THE JOURNAL

OF THE

AMERICAN CHEMICAL SOCIETY

VOL. LXX

APRIL—AUGUST

1948

EASTON, PA.
MACK PRINTING COMPANY
1948

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 70 MAY 3, 1948 NUMBER 4

[CONTRIBUTION OF COLLEGE OF AGRICULTURE, UNIVERSITY OF MISSOURI]

The Electrochemical Properties of Mineral Membranes. VI. Clay Membranes for the Determination of Calcium[1]

BY C. E. MARSHALL[2a] AND A. D. AYERS[2b]

Introduction

Three previous papers in this series[3] have dealt with the use of clay membranes in the potentiometric determination of potassium, ammonium, and sodium. In the course of this work it was found that most of the clay membranes prepared were sensitive also to divalent cations. An important and useful exception was provided by membranes prepared from hydrogen montmorillonite (electrodialyzed Wyoming bentonite) previously heated to 450–550°, which were sensitive to monovalent cations but not appreciably to divalent. These were used for the determination of potassium and ammonium. As regards calcium, some preliminary work had shown that quantitative results could be obtained at low concentrations using membranes prepared from Putnam clay (hydrogen beidellite), previously heated to 500–600°.[4] The present work is concerned with the variations in the properties of clay membranes which affect their suitability for the determination of calcium. We have studied two clays, Wyoming bentonite and Putnam subsoil clay, two exchange cations, hydrogen and calcium, and a range of temperatures of pretreatment from 300 to 600°.

Theoretical Considerations

In all our previous work considerable use has been made of the Teorell–Meyer and Sievers theory of porous, charged membranes. As the work has progressed it has become evident, firstly, that certain of its postulates are not fulfilled by clay membranes; secondly, that quantitative departures from its predictions are generally found. Necessary modifications of the theory for the essentially non-porous clay membranes will be dealt with in a later paper. However, the great importance of the charge A, which can be regarded as the thermodynamic activity of the ions associated with the membrane material itself, cannot be denied, and must be taken into account in any modification of the existing theory. The charge A, sometimes known as the selectivity constant, is responsible for the setting up of two Donnan potentials, one near each surface, which have the effect, in the case of a negatively charged membrane, of greatly reducing the anion activity in comparison with cation activity. Hence, the membrane acts as though the anions possess a greatly reduced or negligible mobility. In the limiting case the potential across it can then be calculated according to the Nernst equation, taking the cations only into consideration. In the practical development of membranes suitable for the determination of various cations, it is important in each case to establish the concentration limits over which accurate results can be obtained. The upper limit is chiefly determined by the magnitude of A. The lower limit varies in different cases; it is affected by the hydrolysis of the membrane itself as well as by hydrolysis of salts of weak bases and strong acids at high dilutions. In the case of potassium it was shown that using 490° hydrogen bentonite membranes accurate results could be obtained in the range 0.1–0.0001 molar.

With divalent cations two factors operate in reducing the charge A. Since the Donnan equi-

(1) Joint contribution from the Department of Soils, University of Missouri, and the U. S. Regional Salinity Laboratory, Bureau of Plant Industry, Soils and Agricultural Engineering, Agricultural Research Administration. Journal Series No. 1064 of the Missouri Agricultural Experiment Station.

(2) (a) Professor of Soils, University of Missouri. (b) Associate Chemist, U. S. Regional Salinity Laboratory.

(3) (a) C. E. Marshall and W. E. Bergman, THIS JOURNAL, **63**, 1911 (1941). (b) C. E. Marshall and W. E. Bergman, *J. Phys. Chem.*, **46**, 325 (1942). (c) C. E. Marshall and C. A. Krinbill, THIS JOURNAL, **64**, 1814 (1942).

(4) C. E. Marshall, *Soil Sci. Soc. Am. Proc.*, **7**, 182 (1942).

libria are evaluated in terms of molality, a membrane having a molal charge A in the monovalent case will automatically have a molal charge $A/2$ in the divalent case. Hence, the upper limit at which the Nernst equation is obeyed will correspond to a lower concentration of divalent than of monovalent cations. Secondly, the dissociation of divalent cations from charged surfaces is in general much less than that of monovalent (hydrogen excepted). The charge A can be regarded as the product of the cation exchange capacity and the fraction of cations active or dissociated. It will therefore be greatly lowered in cases where the cations are only slightly dissociated from the membrane surfaces. These factors are illustrated in Fig. 1. The left hand curve is drawn in the conventional manner from the Teorell–Meyer and Sievers equation for the case in which the anion and cation in solution have equal mobilities, $A = 1$; and the cation activities on the two sides of the membrane are in the fixed ratio $a_1/a_2 = 3.000$ throughout. The next curve is that experimentally found for 550° hydrogen beidellite membranes (Putnam clay), using sodium chloride solutions. Transferring to the divalent scale and allowing for the reduction in A to one-half its value gives the third curve. Finally, the curve farthest to the right is the experimental curve for calcium chloride solutions using the same membrane material. Whereas A for sodium chloride solutions is approximately 0.5, the value for calcium chloride is only 0.026. The practical consequence of this, as may be seen from the figure, is that calcium activities can only be determined with this membrane from 0.002 molar downwards. In order to select the most favorable materials, curves have been obtained for hydrogen and calcium bentonite (montmorillonite) and Putnam clay (beidellite) over a range of pretreatments from 300 to 620° (see below).

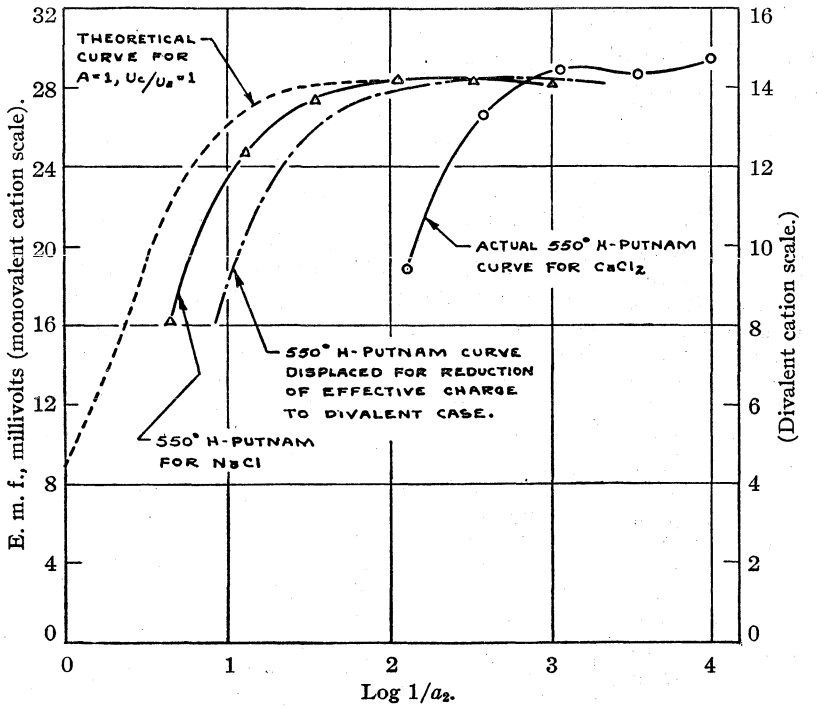


Fig. 1.

The relative behavior of porous membranes as regards different cations can be expressed in terms of mobility ratios. In this formulation the membrane is treated as the limiting case of a liquid junction in which the anions have zero mobility. By application of the Henderson or Planck equations, the potential across the membrane can then be expressed as a function of the activities of the two cations concerned, together with their cationic mobility ratio within the membrane. By measuring the potential when the membrane separates two different salt solutions of known cationic activities, the mobility ratio of the cations can be determined. The equations applicable to different cases have been discussed by Marshall.[5] Once the mobility ratios have been determined it then becomes possible to devise procedures for the analysis of mixtures of cations.

If clay membranes are treated as non-porous then a more rigorous alternative theory (to be discussed in a later paper), relates the potentials observed with different salts to the differential heats of adsorption of the cations concerned. This theory does not as yet facilitate the solution of analytical problems involving mixtures of cations. Hence, in this and the following paper dealing with magnesium, we shall continue to use mobility ratios.

The formulas used for the determination of mobility ratios in the three cases, monovalent–monovalent, divalent–divalent, and monovalent–divalent were derived from the Henderson equation for a liquid junction and are as follows:

Sodium salt on one side of the membrane, potassium salt on the other

$$E = \frac{RT}{F} \ln \frac{a_K^I}{a_{Na}^{II}} \frac{U_K}{U_{Na}} \qquad (1)$$

Calcium salt on one side, magnesium salt on the other

$$E = \frac{RT}{2F} \ln \frac{a_{Ca}^I}{a_{Mg}^{II}} \frac{U_{Ca}}{U_{Mg}} \qquad (2)$$

Potassium salt on one side, calcium salt on the other

(5) C. E. Marshall, *J. Phys. Chem.*, **48**, 67 (1944).

$$E = \frac{RT}{F}\left\{\frac{-a_K^I + \frac{U_{Ca}}{U_K}a_{Ca}^{II}}{-a_K^I + 2\frac{U_{Ca}}{U_K}a_{Ca}^{II}}\right\}\ln\frac{a_K^I}{2\frac{U_{Ca}}{U_K}a_{Ca}^{II}} \quad (3a)$$

As it stands, this equation does not readily lend itself to the determination of U_{Ca}/U_K except by the use of successive approximations. However, if a_K^I is small compared with $U_{Ca}/U_K \times a_{Ca}^{II}$ then we have

$$E = \frac{RT}{F}\frac{1}{2}\ln\frac{a_K^I}{2\frac{U_{Ca}}{U_K}a_{Ca}^{II}} \quad (3b)$$

The way in which mobility ratios so determined can be used may be illustrated by examples which have arisen in investigations of the titration curves of clay acids with bases. Thus in the monovalent–monovalent case we encounter systems comprising a standard potassium salt on one side of the membrane and a clay system containing both hydrogen and potassium ions on the other. Knowing U_H/U_K, a_H^I and a_H^{II} (from a glass electrode measurement) it is possible to calculate the unknown a_K^{II} by applying the equation

$$E = \frac{RT}{F}\ln\frac{a_K^I}{a_K^{II} + \frac{U_H}{U_K}a_H^{II}} \quad (4)$$

Similarly in a calcium–hydroxide titration with a standard calcium solution on one side and a mixture of calcium and hydrogen ions on the other we have

$$E = \frac{RT}{F}\left\{\frac{a_{Ca} - a_{Ca}^{II} - \frac{U_H}{U_{Ca}}a_H^{II}}{2(a_{Ca}^I - a_{Ca}^{II}) - \frac{U_H}{U_{Ca}}a_H^{II}}\right\}\ln\frac{2a_{Ca}^I}{2_{Ca}^{II} + \frac{U_H}{U_{Ca}}a_H^{II}} \quad (5)$$

Substitution of the known quantities E, a_{Ca}^I a_H^{II} and U_H/U_{Ca} does not lead immediately to a solution for a_{Ca}^{II}. This is arrived at by successive approximation, first putting the algebraic quantity before the logarithm equal to one-half and evaluating a_{Ca}^{II}; then using this value to get a better approximation to the quantity before the logarithm; finally using this to calculate an improved value of a_{Ca}^{II}. These three operations are generally sufficient.

Thus the characterization of membrane materials for analytical use involves both the determination of the range of activities over which the Nernst equation is obeyed and a series of mobility ratios. Good methods for the analysis of mixtures can only be developed in cases where the mobility ratio shows reasonable constancy over a sufficiently wide range of concentrations.

Experimental Methods

These were essentially the same as those described in earlier papers dealing with potassium[3a] and sodium.[3c] Since the membranes sensitive to calcium have relatively low resistances (<50,000 ohms) a galvanometer with a sensitivity of 0.025 microamp. per scale division could be used without amplifier in measuring to 0.1 millivolt. The cell measured was Hg, Hg_2Cl_2 Saturated KCl/Solution I/Membrane/Solution II/Saturated KCl Hg_2Cl_2 Hg, the calomel electrodes being of the special type previously described with upturned capillary tip containing saturated potassium chloride in a potassium agar gel. For accurate results fresh calomel electrodes were used whenever the calcium concentration in II was changed. This is important, since if an electrode of this type is transferred from one solution to another, liquid junction potentials which persist for some time can be set up between that part of the first solution which diffused into the capillary tip and the second solution employed. Corrections were applied for the asymmetry potential of the membranes (only those membranes were employed whose asymmetry potentials were less than 1 millivolt) and for the small differences between different calomel electrodes. All results were finally corrected to 25°.

Since the membranes themselves were of relatively low resistance in most cases, the concentrations of the two solutions had a measurable influence upon the total resistance of the cell. A considerable increase in total resistance was noticed in proceeding from $M/1000$ to $M/10{,}000$ solutions of calcium salts.

In membranes prepared from the same sheet of evaporated clay and subsequently treated similarly, individualities still persist, due probably to variation in film structure caused by differences in the rate of evaporation in different parts. They show themselves chiefly in the more concentrated solutions where the theoretical Nernst potential is not attained. Where different salts are employed on the two sides, the mobility ratios are affected and considerable departures from the average value are sometimes encountered. These differences in mobility ratio values are more marked for the monovalent–divalent cases than for monovalent–monovalent or divalent–divalent.

As in previous work, the membranes were first selected for uniformity of thickness and freedom from cracks. They were then mounted and were soaked twenty-four to forty-eight hours—sometimes up to five days—in a calcium chloride solution more concentrated than those employed in measurements. A selection was then made of those with asymmetry potentials below 1 millivolt. The results reported below are averages of from 6–12 membranes so chosen.

In characterizing membranes in their behavior toward calcium ions a series of calcium chloride solutions was required, so adjusted that the calcium ion activities were, for successive pairs, in the fixed ratio 3.000 to 1. The calculations from the activity coefficients of the salt involve two non-thermodynamic assumptions; (1) that in potassium chloride solutions the anion and cation contribute equally to the total activity; (2) that in potassium chloride and calcium chloride solutions of equal ionic strength the chloride ion activities are the same. The primary data used were those of Shedlovsky and MacInnes[6] on potassium chloride and those of McLeod and Gordon[7] on calcium chloride. At any given value of the ionic strength, the following relationship holds.

$$\gamma_{Ca^{++}}^{+} = \frac{(\gamma_{CaCl_2}^{\pm})}{(\gamma_{KCl}^{\pm})^2}$$

where $\gamma_{Ca^{++}}^{+}$ is the activity coefficient of the calcium ion alone, $\gamma_{CaCl_2}^{\pm}$ is the mean activity coefficient of the calcium chloride, and $\gamma_{KCl}^{\pm}$ is that of the potassium chloride. Thus the data are assembled from which a final plot of the activity of the calcium ion against the molality of the calcium chloride could be made. Several such curves were drawn to cover the whole range from 0.1 to 0.0001 molal in suitable steps. Table I presents the data as used for making up standard calcium chloride solutions.

(6) T. Shedlovsky and D. A. MacInnes, THIS JOURNAL, **59**, 503 (1937).

(7) H. G. McLeod and A. K. Gordon, *ibid.*, **68**, 58 (1946).

TABLE I

Calcium ion activity, $a_{Ca^{++}}$	Calcium chloride molality, m	G. $CaCl_2$ per 1000 g. H_2O
0.0001	0.000108	0.01198
.0003	.000350	.03884
.0009	.001150	.12763
.0027	.004250	.47167
.0081	.017300	1.91996
.0243	.077000	8.54546

The Effects of Heat Treatments upon Membrane Potentials.—For the four clays used, hydrogen and calcium bentonite (montmorillonite, fraction <200 mμ), and hydrogen and calcium Putnam clay (beidellite, fraction <200 mμ) the relationships are apparent from Figs. 2–5.

(a) **Hydrogen Bentonite (Fig. 2).**—Only membranes pretreated at temperatures below 450° gave reproducible results for calcium. This is in line with the fact previously discovered,[3a] that 490° hydrogen bentonite membranes were sensitive to monovalent cations, but not to divalent. Membranes pretreated at 300, 350 and 400° were closely alike and gave theoretical results for calcium ion activities below 0.0081.

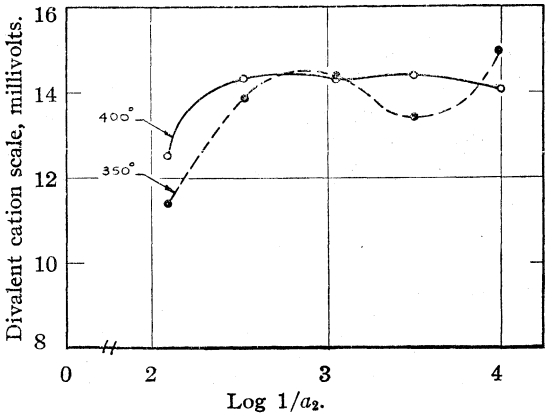


Fig. 2.—Hydrogen bentonite with $CaCl_2$.

(b) **Calcium Bentonite (Fig. 3).**—Between 300° and 600°, increase in the temperature of pretreatment afforded only slight improvement in the electrochemical properties. The 550–600° membranes gave potentials less than 1 millivolt below the theoretical value of 14.1 millivolts even for the 0.0243 and 0.0081 $a_{Ca^{++}}$ solutions. Thus calcium activities below 0.02 extending down to 0.0001 can readily be determined with these membranes.

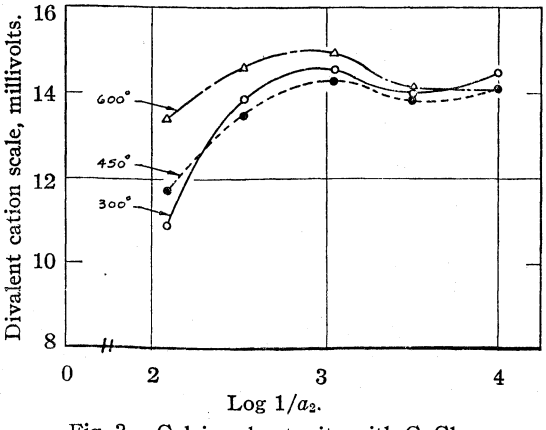


Fig. 3.—Calcium bentonite with $CaCl_2$.

(c) **Hydrogen Putnam Clay (Fig. 4).**—A steady improvement in electrochemical properties with increasing temperature of pretreatments may be seen. None are as good as the corresponding calcium bentonite membranes.

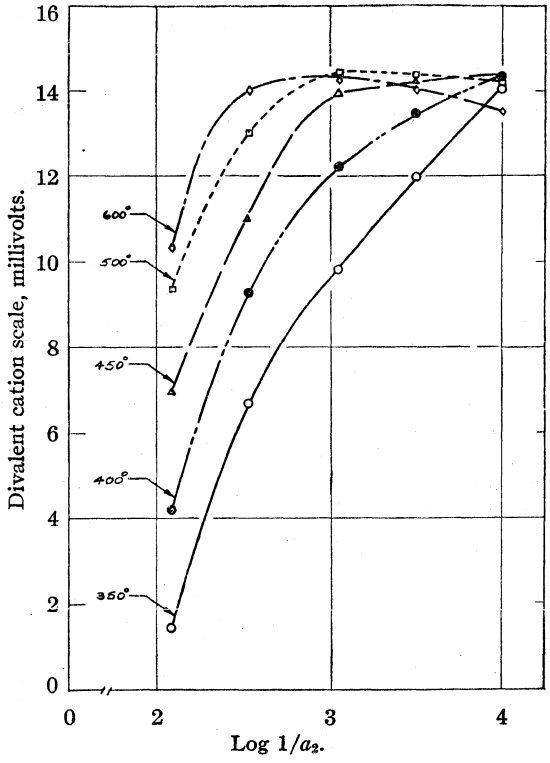


Fig. 4.—Hydrogen Putnam with $CaCl_2$.

(d) **Calcium Putnam Clay (Fig. 5).**—These membranes were consistently a little better than those from hydrogen Putnam clay and in the range 500–600° were very similar to one another, and to the corresponding calcium bentonite membranes. However, at the highest concentration used the latter are somewhat better.

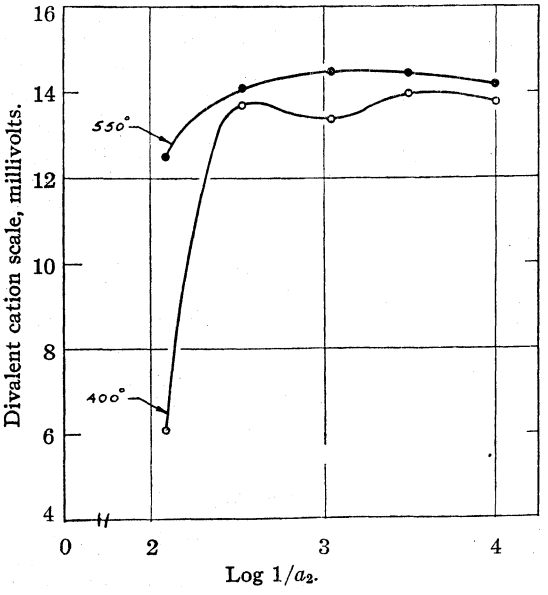


Fig. 5.—Calcium Putnam with $CaCl_2$.

The over-all accuracy of calcium ion determinations in the activity range 0.02–0.0001 using the best membranes is thus around 2–3%. Comparisons of calcium ion activities which are closely alike can be made somewhat more precisely than this, but even here deviations up to 2% are not uncommon.

Cationic Mobility Ratios in Relation to Pretreatment.—More time was needed to establish reproducible potentials with two different cations than where the same cation was present on both sides of the membrane. This was especially true for the monovalent/divalent ratios and in some instances constant values could only be obtained after six to twelve hours contact, with several renewals of the two solutions.

The range of concentrations which can be used in investigating monovalent/divalent mobility ratios is distinctly circumscribed by the fact that if equation 3b is to be used the activity of the monovalent ion must be small compared with the activity of the divalent ion multiplied by the mobility ratio divalent cation/monovalent cation.

As will be evident from the data, monovalent/divalent mobility ratios vary in most cases considerably with concentration. Varying temperatures of pretreatment affect this variation, but not consistently, and change in a somewhat erratic manner the magnitude of the ratio. Table II illustrates the experimental technique for two cases, one of wide variability with concentration and one showing reasonable constancy.

(1) **Calcium–Hydrogen Mobility Ratios.**—In Table III the minimum and maximum values obtained in experiments similar to those of Table II are assembled for clay membranes pretreated at various temperatures. In utilizing these data in the selection of membranes best suited for quantitative work with calcium and hydrogen it must be remembered that if U_{Ca}/U_H is very small, then a_H is multiplied by a large number (U_H/U_{Ca}) and variations in a_H may cause more change in the total potential than variations in a_{Ca}. Other conditions being favorable, the best membranes for this case are those for which U_{Ca}/U_H comes closest to unity.

TABLE II

Membrane material	$a_{Ca^{++}}$	a_{H^+}	Mean mobility ratio, U_{Ca}/U_H
615° Calcium	0.0081	0.000549	0.052
putnam	.0081	.000229	.099
	.0081	.000091	.138
	.0027	.000549	.313
	.0027	.000229	.085
	.0027	.000091	.172
615° Calcium	.0081	.000549	.457
bentonite	.0081	.000229	.545
	.0081	.000091	.466
	.0027	.000549	.674
	.0027	.000229	.615
	.0027	.000091	.496

Hydrogen bentonite membranes pretreated at temperatures between 350 and 420° afford reasonably constant values of U_{Ca}/U_H not far removed from unity. Above 450° these membranes, as previously noted, become insensitive to Ca^{++}.

Calcium bentonite membranes pretreated at 350 and 465° give somewhat lower values, but for 615° membranes the mobility ratio U_{Ca}/U_H varies less with concentration and rises to a value similar to those of the 350 and 415° hydrogen bentonite membranes discussed above.

Hydrogen Putnam membranes show considerable variation with concentration and U_{Ca}/U_H is low, although it rises somewhat with increasing temperature of pretreatment.

Calcium Putnam membranes also show unfavorable properties and the variation with concentration is very marked for those pretreated at 615°.

Thus in work involving mixtures of calcium and hydrogen, such as potentiometric titrations, the most favorable conditions are afforded by the 350–415° hydrogen bentonite and the 615° calcium bentonite membranes. The hydrogen ion activity is first measured using the glass electrode, and by applying equation 5 the calcium ion activity can be computed.

(2) **Calcium-Potassium Mobility Ratios.**—Table III summarizes the minimum and maximum values obtained with calcium chloride and potassium chloride solutions in experiments similar to those with hydrogen chloride. Two calcium activities, 0.0081 and 0.0027, were employed, and three potassium activities, 0.001, 0.00033 and 0.00011. The 360° hydrogen bentonite membranes gave the highest calcium/potassium mobility ratios of any tested, with a moderate degree of variability with concentration.

The 350° calcium bentonite membranes showed considerable variation in mobility ratios, some values being higher than unity and some lower. However, the 615° membranes were much more uniform and closely resembled the 360° hydrogen bentonite membranes in actual values. It is interesting to note that a close similarity exists between 350° hydrogen bentonite and 615° calcium bentonite membranes in their calcium/hydrogen mobility ratios.

The hydrogen Putnam membranes showed extreme variation with concentration at low temperatures of pretreatment, but became much more constant beyond 450° where U_{Ca}/U_K became greater than unity. For the lower temperatures values of U_{Ca}/U_K markedly less than unity were found. Around 450° a considerable change occurs in the electrochemical properties of the hydrogen Putnam membranes. It is much less evident in the calcium/hydrogen series discussed above.

The 465° calcium Putnam membranes showed some variability, but the 615° membranes were relatively constant in their Ca/K mobility ratios.

Thus in selecting membranes for determinations of calcium and potassium in mixtures the 615 calcium Putnam membranes are superior to the others. With some attention to concentration limits, the 360° hydrogen bentonite,

TABLE III

THE RANGE OF MOBILITY RATIOS FOR CALCIUM–HYDROGEN AND CALCIUM–POTASSIUM MEMBRANES PREHEATED TO VARIOUS TEMPERATURES

Membrane material	U_{Ca}/U_H, at temp. 350°	415°	465°	615°
H-bentonite	0.49–0.73	0.35–0.71	.....	
Ca-bentonite	0.13–0.35	.....	0.11–0.28	.46–0.67
H-Putnam	0.021–0.094	.....	0.057–0.13	.46–0.17 (595°)
Ca-Putnam	.....	.....	0.039–0.085	.052–0.31
	U_{Ca}/U_K			
H-bentonite	2.9–5.7 (360°)	.....	.....	.....
Ca-bentonite	0.43–1.81	.....	.....	2.8–5.0
H-Putnam	0.018–0.33	0.026–0.48	0.80–1.86	1.02–1.86 (595°)
Ca-Putnam	.....	.....	0.59–1.70	2.03–2.61

615° calcium bentonite and 595° hydrogen Putnam membranes are probably usable. For the potassium determinations alone, membranes insensitive to calcium, such as the 490° hydrogen bentonite membranes previously described, are required.

(3) **Calcium-Sodium Mobility Ratios.**—Only the 615° calcium bentonite and 615° calcium Putnam membranes were examined. As would be expected, the ratios U_{Ca}/U_{Na} were somewhat greater than the corresponding U_{Ca}/U_{K} values. They showed also more variability with concentration.

(4) **Calcium-Magnesium Mobility Ratios.**—A limited series was determined using high temperature membranes. Much greater constancy was found than with the monovalent–divalent series. These results will be discussed in the succeeding paper, which deals with the determination of magnesium.

Summary

Membranes prepared from hydrogen and calcium bentonite (montmorillonite) and hydrogen and calcium Putnam clay (beidellite), preheated to various temperatures, were examined as to their suitability for the determination of calcium. Hydrogen bentonite membranes heated to 300–415° are suitable; at 450° and higher these are insensitive to divalent cations, but sensitive to monovalent. Calcium bentonite membranes are suitable and are improved only slightly by pretreatment between 300° and 550°. Hydrogen Putnam clay membranes showed great improvement with increasing temperature of pretreatment, but even the 600° membranes were somewhat inferior to the 600° calcium bentonite membranes. The calcium Putnam membranes throughout were better than the hydrogen Putnam, but in the range 500–600° were still slightly inferior to the 500–600° calcium bentonite membranes.

Mobility ratios for calcium–hydrogen, and calcium–potassium were also determined. In many cases this ratio varied greatly with concentration. However, the 350–415° hydrogen bentonite and the 615° calcium bentonite membranes showed reasonable constancy for U_{Ca}/U_{H} and could be employed for the analysis of mixtures containing calcium and hydrogen ions. For calcium–potassium the 615° calcium Putnam membranes were the most favorable.

COLUMBIA, MISSOURI RECEIVED SEPTEMBER 29, 1947

[CONTRIBUTION FROM COLLEGE OF AGRICULTURE, UNIVERSITY OF MISSOURI]

The Electrochemical Properties of Mineral Membranes. VII. Clay Membranes for the Determination of Magnesium[1]

BY C. E. MARSHALL[2a] AND L. O. EIME[2b]

The theoretical and experimental considerations which have been discussed in the preceding paper of this series[3,4] apply in large measure to the determination of magnesium. The same membrane materials were under investigation and no change was needed in the experimental techniques.

The magnesium chloride solutions employed were arranged in a series according to the calculated magnesium ion activities, adjacent members being in the fixed ratio 3.00. The calculations employed for this purpose were precisely similar to those described for calcium. The basic data were taken from Landolt–Börnstein,[5] and because the activity coefficients of magnesium chloride solutions only extend down to 0.05 molal, a more extensive extrapolation to low concentrations was required than for calcium chloride. Table I gives the activities and concentrations employed. The latter were checked by gravimetric determination of the magnesium as pyrophosphate.

TABLE I

Magnesium ion activity, $a_{Mg^{++}}$	Magnesium chloride molality, m	Grams $MgCl_2$ per 1000 g. water
0.0001	0.000106	0.0101
.0003	.000330	.0314
.0009	.001152	.1098
0027	.00398	.379
.0081	.01490	1.419
.0243	.05600	5.340

The Effects of Heat Treatments upon Membrane Potentials.—Figures 1–4 illustrate the general situation for the four clays hydrogen bentonite, calcium bentonite (montmorillonite), hydrogen Putnam clay, and calcium Putnam clay (beidellite). One marked difference is apparent in all cases between these curves for magnesium and those previously given for calcium. In the case of magnesium the curves fall off more or less sharply after attaining the maximum value. This greatly restricts the range over which accurate determinations of magnesium ion activities can be made.

(a) **Hydrogen Bentonite.**—As in the case of calcium, the three curves for 300, 350 and 400° membranes lie very close together. They attain the theoretical e.m.f. at a slightly lower activity of magnesium than of calcium. Down to 0.0003 $a_{Mg^{++}}$ they give good values, but beyond it the

(1) This work was aided by a research grant made by the International Minerals & Chemical Corporation to the Department of Soils, for which the authors wish to express their appreciation.

(2a) Professor of Soils, University of Missouri.

(2b) Research assistant and graduate student in Soils and Chemistry, respectively.

(3) C. E. Marshall and A. D. Ayers, THIS JOURNAL, **70**, 1297 (1948).

(4) Journal series No. 1065 of the Agricultural Experiment Station, University of Missouri.

(5) Landolt–Börnstein, Physikalisch-Chemische Tabellen, 5 Auflage, 2 Ergänzungsband, 2 Teil, 1931.

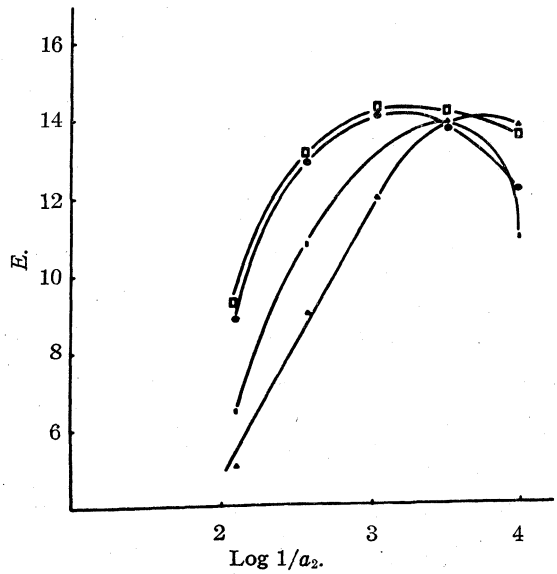


Fig. 1.—Characteristic curves for hydrogen bentonite (montmorillonite) membranes in magnesium chloride solutions: △, 400°; •, 465°; ●, 500°; □, 600°.

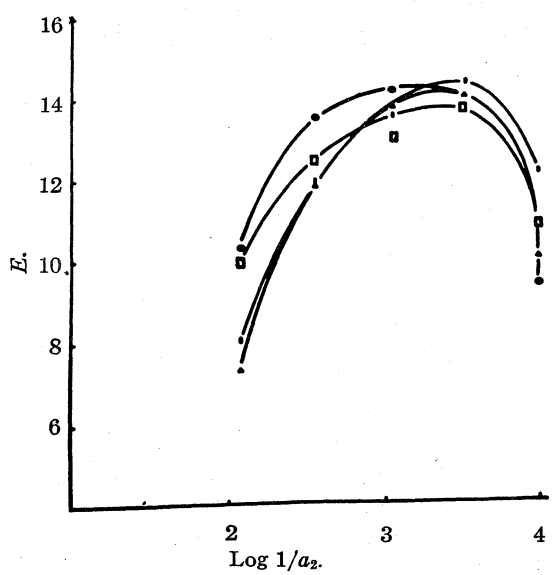


Fig. 2.—Characteristic curves for calcium bentonite (montmorillonite) membranes in magnesium chloride solutions: △, 405°; •, 455°; ●, 500°; □, 550°.

potential shows a rapid falling off. The pair of solutions 0.0003/0.0001 gives only about 10 millivolts instead of 14.1. Thus the range where good accuracy can be secured runs only from about 0.003 to 0.0003.

(b) **Calcium Bentonite.**—These membranes showed considerable improvement with increasing temperature of pretreatment. The 500 and 550° membranes were distinctly superior to the hydrogen bentonite membranes and the usable range of magnesium activities extended from about 0.008 to 0.0003.

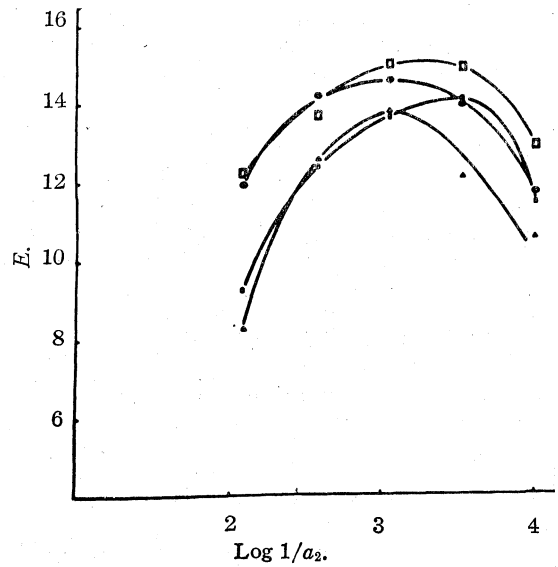


Fig. 3.—Characteristic curves for hydrogen Putnam clay (beidellite) membranes in magnesium chloride solutions: ■, 405°; •, 455°; ●, 500°; □, 550°.

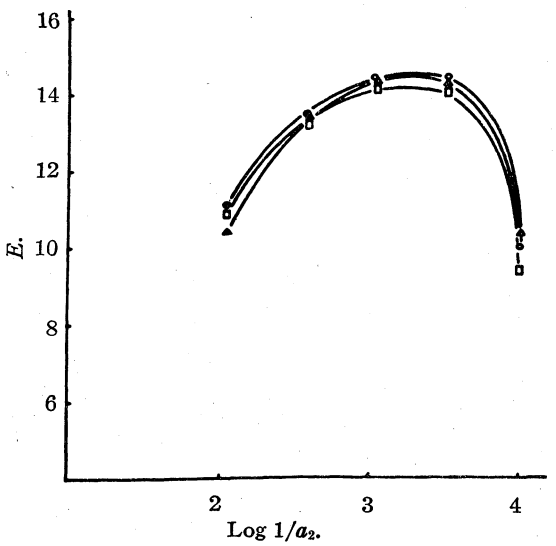


Fig. 4.—Characteristic curves for calcium Putnam clay (beidellite) membranes in magnesium chloride solutions: □, 300°; △, 350°; O, 400°.

(c) **Hydrogen Putnam Clay.**—The properties were considerably improved by higher temperatures of pretreatment. The 600° membranes showed a less marked falling off in potential beyond 0.0003 $a_{Mg^{++}}$ than any of the bentonite membranes. However, the curves were less favorably placed with regard to the higher activities and the usable range runs from about 0.004 to 0.0001.

(d) **Calcium Putnam Clay.**—These membranes were very similar to the corresponding hydrogen Putnam series at the higher activities, but their potentials fell off more below 0.0003.

It can be seen from the curves that the final decline in potential with increasing dilution is general, but that it varies greatly in extent. The basic cause would seem to be hydrolysis, with production of ions such as $(MgOH)^+$. These ions would also affect the membrane potentials, and the preliminary heat treatments would presumably determine to what extent they are potential determining. Unfortunately, the data in the literature on the activity coefficients and equivalent conductivity of magnesium chloride solutions do not extend to sufficiently high dilutions to throw any clear light on their hydrolysis. The same membranes, it should be noted, gave only a very slight indication of a falling off in potential at high dilutions when calcium chloride was used.

One further slight irregularity should be mentioned. There is a tendency for somewhat high potentials to arise at intermediate concentrations, generally with the 0.0027/0.0009 $a_{Mg^{++}}$ pair of solutions. The departure from the theoretical is always less than 1 millivolt, generally around 0.1–0.4 millivolt, but it appears to be real with a given set of membranes. Some of the results with sodium showed similarly high potentials, whereas with potassium and calcium the results were very close to the theoretical.

In consequence, the conditions for the accurate determination of magnesium are distinctly less favorable than for calcium. In the restricted range of magnesium ion activities from 0.008 to 0.0003 using 550° calcium bentonite and 400° hydrogen bentonite membranes, and from 0.004 to 0.0001 using 600° hydrogen Putnam membranes an over-all accuracy of 5% could be relied upon with selected membranes. Comparisons of closely similar magnesium ion activities could be made with greater precision than this.

Cationic Mobility Ratios in Relation to Pretreatment.—The conditions under which divalent–divalent and monovalent–divalent mobility ratios may be determined have been examined in the preceding paper dealing with calcium. The experimental details were essentially the same both for calcium and magnesium.

(1) **Calcium–Magnesium Mobility Ratios.**—When ions of the same valence are employed, the equilibrium potentials are more quickly established and there is less individual variation amongst membranes than for the monovalent–divalent series. Table II gives typical experiments for a series of concentrations; these may be compared with Table II of the preceding paper.

The complete results are summarized in Table III. The variation is much less than for monovalent–divalent ratios. In almost every case where the calcium ion activity is kept constant and the magnesium ion activity decreased, a perceptible fall in the mobility ratio U_{Ca}/U_{Mg} is found. It may be seen that the range of variation is narrow, except for the calcium bentonite and the hydrogen and calcium Putnam membranes heated to around 400°. Excluding these, the range covered is surprisingly similar for the different clays, exchange cations and temperatures of pretreatment. It would not be possible to select from these two sets of membranes with widely different U_{Ca}/U_{Mg} values, which might be used to determine both calcium and magnesium in a mixture by solving two simultaneous equations.

TABLE II[a]

Membrane material	$a_{Ca^{++}}$	$a_{Mg^{++}}$	Mean mobility ratio U_{Ca}/U_{Mg}
615° Calcium Putnam	0.0081	0.0081	1.54
	.0027	.0081	1.59
	.0027	.0027	1.54
	.0009	.0027	1.52
	.0009	.0009	1.33
	.0003	.0003	1.26
	.0001	.0003	1.26
615° Calcium bentonite	.0081	.0081	1.52
	.0027	.0081	1.51
	.0027	.0027	1.40
	.0009	.0009	1.29
	.0003	.0009	1.34
	.0003	.0003	1.24

[a] Determinations by A. D. Ayers.

TABLE III

THE RANGE OF CALCIUM-MAGNESIUM MOBILITY RATIOS OF MEMBRANES PREHEATED TO VARIOUS TEMPERATURES

Membrane material	U_{Ca}/U_{Mg}			
	300°	360°		400°
H bentonite	1.22–1.37	1.36–1.54		1.55–1.66
	405°	455°	500°	615°
Ca bentonite	0.92–1.41	1.08–1.44	1.12–1.45	1.24–1.52[a]
	415°	510°		595°
H Putnam	0.55–1.27 0.64–2.05[a]	1.31–1.45		1.34–1.51 1.38–1.55[a]
	405°	500°	550°	615°
Ca Putnam	0.37–1.18	1.17–1.46	1.38–1.55	1.26–1.59

[a] Determinatons by A. D. Ayers.

(2) **Magnesium–Hydrogen Mobility Ratios.**—Table IV summarizes the range of values obtained with magnesium chloride and hydrochloric acid solutions. The activity of the magnesium ion was held constant at 0.0027 and that of the hydrogen ion ranged downwards from 0.00069. The simplified equation which presupposes that a_H is small compared with a_{Mg} was employed in calculating U_H/U_{Mg} (equation similar to 3b of the preceding paper). Some membranes gave reasonably constant values. In general, the higher temperatures of pretreatment gave the more consistent results. By comparing with Table III of the preceding paper it is apparent that the membranes showing the greatest constancy in U_{Ca}/U_H values are the best also in respect of U_{Mg}/U_H. The actual values of U_{Mg}/U_H are slightly higher than for U_{Ca}/U_H in most cases. The best membranes for use with mixtures of magnesium and hydrogen ions are evidently the

TABLE IV

THE RANGE OF MAGNESIUM–HYDROGEN AND MAGNESIUM–POTASSIUM MOBILITY RATIOS FOR VARIOUS TEMPERATURES OF PRETREATMENT

Membrane material				
H bentonite	Pretreatment at	300°	360°	400°
	U_{Mg}/U_H	0.137–0.201	0.70–0.85	0.81–0.99
Ca bentonite	Pretreatment at	405°		455°
	U_{Mg}/U_H	0.063–0.262		0.250–0.266
H Putnam	Pretreatment at	415°	510°	595°
	U_{Mg}/U_H	0.065–0.139	0.142–0.203	0.126–0.216
Ca Putnam	Pretreatment at	550°		
	U_{Mg}/U_H	0.067–0.24		
H bentonite	Pretreatment at	300°	360°	400°
	U_{Mg}/U_K	0.061–0.602	0.174–0.920	1.60–2.97
Ca bentonite	Pretreatment at	405°	455°	
	U_{Mg}/U_K	0.021–0.236	0.012–0.185	
H Putnam	Pretreatment at	415°	510°	595°
	U_{Mg}/U_K	0.036–0.128	0.239–0.285	0.185–0.201
Ca Putnam	Pretreatment at	500°		
	U_{Mg}/U_K	0.333–0.389		

hydrogen bentonites pretreated at 360 and 400° since these gives ratios of good constancy relatively close to unity. The high temperature calcium bentonite membranes also give good constancy.

(3) **Magnesium–Potassium Mobility Ratios.**—These were also determined under conditions such that a_{K^+} was small compared with $a_{Mg^{++}}$. The latter comprised two values, 0.0081 and 0.0027, and a_K varied from 0.001 to 0.00011. From Table IV it can be seen that U_{Mg}/U_K can be either greater or less than U_{Mg}/U_H for the same membrane, the greater values predominating. On comparing with the ratios U_{Ca}/U_K in Table III of the preceding paper, almost without exception U_{Mg}/U_K is less than U_{Ca}/U_K for the same membrane material. Those showing the greatest constancy in U_{Mg}/U_K are 510° and 595° hydrogen-Putnam, and the 500° calcium-Putnam membranes.

Summary

Using membranes of hydrogen and calcium bentonite (montmorillonite) and hydrogen and calcium Putnam clay (beidellite) preheated over a range of temperatures from 300–600° the conditions most favorable for the determination of the magnesium ion activity have been examined.

Owing probably to the hydrolysis of highly dilute magnesium salt solutions the range was somewhat restricted as compared with calcium. Where magnesium ions alone were concerned, the 400° hydrogen bentonite and 550° calcium bentonite membranes could be used from 0.008 to 0.0003, and the 600° hydrogen Putnam membranes from 0.004 to 0.0001.

Good constancy of the mobility ratio U_{Ca}/U_{Mg} was found with a variety of pretreatments and with the two clays and two exchange cations employed. It was not possible to select membranes with sufficiently widely different values of U_{Ca}/U_{Mg} to make a potentiometric determination of both Mg and Ca in a mixture feasible.

The magnesium–hydrogen and magnesium–potassium mobility ratios were generally variable with concentration. Fortunately, the 400° hydrogen bentonite and 455° calcium bentonite membranes showed reasonable constancy, so that magnesium ions may be determined in the presence of hydrogen ions. The 595° hydrogen Putnam membranes showed the greatest constancy in the magnesium–potassium mobility ratio.

COLUMBIA, MISSOURI RECEIVED SEPTEMBER 28, 1947

[CONTRIBUTION NO. 77 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Kinetics, Mechanism, and Activation Energy of the Cobaltous Ion Catalyzed Decomposition of Ozone[1]

BY GEORGE RICHARD HILL

The rate of decomposition of ozone in an aqueous solution containing hydrogen peroxide and perchloric acid has been investigated by Taube and Bray.[2] The catalytic effect of cobaltous ion on the disappearance of ozone and hydrogen peroxide was noted and the rate constants determined. The purpose of the present investigation has been to study in detail the catalysis by cobaltous ion of the decomposition of ozone in the absence of hydrogen peroxide in order to determine the mechanism of the reaction.

The experimental evidence on the homogeneous catalysis by cobaltous ion is consistent with the mechanism

$$Co^{++} + O_3 + H_2O \longrightarrow CoOH^{++} + O_2 + HO \quad (1)$$
$$HO + O_3 \longrightarrow HO_2 + O_2 \quad (2)$$
$$HO_2 + CoOH^{++} \longrightarrow Co^{++} + H_2O + O_2 \quad (3)$$

Experimental

In each of the experiments, one liter of a solution containing cobaltous sulfate and perchloric acid at known concentrations was saturated with ozone at 0° by bubbling a stream of ozonized oxygen through the container. After a steady state had been achieved, samples of the solution were siphoned through a side arm of the container into calibrated 65 ml. reaction bottles and placed in a constant temperature bath. To each fourth sample was added immediately 3 ml. of a 0.2 *N* buffered potassium iodide solution and the iodide oxidized by the ozone titrated with standard 0.01 *N* thiosulfate.[3] The initial concentration of ozone was computed for each container from these data. The concentration of ozone remaining in the individual reaction vessels after different time intervals was determined using exactly the same procedure. In none of the ozone analyses did the concentration of cobalt ion exceed 1% of the total oxidizing agent present so no correction for oxidation of iodide by cobaltic ion was made.

The concentration of cobaltous ion in the stock solution was determined by amperometric titration with α-nitroso-β-naphthol.[4] C. P. grades of perchloric, acetic and sulfuric acids and of cobaltous sulfate were used. Water, redistilled from Pyrex, was used in all experiments. The ozone was prepared by discharge of a 15,000-volt transformer across a battery of eight Berthelot tubes in series.[5]

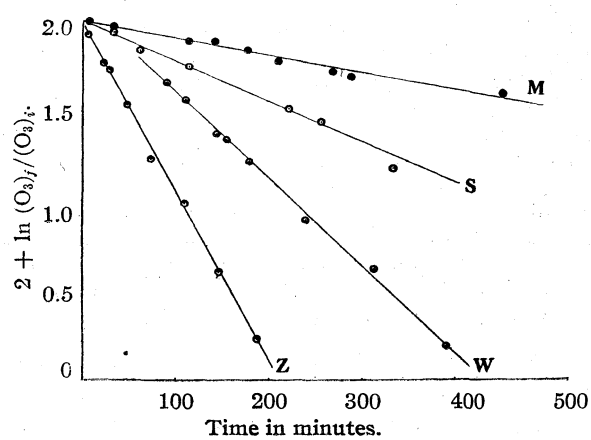


Fig. 1.—The decrease in concentration of ozone at different cobaltous sulfate concentrations: O, S, $(Co^{++})_0 = 6 \times 10^{-5}$ *M*; ●, M, $(Co^{++})_0 = 12 \times 10^{-5}$ *M*; ◒, W, $(Co^{++})_0 = 18 \times 10^{-5}$ *M*; ◓, Z, $(Co^{++})_0 = 36 \times 10^{-5}$ *M*.

Data and Discussion

The reaction was first order with respect to ozone as is shown in Fig. 1. The linear curves are plots of $\ln (O_3)_f/(O_3)_i$ *vs.* time at different concentrations of cobaltous ion. The data for the upper curve on the graph include 8 additional co-linear points determined at longer times.

The reaction was proved homogeneous by experiments in which a 2.3-fold increase in surface area did not change the rate of the reaction appreciably. The reaction rate did not change with substitution of sulfuric acid for perchloric acid as the source of hydrogen ion.

The rate of reaction is independent of hydrogen ion for solutions more acid than *p*H 1.6. From *p*H 1.6 to 3.5 the rate of reaction increases; at the higher value a sol, believed to be $Co(OH)_3$, forms and a heterogeneous reaction no longer first order with respect to ozone ensues. The increased rate with decreasing hydrogen ion can be explained by assuming that the species $CoOH^+$, produced by hydrolysis of Co^{++} in solutions of low acidity, has a higher specific rate of reaction with ozone than does the unhydrolyzed ion.

The rate expression for the disappearance of ozone in acid solution is obtained from equations (1) through (3) as follows

$$-d(O_3)/dt = k_1(O_3)(Co^{++}) + k_2(O_3)(HO)$$

At the steady state

$$\frac{d(Co^{++})}{dt} = \frac{d(HO)}{dt} \backsimeq 0$$

Therefore

$$k_1(O)_3(Co^{++}) = k_2(O_3)(HO) = k_3(CoOH^{++})(HO_2)$$

Since $(Co^{++})_0$, (total cobalt ion) $= (Co^{++}) + (CoOH^{++})$

$$(Co^{++}) = (Co^{++})_0/1 + \frac{k_1(O_3)}{k_3(HO_2)}$$

and

$$\frac{-d(O_3)}{dt} = \frac{2k_1(O_3)(Co^{++})_0}{1 + \frac{k_1(O_3)}{k_3(HO_2)}} = \frac{2k_1(O_3)(Co^{++})_0}{1 + \frac{(CoOH^{++})}{(Co^{++})}}$$

(1) Presented before the Pacific Division of the American Chemical Society meeting in conjunction with the American Association for the Advancement of Science at San Diego, California, June 16–22, 1947.

(2) Taube and Bray, THIS JOURNAL, **62**, 3357 (1940).

(3) Treadwell and Hall, "Analytical Chemistry, Volume II, Quantitative Analysis," 8th ed., John Wiley and Sons, Inc., New York, N. Y., 1935, p. 620.

(4) Kolthoff and Langer, THIS JOURNAL, **62**, 3172 (1940).

(5) L. E. Smith, *ibid.*, **47**, 1844 (1925).

This expression will give first order dependence on initial cobaltous ion concentration and on ozone concentration if the second term in the denominator does not change appreciably during a given experiment. The value of $2k_1/1 + [(CoOH^{++})/(Co^{++})]$ at 0° as determined from a plot of rate *vs.* cobalt ion concentration is 28 mole^{-1} min.$^{-1}$. Spectrophotometric rate measurements leading to the explicit evaluation of k_1 are now being undertaken.

Determination of Activation Energy.—In order to evaluate the heat, entropy, and free energy of activation for the reaction, additional experiments were undertaken at 17.4°, 24.1° and 30.6°. It was found that the spontaneous decomposition of ozone was important at these temperatures and the rate of that reaction determined. The uncatalyzed reaction was found to be of the same order with respect to ozone as the catalyzed reaction.[6] In Table I are given the values for total rate of ozone decomposition, the rate of the uncatalyzed reaction, and the rate of and rate constant for the catalyzed reaction. From a plot of the rate constants (divided by the frequency factor kT/h) *vs.* reciprocal temperature, the following data were obtained: $\Delta H^{\ddagger} = 9{,}000$ cal., $\Delta S^{\ddagger} = -19$ E. U., $\Delta F^{\ddagger}_{298.1} = 14{,}700$ cal. The constants in terms of the Arrhenius equation are: $E_{exp} = 9{,}600$ cal. and $A = 2 \times 10^8$.

TABLE I

RATE CONSTANT DATA FOR OZONE SOLUTIONS CONTAINING 0.0 AND 1.4×10^{-4} *M* $CoSO_4$

Temp., °C.	Total rate of decomposition (ln (O_3)/time)	Rate of uncatalyzed decomposition	$k'(Co^{++})_0$, rate of catalyzed decomposition	k'
0	3.3×10^{-3}	0	3.3×10^{-3}	28
17.4	9.7×10^{-3}	0.02×10^{-3}	9.68×10^{-3}	69
24.1	17.5×10^{-3}	1.0×10^{-3}	16.5×10^{-3}	118
30.6	28.7×10^{-3}	4.1×10^{-3}	24.6×10^{-3}	176

Reaction in the Presence of an Inhibitor, Acetic Acid.—The reaction remains very nearly first order with respect to ozone—in a particular run the rate increases slightly as the ozone concentration becomes low. The data in Fig. 2 show that the rate of decomposition of ozone decreases with increasing acetic acid concentration to a limiting value of 8 mole^{-1} min.$^{-1}$ at 0°. The concentration of perchloric acid and of cobalt sulfate were the same as in the uninhibited reactions. A ratio of acetic acid to cobaltous ion of 2:1 effects a decrease in the rate to 10 mole^{-1} min.$^{-1}$. These data suggest that in the equilibrium $CoOH^{++} + HAc \rightleftarrows CoAc^{++} H_2O$, whose constant is very large, the cobalti–hydroxide complex is converted to cobalti–acetate complex and that the latter is reduced more slowly by HO_2 than is the hydroxide complex. The rate expression for decomposition of ozone in the solution containing acetic acid is

$$-\frac{d(O_3)}{dt} = \frac{2k_1(O_3)(Co^{++})_0}{1 + \frac{(CoAc^{++})}{(Co^{++})}[1 + 1/K(HAc)]}$$

A decrease in the ratio $(CoAc^{++})/(Co^{++})$ during the run would account for the observed increase in rate at low ozone concentrations.

(6) Sennewald, *Z. physik. Chem.*, **A164**, 305–317 (1933).

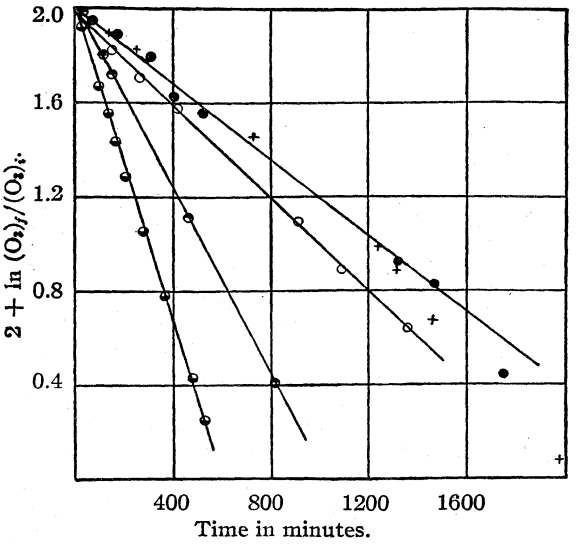


Fig. 2.—Decrease in concentration of ozone at different concentrations of acetic acid: ●, (HAc) = 56×10^{-4} *M*; +, (HAc) = 5.6×10^{-4} *M*; ○, (HAc) = 2.8×10^{-4} *M*; ◒, (HAc) = 0.28×10^{-4} *M*; ◒, (HAc) = 0.0 *M*. $(Co^{++})_0 = 1.4 \times 10^{-4}$ *M* and $(H^+) = 0.2$ *M* in each run.

Summary

1. The heat, entropy, and free energy of activation have been determined for the cobaltous ion catalyzed decomposition of ozone in acid solution.

2. A mechanism involving HO and HO_2 radicals and cobaltous and cobaltic ions is proposed to account for the observed rate dependence of the homogeneous catalyzed reaction on the concentrations of ozone, cobaltous ion and hydrogen ion.

3. The effect of acetic acid in inhibiting the cobaltous ion catalyzed reaction is explained and the rate of the reaction determined at 0°.

4. Differential equations have been obtained which represent the rates of the reactions in the presence and in the absence of acetic acid.

SALT LAKE CITY, UTAH RECEIVED SEPTEMBER 26, 1947

[CONTRIBUTION NO. 147 FROM THE GOODYEAR TIRE & RUBBER CO. RESEARCH LABORATORY]

Kinetics of the Hydrolysis of Ethyl Thiolacetate in Aqueous Acetone[1]

BY JOHN R. SCHAEFGEN

A study of the kinetics of the hydrolysis of ethyl thiolacetate at ordinary temperatures was undertaken in order to compare the behavior of thiolesters with esters and to gain further insight into the mechanism of hydrolysis.

Recorded information concerning thiolesterification and the hydrolysis of thiolesters is limited to qualitative observations and some equilibria and rate studies at elevated temperatures.[2] The data reported in this paper give rate constants and activation energies for the acid catalyzed and the alkaline hydrolysis of ethyl thiolacetate in aqueous acetone solutions containing 24.6, 43.0, and 62.0% acetone by weight. Aqueous acetone was selected as the reaction medium because both thiolester and sodium hydroxide were sufficiently soluble for rate studies in such a mixture over a wide range of composition, and, in addition, a comparison with ester kinetic studies in the same medium was possible.[3]

Experimental

Ethyl thiolacetate was prepared in 77% yield (b. p. 112–115°) by treating ethyl mercaptan with acetyl chloride. The thiolester was purified by fractionally distilling it from anhydrous potassium carbonate through a short packed column. A center constant boiling fraction (113.5° (735 mm.)) was used in the rate studies. This fraction had a refractive index $n^{20.6}D$ 1.4583 and a density d^{20}_4 0.9792. The saponification equivalent was somewhat erratic giving both high and low values depending on the solvent and the length of time allowed for complete hydrolysis. The average value was close to the theoretical, however.

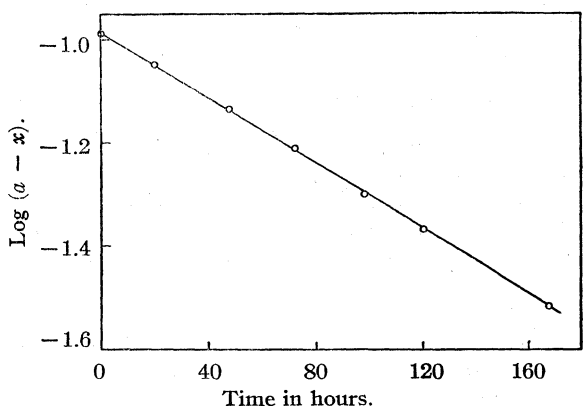


Fig. 1.—The acid catalyzed hydrolysis of ethyl thiolacetate at 40° in 24.6% acetone–water solution: thiolester, 0.1034 *M*; HCl, 0.0985 *M*.

(1) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the New York Meeting, September, 1947.

(2) W. Michler, *Ann.*, **176**, 177 (1875); E. E. Reid and co-workers, *Am. Chem. J.*, **43**, 489 (1910); THIS JOURNAL, **38**, 2746 (1916); **39**, 1930 (1917).

(3) G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940).

The water–acetone mixtures were made up by weight from boiled distilled water and C. P. acetone dried over and distilled from anhydrous potassium carbonate.

Acid Catalyzed Hydrolysis.—The thiolester solutions were prepared by diluting a weighed quantity of ethyl thiolacetate with aqueous acetone of the desired composition in a volumetric flask. The initial concentration was calculated using the theoretical molecular weight. Appropriate quantities of thiolester and of hydrochloric acid solutions (also in aqueous acetone) were mixed at zero time and the initial concentration of acid was determined by titrating a 10-ml. aliquot with standard 0.1 *N* sodium hydroxide. Additional 10-ml. samples were withdrawn from time to time and titrated to follow the reaction. The mercaptan formed in the reaction interferes with the end-point. Therefore, air freed of carbon dioxide was bubbled through the solution for ten to fifteen minutes to remove mercaptan before a final end-point was determined. The reaction mixture was maintained at constant temperature by means of a thermostat. In some solutions, mainly those high in water content, the mercaptan formed by the hydrolysis separated out as the reaction proceeded. This would tend to make the rate constants low in these cases if much thiolester dissolved in the mercaptan layer.

Alkaline Hydrolysis.—Thiolester solutions were made up the same as for acid catalyzed hydrolysis. Base solutions were prepared by diluting the desired quantity of aqueous carbonate-free sodium hydroxide with acetone until the desired composition was obtained, and making up to volume with aqueous acetone. Appropriate volumes of thiolester and of base solutions were pipetted into separate arms of an inverted Y reaction tube which was partially immersed in a thermostat. The solutions were mixed at zero time by tilting the tube. Samples (10 ml.) were withdrawn from time to time by means of a calibrated free-flowing pipet and were delivered into a slight excess of 0.02 *N* hydrochloric acid solution to stop the reaction. The time of the sample was taken as the time of half delivery. The samples were then back-titrated with 0.02 *N* carbonate-free base solution until a faint phenolphthalein end-point was reached. Air freed of carbon dioxide was bubbled through the solution for ten to fifteen minutes to remove mercaptan before the final end-point was determined just as in acid catalyzed hydrolysis.

Discussion and Results

Acid Catalyzed Hydrolysis.—The rate of the acid catalyzed hydrolysis was found to be first order with respect to thiolester concentration in accord with the rate equation

$$dx/dt = k(a - x)[H^+] \qquad (1)$$

where a is the original concentration of thiolester and x is the amount of thiolester hydrolyzed in time t. On integration equation (1) becomes

$$2.303 \log (a - x) = -k[H^+]t + C$$

Graphs of log $(a - x)$ *vs.* t were prepared (such as shown in Fig. 1) to obtain the values of $k[H^+]$. The data for acid catalyzed hydrolysis are summarized in Table I. The lower value of the rate constant observed in the solution 0.2952 *M* in thiolester may be attributed to the decrease in water content of the solution as the hydrolysis proceeds, and to solution of the thiolester in the mercaptan layer formed during the reaction. The rate of the

reaction is directly proportional to the hydrogen ion concentration (*i. e.*, initial hydrochloric acid concentration), k therefore being independent of the hydrogen ion concentration. The lower value of the rate constant observed in the case of the 0.2808 *M* hydrochloric acid solution is probably due to experimental error since there is no trend in the values of k with increasing hydrochloric acid concentration.

The activation energy computed from the Arrhenius equation is independent of the composition of the reaction medium within the accuracy of the measurements.

TABLE I

RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE ACID CATALYZED HYDROLYSIS OF ETHYL THIOLACETATE IN AQUEOUS ACETONE SOLUTIONS

Wt. % acetone	Temp. °C. ±0.03	Initial concn. (m./l.) Thiol-ester	HCl	$k[H^+] \times 10^5$ l./m./min.	$k \times 10^4$ l./m./min.	E, cal./mole
24.6	30.00	0.1050	0.0995	4.81	4.83	17,500
	40.00	.1034	.0985	12.1	12.3	
43.0	30.00	.1030	.1025	2.60	2.54	18,000
	30.00	.0986	.2808	6.04	2.15	
	30.00	.0986	.4700	11.5	2.44	
	30.00	.2952	.0998	2.10	2.10	
	40.00	.0975	.1006	6.54	6.50	
62.0	30.00	.0995	.1009	1.35	1.34	18,000
	40.00	.0985	.1007	3.52	3.49	

Alkaline Hydrolysis.—The rate of the alkaline hydrolysis of ethyl thiolacetate in aqueous acetone solution was found to be second order and to proceed according to the equation

$$\underset{a-x}{CH_3COSC_2H_5} + \underset{b-2x}{2OH^-} \longrightarrow \underset{x}{CH_3COO^-} + \underset{x}{C_2H_5S^-} + H_2O$$

Integrating the rate expression

$$dx/dt = k(a - x)(b - 2x) \qquad (2)$$

leads to

$$[2.303/(2a - b)] \log [(a - x)/(b - 2x)] = kt + C \qquad (3)$$

A graph of log $[(a - x)/(b - 2x)]$ is linear with t in agreement with theory up to 60–70% completion of the hydrolysis, as shown in Fig. 2. If $b = 2a$, equation (2) on integration gives

$$1/(a - x) = 2kt + C' \qquad (4)$$

Accordingly, $1/(a - x)$ is linear with t in this case (Fig. 3).

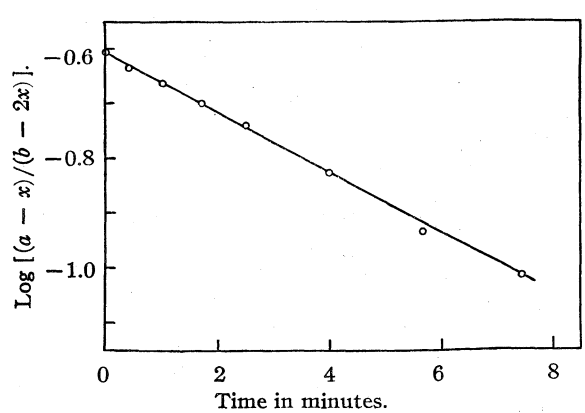


Fig. 2.—The alkaline hydrolysis of ethyl thiolacetate at 20° in 43.0% acetone–water solution: thiolester, 0.0321 *M*; NaOH, 0.1287 *M*.

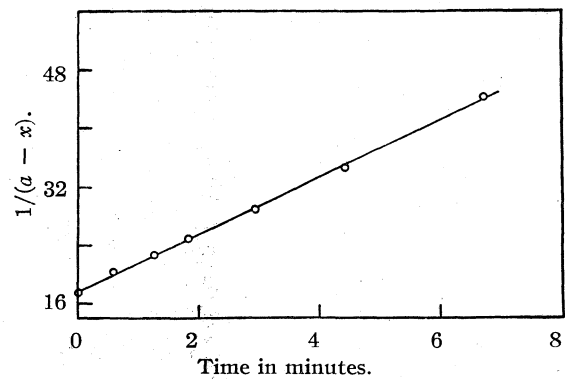


Fig. 3.—The alkaline hydrolysis of ethyl thiolacetate at 20° in 43.0% acetone–water solution: thiolester, 0.0574 *M*; NaOH, 0.1150 *M*.

The data for alkaline hydrolysis are summarized in Table II. The plots from which the energy of activation was determined are shown in Fig. 4. Values of log PZ were calculated from the Arrhenius equation. The rate constant is shown to be independent of thiolester and base concentrations over the small ranges of concentration investigated.

TABLE II

RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE ALKALINE HYDROLYSIS OF ETHYL THIOLACETATE IN AQUEOUS ACETONE SOLUTIONS

Wt. % acetone	Temp. °C. ±0.03	Initial concn. (m./l.) Thiol-ester	NaOH	k (av.)[a] l./mole/min.	E, cal./mole	$\log_{10} PZ$
24.6	10.00	0.0319	0.0637	1.25	13,000	10.2
	20.00	.0369	.0735	2.80		
	30.00	.0319	.0636	5.82		
43.0	10.00	.0570	.1148	0.86	13,800	10.6
	20.00	.0290	.0581	1.91		
	20.00	.0286	.1150	1.98		
	20.00	.0574	.1150	1.98		
	30.00	.0301	.0601	4.39		
62.0	10.00	.0401	.0810	0.638	14,400	10.9
	20.00	.0401	.0802	1.54		
	30.00	.0394	.0795	3.45		

[a] Each of these values is the average of two experiments, the maximum deviation of any value from the mean being 3%.

Comparison with Ester Hydrolysis.—The hydrolysis of ethyl thiolacetate in 62.0% acetone solution is compared to that of ethyl acetate in the same medium in Table III. The rate constant for the acid catalyzed hydrolysis of ethyl acetate at 30° is about thirty times as great as that for ethyl thiolacetate. This difference in k can be attributed almost entirely to the small difference in observed activation energy since the log

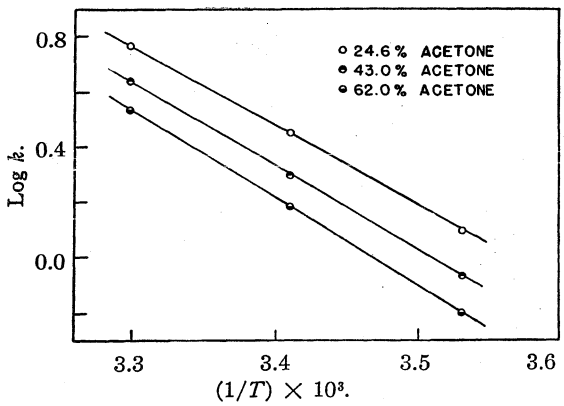


Fig. 4.—The alkaline hydrolysis of ethyl thiolacetate in aqueous acetone. The change of rate constant with temperature.

PZ factor is approximately the same in each case. This would indicate that similar configurational transformations are followed in the acid catalyzed hydrolysis of esters and of thiolesters.

The rate constants for the alkaline hydrolysis of ethyl acetate and of ethyl thiolacetate at room temperature are approximately the same. However, both the activation energy and the log *PZ* factor are much higher for alkaline thiolester hydrolysis than for alkaline ester hydrolysis, indicating that different mechanisms are followed in these two reactions.

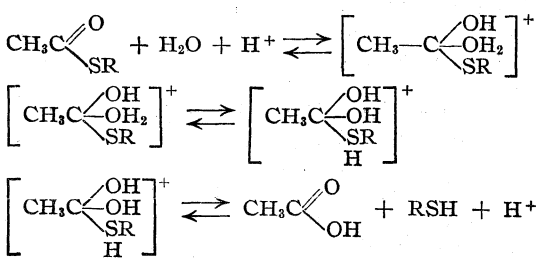
TABLE III

COMPARISON OF THE HYDROLYSIS OF ETHYL ACETATE AND ETHYL THIOLACETATE IN 62% ACETONE SOLUTION

		$CH_3COOC_2H_5$[a]	$CH_3COSC_2H_5$
Acid catalyzed hydrolysis	k at 30°	42.7×10^{-4}	1.34×10^{-4}
	40°	101×10^{-4}	3.49×10^{-4}
	E (kcal./mole)	16.2	17.8
	$\log_{10} PZ$	9.3	9.0
Alkaline hydrolysis	k at 20°	2.13	1.54
	30°	3.74	3.45
	E (kcal./mole)	9.80	14.4
	$\log_{10} PZ$	7.6	10.9

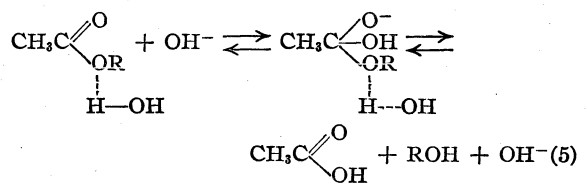
[a] From the data of Davies and Evans, ref. 3.

The mechanism for the acid catalyzed hydrolysis of ethyl thiolacetate is undoubtedly similar to that postulated for ester hydrolysis and may be formulated[4] thus



It should be noted that the addition of the nucleophilic oxygen of the water molecule in the rate controlling first step is favored by polarization of the carbon to sulfur bond; however, the corresponding carbon to oxygen linkage in esters is relatively more polar and the activation energy would therefore be expected to be somewhat lower in the case of ester hydrolysis, in accord with observation (see Table III).

A number of mechanisms have been proposed for alkaline ester hydrolysis, all of which involve an addition of hydroxyl ion at the carbonyl carbon atom in the rate controlling first step with,[5] or without,[6] the aid of a molecule of water to produce the intermediate complex. In the former case the complex then yields the carboxylic acid and the alcohol in a simple decomposition; whereas in the latter case the acid and the alkoxy ion are formed, followed by a second fast reaction with water to produce the alcohol. In view of the work of Kendall,[7] who has demonstrated that solvated ester molecules exist in aqueous solutions of the simple esters, the former mechanism seems more likely, and may be written as follows



The solvated ester complex, formed by hydrogen bonding as shown, reacts with hydroxyl ion in the rate controlling step to produce the intermediate complex which then decomposes to give the observed products. The addition of hydroxyl ion is aided by the small positive charge induced at the carbonyl carbon atom by the added water molecule. The stretching of the C–OR linkage preparatory to rupture is favored by both addition of hydroxyl ion and the electrophilic attack of the hydrogen atom of the water molecule. Thus the activation energy of the reaction, which may be thought[8] of as the energy necessary to add an hydroxyl ion against a negative environment plus a bond stretching energy necessary to break the C–OR linkage, will be much lower by this mechanism than by one in which the coöperation of a water molecule was not involved.

On the other hand, it is quite unlikely that similar solvated thiolester molecules exist in aqueous solution because of the relative weakness of the S---H—O bond compared to the O---H—O bond.[9]

(4) T. Lowry, *J. Chem. Soc.*, **127**, 1381 (1925); I. Roberts and H. Urey, THIS JOURNAL, **61**, 2584 (1939); O. Mumm, *Ber.*, **72**, 1874 (1939).

(5) T. Lowry, *J. Chem. Soc.*, **127**, 1381 (1925); W. B. S. Newling and C. N. Hinshelwood, *ibid.*, 1357 (1936).

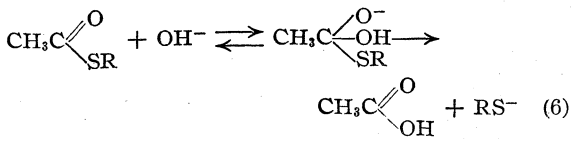
(6) C. K. Ingold and E. H. Ingold, *J. Chem. Soc.*, 756 (1932); J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941); L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 355.

(7) J. Kendall and C. V. King, *J. Chem. Soc.*, **127**, 1778 (1925); J. Kendall and L. Harrison, *Trans. Faraday Soc.*, **24**, 588 (1928).

(8) C. N. Hinshelwood, K. J. Laidler, and E. W. Timm, *J. Chem. Soc.*, 848 (1938).

(9) E. N. Lassettre, *Chem. Rev.*, **20**, 267 (1937).

Therefore the preferred mechanism for alkaline thiolester hydrolysis is



(6)

The activation energy for thiolester hydrolysis by mechanism (6) should be appreciably greater than for ester hydrolysis by mechanism (5) for two reasons: firstly, the coöperation of a water molecule lowers the energy necessary to add hydroxyl ion and to split off alcohol, as pointed out in the preceding paragraph; and secondly, the relatively greater polarization of the C–OR bond in esters compared to the C–SR linkage in thiolesters further lowers the energy necessary for hydroxyl ion addition and bond rupture. The latter reason alone, it should be noticed, is insufficient in itself to account for the large observed difference in activation energies (Table III), since its numerical value will amount to only about 1.6 kcal. as a comparison of acid catalyzed hydrolysis of ester and thiolester reveals (same Table). The steric hindrance to the hydrolysis reaction will be greater for esters (mechanism 5) than for thiolesters (mechanism 6) owing to the shielding effect of the water molecule, thus making the log PZ factor lower for ester than for thiolester hydrolysis, also in accord with observation. On the other hand, the alkaline hydrolyses of ester and of thiolester are similar in that E and log PZ for each reaction both increase with increase in acetone content of the reaction medium[10] (see Table II). The increase of activation energy with change in acetone concentration of the reaction medium is in the expected direction, since a decrease in the dielectric constant of the medium would be expected to decrease the ease of addition of hydroxyl ion at the carbonyl carbon atom.

Acknowledgment.—The author wishes to express his sincere thanks to Dr. Paul J. Flory for his valuable suggestions pertaining to this problem, and to Mr. Daniel Fouser for his assistance in part of the experimental work.

Summary

A kinetic study of the acid catalyzed and the alkaline hydrolysis of ethyl thiolacetate in aqueous acetone has been made. The acid catalyzed hydrolysis is first order with respect to thiolester and with respect to hydrogen ion concentration. The basic hydrolysis is second order. The activation energies are as follows: acid catalyzed hydrolysis 17,800 cal./mole; alkaline hydrolysis 13,000 cal./mole (24.6% acetone solution), 13,800 cal. (43.0% acetone), and 14,400 cal. (62.0% acetone).

A comparison of thiolester and ester hydrolysis has been made, and the mechanisms of hydrolysis have been discussed in view of the results obtained.

(10) R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538 (1937); C. N. Hinshelwood, K. J. Laidler and E. W. Timm, *ibid.*, 848 (1938); R. A. Harman, *Trans. Faraday Soc.*, **35**, 1336 (1939).

AKRON 16, OHIO RECEIVED NOVEMBER 22, 1947

[COMMUNICATION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF NOTRE DAME]

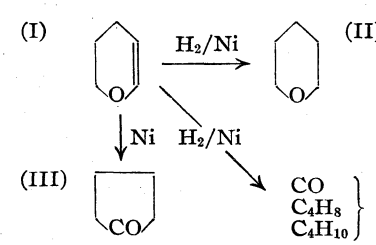
Reactions of Furan Compounds. IX. Catalyzed Rearrangement of 2,3-Dihydropyran into Cyclopentanone[1]

BY CHRISTOPHER L. WILSON

Experiments described in the present paper have shown that 2,3-dihydropyran (I) can be reduced in good yield to tetrahydropyran (II) by passing the vapor with hydrogen over a nickel catalyst at 100°. This confirms an earlier observation.[2] When the temperature was raised to 200° or above, however, two other reactions were noticed. One was ring fission to butane, butene and carbon monoxide and the other rearrangement to cyclopentanone (III). These two reactions have not been recorded before although reference has been made[2] to the formation of unidentified materials of "high molecular weight." Catalysts of nickel or cobalt and mixtures of each of these with copper were effective. On the other hand, copper chromite failed to induce any change whatever.

(1) This paper was presented before the Organic Division at the New York meeting of the American Chemical Society in September, 1947.

(2) British Patent 565,175, Bremner, Jones and Taylor.



The yield of cyclopentanone, calculated on consumed dihydropyran, under favorable circumstances attained almost 30% but the reaction was always accompanied by fission. Replacement of added hydrogen by nitrogen suppressed to some extent both fission and reduction but the rearrangement was only affected to a minor extent. Thus hydrogen does not appear to be essential for this reaction. On the other hand, the catalyst to be active must be so for all three processes and deterioration toward one reaction is accompanied

by inactivation in the other two. These features are illustrated by Tables I and II.

TABLE I

REACTION OF DIHYDROPYRAN VAPOR OVER A NICKEL CATALYST

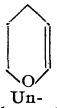
Input: Dihydropyran, 84 g. for each experiment during two hours. Experiments consecutive without catalyst reactivation

Temp., °C.	Carrier and rate (1/hr.)	Unchanged (g.)	Products (g.) n-C_4H_8 n-C_4H_{10}		
100	H_2 45	0	0	77	0
200	H_2 25	7.5	3.3	61	0.9
200	N_2 25	63	0.1	0	2.9
250	N_2 10	44	4.4	1.9	9.2
300	H_2 25	19	11.0	7.5	8.8
300	N_2 10	21	11.0	3.1	7.1

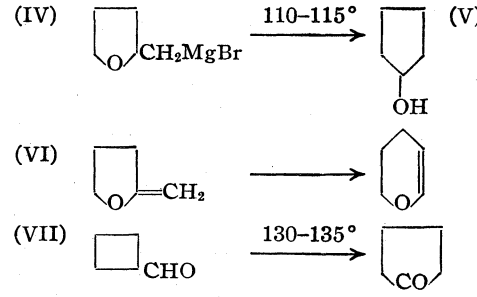
TABLE II

REACTION OF DIHYDROPYRAN VAPOR OVER A COBALT CATALYST

Input: Carrier: 10 l./hr., dihydropyran, 84 g. for each experiment during two hours. Experiments consecutive without catalyst reactivation

Temp., °C.	Carrier	 Unchanged (g.)	Products (g.) n-C_4H_{10}	n-C_4H_8		
250	H_2	27	3.9	1.6	33	7.2
250	N_2	65	0.1	0.1	3.7	6.6
300	H_2	29	4.2	3.6	8.3	10.0
300	N_2	54	0.2	0.6	0.9	5.0
300	H_2	63	0.1	0.1	3.2	2.7

There appears to be no recorded parallel with the reaction leading to cyclopentanone, but certain observations of significance have been made previously. Cyclopentanone is present in the higher ketone fractions from the destructive distillation of wood or lignite which may suggest a connection with furan compounds. Furthermore Paul[3] obtained what he thought was a small amount of cyclopentanol (V) by heating the magnesium derivative of tetrahydrofurfuryl bromide (IV). Later[4] he drew attention to the fact that thermal rearrangement of methylenetetrahydrofuran (VI), which may be made by the elimination of hydrogen bromide from tetrahydrofurfuryl bromide, would be expected to give rise to cyclopentanone if the usual mode of vinyl ether rearrangement was followed.[5] His experiments gave, however, only a poor yield of dihydropyran. At temperatures higher than those Paul used, dihydropyran is known to split into acrolein and ethylene, and it has already been pointed out that if the usual mode of vinyl ether rearrangement obtained here the initial product would be cyclobutane aldehyde.[6] This compound, however, could not be detected but its intervention was not disproved. It has since been noted that cyclobutane aldehyde (VII) on heating in the presence of certain acidic substance rearranges to cyclopentanone.[7] Since this ketone was absent from the pyrolytic products from dihydropyran the intervention of the cyclic aldehyde would appear to be excluded. The catalysed rearrangement of course might proceed in quite another manner, and cyclobutane aldehyde might intervene here before being transformed into cyclopentanone.



The formation of cyclopentanone from dihydropyran offers an explanation of the hitherto unaccountable presence of the cyclic ketone in the products from the reaction of tetrahydrofurfuryl alcohol over a nickel catalyst.[8] It is, however, necessary to suppose the intermediate formation of some dihydropyran which although not detected with a nickel catalyst has since been shown to form using a cobalt catalyst.

The function of the catalyst in the rearrangement is obscure. Activated adsorption involving the C–O links, and particularly the weaker one remote from the carbon double bond, might be expected to be the first step in ring fission and loss of carbon monoxide. On the other hand, adsorption by attachment of the carbon double bond must be an important step in reduction. The type of activation necessary for rearrangement is not so clear but it may be that the second variety which leads to reduction, if hydrogen is also present, might also be responsible for a loosening of the α-hydrogen atom of the double bond. This kind of effect has been recognized ever since it was shown[9] that the rate of hydrogen-isotope exchange with an olefin under the influence of a metallic catalyst is much more rapid than the rate of hydrogen addition to the double bond. If this is so it should be possible to find a catalyst which will cause rearrangement and reduction rather than fission.

Experimental

Catalysts.—These were used in the form of granulated (4–16 mesh) sintered powders. They were placed in the

(3) Paul, *Bull. soc. chim.*, **53**, 424 (1933).
(4) Paul, *ibid.*, **2**, 751 (1935).
(5) Part VII, THIS JOURNAL, **69**, 3002 (1947).
(6) Part VIII, *ibid.*, **69**, 3004 (1947).
(7) Venus-Danilova, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1179 (1938); *C. A.*, **33**, 4203 (1939).
(8) Part III, *J. Chem. Soc.*, 54 (1945).
(9) Farkas, Farkas and Rideal, *Proc. Roy. Soc.* (*London*), **A146**, 630 (1934).

catalyst chamber consisting of a Pyrex glass tube, 1.7 in. diameter, and heated electrically. The metal was activated by oxidation in a stream of air at 500° followed by slow reduction below 300° with hydrogen. The weight of each catalyst and the amount of water produced at the first reduction was as follows, pure nickel (2500 g., 250 cc.), pure cobalt (2300 g., 359 cc.), nickel–copper (50% of each, 2500 g., 607 cc.) and cobalt–copper (50% of each, 2500 g., 425 cc.). Copper chromite (750 g.) prepared by the usual precipitation method was inactive at 225° and 350°. The catalysts were reactivated by oxidation and reduction as above.

Isolation and Analysis of Products.—Dihydropyran was prepared by dehydration of tetrahydrofurfuryl alcohol over aluminum silicate at 350°. After drying over solid sodium hydroxide it had b. p. 86–88°.

The product issuing from the catalytic chamber containing the active metals was passed through a trap at −78° and the condensed portion distilled at atmospheric pressure. Material, b. p. below 20°, consisted of C_4-hydrocarbons. Bromine was added at −78° until addition was complete and the volatile unreacted butane distilled off into a graduated tube where its volume at 0° was measured. The involatile bromide was weighed and the amount of butene to which it corresponded was calculated. The bromide had b. p. 159–160° and would therefore appear to consist essentially of the symmetrical butene dibromide. The boiling point of the 1,2-compound is recorded as 166°.

The fraction of the products collected between 20 and 100° boiled mainly between 70 and 90°. It appeared to contain only di- and tetra-hydropyrans in addition to a little water. The organic substances were estimated in one of three ways depending on the accuracy desired, each method being checked using authentic mixtures. The most accurate was to weigh the precipitated δ-hydroxyvaleraldehyde 2,4-dinitrophenylhydrazone formed by adding a weighed sample to excess of a saturated solution of the hydrazine in hydrochloric acid (2 *N*); the accuracy was 1% with a mixture of equal amounts of the pyrans. A second method, accurate to 6% with the same mixture of pyrans, was to measure the reduction in weight of a sample (5 cc.) after shaking with hydrochloric acid (2 *N*) saturated with sodium chloride. Shaking and separation were carried out in a micro-separatory funnel. This method was only reliable when the pyrans were present in approximately equal amounts. The third method depended on titration of a sample with bromine (about *M*) dissolved in aqueous acetic acid (50%) containing sodium acetate (5%). The last method was the most rapid but least reliable.

Cyclopentanone was estimated in the material, b. p. above 100°, by measuring the reduction in weight after shaking with excess of saturated sodium bisulfite. The method was accurate to within 5% of the ketone which usually amounted to about half the material. A more accurate method for small quantities depended on precipitation with dinitrophenylhydrazine.

In the experiments with nickel, distillation of the material from the last fraction and insoluble in bisulfite gave a small quantity, b. p. 136–142°, which may have been cyclopentanol. It could not be induced to give a solid dinitrobenzoate and was therefore unidentified.

Experiments with cobalt–copper were carried out over a range of temperatures between 200 and 350°. Cyclopentanone was formed in all the experiments above 250° in amounts similar to those with the cobalt catalyst. Reduction and fission were also observed and the catalyst deteriorated in use.

The nickel–copper catalyst was investigated only at one temperature (275°). Dihydropyran (84 g.) was passed over the catalyst with hydrogen (24 l./hr.) during two hours. The product contained *n*-butane, b. p. 0–2° (6 g.), tetrahydropyran, b. p. 87–89° (44 g.), and cyclopentanone, b. p. 129.5–130.5° (7.5 g.), 2,4-dinitrophenylhydrazone, m. p. 142–143°, m. m. p. with an authentic specimen (m. p. 144–145°) was 142–143°. There was no unsaturated material.

Summary

2,3-Dihydropyran has been shown to undergo three simultaneous reactions when passed with hydrogen over catalysts containing nickel or cobalt at a temperature of 200° or above.

The reactions are (1) reduction to tetrahydropyran, (2) fission to butene, butane and carbon monoxide and (3) rearrangement into cyclopentanone.

The mechanism of the reactions is discussed.

NOTRE DAME, INDIANA RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Reactions of Furan Compounds. X. Catalytic Reduction of Methylfuran to 2-Pentanone

BY CHRISTOPHER L. WILSON

Reference was made some years ago[1] to the formation of small amounts of 2-pentanone (II) and 2-pentanol (III) during the gas phase reduction of methylfuran (I) to tetrahydromethylfuran (IV). Experiment has now shown that either tetrahydromethylfuran or 2-pentanone can be the major product depending on conditions. Results obtained using a nickel catalyst at various temperatures are shown in the diagram. At 100° the chief product (86% yield) was tetrahydromethylfuran but as the temperature was raised the quantity decreased and ketone appeared in increasing amounts attaining a maximum (yield 75%) at about 185°. Along with the ketone a small quantity of its reduction product, 2-pentanol, was also formed. Below 150° conversion of methylfuran was complete but surprisingly enough a proportion escaped reaction above this temperature. This coincided with the formation of quantities of gaseous products, with a slight increase in the amount of tetrahydromethylfuran and with a rapid drop in ketone production. No adequate explanation of these variations has yet been found but the reason is undoubtedly connected with complex surface conditions. Furthermore, nuclear hydrogenation of methylfuran might be reversible.

Other metallic catalysts such as cobalt and mixtures of nickel, cobalt or iron with copper as well as copper chromite also gave some ketone but a

(1) French Patent 811,695 (1937).

detailed study of their behavior has not been made.

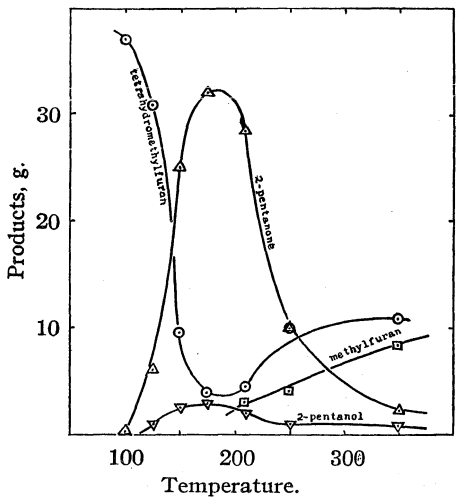


Fig. 1.—Products from methylfuran and hydrogen over a nickel catalyst at various temperatures. Each point corresponds with the passage of 41 g. of methylfuran and 80 liters of hydrogen over the catalyst in two hours.

At present there is little information from which to propose a reaction mechanism. It is particularly uncertain to identify the chemical steps of a catalytic reaction by duplicated experiments with possible intermediates since the conditions on the surface are no longer comparable. Experiment has shown that tetrahydromethylfuran on passage over the catalyst with hydrogen below 200° does not give any ketone. If we ignore the criticism just made of this type of experiment, this fact indicates that ring fission must occur before ring saturation. It may occur therefore either in methylfuran itself or a derived dihydro- compound.

In Part III of this series[2] evidence was presented showing that 2,3-dihydrofuran was much more susceptible to hydrogenative ring fission than either furan or tetrahydrofuran and that the carbon–oxygen bond remote from the carbon double bond was the more readily attacked. Applying these ideas to the reduction of methylfuran would indicate the intermediate formation of an unstable 4,5-dihydromethylfuran (V).

Evidence for the formation of this compound has been presented before[3,4] to account for the formation of some γ-acetopropyl alcohol (VI) during the catalytic reduction of methylfuran in the presence of dilute acid. Presumably dilute acid would hydrolyze 4,5-dihydromethylfuran to acetopropyl alcohol just as it converts 2,3-dihydrofuran into γ-hydroxybutaldehyde.[2]

There still remains the possibility, however, that ring fission occurs in methylfuran itself in the vapor phase by reduction, although the absence of unsaturated products would appear to discount it, and in the experiments in aqueous acid by hydrolysis followed by reduction. In connection with the last point it was shown in the present work during attempts to devise a method for estimating methylfuran that it reacted in the cold with a solution of dinitrophenylhydrazine in dilute hydrochloric acid to give levulinic aldehyde bis-dinitrophenylhydrazone (VII). An analogous reaction is the formation of the dimethylacetal by reaction with methyl alcoholic hydrogen chloride.[5] Levulinic aldehyde might then reduce further to acetopropyl alcohol.

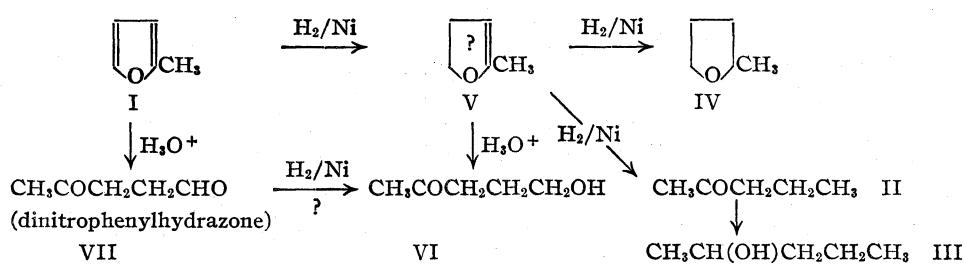
It will be recalled[2] that the reaction of tetrahydrofurfuryl alcohol vapor with a nickel catalyst gave rise to many products including some 2-pentanone. The present work confirms the view then expressed that the ketone arose by fission of methylfuran which was formed from furfuryl alcohol present as an impurity in the commercial tetrahydro-alcohol.

Experimental

Materials.—Methylfuran, b. p. 63–64°, was prepared by reduction of furfuraldehyde using a copper chromite catalyst at 275°. The feed rate was 48 cc. of furfural and 45 liters of hydrogen per hour. The product was distilled, dried over sodium hydroxide and redistilled.

Catalysts.—The description of these excepting iron–copper and pure copper was given in the preceding paper. Iron–copper sintered powder (4% copper, 2200 g., 4–16 mesh) was oxidized at 550° and reduced below 400° giving 64 cc. of water. The pure copper contact material was produced by reducing the granular oxide (1840 g.) below 200°. This metal failed to have any effect on methylfuran either at 280 or 320°. On the other hand, copper chromite gave a 52% yield of 2-pentanone at 340° together with a little pentanol.

Cobalt–copper gave rise to rather more low-boiling materials. The yield of ketone was about 60% at 350°. Iron–copper at 350° gave ketone (4.0 g.), tetrahydro-



(2) Wilson, *J. Chem. Soc.*, 54 (1945).

(3) Topchiev, *Compt. rend. Acad. Sci., U. R. S. S.*, **19**, 497 (1938); *C. A.*, **32**, 8411 (1938).

(4) Schniepp, Geller and Von Korff, THIS JOURNAL, **69**, 672 (1947).

(5) Harries, *Ber.*, **31**, 41 (1898).

methylfuran (10.8 g.) and unchanged methylfuran (16.1 g.) from an input of 41 g.

Isolation and Analysis of Products.—The products from the reaction chamber were caught in a trap at −78° and freed from water either by filtering with exclusion of atmospheric moisture through a small sintered glass funnel kept very cold or by using anhydrous magnesium sulfate. Distillation was effected at atmospheric pressure with a 12-plate fractionating column. Methylfuran constituted most of the fraction, b. p. 60–70°. The amount was checked by conversion into the maleic anhydride adduct using benzene as solvent. Tetrahydromethylfuran was present in the fraction b. p. 70–90° (most 79–80°); 2-pentanone distilled mainly between 101 and 103°, the fraction being collected between 90 and 110°. This fraction was shaken with saturated aqueous bisulfite and correction applied for the small amount of non-ketonic material. The distillation residue contained 2-pentanol, usually too little for separation by distillation. The material from several experiments was collected, any ketone removed by bisulfite and the material shown by distillation to contain 80% of b. p. 117–120°. The figures for 2-pentanol are perhaps the least accurate of those recorded.

The 2,4-dinitrophenylhydrazone of 2-pentanone after recrystallization from ethyl alcohol had m. p. 146–147°. The 3,5-dinitrobenzoate of 2-pentanol recrystallized from ligroin, b. p. 90–120°, had m. p. 61–62°.

Reduction of 2-Pentanone.—The ketone (15 g.) was passed with hydrogen (15 l./hr.) during thirty minutes over the nickel catalyst at 100°. The product consisted of unchanged pentanone (20 g.) and 2-pentanol (12.3 g.).

Dehydrogenation of 2-Pentanol.—The alcohol (10 g.) was passed over the nickel catalyst at 225° together with hydrogen (30 l./hr.). The product contained 95% ketone. Similar results were obtained at 250°.

Tetrahydromethylfuran.—The cyclic ether, b. p. 80–81° (30 g.), was passed during one hour together with hydrogen (30 l./hr.) over nickel at 250°. No ketone was produced but there was considerable gas formation. At 100° the compound was recovered unchanged.

Reaction of Methylfuran with Dinitrophenylhydrazine.—Methylfuran (1 g.) and 2,4-dinitrophenylhydrazine dissolved in hydrochloric acid (2 *N*) were shaken for several days. The yellow precipitate (1.3 g.) was filtered off, washed with water and hot ethyl alcohol. It was insoluble in all ordinary solvents but was crystallized from dimethylformamide forming dark red prisms, m. p. 231° (dec.).

Anal. Calcd. for $C_{17}H_{16}O_8N_8$: C, 44.3; H, 3.5; N, 24.2. Found: C, 44.4; H, 3.5; N, 24.2.

Acknowledgment.—The author is indebted to M. J. While for help with the experiments and to Revertex, Ltd., in whose laboratories some of the work described in this and the preceding three papers in this series was carried out.

Summary

The variation of products with temperature in the reaction of methylfuran vapor with hydrogen over a nickel catalyst has been studied. At 100° the main product was tetrahydromethylfuran while above this temperature 2-pentanone was formed in large amounts. The yield of ketone was a maximum at 185°. Along with the ketone small amounts of 2-pentanol were also formed and at the higher temperatures quantities of gaseous materials.

Other catalysts containing cobalt, copper and iron also resulted in ketone formation but a detailed study of their behavior was not made.

NOTRE DAME, INDIANA RECEIVED AUGUST 18, 1947

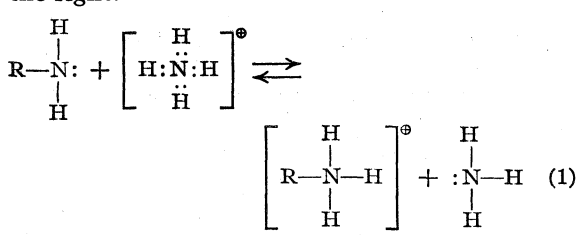
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Low Pressure Reductive Alkylation Method for the Conversion of Ketones to Primary Amines[1]

BY ELLIOT R. ALEXANDER AND ALICE LOUISE MISEGADES[2]

It is well known that carbonyl compounds can be hydrogenated in the presence of ammonia to produce mixtures of primary, secondary, and tertiary amines.[3] Originally the reaction was carried out by the hydrogenation of the carbonyl compound in ethanol, saturated with ammonia, at low pressure over a nickel catalyst.[3a] Better yields and more reproducible results, however, have been obtained over Raney nickel with hydrogen pressures of 20 to 150 atmospheres at temperatures ranging from 40 to 150°.[3b,3c] This technique, while readily carried out, requires high pressure apparatus which is not always available. Accordingly, it was the object of this work to improve Mignonac's low pressure reductive alkylation reaction for the preparation of primary amines.

It appeared that this might be done by taking advantage of the fact that a primary amine is more basic than ammonia. If ammonium ions were introduced into the reaction mixture, the following reaction should occur in which the position of equilibrium should favor the products on the right.



(1)

Since the alkylammonium ion no longer has an electron pair available for combination with the carbonyl group, the process should tend to stop at the formation of primary amines.

(1) Taken from a thesis by Alice Louise Misegades submitted to the faculty of the University of Illinois in partial fulfillment of the requirements for the degree of bachelor of science.

(2) Present address: Albertus Magnus College, New Haven, Connecticut.

(3) (a) Mignonac, *Compt. rend.*, **172**, 223 (1921); (b) Schwoegler and Adkins, THIS JOURNAL, **61**, 3499 (1939); (c) Winans, *ibid.*, **61**, 3566 (1939).

In Table I are summarized the yields which were obtained from a number of reductive alkylations which were carried out in the presence of excess ammonium chloride. The reaction medium was methanol saturated with ammonia and the catalyst was platinum oxide.

TABLE I

REDUCTIVE AMMONATION OF CARBONYL COMPOUNDS IN THE PRESENCE OF AMMONIUM CHLORIDE

Ketone or aldehyde used in preparation[a]	Primary amine prepared	Yield, %
Isobutyraldehyde	Isobutyl-	10
Methyl isopropyl ketone	1,2-Dimethylpropyl-	32
Cyclohexanone	Cyclohexyl-	44–50
Methyl isobutyl ketone	1,3-Dimethylbutyl-[b]	57–65
Benzaldehyde	Benzyl-[c]	14
Dipropyl ketone	1-Propylbutyl-	38–59
Diisopropyl ketone	1-Isopropylisobutyl-[d]	55
Methyl *n*-amyl ketone	1-Methylhexyl-	40
Acetophenone	1-Phenylethyl-	69
Propiophenone	1-Phenylpropyl-	65
Phenylacetone	1-Benzylethyl-	52
Methyl β-naphthyl ketone	1-β-naphthylethyl-[e]	53
Benzophenone	Benzhydryl-	34

[a] Freshly distilled commercial products were used in all cases. [b] Mailhe, *Compt. rend.*, **172**, 693 (1921). [c] The bulk of the product (71%) was dibenzylamine. [d] Reference 3b. [e] Blicke and Maxwell, THIS JOURNAL, 61, 1781 (1939).

It will be observed that the method was only partially successful in preventing the formation of secondary products but that the yields from ketones are quite comparable to those obtained at higher pressures and temperatures.[3b] In the case of isobutyraldehyde, benzaldehyde, methyl isopropyl ketone, cyclohexanone, methyl *n*-amyl ketone, and phenylacetone, considerable amounts of secondary amines were observed. With less reactive ketones such as methyl isobutyl, di-*n*-propyl, diisopropyl, acetophenone, propiophenone, methyl β-naphthyl, and benzophenone there appeared to be very little secondary amine formation. Presumably, the formation of a secondary alcohol was a competing reaction although this point was not investigated.

The improvement ammonium chloride made upon the yield of primary amine can be illustrated with acetophenone and methyl isobutyl ketone. When the reaction was carried out in the absence of ammonium chloride yields of 37 and 49%, respectively, were obtained. Table I shows that yields of 69 and 57–65% were obtained for the same reactions in the presence of ammonium chloride.

Experimental

Reductive Alkylation of Ammonia with Ketones.—An apparatus similar to the one described by Adams and Voorhees[4] was used for the reaction. The carbonyl compounds were all redistilled before use.

In a 300-ml. reduction bottle containing 10 ml. of distilled water, 0.2 g. of platinum oxide[5] was reduced to platinum by shaking in an atmosphere of hydrogen for about ten minutes.[6] The ketone (0.3 mole), ammonium chloride (20.0 g., 0.37 mole), 225 ml. of absolute methanol saturated with ammonia, and 25 ml. of aqueous ammonia were added and the mixture was reduced by shaking with hydrogen at one to three atmospheres. Hydrogenation was continued until a constant pressure reading indicated that reduction had ceased. The shaker was then stopped, The bottle was vented, and the catalyst was allowed to settle. The platinum was removed by filtering the mixture through a Hirsch funnel into a one-liter round-bottomed flask and any salt which collected on the filter was rinsed down with water or methanol. The flask and contents were then removed to a hood and refluxed under a condenser for one hour to remove the excess ammonia.

When the excess ammonia had been removed, the solution was cooled, acidified to congo red paper with concentrated hydrochloric acid, and evaporated to about one-half of its volume under vacuum. Water (200 ml.) was added and the solution extracted with three 25-ml. portions of benzene. The benzene extracts were discarded. The aqueous solution was then made strongly basic with 50% sodium hydroxide solution, the two layers which formed were separated and the water layer was extracted three or four times with ether. The ether extracts and the oily layer were then combined, washed with water and dried over potassium hydroxide. The primary amine was purified by distillation through a 13-cm. column packed with glass helices. The boiling points found agreed well with those recorded in the literature.

In the case of the runs with benzaldehyde, phenylacetone, methyl β-naphthyl ketone, and benzophenone, insoluble salts were formed on acidification. With these compounds the procedure was modified to the extent that the mixture was cooled, the salts filtered with suction and washed thoroughly with water. The filtrate was then extracted with benzene as before and the salts were recombined with it before basing the solution with aqueous sodium hydroxide.

Summary

Experimental conditions have been described for the low pressure hydrogenation of a mixture of a ketone and ammonia to the corresponding primary amine. The reduction was carried out over platinum oxide in methanol saturated with ammonia in the presence of excess ammonium chloride. In general the yields were comparable to those obtained with high pressure equipment.

URBANA, ILLINOIS RECEIVED OCTOBER 18, 1947

(4) Adams and Voorhees, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 61.

(5) Obtained from the American Platinum Works, Newark, N. J.

(6) When an attempt was made to omit this step a long induction period occurred and reduction appeared to proceed much more slowly than normally.

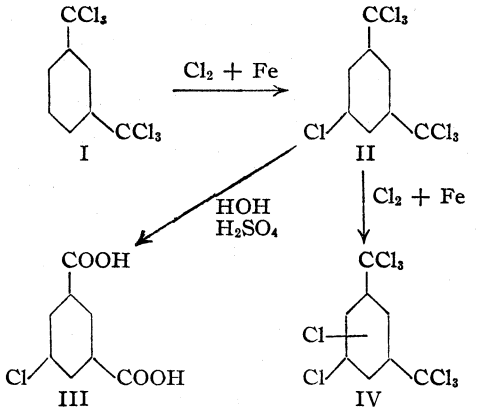
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

Chloro- and Dichloro-*bis*-(trichloromethyl)-benzenes[1]

BY C. K. BRADSHER, P. M. GROSS, M. E. HOBBS, R. S. KITTILA, L. RAPOPORT,[2] P. TARRANT[3] AND G. WEST[4]

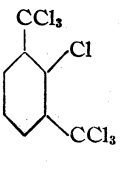
In the course of a program of indirect fluorination carried out in this laboratory, it became necessary to prepare some *bis*-(trichloromethyl)-benzenes containing a chlorinated nucleus. A few such compounds have been mentioned previously, chiefly in the patent literature,[5,6,7,8,9] but with little information as to details of preparation or physical constants. A description of the preparation, physical constants, and, where possible, the proof of structure of some compounds of this class forms the subject of the present communication.

Our investigation followed two general lines, the nuclear chlorination of *bis*-(trichloromethyl)-benzenes and the chlorination of the methyl groups of chloroxylenes. In the nuclear chlorination of 1,3-*bis*-(trichloromethyl)-benzene (I), chlorine enters the position *meta* to the two trichloromethyl groups to yield the new 5-chloro-1,3-*bis*-(trichloromethyl)-benzene (II). Hydrolysis of

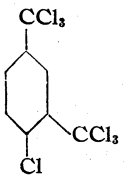


the product yielded the known[10] 5-chloro-isophthalic acid (III).

Introduction of a second chlorine atom into the nucleus of 5-chloro-1,3-*bis*-(trichloromethyl)-benzene (II) or dichlorination of the parent 1,3-*bis*-(trichloromethyl)-benzene (I) alike yielded a viscous liquid which appears to be a dichloro-1,3-*bis*-(trichloromethyl)-benzene (IV). From several of the dichlorination runs there was isolated a small amount of a high melting solid which proved to be 2,5-dichloro-1,4-*bis*-(trichloromethyl)-benzene.[9]



V



VI

The 2-chloro- (V), 4-fluoro-,[11] and 4-chloro-1,3-*bis*-(trichloromethyl)- (VI) and 2-chloro-1,4-bis-(trifluoromethyl)-benzenes were prepared from the corresponding halogenated xylenes by chlorination at elevated temperatures in the presence of a mercury arc, and using the patented technique[6b] of employing a large excess of chlorine in the latter stages. It was found that the 4-chloro-1,3-*bis*-(trichloromethyl)-benzene (VI) obtained from monochlorinated meta-xylene had to be separated from a small amount of the 2-isomer (V). This suggests that nuclear chlorination of the hydrocarbon yields a mixture containing the 2- as well as the 4-isomer, a result that would be predicted by ordinary rules of orientation, but which seems to have escaped earlier workers.[12]

Experimental

5-Chloro-1,3-*bis*-(trichloromethyl)-benzene (II).—A glass reactor was charged with 243 g. of 1,3-*bis*-(trichloromethyl)-benzene[6b] (m. p. 32–36°) and 0.25 g. of iron filings. The reactor was heated to 115–125° and a rapid stream of chlorine bubbled through the liquid for five hours. At the end of this time, the weight increase amounted to 15% more than the theoretical. The fraction distilling at 150–169° (6–7 mm.) amounted to 163 g. and partly solidified on cooling. Recrystallization of the solid portion from alcohol yielded 73 g. of white flakes, m. p. 76–78°. An analytical sample (m. p. 77–78°) gave low values for chlorine, but its identity was established by hydrolysis to 5-chloro-isophthalic acid.

Anal. Calcd. for $C_8H_6Cl_7$: Cl, 71.5. Found: Cl, 71.0.

5-Chloro-isophthalic Acid (III).—The above compound (II) was heated with 100 ml. of 85% sulfuric acid. As the temperature neared the boiling point of the acid,

(1) This research program was sponsored by the Naval Research Laboratory (1942–1944).

(2) Present address: American Cyanamid Co., Stamford, Conn.

(3) Present address: Department of Chemistry, University of Florida, Gainesville, Fla.

(4) Present address: Dayton Rubber Co., Waynesville, N. C.

(5a) Since this manuscript was submitted, but before it was accepted for publication, McBee, Bolt, Graham and Tebbe, THIS JOURNAL, **69**, 947 (1947) have described 4-chloro-1,3-bis-(trichloromethyl)-benzene. The 2-chloro-1,3-bis-(trichloromethyl)-benzene was also prepared but seems not to have been isolated in pure form. No constants are reported for the latter compound.

(5) (a) French Patent 663,791. (b) *Chem. Zentr.*, **100**, II, 2731 (1929).

(6a) U. S. Patent 2,005,712; *ibid.*, **107**, I, 876 (1936).

(6b) French Patent 798,727; *ibid.*, **107**, II, 3360 (1936).

(6c) U. S. Patent 2,132,361; *ibid.*, **109**, II, 4363 (1938).

(7) British Patent 464,859; *ibid.*, **108**, II, 4444 (1937).

(8) French Patent 820,696; *ibid.*, **109**, I, 1661 (1938).

(9) Ruggli and Brandt, *Helv. Chim. Acta*, **27**, 274 (1944); *C. A.*, **38**, 6288 (1944).

(10) Beyer, *J. prakt. Chem.*, [2] **25**, 465 (1882); *cf.* Klages and Knoevenagel, *Ber.*, **28**, 2044 (1895).

(11) We are indebted to Dr. Frances Brown of this Laboratory for the preparation of a quantity of 4-fluoro-1,3-dimethylbenzene from the corresponding amine by diazotization in liquid hydrogen fluoride.

(12) *Cf.* Jacobsen, *Ber.*, **18**, 1760 (1885).

the evolution of hydrogen chloride commenced and proceeded vigorously for several minutes. After cooling, the mixture was poured into a large volume of water and the solid collected. The acidic material was dissolved in sodium carbonate, treated with charcoal, filtered and reprecipitated by addition of concentrated hydrochloric acid. After drying at 120° the white powder melted at 279–280° (lit.[10] 278°). Neutral equivalent calcd. for $C_8H_5O_4Cl$: 100.3. Found: 105, 104.

The dimethyl ester was obtained as white needles, m. p. 79–80°.

Anal. Calcd. for $C_{10}H_9O_4Cl$: Cl, 15.51. Found: Cl, 15.59.

The ethyl ester melted at 50–51° (lit.[10] 45°).

Dichlorination of 1,3-*bis*-(Trichloromethyl)-benzene.—The chlorination was carried out essentially as described above for the preparation of the 5-chloro-1,3-*bis*-(trichloromethyl)-benzene except that chlorination was continued for ten hours, and the temperature was allowed to go as high as 145°. From 204 g. of *bis*-(trichloromethyl)-benzene, 138 g. of a very viscous liquid was obtained b. p. 184–189° (9 mm.). Essentially the same result was obtained by starting with 5-chloro-1,3-bis-(trichloromethyl)-benzene.

Anal. Calcd. for $C_6H_2Cl_2(CCl_3)_2$: active Cl,[13] 55.9. Found: active Cl, 55.4.

In the dichlorination of *bis*-(trichloromethyl)-benzene prepared from research grade *m*-xylene (E. K. 275), a small quantity of a high melting isomer, m. p. 191–192°, was obtained. This was shown to be **2,5-dichloro-1,4-*bis*-(trichloromethyl)-benzene** (lit.[9] 193°).

Anal. Calcd. for $C_8H_2Cl_8$: Cl, 74.3. Found: Cl, 74.8.

2-Chloro-1,3-*bis*-(trichloromethyl)-benzene (V).—The chlorination of 179 g. of 2-chloro-1,3-dimethylbenzene[14] (b. p. 181.5–183°; $n^{25}D$ 1.5241) was carried out at 120–130° in a glass reactor and in the presence of a mercury arc. After the theoretical quantity of chlorine had been absorbed (fifteen hours), the mixture was cooled and the crude crystals collected, m. p. 115–125°; yield 130 g. (30%). On recrystallization from ethanol, white prisms were obtained, m. p. 136–137°.[15]

Anal. Calcd. for $C_8H_3Cl_7$: Cl, 71.5. Found: Cl, 71.5.

4-Chloro-1,3-*bis*-(trichloromethyl)-benzene (VI).[6b,6c]—The chlorination of 166 g. of 4-chloro-1,3-dimethylbenzene (b. p. 181–184°, $n^{17}D$ 1.5269) under similar conditions to those used in the preparation of the 2-isomer yielded 177.5 g. (50%) of 4-chloro-1,3-*bis*-(trichloromethyl)-benzene as a viscous liquid, b. p. 180–185° (8.5 mm.).

Anal. Calcd. for $C_8H_3Cl_7$: Cl, 71.5. Found: Cl, 71.0, 71.5.

The residue from the distillation of 4-chloro-1,3-*bis*-(trichloromethyl)-benzene yielded a small quantity of solid which was identical with the 2-chloro-1,3-bis-(trichloromethyl)-benzene (VI) described above and gave no depression of melting point when mixed with it.

4-Fluoro-1,3-*bis*-(trichloromethyl)-benzene.—The chlorination of 4-fluoro-1,3-*bis*-(trichloromethyl)-benzene[16] was carried out essentially as described for the chloro compounds above, twenty-eight hours being required. Vacuum distillation gave an 82% yield of a colorless oil, b. p. 157.5–159.5° (11 mm.).

Anal. Calcd. for $C_8H_3Cl_6F$: Cl, 64.3. Found: Cl, 64.4, 64.5.

2-Chloro-1,4-*bis*-(trichloromethyl)-benzene[5] was prepared in 79% yield by side-chain chlorination of 2-chloro-*p*-xylene in the manner described above, the crude chlorination product being purified by recrystallization from ethanol, m. p. 78–80°.

Anal. Calcd. for $C_8H_3Cl_7$: Cl, 71.5. Found: Cl, 71.4.

Summary

Some bis-(trichloromethyl)-benzenes containing nuclear halogen have been prepared, and some evidence has been obtained in support of the assigned structures.

(13) The compound was refluxed for eighteen hours with a mixture of 10 ml. of 15% potassium hydroxide solution and 20 ml. of ethanol. After acidification, the chloride ion was determined by the Volhard method.

(14) U. S. Patent 1,796,108; *C. A.*, **25**, 2441 (1931).

(15) This compound has been prepared previously (ref. 6a) but no constants were given.

(16) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

DURHAM, N. C. RECEIVED MARCH 31, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

Chlorination of 1,3-bis-(Trifluoromethyl)-benzenes[1a,b]

BY CHARLES K. BRADSHER AND RICHARD S. KITTILA

In an investigation of methods for the preparation of *bis*-(trifluoromethyl)-benzenes containing nuclear chlorine,[2] the direct chlorination of *bis*-(trifluoromethyl)-benzenes was studied. Recently McBee, Hass, Weimer, Burt, Welch, Robb and Speyer[3] have reported that chlorination in the presence of conventional catalysts, and at temperatures approaching the boiling point of *bis*-(trifluoromethyl)-benzenes is without effect, and this is confirmed by our observations. While it was stated that chloro-*bis*-(trifluoromethyl)-benzenes could be obtained by reaction in the vapor phase at 500°, it was added that "at this high temperature there was extensive chlorinolysis."[4]

We have found that chlorination of *bis*-(trifluoromethyl)-benzenes may be effected readily by carrying out this reaction in an iron reactor at 150–170° and under a chlorine gage pressure of 300 lb./sq. in.

The material used in the majority of our chlorination experiments was a mixture containing both

(1a) This work was sponsored by the Naval Research Laboratory.

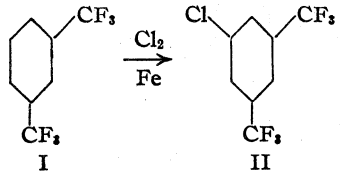
(1b) With the exception of the experiment noted, the material contained in this communication is drawn from a thesis submitted to the faculty of the Graduate School of Arts and Sciences for the degree of Master of Arts, November, 1943.

(2) *Cf.* Bradsher, Gross, Hobbs, Saylor, Tarrant and West, Abstracts of Papers Presented Before the Division of Organic Chemistry at the 111th Meeting of the American Chemical Society, April, 1947.

(3) McBee, Hass, Weimer, Burt, Welch, Robb and Speyer, *Ind. Eng. Chem.*, **39**, 387 (1947).

(4) No yields have been mentioned, and it is clear from the text that this process was abandoned as unworkable.

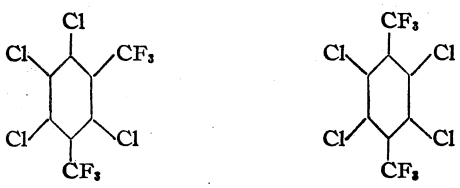
1,3- (I) and 1,4-*bis*-(trifluoromethyl)-benzenes,[5a] but the principal product isolated was 5-chloro-1,3-*bis*-(trifluoromethyl)-benzene[5b] (II), the best yield being 57% (42% conversion).



I II

In each case some material boiling at 170–175° was obtained, and though no chemical individual was isolated with certainty, analysis showed this to consist of dichloro-*bis*-(trifluoromethyl)-benzenes. Similar material could be obtained by the chlorination of either "technical" 4-chloro-[6] or crude 5-chloro-1,3-*bis*-(trifluoromethyl)-benzenes.

Fractionation of the higher boiling material yielded fractions which may have contained trichloro-*bis*-(trifluoromethyl)-benzenes, but no chemical individual other than a crystalline tetrachloro derivative was isolated. The low melting point (47–48°) of the tetrachloro-*bis*-(trifluoromethyl)-benzene suggests that it is 2,4,5,6-tetrachloro-1,3-*bis*-(trifluoromethyl)-benzene (III) rather than the symmetrical 2,3,5,6-tetrachloro-1,4-*bis*-(trifluoromethyl)-benzene (IV).



III IV

The authors are indebted to Dr. Paul M. Gross for his encouragement and many helpful suggestions, to Drs. Marcus E. Hobbs and John H. Saylor for direction of the physical measurements, and to Dr. Carl H. Deal and Miss Virginia Goodbody for most of the physical constants reported.

Experimental

Apparatus.—The reactor used in most of the experiments reported here was made from a 39 in. length of 2.5-in. black iron pipe closed at the bottom by a plate welded on, and at the top by a leaded pipe cap to which was attached a short length of 0.5-in. copper tubing. The copper tubing was connected by flare fittings to a "T" which was provided with a 0–300 lb./sq. in. compressed air gage and a stainless steel exit valve. The gage was protected from the action of the corrosive gas by a coil of 0.25-in. copper tubing, connection being made to the "T" and gage by short lengths of 0.125-in. copper tubing.

General Procedure.—The gage and valve assembly was removed while the reactor was charged through the copper tube at the top with the material to be chlorinated and the apparatus assembled. The end of the tube leading from the exit valve of the reactor was secured to a tank of liquid chlorine and the reactor cooled for one-half to one hour while chlorine distilled into the reactor.

The lower twelve inches of the reactor was next immersed in an oil-bath[7] and the temperature raised. Excess chlorine was valved off until the gage pressure wa 300 lb./sq. in. at the desired bath temperature (usually 150–175°). After heating for a number of hours, the reactor was cooled and the hydrogen chloride and excess chlorine valved off. The gage and valve assembly was removed and the product poured out of the reactor, filtered, washed with dilute acid, dried and distilled.

The reactor was cleaned after each reaction by filling with dilute hydrochloric acid and allowing it to stand for one to three hours. It was rinsed with water and then acetone, and finally dried by evacuation.

5-Chloro-1,3-*bis*-(trifluoromethyl)-benzene.—Using charges of 100–150 ml. of *bis*-(trifluoromethyl)-benzene[5a] and chlorinating for three hours at 150–170°, the best yield of monochloro-*bis*-(trifluoromethyl)-benzene (b. p. 135–145°) obtained under these conditions was 57%, representing a conversion of 42%. Refractionation showed that nearly all of this material boiled at 139–140°, $n^{30}D$ 1.4023, ϵ 3.08. (A sample prepared by the indirect fluorination of 5-chloro-1,3-*bis*-(trichloromethyl)-benzene by the technique of German Patent 575,593 gave: b. p. 138.2–138.3°, $n^{25}D$ 1.4027, ϵ^{23} 3.04.)

Anal. Calcd. for $C_8H_3ClF_6$: Cl, 14.28. Found: Cl, 14.26.

Chlorination of a relatively pure sample of 1,3-*bis*-(trifluoromethyl)-benzene yielded a product boiling at 137.5–138.5°.

Dichloro-*bis*-(trifluoromethyl)-benzene.—(a) By chlorination of *bis*-(trifluoromethyl)-benzene: The chlorination was carried out as in the preparation above except that the reaction was allowed to run longer at slightly higher temperatures. In some cases, the reactor was cooled, the gas pressure released, additional chlorine distilled in, and heating continued for a further period. For example, the chlorination of 280 g. of *bis*-(trifluoromethyl)-benzene for three hours at 175°, recharging with chlorine and heating for an additional four and one-half hours yielded 42% of the dichloro-*bis*-(trifluoromethyl)-benzene (b. p. 167–177°) or a conversion of 39%. This material was refluxed with 6 *M* sulfuric acid to remove hydrolyzable material, washed, dried and redistilled. Most of the material boiled at 173–175°.

(b) By chlorination of "technical" 4-chloro-1,3-*bis*-(trifluoromethyl)-benzene[6]: A small reactor was charged with 67 g. of the 4-chloro-*bis*-(trifluoromethyl)-benzene and chlorinated for two hours at 160–170° to give a 58% yield (45% conversion) of product, b. p. 169–174°.

(c) By chlorination of 5-chloro-1,3-*bis*-(trifluoromethyl)-benzene: Crude 5-chloro-1,3-*bis*-(trifluoromethyl)-benzene (b. p. 135–145°) obtained by chlorination of *bis*-(trifluoromethyl)-benzene was chlorinated for one and one-half hours at 170–185°. The reactor recharged with chlorine and chlorination continued for an additional three hours. An 83% yield (49% conversion) of product (b. p. 168–177°) was obtained.

The material obtained by procedure (a) (b. p. 173–175°) had the properties: $n^{25}D$ 1.4389, ϵ^{27} 2.97, and appeared to be a mixture of isomers.

Anal.[8] Calcd. for $C_8H_2Cl_2F_6$: Cl, 25.06. Found: Cl, 24.75.

(5a) We are indebted to the Hooker Electrochemical Company for this material which is now being manufactured by them on a commercial scale; *cf.* Murray, Beanblossom and Wojcik, *Ind. Eng. Chem.*, **39**, 302 (1947).

(5b) Since this manuscript was submitted but before it was accepted for publication, McBee, Bolt, Graham and Tebbe, THIS JOURNAL, **69**, 947 (1947), have reported some physical properties of 5-chloro-1,3-*bis*-(trifluoromethyl)-benzene; the constants reported are in fairly good agreement with ours. The article referred to indicates that the method of syntheses will be published at a later date.

(6) This material was prepared from monochlorinated technical *meta*-xylene. The low dielectric constant (4.92) suggests that it contains some 2-chloro-1,4-*bis*-(trifluoromethyl)-benzene.

(7) The bath used was made from a larger pipe and was electrically heated by a length of nichrome ribbon insulated with asbestos.

(8) Analysis by Miss Louise Gurney (1947).

Tetrachloro-*bis*-(trifluoromethyl)-benzene.[9]—Chlorination of 238 g. of the dichloro-*bis*-(trifluoromethyl)-benzene obtained above for three hours at 165–215° in the presence of 0.05 g. of aluminum chloride yielded 76 g. of starting material, 55 g. of intermediate fractions (b. p. 180–241°), and finally 31 g. (b. p. 241–244°) which solidified on cooling. Crystallized from ethyl alcohol, it gave colorless crystals, m. p. 47–48°.

(9) Experiment by Jean B. Bond.

Anal. Calcd. for $C_8Cl_4F_6$: Cl, 40.04. Found: Cl, 40.09.

Summary

It has been demonstrated that chlorination of bis-(trifluoromethyl)-benzenes may be effected at elevated temperatures and pressures.

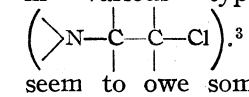
DURHAM, N. C. RECEIVED APRIL 2, 1947

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α-Chloro-β-amino Ketones

BY NORMAN H. CROMWELL AND RONALD A. WANKEL

In a previous communication[1] a study was reported concerning the rate of iodine release from acidified potassium iodide solution by α-bromo β-amino ketones prepared from α-bromobenzalacetophenone. These results were compared with those obtained from similar studies with bromobenzylaminobenzylacetophenone hydrobromides prepared by the reactions of 1-benzyl-2-phenyl-3-benzoylethylenimine with wet and dry hydrogen bromide.[1,2] Also recorded was the fact that at room temperature the chlorobenzylaminobenzylacetophenone hydrochlorides, produced by the action of wet or dry hydrogen chloride, gave a slow iodine release. In this latter case no authentic α-halogenated β-amino ketones were available for comparison as had been the case with the bromo series.

Recently considerable interest has been shown in various types of β-chloroethylamines,  .[3] β-Halogenated ethylamines seem to owe some of their unusual chemical and physiological properties to the ability of their solutions to form the very reactive quaternary ethyleneimmonium ions.[4]

In the present investigation certain α-chloro β-amino ketones have been prepared for iodine release studies and for pharmacological investigation.

Piperidine, morpholine and tetrahydroisoquinoline each added readily to both α-chlorobenzalacetophenone and α-chlorobenzalacetone to give the desired α-chloro β-amino ketones. Attempts to add benzylamine or dibenzylamine or tetrahydroquinoline to α-chlorobenzalacetophenone were not successful. These α-chloro β-amino ketones, especially the α-chloro-β-aminobenzylacetophenones, proved to be considerably more stable than the corresponding bromo compounds reported in the previous studies.[4]

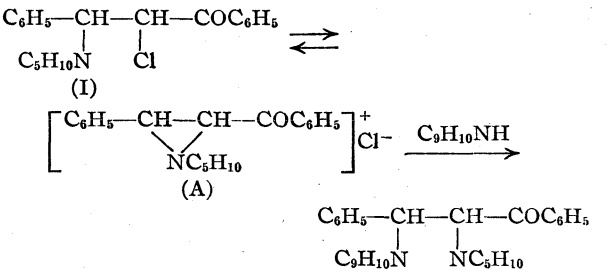
(1) Cromwell and Caughlan, THIS JOURNAL, **67**, 2235 (1945).

(2) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

(3) For example, the nitrogen mustards, Gilman and Philips, *Science*, **103**, 409 (1946); N,N-dibenzyl-β-chloroethylamine, Nickerson and Goodman, *Federation Proc.*, Feb., 1946, p. 195; N-benzohydryl-β-chloroethylamines, Cromwell and Fitzgibbon, THIS JOURNAL, **70**, 387 (1948).

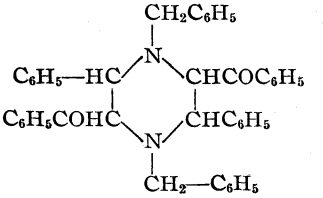
(4) Cromwell and Cram, *ibid.*, **65**, 301 (1943); Cromwell, *Chem. Rev.*, **38**, 118 (1946).

α-Chloro-β-piperidinobenzylacetophenone (I) was quite stable in absolute alcohol solutions at room temperature, showing little tendency to form the quaternary ethyleneimmonium ion (A), as indicated by the slight reaction of such solutions with silver nitrate after standing fifteen hours. However, this α-chloro β-amino ketone reacted readily with tetrahydroquinoline, as did the analogous bromo ketone,[5] to give a good yield of α-piperidino-β-tetrahydroquinolinobenzylacetophenone.



The hydrochlorides of the α-chloro-β-aminobenzylacetophenones were readily prepared and found to be quite stable in alcohol solution, showing no tendency to rearrange to the β-chloro α-amino ketone hydrochlorides. The hydrochlorides of the α-chloro-β-aminobenzylacetones proved to be too unstable to isolate.

For comparative purposes the reactivity of α,β-dichlorobenzylacetophenone with benzylamine was checked and it was found that the yield of the ethyleneimine ketone was about the same as with dibromo ketones.[6] The molecular weight of this product was determined to eliminate the possibility that this compound might be a piperazine such as



(5) Cromwell, THIS JOURNAL, **63**, 2984 (1941).

(6) Cromwell, *ibid.*, **69**, 258 (1947).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR α-CHLORO β-AMINO KETONES

α-Chlorobenzylacetophenones	No.	M. p., °C.	Yield, %	Formula	Chlorine, % Calcd.	Found
β-Piperidino	(I)	124	75	$C_{20}H_{22}ONCl$	10.82	10.64
Hydrochloride	(II)	142	90	$C_{20}H_{23}ONCl_2$	19.47	19.36
β-Morpholino	(III)	127	74	$C_{19}H_{20}O_2NCl$	10.75	10.68
Hydrochloride	(IV)	148	93	$C_{19}H_{21}O_2NCl_2$	19.36	19.27
β-Tetrahydroisoquinolino	(V)	95	69	$C_{24}H_{22}ONCl$	9.43	9.28
Hydrochloride	(VI)	114	91	$C_{24}H_{23}ONCl_2$	17.20	17.01
α-Chlorobenzylacetones						
β-Piperidino	(VII)	57	55	$C_{15}H_{20}ONCl$	13.34	13.12
β-Morpholino	(VIII)	65	66	$C_{14}H_{18}O_2NCl$	13.24	13.04
β-Tetrahydroisoquinolino	(IX)	76	45	$C_{19}H_{20}ONCl$	11.30	11.09

TABLE II

RELEASE OF IODINE BY CHLORO KETONES IN THIRTY MINUTES AT 26° (0.200 G. SAMPLES)

Halogenated ketone	0.0300 *M* $Na_2S_2O_3$, ml. used	required	Per cent. reaction
(III)	1.93	40.40	4.78
(V)	1.35	35.48	3.52
(VI)	0.97	32.38	3.03

As shown in Table II, these various α-chloro β-amino ketones released iodine slowly from acidified potassium iodide solutions at room temperature. At elevated temperatures these compounds reacted with such solutions much more rapidly and at a constant rate. (See Fig. 1 and Table III.) It was also found that the reaction products of 1-benzyl-2-phenyl-3-benzoylethylenimine with wet or dry hydrogen chloride[2] released no iodine under such conditions, and thus both must still be assumed to be β-chloro-α-benzylaminobenzylacetophenone hydrochloride, as was previously decided.[1] This constitutes a method of differentiating between α-chloro β-amino ketones and the very similar β-chloro α-amino ketones.

TABLE III

RELEASE OF IODINE BY CHLORO KETONES AT 66° (0.100 G. SAMPLES)

Sample	Reaction time in minutes	0.0300 *M* $Na_2S_2O_3$, ml. used	required	Per cent. reaction
(I)	20	19.89	20.34	97.8 ± 3.0
(II)	20	18.16	18.34	99.0
	15	16.48	18.34	89.9
	10	10.91	18.34	59.4
	5	5.70	18.34	31.1
(III)	20	19.69	20.20	97.4
(IV)	20	17.43	18.20	95.8
	15	16.90	18.20	92.9
(V)	20	16.95	17.74	95.6
(VI)	20	15.86	16.18	98.0
	15	12.94	16.18	80.0
(IX)	20	20.23	21.24	95.2
β-Chloro-α-benzylaminobenzylacetophenone hydrochloride	30[a]	0.00	17.14	0.0
	30[b]	0.00	17.14	0.0
α-Chlorobenzalacetophenone	20	1.36	27.34	5.0
Morpholine	30	0.00	...	0.0
Blank	30	0.00	...	0.0

[a] From 1-benzyl-2-phenyl-3-benzoylethylenimine and aqueous hydrogen chloride. [b] Using dry hydrogen chloride in benzene, see ref. 2.

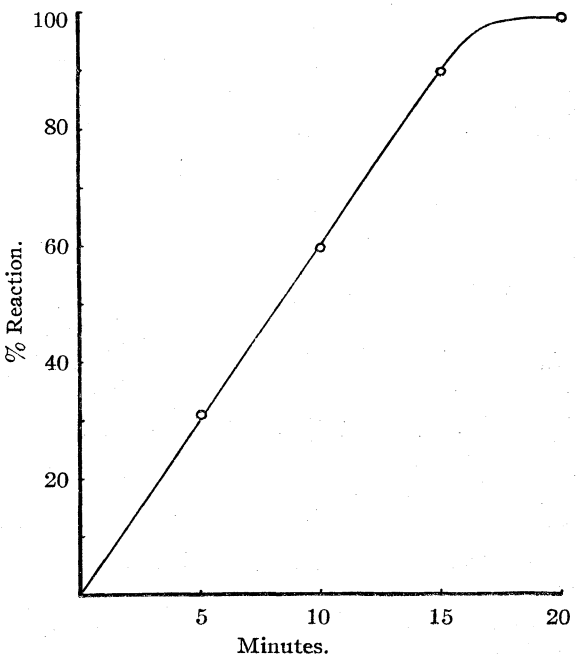


Fig. 1.—Rate of iodine release by (II) at 66°.

Nevertheless, further proof that certain ones of these reaction products of ethylene imine ketones with hydrogen halides actually are β-halogeno α-amino ketone hydrohalides seems to be required. Their very slow reaction with an acidified solution of potassium iodide could conceivably be the result of their being the least reactive of the two possible racemates of the α-halogeno β-amino ketone hydrohalide. This possibility is being investigated.

Experimental[7]

α,β-Dichloro Ketones.—These compounds were prepared by the methods given by Goldschmidt,[8] using an efficient gas–liquid reaction tower, as described by Degering.[9] The yield of α,β-dichlorobenzylacetophenone was the same as previously reported, but the yield of α,β-dichlorobenzylacetone was considerably lower, although the reaction was repeated several times. In a typical experiment, 40 g. (0.274 mole) of benzalacetone was dissolved in 50 ml. of chloroform, cooled to 5° and placed in the glass tower of the chlorination apparatus.[9] Tank grade chlorine gas was bubbled into the solution for one hour. The chloroform was evaporated under reduced pressure to leave an oily solid residue which on recrystallization from absolute alcohol gave 20 g. (33.6% yield) of α,β-dichlorobenzylacetone, m. p. 92–93°. Evaporation of the absolute alcohol solution and vacuum distillation of the residual oil gave 20 g. of α-chlorobenzalacetone, described below.

α-Chlorobenzalacetone.—This compound was obtained in an 83% yield according to the method given by v. Auwers and Brink.[10] The resulting yellow oil distilled at 140–141° at 5 mm. and solidified on cooling in an ice-bath. Recrystallization from petroleum ether (b. p. 60–70°) by cooling to 0° gave large, colorless crystals, m. p. 20–21°.

α-Chlorobenzalacetophenone.—This unsaturated chloroketone was prepared in a 75% yield by the method of v. Auwers and Hügel.[11] The golden yellow oil distilled at 195–200° at 5 mm. and solidified on cooling in an ice-bath. Recrystallization from petroleum ether gave large, colorless crystals, m. p. 29–30°.

Addition of Amines to the α-Chloro Unsaturated Ketones.—Five grams of the α-chloro unsaturated ketone was dissolved in 5 ml. of dry ether and the solution cooled to 0°. A cold solution of an equal molecular amount of the amine in 2 ml. of dry ether and 2 ml. of petroleum ether was added all at once. In five to ten minutes the solution became a solid mass. After standing in the ice-bath for one hour the colorless solid was filtered and washed with petroleum ether. These products were recrystallized by dissolving them in warm petroleum ether and then cooling the solutions to 0°. In this way the α-chloro β-amino ketones (I), (III), (V), (VII), (VIII) and (IX) were prepared (see Table I).

When 0.5 g. of (I) was dissolved in 10 ml. of absolute alcohol and allowed to stand at room temperature for fifteen hours, only a slight precipitate of silver chloride resulted upon addition of alcoholic silver nitrate. The chloro amino ketones (I), (III) and (V) were stable at room temperature for several months, while (VII), (VIII) and (IX) decomposed upon standing for twenty-four hours at room temperature.

Attempts to add benzylamine, or dibenzylamine, or tetrahydroquinoline to α-chlorobenzalacetophenone at various temperatures ranging from −40 to 40° were unsuccessful.

Hydrochlorides of α-Chloro β-Amino Ketones.—Five grams of the α-chloro-β-aminobenzylacetophenone was dissolved in 150 ml. of dry ether and 50 ml. of pure acetone and cooled to 10°. A cold saturated solution of dry hydrogen chloride in dry ether was added slowly with stirring until no further precipitation took place. The colorless solid product was filtered and recrystallized by dissolving in about 40 ml. of alcohol followed by the addition of 120 ml. of dry ether. In this way the hydrochlorides (II), (IV) and (VI) were prepared.

A 0.5-g. sample of (II) was dissolved in 25 ml. of absolute alcohol and allowed to stand at room temperature for forty-eight hours. Addition of 50 ml. of dry ether to this solution gave 0.48 g. of a compound identical with (II) (same m. p. and rate of iodine release).

The hydrochlorides of the α-chloro-β-aminobenzylacetones (VII), (VIII) and (IX) decomposed almost immediately upon isolation from the ether–acetone solutions to give the starting secondary amine hydrochlorides, and thus were not studied.

Reaction of Tetrahydroquinoline with (I).—Three grams (0.00915 mole) of (I) was dissolved in 5 ml. of absolute alcohol and 2.43 g. (0.0183 mole) of tetrahydroquinoline added. This solution was warmed for five minutes on a steam-bath and allowed to stand for forty-eight hours at room temperature. The light yellow product was filtered, washed with water and recrystallized from chloroform and alcohol to give 1.59 g. (41% yield) of yellow crystals, m. p. 166–167°, identical with α-piperidino-β-tetrahydroquinolinobenzylacetophenone,[5] as indicated by a mixed melting point experiment.

Reaction of α,β-Dichlorobenzylacetophenone with Benzylamine.—Nine grams (0.33 mole) of the dichloroketone was mixed with 10 ml. of alcohol and 6 ml. of benzene. This mixture was cooled in an ice-bath and then treated with 10.6 g. (0.097 mole) of benzylamine. Following the previously described procedure,[6] 2.3 g. (23% yield) of a compound, m. p. 107°, identical with 1-benzyl-2-phenyl-3-benzoylethylenimine[2] was obtained.

Mole Weight Determination.—Using 8–12% solutions in benzene and the cryoscopic method, calcd. for $C_{22}H_{19}NO$: 313. Found: 300, 316.

The Determination of Active Chlorine. (a) Reaction with Potassium Iodide at 26°.—Following the directions previously described,[1] the results given in Table II were obtained.

(b) Reaction with Potassium Iodide at 66°.—A mixture of 5 ml. of dry acetone, 5 ml. of absolute alcohol, 0.6 ml. of 3 *N* hydrogen chloride in absolute alcohol, and 16 ml. of 0.2 *N* potassium iodide in 50% absolute alcohol–acetone was brought to reflux temperature in a water-bath. A 0.100-g. sample of the chlorine compound was then dropped into this solution to dissolve immediately. After allowing the solution to reflux for the stated length of time, the flask was removed from the water-bath and 50 ml. of ice-cold water, along with 2 ml. of freshly prepared 2% starch solution was added immediately. The solution was then titrated rapidly with 0.0300 molar sodium thiosulfate until the color changed from blue to colorless (see Table III and Fig. 1).

Summary

1. Piperidine, morpholine and tetrahydroisoquinoline have been found to add readily to both α-chlorobenzalacetophenone and α-chlorobenzalacetone. The stability and reactivity of the resulting α-chloro β-amino ketones have been compared with that of the analogous α-bromo β-amino ketones.

2. The rates of reaction of chloro amino ketones with acidified potassium iodide solution have been studied, and a method of differentiating α-chloro β-amino ketones from β-chloro α-amino ketones proposed.

LINCOLN, NEBRASKA RECEIVED NOVEMBER 24, 1947

(7) All m. p.'s were observed using a strong glass and obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Total chlorine determinations were made by the hydrogen jet method of Caldwell, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935), and Winter, *ibid.*, **15**, 571 (1943), with the assistance and advice of H. Armin Pagel, Department of Chemistry, University of Nebraska.

(8) Goldschmidt, *Ber.*, **28**, 1532, 2540 (1895).

(9) Degering, *Ind. Eng. Chem.*, **24**, 181 (1932).

(10) v. Auwers and Brink, *J. prakt. Chem.*, **133**, 154 (1932).

(11) v. Auwers and Hügel, *ibid.*, **143**, 157 (1934).

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

The Isolation of 1,1-Dichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane from Technical TDE[1]

BY STANLEY J. CRISTOL[1a] AND H. L. HALLER

The recent discovery of the effectiveness of 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethane (called *p,p'*-TDE or *p,p'*-DDD), as an anopheline larvicide made it desirable to have on hand a supply of its *o,p'* isomer, 1,1-dichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane. This compound had been prepared previously by the condensation of chlorobenzene and 2,2-dichloro-1-*o*-chlorophenylethanol,[2] but the synthesis involved a difficultly available reactant, and optimum conditions had not been worked out. Separation of the isomers by fractional crystallization, an operation successful for *o,p'* and *p,p'*-DDT,[2] was also difficult, since both isomers crystallized in similar appearing crystals. The recent successful separation of *o,o'*-DDT from the *o,p'* and *p,p'* isomers,[3] by a procedure making use of the decrease in reactivity toward dehydrochlorination with ethanolic sodium hydroxide caused by the replacement of *para* by *ortho* chlorine atoms, suggested a parallel experiment for the separation of *o,p'*-TDE from *p,p'*-TDE.

A sample of technical TDE was recrystallized, giving pure *p,p'*-TDE. The oil recovered from the mother liquors was treated with ethanolic sodium hydroxide under conditions calculated[4] to effect the dehydrochlorination of substantially all the *p,p'* isomer and expected to leave unreacted most of the *o,p'* isomer. When this mixture of the unreacted *o,p'* isomer and the olefin related to the *p,p'* isomer was treated with chromic anhydride in glacial acetic acid, the olefin was oxidized to *p,p'*-dichlorobenzophenone but the saturated *o,p'*-TDE was not affected. The ketone–ethane mixture was separated by selective adsorption on and elution from activated alumina, the ketone being held more strongly on the column.

The recrystallized *o,p'*-TDE melted at 75.8–76.8°,[2] and was obtained in 7 to 8% yield from the original crude mixture of isomers. Mixed melting points with known samples[2] were not depressed.

Dinitro and tetranitro derivatives of *o,p'*-TDE, m. p. 134–135.5° and 183–185°, respectively, were prepared. Treatment of *o,p'*-TDE with ethanolic potassium hydroxide resulted in elimination of one mole of hydrogen chloride, but the resulting olefin, b. p. 160° (1 mm.), could not be made to crystallize.

The rate constant for the dehydrochlorination with sodium hydroxide of the *o,p'*-TDE was determined in 92.6% (by weight) ethanol at 20.11° (method used same as described earlier),[4] and a value of 0.000144 liter per second per mole (average of two determinations) was obtained. This compares with a value of 0.00567 for the *p,p'* isomer, and again indicates the importance of the steric and/or electrostatic effect of the *ortho* chlorine atom in hindering the elimination reaction.

Experimental

Separation of 1,1-Dichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane from its *p,p'*-Isomer.—A two-hundred gram sample of technical TDE was recrystallized from 450 ml. of 95% ethanol. The solid (129 g.) was fairly pure *p,p'*-TDE and was discarded. The solvent was removed *in vacuo*, and the residual oil was taken up in 1200 ml. of 95% ethanol, brought to 20° in a constant-temperature bath, and treated with 800 ml. of 1 *M* ethanolic sodium hydroxide solution at 20° for exactly thirty minutes. The dehydrochlorination reaction was then stopped by the addition of 40 ml. of concentrated nitric acid in 500 ml. of water. Most of the ethanol was removed *in vacuo*, and the resulting mixture was extracted several times with ether. The ether extracts were washed with water, dilute aqueous sodium hydroxide, and saturated salt solution, and were then filtered. The ether was removed by distillation, leaving 60.4 g. of viscous oil.

This oil was taken up in 200 ml. of glacial acetic acid. To the refluxing solution was added 48 g. of solid chromium trioxide in small portions, violent oxidation occurring at each addition, over a period of one to two hours. Refluxing was continued for about fifteen minutes after the addition was complete. The mixture was cooled and poured onto ice. The presence of excess oxidant was shown by testing with potassium iodide–starch paper. The mixture was extracted twice with ether. The combined ether extracts were washed successively with water, dilute base until washings were basic, and saturated salt solution, and were then filtered. Evaporation of the ether left 49.1 g. of a brown solid mixture.

This solid was divided into two portions, and each portion was treated as follows: The solid was dissolved in 200 ml. of petroleum ether (b. p. 60–70°) and adsorbed on an activated alumina column 42 mm. in diameter and 200 mm. high, which had been washed with 200 ml. of petroleum ether. The column was then washed successively with five 200-ml. portions of petroleum ether, two 200-ml. portions of carbon tetrachloride, and two 200-ml. portions of 95% ethanol. The petroleum ether eluates consisted mostly of *o,p'*-TDE, while the later fractions were mostly *p,p'*-dichlorobenzophenone. The combined petroleum ether eluates from both runs weighed 25.0 g. After two recrystallizations from 95% ethanol, 14.8 g. of *o,p'*-TDE, m. p. 75.8–76.8°, was obtained. This is equivalent to 7.4% of the original technical TDE mixture. The melting point of this sample of *o,p'*-TDE was not depressed when mixed with material isolated from technical DDT[2] or obtained by synthesis.[2]

Dinitro-*o,p'*-TDE.[5]—This derivative was prepared by treatment of 500 mg. of *o,p'*-TDE with 5 ml. of fuming

(1) This work was started as part of a program supported by a transfer of funds from the Office of the Quartermaster General to the Bureau of Entomology and Plant Quarantine, and was completed in the chemical laboratories of the University of Colorado.

(1a) Present address, University of Colorado.

(2) Haller, Bartlett, Drake, Newman and co-workers, THIS JOURNAL, **67**, 1591 (1945).

(3) Cristol, Soloway and Haller, *ibid.*, **69**, 510 (1947).

(4) The calculations were made from the known reaction-rate constant previously determined for *p,p'*-TDE; see Cristol, THIS JOURNAL, **67**, 1494 (1945).

(5) The structure of this compound has not been proved but it is presumably 1,1-dichloro-2-(2-chloro-5-nitrophenyl)-2-(4-chloro-3-nitrophenyl)-ethane.

nitric acid for one-half hour at 50°. The reaction mixture was cooled and poured onto ice. The resulting solid was recrystallized from 95% ethanol to constant m. p., 134–135.5°.

Anal. Calcd. for $C_{14}H_8Cl_4N_2O_4$: N, 6.83. Found: N, 7.02.[6]

Tetranitro-*o,p'*-TDE.[7]—A mixture of 500 mg. of *o,p'*-TDE, 2.5 ml. of concentrated sulfuric acid, and 2.5 ml. of fuming nitric acid was heated on a steam-bath for one hour. The reaction mixture was cooled and poured onto ice. The resulting solid was recrystallized from acetone–ethanol to constant m. p., 183–185°.

Anal. Calcd. for $C_{14}H_6Cl_4N_4O_8$: N, 11.21. Found: N, 11.14.[6]

***o,p'*-TDE Olefin.**—A solution of 500 mg. of *o,p'*-TDE and 0.4 g. of potassium hydroxide in 20 ml. of ethanol was heated at reflux for three hours. The resulting mixture was poured into water. The mixture was extracted with ether, and the ether extract was washed with water and saturated salt solution and filtered. The ether was evaporated off, leaving a viscous oil. This oil, b. p. 160° (1 mm.), was distilled in a vacuum sublimation apparatus. The product remained as an oil after standing at room temperature for over a year.

Acknowledgment.—We are indebted to the Rohm and Haas Company for a generous supply of technical TDE mixture.

(6) The authors are indebted to Mr. Harlan L. Goering for the nitrogen analyses.

(7) The structure of this compound has not been proved, but it is presumably 1,1-dichloro-2-(2-chloro-3,5-dinitrophenyl)-2-(4-chloro-3,5-dinitrophenyl)-ethane.

Summary

1,1-Dichloro-2-*o*-chlorophenyl-2-*p*-chlorophenylethane (*o,p'*-TDE) has been separated from a mixture with its *p,p'* isomer by a procedure making use of the lowered reactivity with ethanolic sodium hydroxide of the *o,p'* isomer compared with the *p,p'* isomer.

Nitration and dehydrochlorination products of *o,p'*-TDE have been described. The rate constant for the reaction of *o,p'*-TDE with ethanolic sodium hydroxide has been determined.

BOULDER, COLORADO RECEIVED NOVEMBER 13, 1947

[CONTRIBUTION FROM PULP MILLS RESEARCH PROJECT, DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Lignin. I. Purification of Lignin Sulfonic Acids by Continuous Dialysis

BY QUINTIN P. PENISTON AND JOSEPH L. MCCARTHY

Introduction

Lignin sulfonic acids[1] have several times been separated from sulfite waste liquor and purified by metal or amine salt precipitations.[2] Although dialysis has been employed as a step in some of these procedures, and has been practically considered by Ogland,[3] no detailed study appears to have been made of the degree of purity and extent of recovery of the lignin sulfonic acids attainable by direct continuous dialysis of sulfite waste liquor. This easily conducted procedure was thought worthy of investigation both as a method for laboratory preparation of purified lignin sulfonic acids for research purposes and as a means of characterization of sulfite waste liquor components.

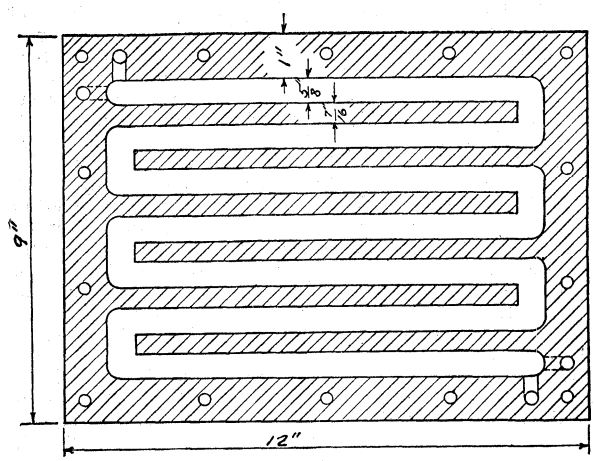


Fig. 1.—Dialyzer plate detail.

Experimental Part

Dialysis Apparatus.—To obtain a high ratio of membrane area to liquor volume and a close approach to true counter-current operation, a multicellular apparatus was constructed from $^1/_8'' \times 9'' \times 12''$ plates of "Plexiglas." This material was chosen for its resistance to chemical attack, dimensional stability in water, workability, and transparency. The last quality is desirable since it aids detection of air blocks or other obstructions to flow. The cells consisted of zig-zag channels $^5/_8''$ wide sawn in the "Plexiglas" plates. Both liquor and water plates were identical except for interplate connections. The design details are indicated in Fig. 1. Fifteen pairs of such plates were used, each pair being isolated by separator plates of $^1/_{16}''$ "Plexiglas." Connections between cells were by means of ports grooved about half through the plates at the ends of the channels. The ports fed into holes which led through membrane and separator to the next appropriate cell. The entire assembly was held between $^1/_4''$ stainless steel plates by means of 14 stainless steel machine bolts.

The total volume of the apparatus amounted to 2780 ml., and the total membrane area to 0.435 square meter. With no bulging of the membrane, the volumes in liquor and water channels were equal.

(1) Hagglund, "Holzchemie," Akademische Verlagsgesellschaft, m. b. h., Leipzig, 1939, 2nd. ed., Lithoprinted 1944 by Edwards Bros., Ann Arbor, Michigan.

(2) (a) E. G. King, F. Brauns and H. Hibbert, *Can. J. Res.* (B) **13**, 88 (1935); (b) G. H. Tomlinson and H. Hibbert, THIS JOURNAL, **58**, 340 (1936); (c) H. Erdtman, *Svensk. Papperstidn.*, **45**, 315–323 (1942); (d) W. Lautsch and Piazolo, *Cellulose chemie*, **22**, 48–54 (1944).

(3) N. J. Ogland, *Svensk. Papperstidn.*, **47**, 288–291 (1944).

Flows of both sulfite waste liquor and distilled water to the apparatus were from constant head reservoirs through small Alyea[4] flowmeters to open funnel receivers. Pressure on the two channels was independently controlled by adjustment of the height of inlet and outlet tubes. In operation the apparatus was placed with plates horizontal and both channels were filled with water using parallel upflow until all air bubbles were removed. Water was then switched from upflow to downflow and sulfite waste liquor was admitted in upflow in the other channel. Steady state operation was obtained over several days' operation without attention. The addition of small amounts of toluene to the input reservoirs was found effective to prevent growth of microorganisms in the apparatus. These if uncontrolled rapidly caused increase in porosity and failure of the membranes.

The membrane used in these studies was a denitrated nitrocellulose casing produced by the Sylvania Industrial Corporation and obtained from the Brosites Machine Company, New York; sample K 412, thickness (dry) 0.0032 inch.

Sulfite Waste Liquor Samples.—The compositions of sulfite waste liquor samples used in this study are shown in Table I. For sample B the alterations brought about by pretreatment before dialysis are indicated. Important differences between Samples A and B are: the higher amount of total reducing substances and fermentable sugar in Sample A, and the high values for total sulfur and loosely combined sulfur dioxide in Sample B. Both samples were obtained from commercial pulping operations using the same wood source: about 85% Western Hemlock and 15% White Fir. In the production of Sample B a much higher "free sulfur dioxide" concentration was present in the pulping liquor.

TABLE I

COMPOSITION OF SULFITE WASTE LIQUOR SAMPLES

Sample	A	B original	B after ion exchange
*p*H	1.77	1.80	2.70
Total solids, g./l.[b]	115.4	121.6	95.9
Ash, g./l.	11.88	20.94	21.63[a]
CaO, g./l.	6.19	9.63	0.05
Free SO_2, g./l.[5]	0.6	8.04	4.02
Loosely combined SO_2, g./l.[5]	3.73	6.17	4.51
Sulfate, g. SO_3/l.[6]	1.14	1.10	0.76
Total sulfur, g. S/l.[7]	8.92	15.75	10.99
Methoxyl, g. OCH_3/l.[8,9]	7.84	8.09	6.16
Total reducing substance, g. glucose/l.	26.78	20.45	14.91
Fermentable sugar, g. glucose/l.[10]	19.05	12.45	...

[a] Sulfated ash. [b] Determined by drying *in vacuo* at 60° on quartz sand.

Method of Calculation of Dialysis Data.—To obtain samples representative of a given set of flow conditions the apparatus was allowed to operate for sufficient time to ensure a steady state condition. Usually a time equivalent to the passage of 2 liters of the more slowly moving fluid was allowed. Samples of dialyzed liquor and dialyzate were then collected over a measured time interval to determine output flow rates. Input flow rates were calculated from a total solids balance. Dialysis rate coefficients and amounts of substances transferred were then calculated from analyses of the effluent samples, the composition of the original liquor and the flow rates established from the total solids balance.

Results and Discussion

The isolation of pure lignin sulfonic acids from sulfite waste liquor by dialysis is dependent on two major factors. Firstly, the non-lignin components, being of relatively low molecular weight, diffuse more rapidly through the pores of the membranes than most of the lignin components, and secondly, the membrane behaves in some degree as an ultra-filter being substantially impermeable to particles above a certain size.

Schwabe and Hasner[11] have shown that for such low molecular weight non-electrolytes, as hexose sugars, the rate of diffusion is determined by Graham's law for certain membranes. With electrolytes in the presence of a high concentration of supporting electrolyte, presumably the dialysis rate is also inversely proportional to the square root of the molecular weight. This relationship has been used by Schwabe and Hasner for estimation of molecular weight of various lignin sulfonic acid preparations. In the absence of extraneous electrolyte, however, potential gradients as well as concentration gradients must be effective in determining the dialysis rate of electrolytic substances. According to Vinograd and McBain[12] the potential gradient in a mixture of electrolytes may be expressed as

$$\frac{d\psi}{dx} = \frac{RT}{F}\left[\frac{\Sigma u_+ G_+/n_+ - \Sigma u_- G_-/n_-}{\Sigma u_+ c_+ + \Sigma u_- c_-}\right]$$

where u_+, u_- are mobilities, G_+ G_- are ionic concentration gradients, c_+, c_- are concentrations and n_+, n_- are valences. An interesting consequence of this relation is that the presence of a high concentration of non-dialyzable high molecular weight lignin sulfonic acid anions should increase the rate of dialysis for low molecular weight anions in the mixture.

In order to aid in the interpretation of dialysis rate coefficients calculated for sulfite waste liquor components, two mixtures of pure substances have been dialyzed under similar conditions using the same dense membrane employed for the sulfite waste liquor experiments. Results with known aqueous mixtures of glucose and sucrose (Table II) dialyzed under four different flow conditions (Experiments 1–4) using newly installed membranes and, again after six weeks of continuous service in sulfite waste liquor dialysis (Experiments 5–8), show (a) that while the free diffusion rate for glucose is 1.37 times that for sucrose,[13] the ratio of dialysis rate coefficients now found for these substances is 1.64 indicating a filtering action by the membrane for molecules as small as sucrose; (b) that apparently the dialysis rate coef-

(4) H. N. Alyea, *Ind. Eng. Chem., Anal. Ed.*, **12**, 686 (1940).

(5) Method 0 403 sm-40, January 15 (1940); Technical Association of the Pulp and Paper Industry, New York.

(6) Q. P. Peniston, V. F. Felicetta and J. L. McCarthy, *Ind. Eng. Chem., Anal. Ed.*, **19**, 332 (1947).

(7) F. H. Yorston, Canadian Pulp and Paper Research Institute, Montreal, Canada, private communication.

(8) E. P. Clark, THIS JOURNAL, **51**, 1479–1483 (1929).

(9) F. Viebock and A. Schwappach, *Ber.*, **63**, 2818 (1930).

(10) H. S. Daniels and J. L. McCarthy, unpublished method.

(11) K. Schwabe and L. Hasner, *Cellulosechemie*, **20**, 61 (1942).

(12) J. R. Vinograd and J. W. McBain, THIS JOURNAL, **63**, 2011 (1941).

(13) "International Critical Tables," Vol. V, p. 71.

TABLE II

DIALYSIS RATES FOR GLUCOSE–SUCROSE MIXTURES[a]

Experiment[c]		1	2	3	4	5	6	7	8
Liquid output, ml./hr.		672	499	296	139	445	316	166	66.7
Dialyzate, ml./hr.		612	422	256	125	359	213	144	78.1
Per cent. dialyzed	Glucose	43.0	47.7	55.7	73.5	51.6	51.2	71.6	87.3
	Sucrose	27.8	35.2	43.9	64.2	38.6	41.2	64.8	86.8
Dialysis rate[b] coefficients	Glucose	0.92	0.95	0.86	0.93	0.93	0.94	1.02	0.81
			Average 0.92				Average 0.93		
	Sucrose	0.56	0.55	0.53	0.54	0.57	0.56	0.64	0.58
			Average 0.54				Average 0.59		
	$\frac{K \text{ glucose}}{K \text{ sucrose}}$	1.64	1.72	1.62	1.72	1.63	1.68	1.60	1.40
			Average 1.67				Average 1.58		

[a] Original mixture: 20.0 glucose g./liter, 20.0 sucrose g./liter. [b] Grams transferred per square meter per hr. per gram per liter concentration difference (logarithmic mean). [c] Experiments 1–4 were carried out using new membranes; experiments 5–8 with membranes after six weeks of service in sulfite waste liquor dialysis.

TABLE III

DIALYSIS RATES FOR GLUCOSE AND SODIUM *p*-TOLUENE SULFONATE[a]

Experiment		1	2	3	4
Average solution rate, ml./hr.		104	215	327	558
Average water rate, ml./hr.		116	232	298	602
Per cent. dialyzed	Glucose	79.8	65.0	52.0	41.7
	Sodium *p*-toluenesulfonate	86.3	74.1	59.7	52.7
Dialysis rate coefficients	Glucose	0.79	0.86	0.85	0.88
	Sodium *p*-toluenesulfonate	1.06	1.22	1.26	1.39
	$\frac{K_{C_7H_7SO_3Na}}{K_{glucose}}$	1.34	1.43	1.49	1.59

[a] Original mixture: glucose 20.60 g./liter, sodium *p*-toluenesulfonate 22.84 g./liter.

ficients for these non-electrolytes, are not dependent on flow rate, and (c) that only a small change if any occurred in the porosity of the membrane during the entire period.

Similar experiments with known aqueous mixtures of glucose with sodium *p*-toluenesulfonate (Table III) showed that (a) although the two substances are of about the same molecular weight, the electrolyte dialyzed considerably faster than the non-electrolyte and (b) that the dialysis rate coefficient of the electrolyte increases with flow rate.

Since sodium *p*-toluenesulfonate is a salt of a relatively large organic anion, it might be expected that similar effects would occur in dialysis of sodium lignin sulfonates and low molecular weight non-electrolytic substances.

The purification of lignin sulfonic acids by dialysis of sulfite waste liquor Sample A was investigated using five different liquid input flow rates corresponding to five different times for dialysis. Dialyzed liquors and dialyzates were analyzed for total solids, methoxyl, total reducing substances and sulfur. The analytical results and the amounts of each analytically determined constituent dialyzed are shown in Table IV as a function

TABLE IV

EFFECT OF DIALYSIS TIME ON LIGNIN SULFONIC ACID PURITY

Sulfite Waste Liquor Sample A

Experiment	1	2	3	4	5
Liquor input, ml./hr.	136	76.7	39.4	37.9	19.0
Water input, ml./hr.	270	273	275	265	256
Average liquor flow rate, ml./hr.	166	93.3	52.7	52.7	31.9
Average time in dialyzer, hours	8.37	14.90	26.7	26.7	43.5
Dilution ratio (liquor out/liquor in)	1.44	1.43	1.67	1.78	2.36
Composition of dialyzed liquor					
Total solids, g./l.	58.25	44.74	32.42	30.69	23.24
Methoxyl, g. OCH_3/l.	5.53	4.70	3.66	3.47	2.72
Total reducing substances, g./l.	7.15	3.23	1.07	0.82	0.48
Sulfur, g./l.	3.70	2.90	2.12	2.00	1.49
Composition of dialyzate					
Total solids, g./l.	20.43	16.40	9.76	9.77	5.02
Methoxyl, g. OCH_3/l.	0.49	0.44	0.30	0.34	0.20
Total reducing substances, g./l.	9.29	7.08	3.93	3.78	1.72
Per cent. of constituent dialyzed					
Total solids	27.4	44.5	53.1	52.8	52.5
Methoxyl	9.7	18.0	21.0	21.3	21.0
Total reducing substance	53.7	82.7	93.3	94.2	94.8
Sulfur	40.2	53.5	60.3	60.1	60.5
Methoxyl equivalent weight dialyzed solids	327	295	274	274	265

of the time of dialysis. Limiting values are approached by all constituents which are characteristic of the calcium salts of the purified lignin sulfonic acids. Interpreting the dialysis of methoxyl groups as proportional to that of lignin sulfonic acids, it appears that about 78% of the original lignin sulfonic acids in Sample A are retained by the membrane used irrespective of the time of dialysis. The remainder pass through the membrane at a rate not greatly lower than that for reducing substances and thus are apparently of lower molecular weight. From the above experiments with known substances and from the recent reports by Gralen[14] and by Pennington and Ritter[15] the molecular weight of lignin sulfonic acids pass-

(14) Nils Gralen, *J. Colloid Sci.*, **1**, 453 (1946).

(15) D. Pennington and D. M. Ritter, THIS JOURNAL, **69**, 665 (1947).

TABLE V

DIALYSIS RATES OF SULFITE WASTE LIQUOR COMPONENTS

Sulfite Waste Liquor B

	As calcium salts			As sodium salts			
Experiment	1	2	3	1	2	3	4
Average liquor flow, ml./hr.	49.6	100.8	179	41.05	65.6	122	179
Average water flow, ml./hr.	59.3	176.1	176	47.3	68.7	144	197
Dilution ratio	1.75	1.45	1.37	2.70	1.76	1.49	1.40
Composition of dialyzed liquor							
Total solids, g./l.	34.34	44.39	59.99	15.24	25.39	33.76	40.56
Reducing substances, g./l.	0.86	2.24	5.59	0.51	1.27	2.20	3.51
Methoxyl, g./l.	3.65	4.46	5.46	1.67	2.69	3.44	3.96
Total sulfur, g./l.	3.02	3.93	5.59	1.40	2.33	3.00	3.58
Free and loosely combined sulfur dioxide, g./l.	0.59	1.02	2.42	0.16	0.42	0.63	1.09
Methoxyl equivalent weight	292	309	342	283	293	304	317
Moles sulfur/mole methoxyl	0.80	0.86	0.99	0.81	0.84	0.84	0.88
Per cent. of constituent dialyzed							
Total solids	50.4	47.0	32.3	57.6	53.4	47.4	40.5
Reducing substances	86.7	82.9	59.2	88.0	83.6	76.3	67.8
Methoxyl	18.1	14.8	9.3	29.4	24.2	17.8	13.8
Free and loosely combined sulfur dixide	29.8	89.6	76.7	97.0	91.4	89.2	82.5
Dialysis rate coefficients							
Total solids	0.10	0.16	0.19	0.09	0.15	0.23	0.26
Reducing substances	.53	.56	.62	.36	.66	.70	.74
Methoxyl[a]	.10	.14	.15	.26	.30	.26	.25
Free and loosely combined sulfur dioxide	.63	.74	.93	1.00	1.15	1.33	1.45

[a] Based on assumption of 35% dialyzable methoxyl.

ing through the membrane is probably not greater than about 2000 and thus these may contain only up to about ten of the structural units postulated by Freudenberg[16] and Hibbert.[17]

The non-dialyzable lignin sulfonic acids may be characterized by a methoxyl equivalent weight (grams of total solids per 31.02 g. of methoxyl). This value for the solids remaining undialyzed was found to decrease with increasing time of dialysis, the data being representable by an equation of the form

$$\text{Methoxyl equivalent weight} = C + A/\text{Time}$$

where A and C are constants. Extrapolation with this relationship of the data to infinite time of dialysis (Fig. 2) suggests a value of about 250 as the methoxyl equivalent weight of the completely purified calcium lignin sulfonate from sulfite waste liquor Sample A. The mole ratio of sulfur, and of the copper reducing value calculated as glucose, to methoxyl in the dialyzed solutions is shown in Fig. 2 as a function of time of dialysis. Both quantities decrease rapidly with increasing purity and approach values of 0.5 mole of sulfur, and less than 0.04 mole of copper reducing groups, per mole of methoxyl, respectively. Thus the nondialyzable lignin sulfonic acids manifest approximately one sulfonic acid grouping for every two structural units. The rate at which the mole ratio of sulfur to methoxyl decreases with increasing purity appears to exclude the possibility that the sulfur-containing impurities can be entirely lignin sulfonic acid salts of higher sulfur content and suggests that they may be, in part, the sulfonic acid derivatives of sugars postulated by Hägglund and Urban[18] and recently studied by Adler.[19]

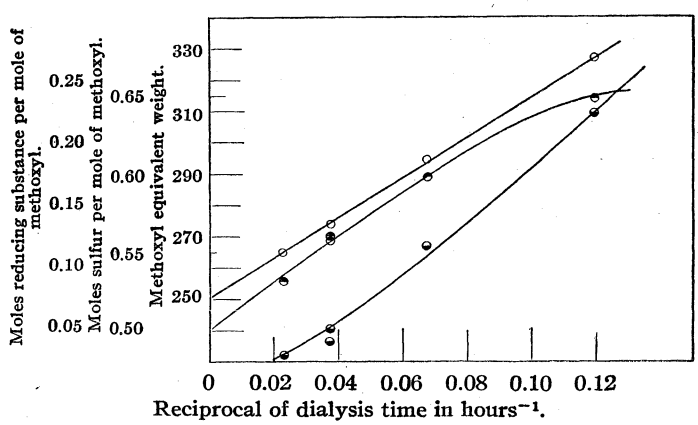


Fig. 2.—Calcium lignin sulfonate composition *vs.* dialysis time: ○, equivalent weight; ◒, sulfur; ◒, reducing substances.

To try to generalize the above trends, a series of experiments was conducted with calcium base sulfite waste liquor Sample B which differs from Sample A in that it was obtained from a separate commercial plant wherein the practice is to use a sulfite pulping liquor very high in concentration of sulfurous acid. In both cases, however, the wood used was the same, namely, about 85%

(16) K. Freudenberg, *Ann. Rev. Biochem.*, **8**, 81 (1931).

(17) H. Hibbert, *ibid.*, **11**, 183 (1942).

(18) E. Hägglund and H. Urban, *Ber.*, **62**, 2046 (1929).

(19) E. Adler, *Svensk Papperstidn.*, **49**, no. 15 (Aug. 15, 1946).

Western Hemlock and 15% White Fir. Sample B, in its original form, and after conversion by ion exchange to sodium salts (Table I), was dialyzed at various flow rates. The dialyzed solutions were analyzed and dialysis coefficients were computed.

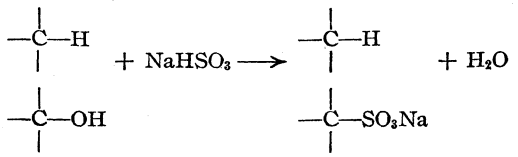
Results (Table V) indicate that dialysis coefficients of electrolyte components of sulfite waste liquor are higher when in the form of sodium salts than as calcium salts. This might be expected from activity considerations.

By extrapolation to infinite time of dialysis of data secured using the sodium salts, it is estimated, on a methoxyl basis, that about thirty-five per cent. of the weight of the original lignin sulfonic acid present in Sample B will dialyze through the membrane, compared to about 22% for Sample A. This evidence for the presence of a larger proportion of lower molecular weight lignin sulfonic acid molecules in the sulfite waste liquor Sample B may correlate with the higher sulfurous acid concentration during the sulfite pulping procedure in this case.

Following completion of these experiments, non-dialyzable sodium lignin sulfonates were prepared by dialyzing Sample B as the sodium salt using a very low flow rate. Also at the conclusion of the above described studies on Sample A, non-dialyzable calcium lignin sulfonates were secured similarly and these were converted to sodium salts by ion exchange. Purified lignin sulfonates A and B were recovered by evaporation to dryness at reduced pressure and then carefully dried under vacuum below 60°. According to Purves[20] erroneous carbon and hydrogen values may result if high temperatures are used. The composition of the two dry samples was found to be

	Sample A (%)	Sample B (%)
Carbon	52.1	50.5
Hydrogen	4.18	3.96
Sulfur	6.66	7.38
Sodium	4.63	4.88
Methoxyl	12.8	12.5

Differences in degrees of sulfonation of these purified non-dialyzable sodium lignin sulfonates can be taken into account to permit comparison of the two samples by calculation of the above analytical data to a sulfur and ash free basis. For such a computation, the mechanism of sulfonation may be postulated either as replacement of one hydroxyl grouping, or else one hydrogen atom, of the lignin for each sulfonic acid grouping becoming attached to the lignin. We have based our calculations on the hydroxyl replacement mechanism, *i. e.*



which yields the following carbon–hydrogen–oxygen–methyl ratios from the experimental data for the average unsulfonated lignin structural unit containing ten carbon atoms

Sample A	$C_{9.00}H_{7.20}O_{2.75}$ $(OCH)_{0.94}$
Sample B	$C_{9.00}H_{7.00}O_{2.84}$ $(OCH_3)_{0.95}$
"Theoretical"	$C_{9.00}H_{7.00}O_{2.75}$ $(OCH_3)_{1.00}$

The "theoretical" ratio given may be secured by assuming that the lignin polymer consists of "*n*" guaiacyl oxygenated propane structural units with the empirical formula $C_{10}H_{10}O_3$ and "3*n*" units with the empirical formula $C_{10}H_{10}O_4$.

Mr. Vincent F. Felicetta's analytical assistance is appreciated.

Summary

1. Lignin sulfonic acids may be isolated in a high degree of purity in about 65 to 80% yield by exhaustive continuous dialysis of sulfite waste liquor.

2. The dialyzable lignin sulfonates are believed to be of molecular weight of less than 2000 and appear to vary in amount depending upon conditions obtaining during the pulping process.

3. Two non-dialyzable lignin sulfonate samples from different commercial sources are found to have nearly the same empirical composition when calculated to a sulfur and ash free basis, and this composition is in agreement with the concept of lignin as a polymer of guaiacyl oxygenated propane structural units.

SEATTLE, WASHINGTON RECEIVED JULY 24, 1947

(20) C. B. Purves, P. F. Ritchie and W. J. Wald, THIS JOURNAL, **69**, 1371 (1947).

[CONTRIBUTION FROM PULP MILLS RESEARCH PROJECT, DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF WASHINGTON]

Lignin. II. Liberation of Phenolic Hydroxyl Groups by Alkaline Cleavage of Lignin Sulfonic Acids

BY QUINTON P. PENISTON AND JOSEPH L. MCCARTHY

The conception of softwood lignin as a polymer of oxygenated guaiacyl propane structural units postulates the occurrence of one phenolic hydroxyl per methoxyl grouping. It has been concluded by most workers within the field that phenolic hydroxyl groupings occur in a free state in at least some structural units of the polymer. Thus, Tomlinson and Hibbert[1] have stated: "The fact that methylated (dimethyl sulfate and alkali) lignin sulfonic acids yield veratric aldehyde affords conclusive proof that the original lignin sulfonic acid contains a free phenolic hydroxyl group," and F. E. Brauns[2] has concluded, from diazomethane methylation studies, that: "...lignin sulfonic acid in addition to the sulfonic group has a free phenolic hydroxyl." Freudenberg and coworkers[3] have suggested that the phenolic hydroxyl group is bound in native lignins by an ether linkage to a secondary aliphatic hydroxyl and that this linkage is broken by sulfonation to yield a sulfonic acid and a free phenolic hydroxyl. From more recent investigations using a technique involving hydrazine reduction of toluene sulfonate esters of phenolic hydroxyl groupings to toluene sulfinate esters, Freudenberg and Plankenhorn[4] have concluded that there are present 0.075, 0.14, and 0.31 free phenolic hydroxyl groups per lignin structural unit in cuproxam lignin, hydrochloric acid lignin, and deacetylated acetic acid lignin, respectively.

To secure further information as to the status of the phenolic hydroxyl groupings in lignin sulfonic acids, conductometric titration studies have now been made of exhaustively dialyzed sulfite waste liquor solutions which, as is established in another communication,[5] consist of salts of lignin sulfonic acids of a high degree of purity.

Experimental Part

Conductometric titrations were conducted in 50% ethanol solution using carbonate-free sodium hydroxide. A 60-cycle Wheatstone bridge circuit with pointer type AC galvanometer was used. The titration cell, of 100-ml. capacity, was constructed with buret delivery tubes and glass stirrer mounted in the lid. This was connected by a ground glass joint to the body containing platinized electrodes. The cell constant was 0.492 cm.$^{-1}$.

Samples from alkali cleavage experiments were adjusted with dilute hydrochloric acid to *p*H 4. A measured excess of standard acid was then added and the samples were boiled to expel carbon dioxide and sulfur dioxide formed by desulfonation of the lignin sulfonic acid. After cooling in stoppered flasks, aliquots were titrated with 0.01 *N* iodine solution to determine residual sulfur dioxide. Weak acids, determined conductometrically on separate aliquots, were corrected for residual sulfite.

Potentiometric titrations were conducted using a Leeds and Northrup glass electrode *p*H electrometer.

Total solids and total sulfur recovery in the fractionation of alkali cleaved lignin sulfonic acid were corrected for sodium sulfate resulting from alkali neutralization by conductometric sulfate[6] determinations.

Other analytical procedures have been described in a separate communication.[5]

Extinction coefficients for the nitroso lignin test were determined using a Coleman Spectrophotometer.

Alkali cleavage experiments were generally conducted in glass apparatus under a reflux condenser using a nitrogen atmosphere. Some experiments were conducted using small stainless steel autoclaves in a constant temperature oil-bath.

The lignin sulfonic acid concentration was generally 20 g. per liter. Free lignin sulfonic acids were prepared from calcium or sodium lignin sulfonate solutions by treatment with an acid regenerated cation exchange resin (Amberlite 1R 100).

Discussion

Typical results with untreated lignin sulfonic acid solutions are illustrated in Fig. 1, which shows comparative conductometric and potentiometric titrations on the same solution of lignin sulfonic acids. From the character of curves obtained, it is clear that only small amounts—certainly less than 0.2 mole per mole of methoxyl of weak acids with *pK* values between 4 and 10—can be contained. Since phenolic hydroxyl groups in lignin sulfonic acids, if free, should fall within this range, the absence, or presence in only low concentrations, of these groupings, is indicated.

However, free phenolic hydroxyl groups do exist in lignin sulfonic acids which have been subjected to an alkaline environment. Such conditions may arise during methylation reactions which have been used to indicate the presence of free phenolic groups[1] and have been found by Karrer and associates,[7] to lead to rapid cleavage of some anthocyanins to simple phenolic substances. Treatment of lignin under more strongly alkaline conditions and at higher temperature yields products which are precipitable with carbon dioxide and thus presumably phenolic in character and under these conditions lignin sulfonic acids yield vanillin and other phenolic substances.

When the lignin sulfonic acid preparation described in Figure 1 was treated with 5% sodium hydroxide at 100° for several time periods, the reaction products showed the conductometric titra-

(1) Tomlinson and Hibbert, THIS JOURNAL, **58**, 350 (1936).

(2) Brauns, *Paper Trade Journal*, **111**, no. 14, 33–39, Oct. (1940).

(3) Freudenberg, Meister and Flickinger, *Ber.*, **70**, 500 (1937).

(4) Freudenberg and Plankenhorn, *ibid.*, **75**, 857–867 (1942).

(5) Peniston and McCarthy, THIS JOURNAL, **70**, 1324 (1948).

(6) Peniston, Felicetta and McCarthy, *Ind. Eng. Chem., Anal. Ed.*, **19**, 332 (1947).

(7) Karrer and co-workers, *Helv. Chim. Acta.*, **10**, 67, 729 (1927); **12**, 292 (1929); **15**, 507 (1932).

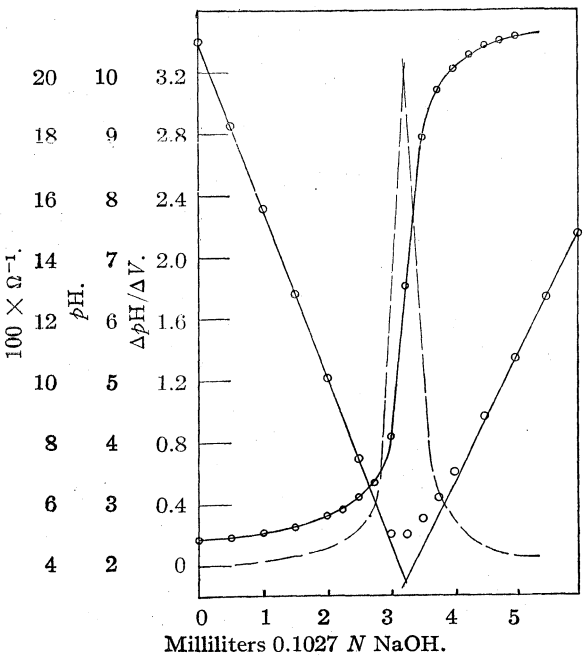


Fig. 1.—Potentiometric and conductometric titrations of lignin sulfonic acid showing low weak acid content: 1.0 ml. NaOH = 0.164 mole of acid per mole of OCH_3.

tion curves given in Fig. 2. After sodium hydroxide addition equivalent to the midpoint of the indicated weak acid lines, all solutions were found to be approximately *p*H 9, indicating that the ionization constants for the acids titrated are in the expected range for phenolic hydroxyl groups. From the above and similar studies on different lignin sulfonic acid preparations, it is concluded that treatment in five per cent. sodium hydroxide solutions at 100°, causes liberation in about two hours of about 0.67 mole of phenolic hydroxyl per mole of methoxyl. Following this there is a more gradual formation of weak acid groups which continues with the time of cleavage.

The rate of the initial phenolic hydroxyl liberation appears to be approximately proportional to the alkali concentration. Thus in aqueous solutions 1% in sodium hydroxide, the rate is found to be roughly one-fifth of that observed in solutions 5% in sodium hydroxide. Also, at the lower alkali concentration, the more gradual acid formation is not discernible. Thus there may be two reactions involved or two different groupings cleaved by the alkaline treatment.

The liberation of phenolic hydroxyl groups in lignin sulfonic acid should result in its increased reactivity in chemical reactions dependent on the presence of active nuclear hydrogen. After alkali treatment there should be evident increased ease of oxidation and of halogenation, increased reactivity in condensation reactions, *e. g.*, with formaldehyde, and in substitution reactions such as coupling with diazonium salts or reaction with nitrous acid. Two such reactions have now been studied in comparison with titration data for the amount of weak acid liberated in alkali cleavage.

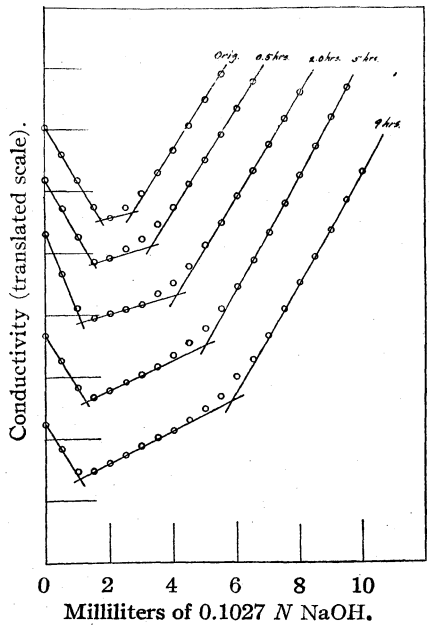


Fig. 2.—Conductometric titrations of L. S. A. after alkali cleavage.

Pearl and Benson[8] have developed a procedure for determination of lignin sulfonic acid in sea water utilizing the color formed by reaction with nitrous acid presumably forming a nitroso lignin. Mr. William G. Westover,[9] in collaboration with H. K. Benson and the authors, has studied the effects of alkali cleavage on the color developed in this reaction.

Pennington and Ritter[10] have recently investigated oxidation of various phenolic substances with periodic acid and have found that substances with guaiacyl nuclei with free phenolic hydroxyl groups are readily oxidized with accompanying demethylation. Dr. Pennington has examined a series of our alkali cleavage samples using the periodate oxidation technique.

Results of the three characterizations of the same series of alkali treated lignin sulfonic acid samples are shown in Fig. 3, in which the conductometric moles of weak acid per mole of methoxyl, the increase in extinction coefficient at 4700 Å. for the nitrous acid reaction product, and the moles of periodate consumed per mole of methoxyl, are each plotted as ordinates against the time of alkali cleavage as abscissa. The three quantities show pronounced increases during the early stages of treatment, indicating an increase in concentration of free phenolic groups. After two hours of treatment, however, there is no further increase in periodate consumption, or in the extinction coefficient, while a continued gradual increase in weak

(8) Pearl and Benson, *Paper Trade J.*, **111**, no. 18, 35–36 (1940).
(9) Westover, B. S. Thesis, University of Washington, 1946.
(10) Pennington and Ritter, THIS JOURNAL, **69**, 187 (1947).

acids is still apparent. It is believed, therefore, that for the experimental conditions used liberation of phenolic groups is substantially complete in two hours, and that generation of other acidic groupings is probably responsible for the subsequent gradual rise in titratable acids. Ritter and Pennington[10] have observed that pure guaiacyl type phenolic substances in general consume three moles of periodate per mole of methoxyl. This would imply that in alkali cleavage under conditions used only two thirds of the potential phenolic hydroxyl groups have been liberated and suggests the possibility that a different type of linkage exists for the remaining third. A similar result is obtained by linear extrapolation to zero time of the gradual weak acid increase. On this basis the amounts of phenolic hydroxyl liberated in the first two hours are in close agreement as determined by periodate consumption or titration (Fig. 3a).

The increase in extinction coefficient for the products of reaction with nitrous acid agrees reasonably well with the assumption that light absorption of the lignin polymer is due to two typical groupings, *i. e.*, structural units with free phenolic hydroxyls, and those remaining as phenolic ethers. The observed extinction coefficient, "K_{obs}," should thus be expressible as a sum of two terms as

$$(C_1 + C_2)K_{obs.} = K_1C_1 + K_2C_2 \qquad (1)$$

where "C_1" and "C_2" represent the molar concentrations of free and combined phenolic hydroxyl groupings per mole of methoxyl, and "K_1" and "K_2" represent the extinction coefficients associated with these respective groupings. If the concentrations of free phenolic hydroxyl found experimentally by periodate oxidation be taken as C_1, then C_2 may be regarded as the difference between unity and C_1. Using values found experimentally by the nitroso technique for the total extinction coefficient, K_{obs}, then the individual extinction coefficients, K_1 and K_2, may be evaluated by simultaneous solution of Equation 1 using data derived from samples hydrolyzed for two different time intervals. Taking K_1 and K_2 as 76 and 20, respectively, calculation of the terms $K_1C_1 + K_2C_2$ as compared to $(C_1 + C_2)K_{obs}$ shows (Table II) satisfactory correlation of the results of the periodate oxidation method with those of the nitroso method except for the original sample in which some phenolic hydroxyl may have been liberated under the alkaline conditions obtaining during the carrying out of the nitroso method.

The liberation of phenolic hydroxyl groups by mild alkaline treatment of lignin sulfonic acid necessarily brings about other changes in molecular structure. If all of the structural units of the lignin polymer are joined together by non-cyclic ether linkages (such as in Formula I), simple cleavage of these ethers would result in conversion of the polymer to the monomer. However, if furan or pyran rings are involved (such as in Formula II), reduction in molecular weight would require not only liberation of the phenolic hydroxyl but also rupture of carbon to carbon bonds.

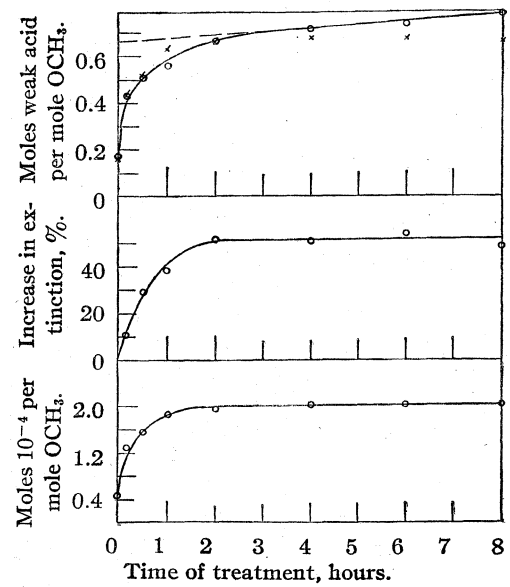
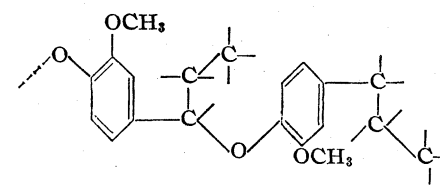


Fig. 3.—Phenolic hydroxyl liberation by alkali cleavage.

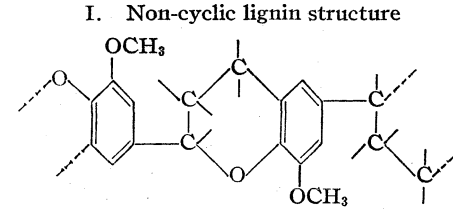
TABLE I

CORRELATION OF EXTINCTION COEFFICIENTS WITH AMOUNT OF FREE PHENOL

Time, hr.	C_1	C_2	K_1C_1	K_2C_2	$(K_1C_1 + K_2C_2)$	$(C_1 + C_2)K_{obs}$
0	0.16	0.94	12.2	18.8	31.0	38.0
0.167	.43	.57	32.7	11.4	44.1	42.1
0.50	.52	.48	39.5	9.6	49.1	49.2
1.00	.63	.37	47.9	7.4	55.3	52.8
2.00	.66	.34	50.1	6.8	56.9	57.8
4.00	.68	.32	51.6	6.4	58.0	57.2
6.00	.68	.32	51.6	6.4	58.0	58.5



I. Non-cyclic lignin structure



II. Cyclic lignin structure

To investigate alteration in molecular size and other changes associated with the alkaline treatment, a fractionation of lignin sulfonic acid after five hours of treatment with 5% sodium hydroxide solution at 100°, has been conducted. Fraction A, which is first apparent after about three hours of treatment and increases with time of the alkali

reaction, is insoluble in water under neutral conditions and after its separation, the remaining soluble Fraction B was dialyzed exhaustively following the same procedure and with the same membranes initially used for preparation of the lignin sulfonic acids from sulfite waste liquor. The non-dialyzable residue (Fraction B-1), the dialyzate (Fraction B-2), and Fractions A and B were then analyzed to determine total material, methoxyl and sulfur balances.

TABLE II

FRACTIONATION OF ALKALI CLEAVED LIGNIN SULFONIC ACIDS

Fraction	Fraction A	Fraction B	Fraction B-1	Fraction B-2
Per cent. of total material	19.1	68.5	32.4	32.3
Per cent. of total sulfur	10.0	58.5	21.5	31.9
Per cent. of total methoxyl	22.5	72.3	36.0	29.7
Extinction coefficient	43	61	49	73

Although considerable material losses occurred particularly in isolation of the peptizable Fraction A, results (Table II) show insoluble Fraction A to be strongly desulfonated (from about 0.50 in the lignin sulfonic acid before alkaline cleavage, to about 0.22 mole of sulfur per mole of methoxyl in Fraction A). The soluble non-dialyzable residue Fraction B-1 is desulfonated to a lesser degree (0.43 mole of sulfur per mole of methoxyl) while the soluble dialyzable Fraction B-2 retains practically the same proportion of sulfur as the original lignin sulfonic acid (0.54 mole of sulfur per mole of methoxyl). Extinction coefficients indicate that a considerable proportion of the phenolic hydroxyl groups remains combined in Fractions A, B, and B-1, while in the dialyzate Fraction B-2 all phenolic hydroxyl groupings appear to be free. That about one-third of the lignin sulfonic acid is readily dialyzable after alkali cleavage whereas the original material had been isolated as a non-dialyzable residue using the same membrane material, appears to demonstrate a substantial decrease in molecular weight for this fraction. Other indications of reduced molecular weight in cleavage products have been obtained from observations of a reduction in specific viscosity.

The liberation of only two-thirds of the potential phenolic hydroxyl groups of lignin sulfonic acid by alkali treatment and the apparent simultaneous formation of sulfonated fragments of lower molecular weight suggest that more than one type of linkage between structural units must exist in the lignin polymer.

The authors are indebted to Mr. Vincent F. Felicetta for analytical assistance.

Summary

1. Examination of a sample of purified lignin sulfonic acids by conductometric and potentiometric titration methods has indicated the absence, or the presence in only low concentrations, of free phenolic hydroxyl groupings in the material as it exists in sulfite waste liquor.

2. By mild alkaline hydrolysis of purified lignin sulfonic acids, weakly acidic groupings are formed which show a pK value of about 9 and are regarded as phenolic hydroxyl groupings.

3. Periodate oxidation studies, and the extent of "nitroso-lignin" formation, as well as conductometric analyses, indicate phenolic hydroxyl liberation by mild alkaline treatment of lignin sulfonic acids.

4. From periodate oxidation values and also conductometric titrations apparently only about 0.67 mole of phenolic hydroxyl per mole of methoxyl are liberated by alkali treatment under the conditions used. The presumed remaining phenolic groups (0.33 mole per mole of methoxyl) thus appear to be bound in a more stable type of linkage.

5. Alkaline hydrolysis of lignin sulfonic acid brings about a decrease in molecular weight of some fractions of the acids, and this and other evidence indicates that more than one type of bond serves to combine structural units in lignin sulfonic acid.

SEATTLE, WASHINGTON RECEIVED JULY 24, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Hydrolysis of Some β-Alkoxypropionitriles[1]

BY ROBERT V. CHRISTIAN, JR.,[2] AND R. M. HIXON

The usual method employed heretofore in the preparation of β-alkoxypropionic acids has involved the hydrolysis[3] of an ester[4] of the desired acid. A variation was introduced by Jones and Powers[5] who obtained sodium β-methoxypropionate from the action of excess sodium methoxide upon β-chloropropionic acid. A single reference to β-alkoxypropionitriles as precursors of acids of this type appears as a patent[6] describing the hydrolysis of di-(2-cyanoethyl)-ether as a step in the preparation of esters of di-(2-carboxyethyl)-ether, although the free acid was not characterized. It should be noted, too, that Kilpi[7] carried out kinetic studies on the hydrochloric acid hydrolysis of β-methoxy- and β-ethoxypropionitrile but did not isolate the products of the reactions.

In the present work, some of the now easily available β-alkoxypropionitriles were examined as intermediates for the preparation of acids of the β-alkoxypropionic type.

Experimental[8]

Materials.—1,4-Pentanediol was prepared by hydrogenation[9] of γ-valerolactone. The other alcohols and glycols were commercially available products which were purified by distillation when necessary. The acrylonitrile (Eastman Kodak Co. Practical Grade) was used without further treatment.

β-Ethoxypropionitrile was prepared by the method of Koelsch.[10] Utermohlen's procedure,[11] employing 40% potassium hydroxide as the catalyst, was followed in the synthesis of the other monofunctional nitriles. Those which have not been described heretofore are listed in Table I with pertinent information. The preparation of 1,4-di-(2-cyanoethoxy)-pentane has been described.[12] The other bifunctional nitriles were obtained in accordance with the procedure of Bruson and Riener.[13]

Alkaline Hydrolysis of β-Alkoxypropionitriles.—1,4-Di-(2-cyanoethoxy)-pentane, when refluxed with 10% sodium hydroxide in the usual manner, gave an undistillable and uncrystallizable oil of neutral equivalent 177 (calculated for the expected dibasic acid, 124). Similar treatment of di-(2-cyanoethyl)-ether with 24% sodium hydroxide gave material from which neither di-(2-carbamylethyl)-ether[13] nor the disodium salt of di-(2-carboxyethyl)-ether[14] could be obtained by suitable procedures.

β-Ethoxypropionic acid[3b] could not be identified as a product of the hydrolysis of β-ethoxypropionitrile with 22% sodium hydroxide. Upon distillation of the reaction products under reduced pressure, partial decomposition took place and a colorless distillate was collected. This liquid liberated carbon dioxide from dilute sodium bicarbonate and reduced alkaline 2% permanganate. The substance polymerized upon standing to form a transparent, elastic solid which was insoluble in ethanol or chloroform but dissolved slowly in sodium bicarbonate solution, with evolution of carbon dioxide, to yield a clear solution of unusually high viscosity.

TABLE I

β-ALKOXYPROPIONITRILES, $ROCH_2CH_2CN$

R	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_{20}	Nitrogen, %[a] Calcd.	Found
n-Propyl	84	87–89	24	1.4131	0.9006	12.4	12.2
		84	19				
Isobutyl	81	91	20	1.4143	.8836	11.0	11.1
s-Butyl	79	90	19	1.4156	.8896	11.0	11.3
Isoamyl	82	99	13	1.4218	.8834	9.93	10.1
s-Amyl	70	98	16	1.4205	.8862	9.93	9.85
Allyl	85	95	24	1.4330	.9396	12.6	12.4

[a] By micro Kjeldahl.

Acid Hydrolysis of β-Alkoxypropionitriles.—The procedure consisted in heating a mechanically stirred mixture of the β-alkoxypropionitrile and twice the calculated quantity of concentrated hydrochloric acid. Only representative experiments are described below. Yields of the liquid acids were based upon the neutral equivalents of the once-distilled compounds. Analytical data and physical constants were obtained upon material purified by fractional distillation using a 20-cm. Vigreux column. The information is summarized in Table II. The yields of the solid acids were determined from the neutral equivalents of the crude products whereas recrystallization to constant melting point furnished analytical specimens. These data are presented in Table III.

The monobasic acids were characterized, when possible, by preparation of solid *p*-bromophenacyl esters (Table IV) in accordance with a standard procedure.[15] Thionyl chloride, followed by cold, concentrated ammonium hydroxide, served to convert the dibasic acids to amides (Table V), of which several have been prepared recently by other methods.[13,16]

β-*n*-Propoxypropionic Acid.—A mixture of 79.1 g. (0.7 mole) of β-*n*-propoxypropionitrile and 140 g. (1.4 moles) of concentrated hydrochloric acid was stirred and heated for three hours at 70–80° and then for thirty minutes at 100°. The reaction mixture was evaporated to dryness *in vacuo* with heating on a water-bath. The product was taken up in acetone (or ether) and filtered. The residual ammonium chloride was washed several times with the solvent. Distillation gave 74 g. of colorless liquid boiling at 117–123° (13 mm.) and having the neutral equivalent 130. This represents a yield of 80%.

The corresponding ethoxy-, isopropoxy-, *n*-butoxy-,

(1) Taken from part of a thesis submitted by Robert V. Christian, Jr., to the Graduate Faculty of Iowa State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Department of Chemistry, University of Wichita, Wichita, Kansas.

(3) (a) Hamonet, *Compt. rend.*, **132**, 260 (1901); *Bull. soc. chim.*, [3], **33**, 518 (1905); (b) Palomaa, *Ann. Acad. Sci. Fennicae*, [A] **3**, No. 2 (1911); *Chem. Zentr.*, **83**, II, 595 (1912); (c) Fichter and Herndl, *Helv. Chim. Acta*, **14**, 857 (1931); (d) Palomaa and Jaakola, *Ber.*, **67**, 949 (1934); (e) Palomaa and Tukkimäki, *ibid.*, **68**, 887 (1935); (f) Fichter and Schnider, *Helv. Chim. Acta*, **25**, 229 (1942).

(4) Methods for preparing the necessary esters have been reviewed by Rehberg, Dixon and Fisher, THIS JOURNAL, **68**, 544 (1946).

(5) Jones and Powers, *ibid.*, **46**, 2518 (1924).

(6) Bruson, U. S. Patent 2,347,627, April 25, 1944; *C. A.*, **39**, 87 (1945).

(7) Kilpi, *Z. physik. Chem.*, **86**, 672 (1913).

(8) Melting points and boiling points are uncorrected.

(9) Folkers and Adkins, THIS JOURNAL, **54**, 1145 (1932).

(10) Koelsch, *ibid.*, **65**, 437 (1943).

(11) Utermohlen, *ibid.*, **67**, 1505 (1945).

(12) Christian, Brown and Hixon, *ibid.*, **69**, 1961 (1947).

(13) Bruson and Riener, *ibid.*, **65**, 23 (1943).

(14) Wislicenus, *Ber.*, **3**, 809 (1870); *Ann.*, **166**, 10 (1872).

(15) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 144.

(16) (a) Bruson, U. S. Patent 2,359,708, October 3, 1944; *C. A.*, **39**, 3972 (1945); (b) U. S. Patent 2,372,808, April 3, 1945; *C. A.*, **39**, 4623 (1945).

TABLE II

β-ALKOXYPROPIONIC ACIDS, $ROCH_2CH_2COOH$

R	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_4	Analyses, % Calcd. Neut. eq.	Calcd. Carbon	Calcd. Hydrogen	Found Neut. eq.	Found Carbon	Found Hydrogen
Ethyl[a]	36	117–120	17	....	1.0635	118.1	..	...	120.0	..	...
n-Propyl[b]	80	87	1	1.4233	1.0237	132.1	..	...	132.0	..	...
		120	13								
Isopropyl[c]	60	85.5–86	1	1.4202	1.0192	132.1	..	...	131.3	..	...
		118	13								
n-Butyl[d]	69	96–97.5	1	1.4268	0.9929	146.1	57.5	9.67	147.3	57.1	10.0
Isobutyl[d]	67	89–90	1	1.4227	0.9843	146.1	57.5	9.67	146.0	57.0	9.74
s-Butyl	56	90–91.4	1	1.4252	0.9946	146.1	57.5	9.67	146.4	57.3	9.76
Isoamyl[e]	69	100	1	1.4285	0.9697	160.2	..	...	162.7	..	...
		137	12		$0.9725(d^{18}_{18})$						
s-Amyl	49	100–101	1	1.4289	0.9833	160.2	60.0	10.1	159.4	59.7	10.3
Allyl	33[f]	84	1	1.4423	1.0604	130.1	55.4	7.75	130.8	55.3	8.17
		111–112	6								
2-Methoxyethyl	75	109–110	0.5	1.4356	1.1146	148.2	48.6	8.16	150.8	48.3	8.35

[a] Previously prepared. Palomaa (3b) gives boiling point 119–120° (19 mm.) and d^{20}_4 1.0641. [b] Previously prepared (3e). Nazarov and Romanov (*Bull. acad. sci. U. R. S. S., Classe. sci. chim.*, 1940, 453; *C. A.*, **35**, 3593 [1941]) report boiling point 110–112° (9 mm.) and $n^{19}D$ 1.4230. [c] Previously prepared (3e). Nazarov and Romanov (*loc. cit.*) report boiling point 125–126° (22 mm.) and $n^{20}D$ 1.4202. [d] Previously prepared (3e) but physical constants not reported. [e] Previously prepared. Constants reported are boiling point 135° (12 mm.) (3c, 3f) and d^{18} 0.974 (3a). [f] Reaction temperature was 60–70°.

TABLE III

β-ALKOXYPROPIONIC ACIDS (DIBASIC), $R(CH_2CH_2COOH)_2$

R	Yield, %	M. p., °C.	Analyses, % Calcd. Neut. eq.	Calcd. Carbon	Calcd. Hydrogen	Found Neut. eq.	Found Carbon	Found Hydrogen
—O—	97	60–61[a,b]	81.07	44.5	6.18	81.77	44.8	6.56
$—O(CH_2)_2O—$	94	66[c]	103.1	46.6	6.86	103.5	47.0	7.24
$—O(CH_2)_3O—$	90	86–87[d]	110.1	49.1	7.32	111.1	49.3	7.62
$—O(CH_2)_2O(CH_2)_2O—$	91	Oil[e]	125	..	..	137[f]	..	..

[a] Recrystallized from an ether–petroleum ether (b. p. 60–70°) mixture by cooling to −40°. [b] Boiling point 189–192° (1 mm. or less) with slight decomposition. [c] Recrystallized from benzene containing a little acetone. [d] Recrystallized from benzene containing a little petroleum ether (b. p. 60–70°). [e] Decomposed at about 225° upon attempted distillation at 0.5 mm. or less. [f] Crude product.

TABLE IV

p-BROMOPHENACYL β-ALKOXYPROPIONATES, $ROCH_2CH_2COOCH_2COC_6H_4Br$-*p*

R	Crystalline form[a]	M. p., °C.	Bromine, %[b] Calcd.	Found
Ethyl	Large leaflets	47–48	25.4	25.1
n-Propyl	Shiny leaflets	57–58	24.3	24.2
Isopropyl	Tiny plates	44–44.5	24.3	23.9
n-Butyl	Shiny leaflets	55	23.3	23.0
Isobutyl	Fibrous needles	58–59	23.3	23.2
s-Butyl	Oil	.....	..	..
Isoamyl	Glistening needles	56	22.4	22.2
s-Amyl	Oil	.....	..	..
Allyl	Tiny plates	38–39	24.4	24.3
2-Methoxyethyl	Oil	*ca.* 15	..	..

[a] Recrystallized by dissolution in aqueous ethanol at room temperature followed by cooling to −20°. [b] By micro pearl tube.

TABLE V

β-ALKOXYPROPIONAMIDS (DIBASIC), $R(CH_2CH_2CONH_2)_2$

R	M. p., °C.	Nitrogen, %[f] Calcd.	Found
—O—[a]	143.5–144	17.5	17.4
$—O(CH_2)_2O—$[b]	123[d,e]	13.7	13.6
$—O(CH_2)_3O—$	124[d]	12.8	12.5
$—O(CH_2)_2O(CH_2)_2O—$[c]	103–103.5	11.3	11.2

[a] Previously prepared by another method (13). M. p. reported, 146°. [b] Previously prepared by another method (16a). M. p. reported, 123–124°. [c] Previously prepared by another method (16). M. p. reported, 103–104°. [d] Mixed melting point of these two substances was 95–110°. [e] Change in crystal structure at 107°. Melted sharply at 104° without resolidification under rapid heating (10° per minute). [f] By micro Kjeldahl.

isoamyloxy-, *s*-amyloxy-, and 2-methoxyethoxy-compounds were prepared by this method.

β-Isobutoxypropionic Acid.—β-Isobutoxypropionitrile (76.2 g., 0.6 mole) was stirred with 120 g. (1.20 moles) of concentrated hydrochloric acid for four hours at 75–80°. The cooled reaction mixture was diluted with sufficient water to dissolve the precipitate of ammonium chloride. The organic layer was separated and the aqueous solution was extracted with ether. Distillation gave 63 g. of material boiling at 105–110° (5 mm.). The neutral equivalent, 157, indicated a yield of 67%.

The *s*-butoxy- and allyloxy- derivatives were prepared in a similar fashion.

1,3-Di-(2-carboxyethoxy)-propane.—A stirred mixture of 98 g. (0.54 mole) of 1,3-di-(2-cyanoethoxy)-propane and 216 g. (2.16 moles) of concentrated hydrochloric acid was heated at 70–80° for four hours and then at 100° for thirty minutes. The mixture was evaporated to dryness *in vacuo* and extracted with warm acetone. Evaporation of the acetone solution under reduced pressure gave 118.5 g. of sirup which crystallized to a white solid (melting

point 65–77°) upon standing overnight. The neutral equivalent was 123, indicating a yield of 90%.

Di-(2-carboxyethyl)-ether, 1,2-di-(2-carboxyethoxy)-ethane, and di-(2-[2-carboxyethoxy]-ethyl) ether were prepared by this method.

Acid Hydrolysis of 1,4-Di-(2-cyanoethoxy)-pentane.—A stirred mixture of 40 g. (0.19 mole) of 1,4-di-(2-cyanoethoxy)-pentane and 76 g. (0.76 mole) of concentrated hydrochloric acid was heated for five hours at 80–90°. Extraction with chloroform gave 40.5 g. of uncrystallizable oil of neutral equivalent 199. This material was esterified by refluxing with absolute ethanol containing a trace of dry hydrogen chloride. Upon distillation the principal fraction consisted of 13 g. of colorless liquid which contained chlorine and was shown by the ferric hydroxamate test[17] to be an ester. The physical constants were boiling point 109–112° (2.5 mm.), d^{25}_4 1.0325, and $n^{25}D$ 1.4386.

The presence of chlorine in the product suggested that cleavage at an ether linkage might have occurred during the hydrolysis. Under the conditions of the experiment this would likely lead to the formation of an ethyl β-(chloroamyloxy)-propionate. The analytical data lend support to this hypothesis.

Anal. Calcd. for $C_{10}H_{19}O_3Cl$: MR_D, 56.63; C, 53.9; H, 8.60; Cl, 15.9. Found: MR_D, 56.75; C, 53.6; H, 8.82; Cl, 15.2.

1,4-Di-(2-carbethoxyethoxy)-pentane.—Sixty grams (0.16 mole) of coarsely pulverized 1,4-di-(2-cyanoethoxy)-pentane bis-(ethyliminoester hydrochloride)[12] was added in small portions to 200 ml. of distilled water at room temperature. The addition was carried out over a period of twenty minutes and the mixture was stirred continuously. The solid dissolved readily and no change in temperature was observed, but an oil began to separate at once. The mixture was finally heated at 45° for thirty minutes, cooled, and extracted with ether. Distillation of the dried ether extract gave 28 g. (58%) of colorless liquid of boiling point 142–145° (0.5 mm.), d^{25}_4 1.0174, and $n^{25}D$ 1.4363.

Anal. Calcd. for $C_{15}H_{28}O_6$: sapn. equiv., 152.2; C, 59.2; H, 9.27. Found: sapn. equiv., 151.4, 152.4; C, 59.5; H, 9.54.

Alcoholysis of 1,4-di-(2-cyanoethoxy)-pentane by the methods of Spiegel[18] and Sabetay[19] gave complex mixtures. 1,4-Di-(2-carbethoxyethoxy)-pentane was obtained in 33% yield, however, by a modification of the procedure described by Kimball, Jefferson and Pike[20] for the preparation of ethyl α-phenylacetoacetate.

With a view to characterization of 1,4-di-(2-carbethoxyethoxy)-pentane by conversion to the sodium salt of the corresponding acid, an attempt was made to saponify the ester by gentle warming with the calculated quantity of alcoholic sodium hydroxide. The experiment was abandoned when the reaction mixture began to exhibit a strong odor of ethyl acrylate.

Discussion

The fact that lower yields of β-alkoxypropionitriles were obtained from secondary alcohols is in agreement with the observations of Utermohlen.[11] Furthermore, it was found unnecessary to employ external cooling to hold the reaction temperature below 40° during the addition of *s*-butyl alcohol and *s*-amyl alcohol to acrylonitrile. This suggests a lower reaction rate or a lower heat of reaction for the secondary alcohols.

Failure to obtain the expected products in the three cases in which β-alkoxypropionitriles were treated with aqueous alkali was unexpected, inasmuch as other investigators have successfully employed basic hydrolysis for the conversion of the cyanoethyl derivatives of active methylene compounds,[21] isatin,[22] pyrrole[23] and ammonia[24] to the corresponding acids. It has been established, however, that the base-catalyzed reaction of an alcohol with acrylonitrile produces an equilibrium mixture which contains, in addition to the β-alkoxypropionitrile, appreciable quantities of the reactants.[10] It is suggested that under the conditions of the basic hydrolytic experiments herein described, partial decomposition of the β-alkoxypropionitriles into their generators took place with subsequent formation of complex hydrolysis mixtures. It is deemed significant that one of the products of the basic hydrolysis of β-ethoxypropionitrile exhibited properties suggestive of acrylic acid or one of its derivatives. Hollihan and Moss[25] have reported that acrylonitrile reacts with commercial viscose solutions to form cyanoethyl ethers of cellulose xanthate, and that during the aging process the latter are hydrolyzed by the approximately 3% sodium hydroxide normally present to form carboxyethyl ethers. These hydrolysis conditions are, of course, much less drastic than those employed in the present study.

Although no attempt was made to determine optimum conditions, hydrolysis in acid media appears to be a fairly general method for the conversion of β-alkoxypropionitriles to the corresponding acids. Slightly lower yields were obtained in the preparation of the β-*s*-alkoxypropionic acids and there was a general decrease in yield as the size of the alkyl group increased. No attempt is made to explain the cleavage which apparently took place upon hydrolysis of 1,4-di-(2-cyanoethoxy)-pentane with hydrochloric acid.

The monobasic β-alkoxypropionic acids were colorless liquids having little or no odor. They were all soluble in the common organic solvents. The ethoxy-, isopropoxy-, allyloxy- and 2-methoxyethoxy- derivatives were easily soluble in water whereas β-*n*-propoxypropionic acid was only slightly so. None of the higher homologs were appreciably soluble in water.

The dibasic acids of the β-alkoxypropionic type were very soluble in water, thus displaying, by comparison with acids of similar molecular weight but having a carbon chain uninterrupted by oxygen, the striking effect of the ether linkage upon solubility. These acids were soluble in acetone or ethanol but insoluble in petroleum ether. Di-(2-carboxyethyl)-ether was highly soluble in ether, but insoluble in benzene. 1,2-Di-(2-carboxyethoxy)-ethane was insoluble in ether and slightly soluble in benzene. 1,3-Di-(2-carboxyethoxy)-

(17) Davidson, *J. Chem. Education*, **17**, 81 (1940).

(18) Spiegel, *Ber.*, **51**, 296 (1918).

(19) Sabetay, *Bull. soc. chim.*, [4] **45**, 534 (1929).

(20) Kimball, Jefferson and Pike, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 284.

(21) Bruson and Riener, THIS JOURNAL, **64**, 2855 (1942); *ibid.*, **65**, 18 (1943).

(22) DiCarlo and Lindwall, *ibid.*, **67**, 199 (1945).

(23) Blume and Lindwall, *J. Org. Chem.*, **10**, 255 (1945).

(24) Ford, THIS JOURNAL, **67**, 876 (1945).

(25) Hollihan and Moss, *Ind. Eng. Chem., Ind. Ed.*, **39**, 929 (1947).

propane was insoluble in ether, but easily soluble in warm benzene.

Summary

1. Six hitherto undescribed β-alkoxypropionitriles have been prepared.

2. A reaction mechanism is proposed to account for the fact that alkaline hydrolysis of β-ethoxypropionitrile, di-(2-cyanoethyl)-ether and 1,4-di-(2-cyanoethoxy)-pentane failed to yield the expected β-alkoxypropionic acids.

3. A series of monobasic and dibasic acids of the β-alkoxypropionic type was prepared by acid hydrolysis of the corresponding nitriles. The acids were characterized, when possible, by the preparation of suitable solid derivatives. The dibasic acids and several of the monobasic acids are described for the first time.

4. Hydrolysis of 1,4-di-(2-cyanoethoxy)-pentane with hydrochloric acid yielded a chlorine-containing acid which was isolated as the ethyl ester. The analysis of this ester was in close agreement with that calculated for an ethyl β-(chloroamyloxy)-propionate.

5. Hydrolysis of 1,4-di-(2-cyanoethoxy)-pentane-bis-(ethyliminoester hydrochloride) or ethanolysis of 1,4-di-(2-cyanoethoxy)-pentane at low temperatures gave 1,4-di-(2-carbethoxyethoxy)-pentane.

WICHITA, KANSAS RECEIVED NOVEMBER 21, 1947

[CONTRIBUTION FROM THE EMERYVILLE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

Decompositions of Di-*t*-alkyl Peroxides. III. Kinetics in Liquid Phase

BY JOHN H. RALEY, FREDERICK F. RUST AND WILLIAM E. VAUGHAN

In the first papers of this set,[1,2] the decomposition of di-*t*-butyl peroxide in the vapor phase was shown to be a clean-cut, first order process, the rate determining step of which was the scission of the peroxy-oxygen linkage. The resultant radicals, *t*-butoxy and the methyl derived therefrom, can react with copresent molecules by steps which follow the generally accepted patterns of chain initiation, propagation and termination. This work has now been extended to a study of decompositions in condensed phases.

It is well established[3a,b,4,5] that the rate of decomposition of benzoyl peroxide varies profoundly with the solvent; further, the first order rate is complicated by higher order processes which become increasingly important at higher concentrations. In contrast, the present work reveals that even in such diverse solvents as cumene, *t*-butylbenzene and tri-*n*-butylamine, the rates of decomposition of di-*t*-butyl peroxide are closely the same and, importantly, nearly equal to that in the vapor phase. Likewise the energies of activation in solution and vapor are approximately equivalent. This implies, obviously, that the same simple dissociation step is rate determining in all cases.

Although these condensed environments do not alter the rate, their differing abilities to donate hydrogen atoms give rise to varying amounts of *t*-butyl alcohol in relation to acetone in the competing steps 2 and 3a

$$(CH_3)_3CO{-}OC(CH_3)_3 \longrightarrow 2(CH_3)_3CO- \quad (1)$$

$$(CH_3)_3CO- + R'H \longrightarrow (CH_3)_3COH + R' \quad (2)$$

$$(CH_3)_3CO- \longrightarrow (CH_3)_2CO + CH_3 \quad (3a)$$

$$CH_3 + R'H \longrightarrow CH_4 + R' \quad (b)$$

Further, in all of the solvents, with increasing temperature the *t*-butoxy radical increasingly dissociates to acetone and methyl (3a). The data permit a rough estimate of the difference in the activation energies of the steps 2 and 3a for the hydrocarbon solvents.

Experimental

Materials

Di-*t*-butyl peroxide, prepared by the method of Vaughan and Rust[6] and vacuum distilled ($n^{20}D$ 1.3890), was used for both the decomposition experiments and calibration of the infrared spectrograph. By titration it analyzed 98% pure. The several solvents were chosen for convenience of boiling points (avoidance of undue pressure build-up in the bombs), obtainability, ease of purification and, importantly, differing abilities as hydrogen donors to free radicals. Commercial **cumene** was carefully distilled and a fraction of b. p. 152° and $n^{20}D$ 1.4912 was collected and stored under nitrogen. ***t*-Butylbenzene** (Eastman Kodak Co.) was similarly treated (b. p. 169°, $n^{20}D$ 1.4922). **Tri-*n*-butylamine** (Eastman) was treated with 3 *N* hydrochloric acid and the water-insoluble impurities removed; the amine was regenerated with aqueous sodium hydroxide, washed, dried, and distilled (b. p. 214°; $n^{20}D$ 1.4291).

Method

The decompositions were carried out in heavy-walled glass bomb tubes (capacity 40 cc.) in an oil-bath regulated to ±0.1°. The seven or more bombs for a given experiment were filled from a stock solution of the peroxide in the particular solvent, chilled, evacuated, sealed, and immersed. After a short equilibration period, they were withdrawn at specified intervals, quenched, and prepared for analysis. They were then opened in an inert atmosphere, the density of the solution determined by pycnometer, and analysis performed by infrared spectrometry. Time "zero" is defined as the time of withdrawal of the first sample. Duplicate experiments were performed in nearly all cases.

Evidence that the decomposition is independent of the

(1) Raley, Rust and Vaughan, THIS JOURNAL, **70**, 88 (1948).

(2) Rust, Seubold and Vaughan, *ibid.*, **70**, 95 (1948).

(3) (a) Nozaki and Bartlett, *ibid.*, **68**, 1686 (1946); (b) Bartlett and Nozaki, *ibid.*, **69**, 2299 (1947)).

(4) Cass, *ibid.*, **68**, 1976 (1946).

(5) Barnett and Vaughan, *J. Phys. Coll. Chem.*, **51**, 926, 942 (1947).

(6) Vaughan and Rust, U. S. Patent, 2,403,771 (July 9, 1946).

vapor volume in the tubes was obtained from the following pair of experiments. Two sets of bombs were charged with a stock solution of the peroxide in cumene, one set having a vapor volume of 35% and the other 66%. The decompositions were then carried out at 135 ± 0.1° to at least 50% completion. The first order constants were 5.1 and 5.2 × 10^{-5} sec.$^{-1}$, respectively, and the *t*-butyl alcohol–acetone ratios, 1.51/0.49 = 3.1 and 1.41/0.59 = 2.4.

Analysis

Analyses were performed by an infrared spectrometric procedure developed for di-*t*-butyl peroxide and its decomposition products, acetone and *t*-butyl alcohol. The bands utilized in the method are found at the (uncorrected) wave lengths of 11.46 μ, 5.88 μ and 2.925 μ, respectively. Tests showed the method to be applicable in the three solvents studied. Since the spectral procedure yields concentrations in terms of unit volume, the density of the sample was needed for conversion to terms of unit weight. This basis is used for expressing concentrations since the weight rather than the volume or total number of moles remains constant throughout the decomposition. The weight of methane which could escape when the bombs were opened was negligible.

Results

Figure 1 gives an example of the precision of measurement in several runs and Fig. 2 that of the correlation of a set of experiments. The reaction is first order to conversions as high as 85% (Fig. 3). In Table I are summarized all of the data and included therein are corresponding values for the vapor phase for the sake of ready comparison. The small variation of the rates in the four media at a given temperature is striking and argues

TABLE I

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE IN VARIOUS ENVIRONMENTS

	Cumene 0.799 mole DTBP/kg. soln. $k = 0.63(10^{16})e^{-37,600/RT}$			*t*-Butylbenzene 0.775 mole DTBP/kg. soln. $k = 1.1(10^{16})e^{-38,000/RT}$		
		Stoichiometry[d]			Stoichiometry	
Temp., ±0.1° C.	$k \times 10^5$[b] sec.$^{-1}$	*t*-Butyl alcohol	Acetone	$k \times 10^5$[b] sec.$^{-1}$	*t*-Butyl alcohol	Acetone
125	1.6 ± 0.1	1.61	0.39	1.5 ± 0.2	0.75	1.25
135	5.2 ± 0.3	1.51	0.49	5.0 ± 0.3	0.56	1.44
145	15.6 ± 1.3	1.23	0.77	15.1 ± 2.2	0.46	1.54

	Tri-*n*-butylamine 0.867 mole DTBP/kg. soln. $k = 0.35(10^{16})e^{-37,000/RT}$			Vapor phase[a] 52–386 mm. $k = 3.2(10^{16})e^{-39,100/RT}$		
		Stoichiometry[f]			Stoichiometry	
Temp., ±0.1° C.	$k \times 10^5$[b] sec.$^{-1}$	*t*-Butyl alcohol	Acetone	$k \times 10^5$[c] sec.$^{-1}$	*t*-Butyl alcohol	Ketones[e]
125	1.7 ± 0.3	*ca.* 1.9	*ca.* 0.1	1.1	0	2.0
135	4.2 ± 0.4	*ca.* 1.9	*ca.* 0.1	3.6	0	2.0
145	16.0 ± 2.1	*ca.* 1.9	*ca.* 0.1	11.5	0	2.0

[a] Interpolated and extrapolated from Ref. (1): temp. range 139.8–159.8° (±0.04°). [b] Calculated from data for the first 50% decomposition. [c] Calculated from data for the first 33% decomposition. [d] Products from one molecule of ROOR (R = *t*-butyl); see equations (2) and (3a) + (3b). [e] Principally acetone with *ca.* 5% methyl ethyl and higher ketones. [f] Acetone formation with this solvent is too small to allow precise determination of the stoichiometry.

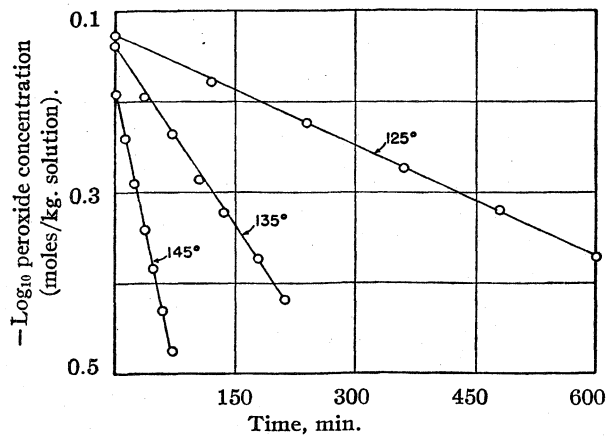


Fig. 1.—Decomposition of di-*t*-butyl peroxide in *t*-butylbenzene: initial concentration, 0.775 mole/kg. solution.

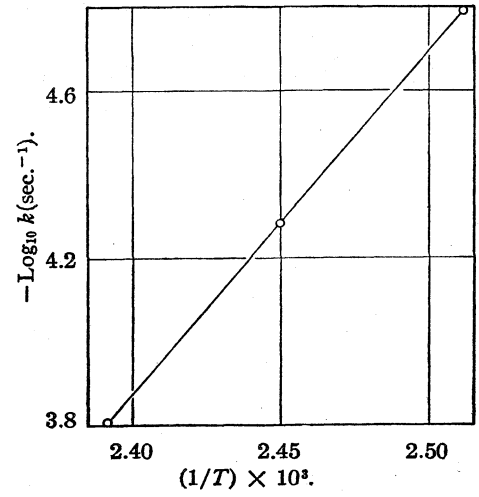


Fig. 2.—Effect of temperature on di-*t*-butyl peroxide decomposition in cumene: initial concentration, 0.799 mole/kg. solution.

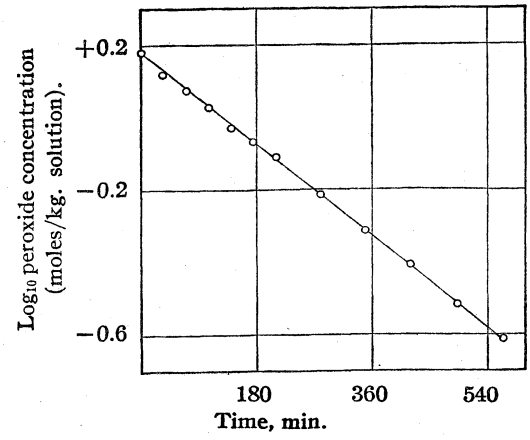


Fig. 3.—Decomposition of di-*t*-butyl peroxide in cumene, 85% decomposition: temperature, 135°; initial concentration, 1.618 moles/kg. solution.

strongly for the unimolecularity of the decomposition,[7] especially in light of the large differences in the fate of the *t*-butoxy radicals. There is a slight trend of k with concentration (Table II), but this variation is no greater than that exhibited by the decomposition of nitrogen pentoxide in carbon tetrachloride.[8]

TABLE II

DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE IN CUMENE

Temp. 135.0 ± 0.1°

Initial concentration (moles/kg. soln.)	$k \times 10^5$[a] (sec.$^{-1}$)
0.455	4.9 ± 0.4
0.799	5.2 ± .1
1.62	5.0 ± .2
2.35	5.7 ± .4

[a] Calculated from data for the first 50% decomposition.

The regular behavior in tri-*n*-butylamine is especially interesting in view of Nozaki and Bartlett's[3,9] finding of explosive reactions of benzoyl peroxide in nitrogen-containing solvents. Di-*t*-butyl peroxide does not behave as an oxidizing agent in the usual sense of the expression.

(7) For comparison with the thermal decomposition of N_2O_5 in various solvents, see F. Daniels, "Chemical Kinetics," Cornell University Press, Ithaca, N. Y., 1938, pp. 100–107.

(8) Eyring and Daniels, THIS JOURNAL, **52**, 1472 (1930).

(9) Also private communication from Dr. Nozaki.

The trends in the stoichiometries enable one to calculate roughly the differences in the activation energies of the steps 2 and 3a. The values of $(E_{3a} - E_2)$ are *ca.* 16 kcal. for cumene and 11 for *t*-butylbenzene. It should be mentioned that calculation shows that step 3a is endothermic to the extent of *ca.* 5 kcal.

Acknowledgment.—The authors wish to thank Mr. William R. Harp and Dr. Robert S. Rasmussen of the Spectroscopic Department of this Company for their extensive coöperation, without which the analytical procedures would have been far more complicated and less accurate. Thanks are also due Mr. Charles E. Fuller and Miss Betty J. Benell for their assistance.

Summary

The small variation in the first order rates of decomposition of di-*t*-butyl peroxide in cumene, *t*-butylbenzene and tri-*n*-butylamine solution and in the vapor state is strong evidence that the same process is rate-determining in all cases. This is thought to be unimolecular scission of the peroxy-oxygen linkage. With increasing temperature the *t*-butoxy radicals become more subject to loss of methyl rather than abstraction of hydrogen from solvent molecules.

EMERYVILLE 8, CALIFORNIA RECEIVED OCTOBER 6, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Effect of Salts on the Solubilization of Insoluble Organic Liquids by Cetylpyridinium Chloride

BY PAUL H. RICHARDS AND JAMES W. McBAIN

Solutions of colloidal electrolytes and of similar non-electrolytic detergents have the power of dissolving otherwise insoluble substances by putting them into or upon the colloidal micelles of the detergent. Salts promote the formation of colloidal micelles of the detergent. Salts promote the formation of colloidal micelles and probably change even their sizes and relative proportions. Therefore they also affect solubilization. Heretofore[1–6] salts have always been reported to enhance solubilization, as well as produce it in solutions of detergents otherwise too dilute to contain colloidal particles.

Materials.—The detergents used in these experiments were cetylpyridinium chloride, obtained in very pure form through the courtesy of Wm. S. Merrell Company, Emulsol 607L (Emulsol Corporation), and Triton X-100 (Röhm and Haas); compare previous publications using these detergents.[3,5,7] The relative effects of a number of detergents with a series of insoluble organic liquids has already been reported.[7]

The organic compounds used were benzene (Kahlbaum "K," thiophene free), *n*-octane (Eastman Kodak Co.) and *n*-octyl alcohol (Eastman Kodak), as well as others previously referred to.[7] The salts employed in the investigation were Kahlbaum sodium and potassium chloride "zür Analyse."

Method.—The method of determining the solubilization of the organic compound by the detergent has been fully described.[7] The turbidimeter was used to detect the saturation or inflection point where solubilization in the clear solution was complete, and any excess of organic liquid began to appear as emulsified droplets. The solutions were shaken in a thermostat maintained at 25° for from ten to twenty hours before readings were taken. The solutions of the detergent and of the salts were prepared at double the desired concentration and 5 cc. of each solution was pipetted

(1) Hartley, *J. Chem. Soc.*, 1968 (1938).

(2) McBain, Merrell and Vinograd, THIS JOURNAL, **63**, 675 (1941).

(3) McBain and Merrill, *Ind. Eng. Chem.*, **34**, 915 (1942).

(4) McBain, in "Advances in Colloid Science," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1942, pp. 129, 131.

(5) McBain and Green, THIS JOURNAL, **68**, 1731 (1946).

(6) McBain, Wilder and Merrill, *J. Phys. Chem.* **52**, 12 (1948).

(7) McBain and Richards, *Ind. Eng. Chem.*, **38**, 642 (1946).

into the reacting bottle to make up a 10 cc. solution of the desired concentration.

As in the previous work, the results were expressed in terms of mole to mole ratio, that is, moles of the organic material solubilized per mole of detergent. The sources of error were the same as previously described. All normalities are volume normalities, N_v.

Results

The initial experiment was to prepare a solution that was 0.1 N in respect to the detergent and 1 N in respect to sodium chloride. It was found that in a few minutes the detergent was precipitated from the solution. This "salting out" of the detergent did not occur when dilute solutions of the salt were used; it began between 0.25 N and 0.5 N sodium chloride with 0.1 N cetylpyridinium chloride. Salting out of detergent depends on its concentration as well as upon that of the salt.[8] Instead of discarding this precipitated solution (1 N sodium chloride, 0.1 N cetylpyridinium chloride), a few drops of benzene were added and the solution was shaken overnight. It was found that the solution had become clear. The turbidimeter reading of this solution was identical with the reading of a 0.1 N detergent solution. This phenomenon is similar to that observed by Lawrence,[9] who found that small amounts of water-insoluble materials cleared up cloudy soap solutions. He called the phenomenon "peptization." However, it is observed that what happens is the spontaneous formation of stable colloidal particles of detergent solubilizing the insoluble benzene, a process that proceeds with positive affinity, that is, diminution of free energy. The benzene promotes the formation of these colloidal particles of detergent which otherwise could not have gone into solution in the presence of the salt. Peptization is merely the separation and protection of aggregates of previously existing particles.

The following results all refer to the solubility of benzene in 100 cc. of aqueous solution. In 0.1 N cetylpyridinium chloride it is 1.88; this includes the small amount, 0.08 cc., molecularly dissolved, but the greater portion of the benzene, 1.8 cc., is solubilized by the detergent. In the same solution, but containing 1 N sodium chloride, 2.5 cc. was dissolved and solubilized. (However, only 0.18 cc. was required to bring the detergent into solution in this mixture. Even the filtrate from a mixture of 1 N sodium chloride and 0.1 N detergent without benzene possesses some solubilizing action because the total solubility of benzene therein was 0.26 cc.)

From the above data it is seen that once the detergent is brought back into solution by the benzene the solubilizing power of the solution with salt, 2.5 cc., exceeds that of the original solution without salt, 1.88 cc.

Table I presents the data for the solubilization of the aliphatic hydrocarbon octane, the aromatic hydrocarbon benzene, and the polar compound octyl alcohol, with and without various additions of sodium and potassium chloride. All results for solubilization in this paper are corrected for the solubility of benzene in pure water (see Table I of ref. 7). For benzene this may be an over-correction in dilute solution because it makes the ratio moles liquid/moles detergent appear to pass through a minimum. The results of Table I are graphically presented in Fig. 1. From the figure it is seen that potassium chloride has the larger effect on the solubilization of benzene in dilute solutions of detergent, and sodium chloride at higher concentrations, but the curves cross at 0.19 N where they are therefore equal. The results also clearly show that the addition of salts increases the solubility of the hydrocarbons, but that it equally definitely, and quite strongly, depresses the solubilization of the octyl alcohol. However, in the case of benzene above a certain concentration of added salt the solubilization begins to be again depressed and there is a slight indication that a similar result might occur with octane in

TABLE I

EFFECT OF VARYING SALT CONCENTRATION ON SOLUBILIZATION OF BENZENE, OCTANE AND OCTYL ALCOHOL BY 0.1 N CETYLPYRIDINIUM CHLORIDE. N_v EQUALS VOLUME NORMALITY

	NaCl		KCl	
N_v of salt	Total in solution cc./100 cc.	Ratio mole/mole solubilized	Total in solution cc./100 cc.	Ratio mole/mole solubilized
	Benzene			
0	1.88	2.03	1.88	2.03
0.0156	2.25	2.40	2.30	2.50
.03125	2.45	2.67	2.50	2.71
.0625	2.65	2.89	2.80	3.06
.125	3.05	3.34	3.40	3.74
.25	3.90	4.29	3.30	3.62
.50	3.50	3.85	2.30	2.49
1.00	2.50	2.72	2.20	2.38
	Octane			
0	0.40	0.242	0.40	0.242
0.0156	.43	.261	.44	.267
.03125	.50	.304	.50	.304
.0625	.55	.335	.60	.366
.125	.63	.383	.65	.396
.25	.75	.458	.70	.427
.50	1.00	.60	.80	.488
.75	1.05	.64	..	...
1.00	1.00	.60	1.00	.60
	Octyl Alcohol			
0	1.10	0.652	1.10	0.652
0.0156	1.08	.639	1.05	.619
.03125	1.06	.628	0.98	.575
.0625	0.97	.569	.90	.525
.125	.90	.515	.85	.493
.25	.80	.462	.75	.429
.50	.60	.335	.60	.335
1.00	.55	.310	.40	.208

(8) McBain and Field, *J. Phys. Chem.*, **30**, 1545 (1930).

(9) Lawrence, *Trans. Faraday Soc.*, **33**, 325 (1937).

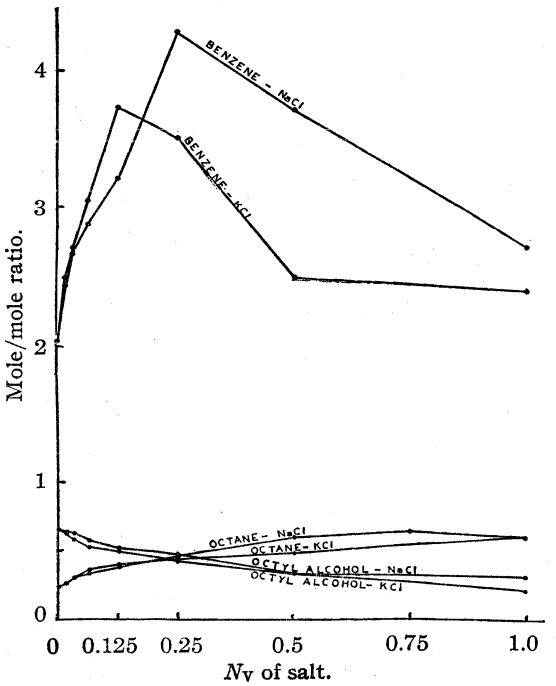


Fig. 1.—Effect of varying salt concentration on solubilization of benzene, octane and octyl alcohol by 0.1 *N* cetylpyridinium chloride.

much higher concentrations of salt, although actually only enhancement was observed.

TABLE II

EFFECT OF VARYING CONCENTRATION OF SODIUM CHLORIDE AND CETYLPYRIDINIUM CHLORIDE ON THE SOLUBILIZATION OF BENZENE, OCTANE AND OCTYL ALCOHOL

N_V cetyl pyr. chl.	No salt Total in solution cc./100 cc.	No salt Mole/mole solubilized	0.125 NaCl Total in solution cc./100 cc.	0.125 NaCl Mole/mole solubilized	0.5 NaCl Total in solution cc./100 cc.	0.5 NaCl Mole/mole solubilized
			Benzene			
0.00625	0.28	3.6		..		
.0125	.40	2.9	0.48	3.6	0.56	4.3
.025	.60	2.3	0.80	3.2	1.00	4.1
.05	.96	2.0	1.50	3.2	1.80	3.8
.1	1.88	2.0	3.05	3.2	3.50	3.7
.2	3.70	2.0	6.00	3.3	7.40	4.2
.4	8.50	2.4				
			Octane			
0.0125	0.02	0.08	0.05	0.23	0.07	0.33
.025	.08	.19	.12	.29	.16	.38
.05	.20	.21	.30	.36	.40	.48
.1	.40	.24	.63	.38	1.00	.60
.2	1.00	.31	1.50	.45	1.90	.67
.4	2.50	.38				
			Octyl Alcohol			
0.0125	0.18	0.56	0.12	0.26	0.08	0.04
.025	.30	.58	.26	.40	.12	.12
.05	.50	.61	.40	.42	.30	.29
.1	1.10	.65	.90	.52	.60	.34
.2	2.30	.70	1.70	.54	1.20	.37
.4	3.60	.56				

In Table II the concentration of cetylpyridinium chloride is varied and two concentrations of sodium chloride are added, and again the same effects of enhancing solubilization of the hydrocar-

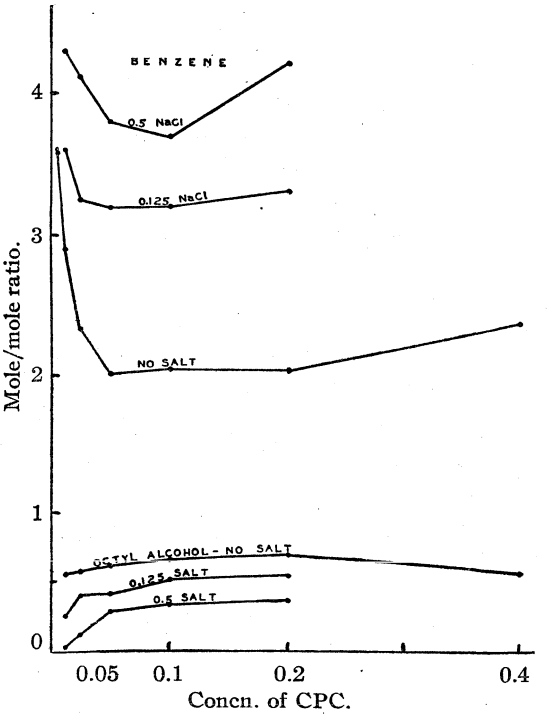


Fig. 2.—Effect of varying concentration of sodium chloride and of cetylpyridinium chloride on the solubilization of benzene and octyl alcohol.

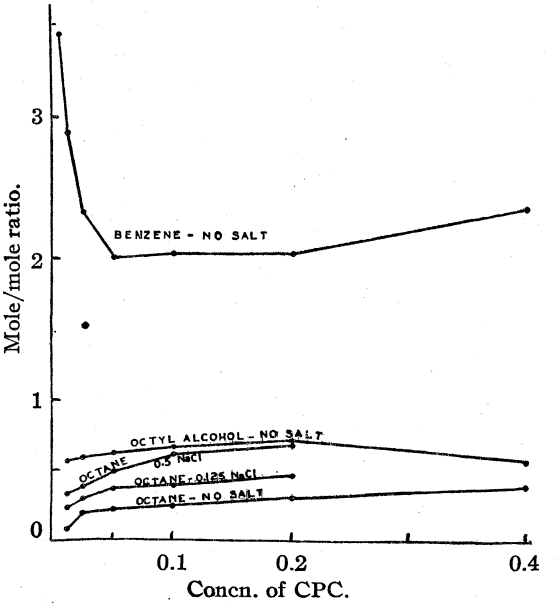


Fig. 3.—Effect of varying concentration of sodium chloride and of cetylpyridinium chloride on the solubilization of octane. Two curves from Fig. 2 are repeated for comparison.

bons, benzene and octane, but of lowering that of octyl alcohol, are noted in all cases, as appears in Figs. 2 and 3.

Discussion

In a dilute solution of detergent one can readily understand favorable effects of added salt because the salt increases the amount of colloid present, as is also shown by the decrease of the osmotic coefficient of the detergent.[10] However, even in dilute solution of detergent the reduction of solubilization of octyl alcohol by added salt is in the opposite direction. It is a requirement of the mass law that in more concentrated solution practically all of the detergent (apart from Gegenions) is already in colloidal form, and the osmotic coefficient is rather increased than decreased. Hence it is clear that the added salt has changed the micelles.

One of us (J. W. M.) has long maintained that many kinds, shapes and sizes of colloidal micelles must occur simultaneously in a soap solution, the relative amounts being determined by such factors as concentration, temperature and presence of added salts or solubilized or other matter. Any manner in which ions, ion pairs or molecules of detergents can associate with a diminution of free energy (including such factors as surface energy, hydrogen bonding or cybotaxis of the solvent), will produce a micelle in competition with all other conceivable micelles of greater and less free energy. Hence, in any given solution all types and sizes of micelles must be present, their relative amounts being determined by the conditions just indicated. Hess and collaborators and McBain have elsewhere given diagrammatic sketches of numerous kinds of small micelles, including the McBain ionic micelle, which may, and probably do, occur.

In most cases of solubilization, the amount solubilized per unit amount of detergent increases from zero at zero concentration of detergent, quite appreciably before the so-called critical concentration is reached; and it rapidly grows to an approximately constant value, but finally increases rapidly again in more concentrated solution where the detergent micelles are evidently more effective solubilizers. In all examples hitherto published, salt has increased the solubilization, first in dilute solutions by producing colloid with which to solubilize, and in more concentrated solutions by promoting or stabilizing those sizes and kinds of micelles which are most effective. Wherever tested, the well known X-ray evidence has indicated that the solubilized material expands the micelles, and in the case of lamellar X-ray micelles much of the solubilized material lies between the hydrocarbon layers, completely shut away from the solvent. This is the only way in which the observed increase in long spacing has been explained.

Now, however, we have a clear case in octyl alcohol where the salts, in all concentrations of detergent and of salt, *lower* the solubilization. We therefore suggest that with this polar compound, the solubilization occurs on or between the *polar* ends of the micelles that are exposed to the water. Hence the salt is now in competition with the solubilized material at the polar ends of the detergent molecules and interferes with its solubilization. Salt itself is sorbed by the micelles.[11]

Benzaldehyde gives results similar to octyl alcohol. With 0.1 *N* cetylpyridinium chloride alone, the mole:mole ratio is 1.94, but in the presence of 0.5 *N* sodium chloride the solubilization is lowered to a mole:mole ratio of only 0.61.

Some Solubilization Data for Detergents without Salt.—The results set forth in Tables III and IV supplement (and in a few instances repeat) those previously reported.[7] In the former investigation thirty-five organic liquids were solubilized by dodecylamine hydrochloride, sodium

TABLE III

SOLUBILIZATION BY 0.1 *N* CETYLPYRIDINIUM CHLORIDE AT 25°

Material	Total in 100 cc. solution	G. solubilized	Mole/mole ratio
Oleic acid[a]	0.22	0.19	0.065
n-Decane	.25	.19	.14
Octane	.4	.28	.24
n-Hexane	.66	.42	.49
Cyclohexane	.75	.55	.66
Xylenol	.88	.60	.49
m-Cresol	.96	.64	.59
n-Octyl alcohol	1.10	.86	.66
p-Xylene	1.2	1.02	.97
Ethylbenzene	1.3	1.11	1.05
Toluene[b]	1.6	1.33	1.45
Benzene[b]	1.88	1.57	2.03
Octylamine[a]	2.6	2.0	1.55
Benzaldehyde	2.24	2.06	1.94
Methyl isobutyl ketone	4.8	2.02	2.02
Methyl *t*-butyl ether	9.6	2.04	2.31

[a] Reaction with octylamine observed to occur with color change; oleic acid might also react with the detergent. [b] The much lower results for benzene and toluene previously published were subsequently found to be in error owing to a wrong factor of calibration being used for the micro pipet.

TABLE IV

SOLUBILIZATION BY 0.0733 *M* TRITON X-100 AT 25° (MOLECULAR WT. 600)

Material	Total in 100 cc. solution	G. solubilized	Mole/mole ratio
n-Decane	0.02	0.015	0.015
Oleic acid	.04	.034	.016
Toluene	.14	.058	.086
Benzene	.16	.07	.123
n-Hexane	.14	.09	.14
Xylenol[a]	.16	.166	.185
n-Octyl alcohol	.36	.238	.245
m-Cresol[a]	.26	.269	.340

[a] Impure, containing water.

(10) McBain and Brady, THIS JOURNAL, **65**, 2072 (1943).

(11) Tartar and Cadle, *J. Phys. Chem.*, **43**, 1173 (1939).

oleate and potassium laurate, and seven of the thirty-five were solubilized by Emulsol 607L and cetylpyridinium chloride. Tables III and IV of the present paper also include solubilization of 8 additional organic liquids by a non-ionic detergent, Triton X-100. Not shown in the tables are the results of solubilization of amyl valerate and of 1-chloronitropropane by decinormal Emulsol 607L at 25°, namely: 0.44 and 1.14 cc. total in 100 cc. solution, or 0.39 and 1.40 g. solubilized, or 0.25 and 1.14 mole ratio, respectively.

The order of solubilization by the six detergents of this and the previous study is maintained for most of the forty-three organic liquids tested, with comparatively minor exceptions or specificities. The non-ionic detergent Triton X-100 is the poorest solubilizer. Next comes potassium laurate. Then come, near together, sodium oleate and Emulsol 607L (one anionic and the other cationic). Much the best are the cationic dodecylamine hydrochloride and cetylpyridinium chloride.

It may have been over-emphasized in the previous publication[7] that high molecular weight of compounds undergoing solubilization hinders their solubilization. This is very true within any one homologous series, and it is emphasized when the volume or percentage solubilized is calculated in mole ratios. However, high molecular weight may be offset for such compounds as oleic acid by their belonging to an homologous series that is especially readily solubilized. Thus, although the mole ratio may be very small the actual volume or weight percentage solubilized may be quite comparable with that of such substances as *n*-decane.

Warren W. Woods and Dr. J. V. Robinson (Stanford Laboratories, unpublished) have found that castor oil is appreciably solubilized in lubricating oil by Aerosol OT, and similarly, sulfonated castor oil was solubilized in lubricating oil by Lead Aerosol OT.

Summary

1. Solubilization of organic liquids in solutions of the cationic detergents cetylpyridinium chloride and Emulsol 607L, and the non-ionizing Triton X-100 have been determined. The results, in general, follow the same order for different liquids as was previously described for three other detergents, dodecylamine hydrochloride, sodium oleate and potassium laurate. The non-ionic detergent Triton X-100 was the poorest solubilizer, and the best were the cationic cetylpyridinium chloride and dodecylamine hydrochloride.

2. Whereas all previous studies have shown that added salts greatly enhance solubility, and this is confirmed for the solubilization of benzene and octane by cetylpyridinium chloride, it is found that the solubilization of the polar compounds octyl alcohol and benzaldehyde is greatly depressed by the addition of sodium or potassium chloride. It is suggested that whereas with hydrocarbons and many other organic liquids solubilization occurs in the hydrocarbon portion of the micelles, with these polar compounds the solubilization occurs at the polar ends of the detergent molecules in the micelles.

STANFORD UNIVERSITY, CALIFORNIA

RECEIVED JUNE 30, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA]

The Polarographic Reduction of Gadolinium

BY SHERMAN W. RABIDEAU AND GEORGE GLOCKLER

On the basis of a dual wave obtained in the polarographic reduction of 0.01 *M* solutions of scandium, yttrium, and the rare earth sulfates without supporting electrolyte, Noddack and Brukl[1] concluded that the reduction proceeded first to the bivalent state and then to the metal. Leach and Terrey[2] observed a single wave in solutions of scandium chloride with 0.1 *N* potassium chloride as the supporting electrolyte. With additions of 1/6 *N* hydrochloric acid, the single wave gradually separated into two waves. The first wave was found to be due to the reduction of hydrogen ions while the second was attributed to the deposition of scandium.

Kolthoff and Lingane[3] expressed doubt that the double wave observed by Noddack and Brukl[1] corresponded in each case to the bivalent state, and suggested that it may have been caused by the discharge of hydrogen from the hydrolyzed solutions. This study was undertaken in an attempt to establish the half-wave potentials of gadolinium and to investigate polarographically the possibility of the existence of a bivalent state for this rare earth.

(1) W. Noddack and A. Brukl, *Angew. Chem.*, **50**, 362 (1937).

(2) R. H. Leach and H. Terrey, *Trans. Faraday Soc.*, **33**, 480 (1937).

(3) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

Experimental Procedure

The Sargent Model XX visible recording polarograph, the characteristics of which have been previously described by Lingane,[4] was used to record the current–voltage curves. The initial and span potentials were determined potentiometrically since the voltmeters supplied with the instrument are not of the requisite accuracy. All polarograms were recorded for uniformity with the damping control in position 5. An Erlenmeyer type flask served as the electrolysis vessel when the mercury pool anode was used. An H-cell of the design described by

(4) Lingane, *Ind. Eng. Chem., Anal. Ed.*, **18**, 734 (1946).

Lingane and Laitinen[5] was used in all other cases. The temperature was maintained at 25.0 ± 0.1°. Oxygen was removed from the solutions with nitrogen or hydrogen. With the exception of the waves recorded using the mercury pool anode, all diffusion currents have been corrected for the residual currents, and the half-wave potentials were corrected for the *iR* drop in the cell. Because of the lag of the recorder, and the difficulty of measuring the diffusion currents, the reported half-wave potentials are believed to be reliable within ±0.01 volt.

A spectrographic analysis of the rare earth confirmed the presence of traces of europium. Small amounts of terbium in the sample are suspected because of the disappearance of the brown color of the oxide in a reducing atmosphere. Because of the limited sample of rare earth it was necessary to recover the gadolinium for subsequent analyses. The gadolinium was precipitated as the oxalate in dilute hydrochloric acid solution, and ignited to the oxide. Before use in preparing a solution for polarographic analysis, the sample was carried through the oxalate–oxide conversion twice to remove salts of the supporting electrolyte and gelatin. The oxide was chosen as the weighing form, and precautions were taken to avoid the interference of carbon dioxide and moisture. The sulfate solutions were prepared from the dry oxide by adding an excess of sulfuric acid, evaporating to dryness, and finally heating to complete removal of fumes of sulfur trioxide. The desired molarities were obtained by dilution with conductivity water.

Experimental Results

The procedure of Noddack and Brukl[1] was followed in an attempt to repeat their work with regard to the polarographic reduction of gadolinium. A 0.01 *M* solution of gadolinium sulfate was electrolyzed using a mercury pool anode. A polarogram of the type illustrated in Fig. 1 was obtained. It is of interest to note that the step height of the wave is much less than would be predicted on the basis of results obtained with supporting electrolyte present. Though Noddack and Brukl[1] reported values of −1.810 and −1.955 volts *vs.* the N.C.E. for the *Knickpunkt* of the two waves, the results of Fig. 1 indicate that the second wave is not sufficiently well enough defined to establish the existence of a second reduction step.

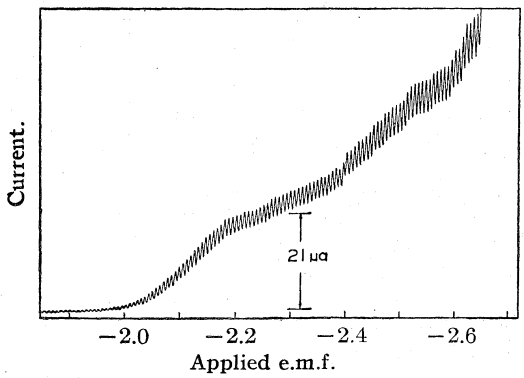


Fig. 1.—0.01 *M* gadolinium sulfate without supporting electrolyte: mercury pool anode.

The polarographic behavior of gadolinium sulfate was studied with a supporting electrolyte of 0.1 *N* lithium chloride plus 0.01% gelatin using the H-cell. A single well-defined wave was obtained with a linear relationship observed between the concentration and the diffusion current (Table I).

(5) Lingane and Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

TABLE I

GADOLINIUM SULFATE IN 0.1 *N* LITHIUM CHLORIDE PLUS 0.01% GELATIN

Millimoles of Gd^{+3} per liter	$E_{1/2}$ *vs.* S. C. E. volts	$m^{2/3}t^{1/6}$	i_d microamp.	i_d/c	I_d
0.80	−1.74	1.693	5.1	6.4	3.8
1.60	−1.74	1.758	10.1	6.3	3.6
4.00	−1.77	1.716	26.2	6.6	3.8

To note the effect of additions of acid on the current-voltage curves, increasing quantities of 0.05 *N* hydrochloric acid were added to 14 ml. of 4.00 millimolar Gd^{+3}. As the solution became more acidic, the hydrogen wave increased proportionately with the half-wave at −1.5 volts *vs.* the S.C.E., but the wave height due to the reduction of gadolinium was not appreciably affected. The half-wave potential of gadolinium was shifted to more negative values with increasing acid concentration as shown in Table II.

TABLE II

EFFECT OF ACID ON THE HALF-WAVE POTENTIAL OF GADOLINIUM IN 0.1 *N* LITHIUM CHLORIDE PLUS 0.01% GELATIN

Ml. of 0.05 *N* HCl	$E_{1/2}$ *vs.* S. C. E., volts
0.00	−1.77
.10	−1.79
.20	−1.80
.40	−1.82
.60	−1.84
.80	−1.86
1.00	−1.86
1.50	−1.91
2.00	−1.93

Fig. 2 illustrates the effect of added acid with a supporting electrolyte of 0.1 *N* tetramethylammonium iodide plus 0.01% gelatin.

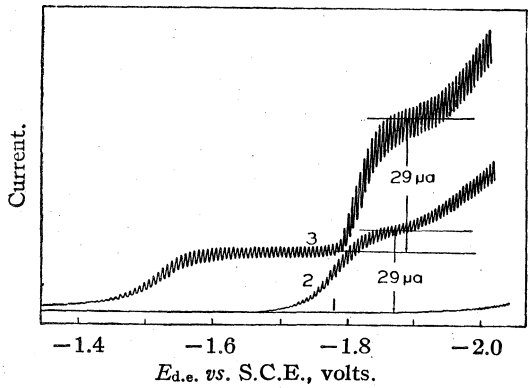


Fig. 2.—Gd^{+3} in 0.1 *N* tetramethylammonium iodide plus 0.01% gelatin: (1) residual current; (2) 4.0 millimolar; (3) 0.30 ml. of 0.05 *N* HCl added to 14 ml. of 4.0 millimolar.

The wave definition in a supporting electrolyte of 0.1 *N* potassium chloride was about the same

as that observed with lithium chloride. The results of the polarographic reduction of gadolinium sulfate in potassium chloride are given in Table III.

TABLE III

GADOLINIUM SULFATE IN 0.1 *N* POTASSIUM CHLORIDE PLUS 0.01% GELATIN

Millimoles Gd^{+3} per liter	$E_{1/2}$ S. C. E. volts	$m^{2/3}t^{1/6}$	i microamp.	i_d/c	I_d
0.80	−1.75	1.780	5.2	6.5	3.9
1.60	−1.75	1.788	10.3	6.4	3.6
4.00	−1.77	1.728	26.9	6.7	3.7

Discussion

The values of the quantity $m^{2/3}t^{1/6}$ were determined at the potential at which the diffusion current was measured. The average value of the diffusion current constant, I_d, for Gd^{+3} was found to be 3.7. Using equivalent conductance data given by Pascal,[6] and extrapolating to infinite dilution, a value of 125 ohm^{-1} $cm.^2$ was obtained for gadolinium sulfate. If the value 80 is used for the sulfate ion, the equivalent ionic conductance of gadolinium is then 45 ohm^{-1} sq. cm. By substituting the value of the ionic conductance of gadolinium into the Nernst relation

$$D_i^0 = 2.67 \times 10^{-7} (\lambda^0/Z)$$

the diffusion coefficient is found to be 4.0×10^{-6} sq. cm. sec^{-1}. With the above quantities substituted into the Ilkovic equation, the number of electrons involved in the electrode reaction is found to be three. Thus the results indicate that the reduction of gadolinium at the dropping electrode takes place according to the reaction

$$Gd^{+3} + 3e \longrightarrow Gd^0$$

An analysis of the polarographic waves was made by noting the slope of the line produced in plotting values of log $i/i_d - i$ *vs.* $E_{d.e.}$ The irreversibility of the electrode reaction is indicated by the fact that the slope is not as steep as would be expected on the basis of a three electron reduction.

(6) Pascal, "Traité de Chimie Minérale," Masson et Cie., Éditeurs, Paris, 1933.

Summary

1. The results of Noddack and Brukl were not confirmed with regard to the polarographic reduction of gadolinium sulfate.

2. An increasing acid concentration shifts the half-wave potential of gadolinium to more negative potentials.

3. A value of 4.0×10^{-6} sq. cm. $sec.^{-1}$ was calculated for the diffusion coefficient of Gd^{+3} at 25°.

4. The results indicate that the reduction of gadolinium at the dropping mercury electrode involves three electrons.

5. The average value of the diffusion current constant for Gd^{+3} was found to be 3.7 at 25° in a supporting electrolyte of 0.1 *N* lithium chloride or 0.1 *N* potassium chloride.

6. The half-wave potential for 4.0 millimolar Gd^{+3} was found to be −1.77 volts *vs.* the S.C.E. with 0.1 *N* lithium chloride, and with 0.1 *N* potassium chloride as the supporting electrolytes.

IOWA CITY, IOWA RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA]

Reduction of Neodymium at the Dropping Mercury Electrode

BY C. R. ESTEE AND GEORGE GLOCKLER

The polarographic behavior of neodymium in the presence of supporting electrolyte has not previously been described. The present study was undertaken to allow the application of the Ilkovic equation[1] to obtain the *n*-value for the reduction of the trivalent neodymium ion, and to establish under proper polarographic conditions the half-wave potential for the reduction. No evidence of the previously reported[2] two-step reduction from water solutions was obtained.

Experimental

The polarograms were recorded with a Sargent Model XX Visible Recording Polarograph of the Heyrovsky type, the design and operating characteristics of which have recently been discussed by Lingane.[3] A conventional dropping mercury cathode assembly was used, the stand tube being provided with an adjustable mercury reservoir. The usual H-type electrolysis vessel[4] with a sintered glass plug and agar bridge was employed. Measurements were made with respect to a mercury anode. Solution temperatures were maintained at 25.0 ± 0.1° by means of a thermostat. The drop time was varied between two and five seconds. Hydrogen or nitrogen was bubbled through the solution to remove dissolved oxygen.

The neodymium salt was obtained as the nitrate and an examination of the absorption curve found with a Bell and Coleman spectrophotometer showed no detectable impurities. Neodymium oxide was prepared by ignition of the oxalate precipitated from a warm acid solution of the nitrate. The oxide was treated with an excess of sulfuric acid and heated for eight hours at 440° to give the octahydrate of neodymium sulfate. Solutions of supporting electrolytes prepared from analytical grade reagents showed no detectable impurities.

Diffusion coefficients of 6.03×10^{-6} sq. cm./sec. for the neodymium ion and 8.15×10^{-6} sq. cm./sec. for

(1) Ilkovic, *J. chim. phys.*, **35**, 129 (1938).

(2) Noddack and Brukl, *Angew. Chem.*, **50**, 362 (1937).

(3) Lingane, *Ind. Eng. Chem., Anal. Ed.*, **18**, 734 (1946).

(4) Lingane and Laitinen, *ibid.*, **11**, 504 (1930).

neodymium sulfate were calculated by means of conductance data[5] and the Nernst equation.[6]

Half-wave potentials were measured in the usual manner, with all values being calculated with respect to the saturated calomel anode and corrected for the iR drop in the cell to an accuracy of ± 0.01 volt.

Data and Discussion

No Supporting Electrolyte.—No indication of the double waves (Inset, Fig. 1) reported by Noddack and Brukl[2] was found; a single wave (Fig. 1) resulted when water solutions of neodymium sulfate were reduced at the dropping mercury electrode. The suggestion[7] has been made that the first wave reported by Noddack and Brukl[2] might be due to the discharge of hydrogen ion from the hydrolyzed solutions. However, although fresh solutions of both neodymium and praseodymium sulfate were slightly acidic, no indication of such a wave could be found. Recent work by Thomas and Kurbatov[8] with yttrium likewise makes doubtful the existence of the two-step waves reported by Noddack and Brukl.[2]

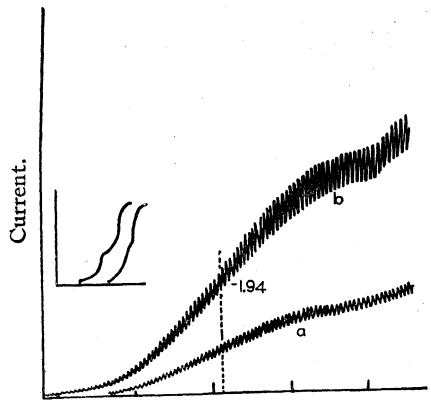


Fig. 1.—Neodymium sulfate, 4.0 molar, no supporting electrolyte. Inset shows curves of Noddack and Brukl.[2]

Lithium Chloride as Supporting Electrolyte.—The half-wave potential was found to vary with the concentration when lithium chloride (0.01% gel added) was used as the supporting electrolyte; no consistent linear relationship between step height and concentration was observed (Table I). The variation in the step heights is probably caused by the simultaneous deposition of hydrogen and neodymium. To separate the two waves sulfuric acid was added to the solutions; as the concentration of acid increased, the hydrogen preceded and was well separated from the neodymium wave (Fig. 2). With the use of

(5) "International Critical Tables, Vol. VI," 233 (1933).

(6) W. Nernst, *Z. physik Chem.*, **2**, 613 (1888).

(7) Lingane and Kolthoff, "Polarography," New York Interscience Publishers, Inc., New York, N. Y., Revised Reprint, 1936, p. 305.

(8) Thomas and Kurbatov, Paper No. 16, Division of Physical and Inorganic Chemistry, Atlantic City Meeting, American Chemical Society, April, 1947.

TABLE I

EFFECT OF CONCENTRATION ON THE HALF-WAVE POTENTIAL OF NEODYMIUM WITH 0.1 MOLAR LiCl AS ELECTROLYTE

Concentration millimoles/l.	$E_{1/2}$	i_d microamp.	i_d/c
1.6	−1.77	17.9	11.2
1.6	−1.78	18.0	11.2
4.0	−1.81	31.1	7.8
4.0	−1.81	28.6	7.2
8.0	−1.83	49.2	6.2
8.0	−1.83	49.6	6.2

2.0 millimolar sulfuric acid solutions fairly well defined waves were obtained (Fig. 3); the half-wave potential was constant, and a linear relationship between concentration and step height was found.

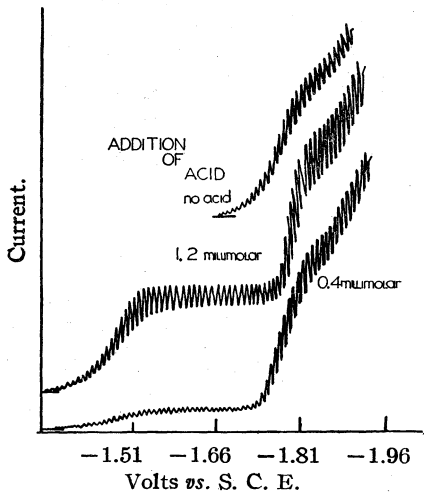


Fig. 2.—Addition of acid with lithium chloride as a supporting electrolyte.

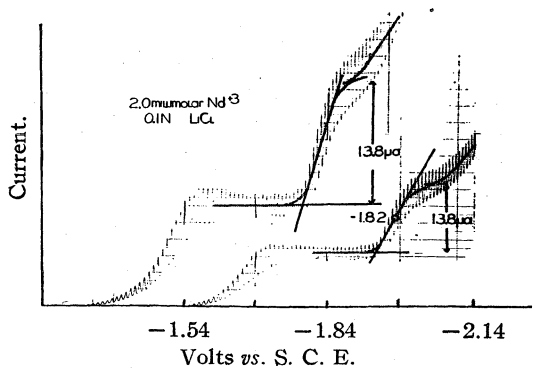


Fig. 3.—Acid solutions with lithium chloride showing separated hydrogen wave.

As shown by Table II the electrode reaction is $Nd^{+3} \rightarrow Nd^0$. The calculated diffusion current was obtained by the use of the Ilkovic equation, assuming that $n = 3$.

Tetramethylammonium Iodide as Supporting Electrolyte.—A single wave (Fig. 4) is obtained from sulfuric acid solutions of this supporting

TABLE II

EXPERIMENTAL VALUES OF n WITH 0.1 M LiCl AS SUPPORTING ELECTROLYTE (0.01% GEL + 2.0 MILLIMOLAR H_2SO_4 ADDED)

Concentration millimoles/l.	$E_{1/2}$	i_d exp.	i_d calcd.	n exp.
0.4	−1.82	2.8	2.9	2.9
0.8	−1.82	5.6	5.8	2.9
1.2	−1.82	8.7	8.9	2.9
2.0	−1.82	13.8	14.4	2.9
4.0	−1.82	28.2	29.4	2.9

electrolyte; the apparent second wave in the range −1.94 to −2.04 being characteristic of the supporting electrolyte used. In the absence of

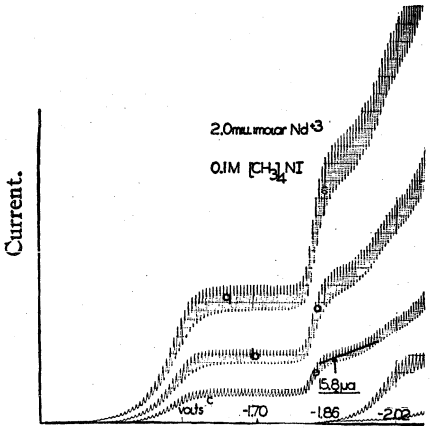


Fig. 4.—Acid solution with tetramethylammonium iodide: recorder sensitivity, (a) 3–75; (b) 3–50; (c) 3–25.

acid, variations in half-wave potentials and diffusion currents occur (Table III) which are not evident when a 2.0 millimolar acid solution is used (Table IV). These data serve to indicate that in neutral media the measured diffusion currents are the result of the simultaneous deposition of neodymium and hydrogen since the measured currents are larger than those expected by the application of the Ilkovic equation. When acid is added to cause a definite prewave due to hydrogen the measured diffusion currents are less than those predicted on the basis of the Ilkovic equation; this is to be expected. The diffusion current constant (I_d) obtained in 2.0 millimolar sulfuric acid solution agrees closely with the theoretical value of 4.46 obtained if the reaction at the electrode is assumed to be $Nd^{+3} \rightarrow Nd^0$.

TABLE III

NEUTRAL SOLUTION OF 0.1 M TETRAMETHYLAMMONIUM IODIDE AS SUPPORTING ELECTROLYTE (0.1% GEL ADDED)

Concentration millimoles/l.	i_d exp.	i_d calcd.	I_d exp.	$E_{1/2}$
2.0	16.2	16.0	4.47	−1.80
2.0	15.8	15.9	4.42	−1.80
0.8	6.9	6.5	4.71	−1.73
.8	6.9	..	..	−1.73
.4	3.6	3.2	4.96	−1.75
.4	3.6	3.2	4.94	−1.75

TABLE IV

SULFURIC ACID (2.0 MILLIMOLAR) SOLUTION OF 0.1 M TETRAMETHYLAMMONIUM IODIDE AS SUPPORTING ELECTROLYTE (0.01% GEL)

Concentration millimoles/l.	i_d exp.	i_d calc.	I_d exp.	$E_{1/2}$
2.0	15.6	16.0	4.32	−1.83
2.0	15.9	16.0	4.41	−1.83
0.8	6.4	6.4	4.48	−1.83
.8	6.4	6.4	4.46	−1.83
.4	3.1	3.2	4.26	−1.83
.4	3.2	3.2	4.45	−1.83

Other Supporting Electrolytes.—A single step curve (Fig. 5) was obtained from potassium chloride solutions; half-wave potential was −1.83 from a 2.0 millimolar sulfuric acid solution of 0.1 M potassium chloride. Again the single step indicates the reduction $Nd^{+3} \rightarrow Nd^0$. Ammonium chloride was not satisfactory as a supporting electrolyte, the curves being poorly defined.

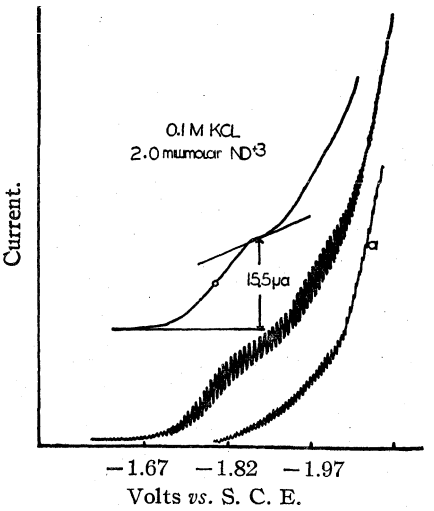


Fig. 5.—Neutral potassium chloride solution: (a) residual current.

Summary

A single wave is obtained from water solutions of neodymium sulfate; this is in contradiction to the results of earlier investigators. Similar single waves are obtained when lithium chloride, tetramethylammonium iodide or potassium chloride is used as supporting electrolyte.

By means of the Ilkovic equation it is shown that the reduction corresponds in all cases to $Nd^{+3} \rightarrow Nd^0$.

The half-wave potentials are found to be dependent upon the concentration and acidity of the solution. From solutions of the above-mentioned electrolytes containing 2 millimoles of sulfuric acid per liter (with 0.01% gel added) diffusion currents

proportional to the concentration of neodymium ion were obtained. The half-wave potentials remained constant in the range studied (0.01 *M* and below) at -1.83 ± 0.01 volt *versus* the saturated calomel electrode in all cases.

IOWA CITY, IOWA RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA]

The Half-Wave Potential of Samarium

BY ANDREW TIMNICK AND GEORGE GLOCKLER

Noddack and Brukl[1] who studied the electrolytic decomposition of 0.01 molar rare earth sulfate solutions, containing no supporting electrolyte, report that samarium undergoes a two-step reduction at the dropping mercury electrode. In an earlier report[2] outlining the progress of the work, Brukl announced their intentions of publishing the inflection points, (Knickpunkte) of the *c–v* curves representing the stepwise reduction of the rare earth ions. In the discussion following the report, Hohn[2] suggested that if the half-wave potentials[3] of the steps were reported, the results would be expressed as a reproducible constant which is independent of concentration. It was also suggested that if an indifferent electrolyte were added to the solutions the diffusion current[4] or step height would be directly proportional to the concentration. The advice evidently was disregarded for only the inflection points were reported.[1]

Holleck[5] electrolyzed 0.02 molar samarium chloride solutions, without supporting electrolyte, at the dropping mercury electrode but his interest was the detection of the conversion of the samarium ion from one isoelectronic form to another. He obtained single and double waves, the form varying with methods of preparation of the salt, the temperature of the solution being electrolyzed and with the addition of zinc chloride. Neither half-wave potentials, nor diffusion currents were reported. Divalent samarium compounds have been prepared.[6,7] It is known that samarous ions are stable in aqueous solutions under limited conditions. A two-step reduction can logically be predicted.

The present study was undertaken to evaluate the diffusion current and half-wave potentials of samarium ion from its chloride and sulfate solutions. The influence of concentration, *p*H and supporting electrolyte was also observed.

Experimental Procedure

A 0.02 molar samarium chloride stock solution was prepared with C. P. $SmCl_3 \cdot 6H_2O$. Spectrographic examination indicated only traces of gadolinium and europium. Samarium sulfate was prepared by converting the chloride to the oxide followed by the conversion to the sulfate. This was done by adding excess sulfuric acid to the oxide, heating the resulting mixture to 450° on a hot-plate until the excess acid was decomposed, and followed by heating in a regulated furnace at 600° for two hours to ensure complete acid decomposition and dehydration. The product was recrystallized from water solutions with subsequent acid and heating treatments. Excellent yellow translucent crystals (octahydrate) were obtained, some 5 mm. long, after the third treatment. These were washed, broken up, mixed with sulfuric acid and heated to the anhydrous form. A 0.01 molar samarium sulfate stock solution was made with this material. The salts employed as supporting electrolyte were of C. P. grade. An H-cell with a saturated calomel anode[8] was used. The salt bridges consisted of saturated potassium chloride solution containing 4% agar. The resistance of the cell and calomel electrode was 230 ohms. This value was used to correct the half-wave potentials for *iR* drop when the magnitude of the diffusion current warranted this procedure.

All measurements were made at $25.0 \pm 0.1°$. Nitrogen was used to remove dissolved air from the solutions. The *m* and *t* values of the Ilkovic equation[4] were found for twenty-five drops of mercury at the applied potential at which the diffusion current was measured. Polarograms were recorded with a Sargent Model XX Polarograph. The operating characteristics of this instrument have been described by Lingane.[9] Accurate checks of applied potential were made with a K-type potentiometer. The polarographic waves for measurement purposes were obtained by connecting the midpoints of the galvanometer oscillations recorded by the instrument. The *p*H of solutions was measured with a glass electrode Type 200 Coleman *p*H Electrometer. This instrument was tested with buffer solutions and found to be accurate to 0.1 unit. The concentration *c* in all cases is expressed in millimoles of samarium ion per liter.

Results and Discussion

Samarium Chloride

No Supporting Electrolyte, No Gelatin.—The preliminary determinations were made with samarium chloride solutions ranging in concentration from 0.5 millimolar samarium ion to 20 millimolar. Some potassium chloride would be expected to diffuse from the agar plug into the solution being electrolyzed, but poorly defined waves were nevertheless obtained.

Supporting Electrolyte, No Gelatin.—Supporting electrolyte media of 1.0 molar potassium chloride, 0.1 molar potassium chloride, 0.1 molar tetramethylammonium iodide, or 0.1 molar lithium chloride, containing 5 millimolar

(1) W. Noddack and A. Brukl, *Angew. Chem.*, **50**, 362 (1937).
(2) W. Noddack and A. Brukl, *ibid.*, **49**, 533 (1936).
(3) J. Heyrovsky and D. Ilkovic, *Coll. Czechoslov. Chem. Commun.*, **7**, 198 (1935).
(4) D. Ilkovic, *ibid.*, **6**, 498 (1934).
(5) L. Holleck, *Z. Elektrochem.*, **45**, 249 (1939).
(6) C. A. Matigon and E. Cazes, *Compt. rend.*, **142**, 83 (1906).
(7) G. Jantsch, H. Rupig and W. Kunze, *Z. anorg. Chem.*, **161**, 212 (1927).
(8) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1946, p. 459.
(9) J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **18**, 734 (1946).

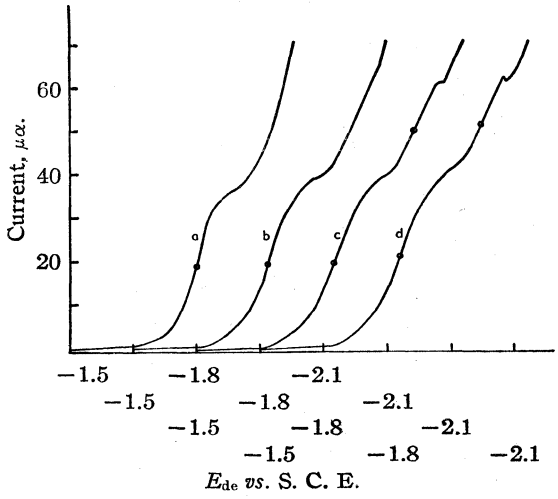


Fig. 1.—Samarium chloride, 5 millimolar, in various media: curves a-d, 1.0 *M* KCl, 0.1 *M* KCl, 0.1 *M* $(CH_3)_4NI$, 0.1 *M* LiCl, respectively.

samaric ion gave rise to well defined first steps as shown by Fig. 1, curves a–d respectively. In the 0.1 molar lithium chloride and 0.1 molar tetramethylammonium medium a second step seems to begin but is apparently terminated by the discharge of the supporting electrolyte. Figure 2 is a representative example of the variation of the ratio i_d/C observed in the polarograms recorded with the samarium chloride solutions shown in Fig. 1. It is evident that the expected proportionality of step height between the first and second step is not attained. Curves a and b are reproductions of the midpoint tracing of polarograms recorded with 0.1 molar tetramethylammonium iodide solutions containing 5 and 2.5 millimoles of samarium chloride, respectively. The residual current is shown by curve c.

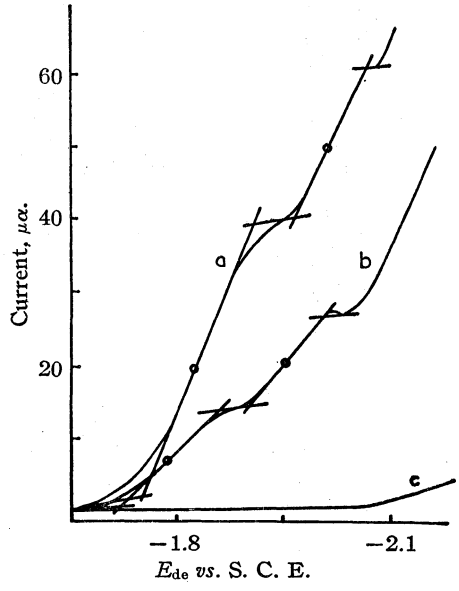


Fig. 2.—Relationship between concentration of samarium chloride and step height in 0.1 *M* tetramethylammonium iodide medium. Curves a and b are recorded with 5 and 2.5 millimolar solutions, respectively; c is the residual current.

Because of this variation in the current–concentration ratio, sulfate solutions of samarium were investigated.

Samarium Sulfate

No Supporting Electrolyte.—Several attempts to reproduce results reported[1] were made employing a mercury pool anode. Stock solutions of samarium sulfate which had stood a month or two yielded no waves, but a three step wave was recorded with a one day old 20 millimolar solution containing no gelatin. Discharge of hydrogen, observed from a wave with a half-wave potential at −1.64 volts against the mercury pool anode, occurred.

Supporting Electrolyte, 0.01% Gelatin.—Polarograms were recorded with various concentrations of samarium in 0.1 molar lithium chloride medium. With concentrations from 5 to 20 millimolar the polarograms consisted of two steps. At lower concentrations the second step terminated in a maximum. The results listed in Table I are corrected for iR drop.

Since the reduction of samarium ion proceeds at a potential more negative than the reduction of hydrogen ion, small amounts of dilute sulfuric acid were added to samarium solutions and polarograms recorded.[10] Two waves, one due to hydrogen and the other due to samarium discharge, were observed. In 0.1 molar lithium chloride solution (0.001 normal in sulfuric acid) containing varying concentrations of samarium, the half-wave potential of the hydrogen wave was −1.5 volts against the saturated calomel electrode. As shown in Table II the addition of acid reduced the

TABLE I

SAMARIUM SULFATE, 0.1 *M* LiCl, 0.01% GELATIN, $E_{1/2}$ *vs.* S. C. E.

Concn. Sm^{+++}	*p*H	i_d First step	i_d Second step	$E_{1/2}$ First step	$E_{1/2}$ Second step
20	...	113.1	17.7	−1.85	−2.07
10	4.0	55.9	15.2	−1.80	−1.97
5	4.4	28.4	15.4	−1.77	−1.92
2	4.8	10.7	Max.	−1.73	Max.

TABLE II

SAMARIUM SULFATE, $E_{1/2}$ *vs.* S. C. E.
0.1 *M* LiCl, 0.01% gel., 0.001 *N* H_2SO_4
$t = 3.074$, $m^{2/3}t^{1/6} = 1.760$

Concn.	*p*H	i_d	$E_{1/2}$
8	3.1	50.1	−1.82
4	3.1	25.3	−1.81
2	3.1	12.6	−1.79
1	3.0	6.5	−1.80
0.5	3.2	3.0	−1.80

(10) R. H. Leach and H. Terrey, *Trans. Faraday Soc.*, **33**, 480 (1937).

half-wave potential shift by 0.03 volt in the samarium ion concentration range of 2 to 8 millimoles as compared to a 0.07 volt shift observed in an approximately similar concentration range without acid addition. The diffusion current varied directly with concentration in the acid series. Stabilization of *p*H could possibly explain the improved regularity.

From equivalent conductivity data[11] and application of Kohlrausch's law and the Nernst[12] equation, D was calculated to be 6.07×10^{-6} sq. cm. sec.$^{-1}$. Calculated I_d values for samarium ion would be 1.49 when n is 1 or 4.47 when n is 3. Experimentally the average I_d for the first step of the lithium chloride, sulfuric acid medium series of runs was found to be 3.57 which lies between the two theoretical values cited above. As shown by Fig. 3, a polarogram of the 4 millimolar solution of this series, the second step is terminated before its complete development and therefore no selection of the proper n value can be made. The two polarograms were recorded with the same solution but with different galvanometer sensitivities. The residual current is shown by curve a'.

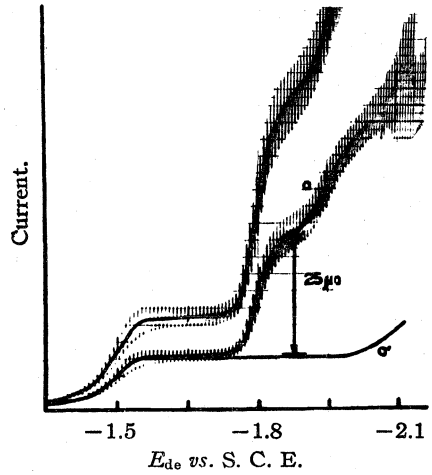


Fig. 3.—Sm^{+++} ion, 4 millimolar, in 0.001 N H_2SO_4, 0.1 M LiCl, 0.01% gelatin medium. Curve a' is the residual current.

Figure 4 is a polarogram recorded with 4 millimolar samarium ion concentration in a 0.1 molar tetramethylammonium iodide and 0.001 N sulfuric acid medium. A well defined two step wave was obtained with an I_d of 3.56 for the first step and 6.49 for the second. As can be seen the two steps are approximately of equal height. This is not the case for a 1 millimolar solution in a similar medium as shown by Fig. 5. I_d for the first step was 3.85 and for the second 12.1 which would indicate a one electron reduction for the first step and a two electron reduction for the second. The multiple polarogram was recorded with various galvanometer sensitivities. The residual current is shown by curve a' in Fig. 5.

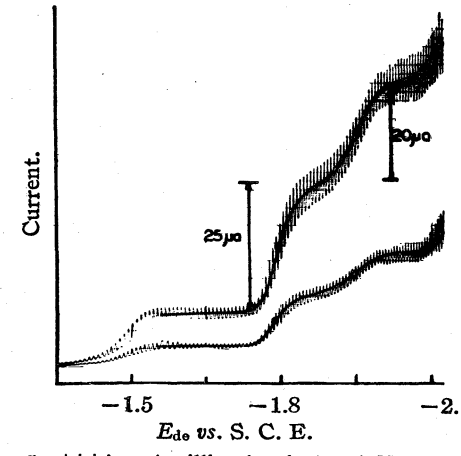


Fig. 4.—Sm^{+++} ion, 4 millimolar, in 0.001 N H_2SO_4, 0.1 M $(CH_3)_4NI$, 0.01% gelatin medium.

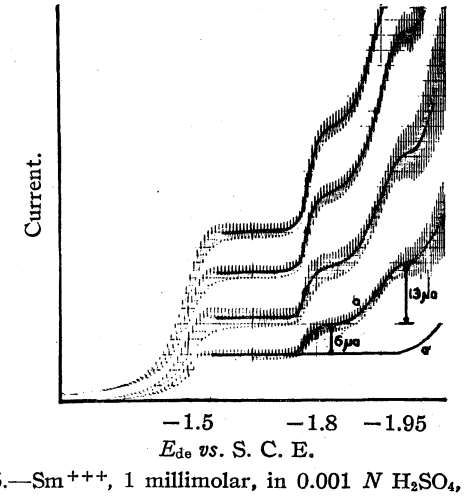


Fig. 5.—Sm^{+++}, 1 millimolar, in 0.001 N H_2SO_4, 0.1 M $(CH_3)_4NI$, 0.01% gelatin medium.

From the preceding observations it is obvious that the discharge of samarium ions at the dropping mercury electrode in aqueous solutions is a complex process. There is evidence of a two-step reduction but in most cases the second step is terminated by discharge of the supporting electrolyte.

It has been noted[6,7] that samarous ion is not very stable in aqueous solutions. It reverts to the samaric state with the evolution of hydrogen. This fact could possibly explain the anomalous results observed, in a manner similar to the case of ytterbium, mentioned by Laitinen and Taebel.[13]

Samarous ion is more unstable[14] than ytterbous ion and therefore hydrogen should be evolved more easily than in the ytterbous case, with greater discrepancy between the expected and ex-

(11) "International Critical Tables," Vol. VI, p. 233.
(12) W. Nernst, *Z. physik. Chem.*, **2**, 613 (1888).
(13) H. A. Laitinen and W. A. Taebel, *Ind. Eng. Chem., Anal. Ed.* **13**, 825 (1941).
(14) W. Klemm and W. Schuth, *Z. anorg. Chem.*, **184**, 352 (1929).

perimentally obtained diffusion currents and thus offer an explanation for the anomalous diffusion current constant in the case of samarium.

Acknowledgment.—This work was undertaken while one of us (A. T.) held a graduate college research assistantship at the State University of Iowa.

Summary

Solutions of samarium chloride and sulfate were studied polarographically without supporting electrolyte and in the presence of lithium chloride, potassium chloride and tetramethylammonium iodide. Addition of sulfuric acid to the sulfate solutions stabilized the half-wave potential. With one millimolar samarium ion, in 0.001 normal sulfuric acid, 0.1 molar tetramethylammonium iodide and 0.01% gelatin medium a two step polarogram was obtained. The half-wave potentials were −1.80 and −1.96 volts against the saturated calomel electrode. The diffusion currents were, respectively, 6.0 and 13.0 microamp., corresponding to $Sm^{+++} \rightarrow Sm^{++}$, and $Sm^{++} \rightarrow Sm^{0}$. However, in 4 millimolar solution the behavior is anomalous.

IOWA CITY, IOWA RECEIVED JUNE 9, 1947

[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heat Capacities at Low Temperatures and Entropies of $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$, and $CaO \cdot 2B_2O_3$[1]

BY K. K. KELLEY,[2] S. S. TODD[3] AND C. H. SHOMATE[4]

In a recent paper, Torgeson and Shomate[5] presented data for the heats of formation of the crystalline calcium borates, $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$, and $CaO \cdot 2B_2O_3$. These are all the compounds in the CaO–B_2O_3 system, according to the work of Carlson.[6] The present paper reports low temperature heat capacity and entropy determinations of these same substances, thus enabling the calculation of their free energies of formation. There are no previous similar data for any of these compounds.

Materials.—The samples of calcium borates used in the present measurements were virtually the same as those employed in the heat of formation studies of Torgeson and Shomate.[5] Their paper included the method of preparation of the samples, their densities, and X-ray diffractions, and repetition here appears unnecessary. About one mole of each compound was used in the present measurements and all weighings were corrected to vacuum. The chemical purity of the samples is indicated by the following analyses:

Substance	Actual analysis CaO, %	Actual analysis B_2O_3, %	Theoretical analyses CaO, %	Theoretical analyses B_2O_3, %
$3CaO \cdot B_2O_3$	70.75	29.31	70.72	29.28
$2CaO \cdot B_2O_3$	61.71	38.41	61.69	38.31
$CaO \cdot B_2O_3$	44.59	55.26	44.61	55.39
$CaO \cdot 2B_2O_3$	28.57	71.02	28.71	71.29

Only the calcium diborate contained any appreciable impurity. As mentioned by Torgeson and Shomate,[5] this material contained 0.42% of insoluble impurity from superficial reaction with the nickel crucible in which it was prepared. No correction for this impurity was made in the present results.

Heat Capacities.—The heat capacities were measured by means of previously described[7] apparatus and methods. The results, expressed in defined calories,[8] are listed in Table I and shown graphically in Fig. 1. The molecular mass figures in the headings of Table I accord with the 1947 International Atomic Weights.[9] The precision error in the results is under 0.1% and it is believed they are accurate on the average to within ±0.3% in the absolute sense.

The heat capacities of all four calcium borates are higher at the lower temperatures, and lower at the higher temperatures, than the sum of the heat capacities of the component oxides. The greatest average deviation from additivity is shown by $CaO \cdot 2B_2O_3$, the heat capacity of which averages over 2 cal. per deg. per mole lower than the sum of the heat capacities of the component oxides in the temperature range 100 to 298.16°K. In this connection it is of interest to note that this substance also has the highest atomic density (lowest mean atomic volume). Other things being equal, high atomic density generally parallels low heat capacity at low temperatures.

Entropies at 298.16°K.—In each instance, the entropy increment between 52.00 and 298.16°K. (measured portion, Table II) was obtained, as usual, by numerical integration of a large-scale plot of C_p against log T. To obtain the entropy

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Supervising Engineer, Pacific Experiment Station, Bureau of Mines.

(3) Chemist, Pacific Experiment Station, Bureau of Mines.

(4) Formerly chemist, Pacific Experiment Station, Bureau of Mines.

(5) Torgeson and Shomate, THIS JOURNAL, **69**, 2103 (1947).

(6) Carlson, *Bur. Standards J. Research*, **9**, 825 (1932).

(7) Kelley, Naylor and Shomate, *Bur. Mines Tech. Paper* 686 (1946).

(8) Mueller and Rossini, *Am. J. Phys.*, **12**, 1 (1944).

(9) Baxter, Guichard and Whytlaw-Gray, THIS JOURNAL, **69**, 731 (1947).

TABLE I

MOLAL HEAT CAPACITIES

T, °K.	C_p, cal./deg.	T, °K.	C_p, cal./deg.
	$3CaO \cdot B_2O_3$ (mol. wt., 237.88)		
52.8	5.978	165.5	30.66
56.6	6.827	175.5	32.13
60.6	7.806	185.6	33.52
64.9	8.863	195.9	34.82
69.0	9.932	205.9	36.09
73.5	11.13	216.2	37.23
77.7	12.21	226.2	38.28
84.7	14.02	235.8	39.27
94.8	16.56	246.1	40.35
104.6	18.92	256.1	41.29
115.1	21.34	266.1	42.22
125.1	23.47	276.2	43.18
135.1	25.45	286.1	43.82
145.7	27.39	296.3	44.77
155.5	29.07	(298.16)	(44.90)
	$2CaO \cdot B_2O_3$ (mol. wt., 181.80)		
53.0	4.914	165.7	23.91
57.0	5.695	175.6	25.04
61.1	6.522	185.8	26.10
65.5	7.399	195.9	27.10
69.8	8.295	206.2	28.08
74.1	9.191	216.2	29.00
78.4	10.06	226.0	29.84
85.6	11.49	235.8	30.60
94.8	13.27	246.2	31.43
104.5	15.03	256.2	32.30
115.2	16.87	266.5	33.07
125.2	18.46	276.2	33.71
135.1	19.96	286.1	34.39
145.4	21.37	296.5	35.03
155.5	22.67	(298.16)	(35.16)
	$CaO \cdot B_2O_3$ (mol. wt., 125.72)		
54.4	4.199	145.5	14.93
56.9	4.554	155.6	15.81
57.7	4.679	165.8	16.68
60.4	5.064	179.1	17.70
61.8	5.265	185.6	18.15
64.4	5.634	195.8	18.87
68.5	6.220	205.4	19.58
71.2	6.604	216.0	20.21
72.6	6.795	226.1	20.84
75.6	7.233	235.4	21.40
80.8	7.924	245.2	21.98
84.8	8.455	255.6	22.55
94.0	9.580	265.5	23.16
104.2	10.80	276.1	23.73
114.3	11.93	286.4	24.24
124.3	12.96	296.3	24.78
135.3	14.02	(298.16)	(24.85)
	$CaO \cdot 2B_2O_3$ (mol. wt., 195.36)		
54.2	4.583	165.7	21.75
57.5	5.092	175.9	23.11
61.6	5.742	189.0	24.84
66.6	6.558	196.0	25.76
71.5	7.366	206.3	27.07
76.3	8.148	215.9	28.31
81.4	8.998	226.4	29.61
86.3	9.776	235.8	30.74
94.4	11.07	245.6	31.88
104.5	12.65	256.0	33.20
114.6	14.22	266.0	34.30
124.1	15.67	276.2	35.33
135.9	17.42	286.5	36.42
146.0	18.90	296.5	37.56
155.8	20.31	(298.16)	(37.75)

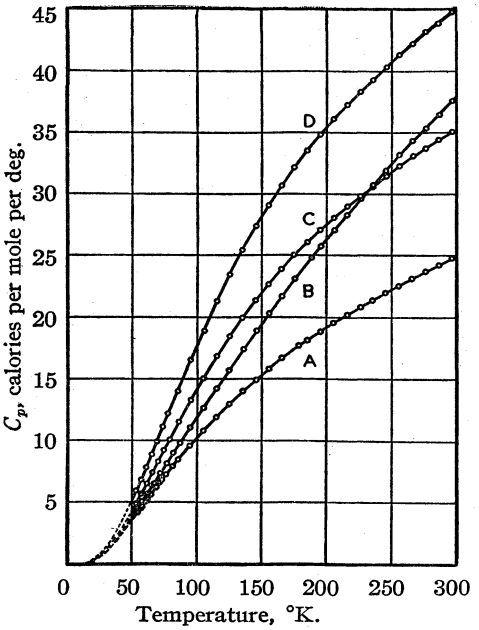


Fig. 1.—Heat capacities: A, $CaO \cdot B_2O_3$; B, $CaO \cdot 2B_2O_3$; C, $2CaO \cdot B_2O_3$; D, $3CaO \cdot B_2O_3$.

increments between 0 and 52.00°K., the measured heat capacities were fitted with the following combinations of Debye and Einstein functions, the maximum deviation between measurements and function sums being shown in parentheses

$$3CaO \cdot B_2O_3 \quad 4D\left(\frac{332}{T}\right) + 4E\left(\frac{534}{T}\right) + 3E\left(\frac{1362}{T}\right) \quad (0.5\%)$$

$$2CaO \cdot B_2O_3 \quad 3D\left(\frac{316}{T}\right) + 3E\left(\frac{511}{T}\right) + 3E\left(\frac{1330}{T}\right) \quad (0.5\%)$$

$$CaO \cdot B_2O_3 \quad 2D\left(\frac{280}{T}\right) + 2E\left(\frac{503}{T}\right) + 3E\left(\frac{1328}{T}\right) \quad (1.0\%)$$

$$CaO \cdot 2B_2O_3 \quad 3D\left(\frac{334}{T}\right) + 4E\left(\frac{700}{T}\right) + 3E\left(\frac{1217}{T}\right) \quad (1.0\%)$$

These function sums were employed in obtaining the extrapolated portions of the entropies in Table II. The extrapolated portion constitutes

TABLE II

ENTROPIES AT 298.16°K., CAL./DEG./MOLE

	$3CaO \cdot B_2O_3$	$2CaO \cdot B_2O_3$	$CaO \cdot B_2O_3$	$CaO \cdot 2B_2O_3$
0°–52.00°K., (extrapolation)	2.16	1.84	1.65	1.59
52.00°–298.16°K., (measured)	41.73	32.84	23.41	30.61
$S^0_{298.16}$	43.9 ± 0.3	34.7 ± 0.2	25.1 ± 0.2	32.2 ± 0.3

only 6.6% of the total entropy for $CaO \cdot B_2O_3$ and is lower for the other substances.

The entropies of $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, and $CaO \cdot B_2O_3$ differ, in order, by 9.2 and 9.6 units, corresponding to successive decreases of one mole of calcium oxide. These figures are to be compared with the measured value for free calcium oxide,[10] $S^0_{298.16} = 9.5 \pm 0.2$. This type of approximate additivity of entropies of some interoxidic compounds has been noted previously in work of this Laboratory and is the result of compensation of plus and minus deviations from additivity of heat capacities. In the case of $CaO \cdot 2B_2O_3$ such compensation is quite incomplete and the entropy difference between $CaO \cdot 2B_2O_3$ and $CaO \cdot B_2O_3$ is only 7.1 units, whereas the entropy of crystalline boric oxide[11] is $S^0_{298.16} = 13.0 \pm 0.1$.

Related Thermal Data.—Free energies of formation at 298.16°K. of the four calcium borates from the oxides and from the elements are given in Table III, being obtained from the relationship $\Delta F^0 = \Delta H - T\Delta S$. The heats of formation, $\Delta H_{298.16}$, are from the paper of Torgeson and Shomate.[5] The entropies employed in calculation of the $\Delta S_{298.16}$ values are from publications of Kelley.[10,11]

Precision uncertainties have been assigned to the free energies of formation from the oxides. It is not possible to do this for the values from the elements because the probable error in the heat of formation of crystalline boric oxide, on which the free energies depend, is not known.

TABLE III

FREE ENERGIES OF FORMATION AT 298.16°K., CAL./MOLE

Substance	$\Delta H_{298.16}$	$\Delta S_{298.16}$	$\Delta F^0_{298.16}$
	From oxides		
$3CaO \cdot B_2O_3$	−60,000 ± 40	2.4 ± 0.7	−60,720 ± 210
$2CaO \cdot B_2O_3$	−45,760 ± 30	2.7 ± 0.5	−46,570 ± 150
$CaO \cdot B_2O_3$	−29,420 ± 20	2.6 ± 0.3	−30,200 ± 90
$CaO \cdot 2B_2O_3$	−42,930 ± 20	−3.3 ± 0.5	−41,950 ± 150
	From elements		
$3CaO \cdot B_2O_3$	−858,200	−136.4 ± 0.6	−817,500
$2CaO \cdot B_2O_3$	−692,100	−111.2 ± 0.5	−659,000
$CaO \cdot B_2O_3$	−524,000	− 86.3 ± 0.5	−498,300
$CaO \cdot 2B_2O_3$	−880,200	−156.2 ± 0.9	−833,700

The free energy of formation values from the oxides follow a normal pattern. The formation of $CaO \cdot B_2O_3$ from the oxides gives a decrease in free energy of 30,200 cal. Smaller decreases in free energy accompany each successive step of adding one mole of oxide to $CaO \cdot B_2O_3$ to form the other calcium borates.

Summary

Low temperature heat capacity measurements of $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$, and $CaO \cdot 2B_2O_3$ were made throughout the temperature range 52° to 298.16°K.

The entropies of the four calcium borates were determined as 43.9 ± 0.3, 34.7 ± 0.2, 25.1 ± 0.2, and 32.2 ± 0.3 cal./deg./mole, respectively.

Free energy of formation values from the oxides and from the elements are included.

BERKELEY, CALIFORNIA RECEIVED OCTOBER 24, 1947

(10) Kelley, *Bur. Mines Bull.*, 434 (1941).

(11) Kelley, THIS JOURNAL, **63**, 1137 (1941).

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1154]

The Reactions of Antiserum Homologous to the *p*-Azosuccinanilate Ion Group[1a]

BY DAVID PRESSMAN,[1b] JOHN H. BRYDEN AND LINUS PAULING

It was discovered by Landsteiner and van der Scheer[2] that the precipitation of azoprotein containing the *p*-azosuccinanilate ion haptenic group by hapten-homologous antiserum (anti-S_p serum) is inhibited just as well by maleate ion as by succinate ion, whereas fumarate ion is practically ineffective, and from this observation the cautious conclusion was drawn[3,4] that "Accordingly, one could suppose that the succinic acid molecule can exist in a form corresponding to the *cis* configuration, or that the antibodies adjust themselves to this." Because of our interest in the use of immunochemical techniques for the determination of the configuration of molecules and haptenic groups,[5] we have extended our quantitative studies of hapten inhibition of serological precipitation to include the S_p system, and have investigated the effect of over fifty haptens on the precipitation of S_p-ovalbumin and anti-S_p serum. The analysis of the data has shown that the normal configuration of the *p*-azosuccinanilate ion group in aqueous solution is a *cis* configuration, presumably stabilized by a hydrogen bond, and has provided information about the configuration of other ions.

Experimental Methods

Haptens.—The following substances used in this work have been described previously[6]: succinanilic acid, *p*-aminosuccinanilic acid, *p*-nitrosuccinanilic acid, and *d*-

(1a) The Serological Properties of Simple Substances. XIII. For No. XII of this series see D. Pressman, A. L. Grossberg, L. H. Pence, and L. Pauling, THIS JOURNAL, **68**, 250 (1946).

(1b) Present address: Sloan-Kettering Institute for Cancer Research, New York.

(2) K. Landsteiner and J. van der Scheer, *J. Exptl. Med.*, **59**, 751 (1934).

(3) K. Landsteiner, "The Specificity of Serological Reactions," Charles C Thomas, Springfield, Illinois, 1936, p. 129.

(4) K. Landsteiner, "The Specificity of Serological Reactions," Revised Edition, Harvard University Press, Cambridge, Mass., 1945, p. 192.

(5) D. Pressman, *Register of Phi Lambda Upsilon*, **29**, 30 (1944).

(6) D. Pressman, J. H. Bryden, and L. Pauling, THIS JOURNAL, **67**, 1219 (1945).

and *l*-N-(α-methylbenzyl)-succinamic acids. The substances prepared in this investigation are described in the following section. All other substances used were commercial preparations purified to the correct melting point and acidic equivalent weight.

Antiserum and Protein Antigens.—The preparation of antiserum and antigens used in this work has been described previously.[6] Only one pool of anti-S_p serum and one preparation of S_p-ovalbumin were used in these experiments.

Reaction of Antiserum with Antigen and Hapten.—One-milliliter portions of S_p-ovalbumin, anti-S_p serum, and hapten solution were mixed and permitted to stand about one hour at 37° and over two nights at 5°. The amount of antigen used, 320 μg. (by Nessler analysis), was that which gave optimum precipitation in the absence of hapten. The hapten solution was made with 0.9% sodium chloride solution and the antigen solution was made with borate buffer of *p*H 8.0.[7] The precipitates were centrifuged, washed three times with 10-ml. portions of 0.9% sodium chloride solution, and analyzed by our standard method.[8]

Preparation of Substances

Malonanilic acid was prepared by the method of Rügheimer,[9] by heating a mixture of 0.24 mole of malonic acid and 0.24 mole of aniline at 105° for one hour. The resultant mass was dissolved in 2 *N* sodium hydroxide solution and filtered, and the filtrate was acidified with hydrochloric acid. Malonanilic acid separated on partial evaporation and cooling. The product was recrystallized from water; m. p. 132.0–132.5°, reported 132°. *Acidic equivalent weight:* calcd. for $C_9H_9O_3N$, 179.1; found 185.6, 186.4.

Glutaranilic acid was prepared by heating a mixture of 0.06 mole of glutaric acid, 0.06 mole of aniline, and 2 g. of fused zinc chloride in an oil-bath at 160 to 170° for forty-five minutes. After cooling, the mixture was extracted with potassium hydroxide solution and was filtered, and the filtrate was acidified with hydrochloric acid. The crystals which separated were recrystallized from water; m. p. 127.0–128.0°, reported 126–127°.[10] *Acidic equivalent weight:* calcd. for $C_{11}H_{13}O_3N$, 207.1; found 208.8, 209.0.

Adipanilic acid was prepared by the method of Dieckmann,[11] by heating a mixture of 0.1 mole of adipic acid, 0.1 mole of aniline, and 2 g. of fused zinc chloride on an oil-bath at 150–160° for one and one-half hours. Upon cooling, the material was dissolved in sodium hydroxide solution and was filtered, and the adipanilic acid was precipitated with hydrochloric acid. The product was recrystallized from water: m. p. 152.0–153.0°, reported 152–153°. *Acidic equivalent weight:* calcd. for $C_{12}H_{15}O_3N$, 221.1; found, 216.9, 218.7.

Maleanilic acid was prepared by the method of Anschütz,[12] by adding 0.3 mole of aniline dissolved in 75 ml. of anhydrous ether to 0.26 mole of maleic anhydride dissolved in 250 ml. of anhydrous ether. The product precipitated as it was formed, and was purified by dissolving it with sodium hydroxide solution and reprecipitating with hydrochloric acid; m. p. 197–198°, reported 198°. *Acidic equivalent weight:* calcd. for $C_{10}H_9O_3N$, 191.1; found, 185.3, 190.5.

Fumaranilic acid was prepared by slowly adding 0.12 mole of aniline in 100 ml. of chloroform to 0.12 mole of fumaryl chloride in 100 ml. of chloroform. The chloroform was evaporated from the emulsion formed by the addition of 350 ml. of 1 *N* sodium hydroxide solution. The solution was filtered and the filtrate was acidified with hydrochloric acid. The precipitate was dissolved with sodium hydroxide solution and reprecipitated with hydrochloric acid; m. p., 238–238.5°, reported, 233–234.0°. *Acidic equivalent weight:* calcd. for $C_{10}H_9O_3N$, 191.1; found, 195.9, 196.9.

d-**Tartranilic acid** was prepared by slowly adding 0.4 mole of aniline to 0.4 mole of *d*-α,β-diacetoxysuccinic anhydride in 400 ml. of chloroform at the refluxing temperature. The cooled solution was extracted with about 400 ml. of 1 *N* sodium hydroxide solution. The aqueous phase was treated with 200 ml. of concentrated hydrochloric acid. A colorless oil separated which dissolved on heating. Subsequent cooling produced crystals; m. p. 181.9–182.4°, reported 180°[13] $[\alpha]^{23}D$ in water, +106.2° (α, +2.13°, 1 dm., 20 g./l.); reported[14] $[\alpha]^{15}D$ +105.6°. *Acidic equivalent weight:* calcd. for $C_{10}H_{11}O_5N$, 225.1; found 224.8, 225.3.

α,β-Diacetylsuccinic anhydride was prepared by the method of Lucas and Pressman.[15]

o-**Bromosuccinanilic acid**, *m*-**bromosuccinanilic acid**, *p*-**bromosuccinanilic acid**, **N-α-naphthylsuccinamic acid**, **and N-β-naphthylsuccinamic acid** were prepared by adding 0.06–0.2 mole of the appropriate amine to a boiling chloroform solution of an equimolar amount of succinic anhydride. The products precipitated as formed and were purified by dissolving in sodium hydroxide solution, extracting with ether, precipitating from the aqueous phase with hydrochloric acid, and finally crystallizing from water or alcohol. The melting points and acidic equivalent weights are as follows:

Substance, acid	Formula	M. p., °C.	Acidic equivalent weight Calcd.	Obs.
o-Bromosuccinanilic	$C_{10}H_{10}O_3NBr$	154.1–156.1	272.2	270.1, 270.1
m-Bromosuccinanilic	$C_{10}H_{10}O_3NBr$	150.9–151.9	272.1	266.7, 266.7
p-Bromosuccinanilic	$C_{10}H_{10}O_3NBr$	187.2–188.2 reported[16] 186–187°	272.1	272.7, 270.8

(7) D. Pressman, D. H. Brown, and L. Pauling, THIS JOURNAL, **64**, 3015 (1942).

(8) D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **51**, 357 (1943). It has been suggested by E. A. Kabat (*Ann. Rev. Biochem.*, **15**, 511 (1946)) that our experimental results are unreliable because the mixtures are allowed to stand only two days, instead of five, before the precipitates are removed and analyzed. We have continued to use the two-day period, for convenience, and we feel that no significant error is introduced thereby. If the tubes containing antiserum and antigen and those also containing hapten were allowed to stand three days longer the amounts of precipitate would increase somewhat, and their ratios might change slightly (by perhaps 5%), leading to correspondingly small changes in the derived values of K_0'. But the values of K_0' obtained with different pools of antiserum differ by as much as two-fold (although usually without changing the order of various haptens), so that the small expected effects of increasing the time of standing are unimportant.

If a true equilibrium were achieved in five days it might be worth while to adopt this longer period. However, on still longer standing the amount of precipitate decreases, presumably as the result of slow degradation of the materials; this suggests that the use of the shorter rather than the longer period may give the more reliable results.

The suggestion has also been made by W. C. Boyd and J. Behnke (*Science*, **100**, 13 (1944)), and repeated by Kabat, that some of the conclusions drawn from our experimental results may be invalidated by the polymerization (aggregation) of some of the haptens or simple precipitating antigens in solution. A detailed discussion of this question will be published shortly; it may be pointed out here that the hapten-inhibition studies reported in the present paper were made with an azoprotein, rather than a polyhaptenic simple substance, as precipitating antigen, and the haptens themselves are so simple as to have little tendency to aggregate, and that for these reasons (as well as others, to be discussed in the later paper) it is unlikely that the arguments presented are to any extent invalidated by the possibility of aggregation of the hapten molecules.

(9) L. Rügheimer, *Ber.*, **17**, 736 (1884).

(10) L. Balbiano and L. Angeloni, *Gazz. chim. ital.*, **35**, I, 150 (1905).

(11) W. Dieckmann, *Ann.*, **317**, 62 (1901).

(12) R. Anschütz, *Ber.*, **20**, 3215 (1887).

(13) A. E. Arppe, *Ann.*, **93**, 352 (1855).

(14) L. Casale, *Gazz. chim. ital.*, **471**, 272 (1917).

(15) H. J. Lucas and D. Pressman, "Theory and Practice in Organic Chemistry Laboratory," to be published.

(16) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **9**, 48 (1890).

Substance, acid	Formula	M. p., °C.	Acidic equivalent weight Calcd.	Obs.
N-α-Naphthylsuccinamic	$C_{14}H_{13}O_3N$	171.1–171.6	243.1	241.4, 241.2
N-β-Naphthylsuccinamic	$C_{14}H_{13}O_3N$	189.4–190.0 reported[17] 184–185°	243.1	240.5, 240.6

p-(p-Hydroxyphenylazo)-succinanilic acid was made by diazotizing 0.01 mole of p-aminosuccinanilic acid, making the solution neutral, and adding it to 0.10 mole of phenol in the presence of sodium hydroxide solution. Coupling was complete within fifteen minutes. The solution was neutralized and was extracted twice with ether, and the free acid was precipitated with hydrochloric acid from the aqueous phase. The product was crystallized twice from dilute alcohol; m. p. 231.5 dec. *Acidic equivalent weight:* calcd. for $C_{16}H_{15}O_4N_3$, 313.2; found, 312.7.

Succinamic acid was prepared by adding an equimolar amount of 15 *N* ammonium hydroxide to solid succinic anhydride. The solid product was recrystallized from acetone; m. p., 156.3–157.8°; reported, 157°.[18] *Acidic equivalent weight:* calcd. for $C_4H_7O_3N$, 117.1; found, 116.9, 116.7.

N-Methylsuccinamic acid was synthesized by adding slowly 0.56 mole of anhydrous methylamine to a mixture of 0.54 mole of succinic anhydride and 200 ml. of anhydrous ether under a "Dry Ice" reflux condenser. The waxy lumps which resulted were broken up several times during the addition. After two days the ether was decanted and the solid residue was recrystallized from absolute alcohol; m. p. 107.7–108.2°. *Acidic equivalent weight:* calcd. for $C_5H_9O_3N$, 131.1; found, 132.1, 132.3.

N,N-Dimethylsuccinamic acid was prepared similarly from dimethylamine; m. p. 81.6–82.6°. *Acidic equivalent weight:* calcd. for $C_6H_{11}O_3N$, 145.1; found, 145.7, 145.1.

N-Isopropylsuccinamic acid was prepared similarly from isopropylamine but at the boiling point of ether; m. p. 97.9–98.9°. Acidic equivalent weight: calcd. for $C_7H_{13}O_3N$, 159.1; found, 162.0, 163.1.

N,N-Diethylsuccinamic acid was prepared similarly from dimethylamine at the refluxing temperature. The product was recrystallized from isopropyl ether; m. p. 82.1–84.1°. *Acidic equivalent weight:* calcd. for $C_8H_{15}O_3N$, 173.1; found 173.2, 173.8.

N-Methylsuccinanilic acid was prepared by the method of Auwers[11] from 0.20 mole of methylaniline and 0.20 mole of succinic anhydride in chloroform solution. The chloroform solution was extracted with sodium hydroxide solution. The aqueous phase was extracted with ether and then treated with hydrochloric acid to precipitate the product, which was then recrystallized from water; m. p. 89.3–89.8°, reported, 91–92.5°. *Acidic equivalent weight:* calcd. for $C_{11}H_{13}O_3N$, 207.1; found, 205.8, 207.8.

N-Benzylsuccinamic acid was prepared similarly from benzylamine; m. p. 137.7–138.2°; reported, 139°.[19] *Acidic equivalent weight:* calcd. for $C_{11}H_{13}O_3N$, 207.1; found, 207.2, 207.4.

N-Cyclohexylsuccinamic acid was prepared similarly from cyclohexylamine; m. p. 166.5–167.0°. *Acidic equivalent weight:* calcd. for $C_{10}H_{17}O_3N$, 199.1; found, 199.1, 200.0.

N,N-Pentamethylenesuccinamic acid was prepared by adding 0.32 mole of piperidine to 0.32 mole of succinic anhydride in 200 mole of anhydrous ether and refluxing. The ether was decanted from the heavier liquid phase, which crystallized upon the removal of residual ether under vacuum. The solid was recrystallized from ethyl acetate; m. p. 93.8–94.8°. *Acidic equivalent weight:* calcd. for $C_9H_{15}O_3N$, 185.1; found, 186.1, 186.1.

γ-Anilinobutyric acid hydrochloride was prepared by the method of Anschütz and Beavis,[20] by hydrolyzing 1 g. of N-phenyl-α-pyrrolidone with barium hydroxide octahydrate in 10 moles of water in a sealed tube for twenty hours. The solution was diluted and carbon dioxide was added to precipitate excess barium hydroxide. The silver salt of the acid was precipitated from the filtrate by adding silver nitrate solution. The dried silver salt was suspended in absolute ether and saturated with hydrogen sulfide. The silver sulfide was removed by filtration and the γ-anilinobutyric acid hydrochloride was precipitated by saturating the ether solution with dry hydrogen chloride; m. p. 135.5–136.5°, reported 135.5–136.5°.

The N-phenyl-α-pyrrolidone was prepared by the method of Anschütz and Beavis,[20,21] by heating 0.21 mole of succinanil with 0.86 mole of phosphorus pentachloride at about 130–140° until all the solid was dissolved to form dichloromaleanil chloride, which was purified by distilling at reduced pressure; b. p. 218–219° at 35 mm. The dichloromaleanil chloride was reduced by slowly adding a solution of 0.05 mole of the compound in 50 ml. of acetic acid and 100 ml. of anhydrous ether to 800 g. of 3% sodium amalgam with agitation and cooling in an ice-bath. The mixture was allowed to stand two weeks. The ether phase was fractionally distilled and the N-phenyl-α-pyrrolidone was collected at 193–195° at 24 mm. The N-phenyl-α-pyrrolidone was recrystallized from petroleum ether containing a few drops of alcohol; m. p. 59.0–61.0°, reported, 68–69°.

Phenylhydantoic acid was prepared by the method of Paal,[22] by stirring 0.21 mole of phenylisocyanate with a solution of 0.21 mole of glycine in sodium hydroxide. After thirty minutes of stirring the odor of the isocyanate had disappeared. The solution was filtered, the phenylhydantoic acid was precipitated with hydrochloric acid, and the solid was recrystallized from water; m. p. 196.5–197.0°, reported, 195°. *Acidic equivalent weight:* calcd. for $C_9H_{10}O_3N_2$, 194.1; found, 195.0, 196.6.

γ-Benzoylbutyric acid was prepared by the method of Somerville and Allen[23] and was recrystallized from water; m. p. 127.5–128.5°, reported, 125–126°. *Acidic equivalent weight:* calcd. for $C_{11}H_{12}O_3$, 192.1; found, 193.7, 194.9.

δ-Phenyl-n-valeric acid was prepared by heating γ-phenyl-n-propylmalonic acid and a few drops of hydrochloric acid on a water-bath for eight hours. The product was crystallized from water; m. p. 54.4–55.5°, reported, 57°[24]. *Acidic equivalent weight:* calcd. for $C_{11}H_{14}O_2$, 178.1; found, 181.2, 181.4.

The γ-phenyl-n-propylmalonic acid used above was prepared as an oil by reducing 0.05 mole of cinnamalmalonic acid in 100 ml. of ethanol with hydrogen in the presence of platinum oxide, removing the catalyst by filtration, and evaporating the alcohol. The cinnamalmalonic acid was prepared by the method of Stuart,[25] by refluxing 0.20 mole of malonic acid, 0.20 mole of cinnamaldehyde, and 25 g. of glacial acetic acid for nine hours. The solid product was filtered off, washed with chloroform, and recrystallized from absolute alcohol.

Citraconic acid was prepared by the method of Shriner, Ford, and Roll[26]; m. p. 92.8–93.8°, reported 92–93°. *Acidic equivalent weight:* calcd. for $C_5H_6O_4$, 65.1; found, 65.3, 65.4.

Mesaconic acid was prepared by the method of Shriner, Ford, Roll[27]; m. p. 204.6–205.6°; reported, 203–205°. *Acidic equivalent weight:* calcd. for $C_5H_6O_4$, 65.1; found, 65.2, 65.2.

Discussion

The Effect of Hydrogen-ion Concentration on the Precipitation Reaction.

—The effect of hydro-

(17) K. Auwers, *Ann.*, **292**, 190 (1896).

(18) L. Wolff, *ibid.*, **260**, 114 (1890).

(19) E. A. Werner, *J. Chem. Soc.*, 630 (1889).

(20) R. Anschütz and C. Beavis, *Ann.*, **295**, 41 (1897).

(21) R. Anschütz and C. Beavis, *ibid.*, **263**, 158 (1891).

(22) C. Paal, *Ber.*, **27**, 975 (1894).

(23) L. F. Somerville and C. F. H. Allen in "Organic Syntheses," Coll. Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 82.

(24) W. Borsche, *Ber.*, **45**, 622 (1912).

(25) C. M. Stuart, *J. Chem. Soc.*, 365 (1886).

(26) R. L. Shriner, S. C. Ford, and L. V. Roll, in "Organic Synthesis," Coll. Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 140.

(27) R. L. Shriner, S. C. Ford, and L. V. Roll, *ibid.*, p. 382.

gen-ion concentration on the precipitation of anti-S_p serum with S_p-ovalbumin is shown in Table I. Optimum precipitation takes place between *p*H values of 7.4 and 8.1, as has been found previously for other azo-protein antigens with negatively charged haptenic groups.[28,29] The antigen concentration for optimum precipitation was found to be between 240 and 480 μg. of antigen added. In the experiments reported in Table II 320 μg. of antigen was used.

TABLE I

THE EFFECT OF HYDROGEN-ION CONCENTRATION ON THE PRECIPITATION OF ANTI-S_p SERUM WITH S_p-OVALBUMIN

Antigen solution, antiserum, and buffer, 1 ml. each.

Initial *p*H	*p*H of supernate	Amount of antigen added, μg., 30	60	120	240	480
		Amount of precipitate, μg.[a]				
6.0	6.5	91	208	333	434	453
7.0	7.4	136	295	543	697	735
8.0	8.1	117	320	519	704	724
9.0	8.9	144	244	394	432	377

[a] Averages of triplicate analyses, with mean deviation ± 2%.

TABLE II

EFFECT OF HAPTENS ON THE PRECIPITATION OF ANTI-S_p SERUM WITH S_p-OVALBUMIN

Antigen solution in borate buffer at *p*H 8, 1 ml. (320 μg.); antiserum, 1 ml.; hapten solution in saline, 1 ml.; *p*H of supernate, 8.1

Hapten	K_0'	σ	Moles of hapten added × 10^8 15.6	62.5	250	1000
			Amount of precipitate[a]			
Series A						
Malonanilate ion	0.03	(1.5)			920	830
Succinanilate	1.00	1.5		670	300	50
Glutaranilate	0.03	(1.5)				830
Adipanilate	.01					920
d-Tartranilate	.00					1030
Maleanilate	.25	2.5		850	640	330
Fumaranilate	.01					900
p-(*p*-Hydroxyphenylazo)-succinanilate	1.38	1.0	920	610	200	
p-Nitrosuccinanilate	1.65	1.0	870	570	120	
p-Aminosuccinanilate	1.03	2.0		650	300	60
p-Bromosuccinanilate	1.31	1.5		640	200	0
m-Bromosuccinanilate	0.72	1.0		920	360	60
o-Bromosuccinanilate	.50	1.0		890	490	110
N-α-Naphthylsuccinamate	.45	1.5		840	540	160
N-β-Naphthylsuccinamate	1.09	1.0		680	220	0
Series B						
Succinanilate ion	1.00	1.5		670	280	100
Succinate	0.01				990	870
Succinamate	.035	(2.5)		970	980	760
N-Methylsuccinamate	.053	(2.5)		890	820	650
N-Isopropylsuccinamate	.064	(2.5)		930	840	600
N-Cyclohexylsuccinamate	.150	2		870	760	400
N-Benzylsuccinamate	.255	2		800	650	280
d-N-(α-Methylbenzyl)-succinamate	.194	2.5		860	660	400
l-N-(α-Methylbenzyl)-succinamate	.169	2		870	(700)	400
N,N-Dimethylsuccinamate	.134	2		(920)	720	460
N,N-Diethylsuccinamate	.122	2		960	760	470
N-Phenyl-N-methylsuccinamate	.128	2		920	740	470
N,N-Pentamethylenesuccinamate	.165	2		910	720	392
Series C						
Succinanilate ion	1.00	1.5		640	270	60
Benzoate	< 0.01					930
Phenylacetate	< .01				990	960
β-Phenylpropionate	.01				(930)	870
γ-Phenylbutyrate	.01				980	890
δ-Phenylvalerate	.02				920	830
β-Benzoylpropionate	.59	1.5		770	(410)	130
γ-Benzoylbutyrate	.053	(2.5)			810	640
Benzylsuccinate	.134	2.0		980	750	440
Phenylhydantoate	.102	2.0		930	790	490
Maleate	.03			930	(900)	790
Fumarate	.00					980
Citraconate	.02				910	860
Mesaconate	.00					1020
Succinate	.01				970	890
Valerate	< .01					950
Levulinate	.066	(2)		1010	845	620
Series D						
Succinanilate ion	1.00	2		670	300	90
γ-Anilinobutyrate	0.01			1030	1030	880
δ-Phenylvalerate	.01			970	930	910
β-Benzoylpropionate	.63	1.5		810	410	160
Succinate	.01			1010	950	900
Glutarate	.00			1040	1030	1000
Adipate	.01			940	890	910
Pimelate	.00			1060	1060	990
Sebacate	.03	(2)		1060	930	790
Aspartate	< .01			990	990	950
Asparagine	.00			1000	1010	1000
Glutamate ion	.00			1000	970	1000

[a] The amounts of precipitate are in parts per mille of the amounts in the absence of hapten: 665, 664, 699, and 649 μg. for series A, B, C, and D, respectively. Blanks of serum and buffer 27, 27, 27, and 17, respectively. Values are averages of triplicate analyses, with mean deviation ±2%, except for duplicate analyses in parentheses.

Inhibition of Precipitation by Haptens.—Data on hapten inhibition are given in Table II. Values of the hapten inhibition constant K_0' and the heterogeneity index σ obtained on application of the theory of heterogeneous antisera[30] are also listed.

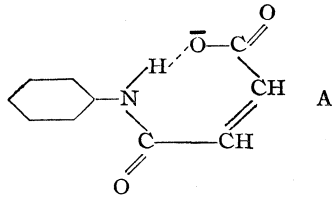
The Structure of the *p*-Azosuccinanilate Haptenic Group.—Through the consideration of the relative inhibiting powers of haptens of known molecular configuration knowledge can be obtained about the configuration of the combining regions of the antibodies, and hence about the normal configuration of the haptenic groups of the immunizing antigen, if we accept the postulate that these regions are complementary to this antigen. In addition, the data for haptens with uncertain configuration may be interpreted to provide information about either the normal configurations of these haptens in aqueous solution or about configurations which do not differ greatly in energy from the normal ones.

(28) D. Pressman, S. M. Swingle, A. L. Grossberg, and L. Pauling, THIS JOURNAL, **66**, 1731 (1944).

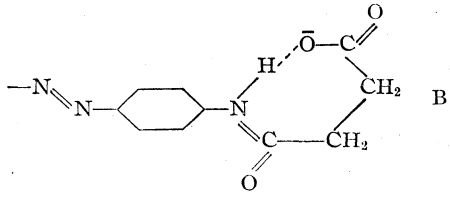
(29) Our work showing the same effect of hydrogen-ion concentration on the precipitation with protein antigen of antiserum specific to the *p*-azophenylarsonate ion and the *p*-(*p*-azophenylazo)-phenyl arsonate ion has not been published.

(30) L. Pauling, D. Pressman, and A. Grossberg, THIS JOURNAL, **66**, 784 (1944).

It was found by Landsteiner and van der Scheer that the maleate ion combines much more strongly with anti-S_p serum than does the fumarate ion, and that the citraconate (methylmaleate) ion combines much more strongly than does the mesaconate (methylfumarate) ion. We have verified these observations (Table II), and have also found that the hapten inhibition constant for the maleanilate ion (0.25) is much greater than that for the fumaranilate ion (0.01). It may accordingly be concluded that the antibody is complementary to a *cis* configuration similar to that of the maleanilate ion, A; and, since there is no reason to believe that the normal configuration of the *p*-azosuccinanilate group is inferior to any other accessible configuration in acting as a template during antibody formation, a corresponding *cis* configuration, presumably B, is indicated for this group.



A



B

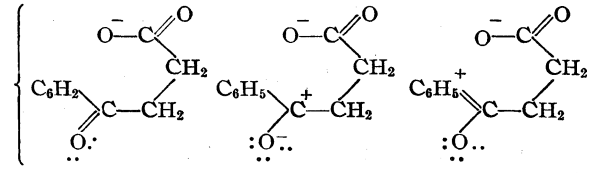
It seems to us likely that the *cis* configuration indicated for this haptenic group is that represented by B, with a hydrogen bond between the amide nitrogen atom and one of the oxygen atoms of the carboxyl group, and that it is largely the energy of this hydrogen bond which stabilizes the *cis* configuration. (The ring closed by the hydrogen bond is probably not coplanar; the two methylene groups may well have nearly the staggered rather than the eclipsed relative orientation.)

The Structure of the Succinanilate Ion, the Succinate Ion, and Related Ions.—The large value of K_0' for the succinanilate ion (1.00, four times the value for the maleanilate ion) indicates strongly that the *cis* configuration is for this ion, too, the normal configuration, and not just an easily accessible one. On the other hand, the value of K_0' for the succinate ion, 0.01, is considerably smaller than that for the maleate ion, 0.03, and it hence seems likely that the *cis* configuration with the two carboxylate groups nearly coplanar with the rest of the ring is not the normal or preferred one for the succinate ion in aqueous solution, but is instead only one of several readily accessible configurations, being itself represented by about 8% of the dissolved ions (the percentage being indicated by the product of ratios of the above K_0' values). The lack of preference for the *cis* configuration presumably is due in part to the inability of the ion to form a hydrogen bond and in part to the electrostatic repulsion of the two carboxylate groups.

The succinamate ion, however, can form a hydrogen bond stabilizing the *cis* configuration, and it contains only one charged group. It is accordingly not surprising that the value of K_0' for this ion (0.035) is considerably greater than that for the succinate ion, and this fact may be taken as verifying that the normal configuration of the succinamate ion, and also of its various monosubstituted derivatives, is the hydrogen-bonded *cis* configuration described above for the succinanilate ion.

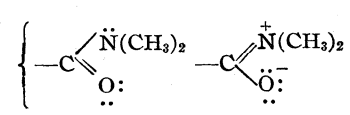
***cis* Configuration without Hydrogen-bond Stabilization.**—It is interesting that there is evidence for predominance of the *cis* configuration, also for some molecules in which this configuration is not stabilized by a hydrogen bond. Thus the large value, 0.59, of K_0' for the β-benzoylpropionate ion requires that the *cis* configuration predominate for this ion in solution, this being essentially the value that would be expected for the *cis* configuration. (The decrease of 41% from the succinanilate ion would be expected to result from the somewhat different orientation of the phenyl group than that for the immunizing haptenic group.)

A reasonable explanation of this observation is that the *cis* configuration for this molecule is stabilized by the electrostatic attraction of the negative charge of the carboxyl ion for a positive charge on the benzene ring and carbonyl carbon atom. The resonance structure places a significant



amount of positive charge in this region, the corresponding negative charge being on the carbonyl oxygen atom, and it is obvious that the electrostatic interactions would stabilize the *cis* configuration, less effectively, however, than would a hydrogen bond.

The sequence of values 0.035, 0.053, 0.134 for K_0' for succinamate ion, N-methylsuccinamate ion, and N,N-dimethylsuccinamate ion strongly indicates that the third of these substances has, like the other two, predominantly the *cis* configuration. For it the positive charge attracting the carboxyl ion is placed on the nitrogen atom by amide resonance



The *cis* configuration indicated for benzylsuccinate ion, $C_6H_5CH_2OCO(CH_2)_2COO^-$, by its rather large value of K_0' (0.134, as compared with 0.255 for N-benzylsuccinamate ion) has a similar explanation, the positive charge being on the oxygen atom to which the benzyl group is attached and on the adjacent carboxyl carbon atom.

The Structural Features Affecting Interaction with Antibody.—The electrically charged carboxyl group is without doubt the structural feature which is of greatest importance in the interaction of haptens and anti-S_p antibody; this feature was, however, not varied in the present investigation.[31] The other structural features which might be important are the imino group, the carbonyl group, the benzene ring, and the framework determining the relative positions of these groups and the carboxyl group.

The data given in Table II indicate that the imino group is not involved directly in attraction of the antibody (hydrogen-bond formation), but exerts only an indirect effect through stabilizing the *cis* configuration for some haptens.

The carbonyl group, on the other hand, makes an important contribution to the attractive forces between hapten and antibody, without doubt by serving as the proton receptor in a hydrogen bond with the antibody. This is strikingly shown by the relative values of K_0' for succinanilate ion (1.00) and γ-anilinobutyrate ion (0.01), and for β-benzoylpropionate ion (0.59) and γ-phenylbutyrate ion (0.01), and is indicated also by other comparisons among the data in Table II (levulinate ion, $CH_3COCH_2CH_2COO^-$ (0.066) and valerate ion (0.01)).

The data also show clearly that the antibody is not pliable, but is rigid: it cannot adjust itself to a change by as much as 1 Å. in the relative position of the carbonyl group and the carboxyl group, but requires for strong combination with a hapten that these groups be the same distance apart as in the haptenic group of the immunizing antigen. This is shown by the comparison of succinanilate ion ($K_0' = 1.00$) with malonanilate ion (0.03) and glutaranilate ion (0.03), and of β-benzoylpropionate ion (0.59) with γ-benzoylbutyrate ion (0.053).

The considerable effect of the van der Waals attraction of the antibody for the benzene ring of the haptenic group is indicated by the 30-fold increase in value of K_0' caused by introduction of a benzene ring in succinamate ion. The effect of the azo group and an additional benzene ring is, however, very small—*p*-(*p*-hydroxyphenylazo) succinanilate ion shows an increase in K_0' of only 38% over the succinanilate ion. We may accordingly conclude that the combining group of the antibody is complementary in structure to the succinamate group and also to the benzene ring, but that it does not extend much farther along the haptenic group.

The value of K_0' for N-cyclohexylsuccinamate ion (0.150), corresponding to decrease to one-seventh on replacing phenyl by cyclohexyl, is probably due to the smaller van der Waals attraction of cyclohexyl, resulting from its smaller polarizability and greater thickness[32] than for the phenyl group.

The value $K_0' = 0.00$ found for the tartranilate ion requires explanation. The great effect of the two hydroxyl groups can hardly be attributed to steric hindrance, since citraconate ion was found to be nearly as effective as maleate ion, and the methyl group is as large as the hydroxyl group. It seems probable that the small effectiveness of the tartranilate ion as an inhibiting hapten results from the fact that hydroxyl groups of the ion in solution are holding water molecules by hydrogen bonds, and that these molecules must be removed in order for the ion to fit into the antibody. This would reduce the free energy of combination with antibody by an amount equal to the free energy of hydration of the hydroxyl groups. This explanation is the same as that previously suggested[33] for the low values of K_0' for *p*-amino and *m*-amino substituted haptens. The same phenomenon explains the low value (0.102, only one-tenth that for the succinanilate ion) of K_0' for the phenylhydantoate ion, $C_6H_5NHCONHCH_2COO^-$. A steric explanation could hardly be invoked here, because the NH group is essentially equal in size to the methylene group which it replaces.

The Effect of Substituents in the Benzene Ring of the Succinanilate Ion.—The effect of various groups in the para position of the benzene ring of the succinanilate ion on the value of K_0' is in the order

$$NO_2 > HOC_6H_4NN > Br > NH_2 > H$$

The action of the nitro group to cause even greater combination than the homologous azo-group was observed previously with anti-R_p serum (antiserum specific for the *p*-azophenylarsonate ion group).[30]

The effect on K_0' of the position of the substituent is in the order $p > m > o$, in agreement with earlier observations,[5,28,30] on *p*-azohaptenic systems.

The magnitude of the effect of substituents in this system is less, however, than for other systems, the spread for the above groups in the para position being by a factor of less than 2 in K_0', as compared with 5 for these groups with anti-R_p serum, 15 with anti-R_p' serum (antiserum specific for the *p*-(*p*-azophenylazo)-phenylarsonate ion group), and 20 with anti-X_p serum (specific to the *p*-azobenzoate ion group). Also in changing a substituent from the *para* to the *ortho* position there is a factor of only 2.6 involved, which is a little larger than the value 2 for anti-R_p' serum but is much smaller than those for anti-R serum (5 to 90) and anti-X_p serum (20 to 1000). The small effect of the substituents in the present system

(31) See ref. 1 and earlier papers.

(32) The effect has been found also in the benzoic acid system, D. Pressman, S. M. Swingle, A. L. Grossberg, and L. Pauling, THIS JOURNAL, **66**, 1731 (1944).

(33) L. Pauling and D. Pressman, *ibid.*, **67**, 1003 (1945).

must be due to a rather poor fit of the antibody to the benzene ring, which probably results from the greater distance from the part of the haptenic group which carries the electric charge.

The values of K_0' for N-α- and N-β-naphthylsuccinamate ions, 0.45 and 1.09, are reasonable when compared with the observed effects of substituents in the *o*-, *m*-, and *p*-positions.

Discussion of Other Haptens.—The order of effectiveness of various groups replacing one hydrogen atom on the nitrogen atom of the succinamate ion in increasing the value of K_0' is $C_6H_5 > C_6H_5CH_2 > C_6H_5(CH_3)CH > cyc\text{-}C_6H_{11} > (CH_3)_2CH > CH_3 > H$. The range of values of K_0' from the benzyl group to hydrogen is through a factor of 8. Replacement of a hydrogen atom by a methyl group presumably increases the value of K_0' from 0.035 to 0.053 through the action of the increased van der Waals attraction, corresponding to the increase in polarizability of the group. Further increasing the size of the alkyl group causes additional increase in K_0'.

The larger value (0.165) of K_0' for N,N-pentamethylenesuccinamate ion than for N,N-diethylsuccinamate ion (0.122) is probably in the main due to the more compact structure of the pentamethylene group than of the two ethyl groups.

In the homologous series of ions of dibasic acids, succinic, glutaric, adipic, and sebacic, the last combines the most strongly with anti-S_p serum, as was reported also by Landsteiner and van der Scheer.[7] We checked this effect for larger amounts of haptens, up to 10^{-4} mole, in both the system S_p-ovalbumin:anti-S serum and the system ovalbumin:antiovalbumin, and found the effect to be specific to the anti-S_p serum. In general an increase in the hapten inhibiting effect would be expected for such a series with increase in the number of methylene groups, because of the increasing van der Waals attraction. In the S_p system, however, it might be expected that the succinate ion would have the maximum effect, because of its close relation to the immunizing para-azosuccinanilate ion haptenic group. It is very probable that the failure of the succinate ion to be active is, as discussed above, due to the predominance of the *trans* configuration for this ion, which does not bring an oxygen atom of the second carboxyl group into the position corresponding to the carbonyl group of the original immunizing antigen.

Asparagine, the aspartate ion, and the glutamate ion were all found to be ineffective as haptens. It is likely that this ineffectiveness is to be ascribed to the effect of the positively charged ammonium ion group in these haptens.

Conclusion.—In general, it has been found that the inhibiting power of haptens in the *para*-azosuccinanilate system depends upon the structural features found previously for other systems, principally the shape of the hapten, the polarizability of groups, and the distribution of charge. The previously recognized phenomenon of decrease in inhibiting power for haptens that are hydrated in solution and must have water removed for combination with antibody has been substantiated by several examples in this system. An interesting result of the studies has been the discovery that the *para*-azosuccinanilate group has the *cis* configuration in the azoprotein used as the immunizing antigen, and that a similar *cis* configuration is shown by the succinanilate ion, the succinamate ion, and many related substances in which this configuration can be stabilized by hydrogen bond formation. The *cis* configuration has also been found to predominate for some other substances in solution, the stabilizing influence presumably being the attraction of the negative charge of the carboxyl group for a positive charge produced elsewhere in the molecule by resonance.

It may be pointed out that the results presented in this paper, like those reported in the preceding papers of this series, strongly support the concept that the forces of attraction between antibody and antigen are interatomic forces operating through distances of a few ångströms, and that the specificity of the resultant integrated attraction depends upon a detailed complementariness in structure of antibody and antigen.

Acknowledgment.—This investigation was carried out with the aid of a grant from The Rockefeller Foundation. We wish to thank Mr. Dan Rice for assisting in the analytical work.

Summary

A quantitative study has been made of the precipitation reaction of S_p-ovalbumin and anti-S_p serum, prepared by injecting rabbits with an azoprotein made by coupling sheep serum with diazotized *p*-aminosuccinanilic acid, and of the inhibiting effect of fifty haptens on this precipitation. The data have been interpreted to show that the normal configuration of the *p*-azosuccinanilate ion haptenic group is a *cis* configuration, which is presumably stabilized by a hydrogen bond between the nitrogen atom of the amide group and an oxygen atom of the carboxyl group. They further indicate that a similar *cis* configuration is the predominant configuration for the succinamate ion and related ions, including some which are not stabilized by hydrogen-bond formation.

The results support the concept that complementariness in structure of antibody and antigen is responsible for their specific combination, and that the forces involved require approximation of the attracting molecules to within one or two ångströms. The values of the hapten inhibition constant show that the principal forces of attraction between the antibody and the hapten are the attraction for the negative charge of the carboxyl group, attraction for the carbonyl group (presumably by formation of a hydrogen bond), and van der Waals attraction for the benzene ring and other parts of the hapten.

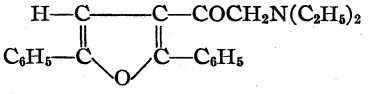
PASADENA 4, CALIFORNIA RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

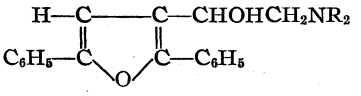
Antimalarials. 2,5-Diphenyl-3-furyl Amino Ketones and Alcohols[1]

BY ROBERT E. LUTZ AND RUSSELL J. ROWLETT, JR.[2]

This research was a part of an exploratory program on quinine-type synthetic antimalarials.[3] The objective was the preparation of some novel α-aryl-β-dialkylamino ketones and alcohols of the type I, II, XI (and its alcohol), and XVI, involving the furyl group as the central aromatic nuclear system. Early leads had indicated slight activity

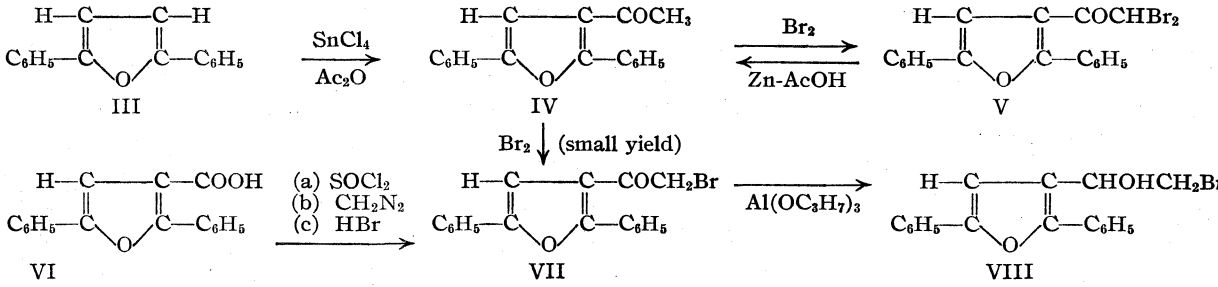


I



II

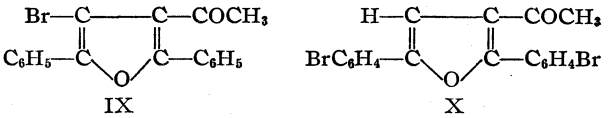
against avian malaria of certain 2,5-diphenylfuran types which contained basic groups,[3c,d] although by present standards of testing[4] few of the compounds so far obtained in this field are to be regarded as active at all, and then only very slightly so. Because of this, although the objectives were only partially achieved, the work was discontinued.



III IV V VI VII VIII

The first attempt to synthesize the key intermediate, 3-bromoacetyl-2,5-diphenylfuran (VII), was through the Friedel–Crafts acylation of 2,5-diphenylfuran followed by bromination. The Friedel–Crafts reaction, although it was unsuccessful using aluminum chloride,[5] proceeds in excellent yields using the combination stannic chloride and acetic anhydride. Bromination of the resulting 3-acetylfuran (IV), however, proved to be difficult to control. Under the various conditions employed only a small amount of the desired bromo ketone (VII) was isolated; the chief product evidently was a mixture which included unchanged material and the dibromo compound (V). This was shown by the reaction of a second molecule of bromine which produced the dibromoacetyl derivative (V) in good yield. It was somewhat surprising to us that the substitution of the second bromine proceeded so rapidly and involved the acetyl group rather than the vulnerable 4-furyl or *para*-phenyl positions, but there is analogy for this in the bromination of 2-acetylfuran.[6]

The nature of the dibromoacetyl compound (V) was demonstrated by the facile reductive dehalogenation back to the acetylfuran (IV), a reaction which showed that the two bromines were aliphatic. The non-reactivity of the 4-nuclear and *para*-phenyl bromines was demonstrated by the stability under the reducing conditions of two compounds, one, the 3-acetyl-4-bromo-2,5-diphenylfuran (IX) which was made from 3-bromo-2,5-diphenylfuran by the Friedel–Crafts reaction, and the other, the isomeric 3-acetyl-2,5-di-(4-bromophenyl)-furan (X), which was made by the Friedel–Crafts reaction with 2,5-di-(4-bromophenyl)-furan.



IX X

The use of chloro and bromoacetyl chlorides in Friedel–Crafts reactions with 2,5-diarylfurans was unsuccessful except in one case. Bromoacetyl chloride and aluminum chloride reacted with 2,5-di-(4-bromophenyl)-furan to give an intractable mixture which on bromination gave a small yield of the dibromoacetyl compound. The latter compound was obtainable in better yields by the bromination of 3-acetyl-2,5-di-(4-bromophenyl)-furan. These experiments showed that the bromoacylation must have produced some of the desired 3-bromoacetyl derivative, even though it was not isolated as such.

The 3-bromoacetyl-2,5-diphenylfuran (VII) was best obtained from the 3-carboxylic acid (VI) by

(1) A part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Devleopment and the University of Virginia.

(2) Philip Francis du Pont Fellow, 1943–1944. Present address: Chemical Abstracts, Ohio State University.

(3) *Cf.* (a) Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946); (b) *J. Org. Chem.*, **12**, 617 (1947); (c) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945); (d) **68**, 2002 (1946).

(4) F. Y. Wiselogle, "Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

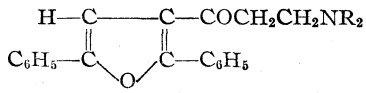
(5) Woodward, Dissertation, Harvard University, 1936.

(6) Brown, *Iowa State Coll. J. Sci.*, **11**, 221 (1937).

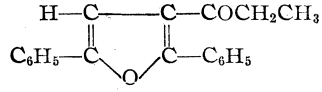
the well known steps, conversion into the acid chloride, diazomethylation, and subsequent treatment with hydrobromic acid.[7]

Condensation of the 3-bromoacetylfuran (VII) with diethylamine gave a typical amino ketone. Condensation of the bromohydrin (VIII) with diethylamine gave a product which resisted crystallization either as the base or the salt. However, a crystalline morpholino alcohol was obtained by this method. Further work in this direction was abandoned because of lack of material.

Six β-dialkylamino ketones of the type XI were made by the Mannich reaction with 3-acetyl-2,5-diphenylfuran, utilizing the following amines: morpholine, piperidine, dimethylamine, diethylamine, dibutylamine and benzylmethylamine. Only two of these compounds were active, and very slightly so, against avian malaria.[4]



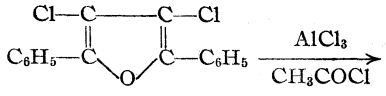
XI



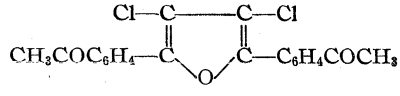
XII

Attempts to reduce these compounds to the amino alcohols by catalytic hydrogen or by aluminum isopropoxide, failed, and only the fission product, the secondary amine, and non-crystalline materials were obtained. From the products of catalytic hydrogenation in one case there was isolated in considerable yields a crystalline deamination product, the ketone XII, which was synthesized independently by the Friedel–Crafts reaction between propionic anhydride and 2,5-diphenylfuran.

In a start toward making an amino alcohol through the *para* position of a phenyl group, a Friedel–Crafts reaction was carried out with 3,4-dichloro-2,5-diphenylfuran (XIII) where the 3,4-furan positions were blocked by chlorine atoms which could be removed later by catalytic hydrogenation. The acylation by means of acetyl chloride and aluminum chloride proceeded twice, however, instead of once as desired, and the di-*para*-acetyl derivative (XIV) was isolated as the chief product. Its structure was demonstrated by oxidation to terephthalic acid.

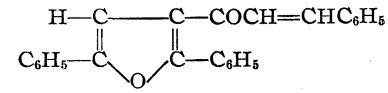


XIII

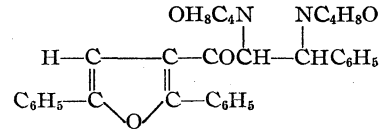


XIV

In connection with the α,β-dimorpholinylbenzylacetophenones,[8] benzaldehyde was condensed with 3-acetyl-2,5-diphenylfuran (IV). The benzal derivative (XV) was brominated and the dibromide reacted with morpholine to give the dimorpholino ketone XVI. This compound showed no activity against avian malaria.



XV



XVI

Acknowledgment.—The synthesis of XII was carried out by Mr. C. R. Bauer.

Experimental[9]

The Preparation of 2,5-Diphenylfuran (III).—Two hundred and fifty grams of *trans*-dibenzoylethylene was added portionwise to a vigorously stirred and refluxing mixture of 250 g. of stannous chloride and 500 ml. each of concd. hydrochloric and concd. acetic acid. The mixture was refluxed for fifteen minutes, and allowed to cool to 50°, and poured into cold water. The solidified product was crystallized slowly from ethanol; yield 154 g. of m. p. 89.5–90° and 36 g. of m. p. 86–87° (86%).

2,5-Di-(4-bromophenyl)-furan.[10]—Twenty-five grams of di-(4-bromobenzoyl)-ethylene was added to a stirred mixture of 50 ml. of concd. hydrochloric and 200 ml. of concd. acetic acids. The addition was rapid enough to keep the mixture boiling gently under the heat of reaction. After refluxing for forty minutes and cooling, the product was isolated by pouring into water. Crystallization from benzene gave 17 g. (73%); melting point 206.5–208°.

Catalytic reduction of 2,5-di-(4-bromophenyl)-furan using palladium on barium sulfate in 95% ethanol at atmospheric pressure and room temperature for eight hours gave 2,5-diphenylfuran.

3-Bromo-2,5-diphenylfuran[11] was made on a large scale by adding 10 ml. of concd. sulfuric acid to a stirred mixture of 120 g. of dibenzoylbromoethane in 500 g. of acetic anhydride. The temperature rose to 54°. Hydrolysis and crystallization of the product gave 94 g. (83%); m. p. 84–86°.

The Preparation of 3-Acetyl-2,5-diphenylfuran (IV).[5]—The Friedel–Crafts acylation of 2,5-diphenylfuran was carried out by means of acetic anhydride and stannic chloride under a variety of conditions in which the solvents tetrachloroethane, carbon disulfide and benzene were used, and in which the mole ratio of stannic chloride was varied between one and two. Acetic anhydride was always used in about 10% excess. The temperature ranges were from 20–50° and the time one-half to eighteen hours. The yields ranged from 64 to 80%. The best procedure is as follows:

Acetic anhydride [28.6 g. (0.28 mole)] was added slowly to a stirred mixture of 55 g. (0.25 mole) of 2,5-

(7) This reaction scheme has been applied at least twice in the furan series starting from furoic acid [Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1219 (1934); Burger and Harnest, THIS JOURNAL, **65**, 2382 (1943)].

(8) A paper to be published shortly from this Laboratory, dealing with a study of this class of compounds with respect to antimalarial activity.

(9) All melting points are corrected.

(10) Lutz and Eisner, THIS JOURNAL, **56**, 2699 (1934); Perkin and Schloesser, *J. Chem. Soc.*, **57**, 94 (1890).

(11) Lutz and Smith, THIS JOURNAL, **63**, 1148 (1941).

diphenylfuran and 250 ml. of dry thiophene-free benzene. A solution of 65 g. (0.25 mole) of anhydrous stannic chloride in 50 ml. of dry benzene was added slowly over thirty minutes with the mixture temperature starting at 13° and not allowed to exceed 20°. Stirring was continued for thirty minutes (15–20°) and the mixture was poured into ice and concd. hydrochloric acid. The product, recovered from the benzene layer, was crystallized from ethanol (with Darco treatment); yield 52 g. (80%) of m. p. 62–64°.

2,5-Diphenyl-3-propionylfuran (XII) was made exactly as was the 3-acetyl analog, but using propionic anhydride. The yield of the product melting at 92.5–95.5° was 72%. A mixture melting point with the sample prepared by reduction of the 3-(β-dialkylamino) ketones showed no depression; melting point 95.5–96°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.53; H, 5.84. Found: C, 82.04; H, 6.19.

2,5-Diphenyl-3-furoic acid[5,11] (VI) was made by passing dry carbon dioxide into a cold ether solution of 2,5-diphenyl-3-furylmagnesium bromide which had been made from carefully purified and dried 3-bromo-2,5-diphenylfuran in the usual way in carefully dried apparatus.

2,5-Diphenyl-3-furoyl chloride.—Five hundred milliliters of thionyl chloride was added cautiously to 49 g. of 2,5-diphenyl-3-furoic acid and the mixture was refluxed for thirty minutes. Unused thionyl chloride was distilled under reduced pressure, and the last traces were eliminated by boiling out with added benzene. Crystallization from ligroin with Norit treatment and cooling to −20° for forty-five minutes gave 44 g. of yellow crystals of m. p. 95–97° (83%).

Anal. Calcd. for $C_{17}H_{11}ClO_2$: Cl, 12.54. Found: Cl, 12.54. (This analysis was carried out by solution of the sample in warm alcohol, addition of alcoholic sodium hydroxide and boiling for ten minutes. After acidification with dilute nitric acid the solution was titrated by Mohr's method with standard silver nitrate and 4% potassium dichromate as indicator.[12])

2,5-Diphenyl-3-furyl Diazomethyl Ketone.—A solution of diazomethane in 1300 ml. of methylene chloride[3a] (0.4675 *N* as determined by titration) was cooled to 0°; and 40 g. of 2,5-diphenyl-3-furoyl chloride was added with gentle stirring. Effervescence continued for thirty minutes. After two hours in the ice-bath and standing overnight, the solvent was evaporated under reduced pressure. A small sample was recrystallized from ethyl acetate and melted at 136.5–138°.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: N, 9.71. Found: N, 9.79.

The bulk of the product was used directly in the preparation of the bromoketone.

3-Bromoacetyl-2,5-diphenylfuran (VII).—Attempts to brominate 3-acetyl-2,5-diphenylfuran (IV) with one equivalent of bromine under a variety of conditions gave mixtures of products. When the bromine in carbon disulfide was added slowly to a carbon disulfide solution of IV at room temperature (over one hour), an oil was obtained which, when treated with a small volume of ethanol, gave a low-melting crude solid. Laborious purification from ethanol gave a small amount of moderately pure VII which was identified. The bulk of the residue on further manipulation gave some dibromo compound (V). That the original crude mixture was largely VII was shown by treatment with diethylamine and isolation of the diethylamino ketone (as the hydrochloride) in 54% yield.

The unsuccessful attempts at Friedel–Crafts reactions between bromoacetyl and chloroacetyl chlorides involved the use of aluminum, ferric and stannic chlorides, with carbon disulfide, benzene or tetrachloroethane as solvent, and temperatures ranging from −5 to 60°.

The best preparation of the 3-bromoacetyl compound is as follows: The ether suspension of the diazoketone (prepared as described above from 40 g. of the acid chloride of VI) in 1 liter of dry ether, was cooled to 0° and treated slowly over three hours under stirring with 23 ml. of 48% hydrobromic acid in 23 ml. of dry ether. Stirring was continued for three hours. After washing and evaporating the solvent, the resulting oil slowly crystallized. Crystallizations from ethanol containing a little ethyl acetate, and from 85% ethanol, gave diamond-shaped light yellow plate-like crystals of melting point 62–64°.

Anal. Calcd. for $C_{18}H_{13}BrO_2$: C, 63.37; H, 3.84. Found: C, 63.17; H, 4.17.

3-(2-Bromo-1-hydroxyethyl)-2,5-diphenylfuran (VIII).—A mixture of 375 ml. of 0.6 *N* aluminum isoproxoxide and 25.6 g. of the bromoacetylfuran (VII) was refluxed for one and one-half hours at which time the evolution of acetone had ceased. Hydrolysis in dilute hydrochloric acid and crystallization of the precipitate from 80% ethanol (with Darco treatment), cooling to −20°, gave 17.4 g. (68%). After crystallization it melted at 124–126°.

Anal. Calcd. for $C_{18}H_{15}BrO_2$: Br, 23.29. Found: Br, 23.26. (The analysis was carried out by warming the sample in alcoholic sodium hydroxide for ten minutes, acidifying with dilute nitric acid, and titrating with standard silver nitrate.[12])

Condensation of the small sample of VIII available, with diethylamine, gave an oil which we were not able to crystallize, either as the base or as the hydrochloride.

3-Acetyl-4-bromo-2,5-diphenylfuran (IX).—Two equivalents of stannic chloride was added dropwise to a stirred and ice-cooled mixture of 3-bromo-2,5-diphenylfuran and a 10% excess of the calculated amount of acetic anhydride in carbon disulfide. Hydrolysis in ice and concd. hydrochloric acid, separation, and evaporation of the solvent gave a crude product which was crystallized from concd. acetic acid to which a small amount of water had been added. Crystallization from 60% ethanol gave pale yellow needles of melting point 81°.

Anal. Calcd. for $C_{18}H_{13}BrO_2$: C, 63.37; H, 3.84. Found: C, 63.18; H, 3.80.

The compound was not affected by zinc dust and concd. acetic acid at boiling-water-bath temperature for thirty minutes.

3-Acetyl-2,5-di-(4-bromophenyl)-furan (X).—To a suspension of 18.9 g. (0.05 mole) of 2,5-di-(4-bromophenyl)-furan in 200 ml. of tetrachloroethane and 26.1 g. (0.1 mole) of stannic chloride, was added over five minutes 5.1 g. (0.05 mole) of acetic anhydride in 20 ml. of tetrachloroethane. After stirring for thirty minutes at room temperature and 1.6 hours at 68–69° (yellow crystals had appeared), and working up the product as above, 22.9 g. (98%) of fairly pure product was obtained.

A reaction using two equivalents of aluminum chloride in the same solvent and adding one equivalent of acetyl chloride (stirring for three hours) gave the same product but in only 77% yield.

After recrystallizations from ethanol containing a small amount of ethyl acetate, the compound melted at 129–130°.

Anal. Calcd. for $C_{18}H_{12}Br_2O_2$: C, 51.46; H, 2.88. Found: C, 52.10; H, 3.21.

3-Dibromoacetyl-2,5-di-(4-bromophenyl)-furan was made in nearly quantitative yield by bromination of X in carbon tetrachloride at room temperature over thirty minutes. It was crystallized from an ethyl acetate–ethanol mixture and melted at 168.5°.

Anal. Calcd. for $C_{18}H_{10}Br_4O_2$: C, 37.41; H, 1.74. Found: C, 37.28; H, 2.41.

In an attempt to obtain the 3-bromoacetyl analog by the Friedel–Crafts acylation of 2,5-di-(4-bromophenyl)-furan with aluminum chloride and bromoacetyl chloride in tetrachloroethane (three hours at room temperature), a difficultly separable mixture was obtained which was evidently largely the desired **3-bromoacetyl-2,5-di-(4-bromophenyl)-furan** (m. p. 128–132°). Bromination of

(12) See Willard and Furman, "Elementary Quantitative Analysis," 2nd ed., D. Van Nostrand Co., New York, N. Y., 1935.

this in carbon tetrachloride gave the 3-dibromoacetyl compound in 83% yield.

The 3-(β-Dialkylaminopropionyl)-2,5-diphenylfurans (XI).—Mixtures in the ratio of approximately 0.1 mole each of the furan (IV) and the secondary amine hydrochloride or hydrobromide, and 0.11 mole of paraformaldehyde in 100 ml. of 99.5% ethanol and 2 ml. of concd. hydrochloric or hydrobromic acid, were refluxed. The products were precipitated as the salts upon cooling (in some cases after first concentrating the solution under reduced pressure). When the hydrobromide of the amine was used in the reaction, usually with concd. hydrobromic acid instead of hydrochloric, the base was liberated by means of alkali, extracted into ether and converted into the hydrochloride. The crystallizations of the salts, and of the one crystalline base which was handled in that form, were from ethanol, except in the last case where the solvent was ethanol containing a small proportion of ethyl acetate.

MANNICH REACTION PRODUCTS

NR_2	SN. No.[a]	Q[b]	Heating time, hr.	Yield, %	M. p., °C.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$N(CH_3)_2 \cdot HCl$	4909	<0.06	22	41	189	$C_{21}H_{21}NO_2 \cdot HCl$	70.88	70.79	6.23	6.57
$N(C_2H_5)_2 \cdot HCl$	2624	.06	72	75	147	$C_{23}H_{25}NO_2 \cdot HCl$	71.95	72.00	6.83	6.77
$N(n\text{-butyl})_2 \cdot HCl$	3541	< .06	120[c,d]	45	144	$C_{27}H_{33}NO_2 \cdot HCl$	3.18	2.88	(nitrogen)	
Morpholinyl(base)	3543	.03+	4[d,e]	58	101.5	$C_{23}H_{23}NO_3$	76.42	76.40	6.41	6.65
Piperidyl·HCl	6639[f]	< .15	20[d,e]	24[g]	194–195	$C_{24}H_{25}NO_2 \cdot HCl$	3.54	3.80	(nitrogen)	
$N(CH_3)CH_2C_6H_5 \cdot HCl$	6638	< .03	24[d,e]	47	193[h]	$C_{27}H_{25}NO_2 \cdot HCl$	3.24	2.96	(nitrogen)	

[a] The SN number identifies the drug in the Survey Tables.[4] [b] Quinine equivalent determined against Gallinaceum in the chick (see ref. 4). [c] Every twenty-four hours an additional 0.05 mole of paraformaldehyde was added. [d] In these reactions the secondary amine hydrobromide was used instead of the hydrochloride. [e] Hydrobromic rather than hydrochloric acid was used. [f] This compound was formulated erroneously as the monoamylamino ketone under this number in the Survey Table.[4] [g] Fully purified material (the other yields listed above were for partially purified material). [h] Unsharp melting point; softens at 182°.

Attempted reduction of the diethylamino ketone (XI) by aluminum isopropoxide (refluxing for three hours) gave only unchanged material. Reduction of the dibutylamino analog (XI) under refluxing involved only very slow evolution of acetone as shown by test with 2,4-dinitrophenylhydrazine. After eight hours the product was worked up and the only compound isolated (and that in large quantity) was dibutylamine (as the hydrochloride).

Catalytic hydrogenation at atmospheric pressure and room temperature of 21.1 g. (0.055 mole) of the β-diethylamino ketone (XI) with 0.5 g. of platinum oxide in 300 ml. of 99.5% ethanol, was stopped after ten hours and absorption of one equivalent of hydrogen (although the rate of absorption had not dropped). Concentration of the solution gave 5.5 g. of a product which, after crystallization from 60% ethanol, melted at 93° and was identified as 2,5-diphenyl-3-propionylfuran (XII) by mixture melting point.

The same compound was obtained by a similar reduction of the dibutylamino analog (XI). Here the hydrogenation had been allowed to go further (1.3 equivalents).

3-Diethylaminoacetyl-2,5-diphenylfuran Hydrochloride (I).—An absolute ether solution (75 ml.) of 3.4 g. of the bromoketone (VII) and 2.9 g. of diethylamine quickly gave a precipitate. After standing for five hours the diethylamine hydrobromide was filtered (81%), and the solution was washed, treated with Norite, and dried over sodium sulfate. Acetone was added and the solution acidified with ethereal hydrogen chloride and cooled to −20° for two hours; yield 1.84 g. Recrystallization from anhydrous ethyl acetate and absolute ethanol mixture, gave long needles of melting point 202–204°.

Anal. Calcd. for $C_{22}H_{23}NO_2 \cdot HCl$: N, 3.79; Cl, 9.59. Found: N, 3.53; Cl, 9.54 (by titration).

2,5-Diphenyl-3-[2-(N-morpholinyl)-1-hydroxyethyl]-furan Hydrochloride (II).—Condensation of morpholine with the bromohydrin (VIII), with no added solvent, and standing for twenty-eight hours, and diluting with ether, gave 88% of the calculated amount of morpholine hydrobromide. Evaporation under reduced pressure and conversion to the hydrochloride in ether gave 2.1 g. (55%). It was recrystallized from ethyl acetate by addition of absolute ethanol; melting point 202–203°.

Anal. Calcd. for $C_{22}H_{23}NO_3 \cdot HCl$: C, 68.47; H, 6.27; Cl, 9.18. Found: C, 68.49; H, 6.27; Cl, 9.21 (by titration).

2,5-Di-(4-acetylphenyl)-3,4-dichlorofuran (XIV).—A mixture of 13.4 g. (0.1 mole) of aluminum chloride, 14.5 g. (0.05 mole) of 3,4-dichloro-2,5-diphenylfuran (XIII) and 100 ml. of tetrachloroethane, was treated with 5.9 g. (0.025 mole) of acetyl chloride in 25 ml. of tetrachloroethane (30°, for two hours). Hydrolysis, washing and steam distillation of the solvent gave a residual oil which partly solidified. Crystallization from ethanol gave 11.2 g. of nearly pure product. It was recrystallized from ethanol; yellow needles of melting point 130.5°.

Anal. Calcd. for $C_{20}H_{14}Cl_2O_3$: C, 64.37; H, 3.78. Found: C, 64.42; H, 4.11.

A higher reaction temperature (68°) gave tars, and no reaction occurred at a lower temperature (0–2°).

Oxidation.—A cooled suspension of the furan (XIV) in ten parts of concd. acetic acid and one of concd. nitric acid, was warmed. Reaction began with evolution of oxides of nitrogen at 40–45° and the solid dissolved. The mixture was heated at 80–85° for fifty minutes and poured into water. The product, which we were unable to crystallize, was then oxidized by potassium permanganate in 10% sodium carbonate, and gave almost two equivalents of terephthalic acid (identified by m. p. 301° and mixture melting point with an authentic sample).

3-Benzalaceto-2,5-diphenylfuran[5] (XV).—Eighty milliliters of 10% sodium hydroxide was added dropwise to a well-stirred mixture of 38 g. of the acetylfuran (IV), 500 ml. of ethanol and 21.2 g. of benzaldehyde. An oil separated. Stirring was continued for two hours. The product solidified, and was filtered and crystallized from ethanol; yield 47 g. (93%). Crystallization from ethanol containing a small amount of ethyl acetate gave pale yellow needles; melting point 123°.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.83; H, 5.77.

The dibromide[5] was made by bromination of XV in ether. The yield of material after crystallization from ethanol–ethyl acetate mixture, was 77%; melting point 180°.

Anal. Calcd. for $C_{25}H_{18}Br_2O_2$: C, 58.84; H, 3.56. Found: C, 58.82; H, 3.94.

3-(2,3-Dimorpholinyl-3-phenylpropionyl)-2,5-diphenylfuran (XVI).—A mixture of 30.8 g. of the dibromide of XV, 26.1 g. of morpholine and 200 ml. of absolute ethanol was refluxed for thirty minutes and allowed to stand overnight. The solid product was filtered, washed with water and recrystallized from an ethanol–ethyl acetate mixture; yield 15 g. (48%); melting point 192°.

Anal. Calcd. for $C_{33}H_{34}N_2O_4$: C, 75.83; H, 6.56. Found: C, 75.59; H, 6.89.

Summary

Six β-dialkylamino ketones, one α-dialkylamino ketone and one α-dialkylamino alcohol, were made, based on the 2,5-diphenyl-3-furyl system.

The synthetic work involved a study of (a) the Friedel–Crafts acylation of 2,5-diarylfurans and bromination of the 3-acetyl group, and (b) conversion of the 3-carboxylic acid through the acid chloride and diazomethyl ketone into the bromoketone and bromohydrin.

The α,β-dimorpholino ketone was made from the benzal derivative of the 3-acetylfuran.

Very little or no antimalarial activity was observed in the limited studies in this field.

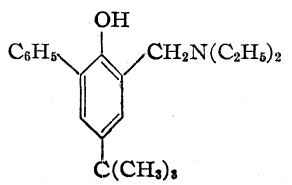
CHARLOTTESVILLE, VIRGINIA
RECEIVED NOVEMBER 20, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & COMPANY]

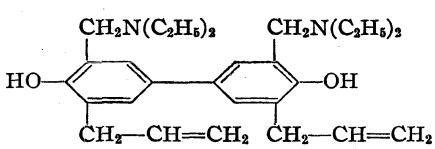
Aminoalkylphenols as Antimalarials. II.[1] (Heterocyclic-amino)-α-amino-o-cresols. The Synthesis of Camoquin[2]

BY J. H. BURCKHALTER,[3] F. H. TENDICK, ELDON M. JONES, PATRICIA A. JONES, W. F. HOLCOMB AND A. L. RAWLINS

In an earlier publication[1] we described a new class of antimalarial compounds represented by 4-*t*-butyl-α-diethylamino-6-phenyl-*o*-cresol (SN 7,744) and 6,6′-diallyl-α,α′-bis-(diethylamino)-4,4′-bi-*o*-cresol (SN 6,771). The high activity of

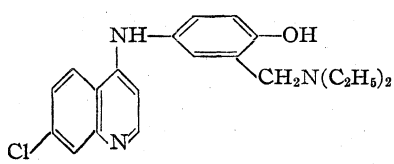


SN 7744



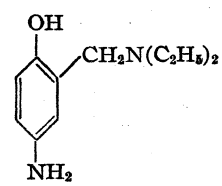
SN 6771

SN 6,771, SN 7,744 and simple analogs led, in 1943, to the synthesis of analogs containing substituent heterocyclic nuclei. This paper describes the work on quinolines, acridines and other heterocyclic compounds which has resulted in the preparation of a new antimalarial, SN 10,751.[2,4]

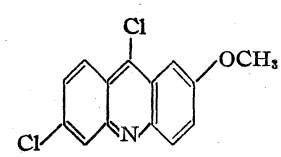


SN 10,751

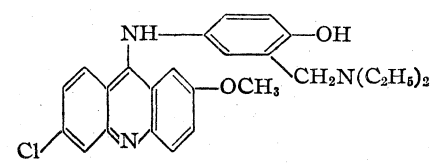
Early attempts to prepare the first member of the new heterocyclic series were unsuccessful. Treatment of 6-chloro-9-(4-hydroxyanilino)-2-methoxyacridine with formaldehyde and diethylamine in the manner of the Mannich reaction failed to yield a product.[5] A method was developed, however, through the preparation of 4-amino-α-diethylamino-*o*-cresol (SN 12,458) and its condensation with 6,9-dichloro-2-methoxyacridine (I) in phenolic solution[6] to give 4-(6-chloro-2-methoxy-9-acridylamino)-α-diethylamino-*o*-cresol (SN 8,617).



SN 12,458



I



SN 8,617

The intermediate 4-amino-α-diethylamino-*o*-cresol (SN 12,458) is new and has been prepared both by acid deacetylation of 4-acetamido-α-diethylamino-*o*-cresol (SN 7,767) and by reduction of 4-nitro-α-diethylamino-*o*-cresol (SN 7,292). The last two compounds were obtained from 4-

(1) For paper I see Burckhalter, Tendick, Jones, Holcomb and Rawlins, THIS JOURNAL, **68**, 1894 (1946).

(2) (a) Camoquin is the Parke, Davis name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-*o*-cresol, SN 10,751. (b) The designation SN identifies a compound in the monograph *A Survey of Antimalarial Drugs*, 1941–1945, F. Y. Wiselogle, Editor, J. W. Edwards, Ann Arbor, Mich., 1946.

(3) Present address: University of Kansas, Lawrence, Kansas.

(4) This drug has been receiving extensive clinical trial in many parts of the world with promising results. Chemical data are summarized in Table VI, compound 9.

(5) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 10. Subsequently, incomplete studies have shown that the reaction can be effected with certain substituted aminophenols, *e. g.*, see compound 3, Table XII (VI).

(6) Because of the objection to the handling of phenol, this and similar condensations were later carried out in dilute mineral acid according to a procedure used by Banks, THIS JOURNAL, **66**, 1127 (1944).

TABLE I

ACETAMIDOPHENOLS[a]

No.	Compound	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	4-Acetamidophenol	56[b]	168							
2	4-Acetamido-2-chlorophenol	55[c]	144	$C_8H_8ClNO_2$	51.77	51.68	4.35	4.24		
3	2-Acetamido-4-chlorophenol	52[d]	186	$C_8H_8ClNO_2$	51.77	51.81	4.35	4.39		
4	4-Acetamido-2-phenylphenol	60[e]	160	$C_{14}H_{13}NO_2$					6.16	6.01
5	2-Acetamido-4-phenylphenol	89[f]	165	$C_{14}H_{13}NO_2$					6.16	6.43
6	2-Acetamido-4-*t*-butylphenol	79[g]	170	$C_{12}H_{17}NO_2$					6.75	6.91

[a] The nitrophenols were obtained through the coöperation of Dow Chemical Co. [b] Identical with the product from Eastman Kodak. [c] Recrystallized from isopropanol as light gray crystals. [d] Recrystallized from ethanol. [e] Recrystallized from methanol. [f] Recrystallized from benzene–ethanol. [g] Recrystallized from benzene.

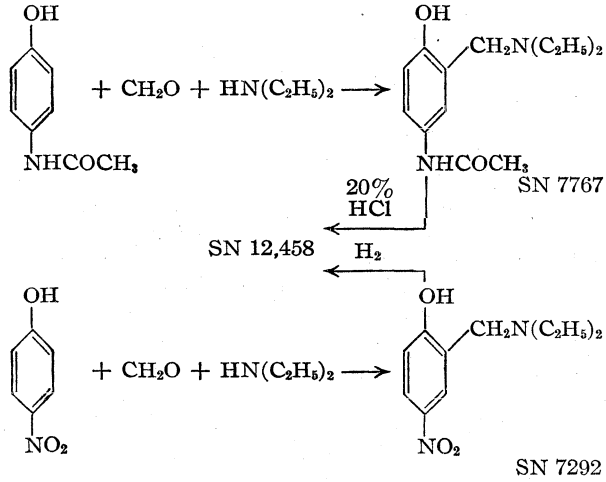
TABLE II

z-ACETAMIDO-α-ALKYLAMINO-*o*-CRESOLS

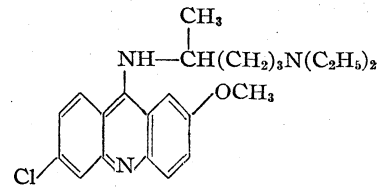
No.	Substituents z	Alkylamino	Other	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	4	Diethylamino		82[a]	135	$C_{13}H_{20}N_2O_2$	66.07	66.45	8.53	8.48	11.85	11.86
2	5	Diethylamino		33[a]	210	$C_{13}H_{20}N_2O_2 \cdot HCl$					10.27	10.19
3	4	Di-*n*-butylamino		87[b]	73	$C_{17}H_{28}N_2O_2$	69.82	70.30	9.65	9.51		
4	4	Dibenzylamino		75[c]	230	$C_{23}H_{24}N_2O_2$					7.77	7.76
5	4	2-Methyl-1-piperidyl		65[d]	175	$C_{15}H_{22}N_2O_2 \cdot HCl \cdot H_2O$	56.86	56.60	7.95	7.96	8.84	8.42
6	4	4-Morpholinyl		27[e]	133	$C_{13}H_{18}N_2O_3$	62.40	62.35	7.25	7.40		
7	4	Methyl-(2-hydroxyethyl)-amino		50[a]	198	$C_{12}H_{18}N_2O_3 \cdot HCl$					10.20	10.09
8	4	Mono-2-hydroxyethylamino		31[f]	230	$C_{11}H_{16}N_2O_3 \cdot HCl$					10.75	10.44
9	4	Mono-2-butylamino		37[g]	156	$C_{13}H_{20}N_2O_2$	66.07	66.27	8.53	8.60		
10	4	Diethylamino	6-Allyl	58[h]	86	$C_{16}H_{24}N_2O_2$	69.53	69.44	8.75	8.69		
11	6	Diethylamino	4-Chloro	66[c]	212	$C_{13}H_{19}ClN_2O_2 \cdot HCl$	50.82	50.89	6.56	6.57		
12	6	Diethylamino	4-*t*-Butyl	53[i]	158	$C_{17}H_{28}N_2O_2 \cdot HCl$	62.08	62.29	8.89	8.91		
13	6	Diethylamino	4-Phenyl	..[d]	183	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41	65.74	7.22	7.07		

[a] Recrystallized from ethanol. [b] From isopropanol–petroleum ether. A monopicrate of this compound was prepared; m. p. 183–185°. *Anal.* Calcd. for $C_{23}H_{31}N_5O_9$: C, 52.96; H, 5.99. Found: C, 53.31; H, 5.85. [c] From methanol. [d] From ethanol–acetone. [e] From isopropanol. [f] From methanol–ethanol. [g] From isopropanol–petroleum ether. [h] From dilute methanol. For intermediate 2-allyl-4-acetamidophenol see Experimental part. [i] From acetone.

acetamidophenol and 4-nitrophenol, respectively, by the Mannich reaction.[5]



SN 8,617 proved to be as active as quinacrine (SN 390) in screening tests and thus provided the impetus for the work which followed. The structural relationship of SN 8,617 to both SN 6,771 and SN 7,744, as well as to SN 390, suggested that a practical antimalarial might be found among its analogs.



SN 390

Many analogs of intermediates SN 7,767 and SN 7,292 were prepared (Tables II and III). Although several others could not be readily crystallized, we found that deacetylation of the crude materials yielded the desired intermediates which, without isolation, could be successfully condensed with reactive chloroheterocycles. Certain analogs of SN 7,292, *e. g.*, α-monoisobutylamino-4-nitro-*o*-cresol (II), were best obtained by conden-

TABLE III

α-ALKYLAMINO-4-NITRO-o-CRESOLS[a]

No.	Substituent: Alkylamino	Substituent: Other	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Diethyl		A	40[b,c]	224 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.67	50.76	6.57	6.47
2	1-Piperidyl		A	68[b]	260 dec.	$C_{12}H_{16}N_2O_3 \cdot HCl$	52.84	52.67	6.28	6.30
3	Diisopropyl		B	19[d]	193 dec.	$C_{13}H_{20}N_2O_3 \cdot HCl$	54.07	54.14	6.98	6.91
4	Di-*n*-butyl		B	75[e]	176 dec.					
5	Diisobutyl		B	43[f,g]	113	$C_{15}H_{24}N_2O_3$	64.26	64.20	8.63	8.18
6	Diisoamyl		B	32[d]	132 dec.	$C_{17}H_{28}N_2O_3 \cdot HCl$	59.20	59.42	8.48	8.67
7	Diethyl	6-Phenyl	A	21[f,g]	125	$C_{17}H_{20}N_2O_3$			9.33	9.29
8	Monoisopropyl		B	38[h]	238 dec.	$C_{10}H_{14}N_2O_3 \cdot HCl$	48.69	48.92	6.13	6.03
9	Monoisobutyl		B	29[i]	247 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.67	50.81	6.57	6.67
10	Mono-*t*-butyl		B	20[h]	275 dec.	$C_{11}H_{16}N_2O_3 \cdot HCl$	50.66	50.86	6.57	6.28
11	Diethyl	4-*t*-Butyl[a]	A	50[f,g]	103	$C_{15}H_{24}N_2O_3$	64.26	64.33	8.63	8.44

[a] Note that compound 11 is a 6-nitro-*o*-cresol. [b] From methanol. [c] Off-white color. [d] From isopropanol–ether. [e] This hydrochloride was not analyzed; it was converted by a procedure similar to the one applied to compounds in Table I into compound 3, Table II. [f] From isopropanol. [g] Yellow colored. [h] From ethanol–ether. [i] From isopropanol–methanol

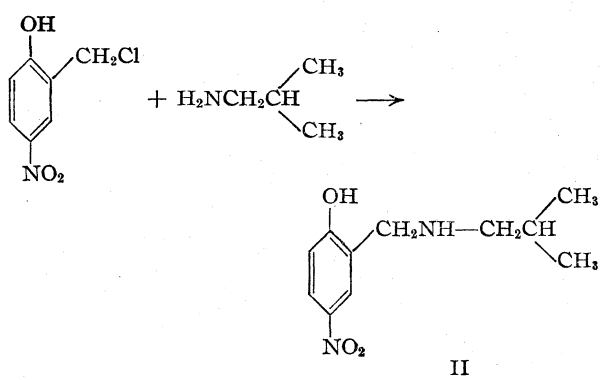
TABLE IV

NITROBENZYLAMINES

No.	Substituents: Amino	Substituents: Benzyl	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	Diethyl	3-Nitro	60[a]								
2	Diethyl	4-Nitro	45[b]	162	$C_{11}H_{16}N_2O_2 \cdot HCl$					11.45	11.12
3	Di-*n*-propyl	4-Nitro	68[c]	138 dec.	$C_{13}H_{20}N_2O_2 \cdot HCl$					10.27	10.43
4	Monoisopropyl	4-Nitro	82[d]	232 dec.	$C_{10}H_{14}N_2O_2 \cdot HCl$					12.15	12.16
5	Monoisobutyl	4-Nitro	64[d]	214 dec.	$C_{11}H_{16}N_2O_2 \cdot HCl$					11.44	11.19
6	Diethyl	5-Nitro-2-methoxy	72[e,f]	178 dec.	$C_{12}H_{18}N_2O_3 \cdot HCl$	52.46	52.38	6.97	6.67		
7	Monoisobutyl	5-Nitro-2-methoxy	63[e,f]	176 dec.	$C_{12}H_{18}N_2O_3 \cdot HCl$	52.46	52.56	6.97	6.90		
8	Diethyl	5-Nitro-2-ethoxy	56[g]	182 dec.	$C_{13}H_{20}N_2O_3 \cdot HCl$	54.07	54.31	7.33	7.36		
9	Mono-*n*-amyl	5-Nitro-2-methoxy[h]			$C_{13}H_{20}N_2O_3 \cdot HCl$						

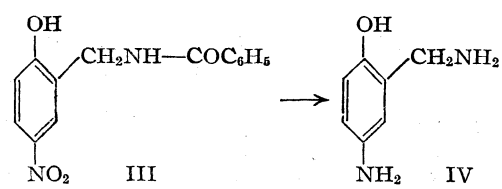
[a] Prepared by the general procedure of this table; b. p. 145–148° (6 mm.); picrate, m. p. 161°. Noelting and Kragczy, *Bull. soc. chim.*, [4], **19**, 336 (1916), prepared the same compound in a pressure bottle; b. p. 206–208° (42 mm.); picrate, m. p. 161°. [b] From acetone–ethanol. [c] From acetone–ligroin. [d] From ethanol–isopropanol. [e] From isopropanol. [f] Intermediate 2-methoxy-5-nitrobenzyl chloride prepared by the method of U. S. Patent 2,278,996. [g] From ligroin–isopropanol. [h] The separation of the hydrochloride of this compound from *n*-amylamine hydrochloride was very difficult. Analytical data indicated the presence of this impurity to a considerable extent. However, compound 8, Table XIII, was readily prepared from the crude product.

sation of α-chloro-4-nitro-*o*-cresol[7] with the proper mono- and dialkylamines.



II

α,4-Diamino-*o*-cresol[8] (IV) was prepared by catalytic reduction of α-benzamido-4-nitro-*o*-cresol (III) followed by acid hydrolysis of the derived 4-amino-α-benzamido-*o*-cresol.



As a part of our studies, certain non-phenolic and O-methylated analogs of SN-8,617 and Camoquin were synthesized. These compounds listed in Table XIII were prepared prior to the appearance of another publication[9] describing 6-chloro-9-(2-diethylaminomethylanilino) - 2 - methoxyacridine, which is a position isomer of compounds 10 and 11. The two necessary types of non-phenolic inter-

(7) "Organic Syntheses," **20**, 59 (1940).

(8) Einhorn, *Ann.*, **343**, 249 (1906).

(9) Hall and Turner, *J. Chem. Soc.*, 694 (1945).

TABLE V

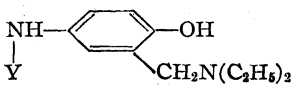
4-CHLOROQUINOLINES

No.	Substituents	Yield,[a] %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7-Ethoxy	53[b]	76	$C_{11}H_{10}ClNO$					6.75	6.96
2	7-*n*-Hexyloxy	41[c,d]		$C_{15}H_{18}ClNO$						
3	5-Chloro-8-methoxy	6[c,e]	127	$C_{10}H_7Cl_2NO$						
4	6,7,8-Trichloro	39[c,e]	156	$C_9H_3Cl_4N$						
5	5-Methyl-8-methoxy	45[c,e]	78	$C_{11}H_{10}ClNO$						
6	6-Methyl	50[e]	55	$C_{10}H_8ClN$	67.61	68.18	4.54	4.58		
7	8-Methyl	71[e]	99	$C_{10}H_8ClN$					7.88	7.75
8	5,7-Dimethyl	51[e]	59	$C_{11}H_{10}ClN$	68.93	68.99	5.26	5.48		
9	5,8-Dimethyl	59[e]	51	$C_{11}H_{10}ClN$	68.93	69.03	5.26	5.40		
10	6,8-Dimethyl	82[e]	90	$C_{11}H_{10}ClN$					7.31	7.44
11	6-Anilino	6[f]	148	$C_{15}H_{11}ClN_2$	70.72	70.86	4.35	4.34		

[a] The yield of each 4-chloroquinoline is an over-all value based on the amount of substituted aniline used in the first step of the synthesis. [b] From dilute alcohol. [c] It is regrettable that analytical data are not available on every compound listed in this table. However, the compounds are tabulated because they are new and necessary intermediates in the preparation of several antimalarials which were more thoroughly characterized. [d] A high boiling liquid which was directly converted into compound 6, Table IX. [e] From ligroin. [f] From benzene–ligroin.

TABLE VI

4-(HETEROCYCLIC-AMINO)-α-DIETHYLAMINO-*o*-CRESOLS (PROCEDURE C)



No.	SN	Q Equiv.[a]	Y	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	12,356	1.5	9-Acridyl	45	265 dec.	$C_{24}H_{25}N_3O\cdot 2HCl$[b,c,d]	64.86	64.48	6.13	6.14		
2	12,355	3	3-Chloro-9-acridyl	52	267 dec.	$C_{24}H_{24}ClN_3O\cdot 2HCl$[b,c,d]	60.19	60.10	5.47	5.42		
3	12,164	0.15	4-Methoxy-9-acridyl	50	245 dec.	$C_{24}H_{27}N_3O_2\cdot 2HCl$[b,c,d]	63.29	62.93	6.16	6.39		
4	8,617		6-Chloro-2-methoxy-9-acridyl	50	175	$C_{25}H_{26}ClN_3O_2$[e,f]	68.87	69.14	6.01	6.20		
					117 dec.	$C_{25}H_{26}ClN_3O_2\cdot H_2O$[e,g]	66.17	66.26	6.22	6.28		
		4		76[w]	280 dec.	$C_{25}H_{26}ClN_3O_2\cdot 2HCl$[e,h]	59.00	58.90	5.55	5.73		
					180 dec.	$C_{25}H_{26}ClN_3O_2\cdot 2HCl\cdot 2H_2O$[e,i]	54.20	53.97	5.82	5.86		
5	11,988	0.25	3-Chloro-5-methyl-9-acridyl	40	275 dec.	$C_{25}H_{26}ClN_3O\cdot 2HCl$[b,c,d]	60.92	60.99	5.73	5.91	8.52	8.30
6	9,559	0.12	2-Quinolyl	48	230 dec.	$C_{20}H_{22}N_3O\cdot 2HCl$[j,k]					10.66	10.53
7	11,537	0.7	6-Methoxy-2-quinolyl	20.5	237 dec.	$C_{21}H_{25}N_3O_2\cdot 2HCl$[l,m,n]					9.90	9.88
8	9,307	<0.07	5-Nitro-2-quinolyl	33	245 dec.	$C_{20}H_{22}N_4O_3\cdot 2HCl$[b,c,k]					12.75	12.82
9	10,751	25	7-Chloro-4-quinolyl	86	208 dec.	$C_{20}H_{23}ClN_3O$[d,f,p]	67.50	67.64	6.23	6.29		
					243 dec.	$C_{20}H_{23}ClN_3O\cdot 2HCl\cdot 1/2H_2O$[h,o]	54.86	54.93	5.76	6.08		
					183 dec.	$C_{20}H_{23}ClN_3O\cdot 2HCl\cdot 1H_2O$[o,q]	53.76	54.09	5.87	6.20		
				90	160 dec.	$C_{20}H_{23}ClN_3O\cdot 2HCl\cdot 2H_2O$[n,r]	51.68	51.88	6.07	5.92		
10	9,591	1.1	2-Amino-4-pyrimidyl	41	258 dec.	$C_{15}H_{21}N_5O\cdot 2HCl$[f,s,t]	50.01	49.71	6.43	6.62		
11	10,177	0.4	2-1′-Piperidyl-4-pyrimidyl	31	156	$C_{20}H_{29}N_5O$[f,t]					19.70	19.70
12	....		2-Amino-6-methyl-4-pyrimidyl	55	245 dec.	$C_{16}H_{23}N_5O\cdot 2HCl$[b,u]					18.71	18.50
13	11,189	<0.07	4-Methoxy-2-benzothiazolyl	47	163 dec.	$C_{19}H_{23}N_3O_2S\cdot 2HCl$[b,k,v]					9.76	9.70

[a] By Dr. Porter's B-4 test; *cf.* ref. 2(b). [b] From methanol–acetone. [c] Orange crystals. [d] Heterocyclic intermediate obtained through Dr. R. C. Elderfield. [e] From absolute ethanol. [f] From 80% ethanol. Calcd. volatile loss, 3.98. Found, 4.13. [g] From methanol. [h] From 50% ethanol. [i] From isopropanol. [j] 2-Chloroquinoline obtained from Eastman Kodak Co. [k] From ethanol–acetone. [l] 2-Chloro-6-methoxyquinoline prepared by the method of Magidson, *J. Gen. Chem.* (*USSR*), **7**, 1896 (1937), and Bachman and Cooper, *J. Org. Chem.*, 9, 302 (1944). [m] Pale yellow crystals. [n] Yellow crystals. [o] See reference 11 for intermediate 4,7-dichloroquinoline. [p] From acetone–water. [q] From water. [r] Light tan crystals. [s] Intermediate 2-amino-4-chloropyrimidine from Dr. H. S. Mosher. [t] Light gray crystals. [u] Off-white crystals. [v] Also prepared in 71% yield by Procedure D.

mediates related to 4-amino-α-diethylamino-*o*-cresol (SN 12,458) were prepared by condensation of nitrobenzyl chlorides and alkoxy nitrobenzyl chlorides with aliphatic amines (Table IV). During the course of this work 2-chloromethyl-4-nitrophenetole was obtained in 75% yield by the chloromethylation of 4-nitrophenetole.

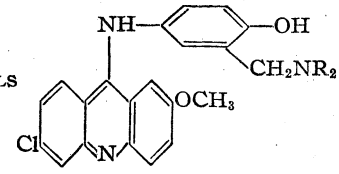
In the preparation of a group of acetamido-α-dialkylamino-*o*-cresols, several new alkyl, phenyl, and chloro acetamidophenols were obtained from the corresponding nitrophenols by catalytic reduction in the presence of acetic anhydride (Table I).

Although several of the intermediate 4-chloroquinolines were first prepared by rearrangement of the corresponding quinoline-N-oxides,[10] the ethoxymethylene malonic ester method of Price

(10) Magidson, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937); Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

TABLE VII

4-(6-CHLORO-2-METHOXY-9-ACRIDYLAMINO)-α-AMINO-*o*-CRESOLS

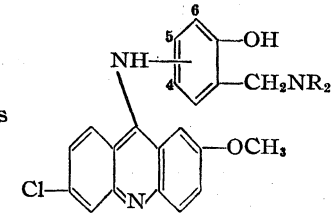


No.	SN	Q Equiv.	R_2	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	8,617	4	Diethyl[a]										
2	....	5	Ethyl (*n*-butyl)	F	36	252 dec.	$C_{27}H_{30}ClN_3O_2 \cdot 2HCl$[b,c]	60.39	60.10	6.01	6.11		
3	11,599	2.5	Di-*n*-butyl	A	69	246 dec.	$C_{29}H_{34}ClN_3O_2 \cdot 2HCl$[c,d]	61.64	61.84	6.42	6.68		
4	13,163	0.5	Diallyl	F	16	158	$C_{27}H_{26}N_2N_3Cl$[c,e]	70.49	70.11	5.69	5.99		
5	....	0.4	Di-*n*-hexyl	F	23	254 dec.	$C_{33}H_{42}O_2N_3Cl \cdot 2HCl$[c,f]	63.81	63.68	7.14	7.12		
6	....	<0.06	Di-*n*-octyl	F	20	285 dec.	$C_{37}H_{50}ClN_3O_2 \cdot 2HCl$[c,g]					6.21	6.30
7	11,536	0.6	1-Piperidyl	D	..	287 dec.	$C_{26}H_{26}ClN_3O_2 \cdot 2HCl$[c,h]	59.95	59.89	5.42	5.71		
8	....	1	Mono-*n*-hexyl	F	7	226 dec.	$C_{27}H_{30}O_2N_3Cl \cdot 2HCl \cdot H_2O$[f,i]	58.43	58.68	6.17	6.25		
9	11,233	0.2	Mono-2-hydroxyethyl	C	90	284 dec.	$C_{23}H_{22}ClN_3O_3 \cdot 2HCl \cdot H_2O$[c,h]	53.66	53.14	5.09	5.10		
10	11,589	<0.04	Benzoyl	D	95	294 dec.	$C_{28}H_{22}ClN_3O_2 \cdot HCl \cdot {}^1/_2H_2O$[c,j,k]	63.52	63.54	4.57	4.71		

[a] See compound 4, Table VI, for chemical data. [b] From methanol–isopropanol. [c] Orange crystals. [d] From ethanol–acetone. [e] From isopropanol. [f] From methanol–acetone. [g] From propylene glycol–acetone. [h] From methanol. [i] Red crystals. [j] From cellosolve–water. [k] Intermediate α-benzamido-4-nitro-*o*-cresol prepared by method of Einhorn.[8]

TABLE VIII

z-(6-CHLORO-2-METHOXY-9-ACRIDYLAMINO)-α-AMINO-*o*-CRESOLS



No.	SN	Q Equiv.	Substituents R_2	z	Other	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	9,614	1	Diethyl	5		C	50	237 dec.	$C_{25}H_{26}ClN_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$[a,b]	57.98	57.97	5.64	5.82
2	11,544	0.6	Diethyl	6	4-*t*-butyl	C	98	271 dec.	$C_{29}H_{34}N_3O_2Cl \cdot 2HCl$[a,c]	61.65	61.87	6.42	6.21
						D	53						
3	11,553	0.5	Diethyl	6	4-phenyl	C	84	274 dec.	$C_{31}H_{30}ClN_3O_2 \cdot 2HCl$[a,c]	63.64	63.74	5.52	5.79
4	11,550	2.0	Diethyl	6	4-diethylaminomethyl	F	73	257 dec.	$C_{30}H_{37}ClN_4O_2 \cdot 3HCl \cdot H_2O$[a,d]	55.56	55.87	6.53	6.53
5	11,234	3	Diethyl	4	6-Allyl	C	65	233 dec.	$C_{28}H_{30}O_2N_3Cl \cdot 2HCl$[f,e]	61.26	60.89	5.87	6.08
6	13,399	0.3	Diallyl	4	6-Allyl	F	12	188 dec.	$C_{30}H_{30}O_2N_3Cl \cdot 2HCl \cdot H_2O$[f,e]	61.92	62.11	5.72	5.67
7	12,701	2	1-Piperidyl	4	6-Allyl	F	44	164 dec.	$C_{29}H_{30}O_2N_3Cl$[f,e]	71.37	71.52	6.20	6.30

[a] Orange crystals. [b] From methanol. Calcd. volatile loss, 2.78. Found 2.77. [c] From methanol–acetone. [d] From methanol–ether. [e] Orange-red crystals. [f] From methanol.

and Roberts,[11] made available to us prior to its publication, was adopted for the preparation of all the 4-chloroquinolines originating in this Laboratory. Since the completion of these studies, many identical data have been reported by others, especially in the January, March and July, 1946, numbers of THIS JOURNAL. Table V therefore lists only a group of 4-chloroquinolines which have not yet appeared in the literature.

The preparation of various intermediates analogous to both SN 12,458 and I made possible the synthesis of many new antimalarial compounds related to SN 8,617. Tables VI to XIII present chemical data, show the development of the SN 8,617 lead, and afford a study of the relationship between chemical structure and pharmacological activity. Some of the most effective compounds appear in Table XII.[12]

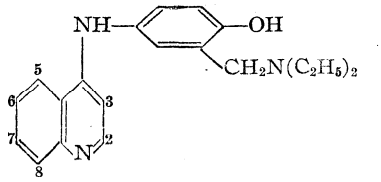
4-(7-Chloro-4-quinolylamino)-α-monoethylamino-*o*-cresol, Table XII, compound 3, (VI) could not be prepared by the usual procedures. It was finally obtained in very low yield by means of the Mannich reaction using 7-chloro-4-(4-hydroxyanilino)-quinoline (V), paraformaldehyde and monoethylamine. This application of the Mannich reaction employing heterocyclic and aromatic ami-

(11) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(12) Compound 25 (Camoquin) was found to be 25 times as active as quinine against *gallinaceum* malaria in chicks, while its monoisobutyl analog (compound 8) is 75 times as active—a considerable improvement over the simpler α-amino-*o*-cresols,[1] as well as over other 4-aminoquinolines heretofore reported [*cf.* tables of 4-aminoquinolines, ref. (2b), pp. 154–163].

TABLE IX

4-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIETHYLAMINO-*o*-CRESOLS



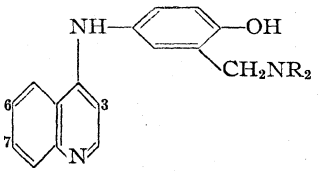
No.	SN	Q Equiv.	Substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	12,452	3	None	C	48	>300	$C_{20}H_{23}N_3O\cdot 2HCl$[a,b,c]	60.91	61.02	6.39	6.75		
2	11,563	0.2	6-Hydroxy	*d*	64	262 dec.	$C_{20}H_{23}N_3O_2\ 2HCl$[b,e]	58.54	58.14	6.14	6.19		
3	10,274	8	6-Methoxy	C	75	270 dec.	$C_{21}H_{25}N_3O_2\ 2HCl$[b,e,f]					9.90	9.80
4	11,554	7	7-Methoxy	C	43	210 dec.	$C_{21}H_{25}N_3O_2\ 2HCl\cdot{}^1/_2H_2O$[b,g,h]	58.20	58.20	6.51	6.43		
5	11,281	7	7-Ethoxy	C	44	136 dec.	$C_{22}H_{27}N_3O_2\ 2HCl\cdot 2H_2O$[b,g]	57.89	58.02	6.85	6.89		
6	11,634	0.5	7-*n*-Hexyloxy-	C	35	153	$C_{26}H_{35}N_3O_2$[i]	74.07	74.20	8.37	8.09		
7	11,594	0.8	8-Methoxy	C	50	241 dec.	$C_{21}H_{25}O_2N_3\cdot 2HCl\cdot 1{}^1/_2H_2O$[b,e,j]	55.87	55.87	6.69	6.62		
8	13,395	2.5	6,7-Dimethoxy	E	68	258 dec.	$C_{22}H_{27}N_3O_2\cdot 2HCl$[e,k,l]	58.15	57.93	6.43	6.49		
9	12,161	0.4	5-Chloro-8-methoxy	E	80	231 dec.	$C_{21}H_{24}ClN_3O_2\cdot 2HCl$[m,t]					9.16	8.94
10	11,986	<0.07	2-Chloro	C	30	248 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl$[b,e,n]					9.80	9.59
11	11,597	3.0	6-Chloro	C	60	220	$C_{20}H_{22}ON_3Cl\cdot 2HCl\cdot{}^1/_2H_2O$[b,e,p]	54.86	54.81	5.76	5.82		
12	10,751	25	7-Chloro[o]										
13	11,551		8-Chloro			212	$C_{20}H_{22}ClN_3O$[b,p,q]	67.50	67.17	6.23	6.50		
		0.5		C	79	253 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl\cdot{}^1/_2H_2O$[b,r]	54.90	55.25	5.76	5.91		
14	12,700	3	5,7-Dichloro	E	65	200 dec.	$C_{20}H_{21}Cl_2N_3O\cdot 2HCl$[s,t,u]					9.07	8.89
15	12,161	5	6,7-Dichloro	C	71.5	257 dec.	$C_{20}H_{21}Cl_2N_3O\cdot 2HCl$[b,s,v]	51.85	51.74	5.00	5.23		
16	11,596	0.25	5,8-Dichloro	C	60	235 dec.	$C_{20}H_{21}ON_3Cl_2\cdot 2HCl\cdot 1H_2O$[b,e,v]	49.91	49.84	5.23	5.31		
17	11,633	<0.3	6,7,8-Trichloro	C	40	277 dec.	$C_{20}H_{20}Cl_3N_3O\cdot 2HCl$[b,s]	48.27	48.30	4.46	4.74		
18	11,559		6-Methyl			172	$C_{21}H_{25}N_3O$[b,q]	75.20	74.80	7.45	7.41		
		4		C	56	238 dec.	$C_{21}H_{25}N_3O\cdot 2HCl$[b,w]	61.76	61.61	6.67	6.80		
19	12,699	9	7-Methyl	E	93	245 dec.	$C_{21}H_{25}N_3O\cdot 2HCl$[s,t,x]					10.29	10.14
20	11,601	0.7	8-Methyl	C	66	253 dec.	$C_{21}H_{25}N_3O\cdot 2HCl\cdot H_2O$[b,e]	59.15	58.85	6.85	6.64		
21	11,561	10	5,7-Dimethyl	C	67	242 dec.	$C_{22}H_{27}N_3O\cdot 2HCl$[b,s]	62.55	62.53	6.92	6.55		
22	11,560	0.6	5,8-Dimethyl	C	80	249 dec.	$C_{22}H_{27}N_3O\cdot 2HCl$[b,s]	62.55	62.80	6.92	6.14		
23	11,990	6	6,7-Dimethyl	C	49	215 dec.	$C_{22}H_{27}ON_3$[y,z,aa]	75.61	75.90	7.78	7.87		
24	11,558	0.6	6,8-Dimethyl	C	54	264 dec.	$C_{22}H_{27}ON_3\cdot 2HCl\cdot 1H_2O$[e,t]	59.86	59.73	7.08	7.27		
25	9,223	1.2	6,-Methoxy-2-methyl	C	45	278 dec.	$C_{22}H_{27}N_3O_2.2HCl$[t,ab]	59.47	59.30	6.88	6.81	9.25	9.18
26	11,632	0.6	8-Methoxy-5-methyl	C	90	210 dec.	$C_{22}H_{27}O_2N_3\cdot 2HCl$[b,s]	60.27	60.02	6.67	6.18		
27	11,985	0.3	5-Chloro-3-methyl	C	48	258 dec.	$C_{21}H_{24}ClN_3O\cdot 2HCl$[e,ac,ad]	56.96	56.94	5.92	6.21		
28	10,492	6	7-Chloro-3-methyl	C	64	260	$C_{21}H_{24}ClN_3O\cdot 2HCl$[b,e,ac]					9.49	9.59
29	11,631	0.4	3-Phenyl	C	31	155	$C_{26}H_{27}ON_3$[ac,ae]	78.56	78.31	6.85	6.68		
30	11,592	0.25	6-Methoxy-2-phenyl	C	61	198 dec.	$C_{27}H_{29}N_3O_2\cdot 2HCl\ 1{}^3/_4H_2O$[b,ac,af]					7.90	7.96
31	11,232	0.3	7-Chloro-2-phenyl	C	41	260 dec.	$C_{26}H_{26}ClN_3O\cdot 2HCl$[b,ac,ag]	61.85	61.74	5.59	5.67		
32	12,228	1	7-Chloro-3-phenyl	C	..	165	$C_{26}H_{26}ClN_3O$[b,e,ac]	72.31	72.94	6.07	6.38		
33	12,361	0.2	6-Anilino	C	63	196 dec.	$C_{26}H_{28}ON_4\cdot 2HCl\cdot H_2O$[e,ad]	62.02	61.80	6.40	6.26		
34	11,984	2.5	6-Dimethylamino	C	73	235 dec.	$C_{22}H_{28}ON_4\cdot 3HCl\cdot{}^1/_2H_2O$[b,e,ah]	54.72	54.73	6.68	6.64		
35	....	0.8	6-Nitro	C	63	210 dec.	$C_{20}H_{22}N_4O_3\cdot 2HCl\cdot 1{}^1/_2H_2O$[ai]					12.01	12.31

[a] Intermediate 4-chloroquinoline was identical with that prepared by Riegel, *et al.*, THIS JOURNAL, 68, 1264 (1946). [b] Yellow crystals. [c] From ethanol. [d] See Experimental part. [e] From methanol–acetone. [f] Same reference as footnote (*m*), Table VI, for preparation of 4-chloro-6-methoxyquinoline. [g] From water–alcohol. [h] 7-Methoxy-4-chloroquinoline melts at 83–85°; Lauer, *et al.*, THIS JOURNAL, 68, 1268 (1946), found 82–83°. [i] From methanol–ethanol. [j] 8-Methoxy-4-chloroquinoline melts at 83°; Lauer, *et al.*, *ibid.*, found 79–80°. [k] Light greenish tan color. [l] Intermediate 4-chloro-6,7-dimethoxyquinoline, independently prepared, was found to be identical with that of Riegel, *et al.*, *ibid.* [m] From ethanol–ethyl acetate. [n] The structure of this compound has not been definitely established. However, a formula has been assigned based on the fact that 4-chloroquinoline was found to condense much more readily than 2-chloroquinoline with aromatic amines. Intermediate, 4,7-dichloroquinoline prepared by the method of Brooker and Smith, THIS JOURNAL, 64, 1357 (1942). [o] For chemical data, see compound 9, Table VI. [p] Intermediate dichloroquinoline was independently prepared by the same procedure of Tarbell, THIS JOURNAL, 68, 1278 (1946). [q] From chloroform–ether. [r] From acetone. [s] From ethanol–acetone. [t] Greenish yellow crystals. [u] Intermediate 4,5,7-trichloroquinoline prepared by the general method of Price[11]; m. p. 108°. *Anal.* Calcd. for $C_9H_4Cl_3N$: C, 46.50; H, 1.73. Found: C, 46.90; H, 1.80. Surrey and Hammer, THIS JOURNAL, 68, 1244 (1946), employed a different procedure. [v] Surrey and Hammer, *ibid.*, also prepared the intermediate trichloroquinoline by a different procedure. [w] From acetone. [z] Intermediate 4-chloro-6-methylquinoline, b. p. 139–140 (10 mm.). *Anal.* Calcd. for $C_{10}H_8ClN$: C, 67.61; H, 4.54. Found: C, 67.23; H, 4.55. Breslow, *et al.*, THIS JOURNAL, 68, 1236 (1946), reported b. p. 140–142 (9 mm.). [y] Pale tan crystals. [z] From methanol. [aa] Independent preparation of intermediate 4-chloro-6,7-dimethylquinoline gave identical results of Price and Roberts.[11] [ab] From methanol–ether; analysis corresponds to the presence of a half

mole of methanol: Calcd. volatile loss, 3.53. Found: 3.30. [ac] Intermediate 4-chloroquinoline obtained through Dr. R. C. Elderfield. [ad] Bright orange crystals. [ae] From ligroin. [af] From water; calcd. volatile loss 5.93. Found: 5.71. [ag] From 20% ethanol. [ah] Intermediate 4-chloro-6-dimethylaminoquinoline hydrochloride obtained as a bright orange powder; m. p. 249° d. *Anal.* Calcd. for $C_{11}H_{11}ClN_2 \cdot HCl$: C, 54.37; H, 4.97. Found: C, 54.12; H, 4.75. Riegel, *et al., ibid.*, p. 1265, reported m. p. 225–230°. [ai] Intermediate 6-nitro-4-chloroquinoline prepared in low yield by the general method of Price and Roberts,[11] but see a better method for this compound by Baker, *et al.*, THIS JOURNAL, 68, 1267 (1946). Orange-red crystals. Calcd. volatile loss, 6.01. Found: 5.79. From methanol–ether.

TABLE X

4-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIALKYLAMINO-*o*-CRESOLS

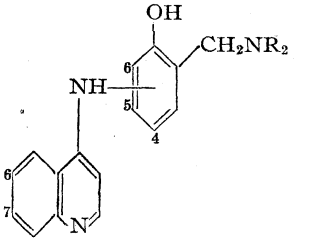


No.	SN	Q Equiv.	R_2	Substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	10,274	8	Diethyl	6-Methoxy[a]								
2	....	9	Di-*n*-butyl	6-Methoxy	C	10	193 dec.	$C_{25}H_{33}O_2N_3 \cdot 2HCl \cdot 1.25H_2O$[b,c]	59.69	59.90	7.51	7.64
3	12,038	8	1-Piperidyl	6-Methoxy	C	80	270 dec.	$C_{22}H_{25}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$[d]	59.32	59.15	6.33	6.25
4	11,989	1	4-Morpholinyl	6-Methoxy	C	57	265 dec.	$C_{21}H_{23}N_3O_3 \cdot 2HCl$[e,f]	57.54	57.48	5.75	5.84
5	13,395	2.5	Diethyl	6,7-Dimethoxy[g]								
6	13,413	4	1-Piperidyl	6,7-Dimethoxy	E	40	230 dec.	$C_{23}H_{27}N_3O_3 \cdot 2HCl$[b,h]				
7	10,492	6	Diethyl	7-Chloro-3-methyl[i]								
8	....	10	Di-*n*-butyl	7-Chloro-3-methyl	C	43	177 dec.	$C_{25}H_{32}ON_3Cl \cdot 2HCl \cdot 1.5H_2O$[b,j]	57.08	57.33	7.09	6.77
9	12,360	2	1-Piperidyl	7-Chloro-3-methyl	C	47	270 dec.	$C_{22}H_{24}ClN_3O \cdot 2HCl$[b,k]	58.09	58.20	5.76	5.67
10	12,362	0.15	4-Morpholinyl	7-Chloro-3-methyl	C	33	242 dec.	$C_{21}H_{22}ClN_3O_2 \cdot 2HCl$[f,k]	55.21	54.92	5.30	5.60
11	11,559	4	Diethyl	6-Methyl[l]								
12	12,456	2.5	1-Piperidyl	6-Methyl	E	41	240 dec.	$C_{22}H_{25}N_3O \cdot 2HCl$[m]				
13	12,457	0.8	4-Morpholinyl	6-Methyl	C	50	239	$C_{21}H_{23}N_3O_2$[n]				

[a] See compound 3, Table IX, for chemical data. [b] From methanol–acetone. [c] Pale greenish-yellow crystals. [d] Light green crystals from ethanol–ethyl acetate. See reference 12 for intermediate 4-acetamido-α-piperidyl-*o*-cresol. [e] Yellowish tan crystals. [f] From methanol–ethyl acetate. [g] See compound 8, Table IX, for chemical data. [h] Off-white crystals. *Anal.* for N: Calcd. 9.01. Found 9.03. [i] See compound 28, Table IX, for chemical data. [j] Yellow crystals. [k] Dark orange crystals. [l] See compound 18, Table IX, for chemical data. [m] Off-white crystals from ethanol. *Anal.* for N: Calcd. 10.00. Found: 10.22. [n] From ethanol. *Anal.* Calcd.: N, 12.02. Found: N, 12.14.

TABLE XI

z-(SUBSTITUTED-4-QUINOLYLAMINO)-α-DIALKYLAMINO-*o*-CRESOLS

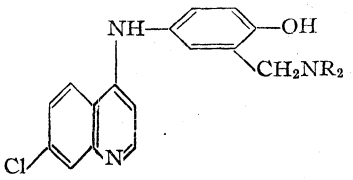


No.	SN	Q Equiv.	R_2	Cresol substituents	z	Quinoline substituents	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	13,730	9	Diethyl	None	5	7-Chloro	C	..	173	$C_{20}H_{22}ClN_3O$[a,b]	67.49	67.80	6.23	6.22
2	....	5	Diethyl	4-Diethylaminomethyl	6	7-Chloro	F	..	145	$C_{25}H_{33}ClN_4O \cdot 1\frac{1}{2}H_2O$[c,d]	64.16	64.06	7.75	7.59
3	12,885	0.5	Diethyl	4-Chloro	6	6-Methoxy	C	50	205 dec.	$C_{21}H_{24}ClN_3O_2 \cdot 2HCl$[c,e]	54.97	54.55	5.71	5.88
4	13,729	12	Diethyl	6-Chloro	4	7-Chloro	F	..	225 dec.	$C_{20}H_{21}Cl_2N_3O$[a,f]	61.54	61.50	5.42	5.38
5	....	[g]	Diethyl	6-Phenyl	4	7-Chloro	D	25	235 dec.	$C_{26}H_{26}ClN_3O \cdot \frac{1}{2}H_2O$[c,e]	70.81	70.50	6.17	5.95
6	12,039	7	Diethyl	6-Allyl	4	6-Methoxy	C	33	161	$C_{24}H_{29}O_2N_3$[h]	73.63	73.11	7.47	7.33
7	11,991	10	Diethyl	6-Allyl	4	7-Chloro	C	44	148	$C_{23}H_{26}ON_3Cl$[a,i]	69.77	69.51	6.62	6.82
8	12,697	4	1-Piperidyl	6-Allyl	4	7-Chloro	F	32	190	$C_{24}H_{26}ON_3Cl$[a,j]	70.65	70.93	6.42	6.59
9	13,394	0.7	Diallyl	6-Allyl	4	7-Chloro	F	25	131	$C_{25}H_{26}ON_3Cl$[a,k]	71.49	71.77	6.24	6.23

[a] Yellow crystals. [b] From methanol–benzene. [c] Light tan crystals. [d] From acetone–ligroin. [e] From ethanol. [f] From dioxane. [g] Sample inadequate for test. [h] Pale greenish-yellow crystals from dilute methanol. [i] From ligroin. [j] From dilute ethanol. [k] From isopropanol–ligroin.

TABLE XII

4-(7-CHLORO-4-QUINOLYLAMINO)-α-AMINO-*o*-CRESOLS

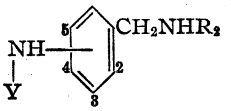


No.	SN	Q Equiv.	R_2	Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	1,603	6	None	E	80	325 dec.	$C_{16}H_{14}ClN_3O\ 2HCl\cdot 0.5H_2O$[a,b,c]	50.35	50.42	4.88	4.49		
2	11,557	0.15	Benzoyl	D	80	289 dec.	$C_{23}H_{18}ClN_3O_2\ HCl$[a,b,d]	62.60	62.82	4.34	4.41		
			α-Monoalkyl										
3	....	40	Ethyl	f		280 dec.	$C_{18}H_{18}ClN_3O\ 2HCl$[a,e]	53.95	53.93	5.03	5.42		
4	....	30	*n*-Propyl	F	24	244 dec.	$C_{19}H_{20}ClN_3O\ 2HCl.0.5H_2O$[a,g]	53.85	54.10	5.47	5.52		
5	....	40	Isopropyl	D	50	287 dec.	$C_{19}H_{20}ClN_3O'2HCl$[a,h]	55.02	54.84	5.35	5.36		
6	....	30	*n*-Butyl	F	6	254 dec.	$C_{20}H_{22}ON_3Cl\cdot 2HCl$[a,h]	56.02	55.68	5.64	5.58		
7	....	50	2-Butyl	C	3	252 dec.	$C_{20}H_{22}ON_3Cl\cdot 2HCl\cdot H_2O$[a,i]	53.76	53.75	5.86	5.57		
8	....	75	Isobutyl	C	33	256 dec.	$C_{20}H_{22}ON_3Cl\cdot 2HCl$[a,i]	56.02	56.03	5.64	5.76		
				D	65								
9	....	40	*t*-Butyl	D	36	285 dec.	$C_{20}H_{22}ClN_3O\cdot 2HCl$[a,h]	56.02	56.17	5.63	5.80		
10	....	50	*n*-Amyl	C	15	266 dec.	$C_{21}H_{24}ON_3Cl\cdot 2HCl$[a,j]	56.95	56.90	5.92	5.50		
11	....	40	2-Amyl	C	22	231 dec.	$C_{21}H_{24}ClN_3O\cdot 2HCl$[a,i]	56.96	57.11	5.92	5.99		
12	....	50	Isoamyl	F	20	279 dec.	$C_{21}H_{24}ON_3Cl\cdot 2CHl$[a,h]	56.95	57.41	5.92	6.31		
13	....	25	*n*-Hexyl	F	56	280 dec.	$C_{22}H_{26}ClN_3O\cdot 2HCl$[a,k]	57.84	57.81	6.18	6.18		
14	....	50	2-Ethylbutyl	F	15	263 dec.	$C_{22}H_{26}ClN_3O\cdot 2HCl$[a,i]	57.84	57.73	6.18	6.04		
15	....	15	*n*-Heptyl	F	29	278 dec.	$C_{23}H_{28}ClN_3O\cdot 2HCl$[a,e]					8.92	8.64
16	....	2.5	*n*-Octyl	F	15	150	$C_{24}H_{30}ON_3Cl$[l]	69.96	70.05	7.34	7.61		
17	....	20	Allyl	F	3	257 dec.	$C_{19}H_{18}ON_3Cl\cdot 2HCl$[a,i]	55.28	55.12	4.88	5.05		
18	....		1-Methallyl	F	..	95	$C_{20}H_{20}ClN_3O\cdot 2HCl\cdot 1.75H_2O$[a,m]	52.41	52.68	5.63	6.03		
19	....	30	Cyclohexyl	F	30	252 dec.	$C_{23}H_{24}ClN_3O\cdot 2HCl\cdot 0.25H_2O$[a,e]	57.52	57.52	5.82	5.98		
20	....	3	2-Hydroxyethyl	C	15	182 dec.	$C_{18}H_{18}ClN_3O_2\cdot 2HCl\cdot H_2O$[a,n]	49.72	50.18	5.10	5.50		
21	....	25	2-Methoxyethyl	F	..	271 dec.	$C_{19}H_{20}ClN_3O_2\cdot 2HCl$[a,h]					9.76	9.79
22	....	16	Benzyl	F	..	270 dec.	$C_{23}H_{20}ClN_3O\cdot 2HCl$[a,i]					9.09	9.11
23	....	25	1-Methyl-2-phenylethyl	F	31	243	$C_{25}H_{24}ClN_3O\cdot 2HCl\cdot 0.25H_2O$[a,h]	60.61	60.66	5.65	5.67		
			α-Disubstituted										
24	....	6	Dimethyl	C	85	290 dec.	$C_{18}H_{18}ClN_3O_2\cdot 2HCl$[a,e,o]	53.95	53.83	5.03	5.18		
25	10,751	25	Diethyl[p]										
26	....	30	Ethyl-(*n*-butyl)	F	65	240 dec.	$C_{22}H_{26}ClN_3O\cdot 2HCl$[a,h]	57.84	57.70	6.18	5.81		
27	13,835	25	Di-*n*-propyl	F	11	181	$C_{23}H_{26}ON_3Cl$[a,q]	68.82	69.20	6.83	6.76		
28	14,105	35	Di-*n*-butyl	C	20	164	$C_{24}H_{30}OH_3Cl$[a,r]	69.96	69.81	7.34	7.50		
29	....	..	Diisobutyl	D	38	166	$C_{24}H_{29}ClN_3O\cdot 0.5H_2O$[s]	68.47	68.86	7.42	7.88		
30	....	..	Diisoamyl	D	..	135	$C_{26}H_{34}ClN_3O\cdot 0.5H_2O$[t]	69.52	69.95	7.85	8.17		
31	....	0.5	Di-*n*-hexyl	F	40	220	$C_{28}H_{38}ON_3Cl\cdot 2HCl$[a,i]	62.16	62.00	7.45	7.78		
32	....	1	Di-*n*-heptyl	F	52	203	$C_{30}H_{42}ON_3Cl\cdot 2HCl$[a,h]	63.32	63.26	7.79	8.04		
33	....	0.2	Di-*n*-octyl	F	46	192	$C_{32}H_{46}ON_3Cl\cdot 2HCl$[a,h]	64.36	64.29	8.10	7.85		
34	....	3	Di-2-ethylhexyl	F	1	154	$C_{32}H_{46}ON_3Cl\cdot 2HCl\cdot H_2O$[a,h]	62.48	62.10	8.19	8.05		
35	11,636	25	1-Piperidyl	C	77.5	302 dec.	$C_{21}H_{22}ClN_3O\cdot 2HCl\cdot 2.5H_2O$[a,n,u]						
36	12,357	20	2-Methyl-1-piperidyl	C	66	288 dec.	$C_{22}H_{24}ClN_3O\cdot 2HCl$[a,h]	58.09	58.22	5.76	5.81		
37	11,987	4	4-Morpholinyl	C	60	292 dec.	$C_{20}H_{20}ClN_4O_2\cdot 2HCl$[a,v]	54.25	54.44	5.01	5.33		
				E	65								
38	12,363	3	Methyl-(2-hydroxyethyl)	C	63	250 dec.	$C_{19}H_{20}ClN_3O_2\cdot 2HCl$[a,e]	52.97	52.96	5.15	5.38		
39	14,824	12	*n*-Butyl-(2-hydroxyethyl)	F	22	149	$C_{22}H_{26}O_2N_3Cl$[r]	66.07	65.94	6.55	6.94		
40	....	0.6	Di-2-hydroxyethyl	F	25	193	$C_{20}H_{23}ClN_3O_3$[w]	62.00	61.90	5.73	6.09		
41	....	2.5	Dibenzyl	C	74	235 dec.	$C_{30}H_{26}ClN_3O\cdot 2HCl$[k,x]	65.16	64.92	5.10	5.40		
42	....	0.07	Methyl-(phenyl)	F	39	140	$C_{24}H_{20}ClN_3O\cdot H_2O$[a,t]					10.77	10.72
43	....	< 0.05	Ethyl-(phenyl)	F	54	131 dec.	$C_{24}H_{22}ClN_3O$[a,t]					10.40	10.19

[a] Yellow crystals. [b] From methanol. [c] Intermediate α,4-diamino-*o*-cresol prepared by the method of Einhorn.[8] [d] See ref. (8) for intermediate. [e] From ethanol. [f] See Experimental part. [g] From ethanol–isopropanol. [h] From methanol–acetone. [i] From ethanol–acetone. [j] From dilute hydrochloric acid. [k] From methanol–ethanol. [l] From alcohol–ether. [m] From isopropanol. Calcd. for volatile loss, 6.87. Found, 7.00. [n] From methanol–ethyl acetate. [o] For intermediate 4-acetamido-α-dimethylamino-*o*-cresol, see ref. (15). [p] See compound 9, Table VI. [q] From ethyl acetate [r] From ethyl acetate–petroleum ether. [s] From dilute methanol. [t] From dilute ethanol. [u] Calcd. volatile loss, 9.27. Found: 8.95. Calcd. ionic chlorine, 14.60. Found, 14.58. [v] From methanol–ethyl acetate. [w] Pale yellowish green crystals from dilute isopropanol. [x] Ivory crystals.

TABLE XIII

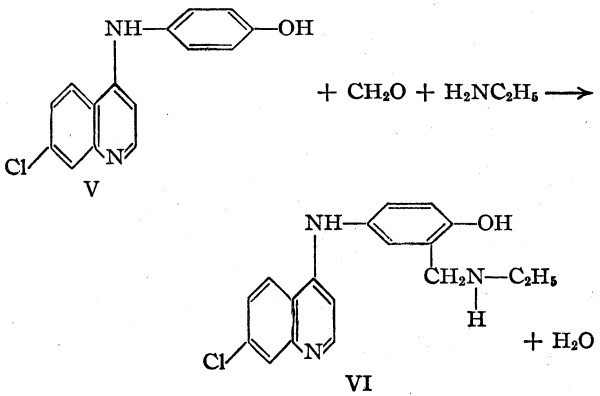
z-(HETEROCYCLIC-AMINO)-BENZYLAMINES (PROCEDURE D)



No.	SN	Q Equiv.	Substituents R₂	2	z	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
						Y = 7-Chloro-4-quinolyl						
1	11,590	1	Diethyl		3	85	128 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl \cdot 2H_2O$[a,b]	53.52	53.26	6.29	6.36
2	12,455	4	Diethyl		4	..	261 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl$[c,d]	58.19	58.39	5.86	6.02
3	....	4	Di-*n*-propyl		4	60	255 dec.	$C_{22}H_{26}ClN_3 \cdot 2HCl$[c,d]	59.94	59.90	6.40	6.31
4	....	10	Monoisopropyl		4	23	303 dec.	$C_{19}H_{20}ClN_3 \cdot 2HCl$[d,e]	54.75	55.05	5.80	5.53
5	....	..	Monoisobutyl		4	76	288 dec.	$C_{20}H_{22}ClN_3 \cdot 2HCl \cdot H_2O$[d,e]	55.76	55.79	6.08	6.40
6	....	25	Diethyl	Methoxy	5	64	203	$C_{21}H_{24}ClN_3O$[a]	68.19	68.03	6.54	6.64
7	....	17	Monoisobutyl	Methoxy	5	76	194 dec.	$C_{21}H_{24}ClN_3O \cdot 2HCl \cdot 1/4H_2O$[d,f]	55.15	55.27	5.84	6.11
8	....	15	Mono-*n*-amyl	Methoxy	5	42	288 dec.	$C_{22}H_{26}ClN_3O \cdot 2HCl$[d,e]	57.84	57.92	6.18	6.44
9	....	8	Diethyl	Ethoxy	5	73	247	$C_{22}H_{26}ClN_3O \cdot 2HCl \cdot 2H_2O$[a,d]	53.61	53.43	6.55	6.54
						Y = 6-Chloro-2-methoxy-9-acridyl						
10	10,984	0.5	Diethyl		3	55	278	$C_{25}H_{26}ClN_3O \cdot 2HCl \cdot 3/4H_2O$[e,g]	59.29	59.25	5.87	5.98
11	10,028	0.4	Diethyl		4	92	260 dec.	$C_{25}H_{26}ClN_3O \cdot 2HCl \cdot 1/2H_2O$[c,h]	59.82	60.06	5.82	6.28
12	....	3	Diethyl	Methoxy	5	67	212 dec.	$C_{26}H_{28}ClN_3O_2 \cdot 2HCl \cdot 1/2H_2O$[c,g]	58.72	58.75	5.88	6.01

[a] From isopropanol. [b] Calcd. volatile loss, 8.03. Found: 8.85. [c] From methanol. [d] Yellow crystals. [e] From methanol–isopropanol. [f] From ethanol–isopropanol. [g] Orange crystals. [h] Red crystals.

nophenols is being continued with the prospect of obtaining better yields.



V

VI

4-(6-Hydroxy-4-quinolylamino)-α-diethylamino-*o*-cresol (Table IX, compound 2) was prepared from the corresponding 6-methoxy analog (compound 3) by demethylation with hydrobromic acid.

Acknowledgments.—The authors are greatly indebted to Drs. R. J. Porter of the University of Michigan, A. L. Tatum of the University of Wisconsin and E. K. Marshall of the Johns Hopkins University for their pharmacological study of the compounds presented in this publication.[13] For the sake of simplicity, only the quinine equivalents of Dr. Porter have been reproduced. Dr. Robert C. Elderfield, who represented the O.S.R.D., kindly supplied several 4-chloroquinolines, 9-chloroacridines and dialkylamines of high molecular weight. We are grateful to Dr. C. K. Banks, Messrs. H. J. Nicholas, D. F. Walker, L. M. Montibeller, M. H. Darwish, M. L. Black and H. A. DeWald, of this Laboratory, who contributed several of the compounds reported, and to Dr. L. A. Sweet, Director of Chemical Research, for his keen interest during the course of the studies. Mr. A. W. Spang and Miss Patricia Keller supplied the microanalytical data.

(13) The facilities for testing the compounds described were provided by the Office of Scientific Research and Development through the Committee on Medical Research and by Dr. A. L. Tatum of the Department of Pharmacology in the University of Wisconsin.

Experimental

Acetamidophenols (Table I).—One-tenth of a mole each of the nitrophenol and acetic anhydride were dissolved in 50 cc. of acetic acid. After the addition of 0.2 g. of platinum oxide catalyst, the mixture was shaken in the customary manner under a pressure of about three atmospheres of hydrogen gas until three molecular equivalents had been absorbed. The catalyst was removed by filtration and the acetic acid removed by distillation under reduced pressure. Usually the crude acetamidophenol separated as a white or light gray crystalline solid pure enough for further syntheses.

2-Allyl-4-acetamidophenol.[14]—A solution of 96 g. (1.1 moles) of the allyl ether of 4-acetamidophenol in 70 g. of diethylaniline was heated at boiling temperature for forty minutes. The solution was cooled and diluted with chloroform prior to thorough extraction with 10% sodium hydroxide solution. Enough ether was added to form a distinct upper layer. The combined alkaline extracts were washed twice with ether, and then treated with a slight excess of acetic acid. Extraction of the product with ether, drying and evaporation of the extracts left an oil which was crystallized from a benzene and petroleum ether mixture; m. p. 91–93°. Recrystallization from the same mixture with charcoal treatment yielded 80 g. (83%) of pure product; m. p. 93–94°.

Acetamido-α-alkylamino-*o*-cresols[15] (Table II).—A mixture of equivalent amounts of the acetamidophenol, formaldehyde and aliphatic amine, suspended in about 250 cc. of alcohol per mole of the phenol, was heated in a steam-bath for one to three hours. Upon cooling a crystalline mass usually formed readily, and the product was washed with acetone, alcohol or dilute alcohol. After drying, the product was ordinarily white and of high enough purity to be used in further syntheses.

In certain cases when a crystalline product could not

(14) Claisen, *Ann.*, **418**, 97 (1919).

(15) German Patent 92,309; *Frdl.*, **4**, 103 (1897).

be readily obtained by the foregoing procedure, the volatile materials were removed under reduced pressure and the residue taken into ether and treated with excess alcoholic hydrogen chloride. The monohydrochloride of the desired acetamido-α-alkylamino-*o*-cresol precipitated as an oil, but after treatment with acetone or ether, it crystallized as a white solid.

4-Amino-α-diethylamino-*o*-cresol Dihydrochloride (SN 12,458).—A mixture of 500 g. (2.12 mole) of 4-acetamido-α-diethylamino-*o*-cresol and one liter of 20% hydrochloric acid was heated at refluxing temperature for an hour. The solution was evaporated under reduced pressure to a thick sirup. A liter of benzene was stirred well into the sirup, and the evaporation repeated. Once again the process was repeated using a liter of denatured absolute alcohol. Finally, the sirup was dissolved in two liters of alcohol. The desired salt was then precipitated by the addition of a liter and a half of ether. A total of 541 g. (96% yield) of off-white product was obtained; m. p. 218–220° (dec.).

For analysis a sample was recrystallized from a mixture of alcohol and ethyl acetate; the melting point of the white product did not change.

Anal. Calcd. for $C_{11}H_{18}N_2O\cdot 2HCl$: C, 49.44; H, 7.54. Found: C, 49.70; H, 7.60.

4-Amino-α-1-piperidyl-*o*-cresol Dihydrochloride.—In the same manner, this analog was obtained in a yield of 91% from 4-acetamido-α-1-piperidyl-*o*-cresol[15]; m. p. 153–155° (dec.). Recrystallized from alcohol for analysis, there was no change in the melting point.

Anal. Calcd. for $C_{12}H_{18}N_2O\cdot 2HCl\cdot H_2O$: C, 48.49; H, 7.46; N, 9.43. Found: C, 48.63; H, 7.43; N, 9.10.

4-Amino-α-4-morpholinyl-*o*-cresol Dihydrochloride.—Similarly this compound was obtained in a yield of 45% from 4-acetamido-α-4-morpholinyl-*o*-cresol; m. p. 259–260° (dec.).

Anal. Calcd. for $C_{11}H_{16}N_2O_2\cdot 2HCl$: N, 9.97. Found: N, 9.93.

α-Alkylamino-4-nitro-*o*-cresols (Table III).—The two synthetic methods used in obtaining these compounds are described in the following procedures.

Procedure A.—One-tenth of a molecular equivalent each of the nitrophenol, paraformaldehyde and aliphatic amine were dissolved in 25 cc. of alcohol. The solution was heated in a steam-bath for at least two hours or until the alcohol had evaporated. The residue was treated with an excess of dilute hydrochloric acid to precipitate an insoluble white hydrochloride.

The yellow crystalline free base could be obtained by trituration of the hydrochloride with ammonia.

Procedure B.—A mixture of one-tenth of a mole of α-chloro-4-nitro-*o*-cresol[7] and two-tenths of a mole of aliphatic amine in 150 cc. of absolute ethanol was heated at refluxing temperature for three hours. The volatile materials were removed by distillation under reduced pressure, and the residue was washed with water for the removal of recovered aliphatic amine hydrochloride. The washed residue was dissolved in acetone and the solution dried over potassium carbonate. An equal volume of ether was added, and an excess of alcoholic hydrogen chloride precipitated the desired product as a white crystalline hydrochloride.

2-Ethoxy-5-nitrobenzyl Chloride.—A mixture of 33.4 g. (0.2 mole) of 4-nitrophenetole, 19.8 cc. (0.26 mole) of 37% formalin, and 16.5 g. of zinc chloride was stirred well at 95 to 100° while a rapid stream of hydrogen chloride gas was allowed to pass through it. After five hours, the mixture was allowed to cool overnight. The temperature was raised to 90°, and 35 cc. of water was added. The mixture was cooled, while stirring in an ice-bath, to precipitate the product in small lumps. The solid was collected on a filter and washed with water. A yield of 32.4 g. (75%) of white material was obtained; m. p. 72–75°. A sample was recrystallized from methanol for analysis, with no change in melting point.

Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67. Found: C, 50.54; H, 4.84.

Nitrobenzylamines (Table IV).—The synthetic method is essentially the same as that of Procedure B, Table III. However, benzene was found more desirable here than alcohol as a solvent since the nitrobenzyl chlorides and the 2-alkoxy-5-nitrobenzyl chlorides, in contrast with α-chloro-4-nitro-*o*-cresol, dissolved quite readily in it. Furthermore, the excess alkylamine hydrochlorides were removed almost quantitatively by their insolubility in benzene, giving an indication of the expected yield of crude product.

In practice, the reaction mixture was cooled and the separated alkylamine salt collected. The filtrate was evaporated under reduced pressure, and the residue was dissolved in ether. After thorough washing of the ether solution with water and finally with saturated salt solution, drying was effected over potassium carbonate. The desired product could be obtained as the hydrochloride by the addition of alcoholic hydrogen chloride to the filtered solution.

4-Chloroquinolines (Table V).—The method of Price and Roberts[11] was employed. Ethoxymethylene malonic ester was condensed with the appropriate aromatic amine by heating them in diphenyl oxide. Ring closure to the 3-carbethoxy-4-hydroxyquinoline was effected in the same medium. The corresponding acid was obtained by alkaline hydrolysis and decarboxylated by heating in diphenyl oxide. The final step was accomplished by treatment of the 4-hydroxyquinoline with phosphorus oxychloride.

Heterocyclic-amino-α-amino-*o*-cresols (Tables VI to XIII, inclusive).—The preparative methods for these compounds, together with the heterocyclic-amino-benzylamines, are described in the following procedures.

Procedure C.—For each mole of acetamido-α-alkylamino-*o*-cresol (Table II), 500 cc. of 20% hydrochloric acid was added, and the mixture was heated at refluxing temperature for an hour. The solution was cooled and treated with concd. sodium hydroxide solution until just acid to congo red. An equivalent amount of chloroheterocyclic was added, and the resulting mixture was then heated in a steam-bath for about two hours. In many cases, a crystalline hydrochloride formed after cooling, and the product was purified by recrystallization. At other times, the reaction mixture was made basic with ammonia or alkali solution and the free base either crystallized or it was extracted with chloroform. In the latter case, the extract was washed with water and dried over potassium carbonate. The filtered solution was then treated with excess alcoholic hydrogen chloride and diluted with ether or acetone for the precipitation of the desired salt. The product was then recrystallized from the solvent indicated in the table.

Procedure D.—The α-alkylamino-4-nitro-*o*-cresol, base or hydrochloride, (Table III) or the nitrobenzylamine (Table IV) was suspended in absolute alcohol and reduced catalytically using platinum oxide catalyst. The solution was treated with a slight excess of alcoholic hydrogen chloride and filtered to remove the catalyst. An equivalent amount of chloroheterocyclic was added to the filtrate, and the directions in Procedure C were followed thereafter.

Procedure E.—In a manner similar to Procedure D, the crystalline 4-amino-α-substituted-amino-*o*-cresol dihydrochloride was simply heated with the desired chloroheterocycle in water or alcohol.

Procedure F.—This method is the same as Procedure C, except that the intermediate acetamido-α-alkylamino-*o*-cresol was not isolated as a pure compound. After the Mannich reaction had been carried out, the volatile materials were removed under reduced pressure. The crude residue was treated thenceforth as the crystalline intermediate in Procedure C. Yields are based on the amount of acetamidophenol used. A by-product of this reaction is the usually relatively insoluble 4-hydroxyanilinoheterocycle; when 4,7-dichloroquinoline is employed, the by-product has been shown to be 7-chloro-4-(4-hydroxyanilino)-quinoline.

7-Chloro-4-(4-hydroxyanilino)-quinoline Monohydrochloride.—To a solution of 72.8 g. (0.5 mole) of 4-amino-

phenol hydrochloride in 500 cc. of water, 99 g. (0.5 mole) of 4,7-dichloroquinoline[16] was added. The mixture was heated in a steam-bath for two hours. After standing for two days, the yellow product was collected on a filter, washed with water and dried at 110°; yield 145 g. (94%); m. p. over 320°. A small sample was recrystallized from methanol for analysis.[17]

Anal. Calcd. for $C_{15}H_{11}ClN_2O \cdot HCl$: C, 58.64; H, 3.94. Found: C, 59.17; H, 4.11.

6-Chloro-9-(4-hydroxyanilino)-2-methoxyacridine.—This compound was obtained as the orange monohydrochloride by the foregoing procedure in 98% yield; m. p. over 300°. Trituration of a small sample with excess ammonia gave the free base. Recrystallized from dioxane, it melted at 266° (dec.).

Anal. Calcd. for $C_{20}H_{15}ClN_2O_2 \cdot H_2O$: C, 65.13; H, 4.65. Found: C, 65.54; H, 4.62.

4-(7-Chloro-4-quinolylamino)-α-monoethylamino-*o*-cresol Dihydrochloride (Table XII, Compound 3).—A mixture of 30.7 g. (0.1 mole) of 7-chloro-4-(4-hydroxyanilino)-quinoline monohydrochloride, 6.3 g. (0.2 mole) of 95% paraformaldehyde, 27.2 cc. (0.2 mole) of alcoholic ethylamine, and 125 cc. of alcohol was heated at refluxing temperature for sixteen hours. Upon cooling, 9 g. of starting material was recovered unchanged. The filtrate was evaporated to dryness and the residue triturated with acetone to yield a solid which was collected on a filter. Treatment of this solid with 100 cc. of warm water left a total of 23.2 g. of unchanged starting material. The aqueous filtrate was made basic with ammonia, and the precipitated free base was extracted with chloroform. After being washed with water, the extract was dried over potassium carbonate. The filtered solution was evaporated to dryness, and the residue taken up in acetone. The addition of excess alcoholic hydrogen chloride precipitated a crude yellow salt. Recrystallized first from alcohol and then from alcohol–methanol, only 1.5 g. (4% yield) of the desired product was obtained; m. p. 280° (dec.).

4-(6-Hydroxy-4-quinolylamino)-α-diethylamino-*o*-cresol Dihydrochloride (Table IX, Compound 2).—A mixture of 10 g. of 4-(6-methoxy-4-quinolylamino)-α-diethylamino-*o*-cresol dihydrochloride (Table IX, compound 3) and 100 cc. of 48% hydrobromic acid was heated at boiling temperature for two hours. The mixture was made basic with ammonia, precipitating a yellow solid base. This was collected on a filter, washed with water, converted to the dihydrochloride by treatment with alcoholic hydrogen chloride.

(16) Obtained through Dr. R. C. Elderfield from the University of Illinois.

(17) Microanalysis by Arlington Laboratories.

Summary

A group of 122 heterocyclic-amino α-amino-*o*-cresols and a related group of 12 heterocyclic-amino benzylamines have been synthesized with the object of finding the most effective antimalarial compounds in the general class. All these compounds are new. For the purpose of studying the relationship of chemical structure to antimalarial effectiveness, they have been classified in seven tables. Preparation of the intermediate acetamidophenols, acetamido-α-alkylamino-*o*-cresols, α-alkylamino-4-nitro-*o*-cresols, nitrobenzylamines, and 4-chloroquinolines is also described.

This general class includes the most active 4-aminoquinolines heretofore reported in trophozoite-induced *P. gallinaceum* infection in the chick. Recent clinical reports on one member of the series (Camoquin) are promising.

DETROIT 32, MICHIGAN RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

A New Synthesis of Cinnoline Derivatives: Heterocyclic Steroid Analogs

BY EDMUND C. KORNFELD

In connection with another synthetic problem in progress in these laboratories *m*-hydroxyphenylacetic acid (I) was coupled in alkaline solution with diazotized *p*-nitroaniline (II) to form the azo dye (III) in the normal fashion. It was planned to carry out reactions on the carboxyl group of this product, and in order to effect these changes it was necessary to protect the free hydroxyl function. The azo compound was, therefore, subjected to the action of acetic anhydride in the presence of a trace of sulfuric acid as catalyst, and from the resulting reaction mixture was isolated in good yield a non-acidic, yellow, crystalline product. The analyses indicated that one acetyl group had been introduced, but they showed also that one molecule of water had been eliminated under the acetylating conditions. From the properties and reactions of the product it was evident that cyclization to a cinnoline derivative (V) had taken place. The steps in the process involved first a cyclization of the azo compound in its tautomeric form (IIIa) to 2-*p*-nitrophenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (IV) and then acetylation of the enol form of IV to yield 2-*p*-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (V).

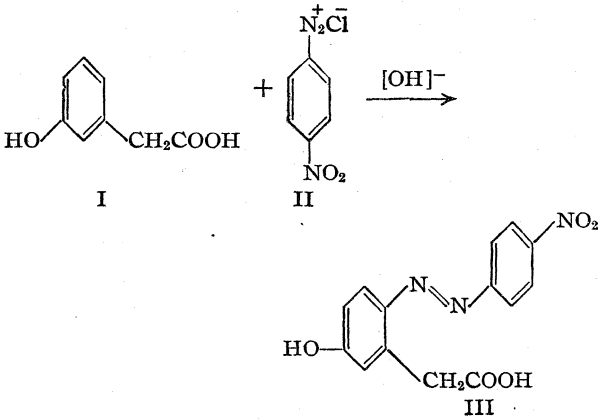
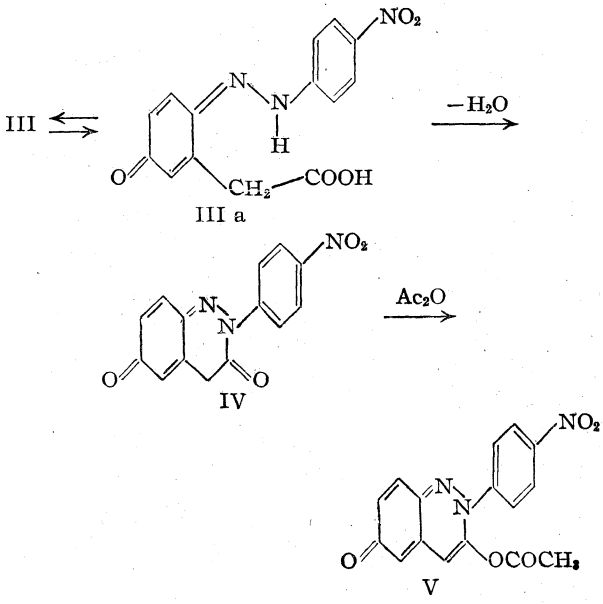


TABLE I

2-ARYL-3-ACETOXY-6-KETO-2,6-DIHYDROCINNOLINES

Aryl =	Yield, %[a]	M. p., °C.	Solvent[b]	Formula	% Composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
-phenyl	72	216–218	A	$C_{16}H_{12}N_2O_3$	68.56	68.30	4.32	4.40
-4-bromophenyl	71	226–228	B	$C_{16}H_{11}BrN_2O_3$[c]	53.50	53.41	3.09	2.98
-4-nitrophenyl	70	239–241	A	$C_{16}H_{11}N_3O_5$[d]	59.08	59.08	3.41	4.19
-4-carboxyphenyl	90	>290	C	$C_{17}H_{12}N_2O_5$	62.96	63.22	3.73	4.24
-4-acetaminophenyl	81	260–265 (dec.)	D	$C_{18}H_{15}N_3O_4$	64.09	64.00	4.48	4.79
-3-pyridyl	67	213–215	E	$C_{15}H_{11}N_3O_3$	64.05	64.20	3.94	4.01
-2-naphthyl	58	188–189	F	$C_{20}H_{14}N_2O_3$	72.72	72.55	4.27	4.51
-4-acetoxyphenyl	70	220–223 (dec.)	C	$C_{18}H_{14}N_2O_5$	63.90	63.56	4.17	3.89
-4-acetylphenyl	83	220–222	C	$C_{18}H_{14}N_2O_4$	67.07	67.03	4.38	4.38
-3-acetylphenyl	84	237–239 (dec.)	C	$C_{18}H_{14}N_2O_4$	67.07	66.22	4.38	4.36
-4-acetoxyacetylphenyl	68	237–238 (dec.)	C	$C_{20}H_{16}N_2O_6$	63.15	62.40	4.24	4.26

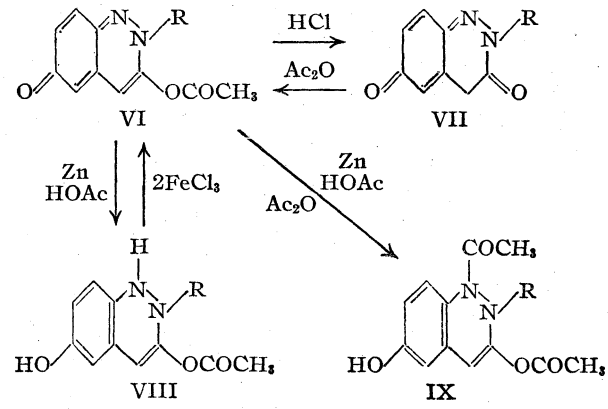
[a] Based on azo compound. [b] Solvent used in recrystallization, A = dioxane–ether, B = dioxane, C = acetic acid, D = dilute acetic acid, E = pyridine–ethanol, F = dilute dioxane. [c] Calcd.: N, 7.80. Found: N, 7.76. [d] Calcd.: N, 12.92. Found: N, 12.36.



Tautomerism of the type III ⇄ IIIa is well known and has been thoroughly studied by previous investigators.[1]

Further investigation proved the above reaction to be quite a general one. A number of diazotized aromatic amines were coupled with *m*-hydroxyphenylacetic acid, and the resulting azo compounds were cyclized with great facility to cinnoline derivatives similar to V. Table I lists the properties of these products. In most cases the azo compounds were used for the cyclization reaction without purification.

Evidence supporting the above proposed formulations was obtained from several of the reactions of the cinnoline derivatives. Hydrolysis of the monoacetyl compound (VI) (R = 3-acetylphenyl) with concentrated hydrochloric acid produced the 2 - *m* - acetylphenyl - 3,6 - diketo - 2,3,4,6 - tetrahydrocinnoline (VII). Reacetylation of VII regenerated the starting material (VI). Reduction of VI (R = 3-acetylphenyl, 2-naphthyl, or 4-acetoxyphenyl) with zinc dust and acetic acid



gave the corresponding colorless, phenolic, dihydro derivatives (VIII), which could be oxidized by means of ferric chloride at room temperature to the original quinonoid compound (VI). When the reduction was conducted in the presence of acetic anhydride, two hydrogen atoms and one acetyl group were introduced. The structure of the product is probably IX (R = 2-naphthyl in this case) since amines are more readily acetylated than phenols under these conditions.[2]

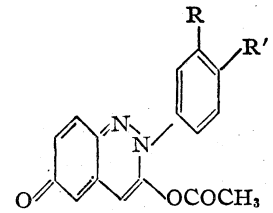
The ultraviolet absorption spectra of the first three cinnoline derivatives in Table I were determined in ethanol, and that of 2-phenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline is shown in Fig. 1. This compound shows maxima at 235, 330 and 413 mμ, while the 4-bromophenyl derivative has peaks at 235, 338 and 415 mμ. The corresponding maxima for the 4-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline lie at 239, 311 and 415 mμ. For clarity and because of the close similarity of these spectra only one is shown in Fig. 1.

The gross structural resemblance of these 2-phenyl-cinnoline derivatives to the basic ring system of the steroid hormones prompted the prepa-

(1) Fierz-David, *et al.*, *Helv. Chim. Acta*, **29**, 1718, 1765 (1946).

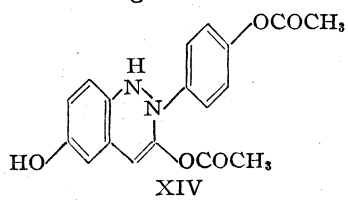
(2) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 398.

ration of several new heterocyclic steroid analogs by the method outlined above. 2-*p*-Acetoxyphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (X)



X R = H, R′ = $OCOCH_3$
XI R = H, R′ = $COCH_3$
XII R = $COCH_3$, R′ = H
XIII R = H, R′ = $COCH_2OCOCH_3$

resembles the testosterone esters, while 2-*p*-acetylphenyl - 3 - acetoxy - 2,6 - dihydrocinnoline (XI), and its isomer (XII) are related to progesterone. Finally, 2-*p*-acetoxyacetylphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (XIII) was prepared as an analog of desoxycorticosterone acetate. In the partially reduced series 2-*p*-acetoxyphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (X) on reduction with zinc and acetic acid gives the corresponding phenolic derivative (XIV) which is a model for the estrogenic hormones.



XIV

The aromatic amine intermediates requisite for the preparation of these analogs were available by published procedures.

Pharmacology.—The various steroid analogs were tested for hormone activity by Drs. K. K. Chen, R. C. Anderson and E. D. Campbell of these laboratories. Compounds X, XIV, and XII showed one mouse unit of estrogenic activity at levels of 1800, 500 and 100γ, respectively. Analogs X and XII, however, had no testosterone or progesterone activity. Compound XIII, the analog of desoxycorticosterone, was found to be ineffective in maintaining adrenalectomized rats.

Acknowledgment.—The author is indebted to Dr. R. G. Jones for helpful suggestions throughout the course of this work.

Experimental[3]

***m*-Hydroxyphenylacetic Acid.**—*m*-Methoxyphenylacetothiomorpholide was prepared by the method of Schwenk and Bloch[4] from *m*-methoxyacetophenone, morpholine and sulfur. The thioamide (600 g.) was dissolved in a mixture of 1.5 l. of glacial acetic acid and 2.5 l. of concentrated hydrochloric acid, and the solution was refluxed for seventeen hours. The solvents were removed *in vacuo*, and water was added to the residue. The crude *m*-methoxyphenylacetic acid was filtered and washed with water and then dissolved in dilute sodium hydroxide. The solution was filtered, and the product was reprecipitated with hydrochloric acid. It was filtered, washed with water, and dried; yield, 60%. The methoxy compound (1.4 moles) was then dissolved in 750 ml. of hydriodic acid (sp. gr., 1.7), and the solution was refluxed for one and one-half hours while continuously separating the methyl iodide which was formed. The solvent was removed by distillation *in vacuo*, and the *m*-hydroxyphenylacetic acid was filtered and washed with a small portion of cold water. The crude, dry product weighed 153 g. (72%), and was easily purified by recrystallization from ethyl acetate–petroleum ether, m. p. 133–134°.

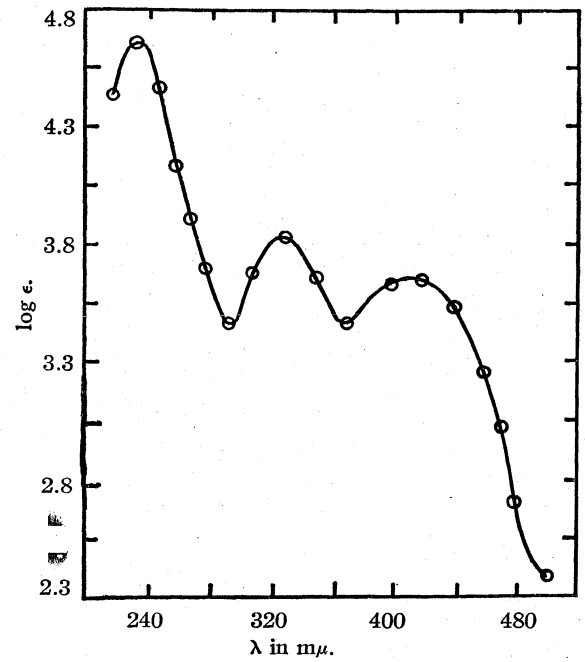


Fig. 1.—Ultraviolet absorption spectrum of 2-phenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.

Coupling of Diazotized Aromatic Amines with *m*-Hydroxyphenylacetic Acid.—The amines used in this study were commercial products except for *p*-acetoxyaniline[5] and *p*-acetoxyacetylaniline.[6] The procedure employed in the preparation of the azo compounds was as follows: The amine was dissolved or suspended in ice and water containing 2.2 equivalents of hydrochloric acid, and the solution was diazotized with a slight excess of sodium nitrite below 0°. The diazo solution was then poured with stirring into a prepared solution of one equivalent of *m*-hydroxyphenylacetic acid and 4.2 equivalents of sodium hydroxide in ice water. Excess ice kept the temperature below 0° throughout. The bright orange solution was then filtered and acidified with acetic acid or hydrochloric acid. The azo compound was filtered, washed with water and dried. The yields averaged 84%. Analytic data for several of these coupling products are given in Table II. The other azo compounds

TABLE II

2-ARYLAZO-5-HYDROXYPHENYLACETIC ACIDS

Aryl =	Solvent	Formula	Percentage N Calcd.	Found
-C_6H_5	[a]	$C_{14}H_{12}N_2O_3$	10.93	10.50
-4-C_6H_4Br	Dil. acetone	$C_{14}H_{11}BrN_2O_3$	50.17[b]	50.10
-4-$C_6H_4NO_2$	Dil. ethanol	$C_{14}H_{11}N_3O_5$	13.95	14.29
-4-C_6H_4COOH	Dil. acetone	$C_{15}H_{12}N_2O_5$	9.33	9.21

[a] Purified by reprecipitation from ammonium hydroxide solution with acetic acid. [b] % C; % H: calcd. 3.31, found 3.06.

(3) All melting points are corrected.

(4) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(5) Ruggli and Courtin, *Helv. Chim. Acta*, **15**, 75 (1932).

(6) Robinson and Robinson, *J. Chem. Soc.*, 1939 (1932).

were not purified but were used directly for the cyclization reaction.

Cyclization of Azo Compounds to Cinnoline Derivatives.—For the cyclization reaction the azo compounds were dissolved in about 10 parts of acetic anhydride containing 0.02 part of concentrated sulfuric acid, and the solutions were refluxed for thirty to sixty minutes. (The sulfuric acid was omitted in the case of the pyridine derivative derived from 3-aminopyridine.) The solutions were then concentrated *in vacuo* to a small volume, and ether was added. The products were filtered and washed thoroughly with ether. The other pertinent details are given in Table I.

Hydrolysis of 2-*m*-Acetylphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (VI).—This acetyl compound (0.5 g.) was dissolved in 50 ml. of concentrated hydrochloric acid, and the solution was refluxed for fifteen minutes. The yellow product began to separate from the reaction mixture toward the end of the reflux period. The solvent was then distilled *in vacuo*, and water was added to the residue. The product was filtered and washed with water and dried. The yield was practically quantitative. Pure 2-*m*-acetylphenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (VII) was obtained by precipitation from pyridine solution with ether, m. p. 290–300°, dec.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. Found: C, 68.53; H, 4.45.

Acetylation of 2-*m*-Acetylphenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (VII).—The diketo compound (VII), when treated with acetic anhydride in the manner described above for the azo compounds, gave a 70% yield of VI.

Reduction of 2-β-Naphthyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.—The quinonoid compound (1.8 g.) was dissolved in 100 ml. of boiling glacial acetic acid, and 3.6 g. of zinc dust was added gradually. After a few minutes the mixture was filtered through sintered glass and the filtrate was concentrated *in vacuo* to a small volume. Addition of water precipitated the product, which was obtained in the theoretical yield. The 2-β-naphthyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline was purified by recrystallization from dilute methanol, and was obtained as colorless plates, m. p. 131–133°.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.27; H, 4.85. Found: C, 72.60; H, 4.98.

Two other dihydro derivatives were similarly prepared: 2-*m*-acetylphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline, m. p. 164–166°, 70%.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97. Found: C, 66.15; H, 4.86. 2-*p*-Acetoxyphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline (XIV), m. p. 164–165°, 83%. *Anal.* Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74. Found: C, 63.32; H, 4.87.

Reductive Acetylation of 2-β-Naphthyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.—This compound (2.0 g.) was dissolved in a mixture of 40 ml. of acetic anhydride and 20 ml. of glacial acetic acid, and 3 g. of zinc dust was added. The mixture was then refluxed for one-half hour, after which it was filtered and the filtrate concentrated *in vacuo* to a straw-colored oil. The oil was taken up in ether, washed with water, and the ether solution was dried over calcium chloride (acetone was added to prevent precipitation of the product at this point). Concentration of the ether solution *in vacuo* gave the product; yield, 32%. The 1-acetyl-2-β-naphthyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline (IX) was recrystallized several times from benzene–petroleum ether for analysis, m. p. 141–143°.

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.57; H, 5.01; N, 7.66, 7.37.

Oxidation of 2-*m*-Acetylphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline.—This colorless dihydro derivative (2.3 g.) was dissolved in 50 ml. of acetic acid at room temperature, and to it was added a solution of 4.0 g. of ferric chloride crystals in 5 ml. of water and 1.0 ml. of concentrated hydrochloric acid. Upon dilution of the solution with two volumes of water the yellow 2-*m*-acetylphenyl-3-acetoxy-6-keto-2-6-dihydrocinnoline separated. It was filtered and washed with water; yield, 84%; m. p. 236–238°, dec.

Summary

1. Azo dyes formed by coupling diazotized aromatic amines with *m*-hydroxyphenylacetic acid have been found to cyclize to 2-aryl-substituted cinnolines under acetylating conditions.

2. This new synthesis of cinnoline derivatives has been used to prepare heterocyclic analogs of the steroid hormones.

3. Several of the compounds show a slight estrogenic activity.

INDIANAPOLIS, INDIANA RECEIVED OCTOBER 20, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

The Synthesis of Palmitic Acid and Tripalmitin Labeled with Carbon Fourteen

BY WILLIAM G. DAUBEN

Isotopic high molecular weight fatty acids, such as palmitic and stearic, have been prepared containing deuterium and radioactive bromine. In order to study the fate of the carbon chain itself, palmitic acid containing radioactive carbon was prepared.

The synthesis of palmitic acid labeled in the carboxyl group with C^{14} was readily accomplished, in a yield of 72%, by the carbonation of *n*-pentadecylmagnesium bromide with radioactive carbon dioxide.[1] Carboxyl-labeled tripalmitin was prepared from this acid in a yield of 75% by employing the acid chloride method of Stephenson.[2] The tripalmitin has a specific activity of 760 cts./min./mg. ester.

The preparation of *n*-hexadecanoic acid (palmitic acid) labeled at carbon atom six with C^{14} was carried out as shown in the scheme.

$$\underset{\text{I}}{C_{10}H_{21}MgBr} \xrightarrow{C^*O_2} \underset{\text{II}}{C_{10}H_{21}C^*OOH} \xrightarrow{CH_2N_2}$$

$$\underset{\text{III}}{C_{10}H_{21}C^*OOCH_3} \xrightarrow{CuCr_2O_4} \underset{\text{IV}}{C_{10}H_{12}C^*H_2OH} \xrightarrow{HBr}$$

$$C_{10}H_{21}C^*H_2Br \xrightarrow[2.\ CdCl_2]{1.\ Mg.}$$

(1) Dauben, Reid and Yankwich, *Anal. Chem.*, **19**, 828 (1947).

(2) Stephenson, *Biochem. J.*, **7**, 429 (1913).

$$(C_{10}H_{21}C^*H_2)_2Cd \xrightarrow[2.\ KOH]{1.\ CH_3OOC(CH_2)_3COCl} \underset{VI}{}$$

$$C_{10}H_{21}C^*H_2CO(CH_2)_3COOH \xrightarrow[NH_2NH_2]{NaOH} \underset{VII}{}$$

$$C_{10}H_{21}C^*H_2(CH_2)_4COOH \quad \underset{VIII}{}$$

Yields: $C^*O_2 \longrightarrow$ III, 83%; III $\longrightarrow$ V, 79%; V $\longrightarrow$ VIII, 54%

It was found necessary to use three times the normal amount of copper chromite catalyst in the hydrogenolysis of ester III to obtain high yields consistently.[3] This was probably due to the fact that the methanol produced in the reaction is a strong enough acid to destroy the activity of the catalyst. The over-all yield of palmitic acid, based on barium carbonate, was 30% and the palmitic acid has a specific activity of 40,000 cts./min./mg. acid.

After this work had been completed, Houston[4] reported the synthesis 4-keto-*n*-hexadecanoic acid by the same general procedure employing *n*-dodecyl bromide and β-carbomethoxypropionyl chloride. However, the yield of the keto-acid isolated, based on the bromide, was only 7.4%. In view of the great discrepancy in this yield and the yield obtained in the above synthesis, the reaction was investigated. It was found when the procedure outlined in this paper for the preparation of the 5-keto-acid was followed, the 4-keto-acid was obtained in 69% yield. The failure of Houston to obtain a high yield may have been due to the fact that insufficient time was allowed for the conversion of the Grignard reagent to the dialkylcadmium compound.

Acknowledgment.—The author wishes to express his appreciation to the Bio-Organic Group of the Radiation Laboratory for their kind assistance.

Experimental[5]

1-Pentadecanol. (a) From Paraformaldehyde.[6]—*n*-Tetradecylmagnesium bromide was prepared in an all-glass apparatus under nitrogen from 1.54 g. (0.0623 mole) of magnesium turnings and 15.5 g. (0.057 mole) of redistilled *n*-tetradecyl bromide in 60 cc. of anhydrous di-*n*-butyl ether. The bromide solution was added to the magnesium during one hour, and the temperature was kept at 35° or below. The temperature was raised to 105° and 2.84 g. (0.094 mole) of paraformaldehyde (dried in a vacuum desiccator) was added in small portions over a period of thirty minutes. After the addition was complete, the clear solution was heated for an additional period of forty-five minutes at 105° during which time the solution became cloudy. The heating was then continued for one hour at 110°, the reaction mixture was cooled, decomposed in the usual manner with dilute sulfuric acid, and the ether was removed by steam distillation. The cooled residue from the distillation was extracted with ether, the solvent was removed and the product was distilled. A small amount of 1-pentadecanol (2.2 g., 17.2%, b. p. 118° (0.3 mm.)) was obtained. The pot residue was heated for six hours on a steam-bath with 15 cc. of absolute ethanol and 3 cc. of concentrated hydrochloric acid but only *n*-octacosane was isolated.

When the Grignard reagent was prepared at a temperature above 35°, the yield was only slightly less, 15.7%.

(b) From the Ester.—Ethyl *n*-pentadecanoate (14.6 g., 0.054 mole) was hydrogenated over copper chromite catalyst (2.5 g.). The initial pressure was 3000 p. s. i. at room temperature and hydrogenolysis took place readily at 250° and was complete in five to six hours. The 1-pentadecanol distils at 112–114° (0.2 mm.), yield 10.5 g. (85.4%).

***n*-Pentadecyl Bromide.**—The bromide was prepared in the usual manner[7] employing anhydrous hydrogen bromide and 1-pentadecanol (27.3 g., 0.12 mole) except that the reaction mixture was diluted with 50 cc. of *n*-hexane before processing. *n*-Pentadecyl bromide boils at 127–128° (0.5 mm.), yield 28.4 g. (82.7%).

Carboxyl-Labeled Hexadecanoic Acid.—*n*-Pentadecylmagnesium bromide was prepared in an all-glass apparatus in a nitrogen atmosphere from 1.6 g. (0.066 mole) of magnesium turnings and 15.9 g. (0.0547 mole) of *n*-pentadecyl bromide in 110 cc. of anhydrous ether. An aliquot of the solution was titrated and the concentration was found to be 0.00044 mole of Grignard reagent per cc. of solution.

A volume of 110 cc. (0.0484 mole) of Grignard solution was carbonated with radioactive carbon dioxide generated from 9.1 g. (0.046 mole) of radioactive barium carbonate with a specific activity of 1060 cts./min./mg.[8] following the procedure described in detail in previous publications. The acid was isolated in the usual manner and converted directly to the methyl ester. The ester distils at 132–133° (0.3 mm.), yield 10.0 g. (80.4%), $n^{25}D$ 1.4386.

The ester (10.0 g., 0.037 mole) was saponified with a solution of 2.3 g. of potassium hydroxide, 35 cc. of methanol, and 2 cc. of water by heating on a steam-bath overnight. The crude acid was recrystallized from 40 cc. of ten per cent. aqueous acetone. The pure acid melts at 60–61°, yield 8.55 g. (90.1%). The over-all yield based on barium carbonate was 72.4%, specific activity × 16: 1050 cts./min./mg. barium carbonate,[9] activity of compound: 810 cts./min./mg. acid.

Carboxyl-labeled Tripalmitin.—Palmityl chloride was prepared as described by earlier workers[10] from 8.3 g. (0.0324 mole) of the carboxyl-labeled palmitic acid prepared above and 10 cc. of purified thionyl chloride.

Tripalmitin was prepared by slow addition, with stirring, of a chloroform solution of palmityl chloride to a cooled mixture of 0.975 g. (0.0106 mole) of redistilled glycerol, 8 cc. of dry pyridine, and 25 cc. of dry chloroform.[2] The light-yellow solution was allowed to stand three days at room temperature during which time it gradually darkened. The mixture was processed in the usual manner, and the residual light-tan solid was recrystallized twice from acetone (Norit) to give white tripalmitin, m. p. 61–62°, sinters 59°, yield 6.15 g. (75.5%). The over-all yield from barium carbonate was 54.7%, specific activity

(3) Adkins and Folkers, THIS JOURNAL, **53**, 1095 (1931).

(4) Houston, *ibid.*, **69**, 517 (1947).

(5) All melting points are corrected. Microcombustions by Mr. C. W. Koch and Mrs. W. B. Dandliker.

(6) Marvel, Blomquist and Vaughn, THIS JOURNAL, **50**, 2810 (1928).

(7) "Org. Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 246.

(8) All measurements of radioactivity were carried out with a thin mica-window Geiger–Müller tube on a scale of 64 circuit with a geometry of 17.6 ± 2.5 disintegrations per count. The activity was determined with thin uniform layers of barium carbonate according to the procedure described in earlier publications. The over-all counting error was ±2%.

(9) This value was obtained by the oxidation of a microsample with Van Slyke's oxidizing solution and precipitation of the carbon dioxide as barium carbonate, which was counted. To correct for the dilution of activity in the compound, the observed specific activity was multiplied by sixteen.

(10) (a) Hann and Jamieson, THIS JOURNAL, **50**, 1442 (1928); (b) Rose, *ibid.*, **69**, 1284 (1947).

× 17: 1040 cts./min./mg. barium carbonate, activity of compounds: 760 cts./min./mg. tripalmitin.

Carboxyl-labeled Methyl *n*-Hendecanoate (III).—*n*-Decylmagnesium bromide was prepared as described for the other Grignard reagents from 1.8 g. (0.074 mole) of magnesium turnings and 15 g. (0.068 mole) of *n*-decyl bromide dissolved in 80 cc. of anhydrous ether. An aliquot of the solution was titrated and the concentration was found to be 0.00075 mole of Grignard reagent per cc.

A volume of 15.7 cc. (0.0117 mole) of Grignard solution was carbonated with radioactive carbon dioxide generated from 1.860 g. (0.00942 mole) of radioactive barium carbonate with a specific activity of 54,400 cts./min./mg. following the procedure described previously.[1] The acid was isolated in the usual manner and was then methylated with an ethereal solution of diazomethane. The ester was distilled in a small sublimation-type still, block temperature 54–58°, pressure 0.3 mm., yield 1.560 g. (82.9%), n^{23}D 1.4275, specific activity × 12: 53,500 cts./min./mg. barium carbonate, activity of compound: 52,800 cts./min./mg. ester.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07. Found: C, 71.97; H, 11.95.

***n*-Hendecyl Bromide Labeled at Carbon Atom One (V).**—Carboxyl-labeled methyl *n*-hendecanoate (1.538 g., 0.00767 mole) was hydrogenated over copper chromite catalyst (1.0 g.) at an initial pressure of hydrogen of 3000 p. s. i. at room temperature. The hydrogenolysis took place at 250° and was complete in six hours. The crude alcohol was converted directly to the bromide by passage of anhydrous hydrogen bromide through the alcohol at steam-bath temperature.[7] The *n*-hendecyl bromide was distilled in a small sublimation-type still, block temperature 70–75°, pressure 0.5 mm., yield 1.432 g. (79.3%), n^{25}D 1.4548, specific activity × 11: 53,100 cts./min./mg. barium carbonate; activity of compound: 44,800 cts./min./mg. bromide.

Anal. Calcd. for $C_{11}H_{23}Br$: C, 56.17; H, 9.86. Found: C, 56.61; H, 10.28.

***n*-Hendecanoic Acid Labeled at Carbon Atom Six (VIII).**—Methyl 5-keto-*n*-hexadecanoate was prepared following the procedure outlined by Cason and Prout except for one modification.[11] The Grignard reagent was prepared from 0.15 g. (0.0062 mole) of magnesium turnings and 1.412 g. (0.006 mole) of *n*-hendecyl bromide labeled at carbon atom one in 50 cc. of anhydrous ether. The resulting Grignard reagent was converted to the dialkylcadmium compound with 0.71 g. (0.00389 mole) of anhydrous cadmium chloride. After the addition of the cadmium chloride, the mixture was heated under reflux until a negative Gilman test for a Grignard reagent was obtained. This required about two hours. The ether was replaced with benzene, and the resulting suspension was treated with 1.00 g. (0.0061 mole) of γ-carbomethoxybutyryl chloride.[12] The reaction mixture, after heating under reflux for one hour, had set to a solid mass and then was decomposed as usual. The crude reaction mixture was directly saponified with a solution of 0.4 g. of potassium hydroxide in 10 cc. of methanol. After dilution to 50 cc. with water, the mixture was extracted with ether to remove the neutral compounds. *n*-Docosane (100 mg.) marked at carbon atoms eleven and twelve was isolated. The alkaline layer was acidified and then extracted with ether.

The crude keto acid was reduced by the modified Wolff–Kishner method[13] using 6.4 cc. of diethylene glycol, 0.8 g. of sodium hydroxide, and 0.77 cc. of one-hundred per cent. hydrazine hydrate. The crude acid was distilled onto a cold-finger type condenser at a bath temperature of 110° and pressure of 1 mm. The distillate was recrystallized from 15 cc. of ten per cent. aqueous acetone (Norit), m. p. 61–62°, yield 700 mg. (45.7%), specific activity × 16: 52,700 cts./min./mg. barium carbonate, activity of compound: 40,500 cts./min./mg. acid.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.55; H, 12.47.

In a practice experiment with non-radioactive *n*-hendecyl bromide (6.71 g., 0.00286 mole) and γ-carbomethoxybutyryl chloride (3.76 g., 0.0228 mole), the keto acid was isolated, and recrystallized from methanol, m. p. 84.5–85°, yield, 4.87 g. (64% based on bromide, 79% based on acid chloride). This acid, when subjected to the Wolff–Kishner reaction, was reduced to palmitic acid in a yield of 82%.

Summary

1. Palmitic acid and tripalmitin, labeled in the carboxyl carbon with carbon fourteen, have been prepared.

2. Palmitic acid, labeled at carbon atom six with carbon fourteen, has been synthesized.

3. A re-examination of the work of Houston on the synthesis of 4-ketohexadecanoic acid by the cadmium procedure, has shown that it is critical to allow sufficient time for the conversion of a Grignard reagent to a dialkylcadmium compound.

BERKELEY 4, CALIFORNIA RECEIVED AUGUST 4, 1947

(11) Cason, THIS JOURNAL, 2078 (1946), and earlier papers.

(12) The acid chloride was prepared from half ester that had been fractionally distilled through a column (b. p. 156° (10 mm.)) and purified thionyl chloride. The chloride boils at 84° (7 mm.); see Harris, Wolf, *et al.*, THIS JOURNAL, **67**, 2096 (1945), and "Org. Syntheses," **25**, 19 (1945).

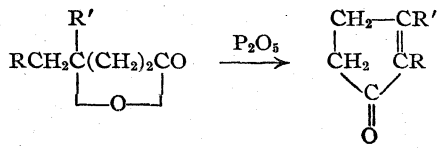
(13) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of Cyclopentenones from Lactones

BY ROBERT L. FRANK, ROSE ARMSTRONG, JACK KWIATEK AND HAROLD A. PRICE

The reaction of lactones with phosphorus pentoxide to form cyclopentenones, by which syntheses of dihydrojasmone (VII)[1] and dihydrocinerone (VI)[2] have been recently accomplished, has now been further investigated to determine its scope and usefulness as an alternative method to those developed by Hunsdiecker[3] and by Johnson and Petersen.[4]

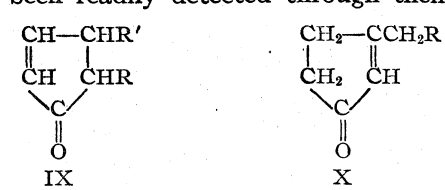


I, R = R′ = H
II, R = H, R′ = CH_3
III, R = n-C_6H_{13}, R′ = H
IV, R = R′ = CH_3
V, R = n-C_3H_7, R′ = CH_3
VI, R = n-C_4H_9, R′ = CH_3
VII, R = n-C_5H_{11}, R′ = CH_3
VIII, R = n-C_6H_{13}, R′ = H

The lactones were prepared in yields of 15–64% by the addition of the appropriate Grignard reagents to esters of levulinic acid, using the low-temperature technique of Cason, Adams, Bennett and Register.[5] Both ethyl and cyclohexyl levulinates were used, the choice depending on the ease of separation by fractional distillation of the lactones from the starting materials.

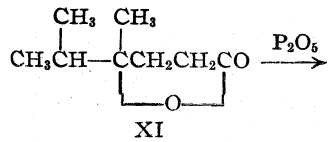
The reaction of the simplest lactones (I and II) with phosphorus pentoxide was found to yield only black tarry products rather than the desired cyclopentenones, probably because of insufficient steric hindrance around the α,β-unsaturation of the products to prevent polymerization in the strongly acidic reaction mixture.

Better results are obtained with increased substitution, the respective yields being 30, 32, 30[2] and 50%[1] of the cyclopentenones represented by Structures IV, V, VI and VII. In these instances, in which R′ = methyl, the transformation gives only 2-cyclopentenones. 2,3-Disubstituted 4-cyclopentenones (IX) were not found; nor were β-substituted products (X), which might have been expected by ring closure involving the γ-methyl group. If formed these latter compounds would have been readily detected through their ultraviolet absorption spectra, as described below. Thus, a methylene group adjacent to the γ-position of the lactone appears to react in preference to a similarly-attached methyl group in the formation of the five-membered ring.

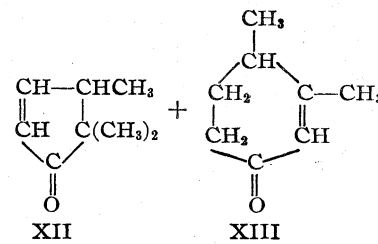


IX X

γ,δ-Dimethyl-γ-caprolactone (XI), however, a *gamma* lactone having a methyl and a methinyl group attached to the *gamma* carbon atom, gives on treatment with phosphorus pentoxide a complex mixture containing at least two α,β-unsaturated ketones. A 6% yield of 2,2,3-trimethyl-4-cyclopentenone (XII), characterized by ozonolysis to trimethylsuccinic acid and reduction to 2,2,3-trimethylcyclopentanone, was isolated by fractional distillation.



XI



XII XIII

The other ketone (6%) has not been positively identified, but its C-methyl determination (1.5)[6,7] and ultraviolet absorption maximum of 231 mμ[8] indicate its structure to be 3,4-dimethyl-2-cyclohexenone (XIII), the reaction product which would result by ring closure involving the δ-methyl group of the lactone (XI).

One additional lactone, γ-undecanolactone (III), gave results similar to those of Plattner and St. Pfau[9] in their study of the action of sulfuric acid on ω-undecylenic acid. The main product was 2-n-hexyl-2-cyclopentenone (VIII), but the yield was low (17%) and high purity of product difficult to attain due to the occurrence of smaller amounts of an isomer, 2-n-hexyl-4-cyclopentenone.

It is significant that when the lactone contains both a methyl and a methylene group, a single product is formed, while a complex mixture results if the methyl group is absent.

The ultraviolet absorption spectra of substituted cyclopentenones have been studied by Gil-

(1) Frank, Arvan, Richter and Vanneman, THIS JOURNAL, **66**, 4 (1944).
(2) LaForge and Barthel, *J. Org. Chem.*, **10**, 222 (1945).
(3) Hunsdiecker, *Ber.*, **75B**, 447 (1942).
(4) Johnson and Petersen, THIS JOURNAL, **67**, 1366 (1945).
(5) Cason, Adams, Bennett and Register, *ibid.*, **66**, 1764 (1944).
(6) Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).
(7) Barthel and LaForge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944); Pregl-Grant, "Quantitative Organic Microanalysis," 4th ed., The Blakiston Co., Philadelphia, Pa., 1945, pp. 167–169.
(8) Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).
(9) Plattner and St. Pfau, *Helv. Chim. Acta*, **20**, 1474 (1937).

lam and West,[10] who have shown for several 2,3-disubstituted 2-cyclopentenones an approximate deviation of −11 mμ from Woodward's average value of 247 ± 5 mμ for open-chain α,β-unsaturated carbonyl compounds triply substituted around the double bond with non-absorbing groups. Gillam and West have suggested that this can be extended as a general amendment to Woodward's rule.[8] The absorption maxima for 2-cyclopentenones unsubstituted, singly substituted, and doubly substituted at the double bond should, therefore, appear at 214 ± 5 mμ, 224 ± 5 mμ and 236 ± 5 mμ, respectively.

Absorption spectra of our cyclopentenones, with one exception (XII), fall within the range of these predictions, with maxima as follows: 2,3-dimethyl-2-cyclopentenone (IV), 235 mμ; 2-*n*-propyl-3-methyl-2-cyclopentenone (V), 235 mμ; 2-*n*-hexyl-2-cyclopentenone (VIII), 229 mμ; 2,2,3-trimethyl-4-cyclopentenone (XII), 221 mμ; 2-*n*-hexyl-4-cyclopentenone, 212 mμ.

Experimental

Cyclohexyl Levulinate.—This was prepared by a procedure analogous to that for ethyl levulinate[1] from 581 g. (5.00 moles) of levulinic acid, 990 g. (9.88 moles) of cyclohexanol and 1 ml. of concentrated sulfuric acid in 500 ml. of benzene. The yield was 803 g. (81.5%) of cyclohexyl levulinate, b. p. 116–118° (2 mm.); $n^{20}D$ 1.4559; sp. gr. $^{20}_{20}$ 1.023; *MR* calcd., 52.35; *MR* found, 52.66.

Anal.[11] Calcd. for $C_{11}H_{18}O_3$: C, 66.54; H, 9.15. Found: C, 66.60; H, 9.35.

Preparation of Lactones.—Procedures similar to that of Cason, Adams, Bennett and Register[5] for γ-methyl-γ-*n*-propylbutyrolactone were used. γ-Methyl-γ-valerolactone was prepared from 200 g. (1.41 moles) of methyl iodide and 34.0 g. (1.40 gram atoms) of magnesium turnings in 500 ml. of dry ether and 318 g. (1.60 moles) of cyclohexyl levulinate in 1 liter of dry ether. The crude product, after shaking with zinc dust, was fractionally distilled through a twelve-inch helix-packed column to give a fore-run of cyclohexanol and 78.8 g. of the lactone, b. p. 85–90° (18 mm.). Redistillation gave 67.4 g. (42%) of colorless product, b. p. 89–91° (17 mm.); $n^{20}D$ 1.4352; sp. gr. $^{20}_{20}$ 1.020; *MR* calcd.: 29.24; *MR* found, 29.22.

γ-Methyl-γ-caprolactone was prepared similarly from 230 g. (2.11 moles) of ethyl bromide and 48.6 g. (2.00 gram atoms) of magnesium turnings in 500 ml. of dry ether and 396.5 g. (2.00 moles) of cyclohexyl levulinate in 2 liters of dry benzene and 500 ml. of dry ether. Fractional distillation of the crude product gave 146.5 g. (65% based on unrecovered cyclohexyl levulinate) of lactone, b. p. 102–103.5° (15 mm.); $n^{20}D$ 1.4412; sp. gr. $^{20}_{20}$ 1.004; *MR* calcd., 33.86; *MR* found, 33.71. There were also obtained 86.5 g. of cyclohexanol and 46.6 g. of cyclohexyl levulinate, b. p. 115° (3 mm.).

γ-Methyl-γ-octanolactone was synthesized from 430 g. (3.14 moles) of *n*-butyl bromide and 73.0 g. (3.00 gram atoms) of magnesium turnings in 800 ml. of dry ether, and 500 g. (3.52 moles) of ethyl levulinate in 3 liters of benzene. The crude product, after shaking with zinc dust, gave on fractional distillation 279.8 g. (60%) of the colorless lactone, b. p. 85–87° (2 mm.) (reported,[12] 120–123° (15 mm.)); $n^{20}D$ 1.4452; sp. gr. $^{20}_{20}$ 0.964; *MR* calcd.: 43.10; *MR* found: 43.11.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.40; H, 10.53.

γ,δ-Dimethyl-γ-caprolactone (XI) was prepared from 1275 ml. (1684 g., 13.70 moles) of isopropyl bromide and 314 g. (12.9 gram atoms) of magnesium turnings in 3900 ml. of absolute ether and 1885 g. (13.08 moles) of ethyl levulinate in 6.5 liters of dry benzene. Fractional distillation of the crude product gave 274.9 g. (15.1%) of the lactone, b. p. 116° (16 mm.); $n^{20}D$ 1.4460; sp. gr. $^{20}_{20}$ 0.991; *MR* calcd., 38.49; *MR* found, 38.26.[13]

The Reaction of Lactones with Phosphorus Pentoxide.—The transformations were carried out similarly with all the lactones. One-fifth mole of phosphorus pentoxide was placed in a distilling flask equipped with a ground-glass joint. The lactone (0.27 mole) was then poured into the flask, which was immediately attached to a distilling column partially filled with glass helices. The mixture was heated gently with a flame to initiate reaction, the pressure was gradually reduced to 2–28 mm., and the products finally distilled directly from the dark reaction mixture by the use of a free flame. They were then redistilled.

2,3-Dimethyl-2-cyclopentenone (IV).—γ-Methyl-γ-caprolactone (in three runs totaling 101.6 g., 0.78 mole) gave 53.0 g. of distillate, b. p. 102–115° (28 mm.). Redistillation yielded 29.6 g. of starting material, b. p. 101–110° (25 mm.), and 18.8 g. (30.4% based on unrecovered lactone) of 2,3-dimethyl-2-cyclopentenone, b. p. 90–92° (25 mm.); $n^{20}D$ 1.4830; sp. gr. $^{20}_{20}$ 0.969; *MR* calcd., 31.89; *MR* found, 32.47; ultraviolet absorption maximum 235 mμ (log ε = 3.04). The semicarbazone of the product melted at 247–250° (dec.) (reported,[3] 247° (dec.)).

3-Methyl-2-*n*-propyl-2-cyclopentenone (V).—γ-Methyl-γ-octanolactone (in five runs totaling 210 g., 1.35 moles) gave 136.4 g. of distillate. Redistillation yielded 39.6 g. (32% based on unrecovered lactone) of 3-methyl-2-*n*-propyl-2-cyclopentenone of mint-like odor, b. p. 55–58° (2 mm.); $n^{20}D$ 1.4778; ultraviolet absorption maximum, 235 mμ (log ε = 3.04); and 71.2 g. of starting material, b. p. 82–88° (2 mm.). The semicarbazone of the product melted at 209–210.5° (reported,[3] 212°).

2,2,3-Trimethyl-4-cyclopentenone (XII) and 3,4-Dimethyl-2-cyclohexenone (XIII).—γ,δ-Dimethyl-γ-caprolactone (XI) was treated with phosphorus pentoxide in ten runs of 32 g. (0.23 mole) each to give 18.8 to 23.7 g. of slightly yellow distillate per run, $n^{20}D$ 1.4563–1.4621. All were combined to total 212.2 g., $n^{20}D$ 1.4601. Careful distillation through a thirty-six inch helix-packed column with a total reflux-partial takeoff head and reflux ratio 20:1 yielded 11.8 g. (6%, based on unrecovered lactone) of 2,2,3-trimethyl-4-cyclopentenone (XII) of camphor-like odor, b. p. 66–66.5° (19 mm.), 169.5–170° (740 mm.); $n^{20}D$ 1.4599; sp. gr. $^{20}_{4}$ 0.911; *MR* calcd., 36.50; *MR* found, 37.06; C-methyl[14] calcd. (2 methyls), 24.2%; found, 19.5, 19.7%; ultraviolet absorption maximum 221 mμ (log ε = 2.77). *Anal.* Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.18; H, 9.80. The semicarbazone of this fraction, recrystallized from ethanol as shiny colorless needles, melted at 189–190°.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34. Found: C, 59.38; H, 8.60.

Attempts to prepare a crystalline oxime were unsuccessful.

A second fraction, probably 3,4-dimethyl-2-cyclohexenone (XIII), weighed 11.0 g. (6%, based on unrecovered lactone), b. p. 100–101° (18 mm.); $n^{20}D$ 1.4779; C-methyl calcd. (2 methyls): 24.2%; found: 18.0, 17.4%; ultraviolet absorption maximum 231 mμ (log ε = 3.02). *Anal.* Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 75.14, 74.91; H, 9.79, 9.78.

The semicarbazone, recrystallized from 40% ethanol as colorless platelets, melted at 183–184°.

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34. Found: C, 59.77; H, 8.48.

(10) Gillam and West, *J. Chem. Soc.*, 486 (1942).

(11) Microanalyses were carried out by Miss Theta Spoor, Miss Lillian Hruda and Miss Betty Alice Snyder.

(12) Wilson, THIS JOURNAL, **67**, 2161 (1945).

(13) Blaise, *Compt. rend.*, **130**, 1033 (1900).

(14) C-Methyl determinations were carried out by Mr. Howard Clark of the Illinois State Geological Survey.

This semicarbazone was shown to be different from that of 2,2,3-trimethyl-4-cyclopentenone (XII) by a depressed mixed m. p., 168–170°.

Attempts to prepare a solid oxime were unsuccessful. As a higher-boiling fraction, 99.3 g. of the starting lactone was recovered.

2-*n*-Hexyl-2-cyclopentenone (VIII) and 2-*n*-Hexyl-4-cyclopentenone.—γ-Undecanolactone (commercial product of Givaudan-Delawanna, Inc., New York) (in two runs totaling 100.0 g., 0.54 mole) gave 25.3 g. of a mixture of ketones, b. p. 74–94° (2 mm.); $n^{20}D$ 1.4728. Redistillation yielded 15.7 g. (17.5%) of 2-*n*-hexyl-2-cyclopentenone, b. p. 97–100° (5 mm.); $n^{20}D$ 1.4675; sp. gr. $^{20}_{20}$ 0.910, *MR* calcd., 50.32; *MR* found, 50.72; ultraviolet absorption maximum 229 mμ (log ε = 2.70). The semicarbazone, recrystallized as a colorless powder from 40% ethanol, melted at 194.5–196° (reported,[9] 196°). A 4-g. lower-boiling fraction, b. p. 60–70° (5 mm.); $n^{20}D$ 1.4854; ultraviolet absorption maximum 212 mμ (log ε = 2.40), yielded a semicarbazone corresponding in melting point (192–193.5°) to that of Plattner and St. Pfau[9] (m. p. 189–190°) for 2-*n*-hexyl-4-cyclopentenone. A mixture with the semicarbazone of 2-*n*-hexyl-2-cyclopentenone melted at 186–187°.

Ozonolysis of 2,2,3-Trimethyl-4-cyclopentenone (XII).—Ozone was bubbled for twelve hours through a solution of 3.3 g. (0.027 mole) of 2,2,3-trimethyl-4-cyclopentenone in 35 ml. of glacial acetic acid. The solution was then added dropwise to 25 ml. of 11% aqueous hydrogen peroxide, the mixture being agitated by a stream of air bubbles, and refluxed for two hours. The acetic acid was removed by steam distillation and the residue evaporated to a volume of approximately 5 ml. To this was added 5 ml. of concentrated nitric acid, followed by reevaporation to 5 ml., the process being repeated three times. On standing the solution then deposited platelets of trimethylsuccinic acid, weighing 0.75 g. (18%) after recrystallization from concentrated nitric acid, m. p. 147.5–149° (reported,[15] 148–149°); neutral equivalent calcd., 80.1; found, 84.6.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.22; H, 7.81.

Distillation of 0.25 g. of the acid gave a colorless solid melting *ca.* 30° (anhydride). On standing with an equimolar amount of *p*-toluidine in benzene this deposited crystals of the mono-*p*-toluidide of trimethylsuccinic acid. Recrystallization from 95% ethanol gave colorless needles melting at 125–126° (reported,[16] 127°).

(15) Auwers, *Ann.*, **292**, 142 (1896).

(16) Auwers and Umgemach, *Ber.*, **68**, 349 (1935).

Hydrogenation of 2,2,3-Trimethyl-4-cyclopentenone (XII).—Two grams of the ketone dissolved in 8 ml. of ethanol was hydrogenated over Raney nickel at room temperature and a pressure of 1900 lb. per square inch. The reaction was stopped after five minutes when one molar equivalent of hydrogen had been absorbed (estimated by pressure drop). The catalyst was removed by filtration and the semicarbazone and oxime prepared from the alcoholic solution. The semicarbazone, recrystallized from 40% ethanol, took the form of shiny plates, m. p. 197–198° (reported,[17] 210–212°).

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.99; H, 9.35. Found: C, 58.76; H, 9.15.

A mixed m. p. with the semicarbazone of 2,2,3-trimethyl-4-cyclopentenone (XII) was depressed, 184–185°.

The oxime, recrystallized from water or aqueous ethanol as colorless needles, melted at 103–104° (reported,[18] 104°).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.05; H, 10.71. Found: C, 67.45; H, 10.56.

Ultraviolet Absorption Spectra.—Miss Ruth Johnston carried out the determinations using a Beckmann Model D Spectrophotometer. The ketones were dissolved in 95% ethanol, concentration 0.006 g. per liter of solution; $\log \epsilon = \log (1/cl) \cdot \log (I_0/I)$, in which c = g./100 ml. of solution, l = 1 cm.

Summary

γ-Methyl-γ-lactones having a methylene group adjacent to the *gamma* carbon atom are converted smoothly by action of phosphorus pentoxide to 2,3-disubstituted 2-cyclopentenones. This method is not applicable, however, for the preparation of 2-cyclopentenone and 3-methyl-2-cyclopentenone.

γ,δ-Dimethyl-γ-caprolactone, when treated with phosphorus pentoxide, is converted in low yield to 2,2,3-trimethyl-4-cyclopentenone and other products.

The ultraviolet absorption spectra of substituted 2-cyclopentenones are briefly discussed.

(17) Blanc and Desfontaines, *Compt. rend.*, **136**, 1141 (1903).

(18) Noyes and Patterson, *Am. Chem. J.*, **27**, 427 (1902).

URBANA, ILLINOIS RECEIVED SEPTEMBER 10, 1947

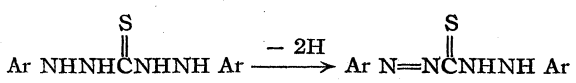
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Synthesis of Some Substituted Thiocarbazones[1]

BY D. S. TARBELL, C. W. TODD,[2a] M. C. PAULSON,[2b] E. G. LINDSTROM[2c] AND V. P. WYSTRACH[2d]

The observation[3] that thiocarbazones, especially di-(*p*-biphenyl)-thiocarbazone, were sensitive reagents for the detection of small amounts of arsenicals, led to the preparation and testing of a number of substituted thiocarbazones. The synthesis of these compounds, and their properties as arsenical detectors, are described in the present paper.

Thiocarbazones (I) are prepared by oxidation of the corresponding thiocarbazides (II) by air in alkaline solution or by hydrogen peroxide



Several methods were used for the preparation of the necessary thiocarbazides in our work.

(1) The work described in this paper was done under Contract OEM-sr-319, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development, and the University of Rochester.

(2) Present address: (a) Experimental Station, E. I. du Pont de Nemours, Inc., Wilmington, Del.; (b) Research Laboratory, Grasselli Chemical Company, Cleveland, Ohio; (c) California Research Corporation, Richmond, Calif.; (d) Research Laboratory, American Cyanamid Company, Stamford, Conn.

(3) By Professor Weldon G. Brown of the University of Chicago.

(1) **The Fischer Method.**—This involves formation of the hydrazine salt of a dithiocarbazinic acid (III), which, on heating, evolves hydrogen sulfide and yields the thiocarbazide II.

$$2ArNHNH_2 + CS_2 \longrightarrow ArNHNHCS_2H\cdot H_2NHNAr \xrightarrow{-H_2S} II$$
III

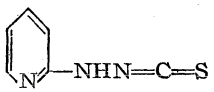
A number of hydrazines were prepared by the usual procedure of reduction of the diazonium compound with sodium sulfite[4] or stannous chloride.[5] Diazonium compounds having electron-donating groups in the ortho- or para-positions were cleaved by reduction, with the formation of the original amine or the corresponding nitrogen-free aromatic compound instead of the hydrazine. This behavior was shown by the diazonium salts from *p*-aminodimethylaniline, 2,6-dimethoxyaniline, 4-dimethylamino-1-naphthylamine, N-(*p*-aminophenyl)-morpholine, and 2-aminodiphenyl sulfide. In order to test the feasibility of a projected synthesis of *p*-dimethylaminophenylhydrazine, a model experiment was tried by treating N-magnesiobromoaniline with monochloroamine; the only product isolated was *p*-bromoaniline, identified through the mixed melting point as the acetyl derivative. Apparently the following reactions took place, instead of the desired formation of phenylhydrazine.

$$C_6H_5NHMgBr + ClNH_2 \longrightarrow C_6H_5NHMgCl + BrNH_2$$
$$\downarrow$$
$$p\text{-}BrC_6H_4NHMgCl + NH_3$$

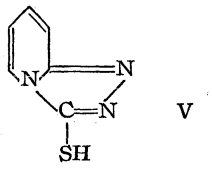
Much variation was noted in the ability of the various arylhydrazines to react with carbon disulfide. *p*-Nitrophenylhydrazine did not react unless a base was present; in the presence of pyridine, a product was obtained which was probably $p\text{-}NO_2C_6H_4NHNHCS_2H\cdot C_6H_5N$, but no thiocarbazide could be obtained from it. *p*-Phenoxyphenylhydrazine did not react normally; the thiocarbazide; if formed, apparently was unstable.[6]

The reaction of thiophosgene with arylhydrazines to form thiocarbazides was also used in a few cases, but it did not offer any advantage over carbon disulfide.[7]

2-Pyridylhydrazine and carbon disulfide gave a compound at first believed to have the structure IV, but it was later found to be V, which had been previously prepared from 2-pyridylhydrazine and potassium trithiocarbonate.[8]



IV



V

In the second stage of the reaction between carbon disulfide and the hydrazine (III → II), long-continued heating after the evolution of hydrogen sulfide has stopped may lead to formation of a thiosemicarbazide from the thiocarbazide III by disproportionation. Thus, when 2-methylthiolphenylhydrazine VI was treated with carbon disulfide and heated overnight on the steam-bath, the thiosemicarbazide VII was the only product isolated. When the heating was limited to about an hour, the thiocarbazide was obtained as usual.

$o\text{-}CH_3SC_6H_4NHNH_2$ VI $o\text{-}CH_3SC_6H_4NHNHCSNH_2$ VII

(2) **The Bamberger Nitroformazyl Method.**[9]—This method avoids the preparation of the hydrazines, and although it requires careful attention to detail and some practice, is usually better than the Fischer method. It involves the coupling of two moles of diazonium compound with sodionitromethane, followed by reduction of the resulting nitroformazyl VIII with ethanolic ammonium sulfide:

$$2ArN_2Cl + CH_3NO_2 \longrightarrow ArN{=}NCHN{=}NAr$$
VIII
$$\downarrow NO_2$$
$$\downarrow EtOH(NH_4)_2S$$
II

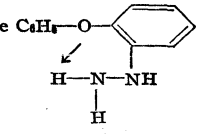
A modified procedure, due to Professor N. L. Drake,[9a] in which the *p*H of the diazonium solution is brought to 6 before adding the sodionitromethane, has been found very useful.

A number of trials runs showed that the procedure could be modified further with advantage by carrying out the coupling reaction in an acetate buffer containing 40% acetic acid at a *p*H of about 4.5; nitromethane itself was found to couple just as well as the sodio derivative under these conditions,[10] since the sodio derivative would obviously revert to nitromethane at this *p*H in an acetate buffer. The mechanism of the coupling reaction can be represented as[11]

(4) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 442.

(5) Graebe and Rateanu, *Ann.*, **279**, 267 (1894).

(6) It may be noted that *o*-phenoxyphenylhydrazine is stable indefinitely, while the *p*-compound is stable for only a few hours; this may be due to chelation of the type



(7) Thiophosgene is much more readily prepared by the method given in Sartori, "The War Gases," D. Van Nostrand Co., New York, N. Y., 1939, p. 213, than by the "Organic Syntheses" method Coll. Vol. 1, 2nd ed., p. 506).

(8) Mills and Schindler, *J. Chem. Soc.*, **123**, 321 (1923).

(9) Bamberger, *Ber.*, **33**, 2043 (1900); **27**, 155 (1894); *Ann.*, **446**, 260 (1926).

(9a) Private communication from Professor N. L. Drake, University of Maryland.

(10) This procedure is based in part on Bamberger's work (ref. 9); a somewhat similar procedure has been published by Hubbard and Scott, THIS JOURNAL, **65**, 2390 (1943).

(11) Coupling of diazonium compounds with phenols and aromatic amines involves the diazonium ion, and the phenoxide ion or the free amine, respectively (Bartlett and Wistar, THIS JOURNAL, **63**, 413 (1941)).

$$ArN_2^+ + CH_2NO_2^- \longrightarrow ArN{=}NCH_2NO_2 \rightleftharpoons ArNHN{=}CHNO_2$$

$$ArN_2^+ + ArN{=}NCHNO_2^- \longrightarrow ArN{=}NCH(NO_2)N{=}NAr$$

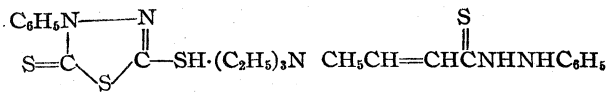
2-Aminodiphenyl sulfide yielded a nitroformazyl by this procedure, but it was unsuccessful with 2-aminofluorene and 4-aminostilbene. The suggestion that the reaction involves the anion in each step is supported by our observation that the phenylmethylhydrazone of nitroformaldehyde, $C_6H_5N(CH_3)N{=}CHNO_2$, which is insoluble in alkali, does not couple with benzenediazonium chloride in an acetate buffer or in glacial acetic acid.

The compound $C_6H_5NHN{=}CHNO_2$, in contrast, is readily soluble in dilute alkali, and couples so rapidly with a diazonium compound to form the nitroformazyl, as above, that it can be isolated from the reaction mixture only with difficulty.

The thiocarbazones obtained in fairly pure form are indicated in Table I; compounds whose preparation in pure form failed are listed in Table II. The *p*-acetyl and *p*-benzoyl derivatives listed in Table II apparently are unstable because they oxidize very readily to the carbodiazone type, $ArN{=}NC(=S){-}N{=}NAr$, in which there is a more extended conjugated system. In order to prevent this oxidation to the diazone type, which seemed to be one cause of the instability of the thiocarbazones when used as detecting agents, much time was spent in attempts to make a methyl substituted thiocarbazone (XX), which should be stable to oxidation of this type. Compound XX should

$C_6H_5N(CH_3)(NHCSN{=}NC_6H_5$ (XX) $\qquad C_6H_5NHN{=}C{=}S$ (XXI)

be obtained, after oxidation, from α-methylphenylhydrazine and compound XXI, but the latter does not seem to have been reported, and an attempt to prepare it from phenylhydrazine, carbon disulfide and triethylamine yielded instead the triethylamine salt of phenyldithiadiazolonmercaptan XXII; the structure of this product is proved by

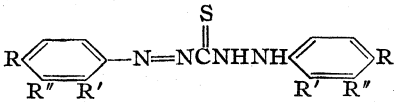


XXII XXIII

its formation from potassium phenyldithiadiazolonmercaptide and triethylamine. The interaction of $C_6H_5NHNHCSSH$ and $C_6H_5N(CH_3)NH_2$, which should yield XX, after oxidation, was also unsuccessful.

The preparation of cinnamic thiophenylhydrazide[12] XXIII was undertaken because of its simi-

TABLE I

THIOCARBAZONES PREPARED 

Compound[a]	Method[b]	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
R′ = OC_6H_5(IX)	1, 2a, 2b	167–168 dec.	$C_{25}H_{20}N_4SO_2$	68.18	4.55	67.69	4.59
R′ = OCH_3(X)	1	186 dec.	$C_{15}H_{16}N_4SO_2$	56.96	5.06	56.88	4.88
R′ = OC_2H_5(XI)	2a	170 dec.	$C_{18}H_{24}N_4SO_3$[c]	57.50	6.38	57.72	6.23
R = OC_6H_5(XII)	2a	145 dec.	$C_{25}H_{20}N_4SO_2$	68.18	4.55	68.44	4.95
R′ = C_6H_5(XIII)	2a	154 dec.	$C_{25}H_{20}N_4S$	73.53	4.90	73.11	4.60
R″ = C_6H_5(XIV)	2a	151.5 dec.	$C_{25}H_{20}N_4S$	73.55	4.90	73.55	5.28
R′ = *p*-$CH_3OC_6H_4O$(XV)	2a	153 dec.	$C_{27}H_{24}N_4SO_4$	64.80	4.80	64.25	4.97
R′ = SC_6H_5(XVI)	2b	131–133 dec.	$C_{25}H_{20}N_4S_3$	63.52	4.27	63.12	4.44
R′ = SCH_3(XVII)	1	145–146	$C_{15}H_{16}N_4S_3$	51.7	4.6	51.6	4.4
R = C_6H_5, R′ = OC_6H_5(XVIII)	2a	159–161 dec.	$C_{37}H_{28}N_4SO_2$	74.98	4.76	75.12	4.84
R = C_6H_5, R′ = SC_6H_5(XIX)	2a	147–149 dec.	$C_{37}H_{28}N_4S_3$	71.13	4.52	70.43	3.40

[a] R, R′, R″ = H, unless otherwise indicated. [b] 1 = Fischer method; 2a = nitroformazyl (Drake); 2b = nitroformazyl in acetate buffer. [c] Calculated for one molecule of methanol of crystallization.

TABLE II

THIOCARBAZONES WHOSE PREPARATION WAS ATTEMPTED

Parent amine	Method	Remarks
p-Aminoacetophenone	2a	Thiocarbazide unstable
p-Aminobenzophenone	2a	Thiocarbazide unstable
2,6-Dimethoxyaniline	1, 2a	Thiocarbazone unstable, thiosemicarbazide isolated
2-Aminofluorene	1, 2a, 2b	
2-Aminodibenzofuran	1	Oxidation to thiocarbazone failed
o-Fluoroaniline	2a	Not obtained analytically pure
2-Amino-5-methylbenzenesulfonic acid	2a	Thiocarbazone apparently obtained, but could not be isolated from aqueous solution
4-Aminostilbene	1, 2a, 2b	
2-Aminothiazole	2a	Diazonium solution unstable
2-Aminopyridine	1	Ring closure occurred
2-(*p*-Aminophenyl)-naphthalene	2b	Not obtained pure

(12) Suggested by Dr. Donald E. Pearson.

larity to the thiocarbazone structure. It could not be obtained by the action of phosphorus pentasulfide on cinnamic phenylhydrazide, and the imido chloride of the phenylhydrazide could not be obtained. Another approach, through styrylnitromethane and the nitroformazyl $C_6H_5CH=CHCH(NO_2)N=NC_6H_5$ was not successful, although styrylnitromethane was apparently obtained from cinnamyl bromide and silver nitrite in acetonitrile solution, and a red product, presumably the nitroformazyl, was obtained by treatment of this with benzenediazonium chloride.

The thiocarbazones listed in Table I were tested as arsenical detectors and the *o*-phenoxy derivative (IX) was found the most promising, considering stability, sensitivity, sharpness of color change and ease of synthesis.

Experimental Part[13]

2-Aminodiphenyl Ether.—Reduction of 78 g. of 2-nitrodiphenyl ether (in three batches) with hydrogen and Raney nickel in alcohol yielded 51.0 g. (78%) of the amine, m. p. 45.5–47°, and a second crop of 9.5 g., m. p. 43–47° (total 94%). Zinc dust and calcium chloride in ethanol gave a 68% yield of the amine from the nitro compound.[14]

2-Phenoxyphenylhydrazine.—Twenty-five grams of the above amine was diazotized, the excess nitrous acid destroyed with sulfamic acid, and 107 g. of stannous chloride in 107 cc. of concentrated hydrochloric acid added. After stirring one hour, the complex tin salt was removed and treated with 77 g. of sodium hydroxide dissolved in 650 cc. of water. The precipitate was treated with 500 cc. of water and 20 cc. of concentrated hydrochloric acid, warmed until solution was effected and cooled to obtain the hydrazine hydrochloride, which melted with decomposition at 171°. The hydrochloride was dissolved in warm water, treated with hydrogen sulfide and filtered; the hydrazine was obtained as a white precipitate, which after recrystallization from alcohol, had the m. p. 152–154°, yield, 12 g. (45%).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.00. Found: C, 72.33; H, 6.10. The benzal derivative melts at 129–130.5°.

The m. p. of the hydrazine is surprisingly high, compared to the *para* isomer, which melts at 52°, and is very unstable.

2-Nitro-4′-methoxydiphenyl Ether.[15]—The potassium salt of hydroquinone monomethyl ether (6.2 g.) was prepared in ethanol, the solvent removed and 7.9 g. of *o*-nitrochlorobenzene added: the temperature was brought to 160° for one hour, the mixture cooled and poured into dilute alkali. The product (8.6 g., 70%) melted, after crystallization from ethanol, at 74–74.5°.

2-Nitrodiphenyl Sulfide.—The procedure of Cullinane and Davis[16] was improved as follows: To a mixture of thiophenol (33 g.), 39 g. of sodium carbonate and 120 cc. of water was added a solution of 47.1 g. of *o*-chloronitrobenzene in 150 cc. of hot ethanol. The mixture was stirred and warmed on the steam-bath for four hours, then poured in 500 cc. of cold water, filtered and washed with water. Recrystallization from 200 cc. of ethanol yielded 61 g. (87%) of bright yellow crystals, m. p. 78–80°. The reported value[16] is 82°.

2-Aminodiphenyl Sulfide.—This compound was obtained by reduction of the nitro compound, and also by the following procedure. 2-Chloroacetanilide (20 g.) and a few tenths of a gram of copper powder were added to a solution prepared by dissolving 13.2 g. of potassium hydroxide and 26 g. of thiophenol in 40 cc. of *n*-butanol with heating. The solvent was removed, the residue heated rapidly and held at 280–300° (inside temperature) for fifteen minutes. The cooled melt, which had darkened considerably, was taken up in hot benzene and 10% sodium hydroxide solution; the two layers were filtered with suction and separated. The benzene layer was evaporated, and the crude acetyl compound hydrolyzed with hydrochloric acid and ethanol. The amine was distilled at 154–160° (3 mm.), and 11 g. (46%) of material, m. p. 33°, obtained. The reported[16] m. p. is 35°.

4-Amino-3-phenoxybiphenyl.—3-Bromo-4-acetaminobiphenyl[17] (3 g.) and 0.1 g. of copper powder were added to the potassium salt from 10 g. of phenol, and the melt heated for thirty minutes at 180°. When worked up as above, 2.9 g. of crude 2-acetamino-5-phenyldiphenyl ether was obtained, which after six recrystallizations from dilute alcohol melted at 166–167°. The free amine obtained by hydrolysis melted at 100.5–101.5° after three recrystallizations from alcohol.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.74; H, 5.79. Found: C, 83.12; H, 5.79.

In a second preparation, the crude acetaminodiphenyl ether was hydrolyzed to the free amine directly, which was obtained in 50% yield by vacuum distillation, m. p. 94–99°. After one crystallization from alcohol, it melted at 99–101°.

4-Amino-3-thiophenoxybiphenyl.—3-Chloro-4-acetaminobiphenyl (20 g.), 20 cc. of thiophenol, 9 g. of potassium hydroxide, 30 cc. of *n*-butanol and a small amount of copper powder were heated at 260–280° for one hour. The reaction mixture was worked up as usual, yielding 13 g. (59%) of the free amine, m. p. 68–70°.

Anal. Calcd. for $C_{18}H_{15}NS$: C, 77.94; H, 5.45. Found: C, 77.87; H, 5.41.

The acetyl derivative melted at 132–134.5°. When the bromoacetaminobiphenyl was used instead of the chloro compound, a 66% yield was obtained.

2-Pyridylhydrazine.—This was prepared more conveniently from 2-bromopyridine than from the chloro compound,[18] and was obtained in 57% yield by heating the halogen derivative with 85% hydrazine hydrate at 125° for twenty-four hours.

3-Mercaptopyrido(2,1-c)-*s*-triazole.[19]—2-Pyridylhydrazine (5 g.) was added to 12 cc. of carbon disulfide in 40 cc. of chloroform. A precipitate was formed, and the mixture refluxed on the steam-bath for twenty hours, with the evolution of hydrogen sulfide. The crystals present were isolated, weighed 6.10 g. (88%), and melted at 209–210°. The product is insoluble in benzene and dioxane, but is soluble in methanol and dilute sodium hydroxide.[20]

Anal. Calcd. for $C_6H_6N_2S$: C, 47.7; H, 3.3; mol. wt., 151. Found: C, 48.1; H, 3.4; mol. wt. (Rast), 165.

This compound was also obtained by action of thiophosgene on 2-pyridylhydrazine.

(13) Analyses by Robert Bauman.

(14) *Cf.* Suter, THIS JOURNAL, **51**, 2583 (1929); the reported m. p. is 44–45°.

(15) *Cf.* Henley, *J. Chem. Soc.*, 1222 (1930); Mole and Turner, *ibid.*, 1720 (1939). The m. p. is reported as 75–76.5°.

(16) Cullinane and Davis, *Rec. trav. chim.*, **55**, 881 (1936).

(17) The preparation of this compound, which involves the separation of the constant melting mixture of 3-bromo-4-acetaminobiphenyl and 3,4′-dibromo-4-acetaminobiphenyl obtained as one of the products in the bromination of 4-acetaminobiphenyl (Kenyon and Robinson, *J. Chem. Soc.*, 3050 (1926); Case and Sloviter, THIS JOURNAL, **59**, 2381 (1937)) is laborious and unsatisfactory. The amine was acetylated and the acetyl derivative purified by recrystallization from dilute alcohol. The yield of fairly pure 3-bromo-4-acetaminobiphenyl, m. p. 158–159° (literature 161°), varied from 8 to 15% based on 4-acetaminobiphenyl. The 3-chloro 4-acetaminobiphenyl was readily obtained by chlorination of 4-acetaminobiphenyl (Scarborough and Waters, *J. Chem. Soc.*, 557 (1926).

(18) *Cf.* Fargher and Furness, *ibid.*, **107**, 688 (1915); Weissberger and Porter, THIS JOURNAL, **66**, 1849 (1944).

(19) Ring Index numbering.

(20) Mills and Schindler report this compound as melting at 205–206°, and their other properties agree with those of our material.

Thiocarbazone Preparations by the Fischer Method.—The preparation of *di-(2-methoxyphenyl)-thiocarbazone* (*X*) is typical of the procedures followed. 2-Methoxyphenylhydrazine (10 g.), 50 cc. of alcohol and 5 g. of carbon disulfide were refluxed on the steam-bath until hydrogen sulfide ceased to be liberated. The thiocarbazide was not isolated, but was treated directly in solution after cooling with enough 10% ethanolic potassium hydroxide to give a clear red color; the solution was allowed to stand with air bubbling through for about five minutes, and was acidified with 1 *N* sulfuric acid. The thiocarbazone was obtained as a black powder, and was isolated by filtration with thorough washing. In the alternate procedure, the alcoholic solution of the thiocarbazide was cooled and treated with 5 cc. of 30% hydrogen peroxide, allowed to stand five minutes, with stirring, and the product was washed with water and cold methanol.

Recrystallization of the thiocarbazone proved difficult. The best method found was to dissolve the substance in the minimum volume of chloroform, filter and precipitate by adding half the volume of methanol. The product formed a finely crystalline material, copper bronze in color. The m. p. and analysis are given in Table I.

Thiocarbazones by the Modified Nitroformazyl Procedure; Di-(2-phenoxyphenyl)-thiocarbazone.—2-Aminodiphenyl ether (b. p. 187–188° (30 mm.)) was dissolved in 160 cc. of concentrated hydrochloric acid and 270 cc. of water. The cold solution was diazotized by adding 23 g. of sodium nitrite in 135 cc. of water. After one hour the excess nitrous acid was removed with sulfamic acid, the solution was filtered through a sintered glass funnel and washed with 50 cc. of water. The solution was poured into 1430 g. of sodium acetate trihydrate in 725 cc. of glacial acetic acid, and stirred at room temperature for fifteen minutes, at which point most of the sodium acetate had dissolved; 25 cc. of nitromethane was added in one portion and the mixture stirred for five hours. The nitroformazyl precipitated rapidly, and the mixture was an almost solid mass after two hours; the product was collected, washed thoroughly with water and twice with alcohol. The nitroformazyl had not dried completely after standing several days on paper towels, and was reduced directly.

Reduction to the Thiocarbazide.—The nitroformazyl was added in one portion to 750 cc. of alcohol saturated with ammonium hydrosulfide. The color of the mixture changed from red to cream in thirty minutes; after stirring one hour, the slurry was poured into 2 liters of cold water, filtered, washed thoroughly with water and air dried on paper towels. It was not completely dry after two days.

Oxidation to the Thiocarbazone.—The thiocarbazide was dissolved in 2 liters of warm alcohol containing 35 g. of potassium hydroxide, and the calculated amount of 3% hydrogen peroxide (175 cc.) added. The mixture was heated almost to boiling on a hot plate, allowed to stand for fifteen minutes, then cooled in an ice-bath. When the temperature had reached 5°, the solution was filtered, and acidified with 100 cc. of concentrated hydrochloric acid. The precipitated thiocarbazone was filtered, and washed thoroughly with water and twice with methanol. The product was bronze colored and microcrystalline, m. p. 162–163.5° with dec., wt. 48 g. after air drying. For purification, it was dissolved in 500 cc. of hot chloroform, filtered and 800 cc. of hot methanol was added to the hot solution. Beautiful bronze crystals were obtained, m. p. 167–167.5° with decomposition (very slow heating), yield 39.5 g. (thoroughly air dried, or 58% based on amine).

Preparation of Diphenylthiocarbazone (Dithizone).—Dithizone was prepared by essentially the same method; 30 g. of clean nitroformazyl, m. p. 146–147°, was obtained from 37 g. of aniline. The sodium acetate and then the acetic acid were added directly to the diazonium solution. The coupling with the nitromethane proceeded quite slowly in the resulting 25% acetic acid solution with acetate–acetic acid ratio of 0.24.

A second preparation was run in the same manner but with an acetate–acetic acid ratio of 0.65. The reaction proceeded more rapidly; after two hours 200 cc. of water was added (changing the acetic acid concentration from 24 to 19%) because the reaction mixture had become too thick to stir. The thiocarbazone obtained from the usual oxidation step was quite pure without the final crystallization, as it melted sharply at 165–166°.

Interaction of Phenylhydrazine, Carbon Disulfide and Triethylamine.—To 15 g. of triethylamine and 25 g. of carbon disulfide in 50 cc. of chloroform was added dropwise 10.8 g. of phenylhydrazine. The mixture was heated on the steam-bath for five hours, causing evolution of hydrogen sulfide. After cooling, the mixture was subjected to steam distillation, and the residue crystallized, giving 18.6 g., m. p. 87–89°. Two crystallizations from benzene raised the m. p. to 91.5–92.5°. This product was shown to be the triethylamine salt of phenyldithiadiazolonmercaptan **XXII** by analysis, and by preparation from potassium phenyldithiadiazolonmercaptide[21] and triethylamine.

Anal. Calcd. for $C_{14}H_{21}N_3S_3$: C, 51.5; H, 6.4. Found: C, 51.9; H, 6.4.

2-Methylthiolphenylthiosemicarbazide (VII).—A mixture of 2-methylthiolphenylhydrazine and carbon disulfide in ethanol was refluxed overnight on the steam-bath. After the solvent was removed, the residue was treated with benzene and a white crystalline product was obtained, which, after two recrystallizations from xylene, melted at 172–173° with decomposition. Two recrystallizations from acetic acid did not change the m. p. or the percentage composition.

Anal. Calcd. for $C_8H_{11}N_3S_2$: C, 45.1; H, 5.2. Found: C, 45.3; H, 5.2.

When the heating with carbon disulfide was limited to an hour, the disproportionation did not occur, and the thiocarbazide and the thiocarbazone (XVII) were obtained.

Summary

A number of new substituted diarylthiocarbazones have been prepared, and several compounds obtained incidental to the work have been described. A modification of the Bamberger nitroformazyl procedure, consisting of coupling the diazonium compound with nitromethane in dilute acetic acid containing acetate ion, has been found useful.

ROCHESTER, NEW YORK RECEIVED DECEMBER 1, 1947

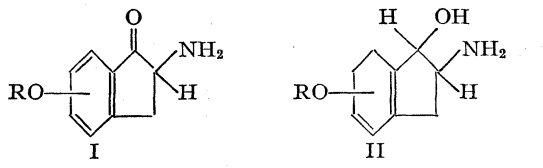
(21) Dubsky and Trtilek, *Z. anal. Chem.*, **96**, 412 (1934); Busch, *Ber.*, **27**, 2510 (1894).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Physiologically Active Indanamines. II. Compounds Substituted in the Aromatic Ring[1]

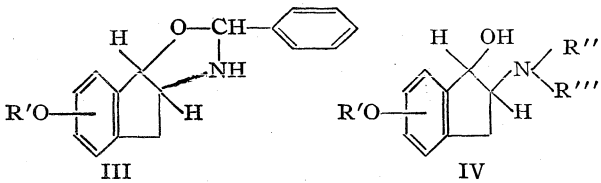
BY R. V. HEINZELMANN, H. G. KOLLOFF AND JAMES H. HUNTER

Previous work in this Laboratory[1] has shown that certain aminoindanes, aminoindanones and aminoindanols unsubstituted in the nucleus possess valuable properties as bronchodilators. For this reason it was considered desirable to prepare some derivatives of these compounds containing one or more hydroxyl or methoxyl groups in the aromatic ring. The present paper deals with indanamines substituted in this manner (I, II, III, IV).



I

II



III

IV

OR = 5-OH, 5-OCH_3, 6-OCH_3, 7-OCH_3, 4,5-di-OCH_3, 5-OCH_3-6-OH, 5,6-di-OCH_3, 5,6-O_2CH_2

OR′ = 5-OCH_3, 6-OCH_3, 7-OCH_3, 4,5-di-OCH_3, 5,6-di-OCH_3, 5,6-O_2CH_2

R″ = H, CH_3

R‴ = CH_3, $CH(CH_3)_2$, CH_2-C_6H_5

Much work has been done and considerable success achieved in efforts to correlate the pressor activity with the structure of phenethylamine derivatives.[2] However, when other physiological phenomena are considered, it is found that in general they do not parallel that of pressor activity. For instance, in the case of bronchodilator activity it is even found in some cases that structural changes which affect the pressor potency adversely tend to produce an increase in the bronchodilator effect.[1,3,4,5] In other cases,[5] no clear-cut relationship appears to exist between the two phenomena. In general, it may be stated that introduction of alkyl or aralkyl groups into the amino group reduces or even reverses the pressor effect, and at the same time favors bronchodilator activity[2,3,5]; large substituents of this type seem to be most effective.[5,6] This variation might thus be expected to result in the formation of an ideal bronchodilator. Extension of the side chain to three carbon atoms results in increased duration of action[7] and, as with the pressor property, confers oral activity due to increased resistance to deamination in the body.[8]

The adverse circulatory effect of alkoxyl substitution, as compared with hydroxyl substitution[2,9] in the benzene ring, has been shown recently not to apply with respect to bronchodilation.[5] Indeed, in twenty-four of thirty-one pairs studied the methoxyl derivative was equal to, or more active than, the corresponding hydroxyl derivative. These facts lend considerable interest to the compounds reported here.

The intermediate hydroxy-, methoxy- and methylenedioxyindanones were prepared from the corresponding substituted phenylpropionic acids by cyclization with anhydrous hydrogen fluoride or phosphorus pentoxide, and in one instance through their acid chlorides *via* the Friedel–Crafts reaction. Cyclization of *o*-hydroxy (methoxy) phenylpropionic acid has not been reported and difficulty in effecting ring closure in these acids having an *ortho*-directing group present was correctly anticipated.[10] Under the usual conditions,[11] attempts to cyclize with anhydrous hydrogen fluoride led to the formation of an amorphous product, insoluble in ordinary solvents,[12] together with a trace of starting material. When phosphorus pentoxide was employed under optimum conditions for this type of reaction,[13] no ring closure occurred. There was isolated a 70% yield of a compound, (m. p. 67–69.5°) whose analysis was in good agreement with the value calculated for the anhydride; on hydrolysis, the starting acid was recovered. Cyclization of *o*-nitrophenylpropionic acid,[14] as well as nitration of indanone with subsequent isolation of the 4-nitro isomer,[15] were not promising procedures because of inaccessibility of starting materials or difficulty in

(1) For the previous paper in this series, see Levin, Graham and Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

(2) For a recent discussion of the status in this field, see Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).

(3) Curtius, *J. Pharmacol.*, **35**, 321 (1929).

(4) Konzett, *Arch. Exptl. Path. Pharmakol.*, **197**, 27 (1940).

(5) Graham, Cartland and Woodruff, *Ind. Eng. Chem.*, **37**, 149 (1945).

(6) See, for instance, the German product "Aludrine" containing an *iso*propylamino group on the side chain; *C. A.*, **40**, 5154[2] (1946).

(7) Alles and Prinzmetal, *J. Pharmacol.*, **48**, 161 (1933).

(8) Beyer and Lee, *J. Pharmacol.*, **74**, 155 (1942); Beyer and Morrison, *Ind. Eng. Chem.*, **37**, 143 (1945).

(9) Tainter, Pedden and James, *J. Pharmacol.*, **51**, 371 (1934); Pedden, Tainter and Cameron, *ibid.*, **55**, 242 (1935); Cameron and Tainter, *ibid.*, **57**, 152 (1936).

(10) See, for example, Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945).

(11) Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).

(12) The substance was partially soluble in pyridine, and dissolved in concentrated sulfuric acid to give a cherry-red solution.

(13) W. S. Johnson, "Organic Reactions," Vol. II, 1944, p. 170.

(14) Hoyer, *J. prakt. Chem.*, **139**, 94 (1934).

(15) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923).

isolating the desired isomer. When the excellent cyclization procedure for *p*-methoxyphenylpropionic acid, using the Friedel–Crafts reaction,[10] was reported by Johnson, these conditions were applied to the *ortho*-isomer. There was obtained 46% of starting material, 45% of amorphous material (m. p. about 220–30°), soluble in pyridine, but not in the usual organic solvents, 6% of an alkali insoluble product (m. p. 103–110°), and a trace of alkali-insoluble material (m. p. about 140°) whose analysis was inconclusive but approached that of the desired indanone.

Of the other three monosubstituted indanones, the 5-hydroxy-(methoxy-) and 7-hydroxy-(methoxy-)indanones were prepared by cyclization of *m*-hydroxyphenylpropionic acid with anhydrous hydrogen fluoride,[16] followed by methylation; the 7-isomer can be prepared in only insignificant yields by this method. 6-Methoxyindanone was made by Johnson's Friedel–Crafts procedure[10]; however, using Ohio-Apex grade aluminum chloride the best yield obtained in a 10-g. batch was 39%.

Cyclodehydration of 2,4-dimethoxyphenylpropionic acid could not be achieved by the methods used; anhydrous hydrogen fluoride yielded a tar, and from an attempted cyclization using phosphorus pentoxide there was recovered 43% of starting material and 35% of an oil which appeared to be the acid anhydride. It is interesting that while 2,3-dimethoxy- and 3-methoxy-4-hydroxy-phenylpropionic acid could be cyclized in excellent yield using liquid hydrogen fluoride, this method was not applicable to 3,4-methylenedioxyphenylpropionic acid.

The substituted indanones were converted, through the 2-isonitroso derivatives, to the amino ketones and amino alcohols essentially as described[1] for the unsubstituted analogs. The tendency for solutions of the aminoketone hydrochlorides to become slightly red was prevented to a considerable extent by the addition of a trace of alcoholic hydrogen chloride during any recrystallization.

Reaction of the aminoindanols with benzaldehyde produced, instead of the Schiff bases, a mixture of bases which could be separated by fractional crystallization and converted to their respective hydrochlorides. In the monosubstituted series one of these proved to be the starting material, and the other, the oxazolidine (III), which is isomeric with the Schiff base.[17] Hydrogenation with active palladium charcoal gave the desired benzylaminoindanol hydrochlorides. In the disubstituted series, reaction of the aminoindanols with benzaldehyde produced, instead of the Schiff bases, racemic mixtures of diastereoisomeric oxazolidines which were separated and purified by fractional crystallization. The isomers on hydrogenation with palladium charcoal gave different benzylaminoalcohols. These benzylaminoalcohols could also be obtained as isomeric mixtures by reductive alkylation with benzaldehyde.

Reductive alkylation of 6-methoxy-2-aminoindanol and 5,6-dimethoxy-2-aminoindanol using acetone yielded the corresponding isopropylaminoindanols; when one mole of formaldehyde was used instead of acetone only the dimethylaminoindanols were formed.

The pharmacology of the aminoketones, aminoalcohols, oxazolidines and substituted aminoalcohols will be reported elsewhere.

The authors wish to acknowledge the technical assistance of Mr. Brooke D. Aspergren in a portion of this work.

Experimental[18]

Substituted Phenylpropionic Acids

The requisite cinnamic acids were prepared from the appropriately substituted benzaldehydes and malonic acid by the Doebner reaction.[19,20]

The cinnamic acids were converted to the corresponding phenylpropionic acids by electrolytic reduction or catalytic hydrogenation using Adams platinum catalyst.[21] The former procedure frequently resulted in products difficult to purify and almost invariably in lower yields.

In view of the difficulty in preparing *m*-hydroxybenzaldehyde,[23] the Schwenk–Papa Raney nickel reduction procedure[24] for preparing *m*-hydroxyphenylpropionic acid from the readily available piperonylacrylic acid was investigated. After numerous attempts and variations of this procedure had been made the maximum yield obtained was only 35%.

(16) Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 218 (1944).

(17) Indeed it appears that the compounds referred to by Levin, Graham and Kolloff[1] as Schiff bases are also oxazolidines. For instance, a sample (m. p. 163–165°) identical with their compound XX and prepared by their procedure was ether-soluble and formed a hydrochloride, m. p. 178–180° (dec.); the oxazolidine free base (m. p. 163–164°) could be regenerated from the hydrochloride. Our oxazolidine hydrochlorides showed a tendency to hydrolyze, even during recrystallization from alcohol and ether.

(18) Melting points are uncorrected. Microanalyses by Mr. C. H. Emerson and the staff of the microanalytical laboratory.

(19) "Organic Reactions," Vol. I, 1942, pp. 226–227.

(20) When condensation was carried out with crude *m*-hydroxybenzaldehyde (m. p. 98.5–100.5°) for four hours on the steam-bath, or for twelve days at room temperature, the yield of *m*-hydroxycinnamic acid after two crystallizations was 68 and 69.5%, respectively; however, when once-crystallized aldehyde (m. p. 102°) was employed under the latter conditions the yield was 93% and the product without purification melted higher than the twice purified acid above and could be hydrogenated directly. In the case of 3-methoxy-4-hydroxybenzaldehyde, the prolonged low-temperature modification (ref. 19, pp. 235 and 250) increased the yield from 50% to 94%.

(21) It was necessary to stop the hydrogenation of *p*-methoxycinnamic acid when one mole of hydrogen had been absorbed since hydrogen uptake continued rapidly until four moles had been consumed; even slight over-reduction caused purification difficulties. Catalytic hydrogenation (PtO_2) of piperonylacrylic acid in ethanol was too slow to be practicable due to its insolubility; hydrogenation was also too slow in glacial acetic acid even at an elevated temperature. The sodium salt of the acid could not be hydrogenated in aqueous alcohol or in distilled water. Toward the end of this work hydrogenation of the acid in warm dioxane was reported.[22] This method proved satisfactory; after having been filtered from the catalyst and concentrated to half the volume, the dioxane solution was mixed with chipped ice and shaken, whereupon the product was deposited as fine, glistening crystals.

(22) Barltrop, *J. Chem. Soc.*, 958 (1946).

(23) "Organic Syntheses," Vol. 25, p. 55.

(24) Schwenk and Papa, *J. Org. Chem.*, **10**, 232 (1945).

Indanones, Aminoindanones and Aminoindanols

Cyclization of the substituted phenylpropionic acids was carried out as indicated in Table I.

5-Methoxy-6-hydroxyindanone.—Fifty grams of crude hydroferulic acid (m. p. 85–88°), prepared by catalytic hydrogenation of ferulic acid and evaporation of the alcoholic solution to dryness, was placed in a pint copper retort. Four hundred grams of chilled anhydrous hydrogen fluoride was added, the top quickly clamped in place, the retort swirled gently once and left overnight with the side arm projecting into the vent of a good hood. The amber liquid was then evaporated gently on the steam-bath in a copper beaker to a purple paste and then to a gray-purple powder. This was suspended in 8 to 10 liters of boiling water, treated with charcoal, filtered quickly while hot, and allowed to cool; yield, 38.2 g. (85%) of beautiful, long, golden needles, m. p. 192–192.5°. Concentration of the filtrate to 3 liters gave 2.0 g. more, and re-extraction of the residue from the first extraction with 750 cc. of boiling water gave an additional 0.8 g.; total yield, 41 g. or 91%.

All cyclizations of this type attempted in open or partially covered copper beakers gave poor to negative results, probably due to condensation of moisture from the air on the cold walls of the beaker.

As indicated in Table I, the isonitrosoindanones were prepared by three methods: using methyl nitrite and anhydrous ethereal hydrogen chloride, butyl nitrite and concentrated hydrochloric acid in methanol, or butyl nitrite and dry hydrogen chloride gas in ether. In general they had to be recrystallized at least twice to attain sufficient purity to undergo subsequent hydrogenation. Conversion (two atmospheres pressure of hydrogen and active palladium Norite) to the aminoketone hydrochlorides was carried out in absolute alcoholic hydrogen chloride, and these were then hydrogenated to the amino-alcohol hydrochlorides in distilled water (Table II); yields were practically quantitative. Occasionally an elevated temperature and two or three additions of catalyst were necessary to effect complete reduction. The aminoindanone hydrochlorides are considerably less soluble in alcohol than the aminoindanol hydrochlorides. With both classes of compounds water was occasionally added in small amounts to dissolve the product away from the catalyst, and during recrystallization to keep the volume down. Raney nickel and also PtO_2 (elevated temperature) were used in the reduction of one of the aminoketone hydrochlorides and were found to be satisfactory catalysts. The hydroxymethoxyamine hydrochlorides seemed to be somewhat more unstable than the corresponding dimethoxy compounds.

Oxazolidines and Benzylaminoindanols (Table III)

Preparation of the monosubstituted oxazolidines may be illustrated by the formation of III from 5-methoxy-aminoindanol hydrochloride.

Two and sixteen-hundredths grams (0.01 mole) of the amino alcohol hydrochloride was heated under reflux for six hours in 50 cc. of 95% alcohol with 1.20 cc. (0.012 mole) of benzaldehyde and 0.84 g. (0.01 mole) of sodium bicarbonate. The solution was filtered from the sodium chloride, concentrated to about one-third, excess water added and the oily suspension chilled, giving 2.52 g. (94%) of buff-colored solid. After recrystallization (Norite) from about 15 cc. of 3A alcohol a product was obtained which proved to be the free base of the starting material.

The filtrate from the alcohol recrystallization of the free base was treated with water and chilled, giving about one gram of white solid, m. p. 85°. Without purification it was converted into the oxazolidine hydrochloride which, after recrystallization from alcohol–ether, melted at 154.5° (dec.).

Anal. Calcd. for $C_{17}H_{18}O_2NCl$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.16; H, 5.69; N, 4.60.

Similarly in the disubstituted series attempts to prepare the Schiff bases by treating the amino alcohol hydrochlorides with an equivalent amount of benzaldehyde and sodium bicarbonate in 3A alcohol resulted in the formation of oxazolidines in all cases; here, however, conditions were such that two racemic mixtures of the latter could often be isolated. For example, with 5,6-dimethoxy-indanol hydrochloride two racemic mixtures of the oxazolidine were formed by this procedure, and also when a dry fusion of the amine hydrochloride, benzaldehyde and sodium acetate was made *in vacuo* at 100 to 150°; a dry fusion at room temperature for several days gave smaller yields of the desired products as well as some starting material as the free base and some which analyzed as the acetate of the starting base. The formation of isomeric mixtures made estimation of yields as well as melting points difficult.

In the case of 5,6-dimethoxyaminoindanol hydrochloride the solid product, obtained by precipitation from the reaction mixture with water, was recrystallized from acetone–ether; fractionation resulted in separation of the isomers. In the remainder of the disubstituted series the oxazolidines were ether-soluble; the precipitate was either recrystallized from dilute alcohol to separate the isomers or converted to the hydrochloride prior to fractionation from alcohol–ether.

TABLE I

INDANONES AND ISONITROSOINDANONES

Indanone	Condensing agent	Yield, %	Yield of isonitroso-indanone, %
4-OCH_3	HF, P_2O_5, $AlCl_3$	0, 0, 0	
5-OH	HF[a]	89.5	78[b]
5-OCH_3	[c]	89	96[d]
6-OCH_3	$AlCl_3$	80[e]	77[d]
7-OH	HF[a]	7	
7-OCH_3	[f]	85	88[g]
4,5-di-OCH_3	HF[h]	80–85	90[i]
4,6-di-OCH_3	HF[j]	0	
5-OCH_3-6-OH	P_2O_5, HF[k]	0, 80–91	81[l]
5,6-di-OCH_3	[m]	92	95[n]
5,6-O_2CH_2	HF, P_2O_5	0, 72[p]	77[q]

[a] For prep., see ref. 16. [b] M. p., 212–214° (dec.). [c] From the -OH compound. [d] See ref. (25). [e] From a 3 g. batch; yield for larger batches much less; using HF yield was 1%, recovery of starting material, 88%, see ref. 10. [f] From the -OH compd., m. p., 99.5–100°; *anal.*: calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.21; found: C, 74.09; H, 6.27. [g] M. p. about 250° (dec.); *anal.* calcd. for $C_{10}H_9O_3N$: C, 62.82; H, 4.74; N, 7.33; found: C, 62.82; H, 4.74; N, 7.32. [h] Previously prepared using P_2O_5, no yield given, see ref. (26); and $AlCl_3$ (yield good), see ref. (27). [i] See ref. 28. [j] This indanone unknown. [k] Previously prepared using H_2SO_4 (yield about 30%), ref. 29. [l] Prepared with butyl nitrite in absolute CH_3OH; recrystallized from 50% alcohol; m. p. 240° (dec.); N: calcd., 6.76; found, 6.89. [m] Prepared from 5-methoxy-6-hydroxyindanone; m. p. 118.5°. [n] Using method of ref. 1; 61% by method of ref. 30; 92% using methyl nitrite, see ref. 31. [p] Based on acid added; 22% of starting material recovered; previously prepared using $AlCl_3$ (yield 15%), ref. 32; P_2O_5 (87%), ref. 32; and since this work was completed, using $SnCl_4$ by the Friedel-Craft reaction (92%), ref. 22. [q] For preparation, see ref. 30.

(25) Chakravarti and Swaminathan, *J. Ind. Chem. Soc.*, **11**, 101 (1934).

(26) Perkin and Robinson, *J. Chem. Soc.*, 2388 (1914).

(27) Ruhemann, *Ber.*, **53**, 280 (1920).

(28) Perkin and Robinson, *J. Chem. Soc.*, 2389 (1914).

(29) Konek and Szamak, *Ber.*, **55**, 106 (1922).

(30) Perkin and Robinson, *J. Chem. Soc.*, 1073 (1907).

(31) "Org. Synth.," Coll. Vol. II, 1944, p. 363.

(32) Perkin and Robinson, *J. Chem. Soc.*, 1084 (1907).

TABLE II

AMINOINDANONES AND AMINOINDANOLS

Ring substituent	Aminoindanone hydrochlorides M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Aminoindanol hydrochlorides M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-OH	[a]	54.17	54.18	5.05	5.10	7.02	7.12	[b]	53.60	53.64	5.96	5.95	6.95	7.13
5-OCH_3	225–227 (dec.)	56.21	56.22	5.66	5.56	6.56	6.44	[c]	55.68	55.78	6.54	6.62	6.50	6.54
6-OCH_3	[d]	56.21	56.32	5.66	5.68	6.56	6.65	[e]	55.68	55.65	6.54	6.53	6.50	6.56
7-OCH_3	[f]	56.21	56.39	5.66	5.62	6.56	6.47	170 (dec.)	55.68	55.69	6.54	6.68	6.50	6.44
4,5-di-OCH_3	185 (dec.)	54.21	54.16	5.79	6.02	5.75	5.48	183 (dec.)	53.77	53.94	6.56	6.64	5.70	6.02
5-OCH_3-6-OH	[g]	48.49	48.49[h]	5.70	5.73[h]	5.66	5.73[h]	[i]	51.83	51.72	6.09	6.20	6.05	6.19[j]
5,6-di-OCH_3	245 (dec.)	54.21	54.11	5.79	5.82	5.75	5.82[k]	[l]	53.77	53.94	6.56	6.59	5.70	5.69[m]
5,6-O_2CH_2	[n]	52.80	53.05	4.41	4.47	6.16	5.98	[p]	52.30	52.60	5.25	5.22	6.10	6.08

[a] Discolors about 227°; melts (dec.) only if immersed at 275°, otherwise gradual softening and decomposition. [b] Darkens at about 120°; no real melting even when immersed at 135°. [c] Softens rapidly (dec.) when immersed at 165°, but only slowly at 160°. [d] Decomposes from 210 to 232° depending on rate of heating and temperature of immersion. [e] M. p. (dec.) from 217 to 222° depending on rate of heating, etc. [f] Decomposes about 250° when immersed at about 245°. [g] Melts (dec.) when immersed at 300° or above. [h] Analysis calcd. for monohydrate. [i] Melts (dec.) when immersed at 258° or above. [j] Cl: calcd., 15.31; found, 15.42. [k] Cl: calcd., 14.56; found, 14.54. [l] Darkens about 200°. [m] Cl: calcd., 14.43; found, 14.50; free base, from benzene–petroleum ether, m. p. 113–116°; *anal.*: calcd. for $C_{11}H_{15}O_3N$: C, 63.16; H, 7.23; N, 6.70; found: C, 63.51; H, 7.21; N, 6.74. [n] Darkens about 230°; m. p. 243° (dec.). [p] Melts (dec.) when immersed at 240° or above.

TABLE III

OXAZOLIDINES AND BENZYLAMINOINDANOL HYDROCHLORIDES

Ring substituents	Oxazolidines (A) Isomers	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Benzylamines (B) Isomers	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5-OCH_3	A-HCl	154.5 (dec.)	67.21	67.16	5.97	5.69	4.61	4.60	B-HCl	189.5	66.77	66.56	6.59	6.60	4.58	4.62
6-OCH_3	A-HCl	137[a]	67.21	[b]	5.97	[b]	4.61	[b]	B-HCl	211–213	66.77	66.56	6.59	6.79	4.58	4.60
7-OCH_3	A-HCl	187.5[c]	67.21	67.01	5.97	5.97	4.61	4.64	B-HCl	181	66.77	66.75	6.59	6.75	4.58	4.52
4,5-di-OCH_3	A	90.5–93	72.71	72.79	6.44	6.19	4.71	4.89								
	A-HCl	148–150 (dec.)	64.75	65.10	6.00	6.43	4.19	4.33	B-HCl	168.5–169[d]	64.37	64.26	6.60	6.72	4.17	4.44
5,6-di-OCH_3	A_1	165.5–166.5	72.71	72.95	6.44	6.65	4.71	4.99	B_1	143–144	72.20	72.23	7.07	7.02	4.68	4.52
	A_1-HCl	192 (dec.)[e]	64.75	65.04	6.00	5.99	4.19	4.35	B_1-HCl	200 (dec.)	64.37	64.39	6.60	6.71	4.17	4.37
	A_2	123–124	72.71	72.54	6.44	6.44	4.71	4.70	B_2	156–156.5[f]	72.20	72.24	7.07	7.11	4.68	[f]
									B_2-HCl	184 (dec.)	64.37	63.90	6.60	6.69	4.17	4.44
5,6-O_2CH_2	A_1	184.5–185.5[g]	72.58	72.80	5.38	5.58	4.98	4.92	B_1	169.5–173	72.07	72.40	6.04	6.07	4.95	4.72
	A_2	95–96	72.58	72.83	5.38	5.67			B_2	148–149.5[h]	72.07	72.03	6.04	6.40		

[a] Approximate; free base melts about 80–82°. [b] Compound hydrolyses progressively on recrystallization, even from absolute alcohol–ether, giving a progressively higher decomposition point; *anal.* after 2 recrystallizations: C, 63.15; H, 6.33; N, 5.12. [c] Free base, m. p. 150.5–152°. [d] Obtained also a second crop, m. p. 180° (dec.) (isomeric?). [e] Without recrystallization; recrystallization, even from absolute alcohol, causes conversion into a product, darkening, but not melting, below 200°, and giving a m. p. depression with the unrecrystallized material; may result from hydrolysis to the original aminoalcohol–HCl. [f] Mixed m. p. with B_1, 130°; compound too highly charged to permit good combustions, or any nitrogen analysis. [g] Hydrochloride darkens about 191°. [h] Mixed m. p. with B_1, 136°.

During the work-up of several of the oxazolidines there were indications that these compounds were gradually hydrolyzing to yield benzaldehyde and the amino alcohol. This was most apparent in the case of the 6-methoxy compound. Here the odor of benzaldehyde persisted throughout the fractionation from dilute alcohol, even though the alcohol solutions were diluted with water at room temperature. During the purification of the oxazolidine hydrochloride considerable amounts of the starting amino alcohol hydrochloride (identified by analysis and mixed melting point) were isolated. The oxazolidine hydrochloride (m. p. about 137° (dec.)) analyzed poorly, and further recrystallization from absolute alcohol–ether caused the melting point to broaden and rise toward that of the amino alcohol; the filtrate from this yielded considerable benzaldehyde, identified as the dinitrophenylhydrazone. Conversion of the oxazolidine to the benzylamino alcohol was considered as sufficient evidence of structure.

Hydrogenation of the bases (platinum oxide or active palladium charcoal) gave the desired benzylamines which were converted into the hydrochlorides. In some cases, however, it was found advantageous to hydrogenate the oxazolidine hydrochlorides to the benzylamine hydrochlorides, using active palladium charcoal; reaction was usually complete in about three quarters of an hour.

Reductive Alkylations

6-Methoxy-2-isopropylaminoindanol-1 Hydrochloride.—Four and thirty-one hundredths grams (0.02 mole) of 6-methoxy-2-aminoindanol-1 hydrochloride, 1.6 cc. (0.022 mole) of acetone and 2.12 g. (0.02 mole) of sodium carbonate were shaken in a Parr hydrogenation apparatus in the presence of 0.5 g. of pre-reduced Adams platinum catalyst in absolute ethanol under a hydrogen pressure of two atmospheres. Hydrogenation was complete in an hour and the filtrate from the catalyst was poured into cold ethereal hydrogen chloride and chilled. After recrystallization from absolute alcohol the white crystals melted at 214° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.57; H, 7.82; N, 5.44. Found: C, 60.54; H, 7.66; N, 5.29.

6-Methoxy-2-dimethylaminoindanol-1 Hydrochloride.—This compound was prepared similarly to that above except that slightly more than two molecular equivalents of formaldehyde (as a 37% solution) were used. The filtrate from the catalyst was concentrated to about a third before conversion to the hydrochloride. After recrystallization the product melted at 215–215.5° (dec.).

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: C, 59.13; H, 7.44; N, 5.75. Found: C, 59.07; H, 7.23; N, 5.84.

5,6-Dimethoxy-2-benzylaminoindanol-1 Hydrochloride.—Four and ninety-one hundredths grams (0.02 mole) of the primary aminoalcohol hydrochloride, 2.12 g. (0.02 mole) of freshly distilled benzaldehyde and 2.12 g. (0.02 mole) of sodium carbonate were added to a suspension of freshly reduced Adams platinum catalyst in absolute ethanol and the mixture subjected to hydrogenation at three atmospheres pressure. The calculated uptake of hydrogen occurred in thirty minutes after which the suspension was warmed, filtered from the catalyst and the filtrate poured into chilled ethereal hydrogen chloride. After chilling, the white precipitate was collected and recrystallized several times from absolute alcohol. The pure white, crystalline product melted at 181.5° (dec.).

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.36; H, 6.58; N, 4.41.

In some cases starting material was isolated by the addition of ether to the alcohol filtrate from the main product.

5,6-Dimethoxy-2-isopropylaminoindanol-1 Hydrochloride.—By a procedure similar to that described above but using acetone, there was obtained a product which, after several recrystallizations from absolute alcohol, amounted to 2.3 g. and melted at 190° (dec.).

Anal. Calcd. for $C_{14}H_{22}O_3NCl$: C, 58.43; H, 7.71; N, 4.87. Found: C, 58.54; H, 7.66; N, 5.05.

5,6-Dimethoxy-2-dimethylaminoindanol-1 Hydrochloride.—By a procedure analogous to that described above but using one mole of formaldehyde there was obtained no monomethylamine, but only the dimethylaminoindanol hydrochloride, melting at 172° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.03; H, 7.36; N, 5.12. Found: C, 56.87; H, 7.46; N, 5.58.

Summary

A series of thirty-six aminoindanones, aminoindanols and N-substituted aminoindanols containing one or more hydroxyl, methoxyl or methylenedioxy groups in the aromatic ring, have been synthesized. The nitrogen substituents were hydrogen, dimethyl, isopropyl and benzyl; the benzylaminoindanols were prepared through the intermediate oxazolidines and were in some cases isolated in two racemic forms.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 29, 1947

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Structures of Some Isopropylidene-*aldehydo*-L-arabinose Derivatives

BY JAMES ENGLISH, JR., AND PAUL H. GRISWOLD, JR.[1]

In a previous paper[2] the positions of the isopropylidene groups in di-isopropylidene-*aldehydo*-L-arabinose and the products of its reaction with Grignard reagents were left indeterminate. An extension of our work on C-substituted pentitols has disclosed evidence leading to the establishment of the structures of these arabinose derivatives in both the D- and L- series.

The triacetone mannitol of Fischer[3] has been shown by Wiggins[4] to be 1,2:3,4:5,6-triacetone mannitol. A graded hydrolysis of this substance[4,5] has been found to yield a diacetone mannitol which Wiggins has converted to an *aldehydo*-diacetone-D-arabinose by lead tetraacetate oxidation. In view of the earlier work of Brigl and Grüner[6] and of Baer and H. O. L. Fischer[7] the structure of this arabinose derivative may be considered established beyond reasonable doubt as 2,3:4,5-diacetone-*aldehydo*-D-arabinose.

2,3:4,5-Di-isopropylidene-*aldehydo*-D-arabinose prepared by the method of Wiggins, or better by periodate oxidation of the same starting material, was treated with cyclohexylmagnesium chloride to form a crystalline di-isopropylidene-1-C-cyclohexylpentitol. This substance was found to be the enantiomorph of the di-isopropylidene-1-C-cyclohexylpentitol previously prepared in this Laboratory[2] from di-isopropylidene-*aldehydo*-L-arabinose. On recrystallizing an equimolar mixture of the two enantiomorphs there resulted a di-isopropylidene-D,L-1-C-cyclohexylpentitol which gave a depression in mixed melting points with both isomers.

In the preparation of di-isopropylidene-L-arabinose diethyl mercaptal the intermediate monoisopropylidene derivative was obtained in a manner analogous to that reported by Gätzi and Reichstein[8] for the D-isomer. Since this substance can be converted into the di-isopropylidene derivative[8] by excess acetone it is evident that the isopropylidene group in this case must be on either the 2,3 or the 4,5 carbon atoms. A lead tetraacetate oxidation of monoisopropylidene-L-arabinose diethyl mercaptal followed by removal of the mercaptal and isopropylidene groups, led to a mixture from which glyoxal was identified as its nitrophenylhydrazone and dinitrophenylhydrazone. This established the structure of this substance as 4,5-isopropylidene-L-arabinose diethyl mercaptal, since no other monoisopropylidene derivative would be expected to yield glyoxal.

Hence it may be concluded that the positions of the isopropylidene groups in this series are as shown in the reaction scheme below.

It is worthy of note that in both the D- and L-series the ratio of the two stereoisomeric pentitols obtained in the reaction of *aldehydo*-di-isopropylidene arabinose with cyclohexylmagnesium chloride is far from unity. In one case as much as

(1) Taken from the thesis presented by Paul H. Griswold, Jr., to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) J. English, Jr., and P. H. Griswold, Jr., THIS JOURNAL, **67**, 2039 (1945).

(3) E. Fischer, *Ber.*, **28**, 1167 (1895).

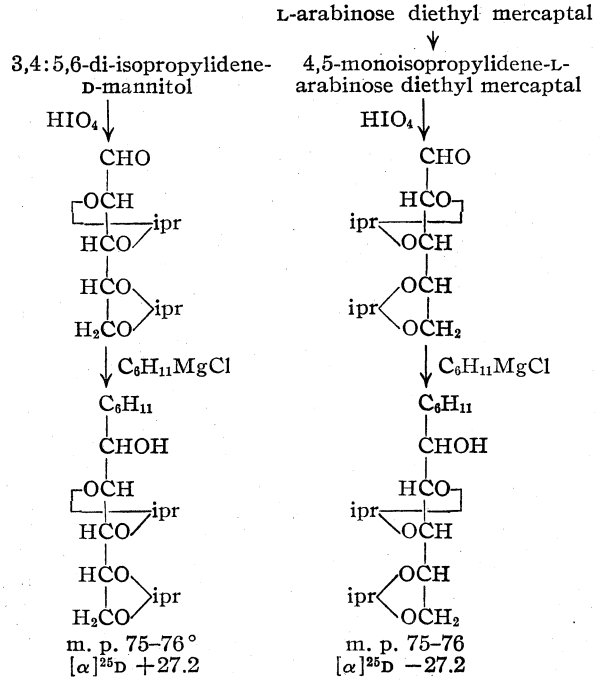
(4) Wiggins, *J. Chem. Soc.*, 13 (1946).

(5) Irvine and Patterson, *ibid.*, 898 (1914).

(6) Brigl and Grüner, *Ber.*, **66**, 931 (1933).

(7) H. O. L. Fischer and Baer, *Helv. Chim. Acta*, **17**, 622 (1943).

(8) Gätzi and Reichstein, *ibid.*, **21**, 914 (1938).



80% of the total 1-C-cyclohexylpentitol was obtained as a pure isomer, crystallized to constant rotation, and it has not yet been possible to isolate any of the other anomer in pure form.

Experimental[9]

2,3:4,5-Di-isopropylidene-*aldehydo*-D-arabinose.—This substance was prepared by oxidation of 3,4:5,6-di-isopropylidene-D-mannitol by the method of Wiggins[4] with a yield of 19%. Improved yields were obtained as follows.

In a well-stirred and cooled flask was placed a solution of 31.4 g. of 3,4:5,6-di-isopropylidene-D-mannitol dissolved in 100 cc. of water. A solution of 28.8 g. of sodium periodate in 450 cc. of water was added, maintaining the temperature at 0–5°. The reaction mixture was allowed to remain at this temperature for thirty minutes, then saturated with salt and extracted with ten 100-cc. portions of chloroform. After drying over sodium sulfate, removing the solvent at room temperature and distillation, there was obtained 24.6 g. (89%) of colorless sirupy 2,3:4,5-di-isopropylidene-*aldehydo*-D-arabinose, b. p. 60–65° (0.08 mm.). This compound was found to be unstable as shown by a change in rotation with time from an initial $[\alpha]^{22}D$ −18.2° in chloroform (*c*, 13.5) to $[\alpha]^{25}D$ +16 after standing for two months. Accordingly the fresh preparations were used immediately for subsequent operations.

1-C-Cyclohexyl-2,3:4,5-di-isopropylidene-D-arabitol.[10]—To a solution of cyclohexylmagnesium chloride prepared from 33.4 g. of chlorocyclohexane and 7.69 g. dry magnesium in 100 cc. dry ether was added 22.5 g. of 2,3:4,5-di-isopropylidene-*aldehydo*-D-arabinose in 100 cc. of ether. The reaction mixture was refluxed for fifteen minutes, cooled in ice, and decomposed with saturated ammonium chloride solution. After ether extraction, drying over sodium sulfate and removal of solvent at low temperatures there remained a solid that was recrystallized from petroleum ether (30–60° b. p.). The yield was 18 g. of 1-C-cyclohexyl-2,3:4,5-di-isopropylidene-D-arabitol after recrystallization to a constant melting point 75–76° and constant rotation $[\alpha]^{25}D$ +27.2 in pyridine (*c*, 2.8). *Anal.* Calcd. for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.96; H, 9.60.

1-C-Cyclohexyl-2,3:4,5-di-isopropylidene-D,L-arabitol.—This substance was prepared by mixing saturated hot petroleum ether solutions of the two enantiomorphs. On cooling the D,L-form separated as large prisms with a melting point 90° which could not be altered by further recrystallization. Mixed melting points with both the D- and L-forms were depressed. *Anal.* Calcd. for $C_{17}H_{30}O$: C, 64.94; H, 9.62. Found: C, 65.05; H, 9.83.

1-C-Cyclohexyl-D-arabitol was prepared by the hydrolysis of its di-isopropylidene derivative as already described for its enantiomorph.[2] After recrystallization from ethanol to constant properties a crystalline product, m. p. 148°, $[\alpha]^{24}D$ −12.6° in pyridine (*c*, 5.2), was obtained. On drying at 60° prior to analysis it was observed that the rotation had changed to $[\alpha]^{24}D$ −15.0° in pyridine (*c*, 4.4). This same phenomenon was then observed with the previously reported L-isomer which was found to change to $[\alpha]^{25}D$ + 15.0°. The loss of weight corresponded to the loss of one molecule of ethanol of crystallization in each case. Since the solvent is reasily lost even in the melting point tube without much change in crystal structure the melting points of both the alcoholate and the free pentitol are apparently the same.

Anal. Calcd. for $C_{11}H_{22}O_5 \cdot C_2H_5OH$: C, 55.68; H, 10.06. Found: C, 55.75; H, 10.37. Calcd. for $C_{11}H_{22}O_5$: C, 56.34; H, 9.47. Found: C, 56.24; H, 9.33. 7.616 g. alcoholate lost 0.848 g. at 60°. Calcd. for $C_{11}H_{22}O_5.C_2H_5OH$: 0.8478 g.

4,5-Monoisopropylidene-L-arabinose Diethyl Mercaptal.—Thirty grams of L-arabinose diethyl mercaptal was shaken with 600 cc. of dry acetone and 150 g. of anhydrous copper sulfate for three days. Some sodium carbonate was added to insure freedom from acidity, the solution filtered and evaporated at room temperature. There was obtained 29 g. of crude product (m. p. 72°) which was recrystallized from ether–petroleum ether to yield pure 4,5-minoisopropylidene-L-arabinose, m. p. 75.6° and $[\alpha]^{23}D$ +7.6° in methanol (*c*, 8.5). Gätzi and Reichstein[3] reported the same melting point and $[\alpha]^{19}D$ −7.4° in methanol for the D-form.

Anal. Calcd. for $C_{12}H_{24}O_4S_2$: C, 48.7; H, 8.2; Found: C, 49.0; H, 8.3.

Lead Tetraacetate Oxidation of 4,5-Isopropylidene-L-arabinose Diethyl Mercaptal.—A fine suspension of 15 g. of lead tetraacetate in 400 cc. of benzene was stirred vigorously at room temperature with 10 g. of 4,5-di-isopropylidene-L-arabinose diethyl mercaptal. In ten minutes all the oxidizing agent had been consumed. The mixture was filtered and the benzene removed through a fractionating column. The residue distilled at 48–52° (14 mm.). After heating with 4 *N* sulfuric acid for ten minutes the distillate yielded a crystalline *p*-nitrophenylhydrazone. After recrystallization from nitrobenzene, pure glyoxal *p*-nitrophenylhydrazone m. p. 306° (dec.) was obtained. *Anal.* Calcd. for $C_{14}H_{12}O_4N_6$: N, 26.5. Found: N, 25.9. The dinitrophenylhydrazone m. p. 321° (dec.) was also prepared. *Anal.* Calcd. for $C_{14}H_{10}O_8N$: N, 26.8. Found: N, 27.0.

1-C-Cyclohexyl-1,2,3,4-tetraacetyl-5-trityl-D-arabitol was prepared in the same manner as already reported for the enantiomorphous pentitol. There was obtained an 82% yield of pure material, m. p. 134°, $[\alpha]^{25}D$ +15° pyridine (*c*, 27.2). *Anal.* Calcd. for $C_{38}H_{44}O_9$: C, 70.79; H, 6.88. Found: C, 70.80; H, 6.97.

Summary

The position of the isopropylidene groups in 2,3:4,5-di-isopropylidene-D- and L-arabinose diethyl mercaptal and related compounds has been

(9) All melting points are corrected.

(10) These pentitols are referred to as arabitols to distinguish them from the corresponding derivatives prepared from other aldehydo sugars. It is recognized that proper nomenclature must await the establishment of the configuration of the new asymmetric carbon atoms in this series.

established by conversion through D- and L-di-isopropylidene-*aldehydo*-arabinose to enantiomorphous, crystalline, 1-C-cyclohexylarabitols. These substances have all been related to 3,4:5,6-di-isopropylidene-D-mannitol of known structure.

The position of the isopropylidene group in 4,5-isopropylidene-L-arabinose diethyl mercaptal has been established by lead tetraacetate oxidation.

1-C-Cyclohexyl-1,2,3,4-tetraacetyl-5-trityl-D-arabitol has been prepared.

NEW HAVEN, CONNECTICUT
RECEIVED SEPTEMBER 20, 1947

[CONTRIBUTION NO. 230 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

1-Thiosorbitol

BY M. W. FARLOW, MADISON HUNT,[1] C. M. LANGKAMMERER, WILBUR A. LAZIER,[2] W. J. PEPPEL[3] AND F. K. SIGNAIGO[4]

The deactivation or poisoning of hydrogenation catalysts by even small amounts of sulfur, hydrogen sulfide, or sulfur-containing organic compounds is a familiar phenomenon of hydrogenation chemistry. Accordingly, the discovery in this laboratory[5] that catalysts, such as cobalt polysulfide, function effectively in the conversion of aldehydes, ketones, and nitriles to thiols by hydrogenation in the presence of sulfur or hydrogen sulfide represents an important advance in this field.

Among the aldehydes and ketones to which this reaction can be applied, sugars are of especial interest since their hydrogenation in the presence of hydrogen sulfide has made available for study a variety of new polyhydroxyalkane monothiols. This paper describes the preparation, properties, and more interesting chemical reactions of 1-thiosorbitol[6] which is derived from D-glucose.

The preparation of thiosorbitol from D-glucose by hydrogenation in the presence of sulfur can be represented by the equations

$$H_2 + S \xrightarrow{\text{catalyst}} H_2S$$

$$CH_2OH\overset{\overset{\text{O}}{\frown}}{CH}(CHOH)_3CHOH + H_2S \longrightarrow \left[CH_2OH\overset{\overset{\text{O}}{\frown}}{CH}(CHOH)_3CHSH\right] + H_2O$$

$$\left[CH_2OH\overset{\overset{\text{O}}{\frown}}{CH}(CHOH)_3CHSH\right] + H_2 \xrightarrow{\text{catalyst}} CH_2OH(CHOH)_4CH_2SH$$

This mechanism is supported by the following facts: (1) thioketones and thioaldehydes readily hydrogenate to thiols under the conditions used here; (2) aldehydes and ketones have not undergone hydrogenation to alcohols under the conditions and with the catalysts used here; and (3) alcohols and hydrogen sulfide have not yielded thiols under these conditions. The reactions indicated have been carried out conveniently in pressure equipment using an aqueous reaction medium, free sulfur, and commercial dextrose. At 125–150° and a hydrogen pressure of 1000–1500 lb./sq. in. the reaction is complete in three to four hours. There is obtained a good yield of crude thiosorbitol sirup from which highly purified thiosorbitol can be isolated by several procedures. The preferred method for the isolation of thiosorbitol involves preparation and separation of the cuprous salt which is suspended in ethanol and treated with hydrogen sulfide to regenerate the free thiol. The aqueous solution is evaporated to dryness, and white crystalline 1-thiosorbitol, m. p. 92–93°, is recovered in 25–30% over-all yields by crystallization at low temperatures from alcohol. Nearly pure varieties of thiosorbitol can be obtained by direct crystallization of concentrated crude sirup from ethanol or by oxidation to the corresponding disulfide, which is recrystallized and subsequently cleaved by catalytic reduction in the presence of sulfactive catalysts. Crude thiosorbitol sirup contains organic sulfur compounds which are not thiols. Some of these products are thought to be the result of side reactions involving thioacetal formation or dehydration of thiosorbitol to cyclic sulfides. Low molecular weight cleavage products are also present in crude sirup. Removal of these prior to the above purification procedure is best accomplished by steam distillation or by extracting the aqueous reaction medium with an immiscible organic solvent.

1-Thiosorbitol is a white, crystalline, water-soluble compound showing the reactions characteristic of aliphatic mercaptans and of polyhydric alcohols. For example, oxidation with iodine in hot absolute alcohol gives the corresponding disulfide in excellent yields. The hexaacetate can be prepared by treatment of thiosorbitol with fused sodium acetate and acetic anhydride at 100°. The corresponding benzoate was obtained as a sirup.

Reaction of 1-thiosorbitol in alkaline dioxane with *n*-dodecyl bromide yields *n*-dodecyl 2,3,4,5,6-pentahydroxyhexyl sulfide.

Perhaps the most unusual property of 1-thiosorbitol is its ability to form water soluble salts with a

(1) Present address, Jackson Laboratory, E. I. du Pont de Nemours & Co., Deepwater, N. J.

(2) Present address, Chas. Pfizer and Co., Brooklyn, N. Y.

(3) Present address, Jefferson Chemical Co., Inc., N. Y., N. Y.

(4) Present address, Rayon Department, Technical Division, E. I. du Pont de Nemours & Co., Buffalo, N. Y.

(5) Signaigo, U. S. 2,230,390, Feb. 4, 1941; Farlow and Signaigo, U. S. 2,402,613, June 25, 1946.

(6) Lazier and Signaigo, U. S. 2,402,640, June 25, 1946.

variety of heavy metals.[7] For example, aqueous 1-thiosorbitol solutions dissolve silver chloride readily with the liberation of hydrochloric acid. Similarly, 1-thiosorbitol forms soluble salts with Cu^+, Cu^{++}, Fe^{++}, Pb^{++}, Hg^{++}, Sn^{++}, Ni^{++}, and Zn^{++} ions. The ability of thiosorbitol to retain these heavy metals in solution in the presence of the usual precipitating negative ions indicates a very low degree of ionization of the thiosorbitol heavy metal derivative. Hydrogen sulfide, however, generally precipitates the metals from thiosorbitol solutions. The preparation of the cuprous salt is described in connection with the purification of 1-thiosorbitol.

The general process described in the experimental part for the conversion of D-glucose to 1-thiosorbitol has been applied successfully to other sugars such as sucrose, maltose, D-fructose and soluble starches. In these cases, the products were sirups from which pure crystalline polyhydroxyalkane thiols have not been isolated.

Experimental

Preparation of Cobalt Sulfide Catalysts.—To 1500 ml. of water in a vessel of 2-liter capacity provided with a stirrer was added 240 g. of $Na_2S \cdot 9H_2O$ and 64 g. of sulfur and the whole was stirred until the sulfur was dissolved. The filtered solution was added over a ten to fifteen-minute period to a solution of 242 g. of $CoCl_2 \cdot 6H_2O$ in 1700 ml. of water contained in a vessel of 4–5 liter capacity equipped with a large paddle stirrer. After the addition, stirring was continued for another half hour. The catalyst was collected by suction filtration and washed with water on the funnel until the filtrate was colorless. The 750–1000 g. of hard paste obtained contains approximately 150 g. of cobalt polysulfide (CoS_3) and is 15–20% solids. If it is not to be used at once, it should be stored out of contact with air.

Preparation of 1-Thiosorbitol.—A 3-gallon, stainless steel, horizontal autoclave equipped with stirrer was charged with 1500 g. of D-glucose, 800 g. of sulfur, 2500 g. of water and 1000 g. of 15% cobalt polysulfide catalyst paste prepared as described above. The autoclave was then sealed and hydrogen introduced from high-pressure storage tanks until the total pressure was 1000 lb./sq. in. The autoclave and contents were heated to a temperature of 125° and maintained at this temperature. The pressure dropped as a result of the reaction of hydrogen with sulfur and additional hydrogen was forced into the autoclave to maintain a pressure of 1000 lb./sq. in. The temperature was then raised to 150° and the pressure was raised to 1500 lb./sq. in. These conditions were maintained for a period of three hours at the end of which time absorption of hydrogen had practically ceased. Excess hydrogen and hydrogen sulfide were vented from the cooled autoclave and then the product was rinsed out with 700 ml. of water. The reaction mixture was filtered to remove catalyst and then evaporated to one-half its original volume at 60° and at 40 mm. pressure. If all the water is removed, 1430 g. of a sirup containing about 13% thiol sulfur and 15% total sulfur is obtained. The viscous liquid remaining from the evaporation was diluted with 2000 g. of water and converted into a solution of the cuprous salt by adding 563 g. of powdered cuprous oxide with stirring at a temperature of 55°. The reaction mixture was kept under an atmosphere of nitrogen during this and subsequent operations. The solution of the cuprous salt was added slowly with vigorous stirring to 13 liters of methanol to precipitate the cuprous salt, which was then separated by filtration and washed twice on the filter with 1500-ml. portions of methanol. The copper salt was suspended in 2400 g. of 90% ethanol in a 3-gallon stainless steel autoclave and treated with hydrogen sulfide under 500 lb./sq. in. pressure until no further pressure drop was observed. The contents of the autoclave were rinsed out with 400 g. of absolute alcohol. The cuprous sulfide was removed by filtration, and the filtrate was treated with 20 g. of carbon black and refiltered. The alcohol solution was evaporated to dryness at 50° and 28 mm. pressure. Seven hundred milliliters of absolute alcohol was added and the evaporation procedure repeated to complete removal of water. The thiosorbitol residue was dissolved in 700 ml. of warm absolute alcohol and filtered. The solution was cooled first to room temperature and finally was kept at 5° overnight. The crystalline 1-thiosorbitol which separated was filtered and washed with cold absolute alcohol and finally with ethyl ether. After drying *in vacuo*, the resulting white crystalline non-hygroscopic material, m. p. 92–93°, weighed 427 g. (27% yield based on *d*-glucose). By titration with standard iodine solution it was found to contain thiol groups corresponding to a purity of 96.2% 1-thiosorbitol.

Anal. Calcd. for $C_6H_{14}O_5S$: C, 36.3; H, 7.12. Found: C, 36.7, 36.7; H, 7.2, 7.2.

1-Thiosorbitol is readily soluble in water, pyridine, ethylene glycol, and formamide. It is insoluble in benzene, petroleum ether, carbon tetrachloride and carbon disulfide. At 20°, 100 ml. of absolute ethanol, dioxane, ethyl ether, trichloroethylene and acetone, respectively, dissolve 1.7 g., 1.2 g., 0.016 g., 0.016 g. and 0.010 g. of 1-thiosorbitol. 1-Thiosorbitol has a specific rotation in water of $[\alpha]^{27}D$ −1.9 at 2% concentration and 27° in a tube 40 cm. in length.

1-Thiosorbitol Disulfide.—Ten grams of 1-thiosorbitol dissolved in 50 ml. of hot absolute alcohol was treated with alcoholic iodine until the iodine color persisted. The solution was then filtered and cooled overnight to allow the product to separate. Recrystallized from alcohol, eight grams of disulfide (80% yield), m. p. 128–130°, was obtained.

Anal. Calcd. for $C_{12}H_{26}O_5S_2$: C, 36.6; H, 6.7. Found: C, 36.7; H, 6.9.

The decaacetate of thiosorbitol disulfide was prepared by treatment with fused sodium acetate and acetic anhydride, m. p. 125–130°.

Anal. Calcd. for $C_{32}H_{46}O_{20}S_2$: S, 7.87. Found: S, 7.82.

1-Thiosorbitol Hexaacetate.—Two grams of thiosorbitol and 1 g. of fused sodium acetate were treated with 10 ml. of acetic anhydride and heated at 90–100° for three hours. The product was poured into water and washed by decantation several times. The solid product purified by recrystallization from aqueous alcohol melted at 87–89°.

Anal. Calcd. for $C_{18}H_{26}O_{11}S$: C, 48.0; H, 5.8. Found: C, 48.4; H, 6.0.

The corresponding benzoate obtained by the reaction of benzoyl chloride with 1-thiosorbitol in pyridine could not be induced to crystallize.

S-Dodecyl-1-thiosorbitol.—Twenty grams of 1-thiosorbitol was dissolved in 50 ml. of water and 4 g. of sodium hydroxide added. To this was added 25 g. of dodecyl bromide in 50 ml. of dioxane and the mixture heated under reflux for two hours. The solid which separated on cooling was washed with water, dioxane and ether. Thirty-one grams (84%) was obtained, m. p. 107°.

Anal. Calcd. for $C_{18}H_{38}O_5S$: C, 58.95; H, 10.48; S, 8.73. Found: C, 58.12; H, 10.37; S, 8.45.

Summary

1-Thiosorbitol has been prepared by the hydrogenation of D-glucose in the presence of sulfur. Methods for the isolation and purification of this new polyhydroxyalkane thiol have been described.

(7) Peppel and Signaigo, U. S. 2,410,844, November 12, 1946.

1-Thiosorbitol has been found to undergo normal mercaptan reactions such as oxidation to the disulfide, acylation, and etherification with alkyl halides. In addition, it has been observed to form water-soluble salts with a variety of heavy metals.

WILMINGTON, DELAWARE RECEIVED OCTOBER 30, 1947

[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

L-α-Glycerylphosphorylcholine

BY ERICH BAER AND MORRIS KATES[1]

Studies with labelled choline (N^{15}) and radioactive phosphorus (P^{32}) have shown that a rapid metabolic turnover of phospholipids, particularly of the small intestine, liver and kidney, takes place. These observations evoke considerable interest in the role of glycerylphosphorylcholine (G.P.C.) as an intermediary metabolite, since it is highly probable that this diester plays an essential part in the biosynthesis and the turnover of lecithins. Until quite recently (1945) an investigation of the metabolic fate of the diester was difficult because it was not obtainable in sufficient quantity or purity.

Attempts to isolate G.P.C. from biological material have been made frequently. In 1935 Contardi and Ercoli[2] incubated lysolecithin with purified rice bran extracts and observed the formation of a water-soluble organic phosphate. Although this substance was not isolated in pure state, its behavior indicated that it was a glycerylphosphorylcholine. Kahane and Lévy[3] on hydrolysis of egg yolk lecithin with lecithinase B (rat intestine) obtained a choline derivative of glycerophosphoric acid which was soluble in water, methanol, ethanol and insoluble in acetone. Further experimental work strongly suggesting the presence of G.P.C. in commercial preparations of dried beef pancreas,[4] and in tissue of fresh heart muscle of frogs and rabbits[5] has been reported.

Schmidt, Hershman and Thannhauser[6] succeeded in isolating from beef pancreas autolysates *levo*-rotatory G.P.C. in fairly pure form and were able to establish its constitution as that of the choline ester of α-glycerophosphoric acid. Utilization of a biological source, however, does not lend itself readily to the preparation of G.P.C. on a laboratory scale in amounts exceeding a few grams.

During the past ten years much of the work in this Laboratory has been directed toward the synthesis of optically pure enantiomers of asymmetrically substituted glycerol derivatives. In the desire to extend our synthetic endeavours to the field of the phospholipids and in the hope of being able to supply the biochemist with a much needed material, the synthesis of L-α-G.P.C., a substance closely related to the lecithins, was attempted.

In a previous communication[7] it was shown that the optically active α-glycerophosphoric acid isolated from lecithins belongs to the L-series and can be synthesized by phosphorylation of D(+)-acetone glycerol. The use of the latter substance insured simultaneously the position of attachment of the phosphate group and the desired L-configuration of the α-glycerophosphoric acid.[8] It was to be expected that the α-G.P.C. obtained from lecithin would have the same configuration and should be obtainable in a similar manner by esterification of phosphoric acid with D(+)acetone glycerol and choline. The synthesis, especially the phosphorylation step offered, however, a number of technical difficulties which had to be overcome before a procedure could be found which would give consistently satisfactory yields of glycerylphosphorylcholine. The method of synthesis of L-α-G.P.C. which was finally adopted and the steric relationships of the various intermediate compounds are illustrated in the accompanying reaction scheme. After trying numerous phosphorylation procedures it was found that the intermediary acetone glycerylphenylphosphorylcholine chloride (C-Cl) is obtainable in adequate amounts by phosphorylation of D(+)acetone glycerol with phenylphosphoryl dichloride in the presence of quinoline, followed by esterification of the reaction product with choline in the presence of pyridine. The isolation of the choline ester from the reaction mixture was greatly facilitated by the observation that its reineckate, in contrast to the reineckates of pyridine and quinoline, precipitates from an alkaline–aqueous solution and can be separated from the similarly alkali-insoluble reineckates of choline and other choline-containing reaction products by means of its solubility in ethyl acetate. The reineckate of (C) was converted to the corresponding sulfate ($C\text{-}SO_4/2$) before removing the protective phenyl and acetone groups in order to avoid complications introduced

(1) This paper forms part of a thesis which will be submitted by M. Kates to the Department of Chemistry, University of Toronto, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. An account of this work was presented before the Canadian Physiological Society, at the London (Ontario) meeting, October 24–25, 1947.

(2) A. Contardi and A. Ercoli, *Arch. sci. biol.*, **21**, 1 (1935).

(3) E. Kahane and J. Lévy, *Compt. rend.*, **219**, 431 (1944).

(4) E. J. King and M. Aloisi, *Biochem. J.*, **39**, 470 (1945).

(5) G. L. Cantoni and A. W. Bernheimer, *Fed. Proc. Am. Soc. Exp. Biol.* (Part II), Vol. **6**, No. 1, 315 (1947).

(6) G. Schmidt, B. Hershman and S. J. Thannhauser, *J. Biol. Chem.*, **161**, 523 (1945).

(7) E. Baer and H. O. L. Fischer, *ibid.*, **128**, 491 (1939).

(8) An optically active α-monoglyceride is considered as being related to the glyceraldehyde which would be obtained by oxidation of the γ-carbon atom.

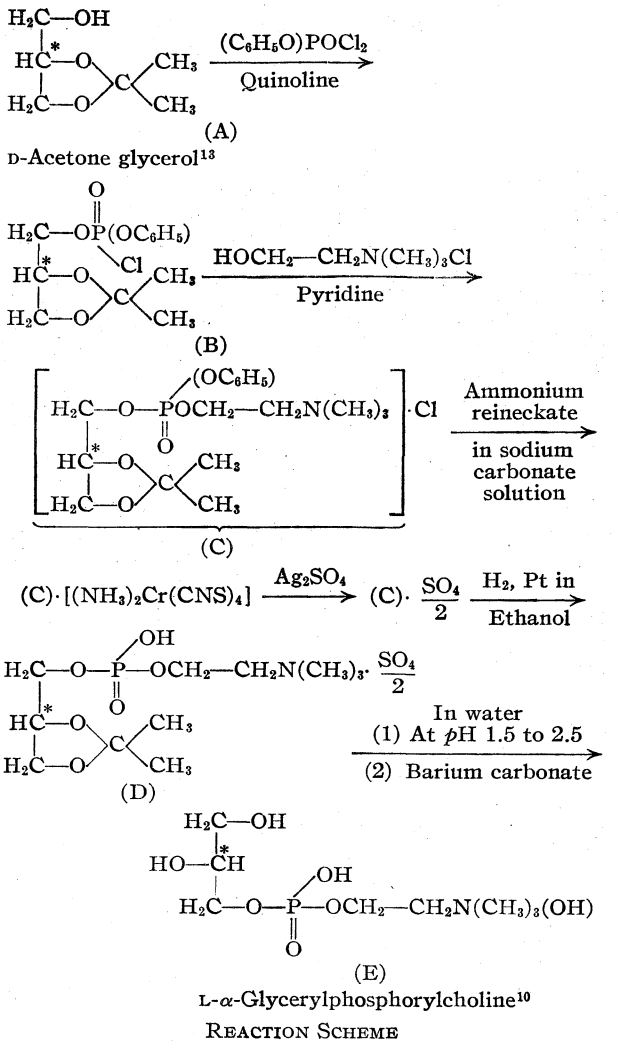
by the reineckate ion. It was found that the order of removal of these groups was a decisive factor in obtaining L-α-glycerylphosphorylcholine. All attempts to prepare the diester by removing first the acetone group of (C-SO_4/2) failed because, at the *p*H required for its removal, liberation of choline and $\alpha \leftrightarrows \beta$ migration of phosphoric acid took place. In contrast, when the phenyl group of (C-SO_4/2) was removed first, the resulting acetone glycerylphosphorylcholine (D-SO_4/2) was found to be stable enough to permit its deacetonation within the *p*H-range of 1.5–2.5 without simultaneous liberation of choline or phosphoric acid migration to give a good yield of the diester (E).

The synthetic L-α-G.P.C. was obtained as a colorless, hygroscopic and viscous liquid in an over-all yield varying from 35–40%; $[\alpha]^{23}D$ −2.85° (±0.1°) in water (average of 15 preparations). The diester is fairly stable in aqueous solution at room temperature within the *p*H-range of 1.5 to 7; in alkaline solution or in strongly acid solution, however, it is rapidly hydrolyzed. The cleavage of its choline-phosphoric acid linkage is also effected by the recently described enzyme preparation from carrots.[9] The diester is precipitated from alcoholic solution by ammonium reineckate or cadmium chloride.

The synthetic L-α-G.P.C. was shown to contain neither inorganic phosphate nor free choline. It analyzed correctly for $C_8H_{22}O_7NP$ and its molecular ratio of *choline : phosphoric acid : α-glycerol ester* corresponded very closely to the theoretical value of 1:1:1. The diester was further characterized by means of an amorphous cadmium chloride compound ($[\alpha]D$ −1.2°) and a crystalline cadmium chloride compound (m. p. 100–102°; $[\alpha]D$ −1.4°), both of which were obtained in excellent yields. On the basis of the analytical data formula $[C_8H_{22}O_7NP]_2 \cdot [CdCl_2]_3$ had to be assigned to the amorphous compound and formula $[C_8H_{22}O_7NP][CdCl_2] \cdot 2H_2O$ to the crystalline compound. On decomposition of the two cadmium chloride addition compounds with silver carbonate the L-α-G.P.C. was recovered unchanged ($[\alpha]D$ −2.9°).

The properties of the synthetic L-α-G.P.C. were similar to those described by Schmidt, Hershman and Thannhauser for the natural G.P.C. except that the rotation of the synthetic diester was considerably lower than that reported for the biological diester ($[\alpha]D$ − 4.87°). This discrepancy could be accounted for either by a partial inactivation of the synthetic α-diester during the later stages of the synthesis or by contamination of the biological diester with compounds of high optical activity.

First of all attempts were made to establish the optical purity of the synthetic diester by degradation to the well known L-α-glycerophosphoric acid.[7] The glycerophosphoric acid obtained by



REACTION SCHEME

acid or alkaline hydrolysis had, however, a much lower rotation than that reported for the synthetic compound and, depending on the method of hydrolysis, containing varying proportions of L-α-, D,L-α- and β-glycerophosphoric acid. The formation of β-glycerophosphoric acid from pure α-G.P.C. must have been caused by acyl-migration during hydrolysis. In order to prevent this migration attempts were made to block both alcoholic hydroxy groups by methylation. The low solubility of the G.P.C. in all solvents commonly used in etherification procedures made the complete methylation of the glycerol-moiety impossible. After several other unsuccessful attempts to establish the optical purity of the synthetic L-α-G.P.C. by relating it to L-α-glycerophosphoric acid, work in this direction was abandoned.

It was then decided to repeat the isolation of G.P.C. from autolyzed beef pancreas as described

(9) D. J. Hanahan and I. L. Chaikoff, *J. Biol. Chem.*, **168**, 233 (1947); **169**, 699 (1947).

(10) The guiding principles in establishing the steric classification of the enantiomeric glycerides and related compounds are outlined by H. O. L. Fischer and E. Baer in *J. Biol. Chem.*, **128**, 475 (1939), and in *Chem. Rev.*, **29**, 287 (1941).

by Schmidt, Hershman and Thannhauser. In view of the complex nature of the autolysate, it was considered possible that small amounts of impurities of high optical activity might still be associated with the product obtainable by this procedure. The rotation of the G.P.C. obtained by us was even higher than that reported by Schmidt, *et al.* However, several repetitions of the Amberlite treatment gradually removed the basic impurities and lowered the rotation to a point where it became not only constant ($[\alpha]_D$ $-2.8°$) but was in complete agreement with that of the synthetic diester. Furthermore, the crystalline cadmium chloride addition compound obtained from the highly purified natural diester was identical with the corresponding compound of the synthetic glycerylphosphorylcholine. The identity of the natural levorotatory G.P.C. and the synthetic L-α-G.P.C. was thus established beyond doubt. The L-configuration, as anticipated, must therefore be assigned to the natural diester. The fact that the optical activities of both compounds, each obtained by a different procedure, and those of their derivatives are in complete agreement suggests with high probability that the synthetic L-α-G.P.C. is optically pure, the possibility that both compounds have been inactivated to the same extent being remote.

By means of the same series of reactions as described for the synthesis of L-α-G.P.C., but starting with L(−)acetone glycerol or racemic acetone glycerol, D-α- or D,L-α-G.P.C. are obtainable. In the course of the present investigation the racemic α-G.P.C. has been prepared. Since, however, its synthesis is identical with that of the optical isomer only the physical and analytical data of the diester and its intermediary compounds are reported.

A kinetic study of the acid and alkaline hydrolysis of the L-α-G.P.C. has shown that the liberation of choline is accompanied by a reversible phosphoric acid migration resulting in the formation of a mixture of L-α-, D,L-α- and β-glycerophosphoric acid. The close relationship of α-G.P.C. to lecithins permits the prediction of similar chemical changes on subjecting lecithins to acid or alkaline hydrolysis. A detailed account of this work which seems to invalidate the methods commonly used in the elucidation of the structure of lecithins, will be published elsewhere. In the light of these findings a critical re-examination of the data in the literature has raised serious doubts as to the natural existence of β-lecithins.

The synthesis of the enantiomeric forms (as well as the racemic form) of α-lysolecithins[11] and α-lecithins of known constitution and configuration *via* the corresponding enantiomers of α-G.P.C. has now become possible. Work along these lines is in progress in this Laboratory.[12] The synthetic α-glycerylphosphorylcholines and the synthetic α-lecithins should be ideal substrates in studies concerning the specificity of the enzymes responsible for the cleavage of the various phosphatide linkages.

Finally it should be mentioned that the synthesis described in this paper should make possible the preparation of α-G.P.C. or of α-lecithins with all or some of their groups labelled by the use of (1) acetone glycerol containing deuterium,[13] (2) choline with heavy nitrogen, (3) phenylphosphoryl dichloride with radioactive phosphorus and (4) fatty acids containing deuterium or preferably heavy carbon.

(11) The α indicates the position of the phosphoric acid.

(12) Attempts to prepare optically active lecithins via the enantiomeric forms of α,β diglycerides by means of the double phosphorylation procedure are also being made.

Experimental Part

I. Synthesis of L-α-Glycerylphosphorylcholine

Monophenylphosphoryl Dichloride.[14]—The chloride was prepared according to Jacobsen,[15] using, however, the slightly modified procedure reported by Brigl and Müller,[14] which yields in approximately equal amounts monophenylphosphoryl dichloride and diphenylphosphoryl monochloride. The acid chlorides were separated and carefully purified by fractional distillation *in vacuo*. Boiling point of the pure phenylphosphoryl dichloride 107–109° (9 mm.)).

D(+)Acetone Glycerol.—The glycerol derivative was prepared according to the simplified procedure reported by Fischer and Baer.[16] The reduction, however, was carried out at atmospheric pressure, using Raney nickel catalyst.[17] It should be noted that the yields of L-α-glycerylphosphorylcholine reported in this communication are obtainable only by using preparations of D(+)acetone glycerol with specific rotations ranging from +13.5° to +14.0°. Preparations of lower optical activity contain moisture; their use reduces greatly the yield of the diester.

Acetone Compound of L-α-Glycerylphenylphosphorylcholine: Phosphorylation, Step 1.—In a 500-ml. round-bottomed, two-necked and thick-walled flask equipped with a mercury-sealed, motor-driven stirrer and dropping funnel were placed 18.2 ml. (0.123 mole) of monophenylphosphoryl dichloride, 16.2 ml.[18] (0.138 mole) of dry quino-

(13) H. Erlenmeyer, H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **20**, 1012 (1937).

(14) Phosphorus oxychloride, widely used as a phosphorylating agent, has the disadvantage of giving rise to the formation of phosphorus-containing by-products which are not only difficult to remove but also reduce the yield considerably. Most of the undesired effects associated with the use of this agent may be avoided by utilizing its phenyl esters. The successful use of the diphenylphosphoryl-chloride as a phosphorylating agent has been reported frequently during recent years but the first successful application of phenylphosphoryl dichloride for the preparation of *mixed* diesters of phosphoric acid will be described in this communication. *Cf.* P. Brigl and H. Müller, *Ber.*, **72**, 2121 (1939). This reagent should prove useful in the synthesis of other compounds of biological interest.

(15) G. Jacobsen, *Ber.*, **8**, 1519 (1875).

(16) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

(17) A detailed description of the most recent procedure for the preparation of D(+)acetone glycerol will appear in "Biochemical Preparations" as a part of the preparation of L-α-glycerophosphoric acid.

(18) Quinoline of a good commercial grade was dried over potassium hydroxide and fractionated within narrow limits of boiling point. By substituting pyridine for quinoline in Step 1, only very small amounts of the acetone compound of glycerylphenylphosphorylcholine are formed in Step 2, presumably because of the increased formation of di-(acetone-glyceryl)-phenylphosphate in Step 1. This assumption is supported by the observation of E. Fischer and E. Pfähler, *Ber.*, **53**, 1606 (1920), that the tendency of phosphorus oxychloride to react simultaneously with more than one of its chloride groups is greater in pyridine than in quinoline.

line[18] and 50 to 60 ml. of glass beads (6–7 mm. diameter).[19] The flask was immersed in a cold bath (−10°) and 16.15 g. (0.123 mole) of freshly prepared D(+)acetone glycerol was added dropwise in the course of four to five minutes to the vigorously stirred phosphorylating mixture. After five minutes the cold-bath was removed and the mixture allowed to come to room temperature. The reaction product, acetone-L-α-glycerylphenylphosphoryl chloride, was not isolated.

Phosphorylation, Step 2.—The reaction mixture was immediately broken up as quickly as possible, covered with 100 ml. of dry pyridine[20] and vigorously stirred until a fine suspension was formed. To this suspension were added 15.8 g. (0.115 moles) of dry choline chloride[21] and 90 to 100 ml. of glass beads. The stirring was continued for a period of at least forty hours.[22]

Isolation of the Phosphorylation Product as Reinecke Salt.—The reaction flask was attached to a receiver and the mixture concentrated *in vacuo* (bath 40°) to a sirup. The residue was poured with stirring into 450 ml. of an ice-cold sodium carbonate solution (60 g. of anhydrous sodium carbonate in 600 ml. of water). The remainder of the carbonate solution was used to rinse the flask and glass beads. The combined aqueous solutions were freed from suspended quinoline by centrifugation and the aqueous layer poured through a wet filter into a freshly prepared solution of 53–55 g. of ammonium reineckate[23] in 1800 ml. of distilled water containing 10 g. of sodium carbonate.[24] After the addition of a small amount of filter-aid (Hyflo-Super-Cel) the mixture was filtered with suction. The precipitate was washed thoroughly with water and dried *in vacuo* over solid sodium hydroxide and phosphorus pentoxide to constant weight. The dry reineckate was powdered, extracted by stirring with 700 ml. of dry ethyl acetate[25] and the suspension was sharply centrifuged. The extraction of the reineckate was repeated with successively smaller amounts of ethyl acetate until the extracts were only faintly colored. Seven to eight extractions, using a total of 2200 ml. of ethyl acetate, were required. The combined extracts, if necessary, were cleared by centrifugation. The supernatant liquid was concentrated *in vacuo* to a volume of approximately 100 ml. and the concentrate diluted gradually with 500 ml. of dry and ethanol-free ether. The precipitate was filtered off with suction, washed thoroughly on the filter with ether and dried *in vacuo*. The yield of already fairly pure reinecke salt of acetone-L-α-glycerylphenylphosphorylcholine varied from 38 to 47 g. (45 to 55%); m. p. 136.5–137.5°. The reineckate is readily soluble in acetone or ethyl acetate, less soluble in ethanol and insoluble in water, ether or benzene. For analytical purposes only, the reineckate was crystallized from 95% ethanol; prisms, m. p. 137.0–137.5°.

(19) By the use of glass beads the choline chloride is brought into a finely dispersed state and the formation of a sticky gum, which would enclose unreacted material, is minimized. The efficiency of the phosphorylating procedure is thus greatly increased.

(20) This base rather than quinoline was used in the second step of the phosphorylation because of the greater activity of the phosphorus oxychlorides in pyridine. Pyridine of a good commercial grade was refluxed over barium oxide and distilled with exclusion of moisture.

(21) The choline chloride was thoroughly dried *in vacuo* over phosphorus pentoxide at 56°.

(22) The reaction vessel was partially immersed in a large water-bath (20–25°) to prevent a rise in temperature due to the friction of the glass beads. Otherwise a marked darkening of the reaction mixture occurs.

(23) The commercial ammonium reineckate is often not sufficiently pure. It was found more economical to prepare the ammonium salt as described in "Organic Syntheses," Coll. Vol. II, p. 555.

(24) The alkalinity of the dilute sodium carbonate solution suffices to prevent the precipitation of pyridine reineckate and quinoline reineckate.

(25) Ethyl acetate, if moist, also dissolves some of the impurities. It suffices to dry the commercial ethyl acetate with anhydrous potassium carbonate.

Anal. Calcd. for $C_{21}H_{35}O_6N_7S_4PCr$ (692.6): C, 36.4; H, 5.52; N, 14.15; P, 4.47. Found: C, 36.5; H, 5.32; N, 14.08; P, 4.41.[26]

Conversion of the Reineckate to the Sulfate.—Ten grams of the reineckate[27] was dissolved in 40 ml. of acetone and the solution was diluted with 60 ml. of 95% ethanol. To this solution was added gradually and with cooling a lukewarm 1% aqueous silver sulfate solution (approximately 225 ml.) until the precipitation of the silver reineckate was complete. The precipitate was removed by centrifugation, washed with 95% ethanol and the combined supernatants were concentrated *in vacuo* as rapidly as possible to a volume of approximately 50–60 ml. at a bath temperature not exceeding 40°.[28] Remaining traces of the original reineckate were decomposed by the dropwise addition of a dilute silver sulfate solution. The silver reineckate was removed, the solution taken to dryness under reduced pressure (bath 35 to 40°) and the residue dried in a vacuum of 0.5 mm. The crude sulfate (5.1 g.) was dissolved in 25–30 ml. of 99% ethanol, freed from insoluble material (100–300 mg.) and the solution taken to dryness *in vacuo*. At this stage the sulfate (4.8 g., 79%) is a glass-like mass which is pure enough for further processing. The sulfate can be obtained in crystalline state by taking it up with warm, dry acetone (7 ml./g.) and keeping the mixture overnight in the ice-box (+5°); recovery approximately 85%.

For analytical purposes the crystalline sulfate was purified further by dissolving it in 99% ethanol, centrifuging the suspension, evaporating the supernatant liquid *in vacuo* to a small volume and adding gradually dry acetone to the concentrate until crystallization set in. After five minutes another portion of dry acetone equal to the first was added and the mixture kept in an ice-box for twenty-four hours. The hygroscopic crystals were filtered rapidly with suction, washed with a small portion of anhydrous acetone and dried *in vacuo* over fresh calcium chloride. Recovery of sulfate approximately 50%; m. p. 108–109.5° (sint. 101°); $[\alpha]^{27}D$ −8.3° in water (*c*, 7.8); $[\alpha]^{28}D$ −3.0° in dry ethanol (*c*, 6.1).[29]

The strongly hygroscopic sulfate is readily soluble in water or ethanol, sparingly soluble in cold acetone or dioxane and insoluble in ether. *Anal.* Calcd. for $C_{24}H_{58}O_{16}N_2P_2S$ (844.5): C, 48.25; H, 6.91; N, 3.31; P, 7.34; SO_4 11.37; acetone, 13.70; choline, 28.8. Found: C, 48.95; H, 7.06; N, 3.29; P, 7.17; SO_4 11.18; acetone, 13.35; choline,[30] 28.8.

L-α-Glycerylphosphorylcholine: Removal of the Phenyl Group by Reductive Cleavage.—Sixteen grams of the L-α-glycerylphenylphosphorylcholine reineckate[27] was converted into the crude sulfate as described above. The sulfate (8.5 g.) was dissolved in 80 ml. of 99% ethanol and freed by centrifugation from insoluble material. The clear solution together with 2 g. of platinic oxide (Adams catalyst) was shaken vigorously in an atmosphere of pure hydrogen at room temperature and a pressure of 40 to 50 cm. of water in excess of atmospheric

(26) The P-determination on the reineckate was carried out according to King (*Biochem. J.*, **26**, 292 (1932)). The determination, however, was somewhat complicated by the presence of chromic acid anhydride, one of the digestion products. At the completion of the digestion the cooled solution was filtered through a sintered glass filter and the chromic anhydride crystals washed with small amounts of 60% perchloric acid. The filtrate and washings were made up to volume and used for the colorimetric determination of phosphorus.

(27) The reineckate obtained directly from the ethyl acetate extraction may be used here.

(28) The aqueous solution of the sulfate is acid. To avoid hydrolysis resulting in the liberation of acetone and choline all operations should be carried to completion as rapidly as possible and at the lowest possible temperature.

(29) The readings were taken immediately after preparing the solutions.

(30) The substance was hydrolyzed in 1.5 *N* hydrochloric acid at 100° (two hours) and the choline determined gravimetrically in form of its reineckate as described by Schmidt, Hershman and Thannhauser.

pressure until the absorption of hydrogen ceased. In about seventy-five minutes 2010 ml. (N. T. P.) or 93% of the theoretical amount of hydrogen were taken up. The catalyst was filtered off, washed with ethanol and the combined filtrate and washings evaporated to dryness *in vacuo* (bath 40°). The residue, a colorless glass weighing 6.0 g., contained in general 20% less acetone than calculated for the acetone compound of L-α-glycerylphosphorylcholine sulfate. No attempt was made to isolate a pure compound.

Deacetonation.—The crude acetone compound (6.0 g.) was dissolved in 150 ml. of distilled water and the solution, which had a *p*H of 1.5, was allowed to stand at room temperature (20 to 25°) for a period of fifteen hours.[31]

To remove traces of nitrogenous impurities, a dilute solution of ammonium reineckate was then added dropwise until the precipitation was complete and after centrifugation, the excess of ammonium reineckate was removed with dilute silver sulfate solution. The supernatant was triturated with barium carbonate until free from sulfate ions and the silver ions were removed with hydrogen sulfide in the presence of the barium salts. The mixture was centrifuged and the aqueous solution concentrated under reduced pressure (bath 35–40°) to a small volume. The deposit of insoluble material (mostly barium carbonate) was removed and the concentration *in vacuo* continued. The drying was completed in a vacuum of 0.1 mm. at a bath temperature not exceeding 40°; yield 4.0 to 4.6 g. of L-α-glycerylphosphorylcholine (65 to 75% of the theoretical from reineckate or 35 to 40% over-all yield). The synthetic diester is a viscous liquid which is readily soluble in water, ethanol or methanol and insoluble in acetone, ether or benzene; $[\alpha]^{23}D$ $-2.85 \pm 0.1°$ in water (*c*, 2.2 determined from P-content; *p*H 6–7). The optical activity of α-G. P. C. seems to decrease slightly with increasing acidity.

Anal. Calcd. for $C_8H_{22}O_7NP$ (275.2): choline, 44.0; P, 11.27. Found: choline, 42.4; P, 10.95.

Vicinal Glycol Titration with Periodic Acid.—0.1157 gram of the diester was dissolved in water and the volume made up to 100 ml. The titration was carried out according to Voris, Ellis and Maynard[32] on 10.0-ml. aliquots. After one hour 0.0422 mM. of the diester had consumed on the average 0.0414 mM. of periodic acid or 98.2% of the theoretical amount calculated for the α-glycerylphosphorylcholine. Ratio of choline:P:α-glycerol ester[33]: calcd. 1:1:1. Found: 0.99:1.00:1.01.

Amorphous Cadmium Chloride Addition Compound of L-α-Glycerylphosphorylcholine.—A solution of 5.8 g. of cadmium chloride (2.5-H_2O) in 4 ml. of water, diluted with 65 ml. of 99% ethanol, was added slowly and with stirring to a solution of 4.0 g. of L-α-glycerylphosphorylcholine in 75 ml. of 99% ethanol. After standing in the ice-box for one hour the dense, white precipitate was filtered with suction, washed with ethanol and ether, and dried *in vacuo;* yield of the amorphous cadmium chloride addition compound 7.3 g. (92%). This compound is quite stable and can be used advantageously for the storage of L-α-glycerylphosphorylcholine. If need arises it can be quickly converted into the free diester; $[\alpha]^{25}D$ $-1.2°$ in water (*c*, 5.0). *Anal.* Calcd. for $(C_8H_{22}O_7NP)_2 \cdot (CdCl_2)_3$ (1100): C, 17.44; H, 4.03; N, 2.54; P, 5.62; Cl, 19.35; Cd, 30.60; choline, 21.9; ratio of $CdCl_2:C_8H_{22}O_7NP = 3:2$. Found: C, 17.6; H, 4.24; N, 2.58; P, 5.58; Cl, 19.90; Cd, 30.15; choline, 21.1; ratio of $CdCl_2:C_8H_{22}O_7NP = 3.01:2.00$. Calcd. for the cadmium chloride-free moiety, $C_8H_{22}O_7NP$ (275): C, 34.9; H, 8.05; N, 5.08; P, 11.27; choline, 44.0. Found by calculation from the analytical values above: C, 35.2; H, 8.48; N, 5.17; P, 11.17; choline, 42.2.

Vicinal-Glycol Titration with Periodic Acid.—The sample of the cadmium chloride derivative in aqueous solution was freed from cadmium by the addition of potassium carbonate. The filtrate was made up to a known volume and the content of diester ascertained by a phosphorus determination. Several aliquots each containing 0.0218 mM. of the diester consumed in two hours on the average 0.0201 mM. (96.3%) of periodic acid.

Crystalline Cadmium Chloride Compound of L-α-Glycerylphosphorylcholine: (a) Prepared from the Amorphous Cadmium Chloride Compound.—A solution of 3.1 g. of the *amorphous* cadmium chloride compound in 38 ml. of water was diluted gradually with 150 ml. of 99% ethanol and a small amorphous precipitate removed immediately by centrifugation. The clear supernatant liquid was first kept at room temperature for twenty-four hours, during which time crystals (prisms) began to form and was then kept in an ice-box (+5°) for two days. The crystals were filtered with suction, washed with a small volume of cold 80% ethanol and *dried in air* to constant weight. The crystalline cadmium chloride compound of L-α-glycerylphosphorylcholine was obtained in a yield of 1.85 g. (66.4%); m. p. 100–102° with sintering from 97° (rise in temperature 3°/min. starting with a bath temperature of 80°); $[\alpha]^{24}D$ $-1.4°$ in water (*c*, 5.5). *Anal.* Calcd. for $(C_8H_{22}O_7NP)(CdCl_2) \cdot 2H_2O$ (494.7): C, 19.46; H, 5.30; N, 2.83; P, 6.27; Cl, 14.33; Cd, 22.7; choline, 24.5. Found: C, 19.31; H, 5.21; N, 2.84; P, 6.28; Cl, 14.50; Cd, 22.8; choline, 24.6. Ratio of $C_8H_{22}O_7NP:CdCl_2$. Calcd. 1.0:1.0. Found. 1.00:1.01. The air-dried cadmium chloride compound lost on drying over phosphorus pentoxide in a vacuum of 0.1 mm. at 56° 10.62% of its weight. Calcd. for a loss of three moles of water 10.92%.[34]

Vicinal-Glycol Titration with Periodic Acid.—Carried out as described for the amorphous cadmium chloride compound. At the end of two hours 0.0235 mM. of the diester had consumed on the average 0.0233 mM. (99.2%) of periodic acid.

(b) **Prepared directly from the diester.** To the combined solutions of 2.0 g. of the diester in 13 ml. of water and of 2.6 g. of cadmium chloride (2.5 H_2O) in 15 ml. of water were added gradually and with swirling 100 ml. of 99% ethanol. The solution was immediately cleared of a small amount of amorphous material by centrifugation. The supernatant liquid was diluted with an additional portion of 10 ml. of 99% ethanol and crystallization induced mechanically. After the mixture had stood for six hours at room temperature and twenty-four hours in the ice-box the crystals (prisms) were filtered with suction, washed with 80% ethanol and dried in air to constant weight; yield of crystalline cadmium chloride compound 80% (2.8 g.); m. p. 97–101° (sintered 94°); $[\alpha]^{27}D$ $-1.4°$ in water (*c*, 5.8). *Anal.* Found: C, 19.14; H, 5.25; N, 2.85; P, 6.22.

Recovery of L-α-Glycerylphosphorylcholine from its Cadmium Chloride Compound.—To a solution of 1.0 g. of the *amorphous* cadmium chloride compound in 35 ml. of water was added 1.6 g. of silver carbonate and the mixture was stirred vigorously until free from chloride ions. After removal of the solids the solution was freed from cations with hydrogen sulfide and the sulfides removed by filtration over Hyflo-Super-Cel. The filtrate was concentrated to a sirup under reduced pressure (bath 35–40°) and the residue was dried to constant weight in a vacuum of 0.1 mm. at a temperature not exceeding 40°. In the event that the residue was still slightly colored by colloidal material it was taken up in ethanol, centrifuged, concentrated and dried *in vacuo* as described above. The recovery of L-α-glycerylphosphorylcholine was 98% (0.49 g.); $[\alpha]D$ $-2.9°$ in water (c, 2.6).

(31) According to our experience a complete hydrolysis of acetone without liberation of choline or migration of phosphoric acid is achieved within the *p*H-range of 1.5 to 2.5 at the stated time interval and temperatures. Hydrolysis at greater acidity liberates choline and at lower acidity is incomplete with regard to acetone.

(32) L. Voris, G. Ellis and L. A. Maynard, *J. Biol. Chem.*, **133**, 491 (1940).

(33) Determined by the periodic acid titration.

(34) The loss of the third mole of water during the process of drying may be explained by the formation of an inner salt of the glycerylphosphorylcholine.

II. Synthesis of D,L-α-Glycerylphosphorylcholine

The synthesis of D,L-α-glycerylphosphorylcholine is identical with that described for the L-form, except that D,L-acetone glycerol[35] is used as starting material. Only the analytical and physical data of the various compounds will be reported here.

Acetone Compound of D,L-α-Glycerylphenylphosphorylcholine: (a) **Reineckate.**—Yield 56%; m. p. 136–137°. *Anal.* Calcd. for $C_{21}H_{35}O_6N_7PCr$ (692.6): C, 36.4; H, 5.52; N, 14.15; P, 4.47. Found: C, 36.6; H, 5.49; N, 14.13; P, 4.40.

(b) **Sulfate.**—Obtained by the decomposition of the reineckate in yields of 70–80% (oil) or 60–68% (crystals). *Anal.* Calcd. for $C_{34}H_{58}O_{16}N_2P_2S$ (844.5); P, 7.34; SO_4, 11.37; acetone, 13.70; choline, 28.8. Found: P, 7.25; SO_4, 11.00; acetone, 13.76; choline, 28.2.

D,L-α-Glycerylphosphorylcholine.—Over-all yield 35–40%; viscous liquid, soluble in water, ethanol, methanol; insoluble in acetone, ether or benzene. **Amorphous cadmium chloride compound.**—Yield 90%. *Anal.* Calcd. for $(C_8H_{22}O_7NP)_2(CdCl_2)_3$: C, 17.44; H, 4.03; N, 2.54; P, 5.62; Cl, 19.35; Cd, 30.60; choline, 21.9. Found: C, 17.68; H, 4.16; N, 2.64; P, 5.72; Cl, 19.45; Cd, 30.05; choline, 21.8. Theoretical values for the cadmium chloride-free moiety $C_8H_{22}O_7NP$: C, 34.9; H, 8.05; N, 5.27; P, 11.27; choline, 44.0. Found by calculation from the analytical values above: C, 35.0; H, 8.23; N, 5.23; P, 11.32; choline, 43.4.

Vicinal-Glycol Titration with Periodic Acid.—Carried out as described for the corresponding cadmium chloride compound of the synthetic L-α-glycerylphosphorylcholine. Aliquots containing 0.0226 mM. of D,L-α-glycerylphosphorylcholine consumed in 15, 45, 90 minutes 0.0204 mM. (90.4%), 0.0215 mM. (95.2%) and 0.0217 mM. (95.9%) of periodic acid, respectively.

III. Isolation of α-Glycerylphosphorylcholine from Beef Pancreas According to Schmidt, Hershman and Thannhauser[6]

Five pounds of beef pancreas treated as outlined by Schmidt, Hershman and Thannhauser yielded 2.9 g. of crude α-glycerylphosphorylcholine with a rotation of $[\alpha]^{25}D$ −7.8° in water (*c*, 2.7). This rotation, much higher than that reported by Schmidt, Hershman and Thannhauser ($[\alpha]^{20}D$ −4.87°), indicated that our biological product still contained extraneous material of high optical activity and needed further purification. The diester was dissolved in 40 ml. of water and a dilute aqueous ammonium reineckate solution added until no further precipitation took place. The excess of ammonium reineckate was removed with dilute silver sulfate solution; the filtrate was triturated with barium carbonate and the silver ions removed with hydrogen sulfide in the presence of the barium salts. The aerated aqueous solution of the diester (approx. volume 60 ml.) was stirred for one hour with 20 g. of Amberlite (I. R.-100), filtered and the filtrate concentrated *in vacuo* at a bath temperature not exceeding 40°. The colorless oil, which weighed 1.15 g. and now had an optical activity of $[\alpha]^{25}D$ −4.2° in water, (*c*, 2.3) was again treated in aqueous solution (60 ml.) with 20 g. of Amberlite for a period of thirty minutes. The filtrate was concentrated *in vacuo* to a volume of 5 ml. and the diester precipitated by the addition of 50 ml. of dry acetone. The precipitate, freed *in vacuo* from solvent, weighed 0.7 g. and had an optical activity of $[\alpha]^{25}D$ −2.7° in water (*c*, 2.5, *p*H 2.8). This rotation, although considerably lower than that reported by Schmidt, Hershman and Thannhauser, is, however, identical with that of our synthetic product $[\alpha]^{23}D$ −2.85° (±0.1°). To ensure that the progressive decrease in optical activity was due to the removal of impurities and not to inactivation of the glycerylphosphorylcholine by the Amberlite, the oil (0.7 g.) was treated once more with the ion-exchanger. The optical activity of the recovered diester (0.6 g.) remained unchanged, $[\alpha]^{25}D$ −2.7° in water (*c*, 2.7, *p*H 2.5) or $[\alpha]^{25}D$ −2.8° (*c*, 2.6; *p*H 5.8). The fact that the optical activity of the synthetic L-α-glycerylphosphorylcholine also remained unchanged after a treatment with Amberlite is further evidence of the harmlessness of this treatment.

Crystalline Cadmium Chloride Compound of the Natural α-Glycerylphosphorylcholine.—For the purposes of analysis and further comparison of the natural L-α-glycerylphosphorylcholine with the synthetic L-α-glycerylphosphorylcholine the natural diester (0.5 g.) was converted via the amorphous cadmium chloride compound (0.88 g.) to the crystalline cadmium chloride addition compound (prisms, 0.56 g.) as described for the synthetic product; m.p. of the crystalline cadmium chloride compound 99–100° (sintered at 90°; rise in temperature 3°/minute, starting with a bath of 80°); $[\alpha]^{24}D$ −1.4° in water (*c*, 5.5). *Anal.* Calcd. for the crystalline cadmium chloride compound $(C_8H_{22}O_7NP)(CdCl_2)\cdot 2H_2O$ (494.7): C, 19.46; H, 5.30; N, 2.83; P, 6.27; choline, 24.5. Found: C, 19.20; H, 5.35; N, 2.83; P, 6.34; choline, 24.9. The air-dried cadmium chloride compound lost on drying *in vacuo* (0.1 mm.) over phosphorus pentoxide at 56°, 11.05% of its weight. Calcd. for the loss of three moles of water 10.92%.

Periodic Acid Titration.—The titration was carried out as described for the amorphous cadmium chloride compound of the synthetic diester: 0.0236 mM. of diester consumed 0.0229 mM. or 97% of periodate.

Acknowledgment.—This work is an extension of studies of enantiomeric derivatives of glycerol conducted during the past ten years by one of us (E. B.) in association with Professor Hermann O. L. Fischer whose continued interest and friendly criticism are gratefully acknowledged.

The authors wish to express their gratitude to the Banting Research Foundation for grants to one of them (M. K.) during part of the investigation.

Summary

1. A synthetic procedure is described by means of which the L- and D,L-α- glycerylphosphorylcholine have been prepared.

2. The synthetic L-α-glycerylphosphorylcholine was found to be identical with a product obtained from autolyzed beef pancreas by a slight modification of the purification procedure described by Schmidt, Hershman and Thannhauser.

3. The first successful application of monophenylphosphoryl dichloride as a phosphorylating agent is described. This reagent may prove useful in the synthesis of other phosphate-containing compounds of biological interest.

TORONTO, ONT. RECEIVED DECEMBER 4, 1947

(35) E. Fischer and E. Pfähler, *Ber.*, **53**, 1606 (1920); M. S. Newman and M. Renoll, THIS JOURNAL, **67**, 1621 (1945).

[CONTRIBUTION FROM MELLON INSTITUTE OF INDUSTRIAL RESEARCH AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Chlorides and Other Derivatives of Tetramethylsilane

BY JOHN L. SPEIER AND B. F. DAUBERT

Chloromethyltrimethylsilane has been prepared[1,2] and some compounds derived from it have been studied.[3,4]

In this paper the study of compounds derived from chloromethyltrimethylsilane is continued and broadened to include two new chlorides of tetramethylsilane with some of their reactions and derivatives. The new chlorides are dichloromethyltrimethylsilane and bis-(chloromethyl)-dimethylsilane.

Trimethylsilylmethylmagnesium chloride[1,4] was found to react vigorously with phenyl isocyanate in absolute ether, but hydrolysis of the addition compound resulted in the formation of acetanilide rather than of α-trimethylsilylacetanilide, thus showing again that a carbonyl group in a position *beta* to silicon decidedly facilitates cleavage of the group.[4] This result perhaps may explain the findings of Kipping[5] who attempted unsuccessfully to prepare benzylethylpropylsilylacetic acid from the appropriate chlorosilane and sodioacetoacetic ester. No silicon-containing acid derivative could be isolated from the hydrolyzed products of the reaction. The reaction products of Gilman and Clark[6] obtained by a similar procedure might be another example of this phenomenon as pointed out by Whitmore, *et al.*,[4] who reported the hydrolytic instability of other *beta* oxygenated organosilicon compounds.

Dichloromethyltrimethylsilane in absolute alcoholic sodium ethoxide rapidly formed methylene chloride and ethoxytrimethylsilane with the liberation of a large amount of heat. Cleavage of the dichloromethyl group from silicon was also brought about by potassium acetate in glacial acetic acid at elevated temperatures. These findings extend those of Krieble and Elliott,[7] who showed that alkaline reagents caused cleavage of chlorinated methyl groups from siloxane structures and that the ease of cleavage increased with the degree of substitution upon the methyl group.

Potassium acetate in glacial acetic acid was found to convert bis-(chloromethyl)-dimethylsilane into the corresponding diacetate ester in good yield. The diacetate yielded the dialcohol, dimethylsilylenedimethanol, [bis-(hydroxymethyl)-dimethylsilane] when subjected to methanolysis in the presence of hydrochloric acid. Chloromethyltrimethylsilane treated in essentially the same manner yielded trimethylsilylmethanol.[3]

(1) Whitmore and Sommer, THIS JOURNAL, **68**, 481 (1946).

(2) Whitmore, Sommer and Gold, *ibid.*, **69**, 1976 (1947).

(3) Speier, Daubert and McGregor, *ibid.*, **70**, 1117 (1948).

(4) Whitmore, Sommer, Gold and Van Strien, *ibid.*, **69**, 1551 (1947).

(5) Kipping, *J. Chem. Soc.*, **91**, 717 (1907).

(6) Gilman and Clark, THIS JOURNAL, **69**, 967 (1947).

(7) Krieble and Elliott, *ibid.*, **67**, 1810 (1945).

Experimental Part

Preparation of Dichloromethyltrimethylsilane and bis-(Chloromethyl)-dimethylsilane.—Chloro-(dichloromethyl)-dimethylsilane[7] and (chloro)-bis-(chloromethyl)-methylsilane[7] were each found to react smoothly with a slight excess of methylmagnesium bromide in ether to yield the expected dichloromethyltrimethylsilane (70% yield) and bis-(chloromethyl)-dimethylsilane (63% yield), respectively. These compounds were found to possess the following properties: dichloromethyltrimethylsilane, b. p. 133° at 730 mm., $n^{25}D$ 1.4430, d^{25}_4 1.0395. Molar Refraction: Calcd.[8] for $Cl_2CHSiMe_3$: 39.96. Found: 40.04. *Anal.* Calcd. for $C_4H_{10}SiCl_2$: Cl, 45.2. Found: Cl, 44.9, 45.1. bis-(Chloromethyl)-dimethylsilane, b. p. 160° at 724 mm., $n^{25}D$ 1.4579, d^{25}_4 1.075. Molar refraction: Calcd.[8] for $(ClCH_2)_2SiMe_2$: 39.96. Found: 39.87. *Anal.* Calcd. for $C_4H_{10}SiCl_2$: Cl, 45.2. Found: Cl, 45.0, 44.8.

The synthesis of chloromethyltrimethylsilane by the above method has been described.[2]

Formation of Acetanilide from Trimethylsilylmethylmagnesium Chloride.—To an ethereal solution of about 0.014 mole of trimethylsilylmethylmagnesium chloride[1,4] was added an excess of phenyl isocyanate. A vigorous reaction occurred and the mixture set to a gelatinous mass. After twenty-four hours the mass was stirred with water and filtered with suction. The solids collected were stirred with 95% ethanol and filtered. To the ethanolic solution thus obtained, dilute aqueous sodium carbonate was added and the mixture was heated to boiling and quickly filtered free of the precipitate that formed. The filtrate on becoming cool yielded carbanilide, m. p. 225–235°. After the removal of this compound, most of the alcohol was driven from the solution by evaporation. When the essentially aqueous solution thus obtained was cooled, acetanilide precipitated, m. p. 110–111°. Further evaporation of the mother liquor yielded a second crop of acetanilide, m. p. 111–112°. These crops were combined and recrystallized from water to yield a product, m. p. 111–112°, (approx. 80%) which showed no change of melting point when mixed with an authentic sample of acetanilide, m. p. 112°, and which contained only a trace of silicon.

Cleavage Reactions of Dichloromethyltrimethylsilane.—Dichloromethyltrimethylsilane (154 g., 0.98 mole) was added to absolute ethanol (350 ml.) at room temperature into which sodium (25 g.) had been dissolved. A vigorous boiling ensued immediately. Before the apparatus could be assembled for distillation through a one-foot Vigreux column, a certain amount of material was lost. Distillate boiling over a range from 40 to 78° was collected. This distillate was washed with dilute hydrochloric acid to remove the ethanol and to hydrolyze any ethoxytrimethylsilane that might be present. The washed product was distilled and found to consist only of methylene chloride (60 g., 71%) b. p. 40–41°, $n^{25}D$ 1.4217, d^{25}_4 1.310, and of hexamethyldisiloxane (57 g., 73%), b. p. 99°, $n^{25}D$ 1.3749.

Dichloromethyltrimethylsilane (14 g.) was sealed into a glass tube with anhydrous potassium acetate (22 g.) and glacial acetic acid (11 ml.) and heated at 200° for three hours. A large amount of potassium chloride formed. The tube was opened and its contents washed with water. A dark liquid was thus obtained which smelled strongly of formaldehyde. A portion of this liquid was treated with 2,4-dinitrophenylhydrazine in acidified ethanol solution and yielded the 2,4-dinitrophenylhydrazone of formaldehyde, m. p. 159°, which

(8) Warrick, *ibid.*, **68**, 2455 (1946).

showed no depression of melting point when mixed with an authentic sample of the derivative of formaldehyde, m. p. 165°. The derivative contained only a trace of silicon. At 150° a similar mixture after nineteen hours showed no signs of having reacted in any way.

Preparation of bis-(Acetoxymethyl)-dimethylsilane (Dimethylsilylenedimethanol Diacetate).—bis-(Chloromethyl)-dimethylsilane (292 g., 1.85 moles), potassium acetate (412 g., 4.2 moles) and glacial acetic acid (300 ml.) were heated together and shaken in a stainless steel autoclave at 118–130° for four hours and at 148–160° for sixteen hours. The contents of the autoclave were then washed once with water to remove the salts and most of the acid present. The water insoluble liquid was distilled. The only compound found, other than acetic acid, was bis-(acetoxymethyl)-dimethylsilane (339 g., 90%), b. p. 124° at 27 mm., 223° at 739 mm., $n^{25}D$ 1.4309–1.4310, d^{25}_4 1.0135. Molar refraction: Calcd.[8] for $(AcOCH_2)_2SiMe_2$: 52.34. Found: 52.17. *Anal.* Sap. equiv. Calcd. for $(AcOCH_2)_2SiMe_2$: 102.2. Found: 102.6, 102.1.

bis-(Acetoxymethyl)-dimethylsilane (110 g.) was dissolved in a ten-fold excess of dry methanol and acidified with three drops of concentrated hydrochloric acid. Periodically during three weeks methyl acetate was removed by distillation. Each time methanol was added to restore the solution to its original volume and the solution was permitted to stand at room temperature for several days before more methyl acetate was removed. The solution was distilled, after no further amount of methyl acetate appeared to form. bis-(Hydroxymethyl)-dimethylsilane (dimethylsilylenedimethanol) was obtained as a colorless, odorless, viscous liquid, completely soluble in water; b. p. 130° at 27 mm., $n^{25}D$ 1.4611, d^{11}_4 0.993. Molar refraction: Calcd.[8] for $(HOCH_2)_2SiMe_2$: 33.38. Found: 33.20. Saponification number, 12.7. *Anal.* Calcd. for $C_4H_{12}O_2Si$: Si, 23.3. Found: Si, 23.2, 23.3.

Summary

Some of the reactions of the chlorides of tetramethylsilane have been studied. These compounds showed a tendency, under certain conditions, toward cleavage of the substituted methyl group from the silicon atom. The dichloromethyl group was found to be more easily cleaved than the chloromethyl group. Hydrolysis of the addition product of trimethylsilylmethylmagnesium chloride and phenyl isocyanate was shown to result in the formation of acetanilide, thus revealing the ease of cleavage of *beta* carbonyl silicon compounds.

The new compounds, bis-(chloromethyl)-dimethylsilane, dimethylsilylenedimethanol diacetate, dimethylsilylenedimethanol, and dichloromethyltrimethylsilane were prepared and characterized during the investigation.

PITTSBURGH, PA. RECEIVED OCTOBER 27, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Basic Strengths of Amines as Measured by the Stabilities of Their Complexes with Silver Ions

BY RICHARD J. BRUEHLMAN[1] AND FRANK H. VERHOEK

The relationship of the basic strengths of amines as determined by the stability of their ammonium ions to their strengths as measured by the stability of their complexes with silver ion has been discussed repeatedly. It has been stated that a parallelism between the two measures exists[2] and that a parallelism does not exist.[3,4] Except for the last paper cited,[4] the conclusions have commonly been based on a consideration of the instability or association constants for the over-all reaction

$$Ag^+ + 2A \rightleftharpoons AgA_2^+ \qquad (1)$$

where A represents the amine. It was pointed out,[5] however, that each such constant contains an equilibrium constant for the reaction

$$AgA^+ + A \rightleftharpoons AgA_2^+ \qquad (2)$$

in which the ion reacting with the amine is different for each amine considered, and that a more just comparison is that between the two reactions

$$Ag^+ + A \rightleftharpoons AgA^+ \qquad (3)$$

$$H^+ + A \rightleftharpoons AH^+ \qquad (4)$$

Accordingly the equilibrium constants of reactions (3) have been measured for several amines and compared with those for reactions (4) measured in similar systems. The equilibrium constants of reactions (2) were also measured.

The equilibrium constants were determined by means of *p*H measurements on solutions of amine, silver ion, acid and neutral salt according to the method of Bjerrum,[6] on selected groups of primary, secondary, and tertiary amines of varied basic strength. The selection was severely limited by the requirements that the amine be reasonably soluble in water, that it form complexes in such a *p*H range that silver oxide would not precipitate out, that it have a basic strength different from other members of the group, and that the complex formed be sufficiently soluble that a solid phase did not form. This paper reports equilibrium constants for the formation of ammines of silver ion with five primary amines, three secondary amines, and four pyridines. In order to estimate the validity of the comparison of equilibrium constants for equations (3) and (4) at a single temperature, temperature coefficients over a ten-degree temperature interval were determined in most cases.

In addition, equilibrium constants were deter-

(1) Present address, Argonne National Laboratory, Chicago, Illinois.

(2) Larsson, *Z. physik. Chem.*, **A169**, 215 (1934).

(3) Britton and Williams, *J. Chem. Soc.*, 796 (1935).

(4) Vosburgh and Cogswell, THIS JOURNAL, **65**, 2412 (1943).

(5) Carlson, McReynolds and Verhoek, *ibid.*, **67**, 1334 (1945).

(6) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Sons, Copenhagen, 1941.

mined for the formation of copper ammines with two of the pyridines.

Experimental

The *p*H measurements were made with a glass electrode and a Coleman Style 200 *p*H Electrometer. The glass and calomel electrodes were mounted in a specially designed glass apparatus that was thermostated at 25 or 35°; the two compartments were connected through ungreased stop-cocks by a saturated potassium nitrate bridge. The electrometer was adjusted for asymmetry and temperature by using buffer solutions prepared from samples of potassium acid phthalate, potassium dihydrogen phosphate and disodium hydrogen phosphate and sodium tetraborate decahydrate furnished by the National Bureau of Standards.

Each *p*H measurement was made on a separate sample prepared by adding a known amount of amine from a weight buret to a 100-ml. sample of a standard solution of metal ion, acid, and neutral salt, precautions being taken to prevent absorption of carbon dioxide. Fifty milliliters of the solution thus prepared was used to rinse the glass electrode chamber and the remaining 50 ml. was used for the measurement.

All of the amines were research grade materials obtained from Eastman Kodak Co. General treatment involved refluxing for eight to twelve hours over barium oxide or potassium hydroxide, followed by distillation through a packed column, taking the middle fraction boiling within 0.2–0.3°. Boiling points in all cases agreed well with those in the literature. As a further precaution, the amines of high basic strength were titrated with standard acid to determine the neutral equivalents; these agreed with the theoretical values. All amines except ethylamine and β-methoxyethylamine, which were used as standardized solutions, were used as the pure amine.

Results

Dissociation Constants of the Amines.—Since it is necessary to know the acid dissociation constants of the amines for the calculation of the formation curves, these were determined in solutions of the same ionic strength as the solutions containing the complex-forming metal ion. Varying amounts of amines were added to standard solutions 0.525 *M* in potassium nitrate and 0.100 *M* in nitric acid. The results are given in Table I. Each value reported here represents an average of 10–12 determinations at different ratios of amine concentration to amine salt concentration.

Metal Ammine Formation.—The over-all and successive association constants for the systems studied were calculated from accurately-drawn large-scale plots of the formation curves ($\bar{n}$, the average number of moles of amine combined with one mole of silver ion, *vs.* $p[A]$, the negative logarithm of the concentration of free amine) by the method of Bjerrum.[5,6] Each formation curve was plotted from 15–25 separate points, each point representing a *p*H measurement on an individually prepared sample of known concentrations of amine, acid, metal ion and neutral salt. The standard solutions to which known amounts of the amines were added were 0.500 *M* in potassium nitrate, 0.1000 *M* in nitric acid and 0.0250 *M* in silver nitrate. Table II gives a summary of the values obtained for the silver ammines at 25° and 35°; k_1 is the equilibrium constant for equation

TABLE I

THE ACID DISSOCIATION CONSTANTS OF AMINES IN 0.5 *M* POTASSIUM NITRATE SOLUTIONS

Amine	pK_{AH} at 25°	pK_{AH} at 35°	$\Delta pK_{AH}/\Delta t$
Pyridine	5.45	5.35	0.010
α-Picoline	6.20	6.08	.012
γ-Picoline	6.26	6.14	.012
2,4-Lutidine	6.99	6.86	.013
Ethylamine	10.81	10.48	.033
Isobutylamine	10.72	10.40	.032
Ethanolamine	9.74	9.51	.023
β-Methoxyethylamine	9.45		
Benzylamine	9.62	9.32	.030
Morpholine	8.70		
Piperidine	11.28		

TABLE II

ASSOCIATION CONSTANTS OF SILVER AMMINES IN 0.5 *M* POTASSIUM NITRATE

Amine	Temp., °C.	log k_1	Δ log $k_1/\Delta t$	log k_2	k_1/k_2	log K_2
Pyridine	25	2.04	0.011	2.18	0.72[a]	4.22
	35	1.93		2.07	.72	4.00
α-Picoline	25	2.27	.011	2.41	.72	4.68
	35	2.16		2.30	.72	4.46
γ-Picoline	25	2.24	.010	2.46	.60	4.70
	35	2.14		2.36	.60	4.50
2,4-Lutidine	25	2.47	.011	2.61	.58	5.18
	35	2.36		2.60	.58	4.96
β-Methoxyethylamine	25	2.95		3.39	.36	6.34
Ethanolamine	25	3.13	.012	3.55	.37	6.68
	35	3.01		3.43	.37	6.47
Isobutylamine	25	3.38	.016	3.86	.33	7.24
	35	3.22		3.70	.33	6.92
Ethylamine	25	3.37		3.93	.28	7.30
	30[c]	3.30	.016	3.84	.29	7.14
	35	3.21		3.77	.28	6.98
Ammonia[b]	25	3.29		3.83	.29	7.12
Benzylamine	25	3.29	.016	3.85	.28	7.14
	35	3.13		3.69	.28	6.82
Morpholine	25	2.25		2.67	.38	4.98
Diethylamine[c]	30	2.98		3.22	.58	6.20
Piperidine	25	3.03		3.45	.38	6.48

[a] Vosburgh and Cogswell (ref. 4) obtained a ratio of 0.78 from solubility measurements. [b] Obtained by Bjerrum (ref. 6) in 0.5 *M* ammonium nitrate solution; pK_{AH} = 9.26. [c] Obtained by Carlson, McReynolds and Verhoek (ref. 5) in solutions of the same concentration as above; pK_{AH} = 10.96.

(3), k_2 that for equation (2) and k_2 that for equation (1). It is estimated that the former values are precise to 0.05 logarithmic unit.

For comparison with the values for the silver ammines, measurements of the equilibrium constants for the reaction

$$Cu^{++} + A \rightleftharpoons CuA^{++} \qquad (5)$$

and those for the addition of further amine molecules to cupric ion were made with pyridine and γ-picoline at 25°. The solutions used were 0.500 M in potassium nitrate, 0.1000 M in nitric acid and 0.0300 M in cupric nitrate. Table III gives the results.

TABLE III

ASSOCIATION CONSTANTS OF CUPRIC AMMINES IN 0.5 M POTASSIUM NITRATE AT 25°

Amine	log k_1	log k_2	log k_3	log k_4	log K_4
Pyridine	2.52	1.86	1.31	0.85	6.54
γ-Picoline	2.82	2.15	1.61	1.16	7.74
Ammonia[a]	3.99	3.34	2.73	1.97	12.03

[a] Measured by Bjerrum in 0.5 M ammonium nitrate solutions.

Discussion

Since silver ion is a Lewis acid, the equilibrium constants for equations (3) and (4) for a series of amines measure the strengths of the amines relative to two different reference acids. If the relative strengths of the amines are independent of the reference acid, a plot of the logarithm of k_1 against the negative logarithm of the dissociation constant of the substituted ammonium ion would be expected to give a straight line of unit slope. Such a plot for the data at 25° from Tables I and II is given in Fig. 1.

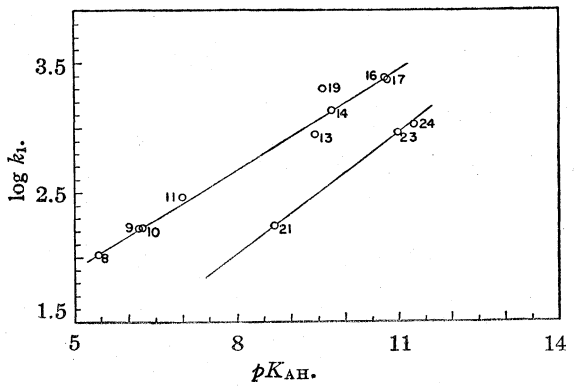


Fig. 1.—Variation of the first association constant of silver ammines with the strength of the amine relative to hydrogen ion at 25°. Amines are numbered as in Fig. 2.

It is evident that a straight line relationship is obtained, but that the data fall into two groups. The pyridines and primary amines lie on one curve, and the secondary amines on another. Thus a secondary amine and a primary amine which have the same strength relative to hydrogen ion will differ in strength by a factor of about 3.5 when measured relative to silver ion.

It is also evident that the lines obtained are not of unit slope; the slopes are about one-fourth. Although the curves are drawn with different slopes for the two groups, it cannot be definitely stated that the slopes should be different, since the number of points is small. The slopes will be changed somewhat by a change in temperature, but the data in the tables show that the temperature coefficients are sufficiently alike that this change will not be great. The slope of approximately one-fourth may then be taken as real, and indicates a very great compression of the range of basicities when silver ion is used as a standard acid to measure the basic strength. Thus two amines which differ in strength by a factor of ten thousand when measured relative to hydrogen ion will differ only by a factor of ten when measured relative to silver ion.

It is seen from Table II that the ratio of k_1/k_2, although larger for the pyridines than for the other amines, is in all cases of the order of unity, and that log K_2 is about twice log k_1. This modifies the statements made in the introduction because it means that log K_2 will vary in a similar fashion to log k_1, so that except for a factor of two, comparisons of log K_2 with pK_{AH} will be valid. This is convenient, because it permits the use of the large number of values of K_2 available in the literature, obtained on systems to which the present technique is not applicable, for comparison. Figure 2 shows a plot of these data as log K_2 *vs.* pK_{AH}; in drawing conclusions from the figure one must remember that the ordinate of each point, and consequently the slopes of the curves

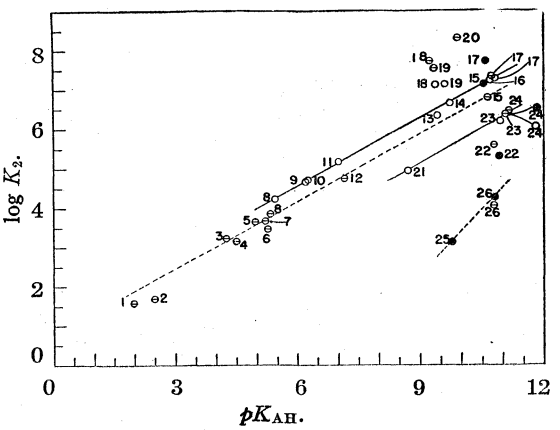


Fig. 2.—Variation of the over-all association constant of silver ammines with the strength of the amine relative to hydrogen ion: ⊖, Larsson; ●, Britton and Williams; O, this paper; 1, *p*-nitroaniline; 2, *m*-nitroaniline; 3, α-naphthylamine and β-naphthylamine; 4, aniline; 5, quinoline; 6, *p*-toluidine; 7, pseudo-cumidine; 8, pyridine; 9, α-picoline; 10, γ-picoline; 11, 2,4-lutidine; 12, *s*-collidine; 13, β-methoxyethylamine; 14, ethanolamine; 15, methylamine; 16, isobutylamine; 17, ethylamine; 18, ammonia; 19, benzylamine; 20, ethylenediamine; 21, morpholine; 22, dimethylamine; 23, diethylamine; 24, piperidine; 25, trimethylamine; 26, triethylamine.

would be decreased by one-half if log k_1 was plotted. The full lines are drawn through the values obtained in this investigation; they are represented by the equations

$$\log K_2 = 0.577\ pK_{AH} + 1.08$$
$$\log K_2 = 0.577\ pK_{AH} - 0.02$$

for the upper and lower curves, respectively. The dotted lines are drawn through the points of Larsson[2] for the primary amines and through the tertiary amine points of Britton and Williams.[3] The curve for Larsson's data lies below that for this investigation because his values are for a 50–50 alcohol water mixture; if, as he reports, the values in water are 0.3 to 0.6 logarithmic units higher than in the alcohol solution, the dotted line will coincide with the full line for the primary amines.

The figure confirms the smaller range of basic strengths relative to silver ion and shows that the aliphatic tertiary amines comprise a third group, although the slope of the curve for the latter is uncertain since only two points are available. It is this difference between primary, secondary, and tertiary amines which has led to the belief that there is no relationship between the basic strengths of the amines measured relative to the two standard acids; actually within the three groups there is a parallelism between the two measures, although the ratios of strengths of two bases is not the same in the two systems.

The explanation for the smaller range of base strengths referred to silver ion as compared to hydrogen ion is not immediately obvious. Evidently a change in the groups attached to the nitrogen atom which makes a great change in its tendency to coördinate with a proton makes little change in its tendency to coördinate with a silver ion. This is probably connected with the larger size of the silver ion as compared to the hydrogen ion, but the exact mechanism is obscure. That the effect is not peculiar to the silver ion is shown by the correspondence of the data on the copper complexes to those for the silver complexes.

Nor is it clear why the silver ion separates the aliphatic amines into three groups. It is tempting to attribute this to the increasing importance of steric effects with increasing substitution on the nitrogen, yet this can hardly be the explanation. The silver ion is not large enough to interfere with any of the groups on the amines investigated.

A further problem appears in the position of the pyridines, which do not lie with the tertiary aliphatic amines. It may be noted, however, that resonance structures are possible in a compound of silver ion with pyridine which are not possible with tertiary aliphatic amines, nor for compounds of hydrogen ion with pyridine. These would tend to cause the pyridine complexes to be more stable as compared to those of the aliphatic amines, raising them above the position of tertiary aliphatic amines of the same strengths relative to hydrogen ion. From this point of view, the fact that the points for the pyridine complexes lie on the same curve as those for the primary aliphatic amines is fortuitous.

Summary

1. The association constants for the reactions of silver ion with groups of primary aliphatic amines, secondary amines and pyridines have been measured, together with similar constants for cupric ion and two pyridines, and temperature coefficients.

2. When the logarithm of the first association constant is plotted against the pK value for the corresponding substituted ammonium ion, two straight lines are obtained: one for the pyridines and primary aliphatic amines, and one for the secondary amines. Data from the literature indicate that tertiary aliphatic amines lie on a third curve.

3. The slope of the curve obtained is approximately one-fourth, indicating a much smaller range of basic strengths when measured against silver ion as a reference acid than when measured against hydrogen ion.

COLUMBUS, OHIO RECEIVED AUGUST 2, 1947

[CONTRIBUTION FROM THE BEACON LABORATORIES, THE TEXAS COMPANY]

The Determination of Pore Size Distribution from Gas Adsorption Data

BY C. G. SHULL*

Introduction

There has been widespread application in the past of gas adsorption data in determining quantitatively the physical structure of finely divided and porous materials. Most notable among the theories of adsorption which have been advanced are those of Brunauer, Emmett and Teller[1] and Harkins and Jura,[2] both of which have proved very successful in evaluating the specific surface of such materials. There are, however, frequent isotherm phenomena which cannot be treated by these theories and, in order to explain some of these, the presence of capillary condensation in the porous structure has been suggested. Excellent summaries of some of the early quantitative or semi-quantitative attempts in this direction have been given by Brunauer[3] and by Cohan.[4] These attempts have all been recognized as merely approximations for one reason or another.

Recently, Wheeler[5] has introduced a composite theory which combines the BET multilayer adsorption and capillary condensation viewpoints. Upon suitable application of this theory to the experimental isotherm, the pore size distribution which would account for the experimental data may be evaluated. It is the purpose of the present paper to point out a simple method by which the Wheeler theory can be applied to isotherm data thereby obtaining the pore size distribution.

The Wheeler theory can be summarized in one simplified equation

$$V_s - V = \pi \int_R^\infty (r - t)^2 L(r) \mathrm{d}r \qquad (1)$$

In this equation, V_s is the volume of gas adsorbed at saturation pressure, V is the volume of gas adsorbed at intermediate pressure p, $L(r)\mathrm{d}r$ is the total length of pores whose radii fall between r and $r + \mathrm{d}r$, R is the corrected Kelvin radius which is obtained as a function of the pressure, and t is the multilayer thickness which is normally built up at pressure p. This equation merely states that the volume of gas $V_s - V$ not yet adsorbed at a pressure p is equal to the total volume of pores which have not been filled.

The left hand side of Equation (1) is known from experimental data and it is desired to determine the pore size distribution function $L(r)$ which when integrated will show agreement with these experimental data. Before this can be done, it is necessary to evaluate R and t as functions of the pressure.

Evaluation of Critical Kelvin Radius and Multilayer Thickness.—Wheeler has introduced a modified Kelvin equation in evaluating the corrected Kelvin radius R. In this equation, the corrected or critical pore radius (critical in the sense that all pores having smaller radii than R have already been filled by multilayer adsorption and capillary condensation) is placed equal to the sum of the multilayer thickness and the radius normally calculated from the simple Kelvin equation. In other words

$$R = t - \frac{2\sigma v}{R_g T \ln p/p_0} \qquad (2)$$

σ being the surface tension, v the molar volume of the condensed liquid, and R_g the gas constant per mole, and T the temperature. This equation states, very reasonably, that the radius determining the presence or absence of capillary condensation is that of the open section (the part not occupied due to multilayer adsorption) in the pore and not that of the entire pore.

An approximate expression from the BET theory of multilayer adsorption has been used by Wheeler for calculating multilayer thickness values. It is known, however, that the BET thicknesses become much larger than experimental thicknesses *for flat surfaces* in the high pressure region. Figure 1 shows a comparison of these thickness values. In the upper part of this figure are shown experimental data taken from nine published isotherms[6] (nitrogen gas) for crystalline materials of large crystal size (1100 to 16,000 ångströms). These data are plotted on a V/V_m basis where V_m is the adsorbed volume corresponding to monomolecular coverage of the surface. Deviations of the experimental points from the average isotherm are seen, but the general trend of the data is well established. The average isotherm is next transferred to a multilayer thickness curve (t values) by assuming the monomolecular thickness to be 4.3 ångströms for nitrogen. This is shown in the lower part of Fig. 1 with the curve corresponding to the BET theory. Pronounced differences between the BET and experimental curves are to be noted in the higher pressure region.

Figure 2 shows curves for the corrected Kelvin radius R as a function of pressure, calculated from Equation (2) by use of the above experi-

* Present address: Oak Ridge National Laboratory, Oak Ridge, Tenn.

(1) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938).

(2) W. D. Harkins and G. Jura, *J. Chem. Phys.*, **11**, 431 (1943).

(3) S. Brunauer, "The Adsorption of Gases and Vapors," Princeton University Press, U. S. A., 1943, Chapter XI.

(4) L. A. Cohan, THIS JOURNAL, **60**, 433 (1938).

(5) A. Wheeler, Presentations at Catalysis Symposia, Gibson Island A. A. A. S. Conferences, June, 1945, and June, 1946.

(6) P. H. Emmett and T. DeWitt, *Ind. Eng. Chem., Anal. Ed.*, **13**, 28 (1941); W. D. Harkins and G. Jura, THIS JOURNAL, **66**, 1362 (1944).

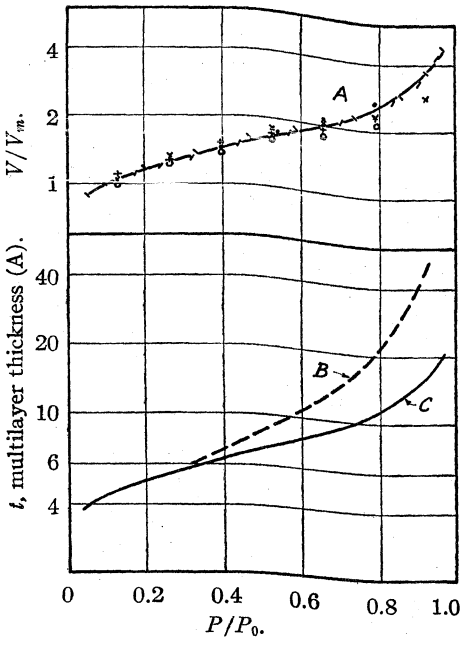


Fig. 1.—Multilayer thickness as obtained for large crystals and as calculated from the BET theory: Curve A, experimental values of the number of adsorbed layers (V/V_m) for crystalline materials of large crystal size; curve B, multilayer thickness for N_2 calculated from BET theory; curve C, multilayer thickness curve derived from curve A.

mental and BET values for multilayer thickness. As expected, the differences between the two curves show up in the high pressure region. Obviously it is necessary to make a decision as to which curve should be used in interpreting experimental isotherms.

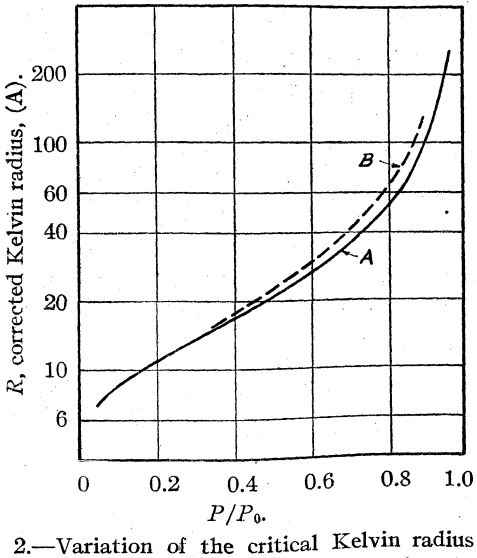
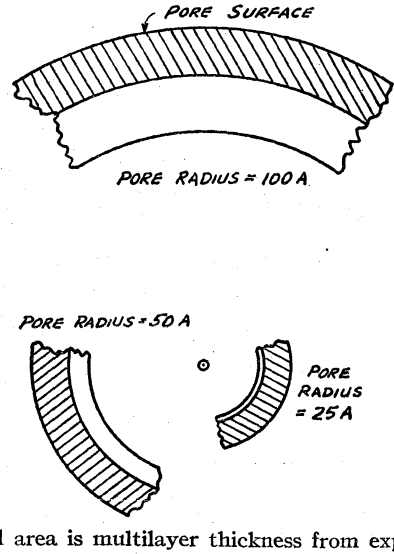


Fig. 2.—Variation of the critical Kelvin radius as a function of the adsorption pressure: curve A, calculated using experimental multilayer thickness values; curve B, calculated using BET thickness values (Wheeler).

Wheeler has argued that since adsorption occurs on the curved surface of a pore, larger thicknesses would be expected than on a flat surface, and hence the use of the BET theory is justified. Notwithstanding this, there are arguments which seem to indicate that the use of BET values is an over-correction for the effect and that it is probably better to use the flat surface experimental data.

Some insight into this can be gained by considering the adsorption process on systems having hypothetical pore structure. Consider first a system where all of the pores are 100 ångströms in radius. According to the curve derived from experimental data, which is shown in Fig. 2, capillary condensation should occur at a partial pressure of 0.895 after a multilayer thickness of 14.8 ångströms had been reached. On the other hand, the BET curve predicts capillary condensation as occurring at a partial pressure of 0.865 with a multilayer thickness of 31 ångströms. Wheeler's argument that the pore curvature would increase the adsorption to BET values seems to be an overcorrection for the effect. It appears very unlikely that the curvature in a pore of radius 100 ångströms would place in effect additional adsorptive forces sufficient to more than double the adsorbed film thickness.

A simple scale drawing with the pertinent relative dimensions indicates a much smaller effect than that given by the BET theory. Figure 3 illustrates the predicted multilayer thicknesses at the time of capillary condensation for pores of radii 100, 50 and 25 ångströms. For a radius of 100 ångströms the BET thickness seems much too large, for a 50 ångström radius it is still larger than would be expected but perhaps not unreason-



Shaded area is multilayer thickness from experimental data for large crystals. Unshaded area is extra thickness predicted by BET theory.

Fig. 3.—Diagram showing multilayer thickness at pressure of capillary condensation for pores of various sizes.

ably so, and for a 25 ångström radius the two multilayer thicknesses are close together. Since the curvature effect becomes more pronounced as the radius is reduced and has little or no effect with large radii pores, it is seen that the BET values are inherently incorrect in their dependence upon the pore radius. If anything, the true curvature values of the thickness should differ from flat surface values most drastically in the small pore region, and this is just the opposite of the result obtained by use of the BET multilayer thickness values. Until a more satisfactory theory accounting for curvature effects is available, the use of flat surface data would appear to be preferable. Accordingly, the curves on Figs. 1 and 2 corresponding to experimental data will be used in the isotherm analysis given below. It should be mentioned that the procedure of isotherm analysis to be discussed in the following section is a general one applicable to whatever multilayer thickness values are selected.

Evaluation of Pore Size Integral.—There does not appear to be a simple method of inversion applicable to the pore size integral, Equation (1), by which the pore size distribution $L(r)$ can be obtained from numerical values of $V_s - V$. Indirect methods are available, however, which permit an easy and convenient solution of the equation. The present method is one of comparison of the experimental isotherm with standard or calculated isotherms.

Wheeler has suggested that pore size distributions may be represented by simple analytical forms of Maxwellian or Gaussian type. Thus for a Maxwellian distribution of pore sizes

$$L(r) = Are^{-r/r_0} \qquad (3)$$

with A and r_0 constants, and when this is substituted into Equation (1) and the integration performed we obtain

$$V_s - V = Ar_0^4 M(R, r_0) \qquad (4)$$

where

$$M(R,r_0) = \frac{\pi}{r_0^3} e^{-R/r_0}\{R(R-t)^2 + 6r_0^3 + 2r_0^2(3R-2t) + r_0(3R-t)(R-t)\} \qquad (5)$$

The function $M(R, r_0)$ has been evaluated for various values of R and r_0, and a family of such curves is shown in Fig. 4. These curves will be referred to as standard inverted isotherms.[7]

Likewise for a Gaussian distribution of pore sizes

$$L(r) = Ae^{-[\beta/r_0(r-r_0)]^2} \qquad (6)$$

with A, β, and r_0 constants, and this integrates into

$$V_s - V = 2A(r_0^3/\beta)G_\beta(R, r_0) \qquad (7)$$

where

$$G_\beta(R, r_0) = \frac{\pi}{4r_0^3}\left\{\frac{r_0}{\beta} e^{-\rho^2}(R - 2t + r_0) + \sqrt{\pi}[1 - H(\rho)][(r_0 - t)]^2 + \frac{1}{2}\left(\frac{r_0}{\beta}\right)^2\right\} \qquad (8)$$

(7) Numerical values for the standard inverted isotherms of Figs. 4 to 6 have been tabulated and are available from the author.

$$\rho = \frac{\beta}{r_0}(R - r_0), \text{ and } H(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-y^2}dy$$

$G_\beta(R, r_0)$ has been evaluated for $\beta = 2$, 5 and 10 and various values of R and r_0, and some of these standard isotherms are shown on Figs. 5 and 6. It may be mentioned that the parameter β determines the width of the pore size distribution while r_0 controls the average pore size.

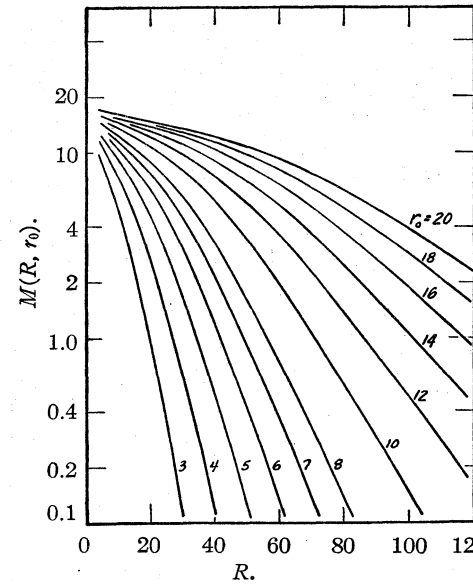


Fig. 4.—Standard inverted isotherms: calculated for a Maxwellian distribution of pore sizes.

The procedure in interpreting experimental data is then the following. The experimental isotherm is replotted as $V_s - V$ (log scale) *versus* the Kelvin radius R. This is conveniently known as an *inverted isotherm*. This inverted isotherm is next matched with one of the standard isotherms of Figs. 4–6. If a satisfactory match is obtained, the pore size distribution is known immediately from the parameters of the standard isotherm.

Sometimes the experimental inverted isotherm cannot be fitted to one of the standard isotherms and it is necessary then to resolve the experimental isotherm into two or more standard isotherms. For instance if an experimental isotherm can be resolved into the sum of a Maxwellian and a Gaussian standard isotherm, then

$$V_s - V = A_0 r_0^4 M(R, r_0) + 2A_1 \frac{r_1^3}{\beta_1} G_{\beta_1}(R, r_1) \qquad (9)$$

and hence

$$L(r) = A_0 re^{-r/r_0} + A_1 e^{-\left[\frac{\beta_1}{r_1}(r-r_1)\right]^2} \qquad (10)$$

In all cases, the coefficients A_n can be evaluated from the relative amplitudes of the component isotherms. Needless to say, as many component isotherms can be used as is necessary to fit the data to the desired accuracy. For all practical cases to date, two terms have been found suf-

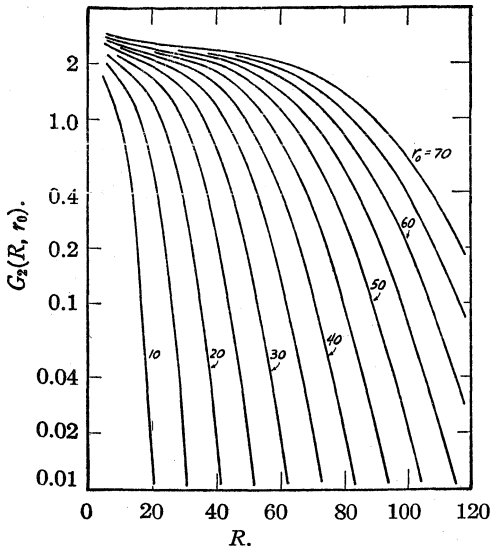


Fig. 5.—Standard inverted isotherms calculated for a Gaussian distribution ($\beta = 2$) of pore sizes.

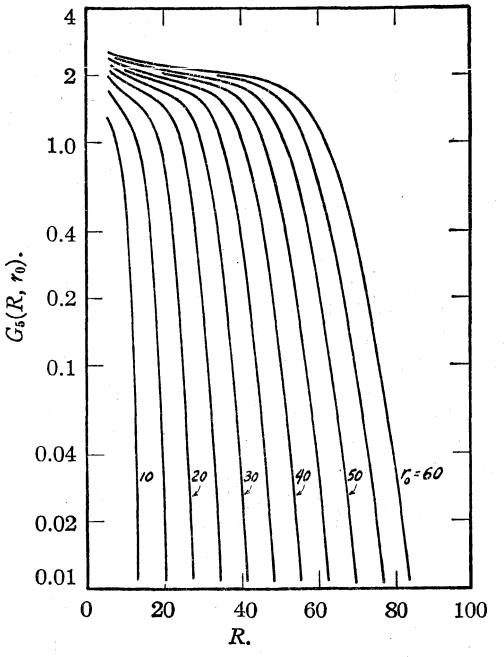


Fig. 6.—Standard inverted isotherms calculated for a Gaussian distribution ($\beta = 5$) of pore sizes.

ficient. The whole procedure can be carried out in fifteen or twenty minutes.

It is obvious that the specific surface may be calculated from the distribution $L(r)$, using the equation

$$S = 2\pi \int_0^\infty rL(r)\, dr \qquad (11)$$

This method of calculation is, of course, independent of the usual BET method[8] of determining the specific surface from adsorption isotherm data, but is more laborious and time-consuming. In particular instances, in which a variety of adsorbates have been adsorbed on the same adsorbent, more consistent values of specific surface have been obtained by this calculation than by the BET method. It should also be pointed out that the Wheeler procedure[5] of isotherm analysis does not permit a wholly independent calculation of the specific surface since the BET surface has entered directly in the pore size evaluation.

The above procedure of matching the experimental data to a calculated curve is, of course, an indirect one in that the mathematical inversion required in Equation (1) is not accomplished in a straightforward fashion. This raises the question of uniqueness in the derived pore size distribution. It has been found that the selection of the matched standard curve is, in general, a well-defined one showing that one type of distribution is in considerably better agreement with the data than any other. In cases where ambiguity in the choice of matching exists (for instance where the matching is equally good with a single curve or with the sum of two other curves), experience has shown that it makes little difference in the final distribution. It would seem that uncertainties in the basic assumptions necessary to the application of the inversion procedure are much more troublesome than the problem of uniqueness in the inversion.

Examples of Isotherm Interpretation.—As examples of the above procedure of analysis, the two isotherms given in Fig. 7 will be considered. These were obtained[9] with samples of silica gel possessing widely different physical properties. Both adsorption and desorption data are presented, there being no hysteresis loop in the case of gel I. The solid line for gel II represents the adsorption data while the broken line corresponds to desorption data. Selected isotherm points from the desorption curves have been replotted as inverted isotherm points (open and shaded circles) in Fig. 8. The isotherm points for gel I are seen to agree closely with the standard isotherm $M(R, 3)$, which has been drawn in from Fig. 4. Therefore the pore size distribution $L(r)$ for this gel can be represented by a Maxwellian distribution with the parameter r_0 having the value 3Å. On the other hand, the isotherm points for gel II cannot be matched to one of the standard curves but they can be matched to the sum of two standard isotherms, $G_5(R, 43)$ and $M(R, 18)$.

(8) It will be recognized that this independence is not strictly true since the BET theory has been used to obtain values of V_m used in the determination of the multilayer thickness t as shown in Fig. 1. However, this procedure has drawn on the validity of the BET determination of specific surface only in the case of materials of large crystal size and this has been shown by many studies to be quite correct. No assumptions regarding the validity of the BET theory for the material being studied have been made. It follows that the specific surface calculated from the pore size distribution is not necessarily the same as that generally calculated from the BET theory since the presence of the pore size distribution may have made questionable the application of the simple BET theory.

(9) I am indebted to Dr. P. B. Elkin for supplying the isotherm data on these materials.

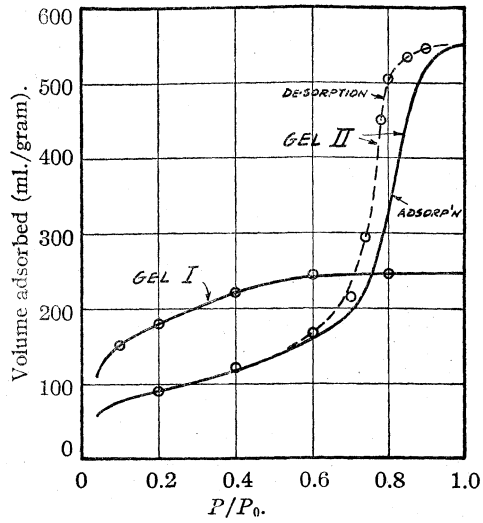


Fig. 7.—Nitrogen isotherms for two samples of silica gel. The solid and broken lines are the experimental isotherms. The circled points are taken from the matched standard isotherms of Figure 8.

The triangular points on Fig. 8 are matched with the standard isotherm $G_5(R, 43)$ and have been obtained by subtracting the standard isotherm $M(R, 18)$ from the experimental data (the open circles) for gel II. Thus the pore size distribution for gel II can be represented by an expression of the type given by Equation (10) with $r_0 = 18$, $r_1 = 43$, $\beta_1 = 5$ and relative values of A_1 and A_0 obtained ($A_1/A_0 = 222$) from the amplitudes of the two standard isotherms.

The differences between the experimental points and the standard isotherms in Fig. 8 have been transferred to the original isotherms given in Fig. 7, since here the fluctuations can be more easily visualized in terms of experimental error. The circled points on the isotherms of Fig. 7 are taken directly from the standard inverted isotherms of Fig. 8. The agreement shown by the matching process is within the experimental error of the adsorption measurements.

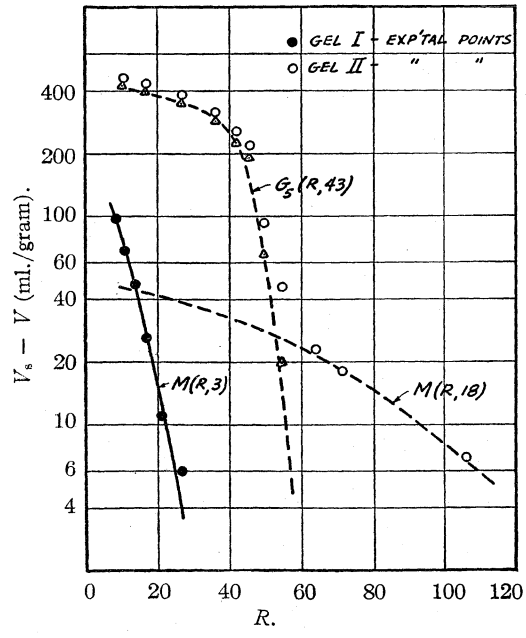


Fig. 8.—Comparison of silica gel isotherm data with selected standard inverted isotherms.

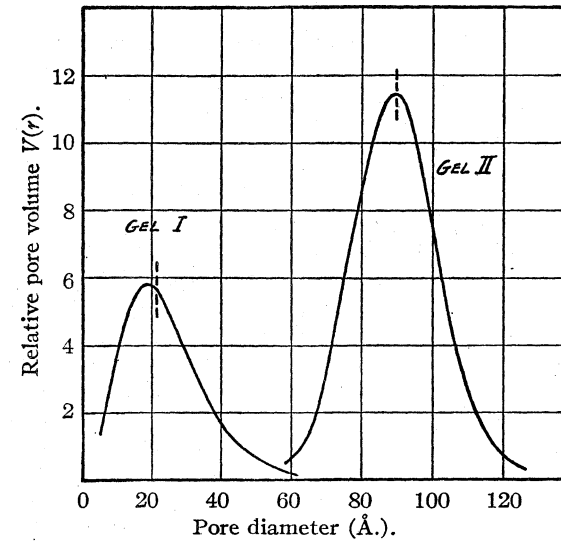


Fig. 9.—Pore volume distributions calculated for silica gel samples.

Pore size distributions for these two gels have been calculated and are shown in Fig. 9. These have been plotted as volume distributions $V(r)$, rather than length distributions, since the former seem to have greater physical significance. This transformation is easily performed since

$$V(r) = \pi r^2 L(r) \qquad (12)$$

Values of the average pore diameter (defined as that size which divides the pore volume distribution into two equal parts) have been marked on the distribution curves. These values are 21 and 90 Å. for gels I and II, respectively. It is interesting to compare these with values of the mean pore diameter calculated from the expression[10] $4V_s/S$ where S is the specific surface determined by the standard BET method. Calculation shows the latter to be 23 and 107 Å., respectively. Comparisons of the pore size distributions obtained by the above procedure with other independent data have been made for a variety of materials and these will be the subject of an accompanying publication.[11]

Summary

The theory of the interpretation of gas adsorp-

(10) If all pore volume is contained in one long cylindrical pore L units long, the diameter of this pore can be written

$$D = 4\,\frac{\frac{\pi D^2}{4}L}{\pi DL} = \frac{4V_s}{S}$$

(11) C. G. Shull, P. B. Elkin and L. C. Roess, THIS JOURNAL, **70**, 1410 (1948).

tion data in terms of capillary condensation as advanced by Wheeler is discussed. It is suggested that the empirical use of experimental adsorption data for materials of large crystal size is preferable to the employment of the BET theory at the higher relative pressures (0.35 to 0.99) in evaluating the multilayer thickness of the adsorbed layers. A simplified procedure for applying the theory of capillary condensation to experimental data, thereby obtaining the pore size distribution, is presented. Examples of this procedure are given in the treatment of data for two silica gels.

BEACON, N. Y. RECEIVED APRIL 3, 1947

[CONTRIBUTION FROM THE BEACON LABORATORIES, THE TEXAS COMPANY]

Physical Studies of Gel Microstructure

BY C. G. SHULL,[1] P. B. ELKIN[2] AND L. C. ROESS

Introduction

During the past few years a number of new techniques have become available for studying the physical microstructure of porous and finely divided materials. Low temperature gas adsorption has found widespread application in the determination of the specific surface available to gases.[3] More recently, attempts have been made to interpret the adsorption isotherm in terms of pore dimensions in addition to specific surface.[4] X-Ray scattering at small angles has been used in obtaining information on the solid discontinuities present in colloidal materials, and these data have been correlated to a certain extent with crystal size data from the broadening of X-ray diffraction lines and with specific surface results.[5,6]

In the application of either of these techniques certain simplifying assumptions must be made with consequent uncertainty or ambiguity in the results of the analysis. One procedure for testing the validity of these assumptions for any particular material presents itself in the correlation of independent data to form a consistent over-all picture of the physical microstructure. Thus, as will be shown later in this paper, the specific surface should show a dependence on the particle size distribution; and the pore size and the particle size distributions should be related through the porosity factor. If the various physical data can be shown to be consistent, then confidence in the validity of the analysis is gained. It is to be emphasized that conclusions of this sort drawn for one material are not sufficient to justify the validity of the assumptions for all cases.

The present paper is concerned with a series of observations of the type outlined above obtained for a series of ten silica and silica–alumina gels. These particular gels were selected because they possessed a wide range of physical properties and hence should serve as good illustrative examples of the correlative procedure.

Experimental Techniques

Nitrogen adsorption–desorption isotherms were obtained in a conventional volumetric apparatus at liquid nitrogen temperature and over a pressure range from a few millimeters of mercury up to near saturation pressure. Measurements in the high pressure region were continued to high enough pressures to determine the plateau of adsorbed volume characteristic of complete filling of the micropore volume. The saturation pressure p_0 was measured continuously throughout the runs by means of a tube containing condensed nitrogen and connected to a manometer. From the data specific surface values were calculated by the Brunauer–Emmett–Teller equation.[3] The data fit the linear plot of this method over the usual range of pressure values.

The micropore size distributions were obtained by analyzing the adsorption and desorption isotherms in terms of a composite multilayer adsorption and capillary condensation theory introduced by Wheeler.[4] A modification in the procedure of applying the Wheeler theory to the experimental data was used in the present study and details of this are given in an accompanying paper.[7] Essentially, the method consists in matching the experimental isotherm with one of a series of standard isotherms which have been calculated for various pore size distributions. Values of median and mean pore diameters (defined in the following section) have been calculated from the size distribution.

Values for the solid density ρ were obtained by displacement in helium gas in an apparatus similar to the one described by Schumb and Rittner.[8] The apparent density ρ_a was determined in a mercury pycnometer. From these values the percentage porosity was calculated by the equation

$$\% \text{ porosity} = 100(\rho - \rho_a)/\rho \qquad (1)$$

(1) Present address: Oak Ridge National Laboratory, Oak Ridge, Tennessee.

(2) Present address: Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

(3) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938); W. D. Harkins and G. Jura, *J. Chem. Phys.*, **11**, 431 (1943).

(4) A. Wheeler, Presentations at Catalysis Symposia, Gibson Island Conferences, June, 1945, and June, 1946.

(5) P. B. Elkin, C. G. Shull and L. C. Roess, *Ind. Eng. Chem.*, **37**, 327 (1945).

(6) C. G. Shull and L. C. Roess, *J. Appl. Phys.*, **18**, 295 (1947).

(7) C. G. Shull, THIS JOURNAL, **70**, 1405 (1948).

(8) W. C. Schumb and E. S. Rittner, *ibid.*, **65**, 1692 (1943).

The small angle X-ray scattering technique has been described[6] previously.

The gels were obtained from several sources and the methods of preparation for some gels were not reported. The emphasis here, however, is placed on physical properties rather than on methods of preparation. It may be mentioned that the gels were heated in a furnace at about 540° prior to all physical measurements so that the residual water content must have been quite small. No correction for this was made.

Experimental Results

A list of the silica–alumina gels which have been studied is given in Table I. The alumina content of these gels is seen to vary between 0 and 28 weight per cent. with most of the samples at the ends of this range. The variety of physical properties obtained are believed for the most part to reflect the various physical and chemical conditions of preparation rather than the alumina content.

TABLE I

SUMMARIZED GAS ADSORPTION AND DENSITY DATA

Gel	Weight per cent. Al_2O_3	Specific surface, sq. m./g.	V_p micropore volume (cc./g.)	Density (g./cc.) by displacement of Helium ρ	Mercury ρ_a	Percentage porosity	Total pore volume, cc./g.
I	25	453	0.563	2.53	1.031	59	0.575
II	23	425	.733	2.45	0.854	65	.774
III	24	475	.681	2.46	.750	69	.927
IV	26	321	.855	2.49	.787	68	.868
V	28	267	.994	2.31	.719	69	.958
VI	13	568	.863	2.30	.755	67	.890
VII	..	344	.870	2.32	.786	66	.840
VIII	0	657	.384	2.39	1.168	51	.436
IX	0	248	.612	2.32	0.911	61	.667
X	0	478	.575	2.19	0.982	55	.562

The nitrogen adsorption–desorption isotherms are shown in Fig. 1. The desorption curves are the upper ones in each case. All except that for sample VIII have similar shapes, but differ in the magnitude and position of the steepest part of the curves. The isotherm for sample VIII, in which the adsorption and desorption data fell on the same curve, is the Langmuir type.

From the adsorption data, the values shown in Table I for the specific surface S and the specific micropore volume V_p (expressed as cc. of void per gram of gel) have been calculated. The solid density ρ obtained by helium displacement, the apparent density ρ_a obtained by mercury displacement and the percentage porosity and total pore volume calculated from the density values are also listed. The specific micropore volume has been obtained from the volume of gas adsorbed at saturation pressure and presumably is indicative of the pore volume in pores of diameter less than about 1000 Å. On the other hand, the percentage porosity and total pore volume given in the last two columns include all pores up to the size which is penetrated by mercury at atmospheric pressure, namely, about 50,000 Å. It is seen that practically all of the pore volume (with the exception of that for gel III) exists in the micropore region. The total pore volume is listed as being slightly smaller than the micropore volume (obviously an impossibility) for three of the gels and this must be due to the presence of small errors in one or more of the measurements.

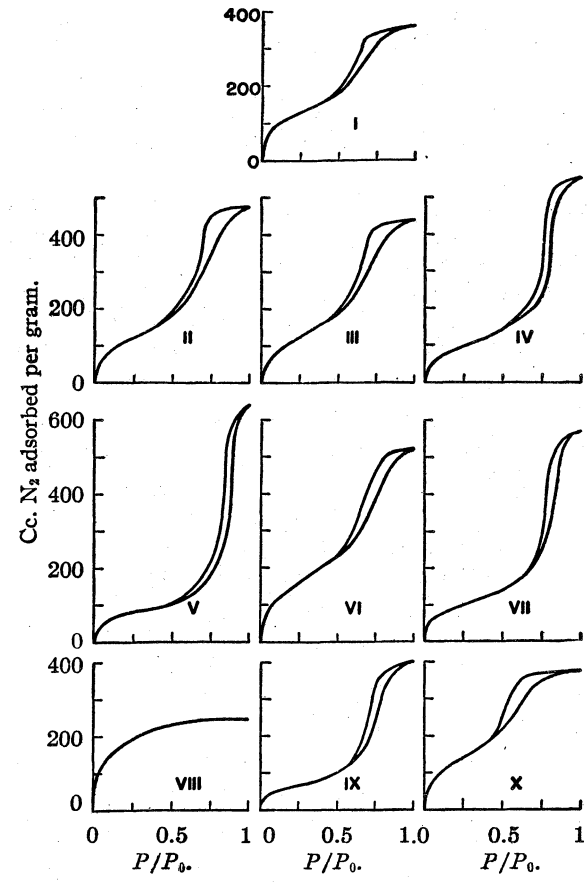


Fig. 1.—Nitrogen adsorption–desorption isotherms (−195°) for gels I to X.

Both the specific surface and the micropore volume are seen to vary over a wide range of values. As is expected, the solid density shows little variation from gel to gel with some indication that the gels with higher alumina content possess somewhat higher solid density values.

Table II summarizes the results of pore size analysis as obtained from both adsorption and desorption isotherms on the assumption that the pores are cylindrical. In this table the mean pore diameter D_0 is defined by

$$D_0 = 4V_p/S \qquad (2)$$

the median pore diameter $\overline{D}$ is defined by

$$\frac{V_p}{2} = \int_0^{\overline{D}} V(D)\, dD \qquad (3)$$

where $V(D)$ is the pore volume distribution function. $\overline{D}$ is thus defined as the pore diameter such that one half of the pore volume is contained in

pores smaller than $\overline{D}$. The mean pore diameter $\overline{D}_0$ is defined as

$$\overline{D}_0 = \frac{\int_0^\infty V(D)\,dD}{\int_0^\infty \frac{V(D)}{D}\,dD} \qquad (4)$$

Since in equation (4) the numerator is the pore volume per gram and the denominator is one-fourth the specific surface, it follows that D_0 and $\overline{D}_0$ represent equivalent mean values. They are designated differently to emphasize that they have been calculated in an independent manner. It is not expected that the median and mean values should agree in magnitude since they represent differently weighted quantities. Also given in Table II is the ratio of the two mean values for the pore diameter.

TABLE II

PORE DIAMETER VALUES CALCULATED FROM ADSORPTION AND DESORPTION DATA (ALL VALUES EXPRESSED IN ÅNGSTRÖMS)

D_0 is mean pore diameter calculated from $4Vp/S$. $\overline{D}$ is median pore diameter calculated from pore size distribution. $\overline{D}_0$ is mean pore diameter calculated from pore size distribution.

		From desorption data			From adsorption data		
Gel	D_0	$\overline{D}$	$\overline{D}_0$	$D_0/\overline{D}_0$	$\overline{D}$	$\overline{D}_0$	$D_0/\overline{D}_0$
I	50	52	48	1.04	59	48	1.04
II	69	65	60	1.15	73	60	1.15
III	57	57	53	1.08	70	57	1.00
IV	107	90	89	1.20	114	105	1.02
V	149	136	126	1.18	170	157	0.95
VI	61	61	56	1.09	74	58	1.05
VII	101	95	94	1.07	131	121	0.84
VIII	23	21	18	1.31	21	18	1.31
IX	99	73	72	1.37	92	85	1.17
X	48	41	41	1.17	46	37	1.30
			Average	1.17			1.08

Figure 2 illustrates the agreement found between values for D_0 and $\overline{D}_0$ using both adsorption and desorption data. The general sequence of the points indicates that D_0 is about 10% larger than $\overline{D}_0$ and, considering the assumptions which are necessary in evaluating the pore size distributions, this can be considered quite satisfactory. Although it is seen that slightly better agreement is obtained when adsorption data are used, it is not felt that this is conclusive of a general criterion on the basis of the present data.

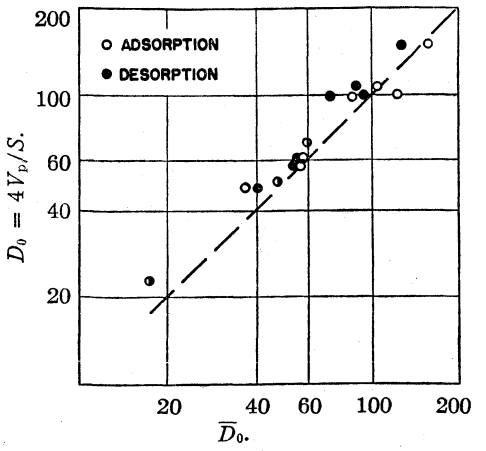


Fig. 2.—Comparison of mean pore diameters (ångströms) calculated from $V_p(D_0)$ and from pore size distribution curves ($\overline{D}_0$).

The results of the small angle X-ray scattering analysis and their correlation with adsorption data for these gels are given in Table III. The scattering analysis has been carried through in terms of a particle size distribution for spherical particles and from this the median particle diameter $\overline{L}$ is evaluated as defined by

$$\int_0^\infty M(L)\,dL = 2\int_0^{\overline{L}} M(L)\,dL \qquad (5)$$

where $M(L)$ is the mass distribution function in terms of the particle diameter L. Values of $\overline{L}$ ranging from 29 to 88 Å. are to be noted in the second column of Table III.

TABLE III

COMPARISON OF PARTICLE SIZE VALUES WITH PORE SIZE AND POROSITY RESULTS

Values of L and D are in ångströms and $S\rho$ in 10^4 cm.$^{-1}$

Gel	$\overline{L}$	$S\rho$	$\overline{D}/\overline{L}$	$V_{p\rho}$
I	48	1147	1.08	1.42
II	47	1041	1.38	1.80
III	45	1170	1.27	1.68
IV	65	799	1.38	2.13
V	88	617	1.55	2.30
VI	48	1308	1.27	1.99
VII	75	798	1.27	2.02
VIII	29	1570	0.72	0.92
IX	81	576	0.90	1.42
X	48	1048	0.85	1.26

In view of the dependence of the X-ray intensity scattered at small angles on differences in electron density, independent evidence is required to establish whether the scattering is characteristic of the particles or of the pores. With crystalline materials, good agreement[6] is found between the crystal size and the average particle size calculated on the assumption that the scattering is characteristic of the particles, and this can be considered as good evidence that the small angle scattering is indeed characterized by the particles. With amorphous materials such evidence is not available, and hence it is particularly interesting to compare the particle size data and the pore size data for the ten amorphous gels being discussed.

It can be shown that the specific surface of an assemblage of particles is given by an expression of the type

$$S = \frac{K}{\rho}\frac{\int_0^\infty \frac{M(L)}{L}\,dL}{\int_0^\infty M(L)\,dL} = K_0/\rho\bar{L} \qquad (6)$$

where K_0 is a constant whose value depends insensitively on the geometrical shape of the particle and the shape of the particle size distribution curve. Values for the product $S\rho$ are given in the third column of Table III and these are plotted versus $\bar{L}$ in the log-log graph of Fig. 3. The inverse relationship between these variables is clearly indicated by the sequence of the points. The line drawn on the figure is the theoretical line to be expected for spherical particles and appears to be shifted from the median correlation line by about 10%. In view of the uncertainties in the interpretation of small angle scattering analysis, this discrepancy of the particle size values by 10% on an absolute basis is certainly not outside of possible error. It should be mentioned that correlation of the type given in Fig. 3 is by no means restricted to one class of materials (*viz.*, silica–alumina gels) but can be obtained with a whole variety of substances whose solid density, specific surface and particle size cover much wider ranges than are indicated in the present data.

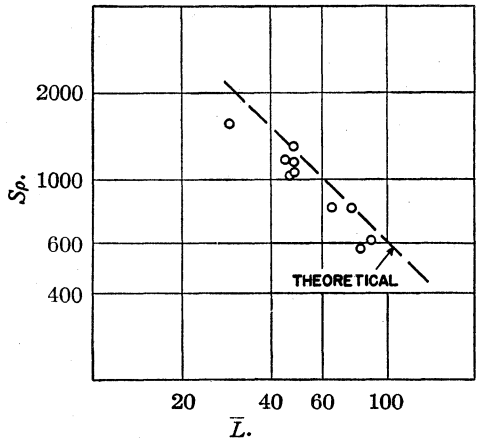


Fig. 3.—Correlation between specific surface times density $S\rho$ and median particle diameter $\bar{L}$. The dashed line is that calculated for spheres. $S\rho$ is given in units of 10^4 cm.$^{-1}$ and $\bar{L}$ in ångströms.

Of particular interest is the comparison of pore and particle size. The ratio of these variables is given in the fourth column of Table III. This ratio is seen to include values between 0.72 and 1.55. Since the surface area of the pores must equal that of the particles, it follows from Equations (2) and (6) that

$$\bar{D}/\bar{L} = k(V_p\rho) \qquad (7)$$

since $\bar{D}$ is proportional to D_0 for a given distribution. The product $(V_p\rho)$ is called the *porosity factor* and is merely the ratio of total micropore volume to total solid volume in the gel. The constant k depends insensitively on the pore and particle size distributions. Figure 4 illustrates the agreement of the experimental data with the correlation predicted by Equation (7). Values for the pore diameter are those obtained from the desorption analysis and the line is the theoretical correlation using a value of 2/3 for the constant k which is the average for the size distributions encountered experimentally. A consistent trend in the values of the pore to particle size ratio with the porosity factor is to be noted and this can be considered evidence that the small angle X-ray scattering is characteristic of the particle size rather than the pore size. If the X-ray scattering were indicative of the pore size, values of $\bar{D}/\bar{L}$ should have remained constant independent of the porosity factor.

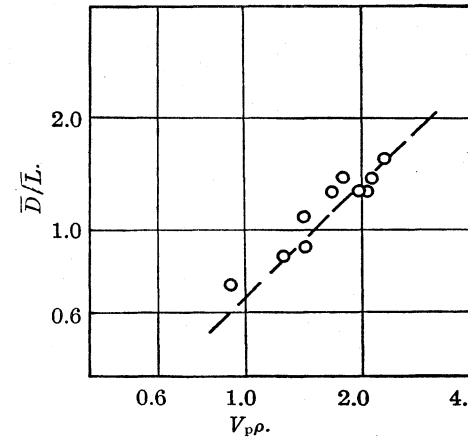


Fig. 4.—Correlation between pore to particle size ratio $\bar{D}/\bar{L}$ and porosity factor $V_p\rho$. The line is the theoretical correlation according to Equation (7).

The over-all agreement of the independently determined variables above appears very satisfactory and is even somewhat surprising in view of the several assumptions which are necessary in interpreting the data. It is recognized immediately that the assignment of a spherical shape to the particles and a cylindrical shape to the pores is inconsistent in a strict sense. The pores and particles are very probably irregular in both shape and size, but it would appear from the data that as far as the determination of average dimensions is concerned, they can be represented by these simple geometrical shapes. Once these discontinuity shapes are decided upon, further assumptions specific to the technique are required. Principal among these are the assumption of incoherence in the X-ray scattering from adjacent particles and the assumption that vapor condensation in a capillary of colloidal size is exactly similar to that in macroscopic capillaries. Neither of these has been the subject of direct experimental test, but as the evidence presented above would indicate indirectly, they appear not far from being correct.

Acknowledgments.—Several of the gel preparations were kindly supplied by the Shell Development Company and the Standard Oil Development Corporation and the remaining ones were prepared by M. M. Stewart of these laboratories. Grateful acknowledgment is also accorded to Dorothy Diener, Bernice Good and Sybil Cumming for assistance in the accumulation of experimental data.

Summary

Physical data on the microstructure of a series of ten amorphous silica and silica–alumina gels have been obtained from studies of low temperature gas adsorption, porosity and small angle X-ray scattering. Good correlations are obtained between (1) the mean pore diameter calculated from the specific micropore volume and the specific surface and the mean pore diameter calculated according to a capillary condensation theory of isotherm analysis, (2) the average particle size and the specific surface and (3) the pore to particle size ratio and the porosity factor. It is concluded that the over-all correlations which are found indicate the validity of the assumptions necessary in the data interpretation at least for the materials which have been studied.

BEACON, NEW YORK RECEIVED OCTOBER 16, 1947

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NAVAL RESEARCH LABORATORY]

The Preparation of Nitrite Salts of Alkyl Amines[1]

BY JOHN K. WOLFE[2] AND KENNETH L. TEMPLE[3]

Alkyl ammonium nitrite salts have been prepared by the reaction of the amine hydrochloride with sodium nitrite[4] or silver nitrite,[5] the amine sulfate with barium nitrite, or the amine with nitrogen sesquioxide,[6] all of these reactions being carried out in aqueous solution. The present study outlines a new method of preparation, employing the amine, sodium nitrite, solid carbon dioxide, methanol and a small amount of water. Sodium carbonate precipitates as the reaction proceeds, leaving a methanol solution of the nitrite. The general reaction, using a primary amine as the example, can be represented by the equation

$$2RNH_2 + CO_2 + H_2O + 2NaNO_2 \longrightarrow 2RNH_2{\cdot}HNO_2 + Na_2CO_3$$

The reaction between the amine and carbon dioxide in methanol in the absence of water formed a white powder which precipitated at about −20° and corresponded to the formula $(RNH_2)_2{\cdot}CO_2$. These substances could be filtered and isolated at room temperature but they sublimed readily. Compounds of this type have been previously observed and identified.[7]

This white powder reacted with sodium nitrite and water in the presence of methanol to produce the ammonium nitrite.

This method has been applied successfully to isopropylamine, diisopropylamine, diisobutylamine and triethylamine, with a yield of about 75% of the nitrite in each case.

The use of methanol instead of water as the solvent permits the use of a lower temperature, thus decreasing the formation of nitrosamines and the decomposition of unstable nitrites. The evolution of carbon dioxide gas during the preparation excludes oxygen and thus tends to prevent the formation of nitrates.

Table I summarizes the various reaction conditions studied. Sodium nitrite is superior to potassium nitrite since potassium carbonate separates in a flocculent condition and is much harder to filter. Absolute ethanol, acetone and isopropanol are inferior to methanol as a solvent, undoubtedly due to the higher solubility of sodium nitrite in methanol. The yield of sodium carbonate is fairly constant in all of the cases in which methanol was used. The yield of sodium carbonate is probably a better measure of the extent of the nitrite reaction than is the yield of the nitrite, since in many cases the nitrites are difficult to isolate.

This new method of synthesis was tried for higher molecular weight amines, whose nitrite salts are not water soluble, and quite low yields were obtained. It was found that some of these nitrites had been described in the literature and were prepared in aqueous solution but the yields reported were often quite low and the methods were poorly described. Dicyclohexylammonium nitrite, a compound not previously described, was prepared in this study in 98% yield and the experimental method used in its preparation is described as an example. Dicyclohexylaminenitrite is easily converted to the N-nitrosamine by warming in dilute acid solution. A comparison of these two materials shows the expected chemical behavior.

A study of the alkyl ammonium nitrite salts which have been investigated indicates that, in general, the salts of primary amines of low molecular weight and the salts of tertiary amines are

(1) The opinions or assertions contained in this paper are the authors' and are not to be construed as official or reflecting the views of the Navy Department.

(2) Present address: General Electric Research Laboratory, Schenectady, N. Y.

(3) Present address: Rutgers University, New Brunswick, N. J.

(4) Van der Zande, *Rec. trav. chim.*, **8**, 205 (1889).

(5) Neogi, *J. Chem. Soc.*, **99**, 1252 (1911).

(6) Bamberger and Muller, *Ber.*, **21**, 847 (1888).

(7) Hayashi, *Abst. Bull. Inst. Phys. Chem. Res.* (*Tokyo*), **11**, 133 (1932).

TABLE I

PREPARATION OF AMINE NITRITE SALTS BY NEW METHOD

Amine	Inorg. nitrite	Solvent	Moles solvent / Moles nitrite	Time, hr.	Na_2CO_3, % yield	Nitrite salt, % yield
Di-isopropylamine	$NaNO_2$	MeOH	7.5	3.5	76	76
Di-isopropylamine	KNO_2	MeOH	12.5	4.5	48[a]	15
Di-isopropylamine	$NaNO_2$	AbsEtOH	10.3	18	56[a]	43
Di-isopropylamine	$NaNO_2$	Acetone	82	8	61[a]	19
Di-isopropylamine	$NaNO_2$	*i*-PrOH	26.6	3.5	28[a]	20
Di-isobutylamine	$NaNO_2$	MeOH	15	3.5	74	66.5
Triethylamine	$NaNO_2$	MeOH	12.5	3.5	75	68
Mono-isopropylamine	$NaNO_2$	MeOH	10	4	75	74

[a] Contained unreacted inorganic nitrite.

hygroscopic while the salts of primary amines of high molecular weight and the salts of secondary amines are not hygroscopic. The salts of highly branched secondary amines appear to be the most stable.

Experimental[8,9]

The following method was used in the preparation of the nitrite salts: A mixture of 200 mesh C. P. sodium nitrite, water and methanol was placed in a three-necked two-liter round-bottom flask fitted with dropping funnel and Hershberg stirrer. The stirred mixture was cooled to 0° by the addition of solid carbon dioxide and the amine was then added over a period of one and one-half to two hours, a temperature of 0–5° being maintained by the addition of solid carbon dioxide. Stirring was continued for about two hours, sufficient methanol being added to wash the foam from the sides of the flask. The precipitated sodium carbonate was filtered at room temperature and washed well with methanol.[10] The solvent was removed from the filtrate under reduced pressure and the solid product recrystallized from a suitable solvent.

The molecular weight of each of the nitrites was determined by boiling a weighed sample of the nitrite with an excess of 0.5 *N* sodium hydroxide solution until the free amine was volatilized and then titrating the residual alkali with standard acid.

Diisopropylammonium Nitrite.—One mole of diisopropylamine (boiling at 81–85°), one mole of sodium nitrite, 0.5 mole of water and 300 ml. of methanol gave 80 g. of sodium carbonate. The solution of the solid nitrite in 500 ml. of anhydrous isopropanol, filtered to remove sodium nitrite, gave 112 g. of nitrite when cooled to −40°. The melting point of 136–7° was unchanged by recrystallization from acetone and ethyl acetate.[11]

Anal. Calcd. for $C_6H_{16}O_2N_2$: C, 48.6; H, 11.0; N, 18.9; mol. wt., 148. Found: C, 48.7; H, 11.5; N, 18.6; mol. wt., 147.

Diisobutylammonium Nitrite.—The salt obtained from 0.5 mole of diisobutylamine (boiling at 136–140°), 0.5 mole of sodium nitrite, 0.25 mole of water and 300 ml. of methanol was dissolved in 250 ml. of isopropanol. By cooling the solution to −40°, 58.6 g. of colorless plates melting at 145–146° was obtained.

Anal. Calcd. for $C_8H_{20}O_2N_2$: C, 54.5; H, 11.5; N, 15.9; mol. wt., 176. Found: C, 54.7; H, 11.2; N, 15.6; mol. wt., 174.5.

Triethylammonium Nitrite.—One mole of triethylamine (boiling at 88–90°), one mole of sodium nitrite, 0.5 mole of water and 500 ml. of methanol gave 81 g. of sodium carbonate. Removal of the methanol in an atmosphere of dry carbon dioxide at a temperature not exceeding 25° gave one hundred grams of light tan crystals melting at 94–97° with decomposition. The product turned brown on standing at room temperature for a few hours but was stable when stored at −40° over calcium chloride in a vacuum desiccator. A solution of 2 g. of the salt in 400 ml. of absolute ether gave white silky needles when cooled to −60°. These needles melted at 96.5–98° in a sealed tube.[12]

Anal. Calcd. for $C_6H_{16}O_2N_2$: mol. wt., 148. Found: mol. wt., 146, 147.

Isopropylammonium Nitrite.—The reaction of one mole of isopropylamine (boiling at 31–35°), one mole of sodium nitrite, 0.5 mole of water and 470 ml. of methanol gave a methanol solution which was evaporated under reduced pressure in an atmosphere of carbon dioxide, the temperature being maintained below 25°. The white crystalline product weighed 79 g. and melted at 47–49°. This substance is very hygroscopic and turns brown when stored in a vacuum desiccator at room temperature, but is stable in a dry atmosphere at −40°. Recrystallization of the product from a solution of four parts of ethyl acetate and one part of isopropanol, by cooling the solution to −60°, gave white crystals which melted at 49–50° in a sealed tube.

Anal. Calcd. for $C_3H_{10}O_2N_2$: mol. wt., 106. Found: mol. wt., 107.

Di-cyclohexylammonium Nitrite $[(C_6H_{11})_2NH\cdot HNO_2]$.—Ten milliliters (9.1 g., 0.045 mole) of di-cyclohexylamine (Monsanto) were mixed with 400 ml. of water, an excess of concentrated hydrochloric acid was added and the mixture was heated almost to boiling to dissolve the salt formed. The solution was adjusted to *p*H 8 with ammonium hydroxide. Solid C. P. sodium nitrite (150 g.) was added, the mixture was stirred at 0° for one hour and the precipitate was filtered and dried. The yield was 11.2 g. (98%) of light tan crystals melting at 176–178° with decomposition. Recrystallization from methanol yielded colorless plates melting at 178–180° with decomposition. Acidification of this product produced the characteristic nitric oxide odor.

Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 58.8; H, 11.8; N, 13.7. Found: C, 58.6; H, 11.7; N, 14.0.

N-Nitroso-Di-cyclohexylamine $[(C_6H_{11})_2NNO]$.—A sample of dicyclohexylamine acetate (m. p. 115–116°) was warmed with an aqueous solution of acetic acid and sodium nitrite. The insoluble precipitate was filtered and recrystallized from acetone, yielding colorless crystals of nitrosamine melting at 104–105°.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.5; H, 10.5. Found: C, 68.6, 68.8; H, 10.3, 10.5.

(8) The authors wish to acknowledge the help of Miss Nyla Mack of the Chemistry Division, NRL, for some of the analyses.

(9) All melting points are corrected.

(10) The identity of the precipitate was established by X-ray diffraction examination, performed by Ens. Birks of the Physical Optics Division of NRL, and by comparison with an authentic sample of anhydrous sodium carbonate.

(11) Van der Zande[4] reported a melting point of 140°. The authors find that the melting point depends on the rate of heating, approaching 140° in a rapidly heated bath.

(12) Neogi [*J. Chem. Soc.*, **99**, 1252 (1911)] and Ray [*ibid.*, **101**, 216 (1912)] reported that this compound forms yellow prisms decomposing at 75°.

A mixed melting point of the nitrosamine with dicyclohexylammonium nitrite showed the normal depression and wide range. N-Nitroso di-cyclohexylamine failed to give nitric oxide fumes on treatment with cold hydrochloric acid.

Summary

1. A new method is described for the preparation of alkyl ammonium nitrites from amines, employing sodium nitrite, carbon dioxide and methanol. The nitrites of isopropylamine, diisopropylamine, diisobutylamine and triethylamine have been prepared.

2. Alkyl ammonium nitrite salts of primary amines of low molecular weight and the salts of tertiary amines are in general hygroscopic while the salts of secondary amines are not hygroscopic.

WASHINGTON, D. C. RECEIVED AUGUST 19, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

The Selective Degradation of Certain Pyrryl Polycarboxylic Esters[1,2]

BY ALSOPH H. CORWIN AND J. LLOYD STRAUGHN[3]

Publication of a method for the conversion of Knorr's pyrrole (2,4-dimethyl-3,5-dicarbethoxypyrrole) into 2-carboxyl-3,5-dicarbethoxy-4-methylpyrrole[4] opened the way for the preparation of many new pyrrole derivatives from this substance, providing that methods for selective degradations of the new acid could be found. The present paper describes these selective degradations. Knorr's pyrrole is already one of the most readily available substitution products of pyrrole. The numerous additional substances that can be prepared from it by transformations recorded below make it the most versatile of all pyrrole derivatives in the number and variety of chemical individuals which can be prepared from it.

Mechanism of Formation of 2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole.—When Knorr's pyrrole is chlorinated with sulfuryl chloride in glacial acetic acid, best yields of the desired acid are obtained if the reaction is performed at as low a temperature as possible. The use of 5% acetic anhydride lowers both the freezing point of the solution and its water content and increases the yield of acid by 5–10%. Increasing the temperature of the reaction, on the other hand, lowers the yield of acid and increases the yield of aldehyde. This observation suggests that the aldehyde represents a by-product of the reaction and not an intermediate in the formation of the acid. This conclusion was confirmed by attempting to halogenate the aldehyde under the conditions of the reaction. No acid could be obtained and the aldehyde was recovered unchanged. When the same reaction was tried using 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole, however, 45% of acid and 36% of aldehyde could be obtained. These results show that the dichloromethylpyrrole can be an intermediate in the reaction and that any of it which is converted to aldehyde in the course of the reaction will not yield acid.

It is possible to convert benzal chloride and acetic acid to benzaldehyde and acetyl chloride.[5] The analogous reaction in the pyrrole series can be represented schematically as

$$RCHCl_2 + CH_3COOH \longrightarrow RCHO + CH_3COCl + HCl$$

It is easily demonstrated that this reaction proceeds at 50° but not rapidly at 17°. At the higher temperature hydrogen chloride is given off and the distillate contains acetyl chloride, as shown by its reaction with aniline to form acetanilide. The dichloromethylpyrrole is best prepared by chlorination in chloroform, to avoid the possibility of aldehyde formation.

It follows from the observations recorded above that the aldehyde is not an intermediate in the formation of the acid, that the dichloro- and trichloro-pyrroles are intermediates and that reaction conditions should be directed toward the stabilization of the dichloromethylpyrrole.

The Stability of Pyrryl-carboxylic Acids.—By methods outlined below several pyrryl-carboxylic acids were prepared which had one methyl group and various combinations of three electron attracting groups, either carboxyl or carboxylic ester groups. None of these acids could be decarboxylated smoothly by the usual methods. When combinations were tried which contained only two electron attracting groups, however, decarboxylation took place smoothly. This behavior is analogous to that found in the benzene series in which electron releasing groups, such as phenolic hydroxyl groups, facilitate decarboxylation and the addition of electron attracting groups, such as carboxyl, to phenolic compounds hinders decarboxylation.[6] Because of this situation, further reactions were directed toward preparation and degradation of derivatives of methyl-dicarboxyl pyrroles.

(1) Studies in the Pyrrole Series, XX; Paper XIX, Erdman and Corwin, THIS JOURNAL, **69**, 750 (1947).

(2) This paper is taken from the doctoral dissertation of John Lloyd Straughn, The Johns Hopkins University.

(3) Present address, Department of Chemistry, Western Maryland College, Westminster, Md.

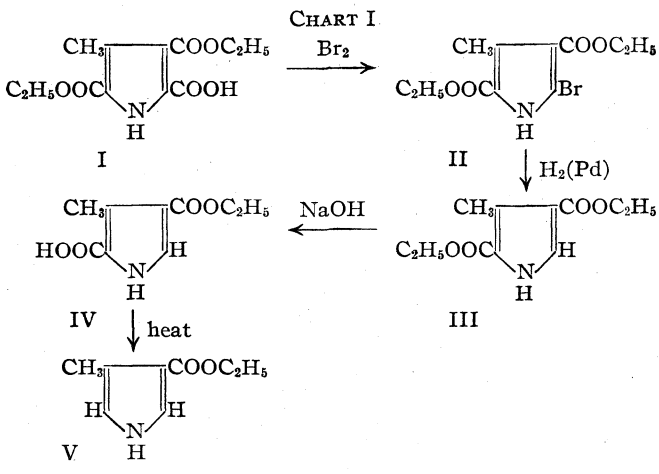
(4) Corwin, Bailey and Viohl, THIS JOURNAL, **64**, 1267 (1942).

(5) Jacobsen, German Patent 11494 (1879), See *Frdl.*, **1**, 24 (1888).

(6) A close analogy is afforded in the resorcylic acids. 2,6-Dihydroxybenzoic acid decomposes in the range of 150–170° while the addition of a carboxyl group in the 3 position increases the stability so that the material melts at 312° without marked decomposition. See Senhofer and Brunner, *Wien. Akad. Ber.*, **80**, 504 (1879), and Brunner, *Ann.*, **351**, 320 (1907).

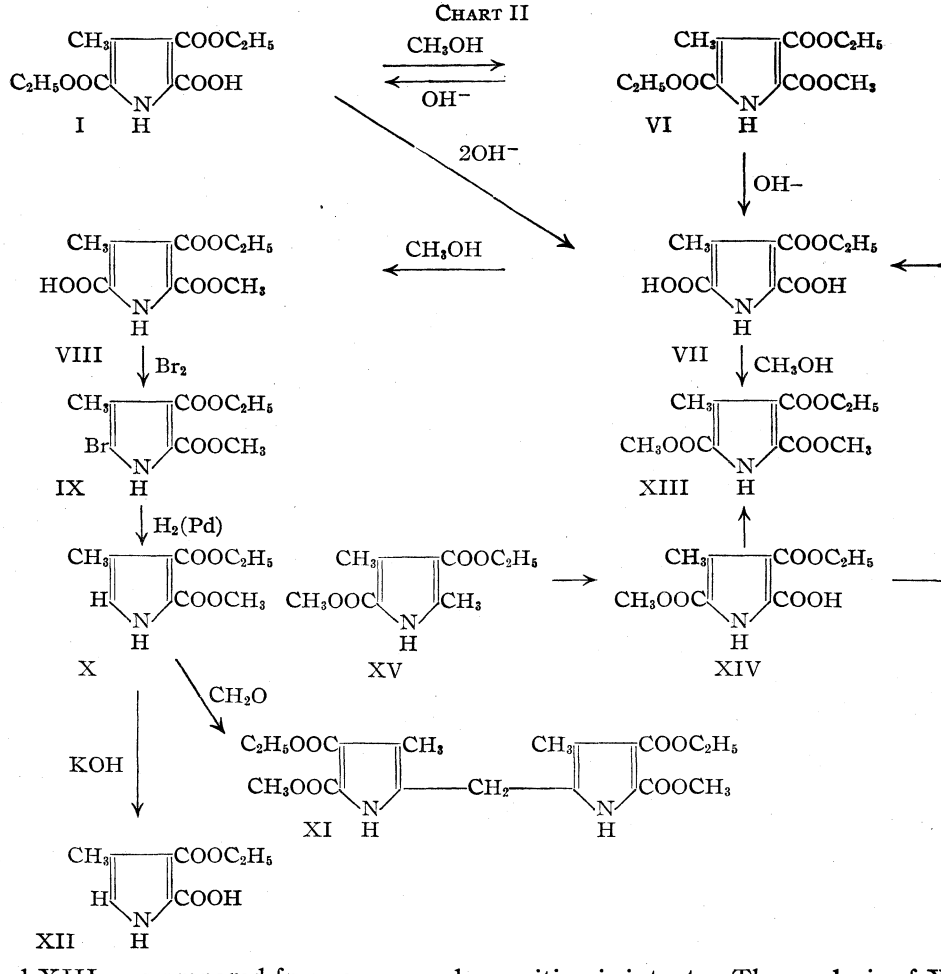
The flow sheet for the reactions to free the 2 and 5 positions is given in Chart I.[4,7]

CHART I



The flow sheet for the reactions to free the 5 position is given in Chart II.

CHART II



Compound XIII was prepared from compound XV by reactions analogous to those discussed in the first section of this paper. These reactions prove that compound XIII has a methyl ester group in the 5 position. Compound X had been prepared previously by Fischer and Wiedemann by esterification of XII.[8] This esterification proves the structure of compound X.

The flow sheet for the freeing of the 3 position is given in Chart III.

Compounds XXI and XIX were prepared by Kordo, Ono and Sato[9] by a method which establishes the structure of XIX.

In addition to the reactions outlined above, certain other derivatives of compound I were made as sketched in Chart IV. Interrelationships with substances with previously tagged ester groups are also shown.

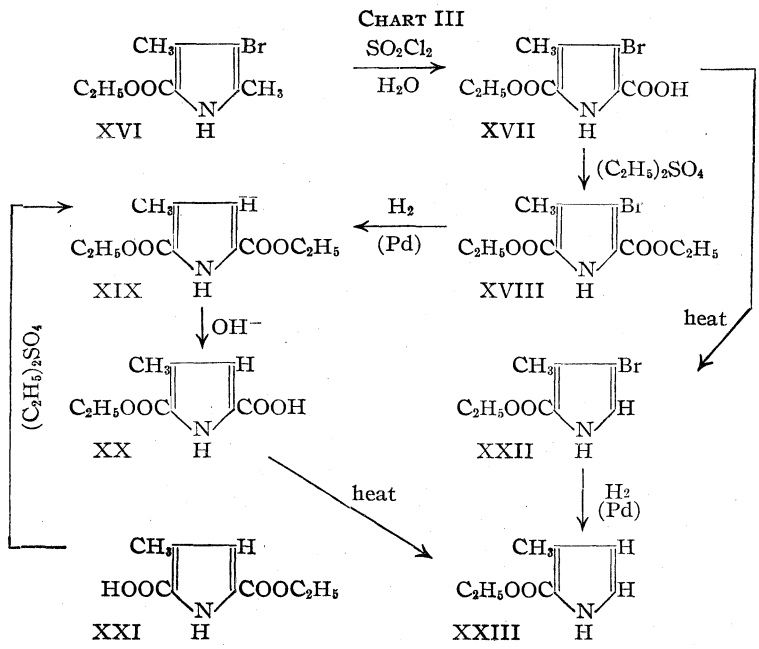
The lack of identity of XXV and XXVII makes possible the location of the free carboxyl group in XXV, since it is known from XXXI that the carbomethoxy group in the 3 position is intact. The analysis of XXXI makes

(7) See Corwin and Viohl, THIS JOURNAL, **66**, 1145 (1944), for the preparation of compounds IV and V.

(8) Fischer and Wiedemann, *Z. physiol. Chem.*, **155**, 58 (1926).

(9) Kordo, Ono and Sato, *J. Pharm. Soc. Japan*, **57**, 1 (1937). See *C. A.*, **31**, 7055 (1937).

CHART III



it possible to deduce the position of the group in compound XXX which has been hydrolyzed by alkali.

Compounds XXXIII, XXXIV and XXXV were all prepared from compound I. The ester interchange observed in preparing compound XXXIV is not unusual when α-esters are treated with strong base.[10a] A corresponding change when esterification takes place under the influence of an acid catalyst is rare. The melting point of the triethyl ester, XXXV, is so low, 45–46°, as to render the substance undesirable for preparational purposes. This is the reason for choosing to make derivatives from the monomethyl ester, VIII, which melts at 75°.

The experiments summarized above add five new cases, compounds I, III, VI, X and XXX to the generalization that attack by an alkaline catalyst upon an ester group is oriented α in preference to β whenever there is a choice.

One of us, J. L. S., wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Experimental Section

2-Carboxy-3,5-dicarbethoxy-4-methylpyrrole (I).—The directions given by Corwin, Bailey and Viohl[4] were modified in an effort to find optimum conditions for the reaction. The use of 10% of anhydrous formic acid in glacial acetic acid gave a slight increase in yield, due to the lower freezing point. A 5% solution of acetic anhydride in glacial acetic acid gave a lower freezing point and a consistently higher yield. At 50°, no acid was obtained but a good yield of aldehyde was formed.

2-Formyl-3,5-dicarbethoxy-4-methylpyrrole was treated with bromine and sulfuryl chloride in acetic acid under the conditions used for the halogenation of 2,4-dimethyl-3,5-dicarbethoxypyrrole. The acetic acid was removed by distillation under reduced pressure and the residue extracted with ether and then with toluene. The ether solution was concentrated by evaporation and the red oil remaining was allowed to crystallize. These crystals give a positive Beilstein test but on treating with alcohol and water the precipitate formed was the starting aldehyde. After partial evaporation of the toluene solution crystals of the aldehyde were also obtained. In still another experiment the halogenation was completed and the hydrolysis with water carried out in a manner identical to that used for the preparation of the acid. No acid was obtained.

When the same reaction was repeated on 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole (see below) a yield of 45% of the acid and 36% of the aldehyde was obtained.

2-Dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole.—Fifty grams of 2,4-dimethyl-3,5-dicarbethoxypyrrole was dissolved in 200 cc. of dry, freshly redistilled C. P. chloroform (U. S. P. chloroform is unsuitable because it contains alcohol); 34 cc. of sulfuryl chloride was added at about 40°. The solution was boiled to remove hydrogen chloride and the chloroform was then removed under vacuum. The crystals which formed were washed with hexane and crystallized from toluene. The use of alcohol for the crystallization, as suggested by Fischer, Sturm and Friedrich,[11] causes decomposition of the substance and is probably responsible for the failure of these investigators to obtain the compound; m. p. 124–125°.

Anal. Calcd. for $C_{12}H_{15}O_4NCl_2$: C, 46.77; H, 4.91. Found: C, 46.83; H, 4.88.

Reaction with Glacial Acetic Acid. (a) Cold.—A solution of 3 g. of the dichloromethylpyrrole in 25 ml. of glacial acetic acid at 17° in a flask was closed with a rubber stopper and placed in an ice-box for eight hours with occasional shaking. The semi-solid mass was then filtered with suction. The filtrate gave no test for acetyl chloride with aniline; 2.3 g. of the starting material was recovered. We conclude that these substances do not react appreciably under the conditions of the trichlorination reaction.

(b) Warm.—A solution of 4 g. of the dichloromethylpyrrole and 25 ml. of glacial acetic acid was placed in a 50-ml. round flask fitted with a small fractionating column with a condenser attached to the side arm. The solution was heated on a water-bath for one hour at 50°, then distilled. The fraction below 60° gave a crystalline precipitate with aniline, identified as acetanilide by its melting point. The solid remaining in the flask was crystallized from dry toluene. A mixed m. p. with 2-formyl-3,5-dicarbethoxy-4-methylpyrrole gave no depression.

2-Carbomethoxy-3,5-dicarbethoxy-4-methylpyrrole (VI). First method.—Five grams of (I) was dissolved in a cold solution of 1.1 g. of potassium hydroxide in 25 ml. of methanol and 2.3 ml. of dimethyl sulfate added dropwise while stirring. After standing half an hour, it was poured into aqueous sodium bicarbonate, filtered and the precipitate crystallized from methanol-water. The methyl ester can be purified by distillation at 235–240° at 20 mm. or by crystallization from hexane, in which it is slightly soluble; m. p. 75°.

Second Method.—This is the method of choice. To a mixture of 25 g. of (I) in 125 ml. of anhydrous methanol in a 250 ml. standard taper Erlenmeyer flask 1.5 g. of dry hydrogen chloride was added and the solution then refluxed for an hour. The solution was stirred into five times its volume of ice water containing 6 g. of sodium

(10) Corwin and Ellingson, THIS JOURNAL, **66**, (a) 1146, (b) 1150, (c) 1149 (1944).

(11) Fischer, Sturm and Friedrich, *Ann.*, **461**, 267 (1928).

bicarbonate to dissolve any starting material. The ester separated as an oil which hardened after two hours of standing and was purified by distillation under reduced pressure and by crystallization from purified hexane; yields, 85–95%; m. p. 75°. This ester is insoluble in bicarbonate but is soluble in sodium hydroxide solutions, due to the acidity of the NH group under the influence of the three electron-attracting groups present.

Anal. Calcd. for $C_{13}H_{17}O_6N$: C, 55.09; H, 6.05. Found: C, 55.17; H, 5.92.

2,5-Dicarboxy-3-carbethoxy-4-methylpyrrole (VII).—This substance is best prepared from (I). Fifteen grams of (I), 4.5 g. of sodium hydroxide and 150 ml. of water were refluxed two and one-half hours in a 500-ml. Erlenmeyer flask. The solution was poured into an equal volume of water and acidified to the congo red endpoint with hydrochloric acid. The precipitate was filtered off, washed well with distilled water and pressed dry. The pyrrole acid was then resuspended in water to remove the hydrochloric acid. After filtering and washing, it was dried to constant weight at 70°. A small amount of the di-acid was obtained from the filtrates by allowing them to stand. The material was crystallized from ethanol and from 60% acetone in water; yield (crude), 85–95%; m. p. 236–237° (dec.).

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.71; H, 4.56.

The crude material is sufficiently pure for subsequent reactions if prepared from starting material which has been recrystallized several times from ethanol.

The same substance is obtained by the alkaline hydrolysis of (VI) and of (XXXV). The acidity of the pyrryl nitrogen is sufficient in each case to dissolve the pyrryl esters in aqueous alkali.

2-Carbomethoxy-3-carbethoxy-4-methyl-5-carboxypyrrole (VIII).—Seven and three-tenths grams of (VII) previously crystallized from acetone-water, and 75 ml. of methanol containing 0.5 g. of dry hydrogen chloride were refluxed in a 250-ml. Erlenmeyer flask for one hour, the solution cooled to room temperature and then poured into 300 ml. of ice water containing sufficient sodium bicarbonate to dissolve the half esterified pyrrole. After standing in the ice-box for one hour, the by-product (XIII) was filtered off (dry yield 0.7 g.) and the 5-carboxypyrrole was isolated by acidification of the filtrate. It was washed with water and dried in the oven at 70°; yield, 6.2 g. or 88%. The pyrrole was crystallized from acetone–water or alternatively from acetone–hexane; m. p. 204–205°.

2-Carbomethoxy-3-carbethoxy-4-methyl-5-bromopyrrole (IX).—To a solution of 2.7 g. of (VIII) in 30 ml. of glacial acetic acid at 45°, 1.8 g. of bromine in 8 ml. of glacial acetic acid was added in ten minutes. The solution became clear. After ten minutes of standing 20 ml. of water was added in twenty minutes. After standing for forty-five minutes it was poured into 200 ml. of ice water and placed in the ice-box for one hour. The precipitate was filtered off, washed with water, dissolved in 50 ml. of methanol and sodium bicarbonate added until no more carbon dioxide was evolved. The bromopyrrole was reprecipitated by pouring the methanol solution into 200 ml. of ice water. After standing for one hour, the precipitate was filtered, washed with water and dried at 50°. It can be recrystallized from methanol-water. A small amount (0.2 g.) of the starting acid was recovered on acidification of the filtrate obtained after the bicarbonate treatment; yield, 1.8 g. or 60%; m. p. 116–117°.

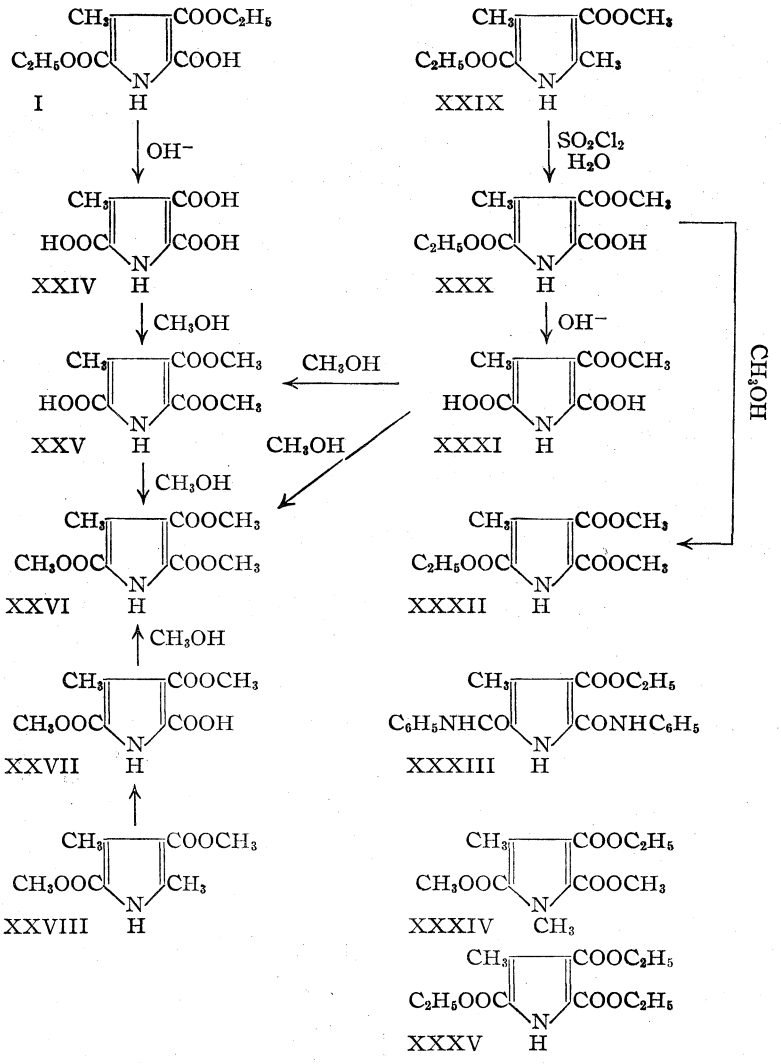
Anal. Calcd. for $C_{10}H_{12}O_4NBr$: C, 41.40; H, 4.17. Found: C, 41.32; H, 4.24. This substance was also obtained by the bromination of compound X (see below).

2-Carbomethoxy-3-carbethoxy-4-methylpyrrole (X).—For the dehalogenation of 2 g. of (IX), it was dissolved in 50 ml. of methanol and 500 mg. of magnesium oxide, 500 mg. of Norite and ten drops of 10% palladium chloride solution were added. The reduction required two hours under a pressure of two atmospheres of hydrogen. The catalyst was filtered off and washed with a few milliliters of hot methanol. The filtrate and washings were combined and dried under reduced pressure below 45°. The solid was dissolved in ether, transferred to a small beaker and the ether evaporated. It was then dissolved in the minimum quantity of ethanol at room temperature and cooled in an ice-bath. Ice water was added, drop by drop, while scratching the sides of the beaker, until the pyrrole crystallized; yield, 1.2 g. or 83%; m. p. 62°.

This pyrrole has also been prepared by the esterification of (XII) with diazomethane[8]; m. p. reported, 59°.

For further identification the pyrrole was brominated in glacial acetic acid. Fine needles of (IX) were obtained, m. p. 116°, mixed m. p., no depression.

CHART IV



2-Carboxy-3-carbethoxy-4-methylpyrrole (XII).[12]—Two hundred milligrams of (X) was hydrolyzed with 70 mg. of potassium hydroxide and 10 ml. of 80% ethanol. After precipitation and separation from unchanged ester the pyrrole was filtered off, washed, and crystallized from ethanol–water; colorless crystals, m. p. 197–197.5° with loss of carbon dioxide. Piloty and Hirsch[12] report 196°.

3,3′-Dimethyl-4,4′-dicarbethoxy-5,5′-dicarbomethoxydipyrrylmethane (XI).—Two hundred milligrams of (X), 3 ml. of 70% acetic acid and 0.3 ml. of 40% formaldehyde were refluxed for five minutes and 0.1 ml. more of formaldehyde was added through the condenser. After refluxing for ten minutes longer, 2 ml. of water was added and the solution was placed in an ice box until crystallization was complete. The product was recrystallized from methanol–water; m. p. 158–159°.

Anal. Calcd. for $C_{21}H_{26}O_8N_2$: C, 58.06; H, 6.03. Found: C, 57.79; H, 6.01.

2-Carboxy-3-carbethoxy-4-methyl-5-carbomethoxypyrrole (XIV).—Twenty-five grams of (XV)[10b] was treated with sulfuryl chloride and bromine by the procedure given for compound I; yields: aldehyde, 36%; acid 38%; m. p. 187°.

Anal. Calcd. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13. Found: C, 51.69; H, 5.17.

2,5-Dicarbomethoxy-3-carbethoxy-4-methylpyrrole (XIII).—This was prepared from (XIV) by esterification with dimethyl sulfate and with methanol and acid, in each case following the procedure used for compound VI. The latter method gave better yields. The product crystallizes from methanol in colorless crystals; m. p. 131–132°.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.52; H, 5.62. Found: C, 53.61; H, 5.59.

2-Carboxy-3-bromo-4-methyl-5-carbethoxypyrrole (XVII).—This was prepared from (XVI)[13] by a procedure essentially the same as for (I), given above; m. p. 254° with decomposition.

Anal. Calcd. for $C_9H_{10}O_4NBr$: C, 39.13; H, 3.65. Found: C, 39.12, 38.98; H, 4.31, 4.29.

2-Formyl-3-bromo-4-methyl-5-carbethoxypyrrole.—This was obtained as a by-product in the preceding preparation. If desired in quantity it can be prepared in a manner exactly analogous to that used for 2-formyl-3,5-dicarbethoxy-4-methylpyrrole.[4b] It was prepared by Fischer, Berg and Schormüller[14a] using ether as a solvent. The use of glacial acetic acid is preferable.

2,5-Dicarbethoxy-3-bromo-4-methylpyrrole (XVIII).[15]—This pyrrole was prepared by the esterification of (XVII) with diethyl sulfate in alcoholic potassium hydroxide by the first procedure under compound VI. The product crystallizes from ethanol–water in colorless needles melting at 85°.

Anal. Calcd. for $C_{11}H_{14}O_4NBr$: C, 43.44; H, 4.64. Found: C, 43.43; H, 4.73.

2,5-Dicarbethoxy-4-methylpyrrole (XIX).—The procedure for the dehalogenation of (XVIII) was the same as that used in the preparation of (X), given above; yield, 62%. Recrystallized from hexane or alcohol–water; m. p. 62°. This pyrrole has also been prepared from (XXI) which in turn was prepared by the condensation of the ethyl ester of glycine hydrochloride with acetylacetoacetic ester in alkaline solution.[9] Kordo, Ono and Sato report m. p. 61°.

2-Carboxy-4-methyl-5-carbethoxypyrrole (XX).—One and five-tenths grams of (XIX) was placed in a solution of 0.25 g. of sodium hydroxide in 25 ml. of 80% ethanol and the mixture refluxed for two hours. An equal volume of water was then added, the solution filtered and the filtrate acidified with hydrochloric acid. The acid was filtered off, washed with water and crystallized from ethanol-water; m. p. 210–215° with decomposition.

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62. Found: C, 54.88; H, 5.58.

2-Carbethoxy-3-methyl-4-bromopyrrole (XXII).—The decarboxylation of (XVII) was carried out by the method of Fischer, Berg and Schormüller.[14b] This method could be used only with quantities less than 2.5 g. The decarboxylation must be performed within five to ten seconds, for the bromopyrrole reacts with hot glycerol to form acrolein; m. p. 179–183°; yield, 40%.

Anal. Calcd. for $C_8H_{10}O_2NBr$: C, 41.38; H, 4.31. Found: C, 41.34; H, 4.38.

2-Carbethoxy-3-methylpyrrole (XXIII).—One and a half grams of (XX) was heated with 6 g. of anhydrous glycerol and the distillate collected in a distilling flask cooled with running water. The new pyrrole distilled between 270 and 290°. Five cc. of ethanol was added to it cautiously and the solution was poured into 25 cc. of ice water. After scratching, the pyrrole precipitated as fine crystals which were filtered off and air-dried; m. p. 56°. Fischer and Wiedemann report 56°.[8]

This substance was also prepared by the dehalogenation by (XXII) by the method used in the preparation of (X) above; m. p. 56°; mixed m. p. with material from the decarboxylation of compound XX, 56°.

2,3,4-Tricarboxyl-4-methylpyrrole (XXIV).—A solution of 25 g. of (I) and 12 g. of sodium hydroxide in 100 ml. of water was placed in a 200-ml. round flask connected to a fractionating column filled with glass helices and fitted with a reflux finger. The side arm of the column was connected to a condenser with a graduated cylinder as the receiver. The flask was heated on a water-bath for two hours. During this time 5 ml. of alcohol was collected below 80°. The flask was then heated with a free flame for four hours longer until the calculated amount, 12 ml., was obtained. The mixture was transferred to a 250-ml. beaker, cooled in an ice-bath and hydrochloric acid added to the congo red end-point. A thick white precipitate was formed which was filtered off with suction and the filtrate used to wash out the beaker. The product was crystallized from boiling water using Norite. It contained some sodium chloride which could be removed by several recrystallizations. The pyrrole is too soluble in cold water to permit washing to remove the salt. The product is insoluble in most organic solvents. It chars slightly when heated to 360°; yield, 15 g. or 76%.

Anal. Calcd. for $C_8H_7O_6N$: C, 45.08; H, 3.31. Found: C, 44.97; H, 3.37.

2,3-Dicarbomethoxy-4-methyl-5-carboxypyrrole (XXV). First Method.—A solution of 400 mg. of (XXIV) in 7 ml. of methanol previously saturated with dry hydrogen chloride was refluxed for five hours and then poured into 40 ml. of ice-cold sodium bicarbonate solution. After standing overnight in the ice box, the precipitate (XXVI) was removed by filtration and the filtrate acidified with hydrochloric acid. It was necessary to add a small amount of salt and to cool the solution before the product (XXV) precipitated. It was filtered off and crystallized from acetone–water; m. p. 211–211.5° with slight decomposition.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.92; H, 4.71.

Second Method.—Five hundred milligrams of (XXXI) and 10 ml. of methanol containing dry hydrogen chloride were allowed to react in the manner described for the preparation of (VIII) above. The pyrrole obtained crystallized from acetone–water and melted at 211–212°; mixed m. p. with XXV prepared from the tricarboxylpyrrole, no depression.

2,3,5-Tricarbomethoxy-4-methylpyrrole (XXVI).—This was prepared from (XXVII) with dimethyl sulfate and with methanol and hydrochloric acid by the procedures described above for (VI). The triester crystallizes from methanol; m. p. 142–143°.

(12) Piloty and Hirsch, *Ann.*, **296**, 70 (1913).

(13) Fischer and Ernst, *ibid.*, **447**, 147 (1926).

(14) Fischer, Berg and Schormüller, *ibid.*, **480**, (a) 155, (b) 114 (1930).

(15) Performed by S. R. Buc.

The same substance was also obtained in small amounts in the esterification of XXIV (see XXV above) and of (XXXI). It was also prepared by the esterification of (XXV). Melting points and mixed melting points of all these preparations are identical.

Anal. Calcd. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13. Found: C, 51.67; H, 5.10.

2 - Carboxy - 3,5 - dicarbomethoxy - 4 - methylpyrrole (XXVII).—Seven grams of (XXVIII)[16] was treated with sulfuryl chloride and bromine by the method given for (I); yield of acid, 4.5 g. or 59%; colorless needles from methanol; m. p. 205–206°.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.69; H, 4.58.

2-Carboxy-3-carbomethoxy-4-methyl-5-carbethoxypyrrole (XXX).—Twenty-one grams of (XXIX)[10e] was treated with sulfuryl chloride and bromine in the manner described for the preparation of (I); yield of acid, 17.3 g., or 73%. This pyrrole crystallizes from ethanol in fine needles; m. p. 157–158°.

Anal. Calcd. for $C_{11}H_{12}O_6N$: C, 51.76; H, 5.13. Found: C, 51.87; H, 5.16.

2,5-Dicarboxy-3-carbomethoxy-4-methylpyrrole (XXXI).—One gram of (XXX) was dissolved in 15 ml. of water containing 0.55 g. of potassium hydroxide and the same procedure followed as for the preparation of (VII). The product obtained was crystallized twice from acetone–water, the first time using Norite; m. p. 243° with decomposition.

Anal. Calcd. for $C_9H_9O_6N$: C, 47.58; H, 3.99. Found: C, 47.59; H, 4.02.

2,3-Dicarbomethoxy-4-methyl-5-carbethoxypyrrole (XXXII).—The same procedure was followed as for the preparation of (VI) using potassium hydroxide and dimethyl sulfate. The product crystallizes from methanol in colorless needles melting at 111°.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.52; H, 5.62. Found: C, 53.45; H, 5.57.

2,5-Dicarbanilido-3-carbethoxy-4-methylpyrrole (XXXIII).—A solution of 10 g. of (I) and 20 cc. of aniline was refluxed for three and a half hours and poured into a mixture of 100 ml. of hydrochloric acid and 500 ml. of water. The precipitate was filtered off, dissolved in hot alcohol and reprecipitated in an ice–hydrochloric acid mixture. The precipitate was then crystallized from methanol; m. p. 196° after sintering at 192°.

Anal. Calcd. for $C_{22}H_{21}O_4N_3$: C, 67.48; H, 5.41. Found: C, 67.34; H, 5.86.

The position of the second anilide group has not been established. It seems probable that it is in the *alpha* position because of the numerous analogies in the pyrrole series.

1,4-Dimethyl-2,5-dicarbomethoxy-3-carbethoxypyrrole (XXXIV).—A solution of 25 g. of (VI) in 250 ml. of dry toluene was treated with 3 g. of metallic sodium, added in small portions between 95 and 100°. When all of the sodium had reacted, 11 ml. of dimethyl sulfate was added slowly to the solution. The solution was refluxed for one hour, filtered while hot and the toluene distilled off with steam. The residue was dissolved in cold methanol and the pyrrole precipitated by pouring into five times its volume of water. After standing for two hours the pyrrole was filtered off and crystallized from methanol–water; m. p. 60°.

Anal. Calcd. for $C_{14}H_{19}O_6N$: C, 57.33; H, 6.33. For $C_{13}H_{17}O_6N$: C, 55.05; H, 6.04. Found: C, 55.19, 55.18; H, 6.11, 6.02.

1,4-Dimethyl-2-carboxyl-3-carbethoxy-5-carbomethoxypyrrole.—A solution of 1 g. of potassium hydroxide in 25 ml. of methanol was added to 5 g. of (XXXIV). A precipitate formed immediately and dissolved on the addition of water. The solution was filtered and the filtrate acidified with hydrochloric acid to precipitate the pyrrole acid. The procedure used for the purification of (VII) was then followed. The product was crystallized from methanol–water; m. p. 88°.

Anal. Calcd. for $C_{12}H_{15}O_6N$: N, 5.21. Found: N, 5.19.

2,3,5-Tricarbethoxy-4-methylpyrrole (XXXV).[17]—This must be prepared from acid (I) which has been recrystallized several times. The preparation is the same as for (VI) except that anhydrous ethanol is used. The alcoholic solution was poured into water containing an excess of sodium bicarbonate. An oil separated and was extracted with ether. The extract was evaporated on a steam-bath. Portions of the residue were purified by distilling three times at 195° and 1 mm. pressure in the Craig microdistillation apparatus.[18] A yellowish oil is obtained that solidifies slowly to give a white, waxy solid; m. p. 45–46°.

Anal.[19] Calcd. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44. Found: C, 56.33, 56.15; H, 6.54, 6.63.

Summary

1. It is shown that 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole reacts with glacial acetic acid to form the pyrryl aldehyde and acetyl chloride.

2. This pyrryl aldehyde is not an intermediate in the formation of 2-carboxyl-3,5-dicarbethoxy-4-methylpyrrole.

3. Carboxylic ester groups hinder decarboxylation in the pyrrole series.

4. Selective freeing of ring positions on tricarboxylpyrrole derivatives may be secured by replacing the first carboxyl group with bromine followed by selective degradations of the resulting dicarboxyl derivatives.

5. Flow sheets are given for the freeing of the 2,3 and 5 positions in derivatives of 2,3,5-tricarboxyl-4-methylpyrrole.

6. Five new cases have been added to the generalization that attack by an alkaline catalyst upon pyrryl-carboxylic ester groups is oriented α instead of β whenever there is a choice.

BALTIMORE 18, MARYLAND RECEIVED SEPTEMBER 6, 1947

(16) Küster, Weber, Maurer, Schlack, Niemann, Willig and Schlayerbach, *Z. physiol. Chem.*, **121**, 135 (1922).

(17) We wish to acknowledge the aid of Bryant Harrell, Jr., in this preparation.

(18) Craig, *Ind. Eng. Chem., Anal. Ed.*, **8**, 223 (1936).

(19) Performed by C. Karr.

[CONTRIBUTION FROM THE WYETH INSTITUTE OF APPLIED BIOCHEMISTRY]

The Leuckart Reaction: A Study of the Mechanism

BY VINCENT J. WEBERS[1] WITH WILLIAM F. BRUCE

The preparation of N-benzhydryl formamide from benzophenone by the Leuckart reaction has been reported by Leuckart and Bach[2] using ammonium formate. The compound has been prepared in this laboratory by the general procedure of Ingersoll[3] with good results. Since Ingersoll[4] stated that somewhat higher yields might be expected in the Leuckart reaction if formamide itself were used rather than ammonium formate, benzophenone was refluxed with 99% formamide; after refluxing for four hours or more, much lower yields of the order of 40% N-benzhydryl formamide were obtained, accompanied by recovery of the benzophenone. This unexpected result led the authors to a study of some factors that influence the Leuckart reaction, in order to determine the conditions under which formamide can be used effectively in the reaction, and to elucidate the mechanism. Catalysis by a selected group of salts was found to be important in securing a good yield in this reaction.

Benzophenone is a good choice for a study of the reaction, as there are apparently no significant side reactions except the decomposition of formamide and the product is readily identified and purified. The reaction of benzophenone with formamide was carried out under a variety of conditions. Since the Leuckart reaction is concerned essentially with the formation of a formyl derivative, and not *per se* with the hydrolysis of the formyl compound to the amine, this formyl intermediate itself was isolated. It was found that one mole of benzophenone gave a homogeneous reaction mixture with six moles of formamide at 180–190°, but not with four moles; hence all the experiments were run using six moles of the reagent. The results of these experiments are summarized in Table I. For convenience, the amounts of reagents are referred to on the basis of one mole of benzophenone, although 0.467 mole was used in each case.

The procedure given in "Organic Syntheses" was followed, and a 92% yield of N-benzhydryl formamide was obtained (Table I, run 1). Schiedt,[5] using a very large excess of formamide, reported excellent yields. In order to test this with the 99% formamide, benzophenone was treated with 18 moles of this reagent for four hours. The amide was obtained in 87% yield, based on the benzophenone used (Table I, run 2). In contrast with this, the use of six moles of formamide gave less than 50% conversion (Runs 3-A and 4-A).

In testing the effect of the addition of various substances to the reaction mixture, all the runs numbered 3 were made in the same oil-bath at the same time and likewise for the runs numbered 4 in order to secure reaction conditions as comparable as possible. Runs 3-A and 4-A, with the same reagents, served as controls so that a comparison might be made between the two sets. The runs were made for four hours in each case. The results given in Table I show that the addition of a base, dimethyl aniline, or the "Zwitterion," pyridine-3-sulfonic acid to the reaction mixture had little effect on the amount of conversion (Runs 3-B and 4-C). The addition of the ammonium salts of sulfuric and formic acids, and of anhydrous magnesium chloride, an acid in the Lewis sense, increased the conversion by significant amounts (Runs 3-C, 4-B, and 4-C).

Mechanism.—The mechanism generally proposed for the reaction was advanced by Wallach[6] and reiterated by Crossley and Moore[7]

$$\underset{\text{I}}{H_2NCHO} \xrightarrow{H_2O} NH_4OCHO \xrightarrow{185^\circ} NH_3 + HCOOH$$

$$\underset{\text{II}}{R_1R_2CO} + NH_3 \longrightarrow \underset{\text{III}}{R_1R_2C(NH_2)OH} \xrightarrow{HCOOH} R_1R_2CHNH_2 + CO_2 + H_2O$$

$$R_1R_2CHNH_2 + HCOOH \longrightarrow R_1R_2CHNH_3OOCH \longrightarrow R_1R_2CHNHCHO + H_2O$$

Doevre and Courtois[8] and Davies and Rogers[9] suggest that in the reaction between ketones and formamide, the first reaction is the addition of formamide to the carbonyl group

$$\underset{\text{II}}{R_1R_2CO} + \underset{\text{I}}{H_2NCHO} \rightleftharpoons \underset{\text{IV}}{R_1R_2C(OH)NHCHO}$$

A compound of the same type as IV is reported by Shive and Shive[10]; they isolated α-hydroxy-α-formaminopropionic acid on mixing pyruvic acid with formamide at 40°. These investigators agree that the first step is the formation of a car-

(1) Present address: Department of Chemistry, University of Minnesota, Minneapolis 14, Minnesota.

(2) Leuckart and Bach, *Ber.*, **19**, 2128 (1886).

(3) Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 503.

(4) Ingersoll, Brown, Kim, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936).

(5) Schiedt, *J. prakt. Chem.*, **157**, 203 (1941).

(6) Wallach, *Ann.*, **343**, 54 (1905).

(7) Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

(8) Doevre and Courtois, *Bull. soc. chim.*, **11**, 545 (1944).

(9) Davies and Rogers, *J. Chem. Soc.*, 126 (1944).

(10) Shive and Shive, THIS JOURNAL, **68**, 117 (1946); for the addition of amides to α-ketoacids, see also Shemin and Herbst, *ibid.*, **60**, 1954 (1938); Herbst and Martell, *J. Org. Chem.*, **6**, 878 (1941). For the addition of amides to aldehydes, see Pandya, *et al.*, *Proc. Indian Acad. Sci.*, **10A**, 282 (1939), and **7A**, 361 (1938) [*C. A.*, **34**, 1980[9] (1940), and *C. A.*, **32**, 7434[8] (1938)].

TABLE I

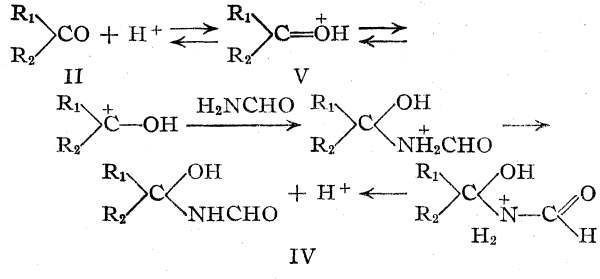
LEUCKART REACTIONS UNDER VARIOUS CONDITIONS WITH BENZOPHENONE (1 MOLE)

Run	Reagent	Temp. of reaction, °C.	Ketone[a] recovered, %	Amide obt., %	M. p. of distilled amide (cor.), °C.
1	("Org. Syn.") 6 moles HCO_2NH_4	180–190	2[b]	92	131–132
2	18 moles 99% $HCONH_2$	180–190	1	87	130–132
3-A	6 moles 99% $HCONH_2$	180–190	46	48	125–129
3-B	Same, plus 2.1 g. $Me_2NC_6H_5$	180–190	40	51	126–129
3-C	Same, plus 6.4 g. $(NH_4)_2SO_4$	180–190	12	80	123–126
4-A	Same as 3-A[c]	180–190	61.5	37.5	123–129
4-B	1 mole NH_4OOCH plus 5 moles 99% $HCONH_2$	170–176[d]	2	95.5	131–133
4-C	4-A plus 6.3 g. pyridine-3-sulfonic acid	180–190	67.5	30.5	124–130
4-D	4-A plus 6.3 g. $MgCl_2$	180–190	2	95.6	129.5–133

[a] These figures for benzophenone recovered on distillation are 1–2% too high; see experimental. [b] This ketone distilled over during the reaction. [c] To compare series 3 with series 4, run on different days. [d] The temperature is lower because of the lower boiling point of this mixture.

bon–nitrogen bond between the carbon atom of the carbonyl group, and the nitrogen atom of ammonia or formamide. This is then followed by the reduction of the alcohol thus formed by means of formic acid or formamide, respectively.

It is probable that the catalytic effects observed by us are due to an initial polarization of the carbonyl group of the ketone. The magnesium chloride, or its reaction product with formamide, $Mg(HNCHO)_2$, or magnesium ion could coordinate with the oxygen atom of the carbonyl group. The function of an ammonium salt as a catalyst for the reaction is probably to furnish a proton from a complex in equilibrium[11] with its dehydration product, the amide. It can be assumed that the formation of an amide from an ammonium salt involves stepwise loss of an hydroxyl ion and a proton from the intermediate, $R\text{-}C(OH)_2NH_2$, proposed by Noyes and Goebel[12]; Krieble and Holst[13] suggest that that the ion $RC(OH)=NH_2^+$ is also intermediate in this reaction; this ion can give up a proton to form the amide. A proton can also coördinate with the carbonyl group, increasing the effective positive charge on the carbon atom (making it more acidic), and facilitating the condensation with the relatively basic nitrogen atom of formamide



II V IV

The reaction sequence in the case of magnesium chloride is similar; and if the reaction proceeds as suggested by Wallach, by the addition of ammonia, the catalysis could be explained on the same basis. The report of Crossley and Moore,[7] that the yield in the Leuckart reaction is lower at higher temperatures, may be due to lower concentrations of ammonium formate at these temperatures.

The Leuckart reaction using monoalkyl formamides[14,15] or dialkyl formamides[6,16,17] has not been investigated by the authors, but it is probable that they show the same catalysis. Wallach[6] found that when formic or acetic acid is added to a mixture of benzaldehyde and ammonium formate, only tribenzylamine was found in the product, whereas Leuckart[17] showed that the reaction without the addition of acid gave a mixture of N-benzyl formamide, N,N-dibenzyl formamide, and tribenzylamine. Nabenhauer[16] found that the addition of formic acid is essential when tertiary amines are prepared by the Leuckart reaction with dialkyl formamides. The mechanism of the reduction of the alcohol, III or IV, with formic acid or formamide is not known, but it may be related to the mechanism of the pyrolysis of alkyl formates to form the corresponding hydrocarbon derivative.[18]

The authors wish to acknowledge the benefit of discussions with Dr. R. T. Arnold in which possible mechanisms were critically examined.

Experimental

Decomposition of Formamide.—Refluxing formamide alone gave slow decomposition to ammonia and carbon monoxide: about one liter of carbon monoxide collected in an hour from 30 cc. of formamide. The formamide, meanwhile, turned black, both in the flask and in the reflux condenser. Replacing the air in the system with nitrogen prevented most of the tar formation. Novelli and Somaglino[19] conducted a current of carbon dioxide through the system, perhaps for the same reason. During the Leuckart reaction, the evolution of carbon dioxide

(11) Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, London, 1942, p. 145.

(12) Noyes and Goebel, THIS JOURNAL, **44**, 2295 (1922).

(13) Krieble and Holst, *ibid.*, **60**, 2978 (1938).

(14) Novelli, *ibid.*, **61**, 520 (1939).

(15) Goodson, Wiegand and Splitter, *ibid.*, **68**, 2174 (1946).

(16) Nabenhauer, Abstracts of April, 1937, meeting of the American Chemical Society.

(17) Leuckart, *Ber.*, **18**, 2341 (1885).

(18) Bowden, Clark and Harris, *J. Chem. Soc.*, 874 (1940).

(19) Novelli and Somaglino, *Anal. Asoc. Quim. Argentina*, **31**, 150 (1943).

and ammonia protects the formamide from the air, and no trouble is encountered unless the heating is interrupted, or unless the heating is continued after the evolution of gases has ceased.

Standard Method of Carrying Out the Reaction.—Eighty-five grams of benzophenone (0.467 mole) and 110 cc. of 99% formamide (6 × 0.467 mole) (obtained from the Eastman Kodak Co.) together with any substances to be tested for catalytic effect, and a chip of porous plate were placed in a 200-cc. balloon flask equipped with an air-reflux-condenser. The air was displaced with nitrogen, and the flask immersed in an oil-bath kept at 190–200°. After boiling had started, the temperature in the flask was at 180–190°. A small quantity of ammonium carbonate sublimed into the reflux condenser, and ammonia and carbon dioxide were evolved. At exactly four hours after boiling started, the flask was removed from the oil-bath, allowed to cool to about 140°, and cautiously poured into about 200 cc. of cold water. (If it was cooled much below 130°, the formyl derivative crystallized, and removal from the flask was difficult.) The flask was washed out with a little water, and the mixture of benzophenone, N-benzhydryl formamide, and water soluble substances was cooled, seeded with a crystal of benzophenone, and the mixture of solids collected on a Buchner funnel, washed with a little water, and dried. The amount of benzophenone and of N-benzhydryl formamide in the mixture of solids was determined by distillation *in vacuo* without a column. Benzophenone boils at 114° at 1.2 mm., but was collected at 120–130° in order to speed up the distillation. When the benzophenone was all gone, the boiling point rose rapidly; at 160° the receiver was changed, and the remaining formyl derivative was distilled with strong enough heating to prevent crystallization in the side arm of the flask. The amide boils at 173° at 1.2 mm., but as before, it saved time to collect it at 185–190°. A small amount of tar (about a gram) remained in the Claisen flask. The amount of benzophenone determined by this method may be too great by one to two grams (estimated), as a small amount of formamide remains with the solids, and distills over with the first few drops of benzophenone.

All of the reaction mixtures were homogeneous, with the exception of 3-C; the ammonium sulfate added is not completely soluble in the reaction mixture. The results are shown in Table I. The melting point determined by Fischer block method was higher when the reaction was more complete. The value for the pure substance in the literature and in our hands is 132°.[2] In order to judge the purity of the amide, a solution of 2% benzophenone in molten N-benzhydryl formamide was made up and allowed to cool. This material melted at 126.5–130.5°, from which it is concluded that the maximum impurity in the amide samples in Table I is about 2 or 3%.

Summary

1. The Leuckart reaction with benzophenone and formamide has been run under various conditions; with pure formamide (99%) the yield is low unless a large amount of the reagent is used.

2. Ammonium formate, ammonium sulfate, and magnesium chloride have been shown to be effective catalysts for the reaction.

3. A partial mechanism is advanced for the reaction.

PHILADELPHIA 30, PA. RECEIVED AUGUST 20, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Gelsemine

BY BERNHARD WITKOP[1]

Several recent papers[1a,2,3] deal with the structure of gelsemine, $C_{20}H_{22}O_2N_2$, the principal crystalline alkaloid of *Gelsemium sempervirens*, the American "yellow jasmine." Marion[2] isolated an indole derivative as the product of soda-lime or selenium treatment of gelsemine. This is the first major degradation product reported, and relates gelsemine to the indole alkaloids. Indole itself occurs in the oils from the enfleurage of jasmine flowers, where it is present in the form of an unknown complex.[4] Marion and other investigators,[1a,2] studying the degradation of gelsemine, report the presence of bases that were difficult to purify and obtainable only in very small yield.

By the use of a modified mild zinc dust distillation three degradation products have been obtained from gelsemine. Two of basic nature were separated by the difference in basicities. The stronger base is an oil with quinoline or isoquinoline odor, and yields a well-crystallized picrate. Analysis of the latter corresponds to an ethyl- or dimethyl- quinoline or -isoquinoline. It is clear from the data of Table I that gelsemine is such a strong tertiary base that the basic nitrogen atom can neither be attached to a benzene nucleus nor form part of an unreduced pyridine ring, as has been suggested already by Forsyth, Marrian and Stevens.[1a] A more weakly basic product, probably $C_{14}H_{11}N$, was obtained in the form of a picrate. According to the analytical data it might be a methylbenzquinoline (or -isoquinoline). Skatole was isolated as the main non-basic product of indolic nature in the form of the picrate.

TABLE I

*p*Ka (negative logarithms of acidity constants of the hydrochlorides)

Quinoline	4.89[5]
Isoquinoline	5.36
Py-tetrahydroquinoline	5.03
Py-tetrahydroisoquinoline	9.41
Gelsemine	9.37[1a]

The dimethylindole reported by Marion[2] has not been observed in the present investigation. It should be pointed out, however, that the identification of alkyl indoles is often rendered difficult

(1) Fellow of the Matthew T. Mellon Foundation.

(1a) Forsyth, Marrian and Stevens, *J. Chem. Soc.*, 579 (1945).

(2) Marion, *Can. J. Res.*, **21B**, 247 (1943).

(3) Chu and Chou, THIS JOURNAL, **62**, 1955 (1940); **63**, 827 (1941).

(4) Hesse, *Ber.*, **37**, 1457 (1904).

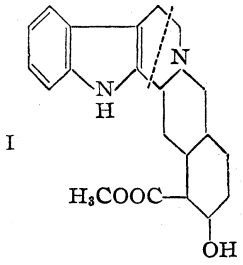
(5) Karrer and Schmid, *Helv. Chim. Acta*, **29**, 1858 (1946).

by the tendency of these substances to form mixed crystals. Soda-lime fusion, zinc dust distillation and dry distillation of yohimbine invariably lead to an isomorphous mixture of 3-ethylindole and skatole,[6] which has been looked upon as an unknown dimethylindole.[7] The same conditions are encountered in the case of C-dihydrotoxiferine-I, an alkaloid of calebash curare. Here, too, an isomorphous mixture of the two β-indole homologs simulates the properties of a new compound.[8] However, in the case of gelsemine purification of skatole could be effected with no great difficulties, which suggests the absence of other homologs.

The isolation from gelsemine of cleavage products containing nine and eleven carbon atoms intimates that the decomposition has taken the simple course

$$C_{20}H_{22}O_2N_2 \longrightarrow C_9H_9N + C_{11}H_{11}N$$

and that the alkaloid may be built up by a combination of the indole and the quinoline or isoquinoline nucleus. The latter possibility further suggests a relationship to the yohimbé alkaloids (*cf.* yohimbine (I)). It must be pointed out however that gelsemine contains an N-methyl group,



and that, if the above hypothesis be accepted, it is necessary to assume a migration of the methyl group from nitrogen to carbon. Since this change is somewhat unlikely,[9] the possibility must be considered that the reactions occurring during the degradation may be much more involved than is indicated by the above argument.

TABLE II

MELTING POINTS OF THE PICRATES

1-Ethylisoquinoline	209–210[10]
1,4-Dimethylisoquinoline	221–222[10,11]
1,3-Dimethylisoquinoline	180–181[12,a]
3,4-Dimethylisoquinoline	224–226
$C_{11}H_{11}N$ from gelsemine	185–187[a]

[a] Mixed melting showed large depression.

(6) Witkop, *Ann.*, **556**, 105 (1944)

(7) *Cf.* Marion, *Can. J. Res.*, **25B**, 1 (1947).

(8) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

(9) Migration of blocking alkyl groups is reported in the case only of quaternary ammonium bases [Reher, *Ber.*, **19**, 2996 (1886)] and certain bicyclic ring systems [norlupinane → quinoline, Prelog and Balenovic, *ibid.*, **74**, 1508 (1941)].

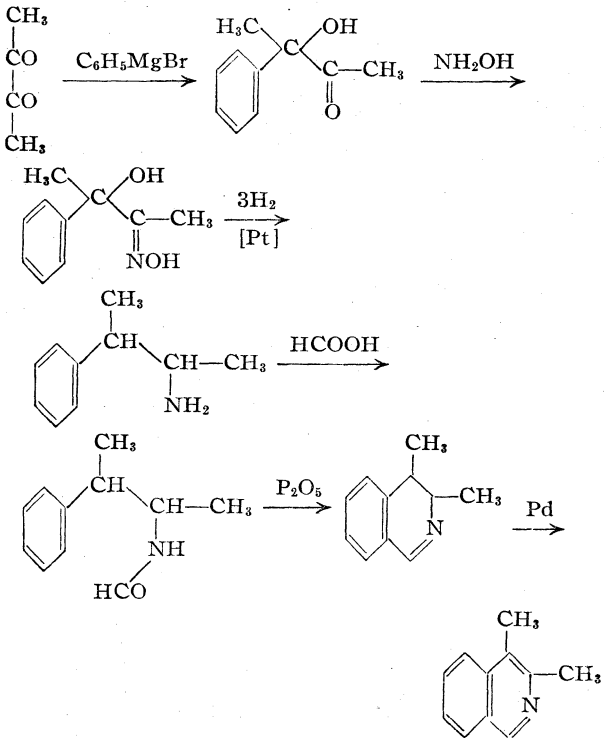
(10) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(11) Krabbe, Schmidt and Eisenlohr, *ibid.*, **74**, 1905 (1941).

(12) Isolated from coal tar, *cf.* P. Karrer, "Organic Chemistry," New York, 1946, p. 898; O. Kruber, *Z. angew. Chem.*, **53**, 69 (1940); E. Jantzen, *C. A.*, **27**, 1064 (1933).

Comparison of the properties of the base $C_{11}H_{11}N$ with those of the previously known dimethyl- and ethylisoquinolines, and further with two new substances, *viz.*, 1,3- and 3,4-dimethylisoquinolines, which have been synthesized in the course of this investigation, has shown that the new base is not identical with any of those substances (Table II).

3,4-Dimethylisoquinoline was prepared by a modification of the method of Pictet and Gams.[13,14] The oxime of dimethylphenylketol,



on catalytic hydrogenation, lost its hydroxyl group and yielded 2-phenyl-3-aminobutane. Formylation, ring closure and dehydrogenation gave the final isoquinoline.

Attempts have been made to prove the presence of an indole ring by ozonolysis[6] or by the very characteristic reaction that is given by indole compounds with perbenzoic acid.[15] Only the reactive double bond present in gelsemine[3] will react with ozone to yield an ozonide explosive in a dry state. Perbenzoic acid gives products that are no longer precipitated on addition of alkali. These findings together with the spectroscopic evidence[16] and the positive "Otto reaction"[17] speak for a hydrogenated indole ring present in gelsemine.

(13) Pictet and Gams, *Ber.*, **43**, 2384 (1910).

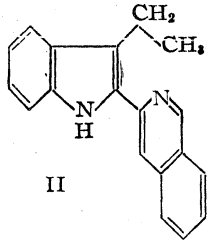
(14) Attempts to use the method of C. Pommeranz, *Monatsh.*, **15**, 299 (1894), recently improved in the synthesis of quinine, Woodward and Doering, THIS JOURNAL, **67**, 860 (1945), failed to give practicable yields in the ring closure reaction of benzylidene-2-aminobutanon (3) diethylacetal with sulfuric acid of varying strength.

(15) Witkop, *Ann.*, **558**, 98 (1947).

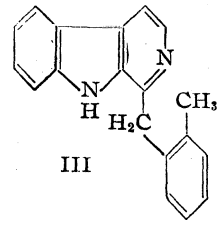
(16) Janot and Berton, *Compt. rend.*, **216**, 564 (1943).

(17) *Cf.* Henry, "The Plant Alkaloids," 1939, p. 507.

Sempervirine.—The concomitant alkaloid sempervirine, $C_{19}H_{16}N_2$, is a very interesting substance. It is isomeric with isoyobyrine (II)[18] and yobyrine (III).[19] In its strong fluorescence and lack of optical activity also it resembles yobyrine.



II



III

On the other hand, the spectra of the three compounds[20,21] are entirely dissimilar. This difference is emphasized by the behavior of sempervirine toward perbenzoic acid. Derivatives of harmine form amine oxides and lose their fluorescence; the reaction is very prompt and characteristic.[15] Sempervirine is very stable to perbenzoic acid; a non-fluorescent amine oxide could not be isolated.[21a]

Experimental[22]

Gelsemine.—*Anal.* Calcd. for $C_{20}H_{22}O_2N_2 \cdot CH_3COCH_3$: C, 72.63; H, 7.42; NCH_3, 9.0. Found: C, 72.90; H, 7.64; NCH_3, 11.4.

Gelsemine Hydrochloride.—*Anal.* Calcd. for $C_{20}H_{22}O_2N_2 \cdot HCl$: C, 67.04; H, 6.42; NCH_3, 8.1. Found: C, 67.21; H, 6.61; NCH_3, 9.49 (no methoxyl; calcd. for NC_2H_5: 12.01).[23]

Zinc Dust Distillation of Gelsemine.—For every distillation 50 mg. of gelsemine is mixed with 5 g. of zinc dust (reagent). The reaction is carried out in an apparatus described previously.[24] The mixture is separated from the constriction by a 2 g.-layer of zinc dust. The temperature inside the oven is regulated to 370°. Nitrogen is passed through a tube at such a velocity that one distillation does not take longer than ten minutes. Eighty such distillations were carried out.

Phenolic Fraction.—The combined ethereal solutions of the volatile degradation products are concentrated to 50 cc. and extracted twice with 5 cc. of dilute alkali. The alkaline solution is acidified and extracted with ether. The solvent is removed and leaves a very small amount of an oil possessing a distinct phenolic odor. It does not give the reaction of Gerngross, Voss and Herfeld[25] and, therefore, cannot be a phenol with a substituent in the *para* position.

Bases.—A.—The ether solution which contains a mixture of bases is extracted first with 10 cc. of 2 *N* acetic acid which removes preponderantly the stronger base. This base is liberated by alkali, taken up in ether, and, after evaporation of the solvent, obtained in the form of an oil with a characteristic quinoline or isoquinoline odor. The crude base is purified by steam distillation in a micro-apparatus similar to that described by Gettler and Siegel.[26] The resulting colorless oil is dissolved in little 0.1 *N* hydrochloric acid and precipitated as the picrate by the addition of the necessary amount of an aqueous solution of picric acid. The flocculent picrate is collected, washed with water and dried. Recrystallized twice from acetone, it forms bright yellow needles, m. p. 185–187°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3$: C, 52.85; H, 3.64. Found: C, 52.95; H, 3.59.

B.—A weaker base is obtained by extracting the ethereal solution from (A) with 2 *N* hydrochloric acid. It is liberated with alkali and taken up in ether. The ether is boiled off, and the oily residue subjected to steam distillation. Here, too, the resulting colorless oil has a characteristic odor reminiscent of isoquinoline. The picrate of this base is prepared in the same way as described for the stronger base. Twice recrystallized from acetone, it forms beautiful needles, m. p. 218–220°.

Anal. Calcd. for $C_{14}H_{11}N \cdot C_6H_3O_7N_3$: C, 56.87; H, 3.36. Found: C, 56.47; H, 3.36.

Non-basic Fraction.—The ethereal solution, which is now free of bases, is evaporated. The residue is separated by steam distillation into a steam volatile and a non-volatile part. The dry volatile part, which has a strong indolic odor, is distilled in high vacuum. The colorless oil which distills at 80–90° is dissolved in 4 drops of benzene. On addition of 4 drops of a cold benzenic solution of picric acid and not too much petroleum ether one obtains a red picrate (m. p. 153°). The addition of eight further drops of picric acid solution to the mother liquor yields a second purer crop of the red picrate. Recrystallized twice from benzene it forms dark red, glossy needles, m. p. 165°.

Anal. Calcd. for $C_9H_9N \cdot C_6H_3O_7N_3$: C, 50.00; H, 3.33. Found: C, 49.99; H, 3.49.

When mixed with a very pure sample of skatole picrate (m. p. 174°) it melted at 172°. Careful study of the picrate from gelsemine on a micro hot stage proves the identity in all respects with skatole picrate. It shows the two transformation points at 138° and 155° characteristic of skatole picrate.[12]

Admixture of 2,3-dimethylindole picrate with the picrate obtained from gelsemine does not lower the melting point below 156°. Equal parts of pure samples of skatole picrate and 2,3-dimethylindole picrate show a mixed melting point of 165°. In the same way, 2,3-dimethylindole (m. p. 106°) and skatole (m. p. 95°) fail to show a characteristic depression on admixture: the mixed melting point is 96°.

The residue from the steam distillation can be purified by high vacuum distillation. At 130° one obtains an oil which partially crystallizes on cooling. Recrystallization from low boiling petroleum ether yields a very small amount of needles, m. p. 195°, which do not give the reaction of Hopkins–Cole. With dimethylaminobenzaldehyde in alcoholic solution and concentrated hydrochloric acid a purple coloration is obtained at room temperature, slightly intensified on heating.

1,3-Dimethylisoquinoline Picrate.—1,3-Dimethyl-3,4-dihydroisoquinoline[27] is easily dehydrogenated by treatment with palladium black at 200° for thirty minutes. The base is dissolved in *N* hydrochloric acid and precipitated as the picrate. Recrystallized from acetone it forms short needles, m. p. 180–181°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3$: C, 52.85; H, 3.64. Found: C, 53.15; H, 3.66.

On admixture with the isomeric picrate from gelsemine (m. p. 185–187°) the melting point is lowered to 145°.

Dimethylphenylketoloxime Hydrochloride.—Dimethylphenylketol[28] (10 g., prepared by the Grignard method)

(18) *Cf.* Julian, Karpel and Magnani, THIS JOURNAL, **70**, 180 (1948).

(19) *Cf.* Clemo and Swan, *J. Chem. Soc.*, 617 (1946).

(20) Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

(21) Private communication and reference (16); the author wishes to express his gratefulness to Prof. Janot, Paris, for his friendly donation of a sample of sempervirine.

(21a) Addendum in proof: very recently Goutarel, Janot and Prelog were able to obtain yobyrine as well as tetrahydroisoyobyrine by dehydrogenation of sempervirine, *Experientia*, **4**, 24 (1948).

(22) All melting points corrected.

(23) Many indole derivatives split off some volatile iodide under the conditions of the N-methyl determination: yohimbol, 3.04%; quinamine [Henry, Kirby and Shaw, *J. Chem. Soc.*, 524 (1945)], 1.63% "NCH_3."

(24) Witkop, *Ann.*, **554**, 123 (1943).

(25) Gerngross, Voss and Herfeld, *Ber.*, **66**, 435 (1933).

(26) Gettler and Siegel, *Arch. of Pathol.*, **19**, 208 (1935).

(27) Hey, *J. Chem. Soc.*, 18 (1930).

(28) Wegmann and Dahn, *Helv. Chim. Acta*, **26**, 101 (1946).

is heated with hydroxylamine hydrochloride (4.1 g.) and anhydrous sodium acetate (4.1 g.) in 200 cc. of absolute ethanol under reflux for four hours. After removal of the sodium chloride the ethanol is evaporated in vacuum. The residue is taken up in 200 cc. of absolute ether. On passing dry hydrogen chloride through the solution the oxime hydrochloride is deposited in form of a sticky oil, which completely crystallizes after twenty hours in the ice box, m. p. 99°.

2-Phenyl-3-aminobutane.—The oxime hydrochloride (4.7 g., 0.2 mole) of 50 cc. of glacial acetic acid with 0.5 g. of platinum oxide takes up somewhat less than three moles of hydrogen. The solvent is removed in vacuum. The residue is taken up in ether, the base extracted with dilute hydrochloric acid, liberated with alkali, and taken up in ether. The amine was obtained as an oil (1.8 g., 60%).

3,4-Dimethyldihydroisoquinoline.—The amine (1.8 g.) is heated with 20 cc. of 87% formic acid on the steam-bath for two hours. The formic acid is evaporated in vacuum and the procedure repeated. The resulting crude formylamino compound still contains some amine which is extracted with dilute acetic acid. The ethereal solution is evaporated to dryness. The carefully dried crude formylamino compound (1.1 g.) is dissolved in 30 cc. of freshly distilled tetralin and treated with 3.5 g. of phosphorus pentoxide. The mixture is refluxed for thirty minutes and another 3.5 g. of pentoxide is added in the middle of this time. The resulting base is isolated in the usual manner and distilled at 120° (10 mm.). It is converted into the picrate and recrystallized from acetone as needles, m. p. 208°.

Anal. Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: C, 52.57; H, 4.12. Found: C, 52.80; H, 4.12.

The hydrochloride is prepared from the picrate by trituration with dilute alkali and extraction with ether. When hydrogen chloride is passed through the dry ethereal solution the hydrochloride crystallizes and forms beautiful needles from ethanol, m. p. 208° (sublimes).

3,4-Dimethylisoquinoline Picrate.—As in the case of the 1,3-dimethyl compound palladium (220°, thirty minutes) easily dehydrogenates the dihydro base in almost quantitative yield. The picrate crystallized immediately from the aqueous solution in short needles, m. p. 224–226°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 50.37; H, 3.95. Found: C, 50.37; H, 3.69.

Acknowledgment.—The author is indebted for support of this work to Prof. L. F. Fieser in whose laboratory part of this work was performed.

Summary

Gelsemine can be degraded to skatole and a base $C_{11}H_{11}N$ which is considered to be a dimethylisoquinoline. None of the three possible dimethylisoquinolines bearing the methyl groups in the pyridine part of the molecule is identical with the base from gelsemine.

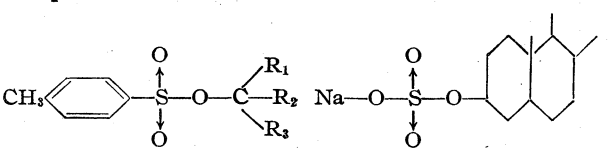
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE 38, MASS. RECEIVED SEPTEMBER 2, 1947

[CONTRIBUTION FROM THE DIVISION OF HORMONE CHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Studies in Steroid Metabolism. V. The Problem of Walden Inversion in the Reactions of Steroid Hydrogen Sulfates and Steroid Sulfites[1,2]

BY SEYMOUR LIEBERMAN, LUCIE B. HARITON AND DAVID K. FUKUSHIMA

This paper deals with the problem of Walden inversion in the reactions of steroid hydrogen sulfates and with the point of cleavage of the S-O-R linkage in these compounds. Since urinary steroids are excreted, at least in part, as water-soluble sulfates,[3] this problem is of biological interest as well as chemical. The isolation of these conjugates is difficult, their quantitative estimation impractical, and therefore it is the general practice to hydrolyze these conjugates with boiling acid in order to estimate or identify the free steroids. Although it has been recognized that various artefacts result from this hydrolytic procedure, the possibility that another type of transformation product might be formed has been overlooked. This type of artefact would result from a Walden inversion accompanying the hydrolysis of those urinary steroids conjugated with sulfuric acid. The supposition is based on the results obtained on the cleavage of analogous sulfonoxy compounds.



I II

Kenyon and Phillips[4] have shown that displacement reactions of *p*-toluenesulfonates of optically active alcohols (I) are accompanied by inversion of configuration, and there are at least three reports[5] demonstrating that steroid toluenesulfonates undergo displacement reactions accompanied by Walden inversion. Esters of sulfonic acids, therefore, unlike esters of carboxylic acids react by a rupture of the alkyl oxygen (SO-R) linkage.

(1) This paper was presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York City, September, 1947.

(2) A portion of this paper was taken from the Master's Thesis of Lucie B. Hariton, June, 1947, Department of Chemistry, New York University.

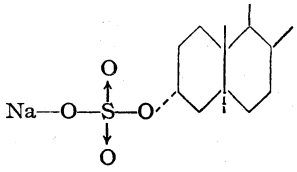
(3) The following steroids have been isolated from urine as their sulfuric acid esters: (a) Estrone [Schachter and Marrian, *J. Biol. Chem.*, **126**, 663 (1938)]; (b) androsterone [Venning, Hoffman and Browne, *J. Biol. Chem.*, **146**, 369 (1942)]; (c) dehydroisoandrosterone [Munson, Gallagher and Koch, *ibid.*, **152**, 67 (1944)]; (d) Δ^{16}-allopregnenol-3β-one-20 [Klyne and Marrian, *Biochem. J.*, **39**, Proc. xlv (1945)]; (e) uranediol [Klyne, *ibid.*, **40**, Proc. lv (1946)].

(4) Kenyon, Phillips, *et al.*, *J. Chem. Soc.*, **123**, 44 (1923); **127**, 399, 2552 (1925); 1676 (1930); 1072, 1663 (1935); *Trans. Faraday Soc.*, **26**, 451 (1930).

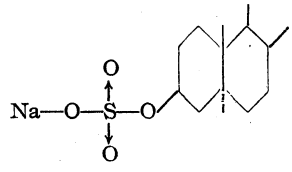
(5) (a) Prelog and Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944); (b) Plattner and Furst, *ibid.*, **26**, 2226 (1943); (c) Gallagher, private communication.

It has been generally assumed[6] that esters of sulfuric acid likewise are cleaved at the SO-R linkage. The 6-sulfates of various hexoses when treated with barium hydroxide for long periods at 100° gave 3,6-anhydro sugars,[7] a result which may be interpreted to indicate that the SO-R linkage had been ruptured. If the urinary steroid sulfates (II) are similarly cleaved at the SO-R linkage by acid hydrolysis, it would be expected that Walden inversion would occur and as a consequence, a steroid which had been excreted as the 3β-sulfate would be isolated and identified after acid hydrolysis as a 3α-hydroxy compound. The direction of cleavage of these steroid sulfates is therefore of considerable biological importance and in addition affords information on the general problem of cleavage of esters.

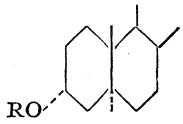
We have studied the fission of the S-O-R linkage by examining the products obtained from the acid hydrolysis and displacement reactions of sulfuric acid esters of several steroid alcohols. The acid hydrolysis has been accomplished by continuous ether extraction of a suspension of the steroid sulfate in aqueous acid. Under these conditions the free steroid accumulates in the ether extract and it is therefore unnecessary to resort to the prolonged heating usually employed for the acid hydrolysis of urinary steroid conjugates. The ether soluble reaction products were separated and were identified by melting point, melting point of mixtures and by their characteristic infrared spectra. Mother liquors and all non-crystalline residues were also submitted to infrared spectral analysis in order that every precaution be made to detect small amounts of an isomer resulting from a reaction involving Walden inversion. Under these conditions, cholestanol-3α sulfate (III) and cholestanol-3β sulfate (IV) yielded the corresponding alcohols (Va and VIIa) without any inversion of configuration. Hydrolysis of the sulfates of cholesterol and dehydroisoandrosterone was similarly accomplished without inversion of configuration.



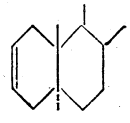
III



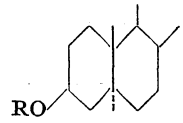
IV



Va, R = H
Vb, R = CH_3CO

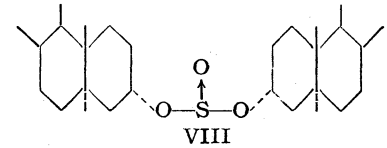


VI

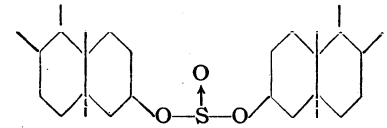


VIIa, R = H
VIIb, R = CH_3CO

In view of these results, a series of reactions were investigated under conditions favorable for a displacement reaction with inversion of configuration. Sodium cholestanol-3α sulfate (III) was heated with silver acetate in acetic acid, and from the reaction mixture, cholestanol-3α (Va) and its acetate (Vb), together with a small amount of neocholestene (VI) were obtained as the reaction products. The isomeric sodium cholestanol-3β sulfate (IV) when treated with silver acetate in acetic acid also yielded products (VIIa and VIIb) without inversion. The results indicated that these reactions were also accomplished with retention of configuration about C_3. Sodium cholestanol-3α sulfate (III) and sodium cholestanol-3β sulfate (IV) when treated at room temperature with dry hydrogen chloride in absolute methanol solution, were converted in high yield to the corresponding alcohols (Va and VIIa) without any evidence of inversion about the asymmetric carbon atom.



VIII



IX

In order to determine whether cleavage of the S-OR linkage was a general phenomenon, we have investigated the cleavage of alkyl sulfites. The sulfites of cholestanol-3α (VIII) and cholestanol-3β (IX) were treated with silver acetate in acetic acid and with dry hydrogen chloride in methanol precisely as were the sulfates, and the products were isolated as in the previous experiments. Here, also, the products retained their configuration about the asymmetric carbon atom and no evidence of Walden inversion was observed.

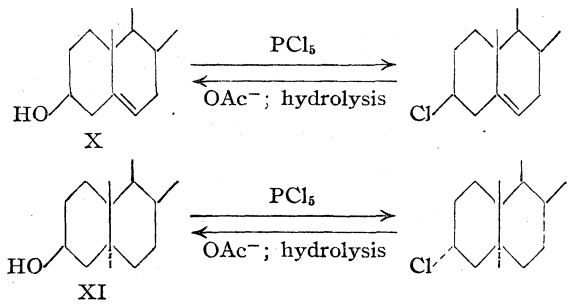
Discussion

The complete retention of configuration in all of the foregoing replacement reactions of the sulfates and the sulfites indicates that the principal course of the reaction was cleavage of the S–OR bond. Double inversion cannot account for retention of configuration because both the sulfates and sulfites were prepared by methods which do not involve the O–R bond. The reagents appear always to have attacked the sulfur rather than the asymmetric carbon atom. In the acid-catalyzed reaction, it may be postulated that a proton adds to the oxygen between the sulfur and carbon atoms. This positive charge weakens the S–OR bond since there already exists a positive formal charge of two on the sulfur; the sulfur–oxygen linkage is then cleaved by an attack of a solvent molecule (water or methanol) on the sulfur atom yielding the alcohol with the original configuration.

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 355.
(7) Percival, *J. Chem. Soc.*, 119 (1945).

That a carbonium ion was formed as an intermediate is possible, but unlikely, from the experimental results. The possibility exists that a carbonium ion is so oriented by virtue of the many asymmetric centers in the steroid nucleus that the entering group could attack the carbonium carbon from one side preferentially. If this were the case, both the isomeric α- and β-sulfates would yield a common carbonium ion and would consequently yield the same isomer or mixture of isomeric alcohols. Since each sulfate was hydrolyzed with complete retention of configuration, this mechanism is unlikely and this view is strengthened by the results of the experiments in methanol with dry hydrogen chloride. Had these reactions taken place by a carbonium ion mechanism, the products would have been the methyl ethers which were in no case isolated. These results eliminate not only the carbonium ion as a possible intermediate but also exclude the displacement reaction involving a cleavage of the SO-R linkage.

In view of some recent work of Shoppee, who has pointed out that derivatives of the unsaturated series[8] (X) react differently from those of the saturated series[9] (XI), the hydrolysis of the sulfates of the two unsaturated steroids, cholesterol and dehydroisoandrosterone cannot be unobjectionably interpreted with respect to the direction of cleavage of the S–O–R linkage.



Replacement of chlorine by acetoxyl and replacement of hydroxyl by chlorine in derivatives of the unsaturated series (X) was accomplished with retention of configuration, whereas these replacement reactions were accompanied by inversion with the saturated compounds (XI) cholestane and androstane. Since the presence of the β,γ-double bond influences the steric course of reactions at the asymmetric C_3, most of the reactions reported here were carried out with derivatives of the saturated steroids in order to facilitate the interpretation of the experimental results.

It is important to note that in the reactions with silver acetate in acetic acid the uninverted **alcohol** was isolated. The cholestanol acetates found among the reaction products were probably not produced by the displacement of the sulfate ion by the acetate ion. Such a displacement must lead to inversion, and since this was not observed in any experiment, the ester must result from the secondary acetylation of the alcohol produced by fission of the sulfate. In agreement with this interpretation we have found that cholestanol-3α acetate is formed from cholestanol-3α under the same experimental conditions employed for the cleavage, whereas cholestanol-3α acetate was recovered unchanged when subjected to this treatment. The formation of the uninverted **alcohols** from the reactions with silver acetate can only be explained by the direct cleavage of the S–OR linkage. In addition to this, it is apparent that under the somewhat more drastic conditions utilized in these reactions, some cleavage of the SO-R bond has occurred as evidenced by the formation of small amounts of neocholestene.

While the formation of unsaturated substances is without significance for the problem of Walden inversion in the displacement reaction, it has considerable interest because similar unsaturated derivatives of steroids have been frequently isolated from urine. Among these are the compounds: $\Delta^{2(\text{or } 3)}$-androstenone-17,[10] $\Delta^{3,5}$-androstadienone-17,[11] Δ^{9}-etiocholenol-3α-one-17[12] and Δ^{9}-androstenol-3α-one-17.[13] The first two of these substances very probably arise from androsterone and dehydroisoandrosterone which have been shown to be, in part at least, excreted as sulfates in human urine. In our experiments, neocholestene was found in only those reactions conducted at elevated temperature and it is likely that it is produced from the steroid sulfate by an elimination reaction. The unsaturated steroid derivatives which are isolated from urine after hydrolysis at reflux temperature are also probably formed by such an elimination reaction and need not necessarily be produced by the prolonged action of the hot acid on the free steroid alcohols resulting from the cleavage of the conjugates. This contention is supported by the results of Talbot, Ryan and Wolfe[14] who, working with the sulfate of dehydroisoandrosterone reported that "acid hydrolysis damages the conjugated dehydroisoandrosterone sterone before hydrolysis to the unconjugated form." Since it appears that temperature is the factor which favors the elimination reaction of these steroid sulfates, the hydrolytic procedure employed in this investigation involving only a room temperature extraction offers marked advantage for the circumvention of this undesirable reaction.

Acknowledgment.—This work has been supported by the Jane Coffin Childs Memorial Fund

(8) Shoppee, *J. Chem. Soc.*, 1147 (1946).
(9) Shoppee, *ibid.*, 1138 (1946).
(10) Hirschmann, *J. Biol. Chem.*, **136**, 483 (1940).
(11) Burrows, Cook, Roe and Warren, *Biochem. J.*, **31**, 950 (1937).
(12) Dobriner, Lieberman, Hariton, Sarett and Rhoads, *J. Biol. Chem.*, **169**, 221 (1947).
(13) (a) Lieberman, Dobriner and Rhoads, *Federation Proc.*, **6**, 270 (1947); (b) Dorfman, Shiller and Sevringhaus, *Endocrinology*, **37**, 262 (1945); Miller, Dorfman and Sevringhaus, *ibid.*, **38**, 19 (1946).
(14) Talbot, Ryan adnd Wolfe, *J. Biol. Chem.*, **148**, 593 (1943).

for Medical Research, the Commonwealth Fund, the New York Foundation Fund, the Lillia Babbit Hyde Foundation and the Albert and Mary Lasker Foundation, Inc. We would also like to express our appreciation to Dr. T. F. Gallagher for his generous assistance in the preparation of the manuscript.

Experimental[15,16]

Sodium Cholesterol Sulfate.—This compound was prepared with pyridine sulfur trioxide according to the method of Sobel[17] and crystallized from methanol–ether as shiny plates, m. p. 182–183°. It was dried for analysis at 100° *in vacuo* for twenty-four hours.

Anal. Calcd. for $C_{27}H_{45}O_4SNa\cdot 3H_2O$: Na, 4.23. Found: Na, 4.14.

Potassium Dehydroisoandrosterone Sulfate.—This substance was prepared according to the method of Sobel.[17] After several recrystallizations from ethanol–ether, potassium dehydroisoandrosterone sulfate melted at 221–223°.

Anal. Calcd. for $C_{19}H_{27}O_5SK$: K, 9.6; S, 7.88. Calcd. for $C_{19}H_{27}O_5SK\cdot H_2O$: K, 9.2; S, 7.55. Found: K, 9.23; S, 7.70.

Sodium Cholestanol-3β Sulfate.—To a cold solution of 1 g. of cholestanol-3β in 30 cc. of dry ether, 0.4 cc. of chlorosulfonic acid was added dropwise with swirling. After the mixture stood for one hour at room temperature, the ether was removed by distillation under reduced pressure. To the residue 4 cc. of 2 *N* sodium hydroxide solution was added slowly while the mixture was cooled in an ice-bath. The crystalline precipitate which formed was collected on a Büchner funnel, washed several times with ether and dried (1.15 g., 91%). Several recrystallizations from methanol yielded pure sodium cholestanol-3β sulfate, m. p. 174–175.5°; $[\alpha]^{29}D$ +16.6 ± 4° (ethanol).

Anal. Calcd. for $C_{27}H_{47}O_4SNa$: C, 66.08; H, 9.65; S, 6.53; Na, 4.69. Found: C, 66.04; H, 9.72; S, 6.61; Na, 4.52.

Sodium Cholestanol-3α Sulfate.—This sulfate was prepared in 76% yield according to the method of Sobel.[17] After three recrystallizations from methanol, sodium cholestanol-3α sulfate melted at 136–137°; $[\alpha]^{29}D$ +15.0 ± 5° (ethanol).

Anal. Calcd. for $C_{27}H_{47}O_4SNa$: C, 66.08; H, 9.65; S, 6.53; Na, 4.69. Found: C, 65.91; H, 9.54; S, 6.39; Na, 4.55.

It was also prepared in 95% yield using chlorosulfonic acid as described for cholestanol-3β sulfate. In general the preparation of the steroid sulfates by the chlorosulfonic acid method was more convenient and gave higher yields than the pyridine sulfur trioxide method.

Cholestanol-3β Sulfite.—To a solution of 1.5 g. of cholestanol-3β in 25 cc. of dry ether and 1 cc. of pyridine was added slowly 5 cc. of dry ether containing 0.2 cc. of thionyl chloride. After standing overnight at room temperature, an equal volume of ether was added to the mixture. The ether solution was washed with dilute hydrochloric acid solution, water, sodium bicarbonate solution and water and dried over sodium sulfate. The ether was then evaporated and the residue digested with 50 cc. of ethanol. The hot suspension was filtered to separate the insoluble starting material (650 mg.), m. p. 135–139°. The filtrate was evaporated to dryness and the residue (720 mg.) was digested in 100 cc. of hot acetone. On cooling, 690 mg. of platelets, m. p. 196–197°, was obtained. Cholestanol-3β sulfite was recrystallized for analysis from ethyl acetate and dried overnight in vacuo at 100°; m. p. 196–197.5°; reported[9] 194°; $[\alpha]^{31}D$ +5.2 ± 2.5° (chloroform).

Anal. Calcd. for $C_{54}H_{94}O_3S$: C, 78.77; H, 11.51; S, 3.89. Found: C, 78.71; H, 10.91; S, 3.97.

Cholestanol-3α Sulfite.—This compound was prepared in the same manner as the 3β isomer. When the reaction product was digested with ethanol, the cholestanol-3α sulfite was separated as the insoluble fraction. Recrystallization from ethyl acetate gave tiny rods, m. p. 210.5–211.5°. After drying *in vacuo* at 100° overnight the m. p. was lowered to 204–205°; $[\alpha]^{31.5}D$ +39.0 ± 2° (chloroform).

Anal. Calcd. for $C_{54}H_{94}O_3S$: C, 78.77; H, 11.51; S, 3.89. Found: C, 79.00; H, 11.28; S, 4.08.

Acid Hydrolysis of Sodium Cholestanol-3α Sulfate.—A suspension of 150 mg. of sodium cholestanol-3α sulfate in 50 cc. of 0.2 *N* hydrochloric acid solution (*p*H 0.9) was extracted with ether in a continuous extractor for forty-eight hours at room temperature. The ether extract was washed with sodium carbonate solution and water, dried over sodium sulfate, and then evaporated to dryness yielding a crystalline residue weighing 116 mg. (97% of the theoretical yield).

The crystalline residue was dissolved in 8 cc. of absolute ethanol and a solution of 100 mg. of digitonin in 2 cc. of 50% ethanol was added. The mixture was allowed to stand overnight at room temperature during which time the digitonide precipitated. About 100 cc. of anhydrous ether was added, the suspension was centrifuged and the supernatant ether was carefully decanted. This process was repeated several times with fresh portions of ether. The ether extracts were combined, washed with small portions of water and dried. Evaporation of the ether left 96 mg. (81%) of cholestanol-3α, m. p. 183–187°. Recrystallization from acetone gave a sample melting at 185–187°; $[\alpha]^{23}D$ +30.0 ± 2° (ethanol); reported[18] $(\alpha)D$ +33.9°, and which did not depress the m. p. of an authentic sample of cholestanol-3α, m. p. 186–187°. Cholestanol-3α acetate was prepared in the usual way, m. p. 94–95.5° (methanol); reported[19] m. p. 95–96°.

The ether insoluble digitonide was dissolved in 5 cc. of pyridine and heated on a steam-bath for one hour. After cooling to room temperature, 100 cc. of anhydrous ether was added to precipitate the digitonin. The suspension was centrifuged, the supernatant carefully decanted, and the process repeated with fresh portions of ether. The ether fractions were combined, washed with 10% sulfuric acid solution and water, and dried over sodium sulfate. Upon evaporation of the ether, 19 mg. (16%) of a crystalline residue, m. p. 175–182° with softening at 150°, was obtained. Recrystallization from acetone gave 12 mg. of cholestanol-3α identified by its infrared spectrum and m. p. 185–186°. The presence of cholestanol-3α in the β-hydroxy steroid fraction was not unexpected since Noller[20] has shown that α-hydroxy as well as β-hydroxy steroids may form insoluble digitonides.

The oily material (7 mg.) remaining in the mother liquor from the above recrystallization was submitted to infrared spectroscopy. The spectrum obtained showed absorption characteristic of cholestanol-3α in the region 1185–875 cm.$^{-1}$. In Figure 1 are shown the infrared absorptions of cholestanol-3α and cholestanol-3β in the region of 1185–875 cm.$^{-1}$. These curves are the tracings obtained directly from the automatic recording instrument. They illustrate the relative characteristic absorption of these compounds in this region of the infrared and they demonstrate how these tracings can be used for the rapid detection and identification of compounds with-

(15) The melting points were determined in a Hershberg melting point apparatus and are correct to about ±1°. The analyses were done by Dr. A. Elek, Rockefeller Institute for Medical Research, and Mr. J. Alicino, Metuchen, N. J.

(16) We wish to express our gratitude to Dr. K. Dobriner and Mrs. P. Humphries for their help in determining and interpreting the infrared spectra reported herein.

(17) Sobel and Spoerri, THIS JOURNAL, **63**, 1259 (1941).

(18) Windaus and Uibrig, *Ber.*, **47**, 2384 (1924).

(19) Ruzicka, Bruengger, Eichenberger and Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

(20) Noller, THIS JOURNAL, **61**, 2717 (1939).

out the necessity of establishing the per cent. transmission curves.[21]

In this experiment 91% (100 mg.) of crystalline cholestanol-3α was obtained from its sulfate by hydrolysis. If any isomeric cholestanol-3β was present in the residue from the mother liquor of the β-hydroxy fraction, it was in too small an amount to be detected by infrared analysis.

Acid Hydrolysis of Sodium Cholestanol-3β Sulfate.—A suspension of 200 mg. of sodium cholestanol-3β sulfate in 50 cc. of 0.2 *N* hydrochloric acid solution (*p*H 0.9) was extracted in a continuous extractor for nineteen hours at room temperature. The ether extract was washed with sodium carbonate solution and water and dried over sodium sulfate. Evaporation of the solvent yielded 156 mg. (98% of the theoretical). This material was recrystallized from acetone (113 mg.), m. p. 143–143.5°, reported[22] 141–142°; $[\alpha]^{29}D$ +33.2 ± 5°; reported[18] $[\alpha]D$ +28.8°; admixture with pure cholestanol-3β did not depress the melting point. Cholestanol-3β acetate was prepared in the usual way. After recrystallization from methanol, it melted at 108–110°; reported[22] m. p. 110–111°; the admixture with an authentic sample did not depress the melting point.

The mother liquor from the recrystallization of the cholestanol-3β was concentrated to dryness and the residue (43 mg.) was separated by digitonin as described above. The crystalline β-hydroxy steroid fraction weighed 26 mg. Recrystallization from acetone gave cholestanol-3β, m. p. 140.5–141°. Infrared analysis of the material remaining in the mother liquor demonstrated the presence of cholestanol-3β; no α-isomer was indicated. The non-crystalline α-hydroxysteroid fraction weighed 11 mg. and showed no characteristic absorption between 1185 and 875 cm.$^{-1}$. The presence of cholestanol-3α in quantities greater than 1 mg. would have been detected in this fraction by this method.

Eighty-eight per cent of crystalline cholestanol-3β was obtained by acid hydrolysis of its sulfate.

Acid Hydrolysis of Sodium Cholesterol Sulfate.—A suspension of 150 mg. of sodium cholesterol sulfate in 50 cc. of 0.2 *N* hydrochloric acid was extracted with ether in a continuous extractor for forty-eight hours at room temperature. The ether extract was worked up in the same manner as that used for sodium cholestanol-3α sulfate. The residue from the ether extract weighed 106 mg. (98% based on hydrated sulfate). After digitonin separation the crystalline β-hydroxy fraction weighed 93 mg. (86%). Recrystallization from acetone gave a sample, m. p. 147–148.5°; $[\alpha]^{22}D$ −30.0 ± 2° (ethanol); which did not depress the melting point of an authentic sample of cholesterol; reported[23] $[\alpha]D$ −29.9° (ethanol). The acetate melted at 114.5–115.5° and did not depress the m. p. of an authentic sample.

The α-hydroxy fraction (10 mg.) was a brown oil which did not crystallize. Infrared analysis indicated no characteristic absorption in the region 1185–875 cm.$^{-1}$.

Acid Hydrolysis of Potassium Dehydroisoandrosterone Sulfate.—By the foregoing procedure 150 mg. of potassium dehydroisoandrosterone sulfate was hydrolyzed. The hydrolysate weighed 96 mg. (94% based on hydrated sulfate) and was separated by digitonin. The β-hydroxysteroid fraction weighed 87 mg. (85%) and after recrystallization from acetone, the product melted at 146–148°; $[\alpha]^{23}D$ +12.5 ± 2° (ethanol); reported[24] 148–149°; $[\alpha]D$ +10.9° (ethanol)[25]; the admixture with dehydroisoandrosterone melted at 145–147°. The acetate melted at 168–170°; reported[26] 170–171°.

The α-hydroxysteroid fraction weighed 8 mg. and was not crystalline. It showed no characteristic absorption in the 1185–875 cm.$^{-1}$ region of the infrared spectrum.

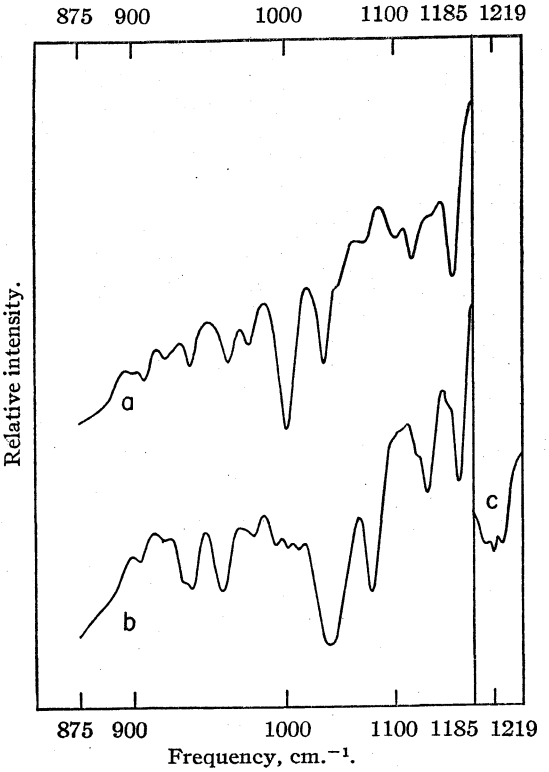


Fig. 1.—Infrared tracings of approximately 1% carbon disulfide solutions of (a) cholestanol-3α and (b) cholestanol-3β taken in a 1-mm. cell. Curve C shows some characteristic absorption bands of acetone vapor which is used as an external standard.

Reaction of Sodium Cholestanol-3α Sulfate with Silver Acetate.—About 20 cc. of anhydrous acetic acid (distilled over triacetyl borate)[27] was distilled into a flask containing 100 mg. of sodium cholestanol-3α sulfate and 200 mg. of silver acetate and the mixture was refluxed for four hours. The acetic acid was distilled *in vacuo* and the residue was extracted several times with ether. The ether extract was washed with sodium carbonate solution, water and dried over sodium sulfate. The oily residue (75 mg.) was dissolved in 7 cc. of ligroin and chromatographed on 2 g. of alumina.[28] Three fractions were obtained: (1) 2 mg. of oil eluted by ligroin and identified by infrared analysis as neocholestene. (2) 51 mg. of crystalline cholestanol-3α acetate, eluted with ligroin. Recrystallization from methanol–acetone gave needles melting at 95.5–96°, which did not depress the melting point of an authentic sample. Infrared analysis of the mother liquor showed the presence of cholestanol-3α acetate, but did not indicate any cholestanol-3β acetate. (3) 22 mg. of crystalline cholestanol-3α after recrystallization from methanol–acetone melting at 186–187°.

(21) Dobriner, Lieberman, Rhoads, Jones, Williams and Barnes, *J. Biol. Chem.*, **172**, 297 (1948).

(22) Willstätter and Mayer, *Ber.*, **41**, 2199 (1908).

(23) Mauthner, *Monatsh.*, **27**, 421 (1906).

(24) Wolfe, Fieser and Friedgood, THIS JOURNAL, **63**, 582 (1941).

(25) Butenandt, Dannenbaum, Hanisch and Kudszus, *Z. physiol. Chem.*, **237**, 57 (1935).

(26) Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 986 (1935).

(27) Eichelberger and LaMer, THIS JOURNAL, **55**, 3633 (1933). This experiment was repeated with acetic acid which was dried simply by freezing and decantation and the results were essentially the same except that more neocholestene was formed. The neocholestene was identified by m. p. (70–71°) and infrared analysis.

(28) This alumina was specially prepared and kindly made available to us by Dr. T. F. Gallagher [Hollander and Gallagher, *J. Biol. Chem.*, **162**, 549 (1946)]. It has been observed that 3-acetoxysteroids are not appreciably hydrolyzed when chromatographed on this acetic acid-washed alumina.

Infrared analysis of the residue from the mother liquor did not indicate any cholestanol-3β.

The total amount of cholestanol-3α corresponds to 68 mg. (46 mg., as the acetate and 22 mg. as the free alcohol) or 86%.

When cholestanol-3α acetate was heated in acetic acid in the presence of silver acetate, cholestanol-3α acetate was recovered unchanged; cholestanol-3α under the same conditions yielded 62% cholestanol-3α acetate and 38% cholestanol-3α.

Reaction of Sodium Cholestanol-3β Sulfate with Silver Acetate.—A suspension of 100 mg. of sodium cholestanol-3β sulfate, 200 mg. of silver acetate and 20 cc. of acetic acid (distilled over triacetyl borate) was refluxed for four hours. The reaction mixture was worked up as above and yielded on chromatographic analysis: (1) 39 mg. of crystalline cholestanol-3β acetate. After recrystallization from methanol–acetone, 29 mg., m. p. 109–110°, was obtained. The residue in the mother liquor was shown by infrared analysis to be cholestanol-3β acetate. (2) 28 mg. of crystalline cholestanol-3β. After recrystallization from methanol–acetone, it weighed 18 mg., m. p. 140–142°. Infrared analysis of the mother liquor again indicated the presence of only the β isomer. The amount of cholestanol-3β recovered was 63 mg. (35 mg. as the acetate and 28 mg. as the alcohol) or 80%.

Reaction of Sodium Cholestanol-3α Sulfate in Methanolic Hydrogen Chloride.—Dry hydrogen chloride gas was bubbled through a suspension of 185 mg. of sodium cholestanol-3α sulfate in 20 cc. of absolute methanol for five minutes. The sulfate dissolved immediately but after the solution remained overnight at room temperature, a precipitate had formed. The product (101 mg., 69%) melted at 186–186.5°, and when mixed with an authentic sample of cholestanol-3α, the melting point was not depressed.

The filtrate was concentrated to dryness and extracted with ether. The ether extract was washed with sodium carbonate solution and water, dried and the solvent removed by distillation under reduced pressure. The residue (31 mg.), m. p. 175–183°, was separated by digitonin. The α-hydroxy fraction (16 mg., 11%) was crystalline cholestanol-3α, m. p. 185–187°. The digitonide was dissociated and yielded 11 mg., m. p. 165–178°. Crystallization from acetone gave cholestanol-3α, m. p. 185–186°. The residue (2 mg.) from the mother liquor had an infrared spectrum characteristic of cholestanol-3α and there was no absorption characteristic of cholestanol-3β. In this experiment 126 mg. (86%) of crystalline cholestanol-3α was obtained.

Reaction of Sodium Cholestanol-3β Sulfate with Methanolic Hydrogen Chloride.—Sodium cholestanol-3β sulfate (200 mg.) was suspended in 20 cc. of absolute methanol into which dry hydrogen chloride gas had been bubbled for five minutes. The mixture was allowed to stand overnight at room temperature and the solvent removed by distillation under reduced pressure. The residue was extracted with ether, the ether solution was washed with sodium carbonate solution and water, and dried. Evaporation of the solvent yielded 144 mg. which was recrystallized from acetone. Sixty-six mg. (42%), m. p. 142–142.5° was obtained which upon mixing with cholestanol-3β did not depress the melting point. The residue (78 mg.) from the crystalline product was separated by digitonin. The β-hydroxy fraction (69 mg., 44%) was crystalline and upon crystallization from acetone gave cholestanol-3β, m. p. 140–142°. The residue (4 mg.) showed absorption bands in the infrared characteristic of cholestanol-3β. The non-crystalline α-hydroxysteroid fraction weighed 7 mg. and exhibited no characteristic absorption in the 1185–875 cm.$^{-1}$ region. The total yield of crystalline cholestanol-3β was 86%.

Reaction of Cholestanol-3α Sulfite with Silver Acetate.—A mixture of 150 mg. of cholestanol-3α sulfite with 200 mg. of silver acetate was refluxed seven hours in 45 cc. of acetic acid (dried by freezing and decantation). After working up in the usual way, 151 mg. of an ether soluble oil, was obtained. It was separated by chromatographic analysis on 4.6 g. of alumina and yielded 14 mg. of neocholestene, 70 mg. of crystalline cholestanol-3α acetate (recrystallized from acetone, 55 mg., m. p. 87–91°), 12 mg. of unreacted sulfite (eluted with benzene–ligroin (1:1)), and 42 mg. crystalline cholestanol-3α (recrystallized from methanol–acetone, 26 mg., m. p. 186.5–187°). The cholestanol-3α recovered amounted to 106 mg. (64 mg. as the acetate and 42 mg. as the alcohol) or 84% based on the sulfite which had reacted.

The compounds were identified by melting point and infrared spectral analysis. The infrared analysis of the residues showed that only cholestanol-3α and its acetate were present. Neither cholestanol-3β nor its acetate was detected.

Reaction of Cholestanol-3β Sulfite with Silver Acetate.—A mixture of 150 mg. of cholestanol-3β sulfite, 200 mg. of silver acetate and 45 cc. of anhydrous acetic acid was refluxed for four hours. The reaction mixture was worked up in the usual way and yielded on chromatographic analysis: (1) 2 mg. of neocholestene; (2) 11 mg. of unreacted sulfite; (3) 58 mg. of crystalline cholestanol-3β acetate which melted at 107–109.5° after a recrystallization from methanol–acetone. The infrared analysis of the mother liquor indicated the presence of only cholestanol-3β acetate; (4) 58 mg. of crystalline cholestanol-3β. After recrystallization from methanol, 43 mg., m. p. 140–142° was obtained. The residue in the mother liquor was shown by infrared analysis to be cholestanol-3β.

Reaction of Cholestanol-3α Sulfite with Methanolic Hydrogen Chloride.—Dry hydrogen chloride was bubbled through 20 cc. of absolute methanol for five minutes. After the solution had cooled to room temperature, 100 mg. of cholestanol-3α sulfite was added and the suspension allowed to stand at room temperature for twenty-four hours. The reaction product was worked up in the usual way and chromatographed on alumina. The fractions obtained were: 4 mg. of an oil eluted with ligroin whose spectra could not be identified, 15 mg. of unreacted sulfite, and 64 mg. (80% based on reacted sulfite) of crystalline cholestanol-3α, m. p. 181–185°.

Reaction of Cholestanol-3β Sulfite with Methanolic Hydrogen Chloride.—Cholestanol-3β sulfite (100 mg.) was treated with methanolic hydrogen chloride as above. The reaction product was worked up in the usual way and chromatographed on alumina. Twenty-four milligrams of cholestanol-3β sulfite, and 69 mg. (95% based on reacted sulfite) of cholestanol-3β were obtained. Recrystallization from methanol–acetone gave 60 mg. of m. p. 141–142°. The infrared analysis of the mother liquor from the recrystallization of cholestanol-3β showed the presence of only the β-isomer.

Summary

The acid sulfates and the sulfites of several steroids have been prepared and their cleavage has been studied. The reaction of these compounds with aqueous acid solution, dry hydrogen chloride in methanol, or silver acetate in acetic acid proceeds with retention of configuration indicating that these compounds react by a rupture of the S-OR linkage. These results are of biological importance because they demonstrate that the steroid acid sulfates excreted in the urine are hydrolyzed without Walden inversion.

NEW YORK, N. Y. RECEIVED NOVEMBER 14, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. I. Synthesis of Cycloöctatetraene from Pseudopelletierine[1]

BY ARTHUR C. COPE AND C. G. OVERBERGER[2]

This paper presents data amplifying our recent communication[3] which reported duplication of the Willstätter synthesis of cycloöctatetraene from pseudopelletierine.[4,5] Indirect evidence of three kinds had been interpreted as indicating that the Willstätter product might not have been 1,3,5,7-cycloöctatetraene[6]: Similarity of the product to styrene; the fact that catalytic dehydrogenation of cycloöctene at 425–455° yielded styrene; proof that application of the Hofmann exhaustive methylation procedure to diaminobutanes (investigated as open chain models of intermediates in the Willstätter synthesis) yielded ethylacetylene and methylallene in addition to the conjugated 1,3-butadiene. Development of a catalytic synthesis of cycloöctatetraene from acetylene[7] has renewed interest in the hydrocarbon. A correspondence in properties[7] made it appear likely that the catalytic and Willstätter products were identical. This has now been fully established by repetition of the Willstätter synthesis and direct comparison of the product with cycloöctatetraene prepared catalytically from acetylene.

Our synthesis began with the preparation of pseudopelletierine (I) from glutaraldehyde, methylamine and acetonedicarboxylic acid.[8] Subsequent steps are shown in the equations, which include yields and a comparison of the melting points of solid intermediates with those recorded previously. The following evidence was obtained for the structures of intermediates. N-Methylgranatenine (III) was hydrogenated quantitatively in the presence of Adams platinum catalyst to the corresponding saturated compound, N-methylgranatanine, m. p. 47–48.5° (lit. 49–50°).[9] The diene resulting from the first Hofmann exhaustive methylation step (α-des-dimethyl-granatenine, V) also was hydrogenated quantitatively and yielded dimethylaminocycloöctane, which was identified by its physical properties and also converted to the methiodide, m. p. 274–275° (dec.) (lit. 270–271°).[4] The ultraviolet absorption curve of V (Fig. 1) showed a maximum at approximately 2200 Å. (log ε 3.9) indicating conjugation of the two double bonds; compare $\lambda_{max.}$ 2170 Å. (log ε 4.32) for 1,3-butadiene.[10] 1,3,5-Cycloöctatriene (VII), the product of the second exhaustive methylation step in the synthesis, absorbed three molar equivalents of hydrogen in a quantitative hydrogenation and yielded cycloöctane. The ultraviolet absorption spectrum of VII (Fig. 2) showed a maximum at 2650 Å. (log ε 3.57) indicating conjugation of the three double bonds. The absorption maximum for an open-chain conjugated triene, 2,4,6-octatriene, is cited as 2600 Å. (log ε 3.90).[11]

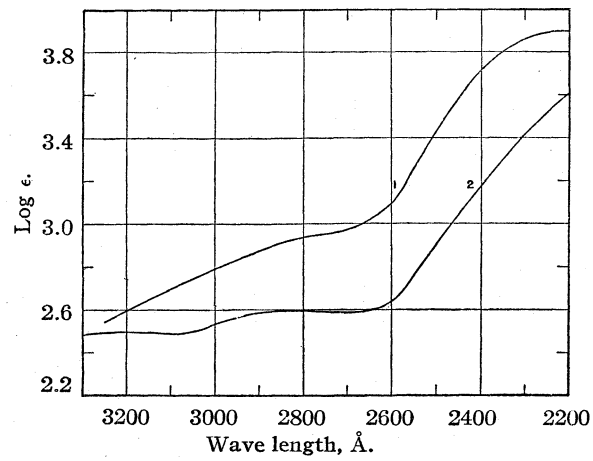


Fig. 1.—Curve 1, absorption spectrum of α-des-dimethylgranatenine (V); curve 2, absorption spectrum of 1,6-*bis*-(dimethylamino)-2,4-cycloöctadiene (VIII).

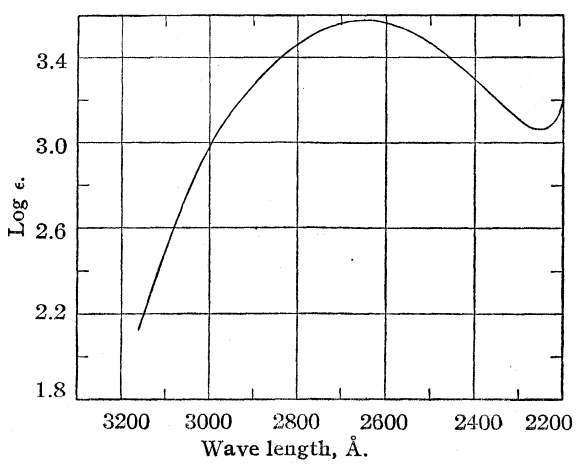


Fig. 2.—Absorption spectrum of 1,3,5-cycloöctatriene (VII).

(1) Presented at the Tenth National Organic Chemistry Symposium, Boston, Massachusetts, June 13, 1947.

(2) du Pont Postdoctorate Fellow, 1946–1947.

(3) Cope and Overberger, THIS JOURNAL, **69**, 976 (1947).

(4) Willstätter and Waser, *Ber.*, **44**, 3423 (1911).

(5) Willstätter and Heidelberger, *ibid.*, **46**, 517 (1913).

(6) The argument has been summarized well by Baker, *J. Chem. Soc.*, 258 (1945).

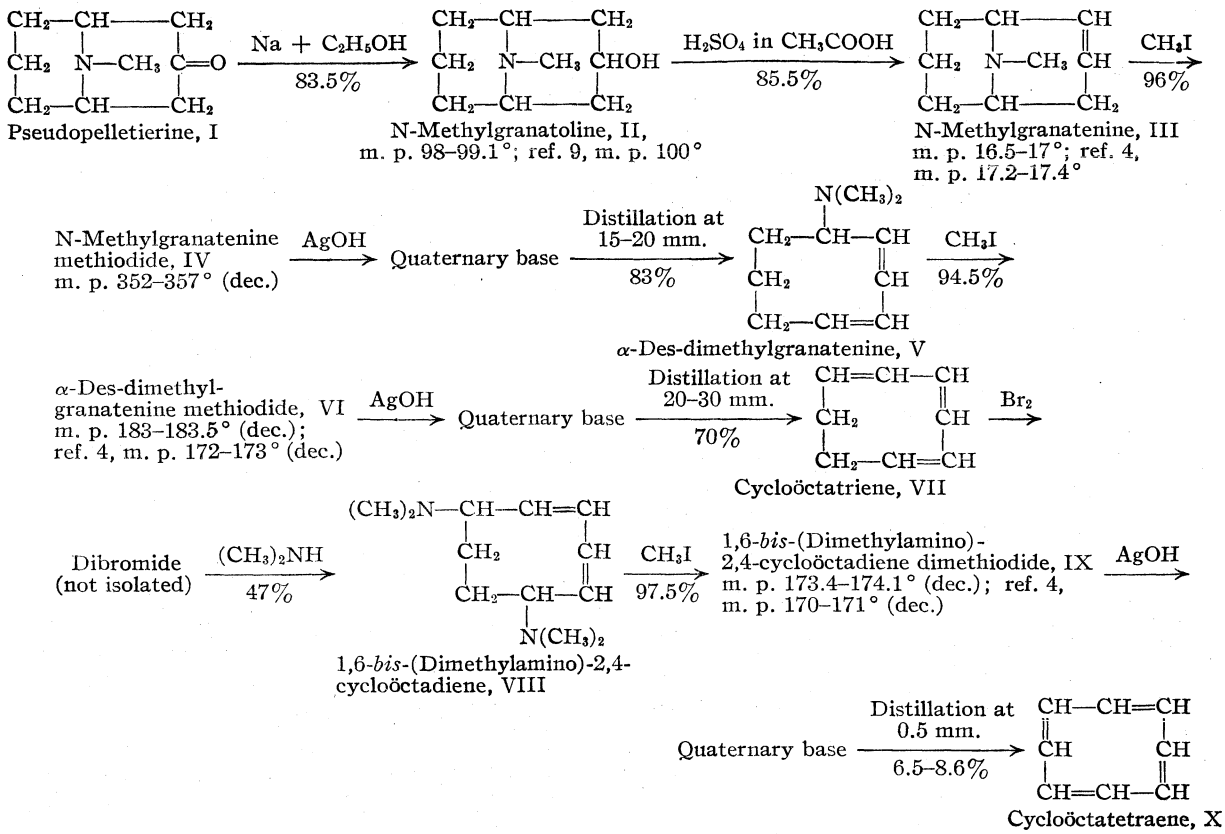
(7) Described in Department of Commerce reports of German technological developments, including a translation of a paper by W. J. Reppe reprinted in "German Synthetic Fiber Developments," p. 631, Textile Research Institute, New York, N. Y., 1946 (P. B. 7416).

(8) By modifications of the procedure described by Schöpf and Lehmann, *Ann.*, **518**, 1 (1935); Cope, D'Addieco and Overberger, to be published.

(9) Ciamician and Silber, *Ber.*, **26**, 2738 (1893).

(10) Dimroth, *Angew. Chem.*, **52**, 549 (1939).

(11) R. A. Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones and Coenzymes," 2d ed., Adam Hilger Ltd., London, 1942, p. 25.



The dibromide prepared by adding bromine to VII was not isolated, but was treated directly with dimethylamine to form a bis-(dimethylamino)-cycloöctadiene which was formulated by Willstätter and Waser[4] as VIII. Our data support but do not rigorously prove this structure, in the absence of information definitely establishing the relative positions of the two dimethylamino groups. Quantitative hydrogenation of VIII yielded a bis-(dimethylamino)-cycloöctane believed to be the 1,4-isomer, which was converted to a dimethiodide, m. p. 258–259° (dec.). The purification of VIII included treatment with warm, dilute hydrochloric acid, which would eliminate easily hydrolyzed vinylamine type isomers. The ultraviolet absorption spectrum of VIII (Fig. 1) approached a maximum below but near 2200 Å., indicating conjugation of the two double bonds. These data appear to eliminate all possible isomeric structures derivable from VII except VIII and 1,2-bis-(dimethylamino)-3,5-cycloöctadiene. It should be noted that both bromines would be allylic in type in the product of 1,6-, 1,4 or 3,4-addition of bromine to 1,3,5-cycloöctatriene, and that the displacement reaction with dimethylamine could proceed with rearrangement, so that the diamine does not necessarily have the same arrangement of groups as the dibromide. Through a combination of displacement with and without rearrangement any of the four possible dibromides (products of 1,2-, 1,4-, 1,6- or 3,4-addition) could lead to either structure VIII or to 1,2-bis-(dimethylamino)-3,5-cycloöctadiene, and accordingly the dibromide could have any of these structures or be a mixture. The diamine (VIII) reacted with methyl iodide to give an excellent yield of a pure, crystalline dimethiodide (IX), and accordingly is homogeneous rather than a mixture of isomers.

The final exhaustive methylation gave a low yield of cycloöctatetraene (X), and a high proportion of polymer. After purification by distillation through a Craig micro-fractionating column[12] the cycloöctatetraene was obtained in 6.5–8.6% yield as a light yellow liquid, $n^{25}D$ 1.5342. The melting point of the product was −5.8 to −5.4°, and was not depressed on mixture with a sample prepared catalytically from acetylene.[13] The maleic anhydride adducts obtained from cycloöctatetraene from the two sources also were identical (m. p. and mixed m. p.). Both samples of cycloöctatetraene had practically identical ultraviolet (Fig. 3) and infrared absorption spectra.[14] The synthetic

(12) Craig, *Ind. Eng. Chem., Anal. Ed.*, **9**, 441 (1937).

(13) By the German procedure described by Copeland and Youker in Fiat Final Report No. 720, 1946, p. 26 (distributed by the Office of the Publication Board, U. S. Department of Commerce).

(14) We are indebted to Dr. R. C. Lord, Jr., and Mr. R. S. McDonald for the infrared data, which will be published separately. Infrared spectra also were determined for intermediates I, II, III, V, VII and VIII. The spectra contain nothing inconsistent with the structures assigned to these compounds, and have no features which would indicate the presence of allene or acetylene structures.

sample absorbed four molar equivalents of hydrogen in the presence of Adams platinum catalyst and yielded cycloöctane.

The melting point observed for the synthetic cycloöctatetraene is of interest, because Willstätter and Heidelberger[5] had reported a freezing point of about −27° for their product, which was purified by vacuum distillation without fractionation. The molal freezing point depression constant of cycloöctatetraene was determined to be approximately 5.5. Using this value and assuming a m. p. of −5° for pure cycloöctatetraene, a m. p. of −27° would correspond to the presence of approximately 30% of an isomeric impurity. Infrared spectra[14] indicated the presence of small amounts of styrene (in the neighborhood of 3%) in our samples of cycloöctatetraene prepared by the Willstätter synthesis and in most samples prepared from acetylene. This impurity may have been responsible for the low freezing point originally reported for cycloöctatetraene, and may have been removed from our product during the fractional distillation, possibly by polymerization.

Experimental[15]

N-Methylgranatoline (II).[9]—A solution of 78.9 g. of pseudopelletierine (b. p. 101° (7 mm.), m. p. 45–46°)[8] in 1550 ml. of commercial absolute ethanol was placed in a 3-liter three-necked flask equipped with an efficient reflux condenser. The solution was heated to the boiling point and 120 g. of sodium was added in small pieces during two to three hours, as rapidly as possible without flooding the condenser. After all of the sodium had reacted, the mixture was cooled, diluted with 600 ml. of water and concentrated under reduced pressure until the residue contained an aqueous phase of approximately 100 ml. After cooling, 300 ml. of water and 500 ml. of ether were added to the residue and the ether solution was separated. The aqueous solution was extracted with 500 and 200 ml. portions of ether, and the combined ether extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the brown solid residue recrystallized from commercial hexane, b. p. 60–66°. II was obtained as brown plates in two crops; yield 66.6 g. (83.5%), m. p. 86–95°. The average yield in four preparations was 82%. The crude product was sufficiently pure for use in preparing III. Several recrystallizations from ligroin (b. p. 74–93°) gave II as small, white plates, m. p. 98–99.1°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.60; H, 11.04; N, 9.02. Found: C, 69.88; H, 11.06; N, 9.31.

Willstätter and Waser[4] stated that II was obtained from natural pseudopelletierine in a yield corresponding to 80%.

N-Methylgranatenine (III).—Glacial acetic acid (34 g.) was added with cooling to 66.6 g. of N-methylgranatoline (II). Concentrated sulfuric acid (122 g.) was added slowly with cooling to the resulting sirup. The solution was placed in a flask attached to a reflux condenser and heated in a bath at 165° for six and one-half hours. The mixture was cooled, 400 ml. of water was added and the solution was made basic by adding a 20% sodium hydroxide solution with good cooling. The dark oil which separated was taken up in 200 ml. of ether and the aqueous layer was extracted with four 300-ml. portions of ether. In some cases emulsions were formed during the extraction. Water was added if necessary to keep inorganic salts in solution. The extracts were dried over magnesium sulfate and the product was distilled through a column with a 20 × 1.2 cm. section packed with glass helices. The yield of III was 50.3 g. (85.5%), b. p. 71–72° (17 mm.). The average yield in four preparations was 85.5%. A sample purified by redistillation had the following physical constants: b. p. 56° (10 mm.); m. p. 16.5–17°; $n^{25}D$ 1.4945; d^{25}_4 0.9549.

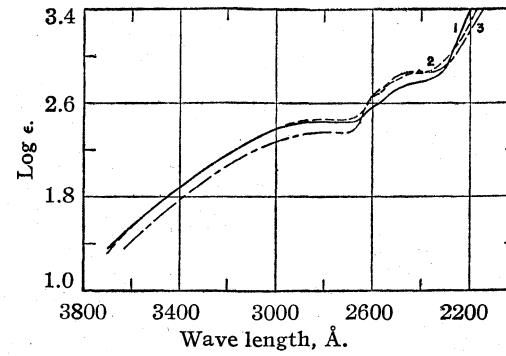


Fig. 3.—Absorption spectrum of cycloöctatetraene. Curve 1, sample prepared from acetylene, freshly distilled; curve 2, sample prepared from pseudopelletierine; curve 3, sample prepared from acetylene, four days after distillation.

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.01; N, 10.20. Found: C, 78.77; H, 11.09; N, 10.55.

This procedure is based upon the preparation of tropidine from tropine described by Ladenburg[16] and Willstätter.[17] Willstätter and Waser[4] reported b. p. 62–62.2° (9 mm.) and m. p. 17.2–17.4° for III prepared in a similar manner in unspecified yield.

Hydrogenation of 1 g. of III in 16 ml. of absolute ethanol in the presence of 0.3 g. of pre-reduced Adams platinum catalyst was complete in two hours and required 103.6% of one molar equivalent of hydrogen. The product, N-methylgranatanine, was isolated by distillation under reduced pressure. It crystallized as a hygroscopic solid and was purified by sublimation at 40° and 3 mm.; m. p. 47–48.5°.

Anal. Calcd. for $C_9H_{17}N$: C, 77.39; H, 12.30; N, 10.06. Found: C, 77.34; H, 12.35; N, 10.00.

Ciamician and Silber[9] reported the m. p. of N-methylgranatanine obtained by the phosphorus and hydroiodic acid reduction of III as 49–50°. Willstätter and Veraguth[18] reported m. p. 55–58° for the compound, prepared by electrolytic reduction of pseudopelletierine. Their product was not analyzed and may have contained some N-methylgranatoline, which also was obtained from the electrolytic reduction.

N-Methylgranatanine was converted to the methiodide by heating to reflux with an excess of methyl iodide in cyclohexane solution. The salt which separated on cooling was recrystallized from 80% ethanol as a white powder, m. p. 353–359° (dec.).

Anal. Calcd. for $C_{10}H_{20}NI$: I, 45.13. Found: I, 45.06.

N-Methylgranatenine Methiodide (IV).—N-Methylgranatenine (III) (50.3 g.), methyl iodide (78 g.) and 500 ml. of cyclohexane were placed in a 1-liter flask attached to a reflux condenser and heated to 40° for three hours. After addition of 5 g. of methyl iodide the mixture was heated at 40° for an additional two hours. Filtration separated 96.5 g. of IV, a white crystalline salt. The filtrate was warmed with 10 g. of methyl iodide for three hours at 40°. An additional 2 g. of IV was obtained, making the yield 98.5 g. (96%). The average yield in

(15) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mr. Philip H. Towle and Mrs. Louise W. Spencer for analyses.

(16) Ladenburg, *Ann.*, **217**, 118 (1882).

(17) Willstätter, *ibid.*, **326**, 28 (1902).

(18) Willstätter and Veraguth, *Ber.*, **39**, 1984 (1905).

four preparations was 96.5%. An analytical sample was recrystallized from 95% ethanol; m. p. 352–357° (dec.) after partial sublimation at 280°.

Anal. Calcd. for $C_{10}H_{18}NI$: C, 43.02; H, 6.49; N, 5.01; I, 45.46. Found: C, 42.79; H, 6.59; N, 4.88; I, 45.15.

α-Des-dimethylgranatenine (V).—Silver hydroxide was prepared by adding a solution of 28.3 g. of sodium hydroxide in 150 ml. of water to 120 g. (0.706 mole) of silver nitrate in 400 ml. of water. The precipitate was washed until free from alkali and added to 98.5 g. (0.353 mole) of the methiodide (IV) and 400 ml. of water in a 1-l. flask. After mechanical stirring and heating at 60° for one hour, the mixture was filtered. The silver iodide–silver hydroxide mixture was washed with water on the filter and then heated with 100 ml. of water at 60–70° with intermittent shaking for fifteen minutes. After again filtering, the combined filtrates were concentrated under reduced pressure. The concentrate was transferred to a 250-ml. Claisen flask attached to a well-cooled receiver and the quaternary base was decomposed (with some foaming) by heating in a bath at 100–110° at 15–20-mm. pressure. The upper parts of the flask were rinsed with 10 ml. of water to dissolve any remaining quaternary base, and the solution was again distilled to dryness in the same manner.

The colorless oil was separated from the water in the distillate by extraction with 50 and 100 ml. portions of ether. The ether extracts were dried over magnesium sulfate and distilled through a column with a 20 × 1.2 cm. section packed with glass helices. Foaming interfered with the distillation, which yielded 44.3 g. (83%) of V, b. p. 80° (12 mm.). The average yield in four preparations was 81.5%. An analytical sample had the following properties: $n^{25}D$ 1.4988; d^{25}_4 0.9038; M_D calcd. 49.18, found 49.12.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.33; N, 9.26. Found: C, 79.46; H, 11.20; N, 9.25.

Willstätter and Waser[4] reported a 90% yield of V, b. p. 71–71.5° (8 mm.); d^{20}_4 0.910.

Hydrogenation of 1.5 g. of V in the presence of 0.2 g. of pre-reduced Adams platinum catalyst in 16 ml. of absolute ethanol was complete in four hours and required 101% of two molar equivalents of hydrogen. After separation of the catalyst, distillation yielded 1.3 g. (85%) of dimethylaminocycloöctane. After redistillation, its properties were b. p. 110° (40 mm.); $n^{25}D$ 1.4707; d^{25}_4 0.877; M_D calcd. 50.14, found 49.76.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.02. Found: C, 77.41; H, 13.45; N, 9.04.

The methiodide of dimethylaminocycloöctane obtained in this manner, prepared in cyclohexane solution and purified by recrystallization from a mixture of acetone and commercial hexane (b. p. 60–66°), had m. p. 274–275° (dec., slight darkening at 270°).

Anal. Calcd. for $C_{11}H_{24}NI$: C, 44.44; H, 8.13; N, 4.71; I, 42.70. Found: C, 44.39; H, 8.13; N, 4.49; I, 42.82.

Willstätter and Waser[4] reported b. p. 86–86.5° (11 mm.), $n^{20}D$ 1.4790, d^{20}_4 0.883 and M_D 49.78 for dimethylaminocycloöctane and m. p. 270–271° for its methiodide.

α-Des-dimethylgranatenine Methiodide (VI).—VI was prepared from 44.3 g. of V and 80 g. of methyl iodide in 500 ml. of cyclohexane. The conditions of reaction were similar to those described for the preparation of IV, and the product was obtained in two crops as slightly pink, chloroform soluble crystals; yield 81 g. (94.5%). The average yield in three preparations was 92.3%. An analytical sample was recrystallized from a mixture of acetone and commercial hexane; m. p. 183–183.5° (dec.).

Anal. Calcd. for $C_{11}H_{20}NI$: C, 45.05; H, 6.88; N, 4.77; I, 43.28. Found: C, 44.96; H, 7.05; N, 4.69; I, 42.90.

1,3,5-Cycloöctatriene (VII).—The freshly prepared, alkali-free silver hydroxide obtained from 77.6 g. of silver nitrate and 18.3 g. of sodium hydroxide was added to a solution of 67 g. of VI in 100 ml. of water. The reaction conditions were similar to those described under V. Foaming occurred during concentration and also during the decomposition of the quaternary base, which was conducted in a 500-ml. Claisen flask at a bath temperature of 90–110° and 20–30 mm. pressure. The organic layer which separated in the receiver, which was cooled with Dry Ice, was extracted with ether, dried over magnesium sulfate and distilled through a column with a 20 × 1.2 cm. section packed with glass helices. A trace of picric acid was added as a polymerization inhibitor before distillation. The yield of VII was 16.8 g. (70%), b. p. 65–66° (60 mm.). After redistillation its properties were: b. p. 45° (18 mm.); $n^{25}D$ 1.5248; d^{25}_4 0.9042; M_D calcd. 35.65, found 35.94.

Anal. Calcd. for C_8H_{10}: C, 90.50; H, 9.50. Found: C, 90.49; H, 9.51.

VII proved to be somewhat unstable and accordingly was used at once.

Willstätter and Waser[4] reported a 72% yield of VII.

Hydrogenation of 1 g. of VII in the presence of 0.2 g. of Adams platinum catalyst in 25 ml. of absolute ethanol was complete in one hour and required 99.5% of three molar equivalents of hydrogen. The cycloöctane formed could not be separated from ethanol by distillation. The alcohol solution was diluted with water and extracted with ether. The extracts were dried over magnesium sulfate, distilled and redistilled through a Craig micro fractionation column[12]; $n^{25}D$ 1.4562; m. p. 11.7°.

Anal. Calcd. for C_8H_{16}: C, 85.62; H, 14.37. Found: C, 85.57; H, 14.18.

1,6-*bis*-(Dimethylamino)-2,4-cycloöctadiene (VIII).—A solution of 28 g. (0.175 mole) of dry bromine in 130 ml. of dry, alcohol-free chloroform was added dropwise during five hours to 18.5 g. (0.175 mole) of VII in 250 ml. of dry chloroform at −20° with mechanical stirring in a flask protected from atmospheric moisture. The solution remained colorless throughout the addition and no hydrogen bromide was evolved. The chloroform was removed under reduced pressure at room temperature and 500 ml. of a benzene solution containing 1.48 moles of dry dimethylamine was added to the residue with cooling. Dimethylamine hydrobromide began to separate after a few minutes. After standing for eleven hours, the mixture was cooled and extracted with an excess of 15% hydrochloric acid. The acid extracts were made basic by adding an excess of 20% sodium hydroxide solution with cooling and extracted with four 200-ml. portions of ether. The ether was removed under reduced pressure, and approximately 300 ml. of 2 *N* hydrochloric acid was added to the residue. The acid solution was heated at 55–70° for three to five minutes to hydrolyze any substituted vinyl amine types present in the crude product. After cooling, the solution was extracted with 100 ml. of ether, made basic with 20% sodium hydroxide solution with cooling, and extracted with three 125-ml. portions of ether. The ether extracts of the basic solution were dried over magnesium sulfate for one hour and distilled under nitrogen through a column with a 20 × 1.2 cm. section packed with glass helices. VIII was obtained as a light straw-yellow liquid which was kept under nitrogen and cooled to prevent rapid darkening which occurred otherwise; yield 15.9 g. (47%); b. p. 116° (8 mm.), $n^{25}D$ 1.4990; d^{25}_4 0.9317.

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.16; H, 11.41; N, 14.41. Found: C, 74.38; H, 11.13; N, 14.53.

The above procedure is similar to the one used by Willstätter and Waser.[4] These investigators purified their product by acid hydrolysis to remove vinyl amine types after distillation of VIII, before conversion to quaternary salts, and do not report physical constants for VIII after purification.

A sample of VIII was treated with picric acid in alcohol solution and converted into the dipicrate, which was recrystallized from a large volume of absolute alcohol containing 5–10% acetone; m. p. 194.6–195.2° (dec.).

Anal. Calcd. for $C_{24}H_{28}N_8O_{14}$: C, 44.17; H, 4.33; N, 17.17. Found: C, 44.41; H, 4.51; N, 16.97.

Hydrogenation of 0.879 g. of VIII in the presence of 0.3 g. of prereduced Adams catalyst was complete in seventeen hours and required 108% of two molar equivalents of hydrogen. Distillation followed by redistillation through the Craig micro column gave 1,4-bis-(dimethylamino)-cycloöctane, b. p. 105° (6 mm.), $n^{25}D$ 1.4823; d^{25}_4 0.9166.[19]

Anal. Calcd. for $C_{12}H_{26}N_2$: C, 72.65; H, 13.21; N, 14.13. Found: C, 72.53; H, 13.12; N, 14.08.

The product of a similar quantitative hydrogenation, in which 1.5 g. of VIII absorbed 103% of two molar equivalents of hydrogen in twenty-two hours, was distilled through the Craig micro column. Methyl iodide (4 g.) in 25 ml. of absolute ethanol was added to several fractions from this distillation (0.85 g.), and the mixture was boiled under reflux for three minutes. The yield of 1,4-bis-(dimethylamino)-cycloöctane dimethiodide was 1.98 g. (96%), m. p. after recrystallization from absolute ethanol 258–259° (dec.).

Anal. Calcd. for $C_{14}H_{32}N_2I_2$: C, 34.86; H, 6.69; N, 5.81; I, 52.64. Found: C, 35.07; H, 6.67; N, 5.60; I, 52.99.

Another sample of 1,4-bis-(dimethylamino)-cycloöctane obtained by hydrogenation of VIII was converted to the dipicrate, which was recrystallized from absolute ethanol; m. p. 171.5–172.2° (dec.).

Anal. Calcd. for $C_{24}H_{32}N_8O_{14}$: C, 43.90; H, 4.90; N, 17.07. Found: C, 43.96; H, 5.07; N, 16.88.

1,6-bis-(Dimethylamino)-2,4-cycloöctadiene Dimethiodide (IX).—Methyl iodide (35 g.) was added to 10.1 g. of VIII in 300 ml. of absolute ethanol. The reaction mixture was boiled under reflux for five minutes, 2 g. of methyl iodide was added, and the mixture was allowed to cool slowly. IX separated as colorless to light yellow crystals in three crops in a total yield of 24.2 g. (97.5%), m. p. after recrystallization from absolute ethanol 173.4–174.1° (dec.).

Anal. Calcd. for $C_{14}H_{28}N_2I_2$: C, 35.16; H, 5.90; N, 5.86; I, 53.08. Found: C, 35.27; H, 6.14; N, 5.87; I, 52.76.

Cycloöctatetraene (X).—The freshly prepared silver hydroxide obtained from 25.5 g. of silver nitrate and 6 g. of sodium hydroxide was added to 23 g. of the dimethiodide (IX) in 100 ml. of water. The suspension was stirred and heated at 30–40° for twenty-five minutes, cooled and filtered. The mixture of silver iodide and silver hydroxide was warmed with 75 ml. of water and shaken intermittently for ten minutes. The mixture was filtered and the combined filtrates were concentrated to a volume of 75 ml. by warming in a bath at 30–35° under reduced pressure. The residue was transferred to a 500-ml. Claisen flask and distilled at 0.5 mm. into a receiver cooled with a Dry Ice–solvent mixture. The decomposition of the quaternary base occurred with foaming at a bath temperature of 40–65° and 0.5 mm. pressure. The light yellow liquid which separated when the distillate was allowed to come to room temperature in a nitrogen atmosphere was extracted with a small volume of ether and dried over magnesium sulfate. The ether solution was concentrated and the product distilled through a Craig micro distillation column under nitrogen at 50 mm. The yellow product was separated from a polymeric distillation residue as six fractions; yield 0.43 g. (8.6%), $n^{25}D$ 1.5342; m. p. −5.8 to −5.4°; mixed m. p. with a sample of cycloöctatetraene prepared from acetylene (melting at −5.9 to −5.3°) −6.0 to −5.3°.

Anal. Calcd. for C_8H_8: C, 92.26; H, 7.74. Found: C, 92.47; H, 7.91.

A repetition of this preparation gave a 6.5% yield of X with the same physical properties.

A maleic anhydride adduct was prepared by heating 30 mg. of the sample of cycloöctatetraene described above and 20 mg. of maleic anhydride under nitrogen until refluxing occurred for two minutes. On cooling the mixture solidified, and was recrystallized from chlorobenzene. The adduct melted at 166.2–167.8° (m. p. determined by the hot-stage microscope technique) and showed no depression in mixed m. p. (165.4–167°, hot stage) with a sample of the adduct prepared from X obtained from acetylene (described below).

Hydrogenation of 0.165 g. of this sample of cycloöctatetraene in the presence of 0.2 g. of pre-reduced Adams catalyst in 20 ml. of glacial acetic acid was complete in seventy-five minutes and required 101.5% of four molar equivalents of hydrogen. After separation of the catalyst, the solution was made alkaline by adding 10% sodium carbonate solution and extracted with ether. The ether solution was dried and distilled through a Craig micro column. The last of three fractions of the cycloöctane obtained melted at 8.8°, presumably depressed by slight contamination with solvent.

Cycloöctatetraene–Maleic Anhydride Adduct.—Cycloöctatetraene (0.5 g.) prepared from acetylene[13] and maleic anhydride (0.48 g.) were heated under nitrogen at a temperature which caused refluxing for five minutes. The solid which separated on cooling was crystallized from 8 ml. of chlorobenzene. The crystalline adduct (0.4 g.) was recrystallized from 6 ml. of chlorobenzene; m. p. 166.5–167.6° (lit. 166°).[20]

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.27; H, 4.95. Found: C, 71.10; H, 5.03.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra of compounds V, VII, VIII and X were determined with a Beckmann quartz ultraviolet spectrophotometer. Purified cyclohexane[21] was used as the solvent in each case. The spectra are shown in Figs. 1–3, in which logarithms of the molar extinction coefficients are plotted against the wave lengths in ångström units.

Summary

The Willstätter synthesis of cycloöctatetraene from pseudopelletierine has been duplicated, and the product has been shown to be identical to cycloöctatetraene prepared catalytically from acetylene. Evidence supporting the structures of intermediates in the synthesis has been obtained.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 13, 1947

(19) Willstätter and Waser[4] reported b. p. 259–261° (718 mm.), d^{20}_4 0.913 for 1,4-bis-(dimethylamino)-cycloöctane prepared in the same way.

(20) Ref. 7, p. 650.

(21) Maclean, Jencks and Acree, *J. Research Natl. Bur. Standards*, 34, 271 (1945).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Structure of Alkali Amylose

BY F. R. SENTI AND L. P. WITNAUER

X-Ray diffraction studies of the structure of amylose and amylose complexes have been limited for the most part to preparations which give powder patterns. Less ambiguous interpretations of structure can be given fiber patterns, but oriented preparations are required, which are difficult to prepare by conventional methods owing to the low wet strength and hydrophilic character of amylose films.

These difficulties can be circumvented by orienting a non-hydrophilic derivative of amylose and then converting this derivative to amylose under such conditions that orientation is retained. Amylose triacetate serves this purpose well, for it is easily oriented by stretching in glycerol at 170°. Oriented alkali amylose is produced directly on deacetylation of clamped filaments in alcoholic alkali solution. Alkali amylose can be converted to the A, B[2] and V structural modifications by methods previously described.[3]

All structural modifications give well-defined fiber patterns. The alkali amyloses give patterns especially rich in reflections and, because they constitute an isomorphous series, their patterns can be more readily interpreted than those of the other modifications.

Experimental

Amylose was prepared by twice fractionating autoclaved potato starch with nitrobenzene.[4] Acetylation was carried out by the method of Whistler, Jeanes and Hilbert,[5] and films about 0.25 mm. thick were cast from chloroform solution. Strips 2 to 4 mm. wide were oriented by stretching in glycerol[6] at 170°. Films stretched 500% are highly oriented, as evidenced by their diffraction pattern, and are suitable for deacetylation.

In the deacetylation experiments, 3- to 10-centimeter filaments of oriented amylose triacetate were held taut in stainless steel clamps and suspended in the various deacetylating solutions. Unless clamped, the filaments retract considerably, especially at higher alkali concentrations, and give disoriented diffraction diagrams. The characteristic diffraction pattern of potassium hydroxide amylose is given by filaments deacetylated at 25° in 0.01 to 0.30 *N* potassium hydroxide (carbonate-free) in 75% ethanol. Completion of deacetylation has been checked by analysis of the filaments and is also evidenced by the disappearance of the amylose triacetate reflections from the diffraction pattern.

That ethanol is not an integral part of the structure is demonstrated by the identical patterns produced by filaments deacetylated in 0.25 *N* potassium hydroxide in 75% ethanol, 75% methanol, saturated butanol or in water. Deesterification proceeds slowly in the last two media and is accompanied by breakage of many filaments in the aqueous alkali solutions.

Filaments from which the alkali has been removed by extraction with absolute methanol give amorphous diffraction diagrams. Extraction with 75% methanol or ethanol results in fiber patterns characteristic of the "V structure. Reconstitution, by soaking in 0.2 *N* potassium hydroxide in 75% ethanol, restores the original diffraction pattern.

Amylose triacetate filaments deacetylated in 75% ethanol, 0.01 to 0.30 *N* in lithium or cesium hydroxide, give the characteristic diffraction patterns of lithium hydroxide amylose and cesium hydroxide amylose. At the higher concentration of alkali (above 0.3 *N* potassium hydroxide, for example) the characteristic fiber pattern diminishes in intensity and is gradually replaced by a diffuse pattern of the V-type.

Sodium hydroxide and guanidine in 75% ethanol likewise deacetylate amylose triacetate and produce the corresponding alkali amyloses with characteristic X-ray diagrams. No systematic study of the composition of these filaments or those of ammonium hydroxide amylose, prepared as described below, has been made. The similarity of their diffraction patterns to those of lithium, potassium, and cesium hydroxide amylose, however, indicates that they have the same structure and composition as the latter.

Preparation of an alkali amylose is not limited to the deacetylation of amylose triacetate by the corresponding hydroxide, but is also accomplished by the exchange of one alkali for another. For example, cesium hydroxide amylose results when potassium hydroxide amylose is immersed in alcoholic cesium hydroxide. Thallium hydroxide amylose has been obtained in similar manner. Barium hydroxide can be exchanged for potassium hydroxide, but the resulting fiber gives a poorly defined diffraction pattern. Attempts to prepare ammonium hydroxide amylose by deacetylation have failed, whereas exchange with alcoholic ammonia solutions has been successful.

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Fiber patterns of the B structural modification have been described by R. E. Rundle, L. Daasch and D. French, THIS JOURNAL, **66**, 130 (1944).

(3) F. R. Senti and L. P. Witnauer, *ibid.*, **68**, 2407 (1946).

(4) R. L. Whistler and G. E. Hilbert, *ibid.*, **67**, 1161 (1945).

(5) R. L. Whistler, H. Jeanes and G. E. Hilbert, *ibid.*, in press (1948).

(6) Method of N. C. Schieltz, private communication.

Many salts in aqueous alcohol solution can be exchanged for the alkali in alkali amylose. By this method we have obtained compounds of amylose with the iodide, bromide, acetate, formate and propionate of potassium. All give excellent fiber diffraction patterns, which will be described in another publication.

Alkali and Water Content.—On removal from the deacetylating solution, the clamped filaments were wiped dry with absorbent tissue to remove adhering alkali solution. Adsorbed alcohol, which is difficult to remove by vacuum drying, was removed by humidification of the filaments over water in a vacuum desiccator for sixteen to twenty-four hours. The vacuum-dried filaments were weighed, excess acid added, and titrated with sodium hydroxide. Figure 1 presents data on the alkali content of the filaments as a function of the normality of the deacetylation solution.

It is to be noted that the alkali content of the filaments increases rapidly with concentration of base in the deacetylation solution up to a normality of 0.02. Above 0.02 *N*, the alkali content of the fibers increases at a much lower rate, and the composition curve is nearly horizontal over a range of normalities, particularly in the case of cesium and potassium hydroxide. At higher normalities, the slope of the composition curve again increases. These observations suggest stoichiometric compound formation between amylose and alkali at a composition corresponding to the horizontal portion of the curve. For cesium hydroxide amylose, this composition corresponds to an alkali content of 26%, whereas for potassium and lithium hydroxide amyloses, the alkali contents are 11 and 5%, respectively. The observed values are in satisfactory agreement with those calculated from the formula $1MOH \cdot 3C_6H_{10}O_5$, which requires 23.7% cesium hydroxide, 10.3% potassium hydroxide and 4.7% lithium hydroxide.

At both extremes of the composition curve, however, the alkali content of the filaments deviates considerably from that corresponding to the stoichiometric ratio $1MOH:3C_6H_{10}O_5$, and the problem of the distribution of the alkali arises. One possibility is that the alkali is distributed at random among a number of crystallographically related sites, which are progressively filled as the alkali content increases. On this hypothesis we should expect the relative intensities of the diffraction maxima to vary with the alkali content. Since the lithium, potassium and cesium amyloses appear to be isomorphous, the magnitude of the shift in relative intensities is indicated by a comparison of the patterns of cesium and potassium amylose having the same mole per cent. alkali. On the cesium amylose ($1CsOH:3C_6H_{10}O_5$) pattern, $I_{(101)} \ll I_{(200)}$, whereas for potassium amylose ($1\ KOH:3C_6H_{10}O_5$), $I_{(101)} \gg I_{(200)}$. If the amount of potassium is increased and the cesium is decreased until the two isomorphous structures contain equivalent alkali on the basis of scattering power, the ratio $I_{(101)}/I_{(200)}$ should be the same for the two patterns. Since the scattering factor of cesium is three times that for potassium, patterns of cesium amylose of composition approximately $0.5CsOH:3C_5H_{10}O_5$ were compared with those of potassium amylose of composition approximately $1.5KOH:3C_6H_{10}O_5$. For each pattern, the ratio $I_{(101)}/I_{(200)}$ was unchanged within the error of visual estimation, and it is certain that the inequalities indicated above were not reversed. Random substitution in a set of sites related by symmetry is thus not consistent with our observations.

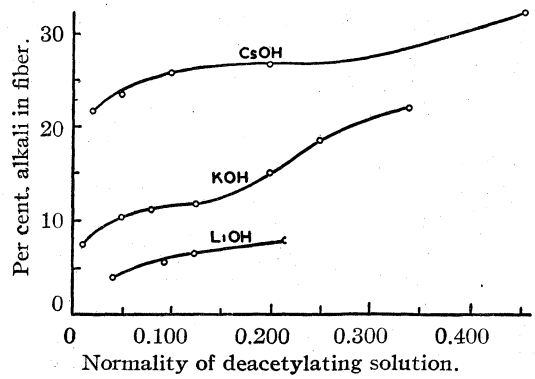


Fig. 1.—Alkali content of lithium, potassium and cesium hydroxide amylose as a function of the normality of alkali in the deacetylating solution.

It appears more likely that the crystalline portions of the fibers are essentially constant in composition with respect to the symmetry-related alkali. Alkali present in other sites would not affect the relative intensities of the discrete diffraction maxima but would contribute to the amorphous background. Any large excess would be expected to distort the structure, causing a change in lattice constants and resulting ultimately in a new or amorphous structure. The possibility that the amorphous regions of the filaments increase in extent and contain an excess or deficiency of alkali at the extremes of composition is not excluded. Experimentally, it is observed that the background scattering increases and the discrete maxima diminish in intensity when the filaments have either a low or high alkali content.

The water content of lithium, potassium and cesium hydroxide amyloses was determined at several humidities after preliminary humidification at 85% R.H. to remove adsorbed ethanol. Humidities were maintained by saturated salt solutions in vacuum desiccators. Water contents on desorption are given in Table I. Diffraction patterns were taken of filaments enclosed in glass capillaries after equilibration at the humidities listed in Table I. Below 30% R.H., corresponding to a water content of about 10%, the patterns diminished in intensity, and there was a slight decrease in lattice dimensions. Precise values of the lattice dimensions of the dry fibers were not determined because accurate measurement of the

weak patterns was impossible. A water content of 10% corresponds to one molecule of water per glucose residue, and this is concluded to be the normal content in the crystalline regions of the filaments.

TABLE I

MOISTURE CONTENT OF ALKALI AMYLOSE AT 25° IN PER CENT. OF DRY WEIGHT ON DESORPTION

Relative humidity, %	Water, %, in LiOH–Amylose	KOH–Amylose	CsOH–Amylose
50	12.6	12.9	11.4
30	9.7	9.9	9.0
12.5	6.3	6.3	6.0

It should be noted that lithium hydroxide amylose also occurs in a more highly solvated structure. Filaments deacetylated in 0.2 *N* lithium hydroxide in 75% ethanol and X-rayed while moist with deacetylating solution give an X-ray pattern showing the same fiber repeat period (22.6 kX), but at least one lateral identity period larger than that of the normal hydrate to which the structure reverts upon drying in air. Under the conditions of deacetylation we have employed, neither cesium nor potassium hydroxide amylose has given any indication of a more highly solvated structure.

X-Ray Diffraction Patterns.—Patterns for indexing were taken in a cylindrical cassette of 5-cm. radius with filtered CuK_α radiation. Filaments mounted with the fiber axis along the cylinder axis show only the second-order reflection of the fiber repeat period. To observe the higher orders, filaments were oscillated with the fiber axis perpendicular to the cylinder axis. Superposition of reflections from planes not perpendicular to the fiber axis on the desired orders of the fiber repeat period was prevented by restriction of the oscillation range. By maintaining a common reflection on succeeding photographs, it was possible to compare the relative intensities of the various orders. Relative intensities of the meridian (orders of the fiber identity period) reflections of lithium, potassium and cesium amyloses were placed on a common basis by the comparison of timed photographs of filaments of known thickness and alkali content. Intensities were estimated visually by comparison with a scale of known relative intensities.

Unit Cell.—The fiber identity period of the alkali amyloses is readily determined from the layer line separation on cylindrical cassette patterns or from the *d*-values of the various orders of the fiber identity period obtained from the oscillation photographs. Determination of the lateral identity periods is ambiguous. The assumption was made that a reflection corresponding to a primitive lateral translation would appear on at least one of the eight layer lines observed. Thus, the first and second nearest reflections to the meridian were indexed as $0kl$ and $lk0$, respectively, where k is the layer line index. On the further assumption that the lattice is orthorhombic, sin θ values were computed and compared with the observed values. The results for potassium hydroxide amylose, based on the orthorhombic unit having $a_0 = 12.7$ kX, $b_0 = 22.6$ kX, and $c_0 = 9.0$ kX, are presented in Table II. A comparison of the dimensions of the orthorhombic unit cells found for the alkali amyloses is given in Table III. All reflections were indexed on the patterns of lithium and cesium hydroxide, whereas the unit cell dimensions of sodium, ammonium and guanidinium hydroxide amylose were derived from measurement of equatorial reflections and layer line separations alone. The lateral dimensions increase regularly with increasing size of the cation except for cesium hydroxide amylose, which has a smaller a_0 than expected. Since the fiber repeat period remains the same, the decrease in a_0 is probably due to a small rotation of the glucose residues about the *b*-axis, and it is unlikely that this will affect the validity of the isomorphous relations which we apply.

Potassium hydroxide amylose containing 10% potassium hydroxide and 13% water has a density (determined by flotation in carbon tetrachloride–petroleum ether mixtures) of 1.53. If it is assumed that the water and alkali are uniformly distributed throughout the filaments, then the number of glucose residues (mol. wt. 162) in the unit cell is

$$N = \frac{12.7 \times 9.0 \times 22.6 \times 1.53 \times 0.77}{162 \times 1.65} = 11.4$$

A similar computation for cesium hydroxide amylose (28.1% cesium hydroxide, 9.0% water, $d = 1.86$) gives a value of 11.3 for N. Consequently, there are twelve glucose residues in the orthorhombic unit cell.

Space Group.—If the alkali amylose structures are based on an orthorhombic lattice, as appears likely from the agreement of observed and calculated sin θ values, the space group must be isomorphous with the point group D_2. All other point groups of the orthorhombic system contain planes of symmetry which are not permitted by the optically active amylose molecules.

Of the reflections $(0k0)$, only those with k even were observed out to $k = 16$ in lithium, potassium and cesium hydroxide amyloses. It is therefore probable that the structures possess a twofold screw axis parallel to the fiber axis. Observed reflections of the form $(h00)$ and $(00l)$ are consistent in all cases with twofold screw axis in the directions *a* and *c*, although not sufficient orders were observed to establish this beyond a possibility of doubt. The observed reflections thus allow space groups $P_{2_12_12_1}$, $P_{2_22_12_1}$, $P_{2_12_12}$, and $P_{2_22_12}$.

Intensity considerations, however, permit only space group $P_{2_12_12_1}$. This follows from the Patterson projections $P_v(uw)$ of the lithium (Fig. 2) and potassium hydroxide (Fig. 3) amyloses. Since the amylose chains lie along *b* (fiber axis), the projection $P_v(uw)$ should give lateral vector distances *u*,

TABLE II

COMPARISON OF CALCULATED AND OBSERVED SIN θ VALUES FOR POTASSIUM HYDROXIDE AMYLOSE

hkl	Sin θ (obs.)	Sin θ (calcd.)	*I* (est.)	*hkl*	Sin θ (obs.)	Sin θ (calcd.)	*I* (est.)
101	0.1049	0.1049	S^+	130	0.1188	0.1183	$W^=$
200	.1207	.1210	$W^=$	131	.1457	.1461	W^-
201	.1488	.1483	W	230	.1571	.1580	M
002	.1708	.1714	S^-	231	.1806	.1797	W
202	.2107	.2098	W^-	330	.2071	.2080	M
302	.2495	.2496	M	132		.2082	
401	.2563	.2567	W^+	331	.2246	.2249	M
003		.2571		133	.2831	.2830	W^+
203	.2843	.2841	W	233	.3009	.3018	$W^=$
501	.3150	.3143	W^+	432	.3148	.3134	W diff.
303		.3147		531	.3303	.3304	W diff.
600	.3637	.3629	$W^=$	532	.3613	.3622	W diff.
204		.3635		234	.3780	.3774	W diff.
602	.4005	.4014	$W^=$				
305	.4653	.4653	$W^=$	140	.1483	.1484	S^-
703	.4954	.4953	$W^=$	041	.1608	.1603	M
				141	.1719	.1714	$W^=$
111	.1097	.1102	S^+	240	.1825	.1817	$W^=$
210	.1254	.1256	S^+	241	.2016	.2009	M^-
211	.1533	.1521	$W^=$	042	.2179	.2185	W^+
012	.1754	.1747	M	142	.2273	.2267	M^+
310	.1845	.1846	M^+	340		.2265	
112		.1849		341	.2427	.2421	W
311	.2034	.2035	M	043	.2905	.2906	W^+
212	.2118	.2125	M^-	441		.2902	
411	.2585	.2589	W^+	244	.3888	.3879	W^-
013		.2593		640		.3874	
113	.2665	.2663	W	642	.4230	.4236	W^-
213	.2862	.2861	W				
412	.3025	.2984	W	150	.1797	.1799	$W^=$ diff.
510		.3043		051	.1901	.1898	M
313	.3160	.3165	W	151	.1993	.1992	W^-
511		.3162		250	.2091	.2082	W^-
512	.3506	.3493	W^-	251	.2254	.2251	M^-
214	.3652	.3651	$W^=$	350	.2486	.2482	W^-
610		.3645		152		.2484	
513	.4000	.3984	W^-	351	.2629	.2626	W
612		.4028		153	.3136	.3138	W
414	.4213	.4209	W^-	253	.3314	.3308	W^+
115	.4337	.4340	W^-	353	.3573	.3574	W^-
711		.4333		551		.3571	
120	.0905	.0908	W	160	.2129	.2121	$W^=$
121	.1253	.1249	S^+	161	.2287	.2287	M
220	.1391	.1387	W^+	261	.2535	.2516	M
221	.1634	.1630	W^-	162	.2718	.2727	M diff.
122	.1945	.1940	S	360		.2725	
320		.1937		262	.2918	.2921	M diff.
321	.2113	.2118	W^-	460	.3162	.3160	W^+
222	.2200	.2205	W^-	163	.3335	.3333	W^+
420	.2512	.2513	W	462	.3593	.3595	W
421	.2672	.2655	W				
023		.2659					
520	.3084	.3099	W				
124	.3574	.3546	M diff.				
423		.3593					
523	.4023	.4027	W^+ diff.				

w between the chains. Resolution of individual carbon and oxygen atoms cannot be expected, since there will be much overlapping in the projection, and furthermore, early termination of the

TABLE III

UNIT CELL DIMENSIONS OF ALKALI AMYLOSES

Amylose	a_0, kX	b_0 (fiber axis), kX	c_0, kX
LiOH	12.1	22.6	8.8
NaOH	12.3	22.6	8.9
KOH	12.7	22.6	9.0
NH_4OH	12.7	22.6	9.0
CsOH	12.4	22.6	8.9
$C(NH_2)_3OH$	13.1	22.6	9.0

series required by the observed reflections results in low inherent resolution. We interpret the maxima in Figs. 2 and 3 at (0, 0) and ($^1/_2$, $^1/_2$) to indicate two amylose chains in the unit cell separated by the vector distance ($^1/_2$, $^1/_2$). Such an

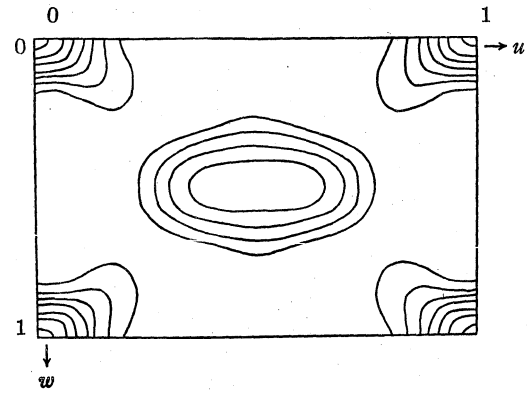


Fig. 2.—Patterson function $P_v(uw)$ for lithium hydroxide amylose.

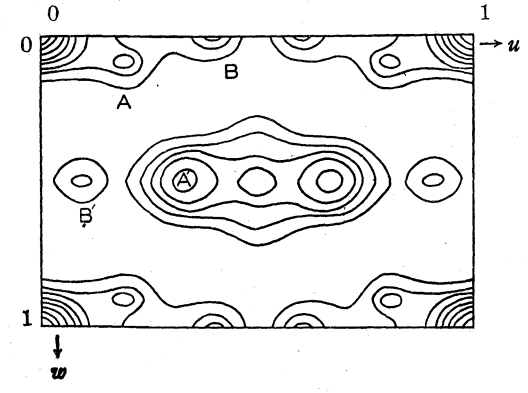


Fig. 3.—Patterson function $P_v(uw)$ for potassium hydroxide amylose.

arrangement is consistent with space group $P_{2_12_12_1}$ as indicated in Fig. 4, where the chains lie on the screw axis along b. Since the amylose molecule does not possess twofold symmetry, it cannot lie on a twofold axis, and a structure based on P_{22_12} would have four chains in the orthorhombic cell. Disposition of the four chains in the unit cell according to symmetry requirements and packing considerations demands a Patterson projection having maxima at approximately ($^1/_2$, 0) and (0, $^1/_2$) in addition to the observed maximum at ($^1/_2$, $^1/_2$). Likewise, structures based on $P_{2_12_12}$ or $P_{22_12_1}$ can be eliminated by comparison of their projected intermolecular vectors with the observed Patterson projection.

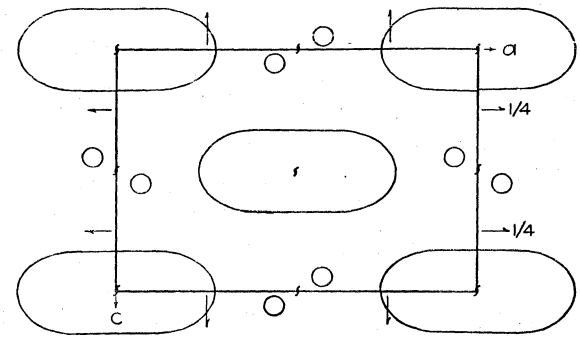


Fig. 4.—Projection of the alkali amylose structure on (010), showing position of amylose chains and alkali ions.

Isomorphism of the Alkali Amyloses.—The near identity of the unit cell dimensions and the fact that all diffraction patterns are consistent with space group $P_{2_12_12_1}$, indicate that the alkali amyloses are isomorphous. Further evidence is provided by a comparison of the $|F|$-values (Table IV) of the ($0k0$) reflections of lithium, potassium and cesium hydroxide amyloses. Filaments having the same content of alkali on a mole basis (1 mole alkali/3 glucose units) were used for this purpose. Appropriate corrections were made for the time of exposure, sample thickness, absorption, Lorentz and polarization factors. The assumption was made that all filaments are equally crystalline. This appears reasonable, since all filaments were prepared from amylose triacetate stretched and deacetylated under identical conditions except for the variation of the alkali. If the structures are isomorphous then

$$\frac{|F|_{0k0}\ (\text{KOH-Amylose}) - |F|_{0k0}\ (\text{LiOH-Amylose}}{|F|_{0k0}\ (\text{CsOH-Amylose}) - |F|_{0k0}\ (\text{KOH-Amylose})} = \frac{f_{K^+} - f_{Li^+}}{f_{Cs^+} - f_{K^+}}$$

where the f's represent the ionic scattering factors. At low angles the value of the ratio is $^1/_2$ and decreases with increasing angles. Thus $|F|_{(0k0}$KOH-Amylose) $-$ $|F|_{0k0}$(LiOH-Amylose) $=$ $^1/_2$ to $^1/_3[|F|_{0k0}$(CsOH-Amylose) $-$ $|F|_{0k0}$(KOH-Amylose)] for the orders considered. These differ-

TABLE IV

F-VALUES FOR THE ($0k0$) REFLECTIONS OF LITHIUM, CESIUM AND POTASSIUM HYDROXIDE AMYLOSES

$0k0$	(1) F_{LiOH}-Amylose	(2) $\|F\|_{KOH}$-Amylose	(3) $\|F\|_{CsOH}$-Amylose	(4) (2)-(1)	(5) (3)-(2)	(6) (3)-(2) Calcd.
020	1	6	22	5	16	−14.7
040	(−) 7	10	18	3	8	− 7.8
060	0	11	35	11	24	+24.0
080	(+) 17	9	9	8	18	−20.4
0·10·0	0	0	0	0	0	0
0·12·0	(−) 25	12	8	13	20	+20.4
0·14·0	<1	4	15	4	11	−19.8
0·16·0	(−) 10	5	17	5	22	+ 7.8

ences are listed in Table IV,[7] in columns 4 and 5, respectively. The agreement is satisfactory, considering the difficulty of making accurate intensity measurements.

Structure of the Alkali Amyloses.—The lateral arrangement of the amylose chains and alkali ions in the isomorphous structures is evident from the Patterson projections of Figs. 2 and 3. Owing to its low scattering, lithium ion contributes little to the Patterson projection, and the maxima in Fig. 2 result from glucose–glucose interactions. Elongation of the maxima in Fig. 2 indicates that the planes of the glucose residues are nearly parallel to the *ab* plane, as represented in Fig. 4. Since there are twelve glucose residues in the unit cell, each of the positions indicated in Fig. 4 must correspond to the projection of six glucose residues. Alkali ion parameters are determined by comparison of Figs. 2 and 3; the additional maxima in the latter result from potassium-potassium and potassium-amylose interactions. Assigning maxima A and A' to the former and maxima B and B' to the latter, the structure represented in Fig. 4 is derived with alkali ions at approximately $x = \frac{24}{60} a_0$, $z = \frac{3}{60} c_0$ and positions derived by symmetry.

Patterson projections of the structure perpendicular to b (the fiber axis) should give the y parameter of the glucose residues and the alkali ions. Unfortunately, the superposition of reflections of different forms having nearly identical $\sin\theta$ values does not permit the assignment of F^2-values to the forms which contribute to the functions $P_w(uv)$ and $P_u(vw)$. The Patterson projections $P_{uw}(v)$ on the fiber axis can be evaluated, however, since only forms $(0k0)$ contribute, and the corresponding F^2-values were determined from oscillation photographs. $P_{uw}(v)$ for cesium hydroxide amylose is given in Fig. 5. Because of the high scattering factor of cesium, the dominant peaks in this function should correspond to Cs^+–Cs^+ distances along b. According to Fig. 5, these distances are $^1/_6\ b_0$.

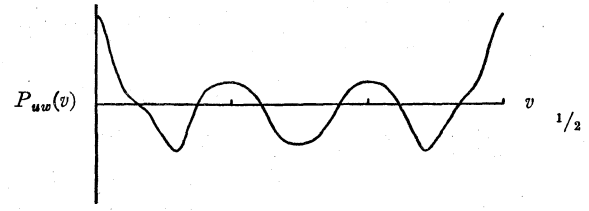


Fig. 5.—Patterson function $P_{uw}(v)$ for cesium hydroxide amylose.

The data of Table IV should also determine the y parameter of the alkali ions, for $|F|_{0k0}$ (Cesium hydroxide–Amylose) $-|F|_{0k0}$ (KOH-Amylose) represents the contribution of an alkali ion of scattering factor $f_{Cs^+} - f_{K^+}$ to the amplitude of the reflection $(0k0)$. Column 6 of Table IV gives the calculated F-values for an alkali ion at $y = 63°$ using a scale factor to give agreement with the observed value for (060). The agreement with the observed values of column 5 are satisfactory except for (0·14·0) and (0·16·0). Part of this discrepancy may be due to error in intensity measurements of the high orders which appeared as weak reflections on the photographs. From the sign of the contribution of the alkali ions to the structure amplitudes of the $(0k0)$ reflections, we can determine the sign of the F-values of lithium hydroxide amylose (as given in column 2 of Table IV). A Fourier series using these values gives the projection of the amylose chain on [010]. This projection appears in Fig. 6 and has maxima at $y = 2/60$, $y = 7.5/60$, $y = 13/60$ and positions related by the center of symmetry of the projection. If it is assumed that these peaks correspond to the centers of the glucose residues of the two amylose chains which have been projected on [010], then we can consider that one chain is displaced with respect to the other by $5.5/60\ b_0$ or by about one half the projected length $(10/60\ b_0)$ of a glucose residue on the fiber axis. This interpretation, however, is somewhat doubtful, because models of extended amylose chains show that there are concentrations of atoms roughly $5/60\ b_0$ along its axis. The Fourier projection would then be explained by placing the two chains in the unit cell with their centers at the same level along b.

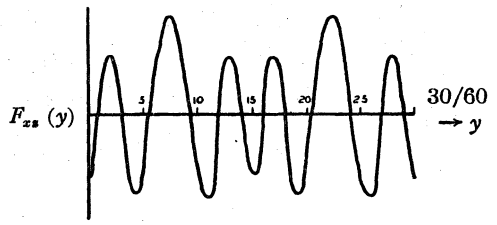


Fig. 6.—Fourier projection of lithium hydroxide amylose on [010].

The exact configuration of the glucose residues in alkali amylose can be determined only by a complete structural analysis, which involves the location of thirty-three atoms of the three independent residues. Fourier series methods have limited application in this case, and the analysis would have to be carried out by trial-and-error methods which we have not attempted. A frequently used but less satisfactory procedure is the comparison of the observed fiber repeat period with that calculated on the basis of various chain configurations.

If it is assumed that all glucose residues have the symmetrical chair configuration[8] with the

(7) The signs of the F_{0k0}'s for lithium hydroxide–amylose which appear in parentheses were determined by the procedure described in the following section.

(8) Pierce, *Trans. Faraday Soc.*, **42**, 545 (1946), has shown that the unit cell dimensions and the intensities of the meridian reflections of cellulose are consistent with the symmetrical chair configuration of the glucose residues. We have used Pierce's bond distances and angles with the exception of the C–C distance, which we take as 1.54 kX instead of 1.52 kX.

bond distances C—C = 1.54 kX, C—O = 1.43 kX and all angles tetrahedral except the ring angle C—O—C, which was taken as 90°, the projection of six maximally extended residues is computed to be 22.4 kX. A chain of maximally extended residues in this configuration does not possess the required twofold screw symmetry, and rotation of the residues to give the required symmetry decreases the fiber repeat period. Bond angles or lengths must be changed, therefore, to obtain agreement with the observed fiber repeat period of 22.6 kX. If the symmetrical chair configuration of minimum steric repulsion is retained, the most reasonable change is to increase the oxygen angle in the ring. Increasing this angle to 109° and using the same values as above for all other angles and distances, the projection of six maximally extended residues is computed to be 26.1 kX. It is evident that models can be constructed having the symmetrical chair configuration and satisfying the requirements of twofold screw symmetry and the observed fiber repeat period by selecting a value for the ring oxygen angle between 90 and 109°. Such agreement, of course, does not eliminate from consideration models of the amylose chain based on other configurations of the glucose ring.

In the structure proposed, the effective thickness of the glucose residue is 4.5 Å., which is consistent with the value found in cellulose and alkali cellulose.[9] The width of the glucose residues plus the contribution of alkali and water (position undetermined) is 12.7 Å., again consistent with the corresponding value found in sodium cellulose III.[8]

Summary

Amylose forms crystalline addition compounds with lithium, sodium, potassium, ammonium, cesium and guanidinium hydroxide. Diffraction patterns indicate these compounds constitute an isomorphous series based on the orthorhombic space group $P_{2_12_12_1}$. Analyses of lithium, potassium and cesium hydroxide amylose shows their composition to be $3C_6H_{10}O_5 \cdot MOH \cdot 3H_2O$, and it is probable that this formula represents the composition of the entire series.

All compounds have the same fiber repeat period, 22.6 kX, corresponding to the extension of six glucose residues. Positions of the alkali ions and the lateral packing of the amylose chains have been determined with the aid of Patterson projections.

(9) K. H. Meyer, L. Misch and N. P. Badenhuizen, *Helv. Chim. Acta*, **22**, 59 (1939).

PHILADELPHIA 18, PA. RECEIVED OCTOBER 20, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO, AND PHYSICAL CHEMICAL RESEARCH, ENGINEERING DIVISION, CHRYSLER CORPORATION]

Surfaces of Solids. XVIII. The Heats of Emersion and Desorption of Water from Graphite at 25°

BY PAUL R. BASFORD, GEORGE JURA AND WILLIAM D. HARKINS

I. Introduction

A recent paper,[1] gives the adsorption isotherms of water and *n*-heptane on a sample of graphite with a content of less than 0.004% ash and presumably free from oxygen. In that paper some of the problems associated with the graphite–water system were indicated, but their discussion was deferred until after the completion of the calorimetric study of the system as presented here.

II. Experimental

The graphite, furnished through the courtesy of Dr. Lester L. Winter of the National Carbon Company, is described elsewhere. The calorimeter and technique of the measurements was that of Harkins and Jura.[2] Because of the low area of the sample, 4.22 sq. m. g.$^{-1}$, the limited supply of the powder and the small amount of water adsorbed per gram, the technique of Harkins and Jura[2] for determining the amount of water adsorbed could not be used. Instead, the equilibrium pressure of the adsorbed vapor was determined. The amount of adsorbed water was then obtained from the data of the isotherm. For high values of p/p_0 this leads to a considerable uncertainty in the exact amount adsorbed. However the actual results in this region are such that this error is insignificant.

(1) W. D. Harkins, G. Jura and E. H. Loeser, THIS JOURNAL, **68**, 554 (1946).

(2) W. D. Harkins and G. Jura, *ibid.*, **66**, 919 (1944).

III. Experimental Results

The heat of emersion of graphite as a function of the amount of water adsorbed (molecules per sq. cm.) is exhibited in Fig. 1. Each value listed in Table I is the average of either two or three determinations, usually three. The table gives also the number of determinations and the average deviation of each determination. From this table it is possible to calculate all the heat values given.

Unfortunately, the results are not very precise, due to (1) low area coupled with small heat effects per unit area, and (2) difficulty of dispersion. The absolute error in a single determination is about twice that of Harkins and Jura[2] in their cor-

TABLE I

THE HEAT OF EMERSION OF GRAPHITE FROM WATER AT 25°, AND THE INTEGRAL HEAT OF DESORPTION OF WATER FROM GRAPHITE AT 25°, AS A FUNCTION OF THE AMOUNT OF ADSORBED WATER

Cc. H_2O (S. T. P.) adsorbed per g.	No. molecules per sq. cm. ($\times 10^{14}$)	$h_{E(SfL)}$ ergs cm.$^{-2}$	$h_{D(VS)}$ ergs cm.$^{-2}$	Number of detns.
0.0000	0	167 ± 3	0	5
.00728	0.046	82 ± 16	89.4	2
.0332	.211	65 ± 7	118.6	2
.0625	.398	58 ± 11	138.7	3
.1450	.923	− 62 ± 54	297.2	2
.2192	1.396	− 73 ± 12	342.0	2
.2820	1.796	−132 ± 29	430.1	3
.3882	2.472	− 32 ± 45	379.8	3
.4970	3.165	− 15 ± 20	413.3	3
1.111	7.076	8 ± 14	675.4	3
1.471	9.369	− 9 ± 23	858.6	3
1.754	11.171	32 ± 11	949.0	2
1.978	12.598	49 ± 11	1035.7	2
2.134	13.591	− 88 ± 47	1245.0	3
2.288	14.572	− 37 ± 47	1265.3	3
2.325	14.807	− 99 ± 42	1345.0	3
2.484	15.820	− 95 ± 52	1414.2	3
2.741	17.457	− 89 ± 56	1527.9	3
3.260	20.762	− 94 ± 44	1773.4	3
4.220	26.876	−124 ± 55	2249.0	3
4.652	29.628	− 62 ± 62	2386.9	3

responding determinations with titanium dioxide of area 13.8 sq. m. g.$^{-1}$. In order to obtain much more precise values, a calorimeter with an increased sensitivity by a factor of 10 would be essential. The present results, however, are the best that can be obtained with our present equipment. Fortunately, many of the changes in energy are so large that certain conclusions can be drawn.

Figure 1 exhibits two points of interest: (1) the heats of emersion are negative when the amount of water adsorbed per gram is between 0.5 × 10^{14} and 7.0 × 10^{14} molecules per sq. cm. and also for all values above 13.5 × 10^{14} molecules per sq. cm.; and (2) there are two discontinuities in the values of the heat of emersion, the first between 1.8 × 10^{14} and 2.5 ×^{14} and the second between 12.6 × 10^{14} and 13.6 × 10^{14} molecules per sq. cm. The first of these is important, since, insofar as is known to the writers, this is the first case in which heat has been found to be absorbed in the process of immersion of a solid. In other later work it was found also that when a sample of clean silver sulfide is immersed in *n*-heptane at 25° heat is absorbed. The detailed set of data for this and other systems will be presented in a later paper.

The general position of the two discontinuities in the heat of emersion corresponds to those in the derivative of the volume with respect to the pressure in the adsorption isotherm. Jura, Loeser, Basford and Harkins[3] have shown that if a second order phase transition occurs there is finite discontinuity in $(\partial v/\partial p)_{T,\Sigma}$. If there is a finite discontinuity in this derivative, it can be shown that there should also be a finite discontinuity in the heat of emersion. Similarly, for a first-order change, the heat of emersion is independent of the amount adsorbed for those values of the amount adsorbed over which the transition occurs. For a third order change there is a finite discontinuity in the derivative of the heat of emersion with respect to the amount adsorbed. Thus, the behavior of the heat of emersion can be used as a criterion for a phase change of the second or third order. The effect of temperature on isotherms in the region of a first order change is so striking that there can be no reasonable doubt of the phenomenon. In the vicinity of second order changes the experimental problem is more exacting, since it is necessary to prove the existence of a discontinuity in the derivative.

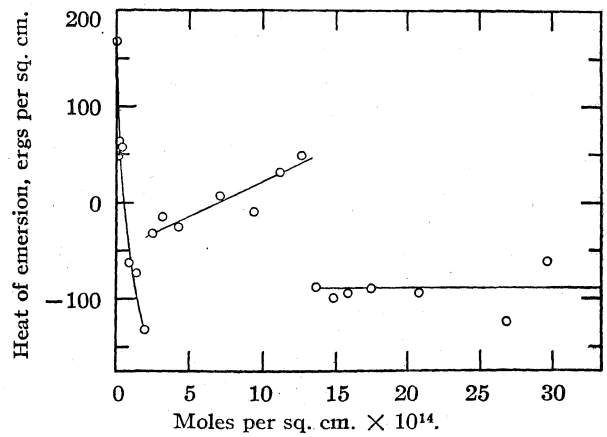


Fig. 1.—The heat of emersion of graphite, with various amounts of water adsorbed in its surface from water at 25°.

However, for the water–graphite system discussed in this paper, the discontinuities in the derivative are supported by a directly measured discontinuity in the heat functions. For the adsorption of water on graphite the discontinuities in the adsorption isotherm are so small that their existence was not entirely certain until the discontinuities in the heats were found. The isotherm is shown in Fig. 2. In this respect the discontinuities found here differ from those previously reported by the writers. Those discontinuities reported earlier were so large that the isotherm was sufficient to establish their existence without doubt.

One of these discontinuities occurs in the monomolecular film at *ca.* 56 Å.^{2} per molecule, but the second does not appear until the film becomes polymolecular at *ca.* 7.5 Å.^{2} per molecule. (The area occupied by a water molecule at 25° is at least 10.6 Å.^{2} in a monolayer.) The regions of the discontinuities in this isotherm are shown on an expanded scale in Fig. 3. The chord-area method

(3) G. Jura, E. H. Loeser, P. R. Basford and W. D. Harkins, *J. Chem. Phys.*, **14**, 117 (1946).

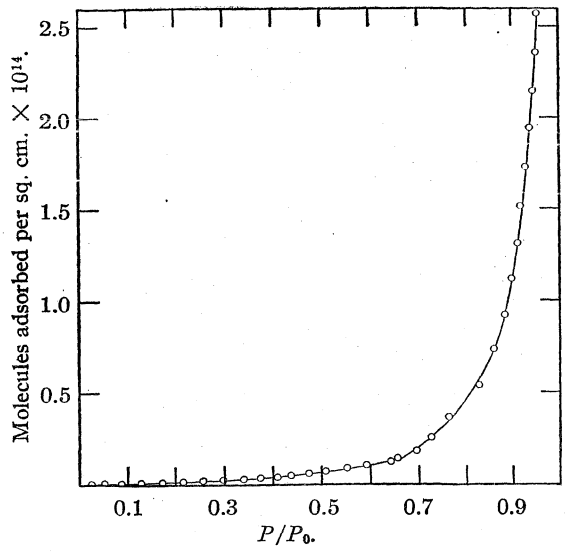


Fig. 2.—Isotherm of adsorption of water on graphite at 25°.

was used to obtain the derivative, $(\partial v/\partial p)_{T,\Sigma}$. This is shown in Fig. 4.

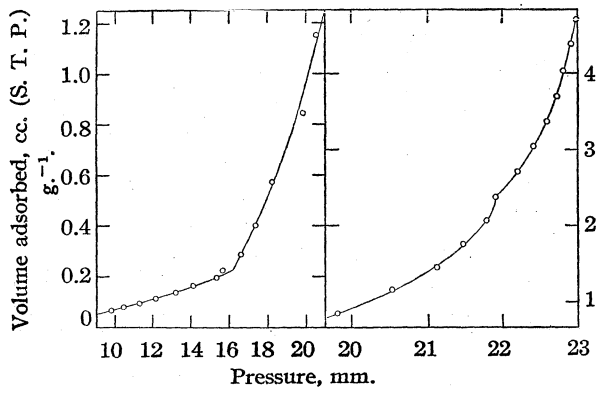


Fig. 3.—Discontinuities in the adsorption isotherm of water on graphite at 25°.

The values of the derivative, $(\partial v/\partial p)_{T,\Sigma}$, and of the heat of emersion, $h_{E(S/L)}$, are shown plotted

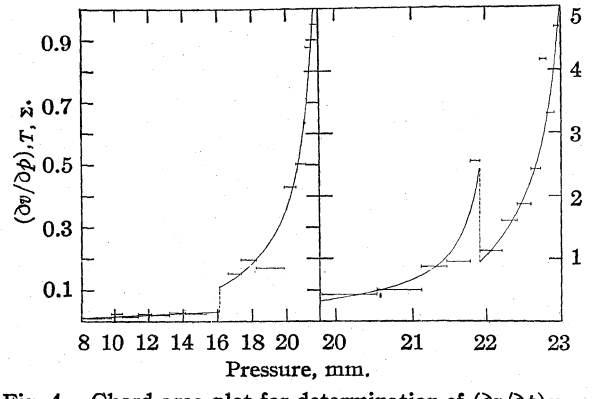


Fig. 4.—Chord area plot for determination of $(\partial v/\partial p)_{T,\Sigma}$, in the region of the discontinuities.

against the number of molecules per sq. cm. in Fig. 5. Both quantities show discontinuities at substantially the same points.

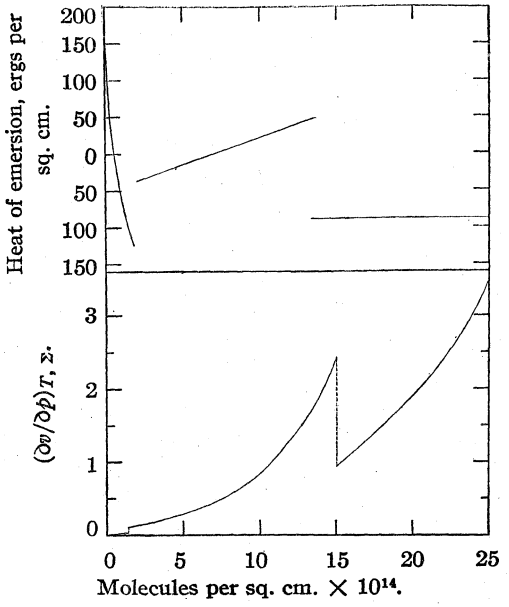


Fig. 5.—The discontinuities in the heat of emersion and in $(\partial v/\partial p)_{T,\Sigma}$.

In addition to the work on water, the heats of emersion from benzene and *n*-heptane of the graphites of 0.004 and 0.46% of ash were determined. These values and those of Harkins and Boyd[4] for a sample of graphite containing 10% ash are listed in Table II.

TABLE II

THE HEATS OF EMERSION OF GRAPHITE FROM LIQUIDS (ERGS CM.$^{-2}$ AT 25°)

Graphite	Water	Benzene	*n*-Heptane
10% ash	265	225	.....
0.46% ash	225 ± 8	147 ± 10	167 ± 10
Less than 0.004% ash	167 ± 3	163 ± 2	146 ± 10

The values indicate that the heat of emersion is highly dependent on the ash content of the graphite. These differences do not seem to be explained by the assumption that a certain fraction of the surface is ash and the remainder is graphite.

In the case of the graphite with 0.46% ash the heat of emersion was determined also in undried benzene. The value found was 219 ± 16 ergs cm.$^{-2}$, while with thoroughly dried benzene it was 147 ± 10 ergs cm.$^{-2}$ (*cf.* 225 ± 8 for water). This indicates that when working with non-polar solids, it is essential to dry even hydrocarbons if correct results are to be obtained.

The absolute method for the determination of area[5] was applied to the graphite of less than 0.004% ash by saturating the powder with *n*-hep-

(4) W. D. Harkins and G. E. Boyd, THIS JOURNAL, **64**, 1195 (1942).

(5) W. D. Harkins and G. Jura, *ibid.*, **66**, 1362 (1944).

tane. The area of the particles covered with the film was found to be 4.6 ± 0.6 sq. m. g.$^{-1}$. For graphite the geometry of the individual particles is not well enough known to correct this figure exactly for the additional area due to the film. If the graphite particles were cubes, the area of the sample would be 4.1 sq. m. g.$^{-1}$, while if they were rectangular parallelopipeds whose dimensions are in the ratio of 10–10–1 the area would be 4.4 sq. m. per gram, and if these dimensions are 100–100–1 the correction is negligibly small. Actually, the particles are thin flakes, so a ratio of 10-10-1 (*i. e.*, $\Sigma = 4.4 \pm 0.6$ sq. m. g.$^{-1}$) is the best that can be estimated. The areas determined by the adsorption of nitrogen, *n*-heptane, and *n*-hexane vary from 4.06 to 4.42 sq. m. g.$^{-1}$, depending on the gas and on whether the relative method of Harkins and Jura[6] or the theory of Brunauer, Emmett and Teller[7] is used. From the available data it is not possible to decide which of the areas determined by adsorption is the correct one, so the weighted average, 4.22 sq. m. g.$^{-1}$ was used. The good agreement between the area as determined by the absolute method and those obtained by adsorption indicates that the sample is non-porous and that capillary condensation need not be considered. If an appreciable fraction of the area were in small pores, the area determined by the absolute method would be less than those by adsorption. Since this is not the case, the solid may be considered to be non-porous.

Figure 6 exhibits the integral heat of desorption of water vapor at 25° from the low ash content graphite. The values were calculated from the data for the heat of emersion by the relationship

$$h_{D(VS)} = h_{E(SL)} - h_{E(SfL)} + n\lambda \qquad (1)$$

where $h_{E(SL)}$ is the heat of emersion of the clean solid from water, $h_{E(SfL)}$, is equal to $-h_{I(SfL)}$ when n moles is adsorbed per sq. cm., and λ is the heat of condensation, 10,480 cal. mole^{-1}. Table I includes the values of $h_{D(VS)}$ so calculated. The two discontinuities correspond to those in the heat of emersion. The data on adsorption available to the writers indicate that these discontinuities are quite common when a sufficiently detailed investigation is made of the heat of adsorption.

The differential heat of adsorption in calories per mole of water is equal to 1.463×10^{16} times the slope of the curve in Fig. 6. It decreases from approximately 100,000 cal. mole^{-1} when 4.65×10^{12} molecules are adsorbed per sq. cm. to 30,000 cal. mole^{-1} at 1.80×10^{14} molecules per sq. cm. When the amount of water adsorbed is between 2.47 and 12.60×10^{14} molecules per sq. cm., the heat is constant, within the limits of the large experimental error, at 9,100 cal. mole^{-1}. Above 13.59×10^{14} molecules adsorbed per sq. cm. the heat is again constant and equal to 10,500 cal. mole^{-1}, which is equal to the heat of condensation. Of these results the high values exhibited by the differential heat of adsorption below 1.80×10^{14} molecules per sq. cm. are not understood at the present time.

(6) W. D. Harkins and G. Jura, THIS JOURNAL, **66**, 1366 (1944).

(7) S. Brunauer, P. H. Emmett and E. Teller, *ibid.*, **60**, 309 (1938).

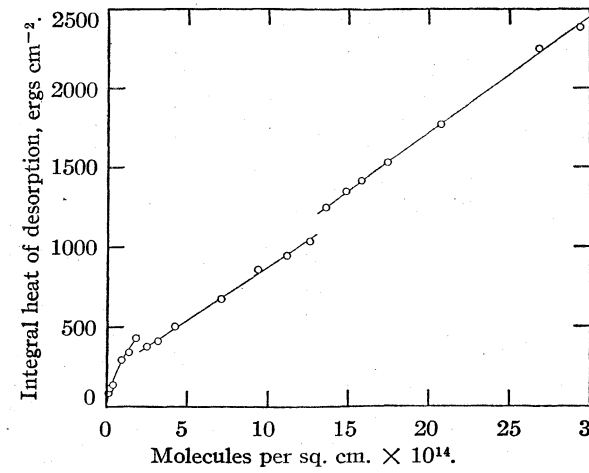


Fig. 6.—The integral heat of desorption of water from graphite in ergs per sq. cm.

There is no precedent in the literature for such high values for the heat of adsorption when physical adsorption is involved. However, to the knowledge of the writers, no data are available in the literature when so few molecules are present on the surface. Analogous results in the very low pressure region have been obtained with water and titanium dioxide. Until more data are available, it is not possible to give any explanation of the seemingly unreasonably high values. The amount of ash is too small to be responsible. The remainder of the values are in complete accord with results which have been obtained when water is adsorbed on charcoal.

Figure 7 shows the change in total surface energy, free surface energy, and the product of the temperature and entropy as a function of the amount of water adsorbed. In this system, in that of water–titanium dioxide, as well as in previously reported systems, the greatest contribution to the heat evolved arises from the entropy rather than from the free energy. The discontinuities in the derivative of the free energy do not show on the scale of Fig. 7.

IV. Discussion

The film of water on graphite exhibits certain relations which are difficult to understand. The results of the calorimetric and adsorption determinations in this and the preceding paper are not sufficient for this purpose. It is probable, before a more complete understanding is possible, that (1) other graphites and other solids which exhibit a similar behavior must be investigated, (2) the precision of the measurements, especially those of the heat involved, must be increased, and (3) experimental procedures other than those used thus far must be used.

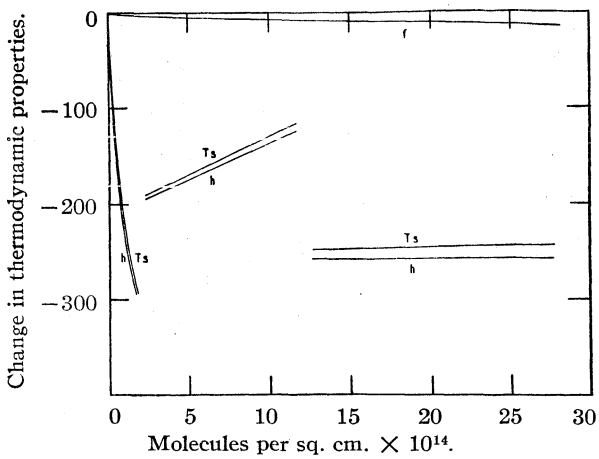


Fig. 7.—The decrease of free surface energy (f), of total surface energy (h), and of the product, temperature times surface entropy (Ts), as a function of the amount of water adsorbed. The uppermost curve is the decrease of free surface energy; this accounts for relatively little of the total surface energy. The two curves to the left below (h below Ts above) very nearly coincide. In the remaining two sets of curves, h is in both cases below and Ts above. All curves are drawn to the same scale.

The two experimental facts which lead to the greatest difficulty are (1) the film is polymolecular at high vapor pressures, and (2) the contact angle is not zero. Unfortunately, the thickness of the film cannot be determined with any certainty. This difficulty arises on account of the fact that there is no reliable estimate of the number of molecules required to form a monomolecular layer. The only method for obtaining this quantity lies in the theory of Brunauer, Emmett and Teller,[7] which, as indicated below, does not seem to be applicable to this case.

Although the simple two-constant equation of this theory apparently reproduces well the experimental data from $p/p_0 = 0.1$ to $p/p_0 = 0.35$, the value of v_m (0.3 cc. g.$^{-1}$) is such that the effective area of the water molecule obtained is 52 Å.^{2} per molecule, or five times that which would be expected for a closely packed monolayer. Though a loosely packed film would not be unexpected, the actual number of molecules required to form a monolayer would seem to be greater than corresponds to this value. Thus, the BET theory does not seem to be applicable. Second, the value of c is less than unity, which means that $E_1 - E_L < 0$. Actually, as is shown later, $E_1 - E_L > 0$, and is over 2300 cal. mole^{-1}. Thus, it appears that *in this particular case* the theory fails. The failure is probably due to the fact that the agreement between theory and experiment in the region $p/p_0 =$ 0.1 to 0.35 is fortuitous, since, at relative pressures above 0.4, $p/v(p_0 - p)$ actually decreases with an increase in p/p_0. This behavior is unusual.

If it is assumed that the water molecules form a tightly packed film, v_m must equal 1.49 cc. g.$^{-1}$ and the average thickness of the film at a relative pressure of 0.985 would be 3 v_m, or about 10 Å. The extrapolation of the observed isotherm to $p/p_0 =$ 1 gives as the thickness about 5 v_m, or 17 Å. Thus, the minimum estimated thickness of the film is 10 Å., but it is more probable that it is 16 Å. On the basis of the theory of Brunauer, Emmett and Teller (v_m = 0.3 cc.) the calculated minimum thickness of the film would be about 50 Å., and probably 83 Å. The value of the contact angle for water–graphite is discussed in an earlier paper.[1]

The fact that the contact angle is not zero indicates that the film is non-duplex, which in turn signifies that in the outermost layer of the film the water molecules do not assume the packing and orientation that exists in the surface of liquid water. If the film were only monomolecular, this state would be understandable and expected. It is difficult to conceive, however, how the effect of the surface can be sufficiently marked at a distance of at least three molecular diameters, and probably more, to affect seriously the packing and orientation of the water molecules.

The available evidence indicates the existence of a polymolecular non-duplex film, a type of film postulated by Harkins.[8] If future work should show that this class of film exists, then this film of water on graphite is the first member of this class to be found.

Thermodynamically, there is no question as to the self-consistency of the available data. This can be shown in the following manner. For the formation of a duplex film it is necessary that

$$\gamma_S - \gamma_{SL} \geqq \gamma_L \qquad (2)$$

while the condition that a duplex film cannot be stable is[9]

$$\gamma_S - \gamma_{SL} < \gamma_L \qquad (3)$$

If the inequalities are combined with the relation

$$\gamma_{Se} = \gamma_{SL} + \gamma_L \cos\vartheta \qquad (4)$$

it is found, if inequality (2) holds for the system under discussion, that

$$\pi_e \geqq \gamma_L (1 - \cos\vartheta) \qquad (5)$$

while if a duplex film cannot be formed

$$\pi_e < \gamma_L (1 - \cos\vartheta) \qquad (6)$$

It is inequality (6) which is of interest. The question is, can π_e have a value less than a pre-assigned positive value for a film of a given thickness. It is possible for the following reasons. π_e is given by the integration of the Gibbs adsorption equation, as suggested by Bangham.[10,11,12] The equation is

$$\pi_e = \frac{RT}{V_M \Sigma} \int_0^{p_0} \frac{v}{p}\, dp \qquad (7)$$

$$\pi_e = \frac{RTp_0}{V_M \Sigma} \left(\frac{v}{p}\right)_{\text{Average}} \qquad (8)$$

(8) W. D. Harkins, in J. Alexander, "Colloid Chemistry," Reinhold Publishing Corp., New York, N. Y., 1945, p. 12.

(9) W. D. Harkins, *J. Chem. Phys.*, **9**, 552 (1941).

(10) D. H. Bangham, *Trans. Faraday Soc.*, **33**, 805 (1937).

(11) D. H. Bangham and R. I. Razouk, *ibid.*, **33**, 1463 (1937).

(12) D. H. Bangham and R. I. Razouk, *Proc. Roy. Soc.* (*London*), **A166**, 572 (1938).

From eq. (8) it is apparent that, even if the values of π_e and the volume of gas adsorbed at saturation are fixed, then, mathematically it is possible to construct an infinite number of isotherms so that eq. (8) is satisfied. The only general statement is that for a given π_e, the larger the value of the volume adsorbed at saturation, the smaller must be the volume adsorbed at low pressures. Whether or not any of these mathematically possible isotherms exist physically can be determined only by experiment. The results of the adsorption of water on graphite indicate that such a case actually occurs.

The preceding paragraphs show also that, from the thermodynamic standpoint, the thickness of the adsorbed film does not determine whether or not the contact angle is zero or greater than zero. The physical evidence also indicates that the film thickness of itself does not determine the contact angle.

The only point upon which there might be a reasonable doubt is the value of the contact angle of water against graphite, but even here all the evidence is that the angle is not zero. The actual determinations of this quantity are discussed in the earlier paper.[1] The present calorimetric data also indicate a contact angle greater than zero. If the contact angle were zero over a small temperature region within which the measurements are made, the heat of emersion at $p/p_0 = 1.0$ would be 119 ergs cm.$^{-2}$. At $p/p_0 = 0.985$ this quantity is -86 ergs cm.$^{-2}$ and is apparently not increasing with p/p_0. To judge from the behavior of the heat of emersion up to a relative pressure of 0.985, another phase transition would be essential if the heat of emersion is to become that characteristic of a zero contact angle. Experimental difficulties encountered in this region preclude any definite statement as to this possibility.

It would be of interest to estimate the decrease of the energy of interaction of the solid as the film thickness increases, but the observed data are not sufficiently accurate to do this quantitatively. The uncertainty in the amount of gas adsorbed in a single layer is even more serious. If it is assumed, as a rough approximation, that the water molecules have an effective cross-sectional area of 10.6 Å.^{2}, *i. e.*, that the film is tightly packed, the energy of interaction between the solid and the first V_m adsorbed is a maximum. If it is also assumed that the second and third layers have the same packing, then the average energy in excess of condensation for the adsorption of the first v_m is 2300 cal. mole^{-1}; for the second, 1500 cal. mole^{-1}; and for the third, zero cal. mole^{-1}. These figures are obtained from Fig. 6 by dividing the appropriate value of $h_{D(VS)}$ by the number of molecules per sq. cm., multiplying by 1.423×10^{16} and subtracting λ (*i. e.*, 10,480 cal. mole^{-1}). Since none of these is very large compared with RT (RT = 600 cal. per mole) it is evident that even the first layer is not nearly complete before an appreciable number of molecules are adsorbed in the second and higher layers. Under these conditions, the 2300 cal. per mole calculated for the first layer must be too low, since many of the molecules included are in the second and higher layers, with lower interaction energies. The figures for the second and third layers must be similarly revised.

Neither the data nor the assumptions about the number of molecules in a monolayer are good enough to attempt to determine $E_1 - E_L$ to any degree of accuracy. The values of 2700, 1300 and -150 cal. mole^{-1} for $E_1 - E_L$, $E_2 - E_L$ and $E_3 - E_L$ approximate the observed values moderately well if the usual assumption is made of a Boltzmann distribution between the layers. Another difficulty with this simple treatment is that the heat must be a continuous function of the amount adsorbed. This is contrary to the experimental results. Even in this respect any simple approach is precluded. It is evident that no analysis based on the simplified theories now available is capable of explaining the observed facts.

Summary

1. The heat of emersion (h_e) from water of a graphite of specific area = 4.22 sq. m. g.$^{-1}$ and of ash content less than 0.004%, presumably free from any oxygen complex, was determined as a function of the amount of water adsorbed on the surface. For the clean graphite (h_e) is 167 ergs cm.$^{-2}$, decreasing to -132 ergs cm.$^{-2}$ when 1.80×10^{14} molecules of water are adsorbed per sq. cm. From 2.47×10^{14} to 12.60×10^{14} molecules per sq. cm. the heat of emersion increases from -32 to $+49$ ergs cm.$^{-2}$. From 13.59 to 29.63×10^{14} molecules adsorbed per sq. cm. the value, within a large experimental error, is constant at -84 erg cm.$^{-2}$.

2. There are two finite discontinuities in the heat of emersion. These discontinuities coincide with two discontinuities in the derivative of the volume with respect to the pressure in the isotherm. Either of the above is sufficient to show that a second order phase change occurs in the film formed by adsorption. The actual determination of both discontinuities is the best evidence which can be obtained for this type of phase change.

3. For the first time negative heats of emersion have been obtained.

4. The area of the solid was determined by the use of the *absolute* method of Harkins and Jura, using *n*-heptane at 25°. The area obtained was 4.4 ± 0.6 sq. m. g.$^{-1}$. This agrees with the area determined by adsorption (4.06 to 4.42 sq. m. g.$^{-1}$). Since the absolute method gives the value at saturation, and adsorption at low relative pressures, it is evident that capillary condensation is negligibly small.

5. From the amount of water adsorbed as determined from the isotherm, the area of the solid,

and the fact that capillary condensation is negligible, it is shown that the film of water on graphite attains a minimum thickness of 10 Å. at a relative pressure very close to saturation. The extrapolation of the isotherm to unit relative pressure indicates a minimum thickness of 16 Å. These figures are obtained on the postulate that the density of the adsorbed material is that of the liquid at the same temperature. The physical relations indicate that the packing must be looser than in the liquid. Consequently, the figures quoted are to be considered minima and not a reliable estimate of the true thickness.

6. It is shown thermodynamically that the film can be polymolecular with a contact angle not equal to zero. It is also pointed out that this situation leads to a difficult problem in the construction of a model compatible with both conditions.

7. It is shown that $E_1 - E_L > 0$, $E_2 - E_L > 0$ and $E_3 - E_L < 0$.

8. The integral and differential heats of adsorption of water on graphite are determined from the heats of emersion.

9. The heats of emersion are used to determine the change in total surface energy caused by the adsorption of water. These values combined with the free surface energy changes as determined from the adsorption isotherm permit the calculation of the change in surface entropy.

CHICAGO, ILLINOIS RECEIVED AUGUST 11, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Synthesis of DL-Methionine

BY EARL PIERSON, MARIO GIELLA[1] AND MAX TISHLER

Consideration of the various syntheses of methionine indicates that the first recorded synthesis, that of Barger and Coyne,[2] using β-methylmercaptopropionaldehyde, is the most direct in approach. The over-all yield of about six per cent. by the modified Strecker reaction and the difficulty in obtaining the required aldehyde discouraged the use and the further development of this synthesis.

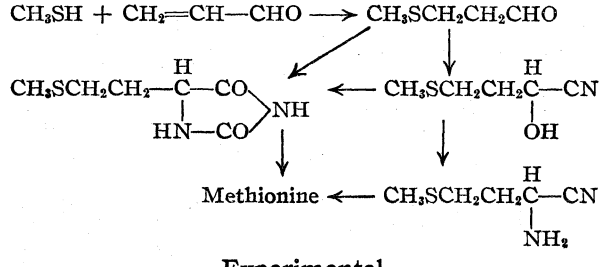
With the recent availability of commercial acrolein, and the reports that β-methylmercaptopropionaldehyde has been prepared from acrolein and methylmercaptan,[3] the development of a practical synthesis of methionine became of interest.

Catch and his collaborators[4] recently prepared methionine from acrolein and methyl mercaptan in 29% yield by a modified Strecker reaction employing liquid hydrogen cyanide. We have also prepared methionine in about the same over-all yield (25%) by the Strecker reaction without resorting to the use of liquid hydrogen cyanide. Further improvement was observed using the well-known Bücherer hydantoin synthesis, whereby an over-all yield of 50% was obtained.

It was found that methyl mercaptan adds smoothly to acrolein at atmospheric pressure when the reaction is catalyzed by a small amount of copper methyl mercaptide.[5]

The conversion of β-methylmercaptopropionaldehyde into 5-(β-methylmercaptoethyl)-hydantoin was accomplished by the usual Bücherer procedure and also by transformation into the cyanohydrin followed by treatment with ammonium carbonate.

The hydrolysis of the hydantoin to methionine was effected by concentrated hydrochloric acid at 135°, by ammonium sulfide solution at 135°, and by aqueous sodium hydroxide at 100°. The routes investigated are indicated.



Experimental

1. **β-Methylmercaptopropionaldehyde.**—Gaseous methyl mercaptan, 48 g., 1.0 mole, was bubbled during the course of thirty minutes under the surface of a cooled, stirred mixture of 56 g. (1.0 mole) of acrolein and 0.5 g. of cupric acetate, while the internal temperature was maintained at 35–40°. The mixture was agitated for an hour and distilled under reduced pressure giving β-methylmercaptopropionaldehyde, 87 g., 84%; boiling 52–54° (11 mm.), $n^{20}D$ 1.4850, d_{20} 1.036; MR_D (calcd.) 28.4, found 28.7. The undistilled aldehyde is sufficiently pure for use in the reactions described below.

The 2,4-dinitrophenylhydrazone was prepared in the conventional manner, m. p. 116–119°.

Anal. Calcd. for $C_{10}H_{12}O_4N_4S$: C, 42.45; H, 4.26; N, 19.70. Found: C, 42.23; H, 4.20; N, 19.61.

2. **α-Hydroxy-β-methylmercaptobutyronitrile.**—β-Methylmercaptopropionaldehyde, 10.4 g., 0.10 mole, was shaken for ten minutes with a solution of 10.4 g., 0.10 mole, of sodium bisulfite in 35 ml. of water. A substantial amount of the adduct crystallized upon cooling to room temperature. A solution of 4.9 g., 0.10 mole, of sodium cyanide in 15 ml. of water was added in three portions, without permitting the temperature to exceed 35°. The oil that separated immediately was extracted

(1) Present address: A. C. Lawrence Leather Company, Peabody, Mass.

(2) Barger and Coyne, *Biochem. J.*, **22**, 1417 (1928).

(3) Kaneko and Mii, *J. Chem. Soc. Japan*, **59**, 1382 (1938); Rothstein, *J. Chem. Soc.*, 1560 (1940).

(4) Catch, Cook, Graham and Heilbron, *Nature*, **159**, 578 (1947).

(5) The English investigators[4] used a tertiary amine as a catalyst.

three times with benzene; the combined benzene extracts were extracted with sodium bisulfite solution and then the solvent was removed under reduced pressure. The crude cyanohydrin was thus obtained as a colorless oil weighing 11.8 g. (90%). For analyses, a small sample of this product was distilled at 100° under a pressure of three microns.

Anal. Calcd. for C_5H_9NOS: C, 45.8; H, 6.87; N, 10.68. Found: C, 46.0; H, 6.88; N, 10.49.

3. 5(β-Methylmercaptoethyl)-hydantoin. A. From β-Methylmercaptopropionaldehyde.—A mixture of 26 g. (0.25 mole) of β-methylmercaptopropionaldehyde, 113 g. (1.17 moles) of finely divided ammonium carbonate, 24.5 g. (0.5 mole) of sodium cyanide, 335 ml. of ethanol and 335 ml. of water was agitated and heated for four hours at 50–55°. The light yellow reaction mixture was filtered, and the filtrate was concentrated at 60° to a volume of 300 ml., acidified with 50 ml. of concentrated hydrochloric acid and heated for five minutes at 90° to cyclize the hydantoic acid, which was found to be present in small amounts. After crystallization, separation and drying, the hydantoin weighed 34 g. (79% yield) and melted at 103–105°. The melting point remained unchanged after recrystallization from ethanol.

Anal. Calcd. for $C_6H_{10}O_2N_2S$: C, 41.38; H, 5.74. Found: C, 41.36; H, 5.81.

B. From α-Hydroxy-γ-methylmercaptobutyronitrile.—The cyanohydrin was prepared by the method given previously from 2.0 moles of the aldehyde. Removal of the benzene solvent left 255 g. of crude cyanohydrin, which was converted into the hydantoin, 174 g. (50% yield based on β-methylmercaptopropionaldehyde), by reaction with 420 g. of ammonium carbonate in 1000 ml. of 50 volume per cent. methanol for two and one-half hours at 50–55°. The product was isolated by the procedure described above.

4. DL-Methionine. A. From the Hydantoin.—5-(β-Methylmercaptoethyl)-hydantoin, 17.4 g. (0.10 mole) was refluxed for six hours with a solution of 8.8 g. of sodium hydroxide in 75 ml. of water contained in a stainless steel flask; an additional 4.4 g. of sodium hydroxide was added, and refluxing was continued for a total of twenty-four hours. The reaction mixture was decolorized with Norit, neutralized to litmus with concentrated hydrochloric acid, and allowed to crystallize at 5°. The product weighed 10.8 g. (73.5%); m. p. 269° with decomposition. An additional 1.7 g. (11%) of material could be isolated by a procedure involving acidification (hydrochloric acid), concentration to dryness, extraction with ethanol, and neutralization of the filtered ethanol extract to Congo with pyridine. After recrystallization of the combined fractions from aqueous ethanol, 10.6 g. of analytically pure methionine was obtained.

By omitting the isolation of both the β-methylmercaptopropionaldehyde and 5-(β-methylmercapto)-hydantoin, pure methionine was obtained in 50% yield based on the charge of acrolein and methyl mercaptan.

B. From the Cyanohydrin.—Gaseous ammonia was passed into 123 g. (0.94 mole) of the stirred cyanohydrin, maintained at 60° for thirty minutes. The reaction mixture was dissolved in benzene, heated to expel excess ammonia, and extracted with dilute hydrochloric acid. The aqueous layer was made alkaline with ammonia water and extracted with benzene; evaporation of the solvent left 49 g. (40%) of crude methionine nitrile. Several futile attempts were made to purify this intermediate and to obtain a crystalline derivative. The crude aminonitrile (10 g.) was hydrolyzed by heating on the steam-bath for five and one-half hours with 20 ml. of concentrated hydrochloric acid. The reaction mixture was diluted with 50 ml. of water, decolorized with Darco, and the solution concentrated to dryness under vacuum. The resulting solid was extracted with hot ethanol, and the ethanolic solution was filtered and neutralized to Congo with pyridine. Methionine in 75% yield (8.5 g.) was obtained.

Summary

A three-step synthesis of methionine has been devised based on the catalyzed addition of methyl mercaptan to acrolein, followed by the Bücherer hydantoin reaction, and then by hydrolysis.

RAHWAY, NEW JERSEY RECEIVED NOVEMBER 7, 1947

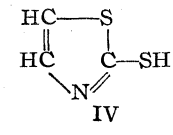
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE B. F. GOODRICH CO.]

A Synthesis of 2-Thiazolethiol and its Disulfide

BY ROGER A. MATHES AND ADOLPH J. BEBER

2-Thiazolethiols, particularly 2-mercaptobenzothiazole, have been used extensively for many years as accelerators for the vulcanization of rubber. The preparation of 2-thiazolethiol (IV), the parent compound of this series, recently has been reported[1] in the patent literature. This synthesis which was effected by treating α-chloroacetaldehyde (I) with ammonium dithiocarbamate (II), has been investigated by us in some detail and under varied conditions. The intermediate, formylmethyl dithiocarbamate (III), was isolated and characterized. The yield of IV was 50% based on I. The synthesis of IV is attended by troublesome side reactions, giving rise to gummy by-products, which apparently result from intermolecular reactions of aldehydes I and III with amino groupings in II and III. Acetaldehyde is known to react with II,[2] and I likewise reacts as a typical aldehyde.[3] Substituted 2-thiazolethiols,[4] on the other hand, can be prepared, usually in high yields,[4c] by the conventional reaction of α-halogen ketones with II. 1,2-Dichloroethyl ether which is known to replace I in thiazole syntheses[5] reacts with II to give a liquid of uncertain composition.[6]

$$\underset{\text{I}}{ClCH_2CHO} + \underset{\text{II}}{NH_2CSSNH_4} \longrightarrow \underset{\text{III}}{NH_2CSSCH_2CHO} \longrightarrow$$



IV

(1) Jones, U. S. Patent 2,426,397.

(2) Levi, *Gazz. chim. ital.*, **59**, 757 (1929).

(3) Natterer, *Monatsh.*, **3**, 442 (1882); Glinsky, *Z. Chemie*, N. F., **6**, 647 (1870).

(4) (a) Miolati, *Gazz. chim. ital.*, **23**, 575 (1893); (b) Levi, *ibid.*, **61**, 719 (1931); (c) Mathes, U. S. Patent 2,186,419.

(5) Traumann, *Ann.*, **249**, 36 (1888); Hantzsch, *ibid.*, **250**, 271 (1889).

(6) Mathes, U. S. Patent 2,411,219.

The preparation of the previously undisclosed disulfide, 2,2′-dithio-bis-thiazole (V), was effected using a number of oxidizing agents; the best of these, ammonium persulfate, gave a 93% yield.

Experimental

Formylmethyl Dithiocarbamate (III).—Fifty-eight grams (0.53 mole) of II was dissolved in a solution of 50 cc. of water and 20 cc. ethanol. While stirring this solution and maintaining the temperature at 20°, 43.8 g. (0.5 mole) of I was added in thirty minutes. An oily layer separated but quickly solidified as agitation was continued. After cooling to −3°, the product was recovered by filtration, and upon drying at room temperature, 47 g. (69% yield), melting at 101–103°, was obtained. As a considerable amount of gum precipitated in the filtrate, the recovery of more product was not attempted. After recrystallizing from water, III was obtained as colorless crystals melting at 110°.

Anal. Calcd. for $C_3H_5NOS_2$: C, 26.65; H, 3.73; N, 10.36; S, 47.43; mol. wt., 135. Found: C, 26.74; H, 3.78; N, 10.31; S, 47.51; mol. wt., 138.5.

2-Thiazolethiol (IV).—One hundred and twenty grams (1.1 moles) of II[7] was dissolved in 250 cc. of water and while stirring vigorously 87.5 g. (1 mole) of I dissolved in 150 cc. of ethanol was added rapidly. The temperature rose from 25 to 82° during this reaction. The water solution of the reaction mixture was decanted from a small amount of sticky, yellow gum and was transferred to an evaporating dish. The solution was evaporated at 50° almost to dryness and was then extracted with 200 cc. of chloroform. The chloroform solution, after evaporating to dryness, gave 95 g. of crude product which upon recrystallizing from water yielded 58 g. (50%) as colorless plates, melting at 79–80°.

Anal. Calcd. for $C_3H_3NS_2$: C, 30.75; H, 2.58; N, 11.95; S, 54.72; mol. wt., 117. Found: C, 30.82; H, 2.64; N, 11.88; S, 54.58; mol. wt., 115.5.

A sample of the gum formed in the reaction, after repeated extractions with hot water, gave positive qualitative tests for nitrogen and sulfur. The composition of the gum was not determined because its physical condition made purification difficult.

It was concluded from further experimental work that no improvement in yield is obtained when the following variations in reaction conditions are employed: reversal of the order of addition, length of time of addition, reaction temperatures of 0 to 50°, concentration of reactants, the absence of air and light, the control of *p*H and the use of organic solvents as reaction diluents.[8]

In an attempt to promote ring closure by the addition of sulfuric acid to the solution resulting from the initial interaction of I and II, a colorless, apparently amorphous product melting at 96–98° was precipitated. The composition of this compound was not determined but it slowly undergoes spontaneous decomposition to form IV in rather low yield (38%).

2,2′-Dithio-bis-thiazole (V).—One hundred and fifty-two grams (1.3 moles) of IV was dissolved in a solution of 500 cc. of water and 54.6 g. (1.35 moles) of sodium hydroxide. While vigorously stirring this solution, 163 g. (0.72 mole) of ammonium persulfate, dissolved in 500 cc. of water, was added in one hour at 8°. During the addition of ammonium persulfate, a crystalline solid precipitated. After stirring for thirty minutes, the product was recovered by filtration, washed with water and dried at room temperature to give 141 g. (93% yield), melting at 79–80°. After recrystallizing from *n*-hexane, the disulfide was obtained as fine, light yellow needles melting at 83°.

Anal. Calcd. for $C_6H_4N_2S_4$: C, 31.01; H, 1.74; N, 12.06; S, 55.19; mol. wt., 232. Found: C, 31.13; H, 1.79; N, 12.13; S, 55.27; mol. wt., 236.

The disulfide decomposed slowly on storage. A similar effect has previously been reported for 2,2′-dithio-bis-(4,5-dimethylthiazole).[9]

Summary

The synthesis of 2-thiazolethiol and its intermediate, formylmethyl dithiocarbamate, from the interaction of chloroacetaldehyde and ammonium dithiocarbamate has been described. The oxidation of 2-thiazolethiol, under mild conditions, is shown to proceed normally to give the disulfide, 2,2′-dithio-bis-thiazole.

(7) Mathes, U. S. Patent 2,117,619. Ammonium dithiocarbamate was prepared according to Example 2.

(8) In these experiments, chloroacetaldehyde was used both as the hemihydrate and as the anhydrous compound which was prepared by passing hot vapors of the hemihydrate over calcium chloride.

(9) Buchman, Reims and Sargent, *J. Org. Chem.*, **6**, 764 (1941).

AKRON, OHIO RECEIVED OCTOBER 6, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE B. F. GOODRICH CO.]

A Synthesis of 2-Pyrimidinethiols

BY ROGER A. MATHES, FLOYD D. STEWART AND FRANK SWEDISH, JR.[1]

In view of the usefulness of heterocyclic thiols as vulcanization accelerators, the authors had occasion to investigate 2-pyrimidinethiols. A new synthesis has been developed which simplifies the preparation, results in improved yields and extends the scope of former methods.

Methods previously employed to prepare 2-pyrimidinethiols include, among others, the interaction of 2-amino-2-methyl-4-pentanone (diacetonamine) and isothiocyanates[2] and the reaction of aliphatic ketones with ammonium thiocyanate.[3]

When mesityl oxide reacts with ammonium thiocyanate in the presence of a strong mineral acid, 2-methyl-2-thiocyano-4-pentanone[4] is formed. When this compound reacts with a primary amine or ammonia and an acid catalyst, a condensation takes place resulting in the formation of a 2-pyrimidinethiol. In the absence of an acid catalyst, ring closure is less readily effected and the intermediate thiourea is formed along with the 2-pyrimidimethiol.

$$(CH_3)_2C{=}CH{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3 + HCl + NH_4SCN \longrightarrow$$

(1) Present address: Marathon Corporation, Rothschild, Wis.

(2) Traube, *Ber.*, **27**, 279 (1894); Traube and Lorenz, *Ber.*, **32**, 3156 (1899).

(3) ter Horst, U. S. Patent 2,234,848, *ibid.*, **35**, 4242[8] (1941).

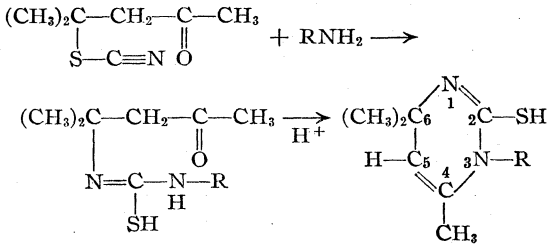
(4) Bruson, U. S. Patent 2,395,453, *ibid.*, **40**, 3467[1] (1946).

TABLE I

2-MERCAPTO-3-SUBSTITUTED-4,6,6-TRIMETHYLPYRIMIDINES

	R[a]	M. p., °C.[a]	Yield, %[b]	Formula	Calcd., % C	H	N	S	Mol. wt.	Found, % C	H	N	S	Mol. wt.
1	Hydro	254–255	90	$C_7H_{12}N_2S$	53.78	7.75	17.94	20.53		53.70	7.84	17.81	20.38	
2	*p*-Tolyl	191	83.5	$C_{14}H_{18}N_2S$	68.29	7.31	11.40	13.00	246	68.22	7.34	11.42	12.97	238
3	α-Naphthyl	216	87	$C_{17}H_{18}N_2S$	72.29	6.43	9.92	11.36	282	72.17	6.45	9.98	11.35	277
4	2-Hydroxyethyl[d]	180	54.5	$C_9H_{16}N_2OS$	53.96	8.05	13.99	16.01	200	54.01	8.05	14.08	16.07	197
5	Isopropyl[e]	267	27	$C_{10}H_{18}N_2S$	60.55	9.15	14.13	16.17	198	60.56	9.14	14.13	16.22	203
6	Cyclohexyl[f]	281–282	[f]	$C_{13}H_{22}N_2S$	65.49	9.30	11.76	13.45	238	65.45	9.28	11.82	13.46	238
7	1,3-Phenylene[g]	202	87	$C_{20}H_{26}N_4S_2$	62.12	6.78	14.50	16.60		62.05	6.77	14.56	16.57	
8	1,4-Phenylene	225	61	$C_{20}H_{26}N_4S_2$	62.12	6.78	14.50	16.60	386	61.76	6.92	14.49	16.64	384

[a] Melting points given are for analytical samples. [b] Yields are based on crude products. [c] Compounds 2, 3, 4, 7 were recrystallized from ethanol; 5, 6, 8 from chloroform; 1 from benzene. [d] During the preparation of this compound, the intermediate, 1-ethanol-3-[2-(2-methyl-4-pentanonyl)]-2-thiourea, was isolated. It melted at 144°. [e] In addition to this compound, 1-isopropyl-2-thiourea (m. p. 168–169°) was recovered from the reaction mixture. [f] This compound was recovered from the reaction mixture in low yield. The principal product of the reaction was 1-cyclohexyl-2-thiourea (m. p. 162°). [g] 1,3-Phenylene-bis-3,3′-(2-mercapto-4,6,6-trimethylpyrimidine).



This method of preparing 2-pyrimidinethiols from 2-methyl-2-thiocyano-4-pentanone and a primary amine or ammonia, in the presence of an acid catalyst, is of quite general application. It can be used successfully to prepare 2-pyrimidinethiols from mono and poly aromatic amines, alicyclic amines, aliphatic amines and hydroxy aliphatic amines. The reactions take place more readily and result in higher yields when aromatic amines are employed.

A second method was developed whereby the reaction can be carried out in one step, thus eliminating the initial preparation of 2-methyl-2-thiocyano-4-pentanone. In this modified procedure, acid is added to an agitated aqueous mixture of ammonium thiocyanate, mesityl oxide and a primary amine. Under the experimental conditions employed, this method was found to be applicable only to aromatic amines. Cyclohexylamine, isopropylamine, *n*-amylamine and ethanolamine were tried but in no case was a reaction product isolated. Apparently amines having dissociation constants greater than about 10^{-9} do not form 2-pyrimidinethiols in the modified procedure.

Experimental[5]

2-Methyl-2-thiocyano-4-pentanone.—Forty-nine grams (0.5 mole) of sulfuric acid dissolved in 50 ml. of water was added over a period of fifteen minutes to 98 g. (1 mole) of mesityl oxide at 15°. Seventy-six grams (1 mole) of ammonium thiocyanate dissolved in 100 ml. of water was added quite rapidly to this mixture at 20°. After stirring for fifteen minutes, the upper, red, oily layer was separated and was washed with water until free from acid. The crude product weighed 145 g., a yield of 92%. An analytical sample boiled at 97° (10 mm.), $n^{20}D$ 1.5030, d^{20}_{20} 1.0363.

Anal. Calcd. for $C_7H_{11}ONS$: C, 53.50; H, 7.00; N, 8.91; S, 20.38; mol. wt., 157. Found: C, 53.47; H, 7.06; N, 8.88; S, 20.30; mol. wt., 161.

The 2,4-dinitrophenylhydrazone derivative was prepared and when purified melted at 204°.

Anal. Calcd. for $C_{13}H_{15}O_4N_5S$: N, 20.77; S, 9.49. Found: N, 20.75; S, 9.45.

2-Mercapto-3-phenyl-4,6,6-trimethylpyrimidine—General Procedure.—A mixture of 78.5 g. (0.5 mole) of 2-methyl-2-thiocyano-4-pentanone, 46.5 g. (0.5 mole) of aniline, 2 g. (0.02 mole) of sulfuric acid and 150 ml. of water was agitated and warmed to refluxing temperature. The buff-colored crystalline product precipitated almost immediately. After cooling to room temperature, filtering, washing with water and drying, 96 g. (82.8% yield) of crude product melting at 188–190° resulted. On recrystallizing twice from alcohol, the melting point was 192–193°.

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.25; H, 6.90; N, 12.05; S, 13.80; mol. wt., 232. Found: C, 67.11; H, 6.98; N, 11.97; S, 13.84; mol. wt., 232.

3-*o*-Tolyl-2-mercapto-4,6,6-trimethylpyrimidine—Modified Procedure.—A mixture of 49 g. (0.5 mole) of mesityl oxide, 38 g. (0.5 mole) of ammonium thiocyanate, 53.5 g. (0.5 mole) of *o*-toluidine and 100 ml. of water was agitated in the reaction flask. Fifty-five grams (0.55 mole) of hydrochloric acid was added in ten minutes at a temperature of 20°. When heated to reflux, the buff-colored, crystalline product precipitated. After cooling to room temperature, filtering, washing with water and drying, 104.6 g. (85% yield) of crude product melting at 199–201° resulted. On recrystallizing twice from alcohol, the melting point was 202°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.29; H, 7.31; N, 11.40; S, 13.00; mol. wt., 246. Found: C, 68.08; H, 7.30; N, 11.41; S, 13.08; mol. wt., 253.

Summary

1. A new synthesis for 2-pyrimidinethiols, which consists of the reaction of 2-methyl-2-thiocyano-4-pentanone with primary amines, has been developed.

2. In a modified method it is shown that 3-aryl-2-pyrimidinethiols can be prepared in one step, with no evidence of the intermediate formation of 2-methyl-2-thiocyano-4-pentanone.

3. The preparation by these methods of ten representative compounds is described.

AKRON, OHIO RECEIVED DECEMBER 6, 1947

(5) The melting points given are uncorrected.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

A New Method for the Preparation of 17(α)-Hydroxy-20-ketopregnanes

BY LEWIS H. SARETT

Two methods[1,2] have been described for the fabrication of 17(α),21-dihydroxy-20-ketopregnanes.[3] Both of these methods suffer from the circumambience involved in total degradation of the sterol or bile acid side chain to a 17-ketone, followed by reassembly of the two carbon side chain. One of these processes comprises five steps, the other seven, with respective yields of about 3.5 and 5%. The present reaction series, however, employs 20-ketopregnanes as starting material and gives yields of 15 to 50%, depending on the nature of the other substituents in the molecule.

Pregnane-3(α)-ol-11,20-dione acetate (I) reacted with hydrogen cyanide in alcohol solution to give 60–80% of a crystalline cyanhydrin (V). The mother liquors consisted of somewhat lower melting crystals, which presumably contained the epimeric cyanhydrin. Some very interesting properties of the pure cyanhydrin and of the lower melting mixture were observed. While both were stable to hot alcohol, to alcohol–pyridine mixtures and to silver acetate in alcohol, they decomposed when eluted from chromatographic alumina. However, the nature of the products depended on how the alumina had been prepared. With acid-washed alumina, dehydration was the principal reaction. A small yield of a mixture of unsaturated nitriles was obtained. With alumina which had not been treated with acid and which therefore was, as is almost invariably the case, alkaline to phenolphthalein, loss of hydrogen cyanide occurred. About 90% of the parent ketone was recovered from the eluate.

The presence of the acetate group at C_3 was found to affect greatly the stability of the C_{20} cyanhydrin group. When pregnane-3(α)-ol-11,20-dione (II) was converted to the corresponding cyanhydrin (VI), the latter rapidly decomposed to the parent ketone in warm alcohol solution, with or without the addition of pyridine. It was, however, perfectly stable to dilute acetic acid and could be smoothly oxidized with chromic acid to the 3-keto derivative (IX). In this compound also the tendency to lose hydrogen cyanide in alcohol or alkaline alumina was marked. Even acid-washed alumina gave 40% of the 20-ketone, together with oily fractions representing dehydration or rearrangement products.

(1) Reichstein and von Euw, *Helv. Chim. Acta*, **23**, 1258 (1940); von Euw and Reichstein, *ibid.*, **24**, 1140 (1941).

(2) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(3) The stereochemical conventions used in this paper are based upon the recent findings of Gallagher and Long [*J. Biol. Chem.*, **162**, 495 (1946)], of Sorkin and Reichstein [*Helv. Chim. Acta*, **29**, 1218 (1946)] and of von Euw and Reichstein, *ibid.*, **30**, 205 (1947)]. The data presented in the last-mentioned contribution show that the configuration of the two carbon side chains in those naturally-occurring pregnane derivatives which bear a hydroxyl group at the 17 position is probably β.

The reactions of the cyanhydrins of 17-keto-steroids have been investigated by Butenandt and Schmidt–Thomé[4] who showed that they can be dehydrated with phosphorus oxychloride in pyridine at 150°. Upon testing the action of this agent with the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione acetate (V), it was found that the α,β unsaturated nitrile (XI) was produced very smoothly at room temperature. When the C_3 substituent was a keto group, however, the more facile loss of hydrogen cyanide from the cyanhydrin group reflected an increased difficulty in the dehydration reaction. Thus, the 20-cyanhydrin of pregnane-3,11,20-trione (IX) gave only 20% of the unsaturated nitrile (XII). Accompanying, XII, however, there was a considerable quantity of a lower melting mixture, consisting apparently of isomeric nitriles or rearrangement products. When the dehydration of the cyanhydrins was effected by boron trifluoride or acid-washed alumina, similar mixtures, from which no pure compound was isolable, were obtained.

The reaction of the unsaturated XI and XII with osmium tetroxide in benzene was extremely slow, as would be predicted from the presence of the negative cyano group attached to the ethylene linkage. However, a small amount of pyridine[5] accelerated the addition so that formation of the osmate was complete in a few hours. Hydrolysis of the osmate ester proceeded smoothly with sodium sulfite at room temperature but the corresponding 17,20-dihydroxy-20-cyano-pregnane (XVII) could not be isolated. The 17(α)-hydroxy-20-ketopregnane derived from it by loss of hydrogen cyanide was indeed the only product. This result is in accord with the previously mentioned instability of 3-hydroxy- and 3-keto-20-cyanhydrins, but it is mildly surprising that the 17(α)-hydroxy-20-ketones are stable in the decidedly alkaline (*p*H 10) hydrolysis medium.

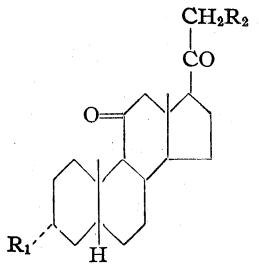
From Δ^{17}-20-cyanopregnene-3,11-dione (XII), pregnane-17(α)ol-3,11,20-trione (XX) was obtained. The latter was identical with the previously described oltrione obtained by oxidation of a pregnane-17,20-diol-3,11-dione.[6] Hence this dioldione also belongs in the 17(α)-hydroxy series. Δ^{17}-20-Cyanopregnene-3(α)-ol-11-one acetate (XI) gave upon hydroxylation a mixture of pregnane-3(α),17(α)-diol-11,20-dione (XVIII) and its 3-acetate (XIX). That the 17-hydroxyl in XVIII and XIX is α was demonstrated by oxidation of XVIII to XX.

The addition of a 21-acetoxy group to the 20-

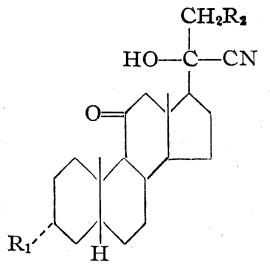
(4) Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

(5) Criegee, Marchand and Wannowius, *Ann.*, **550**, 99 (1942).

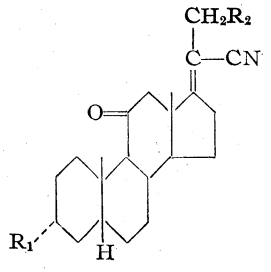
(6) Sarett, THIS JOURNAL, **68**, 2478 (1946).



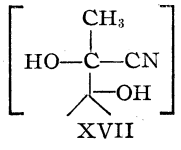
I. R_1 = AcO, R_2 = H
II. R_1 = HO, R_2 = H
III. R_1 = R_2 = OAc
IV. R_1 = HO, R_2 = OAc



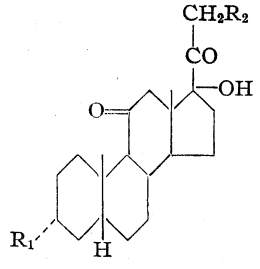
V. R_1 = AcO, R_2 = H
VI. R_1 = HO, R_2 = H
VII. R_1 = R_2 = OAc
VIII. R_1 = HO, R_2 = OAc
IX. R_1 = O=, R_2 = H
X. R_1 = O=, R_2 = OAc



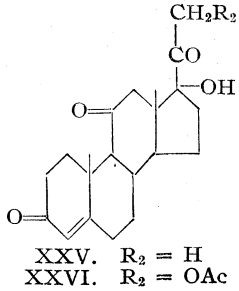
XI. R_1 = AcO, R_2 = H
XII. R_1 = O=, R_2 = H
XIII. R_1 = R_2 = AcO
XIV. R_1 = O=, R_2 = OAc
XV. R_1 = O=, R_2 = OH
XVI. R_1 = R_2 = HO



XVII



XVIII. R_1 = HO, R_2 = H
XIX. R_1 = AcO, R_2 = H
XX. R_1 = O=, R_2 = H
XXI. R_1 = R_1 = HO
XXII. R_1 = R_2 = OAc
XXIII. R_1 = O=, R_2 = OH
XXIV. R_1 = O=, R_2 = OAc



XXV. R_2 = H
XXVI. R_2 = OAc

ketopregnane structures did not materially alter the course of the synthesis. Pregnane-3(α),21-diol-11,20-dione diacetate (III) and the corresponding 21-monoacetate (IV) gave the respective cyanhydrins (VII and VIII). Dehydration of the diacetate cyanhydrin afforded a good yield of the unsaturated nitrile, (XVI), but the 20-cyanhydrin of pregnane-21-ol-3,11,20-trione acetate (X) gave only 20% of the unsaturated compound (XIV). The adverse influence of the 3-keto group on the dehydration is again evident. The hydroxylation of XIV and XV proceeded normally to yield 70–80% of pregnane-3(α),17(α),21-triol-11,20-dione (XXI) and pregnane-17(α),21-diol-3,11,20-trione (XXIII). Treatment with acetic anhydride–pyridine replaced the 21-acetate groups which were removed during the sodium sulfite hydrolysis.

The surprising durability of the side chain permitted conversion of the 3-keto derivatives (XX and XXIV) to the corresponding unsaturated ketones, Δ^4-pregnene-17-ol-3,11,20-trione (XXV) and Δ^4-pregnene-17,21-diol-3,11,20-trione acetate (XXVI, Kendall's compound E acetate).

The assignment of the α or "natural" configuration to the C 17 hydroxyl group in the dioltrione XXIII follows from its conversion into Compound E. Evidence indicates that the other 17-hydroxy-20-ketones described (XVIII, XX and XXII) also belong in the 17(α)-hydroxy series. First, the method of preparation is identical in each case and only one compound is obtained. Second, the rotations fall in the range predicted for 17(α)-hydroxy compounds,[3] the rotations for the 17(β)-hydroxypregnanes being of the order of 100° more toward the *levo* side.

The conversion of Δ^5-pregnene-3(β)-ol-20-one into 17-hydroxyprogesterone was also attempted but the drastic conditions required for hydroxylation of the 17,20 double bond, when conjugated with the 20-cyano group, led to an extensive attack on the $\Delta^{5,6}$ linkage. Oppenauer oxidation of $\Delta^{5,17}$-20-cyanopregnadiene-3(β)-ol gave $\Delta^{4,17}$-20-cyanopregnadiene-3-one but osmium tetroxide in the presence of pyridine appeared to attack both double bonds here also.

Experimental

Rotations were taken in acetone, $c \sim 1.0$. Melting points are corrected.

20-Cyanhydrin of Pregnane-3(α)-ol-11,20-dione Acetate (V).—A solution of 1.70 g. of pregnane-3(α)-ol-11,20-dione acetate (I) in a mixture of 17 cc. of alcohol and 6.4 cc. of acetic acid was cooled to 0° and treated with 6.0 g. of potassium cyanide. The mixture was stirred for one-half hour, then permitted to warm to room temperature. After two hours the solution was diluted with water and the crystalline precipitate was filtered and washed. The wet cake was dissolved in ethyl acetate, excess water removed and the solution concentrated *in vacuo* to a small volume. The addition of petroleum ether gave 1.64 g. of crystals which melted with decomposition at 205–220°. Recrystallization from ethyl acetate gave 1.3 g. of product; m. p. about 221–223° (dec.). A second recrystallization afforded a sample of melting point 217–232° (dec.). Recrystallization from alcohol lowered the melting point to 205–210°.

Anal. Calcd. for $C_{24}H_{35}NO_4$: C, 71.78; H, 8.80. Found: C, 71.50; H, 8.67.

A sample (35 mg.) dissolved in a minimum volume of benzene was put on a column of 1 g. of untreated chromatographic alumina. Elution with 20 cc. of ether gave 29 mg. of pregnane-3(α)-ol-11,20-dione acetate (I); m. p.

and mixed m. p. 135–136°. The experiment was repeated using acid-washed[7] alumina. A crystalline mixture, which melted at 149–170°, was obtained. Repeated recrystallization from methanol yielded a small amount of product of melting point 152–160°.

20-Cyanhydrin of Pregnane-3(α)-ol-11,20-dione (VI).—This cyanhydrin was prepared from II by the procedure given above. From 1.8 g. of ketone, 1.5 g. of recrystallized cyanhydrin, dec. 160–170°, was obtained.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.49; H, 9.26. Found: C, 73.60; H, 9.51.

20-Cyanhydrin of Pregnane-3(α),21-diol-11,20-dione 21-Acetate (VIII).—This cyanhydrin failed to crystallize readily upon dilution of the alcohol–hydrogen cyanide reaction mixture. The diluted solution was consequently extracted with ethyl acetate, the latter solution washed with water and concentrated *in vacuo* to a small volume. From 2.0 g. of ketone (IV) 1.3 g. of recrystallized cyanhydrin was obtained. It decomposed at 175–185° and lost hydrogen cyanide in alcohol or dilute pyridine solution. A trace of acetic acid appeared to stabilize the compound completely, however.

Anal. Calcd. for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.35. Found: C, 68.91; H, 8.37; N, 3.60.

Pregnane-3(α),21-diol-11,20-dione Diacetate (III) and its 20-Cyanhydrin (VII).—A sample of pregnane-3(α),21-diol-11,20-dione 21-acetate (IV) was warmed on the steam-bath with pyridine–acetic anhydride for ten minutes. The solution was diluted with water and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, dilute sodium carbonate, finally with water and concentrated to a small volume. The addition of petroleum ether gave crystals of the diacetate, dec. 100–110°, which contained 10% of solvent of crystallization. From benzene–petroleum ether a sample of dec. p. 82–90° was obtained. Conversion of 3.0 g. of this ketone (solvated) to the cyanhydrin gave 2.2 g. of crystals; dec. 148–160°.

Cyanhydrin of Δ⁵-Pregnene-3(β)-ol-20-one Acetate.—The usual procedure afforded 88% of a product of melting point 194–198° with decomposition.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.96; H, 8.92; N, 3.64. Found: C, 74.70; H, 9.05; N, 3.71.

20-Cyanhydrin of Pregnane-3,11,20-trione (IX).—A solution of 1.4 g. of the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione (VI) in 70 cc. of glacial acetic acid was cooled to 16° and treated over a period of twenty minutes with a solution of 0.9 g. of chromic acid in 7 cc. of acetic acid and 7 cc. of water. After one hour the solution was diluted with water, the precipitate filtered and dissolved in ethyl acetate. Excess water was removed and the solvent was taken off *in vacuo*. The crystalline residue weighed 1.1 g. Recrystallization from ethyl acetate gave 930 mg. of cyanhydrin; dec. 170–180°. For analysis the compound was dried *in vacuo* at room temperature, as with the other cyanhydrins, but, presumably because of solvation, no agreement with theory could be obtained.

20-Cyanhydrin of Pregnane-21-ol-3,11,20-trione Acetate (X).—A solution of 1.2 g. of the 20-cyanhydrin of pregnane-3(α),21-diol-11,20-dione acetate (VIII) in 20 cc. of acetic acid and 2 cc. of water was treated over a period of five minutes with a solution of 600 mg. of chromic acid in 1.2 cc. of water and 11 cc. of acetic acid. After the mixture had stood at room temperature for an hour, water was added and the product worked up as in the preceding oxidation. After purification, 1.0 g. of cyanhydrin, dec. 214–217°, was obtained.

Anal. Calcd. for $C_{24}H_{33}NO_5$: C, 69.36; H, 8.01; N, 3.37. Found: C, 69.31; H, 8.30; N, 3.36.

Samples of this cyanhydrin and of the cyanhydrin IX were treated with alkaline alumina in the manner described above. In both cases the parent ketone was obtained in high yield. Even acid-washed alumina gave 30–40% of the ketone, the remainder of the product being non-crystalline.

Δ¹⁷-20-Cyanopregnene-3(α)-ol-11-one Acetate (XI).—A solution of 2.5 g. of the 20-cyanhydrin of pregnane-3(α)-ol-11,20-dione acetate (V) in 8 cc. of pyridine was treated with 1.2 cc. of phosphorus oxychloride. After standing at room temperature overnight, the solution was diluted, the crystalline precipitate filtered and recrystallized from dilute alcohol. The product weighed 1.9 g. and melted at 199–201°. A sample was recrystallized from methanol for analysis and melted at 201.0–201.5°; $[\alpha]^{25}D$ +40°.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.15; H, 8.67; N, 4.05. Found: C, 75.10; H, 8.62; N, 4.07.

With crude cyanhydrin the yield of the desired unsaturated nitrile was decreased out of all proportion to the amount of impurities initially present. A sample of cyanhydrin (V) which had been crystallized once from ethyl acetate–petroleum ether (90% of theory, dec. 200–210°) was dehydrated as above. Chromatography of the product gave only 20% of the unsaturated nitrile XI. The remaining crystalline fractions consisted of a mixture, m. p. 172–182°, the properties of which could not be greatly altered by recrystallization and for which the analytical data corresponded most closely to the same empirical formula as the nitrile XI.

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.15; H, 8.67; N, 4.05. Found: C, 75.57; H, 8.33; N, 3.55.

Δ¹⁷-20-Cyanopregnene-3,11-dione (XII).—The dehydration of the cyanhydrin IX was carried out in the manner described above. After chromatography of the crude product, 20% of XII was obtained; m. p. 229–237°; $[\alpha]^{25}D$ +38°.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.62. Found: C, 78.05; H, 8.67.

Δ¹⁷-20-Cyanopregnene-3(α),21-diol-11-one (XVI).—The dehydration of 2.2 g. of the cyanhydrin VII was carried out in the usual manner. The product was an oil (2.0 g.) which was chromatographed and the portions eluted with petroleum ether–ether mixtures combined. This material, which was presumably XIII, weighed 1.84 g. and failed to show signs of crystallizing. Hence it was saponified by dissolving in a mixture of 10 cc. of benzene and 10 cc. of 1.1 *N* methanolic potassium hydroxide. After ten minutes the solution was acidified with acetic acid, the benzene removed *in vacuo* and the residue crystallized from dilute methanol. The free diol melted at 242–254° and weighed 1.45 g. After recrystallization from acetone and from dilute alcohol it melted at 256–257°; $[\alpha]^{25}D$ +19.5°.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.92; H, 8.73; N, 3.92. Found: C, 73.68; H, 8.48; N, 4.22.

Δ¹⁷-20-Cyanopregnene-21-ol-3,11-dione Acetate (XIV).—Dehydration of 6.2 g. of the cyanhydrin X according to the usual procedure gave a mixture which was diluted with water and extracted with benzene. The benzene solution was concentrated to dryness and the residue (4.7 g.) was chromatographed. The unsaturated nitrile (XIV) was isolated in 28% yield. Some samples melted at 181–182° with resolidification and remelting at 195–196°, while others only showed the higher melting point; $[\alpha]^{25}D$ +50°.

Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.85; N, 3.53. Found: C, 72.68; H, 7.85; N, 3.57.

Δ¹⁷-20-Cyanopregnene-21-ol-3,11-dione (XV).—Hydrolysis of the acetate (150 mg.) was accomplished by dissolving it in 5 cc. of methanol and adding 2 cc. of water containing 200 mg. of potassium carbonate. The solution was kept at 50° for fifteen minutes, the methanol was then removed *in vacuo* and the crystalline precipitate filtered. Recrystallization from ethyl acetate gave a product of melting point 263–265° (sample introduced at 250°); $[\alpha]^{25}D$ +36°.

(7) Chromatographic alumina was suspended in water and sufficient dilute sulfuric acid added to bring the *p*H to 3.0. The alumina was then washed repeatedly with sufficient distilled water to bring the *p*H to 5.5–6.0, then dried at 150°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.34; H, 8.22; N, 3.94. Found: C, 74.23; H, 8.00; N, 4.22.

$\Delta^{5,17}$-20-Cyanopregnadiene-3(β)-ol Acetate.—The dehydration of the cyanhydrin of Δ^5-pregnene-3(β)-ol-20-one acetate (900 mg.) in the usual manner gave 60% of a product of melting point 170–172°. This was chromatographed and recrystallized, but this treatment failed to produce an analytically pure sample. Hence, it was converted to the free alcohol.

$\Delta^{5,17}$-20-Cyanopregnadiene-3(β)-ol.—The benzene–methanolic potassium hydroxide method described above was used to hydrolyze $\Delta^{5,17}$-20-cyanopregnadiene-3(β)-ol acetate. Recrystallization of the crude product from dilute methanol gave 85% of the free alcohol; m. p. 176–177°; $[\alpha]^{25}D$ −86°.

Anal. Calcd. for $C_{22}H_{31}NO$: C, 81.18; H, 9.60. Found: C, 81.22; H, 9.16.

Attempted hydroxylation of this compound or of the corresponding Δ^5-3-acetoxy derivative by the osmium tetroxide–pyridine procedure described below gave oily products. Milder treatment gave only starting material.

Pregnane-3(α),17(α)-diol-11,20-dione (XVIII) and Its 3-Monoacetate (XIX).—To a solution of 1.65 g. of Δ^{17}-20-cyanopregnene-3(α)-ol-11-one acetate (XI) in 16 cc. of dry benzene was added 1.7 g. of osmium tetroxide and 0.75 cc. of pyridine. After standing at room temperature overnight, the mixture was treated with 50 cc. of water containing 3.0 g. of sodium sulfite. The benzene was then concentrated *in vacuo* to about 5 cc., and the whole was diluted with 50 cc. of alcohol. The mixture was stirred at room temperature for twenty hours, filtered, acidified with a few drops of acetic acid and concentrated *in vacuo* to a small volume. The aqueous mixture was extracted with chloroform, the chloroform solution concentrated to dryness *in vacuo* and the residue crystallized from acetone–ether. The 800 mg. so obtained was recrystallized from dilute alcohol, giving pregnane-3(α),17(α)-diol-11,20-dione; m. p. 207–208°; $[\alpha]^{25}D$ +68.5°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.54; H, 9.19.

The mother liquors (850 mg.) consisted of a crystalline mixture of the dioldione and its 3-acetate. It was converted entirely to the latter by dissolving it in 3 cc. of pyridine and 3 cc. of acetic anhydride. The addition of water after three hours gave 850 mg. of crystals; m. p. 206–208°. Recrystallization from dilute alcohol gave the pure 3-acetate (XIX); m. p. 208–209°; $[\alpha]^{25}D$ +84°. A mixed melting point with XVIII showed a depression of 30°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.83; H, 8.96.

Pregane-17(α)-ol-3,11,20-trione (XX) from Δ^{17}-20-Cyanopregnene-3,11-dione (XII).—The hydroxylation of XII was carried out according to the procedure described above. A yield of 83% of the oltrione, m. p. 205–206°, was obtained. A mixed melting point with the pregnane-17(α)-ol-3,11,20-trione prepared by oxidation of pregnane-3(α),17(α),20-triol-11-one showed no depression.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.81; H, 8.70.

Pregnane-17(α)-ol-3,11,20-trione (XX) from Pregnane-3(α),17(α)-diol-11,20-dione (XVIII).—A solution of 75 mg. of XVIII in a mixture of 0.8 cc. of acetic acid and 0.2 cc. of water was treated with a solution of 60 mg. of chromic acid in 0.06 cc. of water and 1.14 cc. of acetic acid. After standing at room temperature for ten minutes the solution was diluted with water and extracted twice with chloroform. The washed chloroform solution was concentrated to dryness *in vacuo* and the residue crystallized from ether. Recrystallization from dilute acetone gave the pure oltrione; m. p. and mixed m. p. 205–206°.

Pregnane-3(α),17(α),21-triol-11,20-dione Diacetate (XXII).—The osmium tetroxide–sodium sulfite procedure described above was applied to 1.1 g. of Δ^{17}-20-cyanopregnene-3(α),21-diol-11-one diacetate (amorphous, prepared by acetylation of the pure Δ^{17}-20-cyanopregnene-3(α),21-diol-11-one (XVI) in the usual manner). The crude product was amorphous and presumably consisted of equal amounts of pregnane-3(α),17(α),21-triol-11,20-dione and its 3-monoacetate. In addition, the product was contaminated with some green osmium salts. These were partially removed by dissolving the product in a small volume of acetone and diluting with 100 cc. of absolute ether. The flocculent precipitate was separated, the supernatant yellowish solution was concentrated to dryness and dissolved in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride. After standing at room temperature for several hours, the solution was diluted with water and the crystalline precipitate was filtered. Recrystallization from dilute acetone and from alcohol gave 504 mg. of the diacetate; m. p. 233–236°. Additional recrystallization from benzene and from acetone–ether failed to raise the melting point or to remove a trace of greenish discoloration; $[\alpha]^{25}D$ +93°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.08. Found: C, 66.41; H, 8.08.

Pregnane-17(α),21-diol-3,11,20-trione (XXIII).—One gram of Δ^{17}-20-cyanopregnane-21-ol-3,11-dione acetate (XIV) was treated with osmium tetroxide–pyridine and then hydrolyzed with sodium sulfite in the fashion described above. After concentration of the aqueous-alcoholic solution to a small volume *in vacuo*, it was extracted with four 150-cc. portions of chloroform which were then combined and washed with successive small portions of sodium bicarbonate, dilute hydrochloric acid and water, the washes being back extracted each time. The chloroform solution was then concentrated to dryness *in vacuo* and the residue (861 mg.) crystallized from acetone. A yield of 60% of dioltrione, m. p. 233–235°, was obtained. The pure material was sparingly soluble in chloroform, ethyl acetate and acetone.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.59; H, 8.33. Found: C, 69.45; H, 8.13.

The 21-monoacetate was prepared by treatment of the dioltrione with pyridine–acetic anhydride at room temperature. The initially insoluble starting material dissolved after five to ten minutes of stirring. After an additional five minutes the acetate was precipitated by addition of water. It melted at 228–230°; $[\alpha]^{25}D$ +82°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.14; H, 7.91.

Δ^4-Pregnene-17(α)-ol-3,11,20-trione (XXV).—To a solution of 86 mg. of pregnane-17(α)-ol-3,11,20-trione (XX) in 1.0 cc. of acetic acid was added a solution of 41 mg. of bromine in 0.41 cc. of acetic acid. After two minutes the bromine color suddenly disappeared, the solution was poured into water and extracted with chloroform. The chloroform solution was washed with dilute potassium carbonate and water, then concentrated to dryness *in vacuo*. The residue was crystallized from ether to give 71 mg. of crude crystalline 4-bromopregnane-17(α)-ol-3,11,20-trione; dec. *ca.* 185°. This substance was refluxed for five hours in pyridine, the latter removed *in vacuo* and the residue dissolved in ether and dilute hydrochloric acid. The washed ether layer was concentrated to a small volume and the crystalline precipitate (19 mg.) recrystallized twice from methanol. It then melted at 236–239°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.18. Found: C, 73.43; H, 7.49.

Δ^4-Pregnene-17(α),21-diol-3,11,20-trione Acetate (XXVI) (Kendall's Compound E Acetate).—A solution of 333 mg. of pregnane-17(α),21-diol-3,11,20-trione 21-acetate (XXIV) in 5.0 cc. of acetic acid was treated with a solution of 132 mg. of bromine in 1.0 cc. of acetic acid. After decolorization had ensued, the solution was worked up as above. Crystallization of the chloroform residue gave 300 mg. of the 4-bromo derivative; dec. 190°. This material was then refluxed with 12 cc. of pyridine for five hours and the mixture then concen-

trated *in vacuo*, dissolved in chloroform, washed with dilute hydrochloric acid and with water, and concentrated to dryness *in vacuo*. The residue (170 mg.) was crystallized from benzene by the addition of ether, giving 118 mg. of crude crystalline XXVI. This product was dissolved in 2.5 cc. of hot alcohol and the solution permitted to cool slowly to room temperature. It was then kept at −5° for two days at the end of which time the initial precipitate of long dense needles had become contaminated by a small superficial layer of fluffy crystalline balls, apparently containing the saturated dioltrione (XXIV). The needles were easily separated mechanically and after two further recrystallizations from alcohol melted at 236–238°. A total of 83 mg. was obtained; $[\alpha]^{25}D$ +170°. A mixed melting point with an authentic sample of Compound E acetate gave no depression.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.61; H, 7.52. Found: C, 68.85; H, 7.34.

Acknowledgment.—The author wishes to thank Dr. K. Folkers and Dr. R. T. Major of these laboratories and Dr. E. S. Wallis of Princeton University for their suggestions in connection with this work. The author is indebted to Miss Jean Andrews for assistance. Acknowledgment for microanalyses is made to Messrs. R. Boos, W. H. Humphrey, E. Thornton, J. McGregor and R. Funk.

Summary

A new method for the preparation of 17(α)-hydroxy-20-ketopregnanes is described. A 20-ketopregnane is converted to its cyanhydrin which is then dehydrated to give a Δ^{17}-20-cyanopregnene. With osmium tetroxide followed by aqueous sodium sulfite, the unsaturate nitrile is converted to the 17(α)-hydroxy-20-ketopregnane, hydrogen cyanide being spontaneously eliminated from the hypothetical intermediate, 17,20-dihydroxy-20-cyanopregnane. The method is also feasible for introducing a 17(α)-hydroxy group into a 20-keto-21-acetoxypregnane. This permits the synthesis of Kendall's Compound E.

RAHWAY, NEW JERSEY RECEIVED DECEMBER 5, 1947

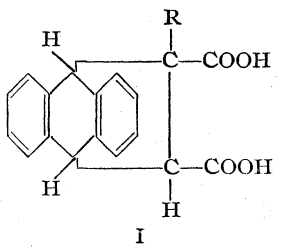
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Reaction of Anthracene with Maleic and Fumaric Acid and their Derivatives and with Citraconic Anhydride and Mesaconic Acid

BY W. E. BACHMANN AND L. B. SCOTT[1,2]

In the present work the addition of seven dienophiles to anthracene is described, the relative rates of reaction are compared, and the effects of changes in some of the reaction variables are noted. By the addition of both the *cis* and *trans* forms of a dienophile, information on the application of the rule of *cis* addition in the Diels–Alder reaction was obtained.

The reaction of maleic anhydride and anthracene to give *cis*-9,10-dihydroanthracene-9,10-endo-α,β-succinic anhydride[3] is well known. We obtained the same anhydride (and not the acid) in high yield from the reaction of maleic acid with anthracene in boiling dioxane. It is not known whether the molecule of water is lost before or after addition, but the latter seems probable in view of the ease with which the *cis*-diacid (I, R = H) is converted to the anhydride (*e.g.*, on recrystallization or on standing in a vacuum desiccator). Diels, Alder and Beckmann[4] prepared the *cis*-dimethyl ester from the anhydride. We have obtained this ester by the addition of dimethyl maleate to anthracene.



I

In spite of the impression that fumaric acid does not engage in the Diels–Alder reaction,[5] we tried its reaction with anthracene and obtained the addition product, the *trans*-acid (I, R = H) in 95% yield. Fumaric acid[6] reacts more slowly (see Table I) than maleic anhydride, requiring days of refluxing in a given solvent to hours for the anhydride. The reaction of anthracene with maleic acid (or maleic anhydride) to give the *cis* adduct and with fumaric acid to give the *trans* acid offers a simple classroom illustration of the

(1) From the Ph.D. dissertation of L. B. Scott, 1944.

(2) Present address: Shell Development Company, Emeryville, California.

(3) In this paper the prefixes *cis* and *trans* refer solely to the configuration at the two carbon atoms attached to the carboxyl groups and not to the configuration at the 9,10 positions.

(4) Diels, Alder and Beckmann, *Ann.*, **486**, 191 (1931).

(5) Alder and Stein, *Ann.*, **514**, 203 (1934) mention that fumaric acid does not add to cyclopentadiene. On page 309 of Richter's "Textbook of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y. 1943, the following statement appears in the section on the Diels–Alder reaction: "This type of reaction does not occur with the *trans* isomer, fumaric acid."

Dilthey and Henkels, *J. prakt. Chem.*, **149**, 85 (1937), stated that the product obtained from acecyclone and fumaric acid was identical with that obtained with maleic acid (or anhydride) and attributed this result to the addition of maleic acid formed by rearrangement of the fumaric acid. After our work had been completed (1942; publication delayed by the war), Bergmann, Eschinazi and Neenam, *J. Org. Chem.*, **8**, 179 (1943), reported the formation of an amorphous acid adduct from 1,1′-bicyclohexenyl and fumaric acid at 190–200°. The nature of the adduct, which was characterized as a dianilide, was not clearly indicated.

(6) In the paper which follows a Diels–Alder reaction is reported in which fumaric acid was superior to maleic anhydride in that it gave a higher yield of adduct and a lower yield of copolymer.

principle of *cis* addition of the diene to the double bond of the dieneophile. We have also prepared the *trans*-dimethyl ester in high yield by the direct addition to anthracene of dimethyl fumarate. Unlike the *cis*-diacid, the *trans*-diacid showed no tendency to lose water and form an anhydride and could be recrystallized unchanged from a mixture of acetic anhydride and acetic acid.

cis-9,10-Dihydroanthracene-9,10-endo-α-methyl-α,β-succinic anhydride (anhydride of I, R = CH_3) had been prepared previously in unspecified yield, by melting together anthracene and citraconic anhydride.[4] We have prepared it in 96% yield by refluxing the same reactants in either toluene or xylene solution. The *trans*-diacid was obtained directly through the reaction of anthracene and mesaconic acid. Here, too, the *cis*-diacid lost water readily to form the corresponding anhydride whereas the *trans*-diacid did not; in fact, the latter could be sublimed unchanged at 200°. The *cis*-dimethyl ester and the *trans*-dimethyl ester were prepared by treating the corresponding diacids with diazomethane. The *cis*-diester was isomerized to the *trans*-diester by prolonged treatment with methanolic potassium methoxide. The rearrangement of this *cis*-ester with an α-methyl group to the *trans* configuration proceeded much more slowly than the rearrangement of the *cis*-ester without the α-methyl group.

The reaction of bromomaleic anhydride and anthracene yielded *cis*-9,10-dihydroanthracene-9,10-endo-α-bromo-α,β-succinic anhydride. When this anhydride was warmed gently with potassium hydroxide, the bromine group was replaced and the corresponding α-hydroxy diacid was isolated. No attempt was made to determine whether the hydroxy diacid was *cis* or *trans*, but its method of preparation and its stability toward anhydride formation during recrystallization favor the *trans* configuration. These compounds should prove useful for a study of the Walden inversion.

The relative rates of most of the above Diels–Alder reactions were compared in a series of experiments in which homogeneous dioxane solutions of equimolar quantities of the two reactants were refluxed for measured periods of time. The yields of the product are recorded in Table I; the relative accuracy of the results is considered to be ±2–3%.

TABLE I

RELATIVE RATE OF ADDITION OF DIENOPHILES TO ANTHRACENE

Anthracene, 0.0112 mole; dienophile, 0.0112 mole; dioxane, 50 cc.; reaction temperature, *ca.* 102°

Dienophile	Reaction time, hr.	Anthracene isolated, %	Yield[a] of product, %
Maleic anhydride	2	31	67
Bromomaleic anhydride	2	62	36
Maleic acid	2	92	6.5
Maleic acid	24	52	47
Dimethyl fumarate	24	58	41[b]
Fumaric acid	24	70	28
Citraconic anhydride	24	70;73	28;26
Mesaconic acid	24	92	7.5

[a] High yields of the adducts were obtained by increasing the reaction time, the concentration or the temperature (by means of a higher boiling solvent) (see Experimental). [b] Product isolated as the *trans*-diacid.

Slower rates resulted when the maleic anhydride was replaced by a *cis*-diacid, a *trans*-diacid or a *trans*-diester, or when a hydrogen on one of the double-bond carbons was replaced by a bromine or a methyl group. It is of interest that bromomaleic anhydride reacts very much more rapidly than does citraconic anhydride although the bromine atom and the methyl group are thought to be similar in size.[7] The substitution of a hydrogen by a bromine would increase the electron affinity of the dienophile while replacement by a methyl group would not. The rate of addition of chloromaleic and fluoromaleic anhydride would be of interest in this connection as the steric factor should have a lesser magnitude and the electronic factor a greater one.

In another series of runs (Table II) the rate of reaction of citraconic anhydride with anthracene in equal volumes (sufficient for complete solution) of different solvents was determined. As expected, the rate of reaction increased as the reaction temperature was increased. The rate of reaction was greater than expected from the increase in temperature when a mildly polar solvent such as acetic or propionic acid was used instead of low polarity solvents such as toluene and xylene.[8] An experiment was conducted in 2-nitropropane because of this solvent's somewhat polar nature, but no enhancement of the rate was observed.

TABLE II

EFFECT OF REACTION TEMPERATURE AND SOLVENT ON THE RATE OF REACTION OF ANTHRACENE AND CITRACONIC ANHYDRIDE

Anthracene, 0.0112 mole; citraconic anhydride, 0.0112 mole; solvent, 25 cc. except as noted; reaction time, 24 hours

Solvent	Approx. reaction temperature, °C.	Anthracene isolated, %	Yield of product, %
Benzene	78	91	8
Dioxane	102	59;58	40;41
Toluene	111	52;49	47;49
2-Nitropropane	122	38	62
Xylene	142	21;21;18	78;78;80
Acetic acid (50 cc.)	119	40	59
Acetic acid (30 cc.)	119	15	83
Propionic acid	144	13	86

The effect of the concentration of the reactants on the rate of addition of anthracene to citraconic anhydride was studied in still another group of experiments (Table III). Different volumes of dioxane were used for equimolar quantities of the

(7) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1939.

(8) *Cf.* Fairclough and Hinshelwood, *J. Chem. Soc.*, 236 (1938), and Wasserman, *ibid.*, 1028 (1936).

reactants, and the homogeneous solutions were refluxed for twenty-four hours. The values calculated for a bimolecular reaction rate constant were in fairly close agreement.

TABLE III

EFFECT OF CONCENTRATION OF REACTANTS ON THE RATE OF REACTION OF ANTHRACENE AND CITRACONIC ANHYDRIDE

Anthracene, 0.0112 mole; citraconic anhydride, 0.0112 mole; reaction time, 24 hours; reaction temperature, *ca.* 102°

Volume of dioxane, cc.	Anthracene isolated, %	Yield of product, %	k^a
12.5	43	57	69
25	58; 59	41; 40	69
50	70; 73	28; 26	71
100	85	14.5	67

[a] Bimolecular reaction rate constant (cc./hr. moles) calculated using the higher value for "% anthracene isolated" where there was a choice. The volume of the solution was taken as the volume of the solvent + 1.5 cc.

Experimental

Reactions of Anthracene

With Maleic Acid.—A solution of 2 g. (0.0112 mole) of anthracene and 3.9 g. (0.0336 mole) of maleic acid in 17 cc. of dioxane was refluxed for thirty hours. The dioxane was removed in a current of air on a steam-bath and the residue was shaken for two hours at room temperature with excess, dilute sodium bicarbonate (this treatment had been shown to have no effect on the anhydride). The mixture was filtered and the filtrate was added to an excess of hydrochloric acid; yield of *cis*-9,10-dihydroanthracene-9,10-endo-α,β-succinic acid, 0.035 g. (1%). The bicarbonate-insoluble residue (the anhydride) was warmed gently with 45% potassium hydroxide, water and benzene (in that order) and the clear layers were separated. The benzene layer contained 0.065 g. (3%) of anthracene while the aqueous layer, upon addition to excess hydrochloric acid, yielded 3.10 g. (94%) of *cis*-diacid (I, R = H). As has been reported,[9] the *cis*-diacid crystallized from ethyl acetate as colorless prisms of the corresponding *cis*-anhydride; m. p. 264–264.5° cor. (reported,[4] 262–263° for the product prepared directly by the addition of maleic anhydride to anthracene). When a small sample of the diacid in a melting point tube was plunged into a bath at 255° cor., it melted with gassing, solidified after 20–30 seconds and remelted (presumably as the *cis*-anhydride) at 261–263° cor.

With Fumaric Acid.—A solution of 6 g. (0.0336 mole) of anthracene and 1.3 g. (0.0112 mole) of fumaric acid in 50 cc. of dioxane was refluxed for three days, the solvent was removed, and the residue was shaken several hours with dilute sodium bicarbonate and then worked up in the same manner as was the maleic acid mixture; the benzene layer contained 4.08 g. of anthracene. The bicarbonate solution was slowly added with stirring to warm, dilute hydrochloric acid and the mixture was filtered while warm (to keep fumaric acid in solution); yield of *trans*-9,10-dihydroanthracene-9,10-endo-α,β-succinic acid, 3.13 g. (95%); m. p. 240–242° dec. with previous softening at 238° (reported,[4] 241–242° dec.). A portion of the diacid treated with ethereal diazomethane gave the *trans*-dimethyl ester which crystallized from methanol in colorless, rhombic plates; m. p. 108.4–108.9° cor. (reported,[4] 106–107° for the product obtained by isomerization of the *cis*-diester by sodium methylate). The *trans*-diacid showed no tendency to form either a *cis* or a *trans*-anhydride when recrystallized from acetic anhydride–glacial acetic acid or when stored for several days in a vacuum desiccator.

(9) Bachmann and Kloetzel, THIS JOURNAL, **60**, 481 (1938).

With Dimethyl Maleate.—Two grams (0.0112 mole) of anthracene, 2.43 g. (0.0168 mole) of dimethyl maleate[10] and 10 cc. of dioxane were refluxed for eight days. The clear solution was transferred to a sublimation tube, the solvent was removed and the residue was evaporatively distilled at about 0.05 mm. The light-yellow material distilling between 140 and 175° (*cis*-dimethyl ester contaminated with a small amount of anthracene) weighed 3.56 g. and melted at 139–146° with previous softening; estimated yield of diester, 90–95%. After three recrystallizations from methanol, the square, colorless plates of the dimethyl ester of *cis*-9,10-dihydroanthracene-9,10-endo-α,β-succinic acid melted at 150–150.5° cor. This ester (m. p. 150–151°) has been prepared previously by the action of methanolic hydrogen chloride on the *cis*-acid.[4]

In a second experiment a solution of 2 g. (0.0112 mole) of anthracene, 8.1 g. (0.056 mole) of dimethyl maleate and 65 cc. of xylene was refluxed for three days. The xylene was removed and the residue was refluxed for seventeen hours with 50 cc. of methanol and 25 cc. of 45% potassium hydroxide. The methanol was removed, water and benzene were added and the clear layers were separated. The benzene layer contained 0.24 g. (12%) of anthracene and the aqueous layer 2.89 g. (87%) of *trans*-diacid; m. p. 239.5–241° dec. The product was converted to the *trans*-dimethyl ester with diazomethane and was crystallized from methanol; m. p. 108–108.5° cor. alone and when mixed with an authentic sample of the *trans*-diester.

With Dimethyl Fumarate.—A solution of 2 g. (0.0112 mole) of anthracene and 2.43 g. (0.168 mole) of dimethyl fumarate (prepared by the action of methanolic hydrogen chloride on maleic anhydride; m. p. 101–100.5° after recrystallization from methanol) in 12 cc. of dioxane was refluxed for three days. The solvent was removed and the residue was evaporatively distilled at about 0.05 mm. A total of 3.63 g. of light-yellow *trans*-dimethyl ester contaminated with a small amount of anthracene distilled at 140–175°; estimated yield of diester, 90–95%. Three recrystallizations from methanol raised the melting point of the product from 90–96° to 107–108° cor.

In another experiment a solution of 2 g. (0.0112 mole) of anthracene and 16.2 g. (0.11 mole) of dimethyl fumarate in 150 cc. of xylene was refluxed for three days, and the reaction product was hydrolyzed with methanolic potassium hydroxide and worked up in the manner described in the corresponding dimethyl maleate experiment; anthracene, 0.20 g. (10%); *trans*-diacid, 2.87 g. (87%).

With Citraconic Anhydride.—A solution of 2 g. (0.0112 mole) of anthracene and 2.52 g. (0.0224 mole) of citraconic anhydride[11] in 25 cc. of xylene (or toluene) was refluxed for eighty-four hours. Most of the solvent was removed in a current of air, the residue was treated with 45% potassium hydroxide, water and benzene, and the clear layers were worked up in the usual manner; anthracene, 0.06 g. (3%); *cis*-9,10-dihydroanthracene-9,10-endo-α-methyl-α,β-succinic acid (I, R = CH_3), 3.33 g. (96%). When a small sample of the diacid in a melting point tube was plunged into a bath at 173°, it melted with gassing, solidified after 15–20 seconds and remelted (presumably as the *cis*-anhydride) at 181–182°.

The *cis*-diacid was readily converted into the *cis*-anhydride by prolonged drying in a vacuum desiccator or recrystallization from ethyl acetate. The anhydride product evaporatively distilled at 160–190° and *ca.* 0.05 mm. without appreciable decomposition and crystallized from ethyl acetate in fine, colorless prisms; m. p. 185.1–185.5° cor. (reported,[4] 182° after repeated recrystallizations). The *cis*-anhydride was formed in about 60% yield by heating 1.8 g. of anthracene with 1.3 g. of citraconic anhydride at 155–165° for two hours according to the procedure of Diels, Alder and Beckmann.[4]

(10) Wolf and Straete, *Bull. classe sci., Acad. roy. Belg.*, **21**, 216 (1935).

(11) Shriner, Ford and Roll, "Organic Syntheses," **11**, 28, 70 (1931).

Three grams of recrystallized *cis*-anhydride was hydrolyzed by warm dilute sodium hydroxide, and the clear solution was added to an excess of hydrochloric acid. The damp *cis*-diacid was treated with ethereal diazomethane and the product was triturated with dilute sodium bicarbonate; yield, 3.40 g.; m. p. 133–134.5°. After recrystallization from methanol and evaporative distillation at 135–145° and *ca.* 0.05 mm., the **dimethyl ester of *cis*-9,10-dihydroanthracene-9,10-endo-α-methyl-α,β-succinic acid** crystallized from methanol in colorless plates; m. p. 140.9–141.2° cor.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 75.00; H, 6.01.

The same compound was prepared in only slightly lower yield by refluxing for eight hours a solution of 5 g. of the anhydride in 250 cc. of methanol which had been saturated with dry hydrogen chloride at 0° and which was treated with hydrogen chloride during the refluxing period.

With Mesaconic Acid.—Two grams (0.0112 mole) of anthracene, 7.3 g. (0.056 mole) of mesaconic acid[12] (m. p. 204–205° cor.) and 40 cc. of propionic acid were refluxed for ninety-six hours at about 144°. The temperature was then held at 90–95° for seventy-two hours more, a total reaction time of seven days. The light-yellow solution gradually darkened but remained clear. The reaction mixture was worked up as before; anthracene, 0.35 g. (17.5%); *trans*-diacid, 2.79 g. (80%). The ***trans*-9,10-dihydroanthracene-9,10-endo-α-methyl-α,β-succinic acid** (I, R = CH_3), after a treatment with Norit in acetone, crystallized from acetone–ethyl acetate as a colorless powder; m. p. 232.1–232.4° dec. cor.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.23; neut. equiv., 154. Found: C, 74.04; H, 5.29; neut. equiv., 154.

The *trans*-diacid showed no tendency to form an anhydride. When an unpurified sample (m. p. 214–219° dec.) was heated in a sublimation tube at 200–220° and *ca.* 0.05 mm., some decomposition occurred; but most of the material sublimed as colorless, bicarbonate-soluble, *trans*-diacid.

The ***trans*-dimethyl ester,** prepared from recrystallized acid and diazomethane, crystallized from methanol in colorless, rhombic prisms; m. p. 119.2–119.7° cor.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 75.17; H, 6.05.

The *trans*-diester was also prepared from the *cis*-isomer. A solution of 1 g. of the *cis*-dimethyl ester, 60 cc. of methanol and 30 cc. of 45% potassium hydroxide was refluxed for thirty-two hours. From it 0.78 g. of diacid was isolated, which on treatment with diazomethane and recrystallization of the product from methanol yielded 0.6 g. (60%) of *trans*-dimethyl ester; m. p. 117–118.5°. In another experiment, 1 g. of the *cis*-dimethyl ester and 0.03 g. of potassium metal were dissolved in 75 cc. of anhydrous methanol, and the solution was refluxed for forty-five hours. The recovered product was shown to be a mixture of about 75% *trans*- and 25% *cis*-diester by fractional crystallization. When a solution of 1.91 g. of the ester in 60 cc. of anhydrous methanol in which 20 mg. of sodium had been dissolved was refluxed for thirty minutes, no change occurred. Under the same conditions the corresponding maleic ester addition product was isomerized to the *trans*-ester.

With Bromomaleic Anhydride.—A mixture of 2 g. (0.0112 mole) of anthracene, 3 g. (0.0169 mole) of bromomaleic anhydride (prepared from dibromosuccinic acid by the method of Walden[13]; b. p. 72–75° at 2–3 mm.) and 15 cc. of toluene was heated on a steam cone for forty-eight hours. The reaction mixture was cooled, a few dark-brown particles were removed by filtration, and the filtrate was concentrated to about one-half of its original volume in a vacuum desiccator. The crystals of ***cis*-9,10-dihydroanthracene-9,10-endo-α-bromo-α,β-succinic anhydride** which precipitated were filtered and washed with ether; yield, 2.59 g.; m. p. 169–170° cor. A single recrystallization from acetone raised the melting point to 171.5–172.9° cor.

Anal. Calcd. for $C_{18}H_{11}BrO_3$: C, 60.87; H, 3.12. Found: C, 60.81; H, 3.13.

The solvent was removed from the filtrate and the residue was warmed gently with 45% potassium hydroxide, water and benzene. The benzene layer contained 0.06 g. (3%) of anthracene and the acidified and concentrated aqueous layer yielded 1.02 g. (31%) of **9,10-dihydroanthracene-9,10-endo-α-hydroxy-α,β-succinic acid**; m. p. 224–230° dec. cor. with previous softening. The hydroxy diacid crystallized from ethyl acetate in colorless prisms; m. p. 232.5–233.2° dec. cor.

Anal.[14] Calcd. for $C_{18}H_{14}O_5$: C, 69.66; H, 4.55; neut. equiv., 155. Found: C, 69.63; H, 4.69; neut. equiv., 155.

Summary

The reaction of anthracene with seven dienophiles is described. The order of reactivity with anthracene was found to be: maleic anhydride > bromomaleic anhydride > maleic acid > dimethyl fumarate > fumaric acid, citraconic anhydride > mesaconic acid.

The addition of the *trans*-dienophiles fumaric acid and mesaconic acid yielded *trans*-acids in agreement with the rule of *cis*-addition.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 1, 1947

(12) Shriner, Ford and Roll, "Organic Syntheses" **11**, 74 (1931).

(13) Walden, *Ber.*, **30**, 2886 (1897).

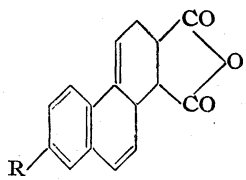
(14) Semi-microanalysis by Dr. Marjorie Horning.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Reaction of 1-Vinylnaphthalene and 6-Methoxy-1-vinylnaphthalene with Citraconic Anhydride, Fumaric Acid and Mesaconic Acid[1]

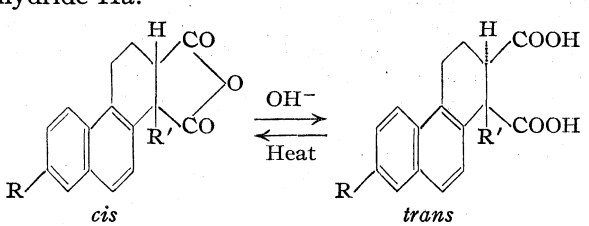
BY W. E. BACHMANN AND L. B. SCOTT[2]

Cohen[3] made the interesting discovery that 1-vinylnaphthalene can function as a diene in the Diels–Alder reaction. From the reaction of this hydrocarbon with maleic anhydride in xylene, *cis*-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (Ia) was obtained.[4] The product was isomerized to the naphthalenic compound 1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (IIa) by treatment with glacial acetic acid saturated with dry hydrogen chloride.



Ia, R = H
Ib, R = OCH_3

We have investigated this reaction and similar ones and have examined the by-products. It was found that when 1-vinylnaphthalene and maleic anhydride reacted in toluene at 90–100° a mixture of monomeric and copolymeric addition products was formed.[5] The monomeric portion which was essentially the non-naphthalenic anhydride (Ia) could be isolated from the mixture in 16% yield by recrystallization. When the crude mixture was subjected to evaporative distillation at low pressure, the distillate was the *cis*-naphthalenic anhydride IIa.

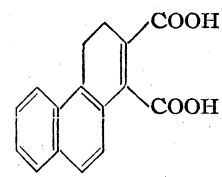


cis *trans*

IIa, R = R′ = H
IIb, R = OCH_3, R′ = H
IIc, R = H, R′ = CH_3
IId, R = OCH_3, R′ = CH_3

IIIa, R = R′ = H
IIIb, R = OCH_3, R′ = H
IIIc, R = H, R′ = CH_3
IIId, R = OCH_3, R′ = CH_3

Various procedures were tried to separate the maximum amount of monomeric product from the mixture. The best procedure consisted in hydrolysis of the crude mixture, esterification of the resulting diacid with diazomethane, and evaporative distillation. In this manner the dimethyl ester of *cis*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (acid corresponding to IIa) was obtained in 60% yield. Recently, Cohen's structure for this ester was confirmed by Fujimoto[6] in this Laboratory, who obtained the same ester by esterifying the acid prepared by sodium amalgam reduction of the acid IV derived from the 3,4-dihydrophenanthrene-1,2-dicarboxylic anhydride of Fieser and Hershberg.[7] The formation of the *cis* acid showed that *cis* addition of hydrogen to the double bond had taken place.



IV

When vinylnaphthalene and maleic anhydride were refluxed in acetic or propionic acid, the monomeric addition product was entirely naphthalenic and consisted of a mixture of anhydride and diacid that contained some of the *trans*-isomer. It is considered that the primary product Ia is isomerized under the conditions of the experiment.

Of considerable interest is the result with the *trans*-dienophile, fumaric acid. Although fumaric acid reacts more slowly than maleic anhydride (110 hours required compared with 3 hours for maleic anhydride), it was found to be superior: the yield of monomeric adduct was higher and that of copolymer was lower. The addition product from fumaric acid and vinylnaphthalene in boiling propionic acid was entirely naphthalenic. After esterification with diazomethane and evaporative distillation of the product, an 89% over-all yield of *trans*-diester (ester of IIIa) containing some *cis*-diester was obtained. The presence of the *cis*-isomer may have been the result of a conversion of some of the fumaric acid to maleic anhydride during the long reflux period at elevated temperatures.

Pure *trans*-diacid (IIIa) can be prepared by treating either the *cis*-diacid or diester (or *cis*–*trans*-mixtures) with methanolic potassium hydroxide, while pure *cis*-diacid can be obtained by gentle alkaline hydrolysis of distilled and recrystallized *cis*-anhydride (IIa). Both the *cis*- and

(1) Presented by W. E. Bachmann in Basel, Zürich, and Geneva, Switzerland, May 9–16, 1947, under the auspices of the American-Swiss Foundation for Scientific Exchange.

(2) From the Ph.D. dissertation of L. B. Scott, 1944. Present address: Shell Development Company, Emeryville, California.

(3) Cohen, *Nature*, **136**, 869 (1935).

(4) Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).

(5) In the light of our present results, the products reported by Bachmann and Kloetzel, THIS JOURNAL, **60**, 2204 (1938), as powders and melting over a wide range may have contained polymeric material.

(6) From the Ph.D. dissertation of George Fujimoto, 1947.

(7) Fieser and Hershberg, THIS JOURNAL, **57**, 1851 (1935).

trans-diacids can be recrystallized unchanged but each is converted to the *cis*-anhydride by evaporative distillation at 160–200° under reduced pressure. The pure diesters were prepared by treating the corresponding diacids with diazomethane; *cis*-dimethyl ester was also obtained by refluxing pure *cis*-anhydride with methanol and treating the resultant acid-ester with diazomethane. Both esters can be evaporatively distilled unchanged. The above results indicate that the best preparative procedure for this group of compounds involves the addition of fumaric acid to vinylnaphthalene in acetic or propionic acid followed by conversion of the *cis–trans*-mixture so obtained to either a pure *cis*- or a pure *trans*-addition product by the methods outlined above.

The results from 6-methoxy-1-vinylnaphthalene and maleic anhydride to give IIb and with fumaric acid to yield IIIb were entirely analogous. Here, too, the *cis–trans* and *trans–cis* interconversions could be carried out. The only previous work with these compounds was that of Cohen and Warren,[4] who obtained the methoxy derivative Ib from the reaction of 6 methoxy-1-vinylnaphthalene and maleic anhydride in xylene.

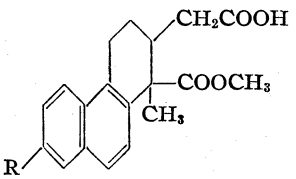
It has been reported[8] that citraconic anhydride does not react with 1-vinylnaphthalene. We found that reaction did occur in benzene, toluene, xylene, and dioxane but only alkali-soluble copolymers were formed. However, when the reaction was carried out in boiling acetic or propionic acid, the product was a mixture of copolymeric material and *cis*-naphthalenic monomer (44–49%). The Diels–Alder reaction followed by isomerization could give rise to two *cis*-naphthalenic anhydrides, one with the methyl group in the 1-position (IIc) and the isomer with the methyl group in the 2-position. Only a single isomer was isolated and all the evidence indicates that it is the product with the methyl group in the 1-position, namely, *cis*-1 methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (IIc).[9] The *trans*-diacid (IIIc) was prepared directly in yields as high as 57% from mesaconic acid and 1-vinylnaphthalene in propionic acid.

The *cis*- and the *trans*-diacids were both converted to the *cis*-anhydride by evaporative distillation. When the *cis*-diester was refluxed with methanolic potassium hydroxide for twenty-four hours, a *cis–trans*-diacid mixture was obtained.

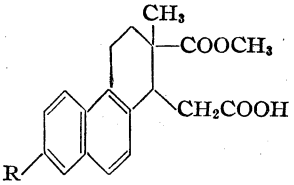
The evidence for the location of the methyl group in the 1-position is three-fold. A methyl group was introduced into the alicyclic ring of the dimethyl ester of *trans*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (ester of IIIa) by forming a sodio derivative with triphenylmethylsodium and adding methyl iodide. It was expected that the α-H adjacent to the naphthalene ring would be the one to be replaced by the methyl group in this reaction. The complex mixture of *cis*- and *trans*-compounds that resulted was converted to a totally *cis*-mixture and was fractionally crystallized. The only product isolated in pure form was the dimethyl ester of *cis*-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (ester of acid of IIc).

The calcium salt of the *cis*-diacid (derived from IIc) was dry-distilled and the distillate was dehydrogenated. The product was a mixture but it gave a single, pure picrate: the picrate of 1-methylphenanthrene.

The *trans*-diester of IIIc was half-hydrolyzed in 99% yield by refluxing its methanolic solution with one equivalent of sodium hydroxide. Since esters of secondary carboxyl groups are saponified much more rapidly than esters of tertiary carboxyl groups, the half-ester probably has the free carboxyl group in the 2-position. When a sample of *cis*-diester was similarly half-hydrolyzed a *cis–trans*-acid ester mixture resulted. An Arndt–Eistert synthesis was carried out on the *trans*-acid ester. The product, which is considered to be IV (R = H) depressed the melting point of both the *cis*- and *trans*-forms of V[10] (R = H) one of which was expected if the original adduct had the methyl group in the 2-position.



IV



V

The addition of 1-vinyl-6-methoxynaphthalene in boiling acetic or propionic acid to citraconic anhydride gave IId (60% yield isolated as the ester) and to mesaconic acid yielded IIId (72% yield isolated as the ester). The properties of the products were similar to those of the desmethoxy compounds. The *cis* and *trans* forms of the dimethyl ester of 7-methoxy-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid were obtained by C-methylation of the ester of IIIb. The product (probably IV, R = OCH_3) obtained by an Arndt–Eistert reaction on the half-ester differed from the *cis* and *trans* forms of V (R = OCH_3). Further confirmation of the structures is being sought by synthesis by other methods.

Experimental

Reactions of 1-Vinylnaphthalene

With Maleic Anhydride. (a) In Toluene.—A solution of 4.45 g. (0.0289 mole) of freshly prepared and distilled 1-vinylnaphthalene[4] (b. p. 93–99° at 9–10 mm.), 3.36 g. (0.0342 mole) of freshly sublimed maleic anhydride and 10 cc. of dry toluene was warmed on a steam-cone for three hours. Light-yellow solid began to precipitate almost immediately. The mixture was cooled and the precipitate was filtered and washed with 10 cc. of toluene; yield, 6.63 g. of a mixture of monomeric and copolymeric

(8) Bergmann and Bergmann, THIS JOURNAL, **59**, 1443 (1937).

(9) The preparation of the isomer with the methyl group in the 2-position is described in the paper by Bachmann and Chemerda which follows.

(10) Bachmann and Wilds, THIS JOURNAL, **62**, 2084 (1940).

addition products, which sintered at 125°, softened at 170° and melted at 177–191° dec. It was soluble in warm, dilute sodium hydroxide but not in dilute sodium bicarbonate, and it reacted with neutral permanganate and 5% bromine in carbon tetrachloride, in agreement with results previously reported. The solvent was removed from the filtrate in a current of air on a steam cone and the residue was treated with 45% potassium hydroxide, water and benzene (in that order). A minimum of gentle warming was used to effect solution, the clear layers were separated, and an additional 0.34 g. of almost completely copolymeric product and 0.15 g. (3% of the charged diene) of viscous, brown oil were isolated from the aqueous and benzene phases, respectively. The hydrocarbon fraction, which reacted instantly with permanganate, was presumably 1-vinylnaphthalene and its homopolymers.

A portion of the initial 6.63 g. of product was dissolved in dilute sodium hydroxide with a minimum of gentle warming and was added to excess hydrochloric acid. The resultant diacid mixture was treated with diazomethane and was evaporatively distilled at 160–200° and *ca.* 0.05 mm. A light-yellow distillate of the dimethyl ester of *cis*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (ester of IIa) was obtained in what corresponded to a 60% yield based on 1-vinylnaphthalene; a residue, presumably polymeric, remained undistilled after two hours at 200°. The diester distillate which was inactive toward neutral permanganate and 5% bromine in carbon tetrachloride crystallized from methanol in stout colorless prisms, m. p. 105.5–106.5° cor. Cohen[3,4] prepared this compound by the action of methanolic hydrogen chloride on the naphthalenic anhydride and by the action of dilute sodium hydroxide and dimethyl sulfate on the non-naphthalenic anhydride (Ia).

A second portion of the initial product was dissolved in glacial acetic acid saturated with dry hydrogen chloride and was refluxed for ninety minutes with the constant addition of a slow stream of hydrogen chloride.[4] It was then converted to the diacid, esterified with diazomethane, and evaporatively distilled as above. Approximately the same over-all yield of monomeric product was obtained as above, but it proved to be a mixture of the *cis*- and *trans*-naphthalenic dimethyl esters; m. p. 92–96.5° with previous softening at 90° after one crystallization from methanol. Fractional recrystallization using seeds of pure *cis*- and *trans*-diesters (m. p. 106° and 68°, respectively) resulted in the isolation of pure, colorless samples of each of these compounds.

A third portion was treated with acetic acid–hydrogen chloride as above and was evaporatively distilled without further treatment at 180–200° and *ca.* 0.05 mm. Yellow *cis*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (IIa) distilled in what corresponded to a 36% over-all yield based on 1-vinylnaphthalene. The *cis*-anhydride showed no activity toward neutral permanganate or 5% bromine in carbon tetrachloride and crystallized from ethyl acetate in light-yellow prisms melting at 168.5–170° cor. After treatment with Norit in acetone and recrystallization from acetone-ethyl acetate, the pale-yellow prisms melted at 170.3–170.8° cor. (reported,[3,4] 167–168° for a sample of adduct treated with acetic acid-hydrogen chloride; 169–170°[8] for a solid treated with hot glacial acetic acid and recrystallized from acetic acid–acetic anhydride and from toluene). A portion of the recrystallized *cis*-anhydride was converted to the *cis*-diacid which crystallized from glacial acetic acid in colorless, powdery crystals melting at 228–229° dec. (reported,[4] 220° dec.). Another portion of the anhydride was refluxed in methanol for twenty hours. After about one and one-half hours the pale-yellow crystals had completely dissolved to form a faintly yellow solution, which became colorless during the next few hours. The solution was cooled and treated with diazomethane without the isolation of the intermediate acid-ester. The *cis*-dimethyl ester melted at 108.5–109° cor.

When a portion of the initial addition product was evaporatively distilled without prior treatment of any kind, much decomposition occurred and some maleic anhydride was collected; over-all yield of *cis*-anhydride (IIa), *ca.* 10%.

With the rest of the initial product it was shown that the polymeric material was more soluble than the monomeric in toluene, in ethyl acetate, in glacial acetic acid and in acetone. Accordingly, the above Diels–Alder reaction was duplicated on a 0.13-mole scale and the initially precipitated addition product was recrystallized once from toluene and twice from acetone. The colorless crystals of *cis*-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid anhydride (Ia) weighed 5.3 g. (16%); m. p. 187.5–190° dec. with previous softening at 186° (reported,[4] 186–189° for a product obtained in a similar manner).

(b) **In Acetic or Propionic Acid.**—A solution of 4.2 g. (0.027 mole) of 1-vinylnaphthalene and 3.35 g. (0.034 mole) of maleic anhydride in 10 cc. of acetic acid was warmed on a steam cone for three hours. The clear, yellow solution was cooled and the colorless precipitate was filtered and washed, yield 2.91 g. (39%). The solvent was removed from the filtrate and the residue was warmed with 45% potassium hydroxide, water and benzene as before. The aqueous layer gave 3.38 g. (45%) of product; the hydrocarbon fraction weighed 0.61 g. (14%). Experiments similar to those conducted above established the following facts: (a) the product was a mixture of monomeric and copolymeric solids that reacted sluggishly and to only a slight extent with neutral permanganate and 5% bromine in carbon tetrachloride; (b) the monomeric product, a mixture of anhydride and diacid, was essentially *cis* but contained some *trans;* (c) by esterification of the total addition product, followed by evaporative distillation, the naphthalenic diester (ester of IIa) could be obtained in 45% over-all yield.

With Fumaric Acid.—A solution of 5.2 g. (0.034 mole) of 1-vinylnaphthalene and 15 g. (0.129 mole) of recrystallized fumaric acid in 250 cc. of propionic acid and 2.5 cc. of propionic anhydride was refluxed for 110 hours. The solvent was removed and the residue was treated with 45% potassium hydroxide, water and benzene as before. The aqueous layer was added with stirring to an excess of hot, dilute hydrochloric acid and the mixture was filtered hot (to keep fumaric acid in solution). The product was esterified with diazomethane and was fractionally and evaporatively distilled at *ca.* 0.05 mm., a small dimethyl fumarate fraction being discarded. The main fraction, which came over at 180–220°, was the dimethyl ester of *trans*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid mixed with 20–30% of the *cis*-diester, yield, 8.95 g. (89% yield based on 1-vinylnaphthalene). The diester mixture crystallized from methanol in large, stout prisms, m. p. 88–93.5° cor.

***cis*- to *trans*-Inversion.**—A mixture of 2 g. of the *cis*–*trans*-diester product from the fumaric acid experiment and 1.56 g. of *cis*-diacid from distilled *cis*-anhydride when refluxed with 20 cc. of 45% potassium hydroxide and 40 cc. of methanol for twenty-four hours gave 3.2 g. (95%) of ***trans*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid** (IIIa), m. p. 222–223° dec. cor. with previous softening at 221°. The acid crystallized from glacial acetic acid in powdery, colorless crystals, m. p. 225–227° dec. cor.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.09; H, 5.22; neut. equiv., 135. Found: C, 70.97; H, 5.39; neut. equiv., 136.

A portion of the above recrystallized *trans*-diacid was esterified with diazomethane and the ***trans*-dimethyl ester** was recrystallized from methanol. The colorless mixture of glistening prisms and clusters of needles melted at 67.8–68.6° cor.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.32; H, 6.13.

***trans*- to *cis*-Inversion.**—One gram of recrystallized *trans*-diacid (XVII) was evaporatively distilled at *ca.* 0.05 mm. and 160–200° (residue, 0.02 g.). The light-yellow distillate was triturated with dilute sodium bicarbonate and with water and dried, yield, 0.895 g. (96%) of the *cis*-anhydride (IIa). Its identity was established

by mixed melting points of the anhydride and the derived *cis*-dimethyl ester.

Reduction of 3,4-Dihydrophenanthrene-1,2-dicarboxylic Acid by Sodium Amalgam.[6]—A solution of the disodium salt of the acid, prepared by warming 0.78 g. of the anhydride[7] with 0.28 g. of sodium hydroxide and 2.8 cc. of water, was swirled with 28 g. of 2% sodium amalgam for twenty-five minutes while the mixture was warmed on a steam-bath. Acidification yielded 0.69 g. of acid which crystallized from acetic acid in colorless prisms, m. p. 219–221°. The dimethyl ester, prepared by means of diazomethane, crystallized from methanol in colorless prisms, m. p. 102–104°, and, after evaporative distillation, 104–105.5° alone and when mixed with the dimethyl ester of *cis*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid.

With Citraconic Anhydride.—In twenty-one different experiments in which 1 g. of freshly prepared 1-vinylnaphthalene and various weights of citraconic anhydride[11] were brought into reactive relationship with or without a solvent of low dipole moment, no monomeric product was isolated. These experiments involved reaction temperatures of 25° to 215°, reaction periods of one hour and twenty minutes to fourteen days, solvents such as benzene, toluene and xylene, and the use of sulfur, an atmosphere of nitrogen, hydroquinone and a commercial rubber-polymerization inhibitor. The copolymeric addition products that were obtained reacted sluggishly or not at all with neutral permanganate, gave indefinite neutral equivalents ranging from 165–220 (calculated for the monomer, 142), had molecular weights of more than 400 (calculated for the monomer, 284) as determined in camphor by the Rast method, and did not evaporatively distil at 240° and 0.05 mm.

A subsequent series of ten experiments conducted in acetic, propionic and valeric acids gave addition mixtures of monomeric and copolymeric addition products from which a single *cis*-naphthalenic monomer was isolated by means of evaporative distillation or fractional crystallization in yields up to 49%. In a typical run a clear solution of 8 g. (0.052 mole) of 1-vinylnaphthalene and 17.5 g. (0.156 mole) of citraconic anhydride in 50 cc. of propionic acid was refluxed for seventeen hours. The solvent was removed on a steam cone in a current of air, excess citraconic anhydride was distilled at 0.3–0.4 mm., and the residue was warmed gently with 45% potassium hydroxide, water and benzene (in that order). The benzene layer contained 1.75 g. (22%) of viscous, brown oil which reacted instantly with neutral permanganate. The dark-brown, gummy diacid addition product isolated from the aqueous layer was evaporatively distilled at 0.05 mm. and 160–200°. The light-yellow distillate of **cis-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride** (IIc) weighed 6.1 g. A sample after decolorization in acetone, crystallized from acetone–ethyl acetate in fine, colorless prisms, m. p. 140.8–141.1° cor.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.64; H, 5.42.

Distilled anhydride was dissolved in a moderate excess of warm sodium hydroxide and the solution was added to an excess of hydrochloric acid. The precipitated *cis*-diacid was isolated and 1 g. was esterified with diazomethane, yield, 1.08 g. (98%), m. p. 100–101°. The **dimethyl ester of *cis*-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid** crystallized from methanol in fine, colorless needles, m. p. 101–101.5 cor.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.97; H, 6.26.

With Mesaconic Acid.—A solution of 9.6 g. (0.062 mole) of 1-vinylnaphthalene and 20 g. (0.154 mole) of mesaconic acid[12] in 60 cc. of propionic acid was refluxed for one hundred and six hours. The solvent was removed on a steam cone in a current of air and the residue was treated with warm potassium hydroxide, water and benzene. Undissolved copolymeric material (3.35 g.) was filtered off and the clear layers were worked up as before; neutral oil in benzene layer, 1.85 g. (19%); unpurified diacid addition product, 10.35 (59%). An aliquot of the product was esterified with diazomethane and the ester was evaporatively distilled at 0.01 mm. and 160–190°; yield 57% based on 1-vinylnaphthalene. The **dimethyl ester of *trans*-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid,** after decolorization in acetone, crystallized from acetone–methanol in large, colorless prisms, m. p. 118.8–119.5° cor.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.18; H, 6.35.

The rest of the addition product was treated with Norit in acetic acid solution and was recrystallized from acetic acid. The ***trans*-diacid (IIIc)** crystallized in small, colorless prisms; m. p. 251–252° dec. cor.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 72.07; H, 5.69.

***cis*- to *trans*-Inversion.**—A solution of 0.5 g. of *cis*-dimethyl ester in 25 cc. of 45% potassium hydroxide and 50 cc. of methanol was refluxed for twenty-four hours, and the resulting mixture of *cis*- and *trans*-diacids was esterified with diazomethane. A 30% yield of *trans*-diester melting at 112–114° was isolated from the mixture.

***trans*- to *cis*-Inversion.**—Evaporative distillation of 2 g. of unpurified *trans*-diacid at 190–200° and 0.01 mm. gave 1.78 g. (95%) of the *cis*-anhydride (IIc), m. p. 136.5–138.5°. The distillate was insoluble in dilute sodium bicarbonate; its identity was established by mixed melting points of the anhydride and the derived *cis*-dimethyl ester.

Introduction of a Methyl Group into the Alicyclic Ring.—A solution of triphenylmethylsodium (prepared from 1.1 g. of triphenylchloromethane in 40 cc. of ether–benzene) was added dropwise to an ether–benzene solution of 0.75 g. of the dimethyl ester of *trans*-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid in a nitrogen atmosphere. The blood-red solution reacted immediately with the ester and a yellow-green solid precipitated. The addition was continued until a blood-red color persisted for fifteen minutes. The mixture was then shaken with 15 g. of methyl iodide for twenty-four hours. A slight excess of dilute acid was added, the solvent was removed and the residual oil was refluxed with methanolic potassium hydroxide for six hours. Preliminary crystallizations indicated that the resulting diacids were a complex mixture of *cis*- and *trans*-compounds. In order to reduce this complexity, the *cis*- and *trans*-diacids were converted to the *cis*-anhydride by evaporative distillation at 0.01 mm. and 160–200°. The light-yellow distillate was refluxed in methanol and the solution was treated with diazomethane. Fractional crystallization yielded 0.47 g. (60% yield based on starting diester) of the dimethyl ester of *cis*-1-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid; m. p. 96–99°. Recrystallization of this fraction from methanol gave colorless prisms; m. p. 99.5–100.5° alone and when mixed with an authentic sample. The m. p. was depressed by the original diester.

Degradation to 1-Methylphenanthrene.—The calcium salt of IIc prepared from 1 g. of recrystallized *cis*-anhydride was intimately mixed with 1.5 g. of calcium oxide and a little water, and the mixture was distilled. The gummy distillate was triturated with warm, dilute sodium hydroxide and was evaporatively distilled at 110–135° and *ca.* 0.05 mm. The light-yellow oil (0.35 g.) proved to be a mixture, at least a part of which contained active double bonds. Accordingly, 90 mg. of the oil was treated with 10 mg. of 30% palladium-charcoal catalyst[13] at 310° for thirty minutes in an atmosphere of nitrogen, and the aromatized product was redistilled. From the colorless distillate (m. p. 98–105°) and picric acid in absolute ethanol was obtained the picrate of 1-methylphenanthrene in fine, yellow needles; m. p. 135.7–136.2°; mixed melting point with the picrate of authentic 1-methylphe-

(11) Shriner, Ford and Roll, *Org. Syntheses*, **11**, 28, 70 (1931).

(12) Shriner, Ford and Roll, *ibid.*, **11**, 74 (1931).

(13) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

nanthrene (136–136.5°), 136–136.5°. The hydrocarbon, regenerated from the picrate by treatment with ammonium hydroxide, crystallized from ethanol in thin, colorless plates, m. p. 116–118°; mixed melting point with 1-methylphenanthrene (120–121°), 118.5–120.5° with previous softening at 117°. A portion of the regenerated hydrocarbon was converted to the trinitrobenzene complex, which crystallized from ethanol in fine, yellow needles melting at 157.5–158.5° alone and when mixed with an authentic sample (m. p. 157.5–158.5°). 2-Methylphenanthrene melts at 55–56°; its picrate at 118–119°.

Hydrolysis to the Acid Ester.—A solution of 1.5 g. of recrystallized *trans*-dimethyl ester, 9.7 cc. of 0.5 *N* sodium hydroxide (1.01 equivalents) and 35 cc. of methanol was refluxed for twenty-four hours. From the solution was isolated 1.425 g. (99.5%) of the acid ester, presumably *trans*-**1-methyl-1-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid,** melting at 186–189.5°. The acid ester crystallized from methanol in colorless prisms, m. p. 193–195° cor.; after another recrystallization from acetone, 194.2–195° cor.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08; neut. equiv., 298. Found: C, 72.47; H, 6.11; neut. equiv., 301.

When the above hydrolysis was carried out on the *cis*-dimethyl ester, the product was a mixture of *cis*- and *trans*-acid esters, m. p. 169.5–181° with previous softening at 162°. Esterification of this acid ester mixture with diazomethane and fractional crystallization of the product gave crystals of pure *cis*-diester and of pure *trans*-diester.

Arndt–Eistert Reaction on the Acid Ester.—A mixture of 4.54 g. of unpurified *trans*-acid ester, 5 cc. of dry ether, 5 cc. of dry benzene and 4 cc. of oxalyl chloride (a large excess) was allowed to react for six hours. A solution was obtained in three hours and gassing ceased after about five and one-half hours. Volatile compounds were removed completely *in vacuo*, the acid chloride was dissolved in dry ether–benzene, and the solution was added dropwise with swirling to a 3-mole excess of ice-cold, ethereal diazomethane. After two hours at room temperature, the solvents were removed and the crystalline yellow diazoketone was refluxed with silver oxide in absolute methanol for six hours. A total of seven 0.05-g. portions of silver oxide was added during this period; no evolution of nitrogen was noted after the first three hours. The diester isolated from the filtered mixture was evaporatively distilled at 175–195° and *ca.* 0.05 mm. Since the viscous, yellow oil (4.28 g.) did not crystallize readily, it was dissolved in methanol and refluxed for two and one-half hours with 1.01 equivalents of *N* methanolic sodium hydroxide.[10] The acid ester (4.05 g.), presumably **1-methyl-1-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid** (IV, R = H), after decolorization in acetone, crystallized from acetone-methanol in colorless prisms; yield, 2.48 g. (52%), m. p. 148–149.5° cor. After a second recrystallization, a sample melted at 150.9–151.7° cor.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.27; H, 6.43.

This compound depressed the melting points of samples of α- (m. p. 133–134°) and β- (m. p. 158–160°) 2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid.[10]

Reactions of 1-Vinyl-6-methoxynaphthalene

With Maleic Anhydride.—Two grams (0.011 mole) of freshly prepared and recrystallized 1-vinyl-6-methoxynaphthalene (obtained in 68–79% yield[4]) and 2.2 g. (0.022 mole) of sublimed maleic anhydride were refluxed in 8 cc. of glacial acetic acid for two and one-half hours. The yellow color that appeared at the instant of mixing gradually deepened to a red-orange. The solvent was removed from the clear solution and the reaction mixture was treated with 45% potassium hydroxide, water and benzene. The mixture was filtered and the clear layers were separated and worked up as in the case of desmethoxy experiments. From the benzene layer was isolated 0.98 g. (49%) of a brown oil (presumably the starting vinyl compound and/or its homopolymers) that reacted instantly with neutral permanganate and from the aqueous phase there was obtained 1.27 g. of red-orange diacid that showed little double bond activity, m. p. indefinite. A portion of the diacid evaporatively distilled at 185–225° and *ca.* 0.03 mm. gave yellow *cis*-anhydride (26% over-all yield). After treatment with Norit in acetone solution, the ***cis*-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride** (IIb) crystallized from ethyl acetate in glistening yellow prisms, m. p. 160.5–161° cor. A recrystallization from acetone did not change the color or the melting point.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.37; H, 4.95.

Cohen and Warren reported 171–175° for the non-naphthalenic adduct (Ib). The rest of the diacid was esterified with diazomethane and the *cis*-dimethyl ester (30% over-all yield) was evaporatively distilled, m. p. 117.5–118° after recrystallization from methanol. There was some indication that a small impurity of *trans*-diester was present.

When distilled *cis*-anhydride was refluxed with methanol for five hours, the yellow crystals dissolved to give a solution which gradually became colorless. Upon cooling, thin, colorless flakes of *cis*-acid ester precipitated, m. p. 208.5–210.5° cor. The mixture was treated with diazomethane; the **dimethyl ester of *cis*-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid** crystallized from methanol in large, colorless prisms, m. p. 119.5–120° cor.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.50; H, 6.24.

Several other similar runs were made with quantities of reactants identical to the above but varying one or more of the reaction conditions. In an experiment in which only half as much acetic acid (4 cc.) and a reaction temperature of only 90–95° was used, solid began to precipitate after six minutes of the two and one-half hour reaction period. The addition product (2.38 g.) was mainly copolymeric and only a 9% over-all yield of *cis*-diester distilled. When 4 cc. of toluene was used as a solvent only 7% yield of *cis*-diester was obtained. When additional maleic anhydride was used as the solvent in a two and one-half hour run at 90–95°, the addition product was one-half monomeric (15% yield).

With Fumaric Acid.—A solution of 2 g. (0.011 mole) of 1-vinyl-6-methoxynaphthalene and 1.5 g. (0.013 mole) of recrystallized fumaric acid in 10 cc. of glacial acetic acid was refluxed for eighteen hours, and the reaction mixture was worked up as above; 0.42 g. (21%) of brown oil with active double bonds was isolated from the benzene layer. The aqueous suspension of the nearly colorless diacid addition product was filtered while hot; yield 2.44 g. A portion of the diacid was esterified with diazomethane and was fractionally and evaporatively distilled at *ca.* 0.05 mm. After traces of dimethyl fumarate had distilled at 100–140°, the *trans*-dimethyl ester came over at 170–225° in what corresponded to a 71% over-all yield, m. p. 117–118° after recrystallization from methanol. Fractional crystallization of the diester indicated that it contained about 5–12% of the *cis*-isomer.

In a second experiment identical with the preceding one except that a fifty-six hour reflux period was used, a 72% over-all yield of distilled diester (80–90% *trans*- and 10–20% *cis*-) was obtained. Addition had taken place to the extent of 90%, but more copolymeric material was produced.

Part of the diacid addition product from the first experiment was dissolved in methanol and was refluxed for ten hours with 45% potassium hydroxide to isomerize the *cis*-impurity. The resultant ***trans*-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid,** after decolorization with Norit and recrystallization from glacial acetic acid, crystallized from acetone in colorless prisms; m. p. 220.5–221.5° dec. cor.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; neut.

equiv., 150. Found: C, 68.16; H, 5.45; neut. equiv., 152.5.

The *trans*-**dimethyl ester** prepared by means of diazomethane crystallized from methanol in fine, colorless crystals; m. p. 118.5–119° cor.; after another recrystallization from methanol–acetone, 119.4–119.8° cor.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.50; H, 6.15.

The mixed melting point of the *cis*- (m. p. 119.5–120° cor.) and *trans*- (m. p. 118.8–119.3° cor.) dimethyl esters was 100–115° with previous softening at 98°.

***cis*- to *trans*-Inversion.**—A solution of 1 g. of the *cis*-diester in 10 cc. of 45% potassium hydroxide and 20 cc. of methanol was refluxed for twenty-three hours. The diacid was treated with diazomethane and the resultant *trans*-diester was crystallized from methanol; yield, 95%; m. p. 118.8–119.5° cor. alone or when mixed with an authentic sample.

***trans*- to *cis*-Inversion.**—Evaporative distillation of the unpurified *trans*-diacid at 100–225° and *ca.* 0.03 mm. yielded the *cis*-anhydride as shown by mixed melting points of the recrystallized anhydride and of the derived *cis*-dimethyl ester.

With Citraconic Anhydride.—A solution of 4.75 g. (0.026 mole) of 1-vinyl-6-methoxynaphthalene and 6.2 g. (0.055 mole) of citraconic anhydride in 50 cc. of propionic acid was refluxed for twenty-one hours. The diacid (5.84 g.), which showed no olefinic activity, was divided into two portions. One part on evaporative distillation at 200–225° and *ca.* 0.02 mm. gave ***cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (IId)** (56% yield), which crystallized from ethyl acetate in fine, colorless prisms; m. p. 127.5–128.5°, and after two more recrystallizations, 129–129.7° cor.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.74; H, 5.28.

The rest of the diacid was treated with excess diazomethane, and the *cis*-**dimethyl ester** was evaporatively distilled (60% yield) and crystallized from methanol in fine, colorless needles; m. p. 165–166°, and after another recrystallization from acetone, 168.3–168.8° cor.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.32; H, 6.55.

With Mesaconic Acid.—A solution of 4.75 g. (0.026 mole) of 1-vinyl-6-methoxynaphthalene and 7.07 g. (0.055 mole) of mesaconic acid in 40 cc. of propionic acid was refluxed for four days. Considerable copolymeric material insoluble in both warm benzene and warm base was filtered off during the isolation procedure. Grayish-white *trans*-diacid (5.43 g.) was esterified with diazomethane and the ester was evaporatively distilled under reduced pressure, 64% yield. The **dimethyl ester** of the *trans*-acid after two recrystallizations from methanol and two from acetone–methanol formed colorless platelets; m. p. 134.4–135° cor.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.47; H, 6.54.

The ***trans*-1-Methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (IIId)**, obtained by methanolic alkaline hydrolysis of the distilled ester, after decolorization with Norit in glacial acetic acid, crystallized in fine, colorless crystals; m. p. 227–232° dec. with previous softening; after further recrystallization from acetic acid and then from acetone, 243–244° dec. cor.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77; neut. equiv., 157. Found: C, 68.96; H, 5.81; neut. equiv., 158.

***cis*- to *trans*-Inversion.**—When 0.5 g. of the *cis*-diester 30 cc. of 45% potassium hydroxide and 60 cc. of methanol were refluxed for thirty-six hours, the diacid (0.44 g., m. p. 195–199.5° dec.) was mainly *trans* as judged by fractional crystallization of the *cis*-*trans*-diester mixture obtained by esterification. About a 40% yield of *trans*-dimethyl ester melting at 130–132.5° was isolated.

***trans*- to *cis*-Inversion.**—Evaporative distillation of a sample of crude *trans*-diacid at 180–225° and *ca.* 0.01 mm. gave the *cis*-anhydride in about 90% yield.

Introduction of a Methyl Group into the Alicyclic Ring.—The reaction between 1 g. of the dimethyl ester of *trans*-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid and a solution of triphenylmethylsodium was carried out as described for the desmethoxy analog; much dark-green solid precipitated. The mixture was then shaken with 20 g. of methyl iodide for fourteen hours and was worked up as before. The diacid mixture (from which 0.2 g. of the *cis*- and a few mg. of the *trans*-diester can be isolated if it is esterified) was evaporatively distilled at *ca.* 0.01 mm. and the resultant *cis* anhydride was refluxed with methanol for ten hours. The *cis*-acid ester was treated with diazomethane and the product was recrystallized from methanol; yield, 0.79 g. (76% over-all yield) of the dimethyl ester of *cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid; m. p. 163.5–165°, and after another recrystallization 164.5–165.5° alone or when mixed with an authentic sample.

Hydrolysis of the *trans*-Dimethyl Ester to the Acid Ester.—Two grams of *trans*-dimethyl ester, 5.46 cc. of 1.07 *N* sodium hydroxide and 75 cc. of methanol were refluxed for twenty-four hours. An aqueous suspension of the sparingly soluble sodium salt of the acid ester was added slowly with stirring to an excess of hydrochloric acid, stirring was continued for three hours, and the mixture was left overnight before filtering; yield 1.81 g. (95%), m. p. 186.5–188.5° with previous softening. The acid ester, presumably ***trans*-1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid**, was decolorized with Norit and recrystallized from acetone; m. p. 194.5–195.5° cor.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; neut. equiv., 328. Found: C, 69.52; H, 5.98; neut. equiv., 328.

Arndt–Eistert Reaction on the Acid Ester.—By the method described for the desmethoxy analog, the acid ester (2.5 g.) gave yellowish crystals of the diazoketone; m. p. 151–153° dec. This was refluxed for five hours with absolute methanol and several portions of silver oxide, and the resulting dimethyl ester was evaporatively distilled at 170–190° and *ca.* 0.03 mm.; yield of light-yellow, glassy solid, 2.39 g. This was refluxed in methanolic solution with one equivalent (+1.5% excess) of *N* sodium hydroxide for two and one-half hours; yield, 2.11 g. The acid ester, presumably ***trans*-1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid (IV**, R = OCH_3), after decolorization in acetone, crystallized from methanol in colorless prisms; yield, 1.16 g. with m. p. 171–172° and 0.52 g. with m. p. 169–170.5°; total, 64% over-all yield. After a recrystallization from ethyl acetate, the acid ester crystallized from acetone–methanol in stout, colorless plates; m. p. 173.4–173.8° cor.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.47; H, 6.51.

This compound markedly depressed the melting points of samples of α- (m. p. 137–138°) and β- (m. p. 211–212°) 2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid.[14]

The **dimethyl ester** prepared by means of diazomethane, after one crystallization from ligroin–benzene and two recrystallizations from acetone–methanol, formed colorless prisms; m. p. 85.2–86.3° cor.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.73; H, 6.59.

This compound depressed the melting points of samples of α- (m. p. 126–126.5°) and β- (m. p. 114–114.5°) dimethyl ester of 2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid.[14]

Summary

The addition of fumaric acid to 1-vinylnaphtha-

(14) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

lene gave a higher yield of monomeric adduct than did maleic anhydride.

Citraconic anhydride and mesaconic acid add to 1-vinylnaphthalene and to 1-vinyl-6-methoxynaphthalene to give the *cis* and *trans* forms of adducts in which the methyl group is in the 1-position of the hydrophenanthrene nucleus.

cis–trans Interconversions of the products are described.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 1, 1947

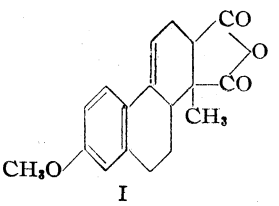
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Diels–Alder Reaction of 1-Vinyl-6-methoxy-3,4-dihydronaphthalene with Citraconic Anhydride[1]

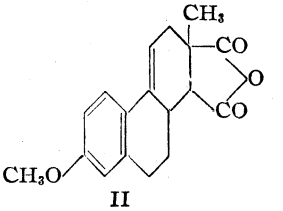
BY W. E. BACHMANN AND J. M. CHEMERDA[2]

1-Vinyl-6-methoxy-3,4-dihydronaphthalene has been allowed to react with a number of dienophiles in order to obtain estrogens or suitable intermediates for the synthesis of estrone.[3,4,5] In 1941 we began an investigation[6] of the reaction of this diene with citraconic anhydride.[7] Theoretically, two sets of products were possible: I, with the methyl group in the 1-position, and II, with the methyl group in the 2-position. In virtue of the three asymmetric carbon atoms, each of the structures can exist in eight stereoisomeric forms (four racemic mixtures). However, the principle of *cis* addition reduces the number to two racemic mixtures for each structure; and, if the rule of the "maximum accumulation of double bonds" prior to addition is applicable, only one racemic mixture for each structural isomer should be obtained. The configuration of the 2-methyl derivative should be IIa; similarly, the single racemic mixture of I would have the H's on C_2 and C_{10a} and the methyl group on C_1 *cis* to each other.

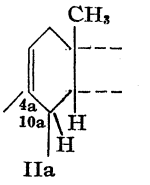
Citraconic anhydride reacted with 1-vinyl-6-methoxy-3,4-dihydronaphthalene in boiling benzene to give a mixture of adducts in 70% yield, from which two pure, crystalline anhydrides were isolated. The anhydrides, m. p. 128° (one part)



I



II



IIa

and m. p. 163° (two parts), comprised at least 60% of the mixture.[8] These results illustrate the pronounced steric selectivity of the Diels–Alder addition. For convenience in isolation, the crude product was hydrolyzed, and the acid portion was separated from neutral material and reconverted to anhydrides by fusion at 190–200°. It was not determined whether the original compounds were regenerated or whether this treatment shifted the double bond (for example, to the 4a-10a position).[9]

The 128° anhydride is *cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (I), since treatment of it or the corresponding acid with palladium on charcoal[10] at 315° for a short time yielded 1-methyl-7-methoxyphenanthrene and (after hydrolysis) the *cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V) of Bachmann and Scott.[7] The 163° anhydride is *cis*-2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (II); it and the acid (IV) derived from it were transformed smoothly into 2-methyl-7-methoxyphenanthrene[11] and the anhydride of

(1) Presented by W. E. Bachmann in Basel, Zürich, and Geneva, Switzerland, May 9–16, 1947, under the auspices of the American-Swiss Foundation for Scientific Exchange.

(2) Research Associate supported by a grant from the Horace H. Rackham Fund at the University of Michigan, 1941–1942. Present address: Merck and Co., Rahway, N. J.

(3) Dane and co-workers, *Ann.*, **532**, 29, 39 (1937); **536**, 183, 196 (1938); **537**, 246 (1939).

(4) Goldberg and Müller, *Helv. Chim. Acta*, **23**, 831 (1940).

(5) Bockemuller, U. S. Patent 2,179,809; *C. A.*, **34**, 1823 (1940).

(6) This investigation, which was interrupted by the war, is now being resumed. Further work on the reaction of the diene with citraconic anhydride and a study of the reaction with mesaconic acid are in progress.

(7) See Bachmann and Scott, THIS JOURNAL, **70**, 1458 (1948), for the addition of citraconic anhydride and of mesaconic acid to 1-vinyl-6-methoxynaphthalene.

(8) *Cf.* Breitner, *Med. u. Chem.*, **4**, 317 (1942); *Chem. Zentr.*, **114**, I, 2688 (1943); *C. A.*, **38**, 4953 (1944). The German abstract appeared after most of our experimental work had been completed. Breitner obtained a potent estrogen from an anhydride adduct (m. p. 210°) prepared from the diene and citraconic anhydride. Later the Government Intelligence Team (Report No. 248, Pharmaceuticals at the I. G. Farbenindustrie Plant, Elberfeld, Germany, Office of the Publication Board, Department of Commerce, Washington, D. C.) reported that Breitner's product was prepared from an adduct melting at about 125° and at 160° after several recrystallizations.

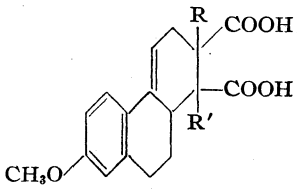
(9) The structures I, II, III, and IV are written with the double bond in the 4–4a position until more information is available.

(10) Hartung, THIS JOURNAL, **50**, 3370 (1928); **66**, 888 (1944).

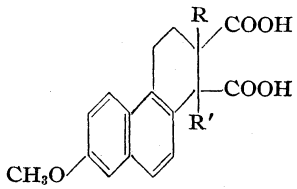
(11) Heer and Miescher, *Experientia*, **3**, 322 (1947), recently reported the formation of 1-methyl- and 2-methyl-7-methoxyphenanthrene from the adducts which they obtained from the diene and citraconic anhydride. An example of a 1-methyl-1-carboxyhydrophenanthrene derivative which has been decarboxylated and dehydrogenated is abietic acid (Ruzicka, *et al.*, *Helv. Chim. Acta*, **6**, 692 (1923); **16**, 842 (1933)) and of a 2-methyl-2-carboxy derivative is estric acid (Butenandt, Weidlich and Thompson, *Ber.*, **66**, 601 (1933)).

cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (anhydride of VI).[12] The formation of the 2-methyl- as well as the 1-methylhydrophenanthrene adduct is in contrast to the behavior of 1-vinylnaphthalene and 1-vinyl-6-methoxynaphthalene, which yielded only the 1-methyl derivatives with citraconic anhydride and with mesaconic acid.[7]

The 1-methylhexahydro acid III, derived from the 128° anhydride, was hydrogenated smoothly in the presence of palladium-charcoal to a mixture of stereoisomeric octahydro acids (VIIa) from which a single pure compound was isolated in 70–80% yield *via* the dimethyl ester or more efficiently through the anhydride. It is of interest that a single compound was formed in such a high yield on reduction.

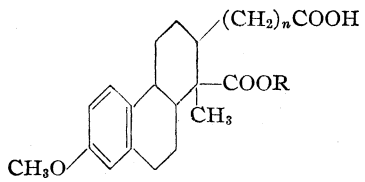


III, R′ = CH_3; R = H
IV, R = CH_3; R′ = H

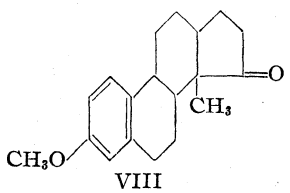


V, R′ = CH_3; R = H
VI, R = CH_3; R′ = H

Two Arndt–Eistert reactions were carried out on the acid ester (presumably VIIb) obtained by half hydrolysis of the dimethyl ester of VIIa. Pyrolysis of the lead salt of the product (presumably VIId) yielded a neutral product, m. p. 100–101°, whose analysis was in fair agreement with that of the methyl ether of an isomer of estrone (VIII). The small amount of material available prevented us from fully characterizing the compound.

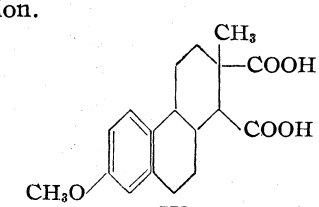


VIIa, n = 0, R = H
VIIb, n = 0, R = CH_3
VIIc, n = 1, R = CH_3
VIId, n = 2, R = H
VIIe, n = 2, R = CH_3



VIII

The 2-methylhexahydro acid IV, derived from the 163° anhydride, absorbed hydrogen rapidly in acetic acid only when a large proportion of Adams catalyst was employed. Whether this is indicative of the double bond lying in the 4a-10a position is left undecided at this time. From the mixture of products a crystalline octahydro acid IX could be isolated but only in low yield. After conversion of the non-crystallizable acids to anhydrides by distillation, a crystalline anhydride of the octahydro acid was isolated readily. Crystalline derivatives of the same octahydro acid were obtained by reduction of the hexahydro acid ester and the dimethyl ester. Various methods suggest themselves for converting these compounds to estrone or its stereoisomers and these are now under investigation.



IX

Experimental

Preparation of 1-Vinyl-6-methoxy-3,4-dihydronaphthalene.—Purified acetylene was bubbled at the rate of 2–3 bubbles per second for twenty-four hours through an ice-cold, ethereal solution of ethylmagnesium iodide (the iodide was used instead of the bromide[3] because of the greater solubility of the acetylene Grignard reagent in ether–benzene) prepared from 28 g. of magnesium and 110 cc. of ethyl iodide in 500 cc. of ether. The ether layer was decanted from the heavy, viscous purple layer of the acetylene-bis-magnesium iodide, which was then dissolved in 300 cc. of dry thiophene-free benzene. To the filtered Grignard solution, 20 g. of 6-methoxy-1-tetralone[13] was added in one portion. After eight hours at room temperature, the reaction mixture was hydrolyzed with ice-cold ammonium chloride solution, and the filtered organic layer was evaporated under reduced pressure at 35–40°. The partly solid residue was filtered and the solid diol, —C(OH)C≡C(OH)C—, on the filter was washed with small amounts of ether; after a second evaporation, a second crop of diol was removed. The filtrate was evaporated in a modified Claisen flask with an 8-inch Vigreux column, and the apparatus was filled with nitrogen and then evacuated before the dehydration was carried out. At 100–110° (0.5–0.6 mm.) the liquid bubbled vigorously as water was evolved; the eneyne, 1-ethynyl-6-methoxy-3,4-dihydronaphthalene, distilled smoothly at 118–123° (0.5–0.6 mm.) (reported, 124–130° at 0.5 mm.[3] and 120° at 0.1 mm.[4] for a purer sample); yield, 10.9 g. (52%). The eneyne reacted instantly with ammoniacal silver nitrate solution and with an alcoholic mercuric chloride solution in the presence of sodium ethoxide.[14]

For best results exposure of the carbinol to air should be avoided throughout. Midway in the distillation of a batch of acetylenic carbinol which had been kept overnight in a refrigerator, a sudden violent reaction set in with the formation of a green tar in the flask and the receiver. This danger can be partially averted by storage of the carbinol in an atmosphere of nitrogen at 0°, but it is better to carry out the entire sequence of steps from the hydrolysis of the Grignard reaction mixture to the distillation without interruption. Because the eneyne oxidized rapidly in the presence of air even at 0°, the partial hydrogenation to the diene was carried out immediately after the distillation.

(12) This compound should prove useful in a project now in progress concerned with the determination of the configuration at C/D ring fusion of equilenin, estrone and other steroids.

(13) Burnop, Elliot and Linstead, *J. Chem. Soc.*, 727 (1940). In place of steam distillation, we distilled under reduced pressure the crude 6-methoxy-1-tetralone obtained by chromic acid oxidation of 6-methoxytetralin.

(14) Shriner and Fuson, "The Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd edition, 1940, p. 59.

The eneyne (10.9 g.) in 30–40 cc. of absolute alcohol with 0.5 g. of palladium-charcoal absorbed the equivalent of one mole of hydrogen at slightly more than one atmosphere pressure in one to three hours. After filtration from the catalyst and concentration *in vacuo* at 35–40°, 1-vinyl-6-methoxy-3,4-dihydronaphthalene was obtained as a practically colorless liquid. Since the product gave no test for an ethynyl group, it was used in the Diels-Alder reaction without further purification. A sample reacted instantly with maleic anhydride in benzene to give an adduct melting at 201–202° (reported,[3] 201°) after one recrystallization.

Reaction of the Diene with Citraconic Anhydride.—A solution of 31 cc. of citraconic anhydride and 10.9 g. of the diene in 150 cc. of dry thiophene-free benzene was refluxed for forty-eight hours, the solvent was removed from the mixture in a current of air, and the residual citraconic anhydride was distilled at 100° (0.5 mm.). The sticky, semi-crystalline residue was warmed gently on a steam-bath with 10 cc. of 45% aqueous potassium hydroxide solution and 40 cc. of water until the anhydrides were hydrolyzed (fifteen minutes). After the removal of 1.5 g. of alkali-insoluble material by extraction with ether, the aqueous solution was added with stirring to a solution of 15 cc. of concentrated hydrochloric acid and 15 cc. of water. The precipitated acid, after it had crystallized (on standing or when seeded and scratched) was filtered and washed thoroughly with water. A solution of the product in ethyl acetate deposited crystalline acid (m. p. 174–179°) which on continued recrystallization was transformed to an anhydride (m. p. 161.5–165°). The product was separated more efficiently by recrystallization of the anhydrides (12.3 g. or 70%) which were prepared by fusion of the above mixture of dicarboxylic acids at 190–200° in an atmosphere of nitrogen. Breitner[8] obtained about the same yield of adduct by heating the diene with citraconic anhydride at 50–60° and allowing the temperature to rise to 160–190°.

A hot solution of the anhydrides in 25 cc. of ethyl acetate and 10 cc. of acetone was concentrated and then seeded with the high melting isomer. After one to two hours at room temperature, 4.6 g. of ***cis*-2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (II)** was obtained as square yellowish tablets, m. p. 158–162°. A colorless, constant-melting product was obtained after evaporative distillation at 160–200° (0.01 mm.) and one recrystallization from ethyl acetate, m. p. 163–163.5°.

Anal.[m15] Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 73.1; H, 6.2.

The anhydride reacted readily with a dilute solution of potassium permanganate in acetone.

The mother liquor from the first crop of high melting anhydride was concentrated to a volume of about 10 cc. and allowed to cool undisturbed. A mixture of crystals was obtained consisting of small yellow tablets (m. p. *ca.* 160°) and large, jagged, rectangular, colorless masses, m. p. 125–150°. The two forms were separated mechanically and 2.6 g. of fairly pure ***cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (I)** was obtained. After one recrystallization from ethyl acetate the anhydride melted at 125–128°; yield 2.1 g. After evaporative distillation at 0.01 mm. and recrystallization from ethyl acetate–ligroin, the anhydride melted at 127–128°.

Anal.[m] Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 72.8; H, 6.2.

Additional crops of material were obtained from the mother liquor after removal of the second crop. These usually were rich in the lower melting anhydride. In one experiment there appeared to be some indication of the presence of an additional isomer but complete characterization of this substance has not been accomplished.

(15) Analyses marked "m" are by Dr. T. S. Ma and those marked "k" are by Mr. Fred Kaufmann.

Derivatives and Reactions of 1-Methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic Acid

Proof of Structure of the 128° Anhydride.—Three hundred milligrams of the 128° anhydride (I) and 150 mg. of palladium charcoal[10] were heated in an atmosphere of nitrogen at 310–315° for fifteen minutes when gas evolution ceased. The product after separation from the catalyst was digested with *N* sodium hydroxide. The insoluble portion (10 mg.) gave a yellow trinitrobenzene derivative in alcohol; m. p. 136–138°. Mixed melting point determinations with samples of the trinitrobenzene derivatives of synthetic 1-methyl and 2-methyl-7-methoxyphenanthrene proved conclusively that the neutral material was 1-methyl-7-methoxyphenanthrene.

Acidification of the alkaline filtrate followed by recrystallization of the product from aqueous acetone yielded 150 mg. of an acid as colorless needles, m. p. 196–198° dec. (bath pre-heated to 185°). The dimethyl ester, prepared by means of diazomethane crystallized from methanol in colorless needles, m. p. 168–169° alone and when mixed with dimethyl ester of *cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V).[7]

1-Methyl-7-methoxyphenanthrene was prepared in the following manner. One gram of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene was added to a solution of methylmagnesium iodide prepared from 0.3 g. of magnesium. After forty-eight hours at 0°, the reaction mixture was hydrolyzed with ice-cold ammonium chloride solution and the desired carbinol, 1-methyl-1-hydroxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, was isolated by evaporation of the filtered organic layer; yield of product after trituration with ethyl acetate–ligroin, 0.48 g., m. p. 78–92°. More material was isolated from the mother liquor.

A mixture of 480 mg. of the carbinol and 100 mg. of palladium charcoal[10] was heated at 300–320° in an atmosphere of nitrogen for thirty minutes. An acetone extract of the reaction mixture was filtered, concentrated and diluted with alcohol. The 1-methyl-7-methoxyphenanthrene which crystallized in nacreous colorless leaflets (200 mg., m. p. 131–132.5°) was recrystallized from alcohol, purified through the picrate and recrystallized from absolute alcohol; m. p. 135–136° (reported,[16] 133.5–134°).

The **trinitrobenzene derivative** crystallized from hot alcohol–benzene in bright yellow needles, m. p. 143–143.5°.

Anal.[k] Calcd. for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94 Found: C, 60.59; H, 3.93.

Dimethyl Ester of the Acid III.—**The dimethyl ester of *cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic acid,** obtained from the crude diacid and diazomethane, crystallized from aqueous methanol in rectangular prisms; m. p. 83.5–85°.

Anal.[m] Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.6; H, 6.8.

Reduction of the Hexahydro Acid.—The crude diacid from 4.3 g. of the 128° anhydride (I) in 75 cc. of acetic acid with 1.5 g. of palladium–charcoal absorbed one mole equivalent of hydrogen in one to two hours at slightly more than one atmosphere pressure. When 10 to 20% of catalyst by weight was used, about twenty-four hours was required for the hydrogenation. The filtered solution was evaporated to dryness and the solid diacid mixture was converted either to the anhydrides or to the dimethyl esters for purification. The anhydrides were obtained by refluxing the diacid with 40 cc. of acetic anhydride and 25 cc. of acetyl chloride for three hours. After removal of the solvents under reduced pressure, 2.85 g. of an anhydride crystallized from ethyl acetate as glistening thick prisms; m. p. 161–163.5°. From the filtrate an additional 0.7 g. of anhydride, m. p. 162–164°, was obtained; total yield, 83%. After one more recrystalliza-

(16) Short and Stromberg, *J. Chem. Soc.*, 319 (1936); *ibid.*, 516 (1937).

tion, ***cis*-1-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic anhydride (anhydride of VIIa)** was pure and melted at 163–164°.

Anal.[k] Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 72.0; H, 7.0.

The same dimethyl ester was obtained by diazomethane treatment of the diacid mixture and of the hydrolysis or methanolysis product of the pure anhydride. The **dimethyl ester of *cis*-1-methyl-7-methoxy-1,2,3,4,4a,9,-10,10a-octahydrophenanthrene-1,2-dicarboxylic acid** crystallized from methyl alcohol in colorless needles, m. p. 126–127.5°.

Anal.[m] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.5; H, 7.4.

Hydrolysis of the Dimethyl Ester of VIIa to the Acid Ester.—A solution of 3.7 g. of the above *cis*-dimethyl ester in 50 cc. of methanol and 10.5 cc. of 1.04 *N* sodium hydroxide solution was refluxed for thirty-eight hours. After removal of methanol in a current of air, the residue was treated with water and ether. The ethereal solution contained 0.7 g. of a mixture of *cis* and *trans* esters. Acidification of the aqueous layer gave the acid ester (2.7 g.; m. p. 169–183°) which crystallized from ethyl acetate in colorless prisms; yield, 2.56 g. (85%); m. p. 184–188°. After a few recrystallizations from ethyl acetate the acid ester, presumably ***trans*-1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-carboxylic acid (VIIb)** melted at 186–187° dec.

Anal.[m] Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.3. Found: C, 69.0; H, 7.3.

The acid ester is assigned the *trans* configuration because on treatment with diazomethane it gave a practically quantitative yield of a **dimethyl ester** (different from the original diester) which crystallized from methanol in colorless rhombs; m. p. 134–135°. A mixture of this ester and the original diester melted at 107°.

Anal.[m] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.7; H, 7.4.

Partial hydrolysis of the *trans*-dimethyl ester gave the same acid ester in 85% yield.

Arndt–Eistert Synthesis on the Acid Ester VIIb.—Oxalyl chloride was found to be superior to thionyl chloride and phosphorus pentachloride for preparing the ester acid chloride. The acid ester (50 mg.) was added to 0.25 cc. of oxalyl chloride in 1 cc. of dry thiophene-free benzene and after two hours at room temperature the solution was evaporated. Treatment of the residual yellow gum with methanol gave 40 mg. of pure *trans*-dimethyl ester; no acidic products were isolated.

After many failures the following procedure was found to be successful for the Arndt–Eistert synthesis. The acid chloride solution, prepared as above from 500 mg. of pure *trans*-acid ester, was evaporated under reduced pressure at room temperature. Twice, the residue was redissolved in benzene and the solution evaporated. A solution of the colorless acid chloride in 15 cc. of dry benzene was added slowly to an ice-cold distilled, ethereal solution of diazomethane (prepared from 4.5 cc. of nitrosomethylurethan). The reaction appeared to be slow. After one day at 0° and another day at room temperature, the reaction mixture was filtered and evaporated to dryness under reduced pressure. The semicrystalline mass yielded 390 mg. (72%) of crystalline diazoketone upon trituration with ether–ligroin, m. p. 131–133° dec.

For the rearrangement, a silver mirror was prepared by refluxing a suspension of 0.1 g. of silver oxide in 15 cc. of methanol for one and one-half hours. To the hot mixture, the diazoketone was added in one portion. After one-half hour of refluxing another portion of silver oxide was added and refluxing was continued for another half-hour. After filtration of the suspension and evaporation of the solvent, the yellow oil was evaporatively distilled at 180–230° (0.03 mm.) and saponified by refluxing with 0.9 cc. of 1.04 *N* sodium hydroxide solution for three hours; weight of acid ester, 270 mg. The acid ester, presumably **1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,-9,10,10a-octahydrophenanthrene-2-acetic acid (VIIc)**, crystallized from ethyl acetate in glistening prisms; yield 180 mg. (57%), m. p. 182–186°; after several recrystallizations of the compound the m. p. was 186–187°.

Anal.[k] Calcd. for $C_{20}H_{26}O_5$: C, 69.33; H, 7.56. Found: C, 69.95; H, 7.76.

A portion of the pure acid ester with diazomethane gave the **dimethyl ester** which crystallized from methanol in tiny colorless prisms; m. p. 78–79°.

Anal.[k] Calcd. for $C_{21}H_{28}O_5$: C, 70.0; H, 7.8. Found: C, 69.9; H, 8.0.

For the next Arndt–Eistert synthesis, 500 mg. of the acid ester (VIIc) was allowed to react with 3 cc. of oxalyl chloride in 2 cc. of dry benzene for three hours at room temperature. The reaction of the acid chloride with diazomethane at 0° was rapid; after twelve hours at 0°, the suspension of crystalline diazoketone in ether was evaporated to dryness. In this manner 570 mg. of a light cream-colored diazoketone was obtained, m. p. 138–140°.

The crude diazoketone was submitted to a rearrangement in methanol as described, and the product was hydrolyzed by refluxing with 1.45 cc. of 1.03 *N* sodium hydroxide solution in 10 cc. of methanol for one and one-half hours; weight of acid ester, 530 mg.; m. p. 171–180°. The acid ester, presumably **1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-propionic acid (VIIe)**, crystallized from ethyl acetate in small thin plates, yield 380 mg. (70%), m. p. 183–184° with previous sintering; after one more recrystallization the m. p. was 184.5–186°.

Anal.[k] Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.52; H, 7.78.

Cyclization of the Diacid VIId.—A mixture of 130 mg. of the acid ester (VIIe), 3 cc. of 45% aqueous potassium hydroxide and 6 cc. of methanol was refluxed for twenty-one hours. Acidification of the alkaline solution gave a crystalline diacid (presumably VIId), m. p. 214–215°, which was used without further purification. In our best experiment, 61 mg. of the diacid was heated in methanol with 60 mg. of lead acetate and the white suspension was evaporated to dryness.[17] The solid was heated at 290–310° at 0.01 mm. until distillation stopped. The distillate was digested with 5% sodium hydroxide solution and the neutral product isolated by extraction with benzene. The compound, presumably **7-methoxy-1′-keto-1-methyl-1,2,3,4,4a,9,10,10a-octahydro-1,2-cyclopentenophenanthrene (VIII)** crystallized from methanol in small prisms, yield 10 mg., m. p. 99–100.5°, unchanged by another recrystallization. In another run, less well-defined crystals were obtained by recrystallization from aqueous methanol, m. p. 100–101°. Both samples were analyzed.

Anal.[k] Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.47, 79.93; H, 8.42, 8.54.

Derivatives and Reactions of 2-Methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic Acid

Proof of Structure of 163° Anhydride.—A mixture of 1 g. of the 163° anhydride (or the corresponding acid) and 500 mg. of palladium–charcoal was heated in an atmosphere of nitrogen at 315–320° for fifteen minutes. The filtered acetone extract of the product was treated with Norit, concentrated and diluted with ethyl acetate. Practically colorless rectangular prisms of the **anhydride of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (VI)** crystallized; yield 610 mg.; m. p. 183–186°. After several recrystallizations from ethyl acetate and benzene the pure anhydride melted at 185–186°.

Anal.[k] Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.0; H, 5.5

A mixture of 1.08 g. of the 185–186° anhydride and 50 cc. of methanol was refluxed for twenty-two hours.

(17) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).

Upon concentration of the solution chalky prisms of an **acid ester** crystallized; yield, 650 mg., m. p. 186–188°.

Anal.[k] Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.56; H, 6.02.

Additional crystalline material could be obtained from the mother liquor, but it was not pure. Both the material from the mother liquor and the pure acid ester above reacted with diazomethane to give the *cis*-**dimethyl ester**, m. p. 100–101°, which crystallized from aqueous methanol in chalky white needles.

Anal.[k] Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.22; H, 6.44.

The same dimethyl ester was obtained by the dehydrogenation of the hexahydro dimethyl ester and the octahydro dimethyl ester. The yield of ester was inferior to the yield of the aromatic anhydride because of its less favorable solubility in organic solvents.

Digestion with *N* sodium hydroxide of the material in the filtrate after removal of the anhydride left 47 mg. of solid (m. p. 105–135°), which after two recrystallizations from methanol gave 10 mg. of 2-methyl-7-methoxyphenanthrene, m. p. 141–144° alone and when mixed with a synthetic specimen. The m. p. (141–143.5°) of the trinitrobenzene derivative was not depressed by a sample of known structure.

2-Methyl-7-methoxyphenanthrene was synthesized by reducing 1.2 g. of 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene[18] to the corresponding 1-hydroxy derivative by means of a ten-fold excess of aluminum isopropoxide. The reaction mixture was hydrolyzed with ice-cold dilute sulfuric acid solution, the product extracted with benzene and the benzene extract washed with dilute ammonia. Evaporation of the extract gave 1.2 g. of a stereoisomeric mixture of carbinols, m. p. 102–115°; after one recrystallization from benzene–petroleum ether, the m. p. was 109.5–117°.

A mixture of 500 mg. of the recrystallized carbinols and 100 mg. of palladium–charcoal[10] was heated at 315° in an atmosphere of nitrogen for fifteen minutes. A filtered acetone extract of the product was concentrated, diluted with alcohol. After a few recrystallizations of the plate-like crystals (310 mg., m. p. 142–143.5°) and purification through the picrate, the melting point was not changed significantly but the analysis was low in carbon. The following treatment with alkali removed the impurity and led to an analytically pure sample. The crude product was dissolved in methyl alcoholic potassium hydroxide with the aid of warm acetone and water was added until crystallization began. The **2-methyl-7-methoxyphenanthrene** crystallized from alcohol–acetone in slender rectangular prisms, m. p. 144.5–145.5° (reported,[3] 143–144°).

Anal.[k] Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.57; H, 6.26.

The **trinitrobenzene derivative** crystallized from hot alcohol–benzene in fine orange needles, m. p. 146–147°.

Anal.[k] Calcd. for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94. Found: C, 60.62; H, 3.96.

Dimethyl Ester of the Acid IV.—The 163° anhydride did not appear to react with warm dilute sodium bicarbonate solution but was hydrolyzed rapidly by hot *N* sodium hydroxide solution. Upon acidification of the alkaline solution, the dicarboxylic acid (IV) was obtained which melted at 179–180° after one recrystallization from ethyl acetate.

The **dimethyl ester of 2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic acid** prepared from the crude dicarboxylic acid by means of diazomethane, crystallized from aqueous methanol as hexagonal plates, m. p. 90–93°. After two more recrystallizations from aqueous methanol, the pure ester melted at 91–92°.

Anal.[m] Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.9; H, 7.0.

(18) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

Preparation of the Acid Ester.—A solution of 2.57 g. of the aforementioned dimethyl ester in 30 cc. of methanol containing 7.1 cc. of 1.1 *N* sodium hydroxide was refluxed for forty-six hours. After evaporation of the methanol, addition of water and extraction of the insoluble material (0.08 g.) with benzene, dilute hydrochloric acid was added to the aqueous layer. The product crystallized when stirred with ether and after evaporation of the ether, 2.45 g. of solid was filtered and washed with water, m. p. 117–170° dec. The **acid ester** crystallized from ethyl acetate in silken colorless needles, yield 730 mg., m. p. 185–187° dec. At the melting point the acid ester gave the anhydride (II), m. p. 163°.

Anal.[m] Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7. Found: C, 69.1; H, 6.7.

When a solution of 5 g. of the 163° anhydride in methanol was refluxed for twelve hours and concentrated, 2.16 g. of needles was obtained; m. p. 182.5–184° dec. alone and when mixed with the acid ester obtained by alkaline hydrolysis. Both acid esters were converted to the dimethyl ester, m. p. 91°, obtained from the anhydride in the manner described.

Hydrogenation of Derivatives of the 163° Anhydride. (a) **Dicarboxylic Acid.**—Attempts to hydrogenate derivatives of the hexahydro anhydride to octahydro derivatives using 5–10% by weight of Adams catalyst were unsuccessful. When 40–50% by weight of the catalyst was used, hydrogenation was rapid. A mixture of 850 mg. of the diacid IV, 35 cc. of acetic acid, and 300 mg. of pre-reduced Adams catalyst absorbed one mole equivalent of hydrogen at slightly more than one atmosphere pressure in forty-five minutes. On concentration of the filtered solution in a current of air, 56 mg. of the octahydro dicarboxylic acid IX crystallized in colorless prisms, m. p. 202–203° dec. Since it was difficult to obtain more crystalline material from the mother liquor, the residual material was evaporatively distilled at 200–250° (0.01 mm.) to convert the diacids into the corresponding anhydrides. The solution of the distillate in ethyl acetate yielded 335 mg. of anhydrides in two crops, m. p. 165–166° and m. p. 150–155°. *cis*-**2-Methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic anhydride,** the material from the first crop, was recrystallized from ethyl acetate without any change in melting point.

Anal.[k] Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.23; H, 6.74.

(b) **Acid Ester.**—Hydrogenation of 1.3 g. of the acid ester of IV was accomplished with 0.45 g. of pre-reduced Adams catalyst in 50 cc. of acetic acid in three hours. The filtered solution was concentrated and the residue crystallized from ethyl acetate, yield 420 mg., m. p. 194–204° dec. The pure **octahydro acid ester** crystallized from ethyl acetate in small cubes, m. p. 206–208° dec. (bath preheated to 180°). The melting point varied markedly with the rate of heating.

Anal.[m] Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.3. Found: C, 68.8; H, 7.2.

(c) **Dimethyl Ester.**—A mixture of 1.15 g. of the dimethyl ester of IV and 0.4 g. of pre-reduced Adams catalyst in 35 cc. of acetic acid absorbed one mole equivalent of hydrogen at slightly more than one atmosphere pressure in forty-five minutes. A methanol solution of the product deposited colorless needles of the **dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic acid,** yield 470 mg., m. p. 104.5–108.5°; after several recrystallizations the m. p. was 108.5–109.5°.

Anal.[k] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.3; H, 7.6.

The configurations of the derivatives isolated from the three hydrogenations were the same. Both the anhydride and the acid ester were converted to the 109.5° dimethyl ester.

Hydrolysis of the Dimethyl Ester.—Alkaline hydrolysis of the dimethyl ester gave **2-methyl-7-methoxy-1,2,3,4,-**

4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic acid (IX) which crystallized from ethyl acetate in colorless prisms, m. p. 211–213° dec.

Anal.[m] Calcd. for $C_{18}H_{22}O_5$: C, 68.0; H, 7.0. Found: C, 68.0; H, 7.1.

Summary

Two structurally isomeric adducts are formed in the reaction of citraconic anhydride with 1-vinyl-6 methoxy-3,4-dihydronaphthalene. One is a derivative of 1-methylhexahydrophenanthrene; the other has the methyl group in the 2-position of the hexahydrophenanthrene nucleus. From one a compound was synthesized whose analysis agreed with that of the methyl ether of an isomer of estrone. Preliminary studies have been carried out on the conversion of the other isomeric Diels–Alder adduct to estrone.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 1, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF INDIANA UNIVERSITY AND YALE UNIVERSITY]

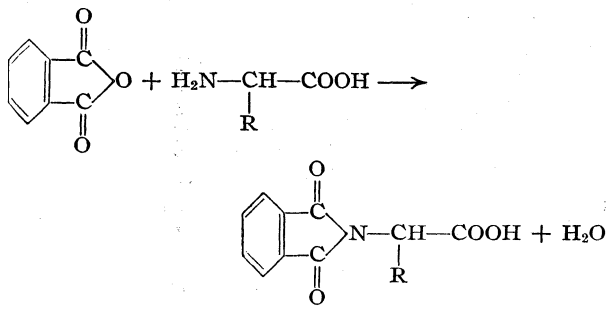
Amino Acids. V.[1] Phthalyl Derivatives

BY JOHN H. BILLMAN[2] AND WILLIAM F. HARTING[3]

Interest in amino acids has increased enormously during recent years mainly because of the many new uses which have been found for these compounds in the nutritional and medicinal fields. Additional reagents for the characterization of amino acids are accordingly useful.

Succinic anhydride and maleic anhydride were investigated as reagents but proved to be unsatisfactory. However phthalic anhydride gives compounds of excellent properties with a large number of amino acids.

Table I contains a list of the phthalyl derivative prepared in these laboratories. Phthalic anhydride condenses with amino acids according to the following general equation, the reaction being complete in fifteen minutes at 180–185°.



The recorded yields are those obtained from 0.2 to 0.5 g. of the amino acid. Much smaller amounts of the amino acid can be used with equal success. Large amounts, such as 5 g. of several of the amino acids were tried and in most cases the yields were considerably higher than those reported in the table. All of the derivatives were easily and

TABLE I

PHTHALYL DERIVATIVES OF AMINO ACIDS

Amino acid used	M. p. of derivative °C. (uncor.)	Yield, %	Analyses, % Calcd.	Found	Neutral equivalents Calcd.	Found
Glycine[a]	191–192	90	C 58.54	58.57	205	205
			H 3.41	3.56		
DL-Alanine[b]	160–161	92	N 6.39	6.45	219	218
DL-α-Amino-*n*-butyric acid[c]	95.5–96.5	65			233	231
DL-α-Amino-isobutyric acid[d]	152–153	79			233	231
DL-α-Amino-*n*-valeric acid	103–104	53	N 5.66	5.84	247	244
DL-Valine	101.5–102	54	N 5.66	5.82	247	249
DL-α-Amino-α-methylbutyric acid[e]	139–140	53	C 63.16	62.97	247	248
			H 5.26	5.44		
DL-Norleucine	111.5–112.5	38	N 5.36	5.25	261	259
DL-Leucine[f]	140–141	41			261	260
L-Leucine[5,6,g]	115–116	70	N 5.36	5.22	261	264
DL-Isoleucine	120–121	66	N 5.36	5.34	261	264
L-Glutamic acid	188–189	45	N 5.05	4.93	277	275
DL-α-Aminophenylacetic acid[h]	167–168	64	C 68.3	68.5	281	280
			H 3.9	4.0		
DL-Phenylalanine	174–175	79	N 4.74	4.81	295	300
DL-Threonine	102–103	30	N 5.62	5.81	243	246

[a] Reese, *Ann.*, 242, 1 (1887). [b] Gabriel, *Ber.*, **38**, 634 (1905). [c] Hildesheimer, *Ber.*, **43**, 279 (1910). [d] Gabriel, *Ber.*, **44**, 59 (1911). [e] Freytog and Gabriel, *Ber.*, **48**, 648 (1915). [f] Ulrich, *Ber.*, **37**, 1695 (1904). [g] Fling, Minard and Fox report the m. p. of 118–119°. [h] McKenzie and Barrow, *J. Chem. Soc.*, **103**, 1332 (1913) (m. p. 170.5–171.5°).

(1) Paper IV, Billman and Parker, THIS JOURNAL, **67**, 1069 (1945).
(2) On leave at Yale University, September, 1946–June, 1947.
(3) Present address: Coca-Cola Company, Linton, Indiana.

quickly prepared and melted in a convenient temperature range.

Since the basic function of the amino group is suppressed by this reaction, the derivatives behave as ordinary carboxylic acids. The neutral equivalent of the derivative can therefore be used as a criterion of identity. This is particularly useful when the melting points of two derivatives are separated by only a few degrees.

A solution of phthalyl L-leucine when examined polarimetrically was found to be optically active. This confirms the findings of Fox[4] and Reese.[5] Phthalyl L-glutamic acid likewise was found to be optically active. Since racemization does not appear to occur during their preparation, phthalyl derivatives should be valuable for the rapid characterization of optically active amino acids.

Tryptophan, tyrosine, serine and taurine did not give the desired derivatives.

Preparation of Phthalyl Derivatives of Amino Acids.—In a Pyrex test-tube is placed a mixture of 0.5 g. of an amino acid and 1.0 g. of phthalic anhydride. The tube is then placed in an oil-bath, which has previously been heated to 180–185°, for fifteen minutes. During the first ten minutes, the mixture is stirred occasionally and the phthalic anhydride which sublimes and deposits on the walls of the tube is pushed down into the reaction mixture by means of a glass rod. The mixture is left undisturbed during the remaining five minutes. At the end of fifteen minutes, the test-tube is carefully removed and cooled until the liquid mass solidifies. It is then inverted and the excess phthalic anhydride sublimed on the walls is scraped out. The residue is recrystallized from 10% ethyl alcohol or water. Most of the phthalyl amino acids are very soluble in dilute alcohol. When alcohol is used, some of the derivatives oil out if too concentrated a solution of the derivative is made or if the solution is cooled too rapidly.

When working with a specific amino acid it is desirable to use an approximately one to one molar ratio of amino acid to phthalic anhydride.

(4) Fling, Minard and Fox, THIS JOURNAL, **69**, 2468 (1947).
(5) Reese, *Ann.*, **242**, 9 (1887).

Summary

A series of phthalyl derivatives of amino acids has been prepared by a general procedure and it has been shown that phthalic anhydride is a useful reagent for the identification of most of the simple amino acids.

BLOOMINGTON, IND.
NEW HAVEN, CONN. RECEIVED NOVEMBER 20, 1947

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Condensation of Some Tertiary Octyl Alcohols with Phenol

BY RALPH C. HUSTON, WILLIAM K. LANGDON[1a] AND LOUIS J. SNYDER[1b]

In previous communications from this Laboratory,[2] the condensations of eleven tertiary alcohols with phenol have been described. The present paper reports the condensation of the five tertiary alcohols shown in Table I.

These alcohols were prepared as described by Huston and co-workers[3] and condensed with phenol in the presence of anhydrous aluminum chloride. The yields of the *p-t*-octylphenols varied from 36 to 80%. No isomers or disubstituted products were isolated. In addition to the benzoyl esters and α-naphthylurethans of these *p-t*-octylphenols, the phenylurethans of three of them were prepared.

The position of the alkyl group in each phenol was proven by oxidation of the corresponding nitro-octylbenzene,[4] by heating in a Carius tube with 6 *N* nitric acid at 130°, to yield only *p*-nitrobenzoic acid. The corresponding *t*-octylbenzene[3] was also converted into the phenol by nitration, reduction to the amine, diazotization and hydrolysis.[2] The phenol thus synthesized was shown to be identical with the one obtained through direct condensation of the alcohol and phenol by means of melting point and mixed melting point determinations. The assignment to the alkyl group of the phenol the same structure as that of the alkyl group of the alcohol from which it is formed is based upon the following considerations:

(a) There are theoretically possible seventeen *p-t*-octylyhenols.

(b) In the rearrangement of alkyl groups during processes of condensation, primary groups may change to secondary or tertiary, secondary may change to tertiary, and tertiary may change to tertiary. Instances of the formation of appreciable yields of isomeric primary or secondary groups from tertiary groups are not known.[2b]

(c) Fifteen different *p-t*-octylphenols, corresponding to the fifteen tertiary octyl alcohols, other than 2,3,3-trimethyl-2-pentanol and 2,2,3-trimethyl-3-pentanol, have been described[2,5] or are described in this article.

When 2,3,3-trimethyl-2-pentanol is condensed with phenol, *two* *p-t*-octylphenols are formed, neither of which is identical with any of the other fifteen. The condensation of 2,2,3-trimethyl-3-pentanol with phenol gives the same two *p-t*-octyl-

(1) Present location: (a) Wyandotte Chemical Corp., Wyandotte, Mich.; (b) Ethyl Corp., Baton Rouge, La.
(2) (a) Houston and Guile, THIS JOURNAL, **61**, 69 (1939); (b) Huston and Meloy, *ibid.*, **64**, 2655 (1942).
(3) Huston, Goerner, *et al.*, *ibid.*, **70**, 1090 (1948).
(4) Malherbe, *Ber.*, **52**, 319 (1919).
(5) Huston and Krantz, *J. Org. Chem.*, **13**, 63 (1948).

TABLE I

SOME TERTIARY OCTYL PHENOLS AND DERIVATIVES

Alcohols		3-Methyl-3-heptanol	3-Ethyl-3-hexanol	2,4-Dimethyl-4-hexanol	3,4-Dimethyl-3-hexanol	2-Methyl-3-ethyl-3-pentanol
p-*t*-Octylphenols, yield, %		80	36	61	40	54
B. p., °C. (mm.)		293.7 (758)	265 (741)	287.5 (758)	294 (758)	270 (756)[a]
		128–130 (3)	134–137 (6)	125 (3)	130–133 (3)	110–112 (2)
$n^{20}D$		1.5164	1.5212 (14.5°)	1.5162	1.5247	
d^{20}_4		0.9516	0.9561 (d^{20}_{20})	0.9530	0.9717	
Carbon, % (calcd. 81.50)		81.38	81.60	81.47	81.41	81.42
Hydrogen, % (calcd. 10.75)		10.78	10.92	10.73	10.57	10.69
Benzoyl esters, m. p., °C.		122	40–40.5	123	125	38.2–38.6
Carbon, % (calcd. 81.25)		81.13	81.18	81.18	81.23	81.06
Hydrogen, % (calcd. 8.44)		8.23	8.42	8.31	8.29	8.64
α-Naphthylurethans	M. p., °C.	94	106.7–107	90	129	128–128.5
	N, % (calcd. 3.73)	3.58	3.66	3.67	3.51	3.68
Phenylurethans	M. p., °C.	104		94	119	
	N, % (calcd. 4.30)	4.28		4.21	4.18	
p-Nitro-*t*-octylbenzenes	B. p., °C.	145–147 (3)	125–130 (3)	160–163 (9)	159–160 (9)[b]	130–135 (6)
	N, % (calcd. 5.95)	5.72	6.07	5.81		5.97
p-Amino-*t*-octylbenzenes	B. p., °C.	129–130 (3)	120–125 (3)	130–131 (3)	134–136 (3)	125–130 (6)
	N, % (calcd. 6.82)	6.74	6.80	6.67		6.75

[a] M. p. 33.5–34°. [b] Distilled with decomposition.

phenols. These are now being studied in this Laboratory. The only other evidence of rearrangement noted is the formation of some 2,4,4-trimethyl-2-*p*-hydroxyphenylpentane together with 2,3,4-trimethyl-2-*p*-hydroxyphenylpentane when 2,3,4-trimethyl-2-pentanol is condensed with phenol.[5]

(d) Seventeen different *p*-*t*-octylphenols have been formed by the condensation of seventeen isomeric octyl alcohols. In cases where only one phenol is isolated, the assignment of the structure of the alkyl group of the alcohol to the side chain of the octylphenol is justified.

Experimental

Melting points and boiling points are uncorrected.

The alcohols were prepared as indicated by Huston, Goerner, *et al.*,[3] with one exception. Part of the 3-ethyl-3-hexanol was made by adding one mole of chloroacetyl chloride to slightly over three moles of ethyl Grignard reagent. The ether was then removed and the dry reaction mixture heated on the steam-bath for twenty-four hours in order to insure the hydrocarbon type of synthesis on the α-carbon atom. The average yield was 75%.

Condensations with Phenol. (a) Using 3-Ethyl-3-hexanol and 2-Methyl-3-ethyl-3-pentanol.—Thirty-two grams (0.25 mole) of octyl alcohol, 47 g. (0.5 mole) of phenol and 200 ml. of petroleum ether were mixed in a 500 ml., three-neck flask equipped with a thermometer, condenser and mechanical stirrer. Anhydrous aluminum chloride (17 g., 0.125 mole) was added portionwise during the course of an hour. The temperature was maintained between 25 and 30° by external cooling when necessary.

(b) **Using the Other Three *t*-Octyl Alcohols.**—The proportions of reactants were: alcohol, 32.5 g. (0.25 mole); phenol, 23.5 g. (0.25 mole); aluminum chloride, 17 g. (0.125 mole); petroleum ether, 80 ml. The method was the same as in (a).

After the addition of the aluminum chloride, stirring was continued for four hours and the reaction mixture allowed to stand overnight. After hydrolysis by ice and hydrochloric acid, the layers were separated and the aqueous layer extracted with ether. The combined ether–petroleum ether layers were washed with 10% sodium carbonate solution and dried. Distillation through a modified Claisen flask with a 30 to 45 cm. Vigreux column gave the following fractions: (1) b. p. below 65° (5 to 10 mm.), probably unreacted alcohol or the corresponding chloride; (2) b. p. 65 to 100° (5 mm.), chiefly recovered phenol; (3) b. p. 100 to 140° (3 mm.). The last fraction was redistilled until a product with a narrow boiling point range was obtained. 2-Methyl-3-ethyl-3-(*p*-hydroxyphenyl)-pentane, the only solid phenolic product, was recrystallized from petroleum ether.

The benzoyl esters were prepared by the method of Shriner and Fuson.[6] Since the esters did not solidify when poured into water, it was necessary to separate the oil, extract the aqueous layer with ether, wash the ether extract successively with dilute acid and sodium carbonate solution and distil under diminished pressure. The esters crystallized at once or when chilled in the refrigerator. They were recrystallized from petroleum ether or ethyl alcohol.

The phenylurethans and α-naphthylurethans prepared by the method of Bickel and French[7] or by the method of French and Wirtel,[8] were recrystallized from alcohol or petroleum ether.

Summary

1. Five *t*-octyl alcohols have been condensed with phenol in the presence of aluminum chloride.

2. The benzoyl esters and α-naphthylurethans of the resulting *p*-*t*-octylphenols have been prepared. The phenylurethans of three of these phenols were also prepared.

3. The structures of the phenols have been established.

EAST LANSING, MICHIGAN RECEIVED AUGUST 25, 1947

(6) Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 137.

(7) Bickel and French, THIS JOURNAL, **48**, 747 (1926).

(8) French and Wirtel, *ibid.*, **48**, 1736 (1926).

[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Synthesis of 6-Nitro-6-desoxy-D-glucose and 6-Nitro-6-desoxy-L-idose

BY J. M. GROSHEINTZ AND HERMANN O. L. FISCHER

The synthesis of 6-carbon C-nitrodesoxy-aldoses, in which the hydroxyl group on carbon atom 6 is replaced by a nitro group, thus forming the grouping $-CH_2NO_2$, was of interest, since these compounds represent a new type of sugar derivative and also show, as was anticipated, a remarkable tendency to form cyclic compounds of the cyclohexane and benzene series, on which we shall report in a subsequent paper.

Two of these sugars, 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose, have been prepared by the condensation of 1,2-acetone-D-*xylo*-trihydroxyglutaric dialdehyde (II) with nitromethane. Such a condensation reaction of an aldehyde with a nitroparaffin, which dates back to Henry[1] has received much attention in recent years.[2] It has been used previously in this Laboratory for the preparation of nitrolactaldehyde,[3] and recently for the preparation of carbohydrate C-nitroalcohols.[4] In the case under consideration the condensation was effected in ethanol with sodium methoxide in the presence of an excess of nitromethane. When no further change in optical rotation occurred (after eighteen hours), the solution was processed and a crystalline **Mixture A** of the two diastereoisomers III and IV was obtained in a yield of 50% of the theoretical amount (calcd. on the dialdehyde).

The 1,2-acetone-D-*xylo*-trihydroxyglutaric dialdehyde, which is made from monoacetone-D-glucose (I)[5] by oxidation with lead tetraacetate, has been described previously with a rotation of $[\alpha]^{10}D + 20 \pm 3°$.[6] On preparing this compound we obtained products of varying rotations. Therefore, in the experimental part we describe our method of preparing the dialdehyde for our present purpose. Further investigations of the sirupy dialdehyde are being conducted.

It was found impracticable to separate the two isomers from the mixture **A** by fractional crystallization. A very small amount of IV (less than 5%) was obtained on extraction with absolute ether and repeated crystallization from dibutyl ether. However, separation could be effected satisfactorily by a process we would like to call "fractional acetonation." We found that under similar conditions, IV was acetonated to a diacetone derivative in a yield of about 90%, whereas III was acetonated in a yield of only about 25%. Thus acetonation of the mixture **A** resulted in practically complete acetonation of IV and only partial acetonation of III. This mixture could then be separated easily into the monoacetone derivative III, the diacetone derivative VI, and a residual amount of a crystalline mixture of the two diacetone derivatives V and VI, from which V could not be separated. The latter was, however, obtained from acetonation of III.

On desacetonation of III and V, 6-nitro-6-desoxy-D-glucose was obtained as a white powder which crystallized on slow cooling from a mixture of butanol and dibutyl ether. The crystalline 6-nitro-6-desoxy-D-glucose shows a downward mutarotation in water. Acids slightly accelerate the mutarotation, whereas traces of alkali induce secondary reactions. The downward direction of the mutarotation indicates that the 6-nitro-6-desoxy-D-glucose crystallizes in its α-form.[7]

On desacetonation of IV and VI, 6-nitro-6-desoxy-L-idose was obtained as a resinous, slightly colored mass, which so far has resisted crystallization. The initial and final values of the rotation of this amorphous material were considerably dependent on the degree to which it had been previously dried. Acids accelerate the mutarotation whereas traces of alkali induce secondary reactions.

To establish the configuration of III, it was reduced to the known 1,2-acetone-6-amino-6-desoxy-D-glucose,[8] which was isolated in the form of its *p*-toluenesulfonate in a yield of 85%. Further evidence that III and V possess the D-glucose configuration was obtained by the reduction of V to the known 1,2,3,5-diacetone-6-amino-6-desoxy-D-glucose *p*-toluenesulfonate.[9] This establishes the D-glucose configuration for III and for V and for the acetone-free nitrodesoxysugar VII obtained from III and V. It leaves for IV, VI and VIII the L-idose configuration, as indicated in the table.

On reduction of VI, as above, the crystalline *p*-toluenesulfonate of 1,2,3,5-diacetone-6-amino-6-desoxy-L-idose could be isolated in a yield of 80%.

Experimental

(1) **Condensation of 1,2-Acetone-D-xylo-trihydroxyglutaric Dialdehyde with Nitromethane.**—One hundred grams of monoacetone-D-glucose (m. p. 159–160°) was added to 1.6 liters of dry benzene and the suspension just brought to the boil while stirring moderately. Then 205 g. of lead tetraacetate was added in five equal portions at intervals of about three minutes without further heating, and the stirring was continued for an additional quarter of an hour at 70°. Any slight excess of lead tetraacetate

(1) L. Henry, *Compt. rend.*, **120**, 1265 (1895).

(2) Reviews by H. B. Hass and Riley, *Chem. Reviews*, **32**, 373 (1943); H. B. Hass, *Ind. Eng. Chem.*, **35**, 1146 (1943); Hass and Bouriand, *C. A.*, **38**, 2969 (1944).

(3) H. O. L. Fischer, E. Baer and H. Nidecker, *Helv.*, **18**, 1079 (1935).

(4) J. C. Sowden and H. O. L. Fischer, THIS JOURNAL, **66**, 1312 (1944); **67**, 1713 (1945); **68**, 1511 (1946); **69**, 1048, 1963 (1947).

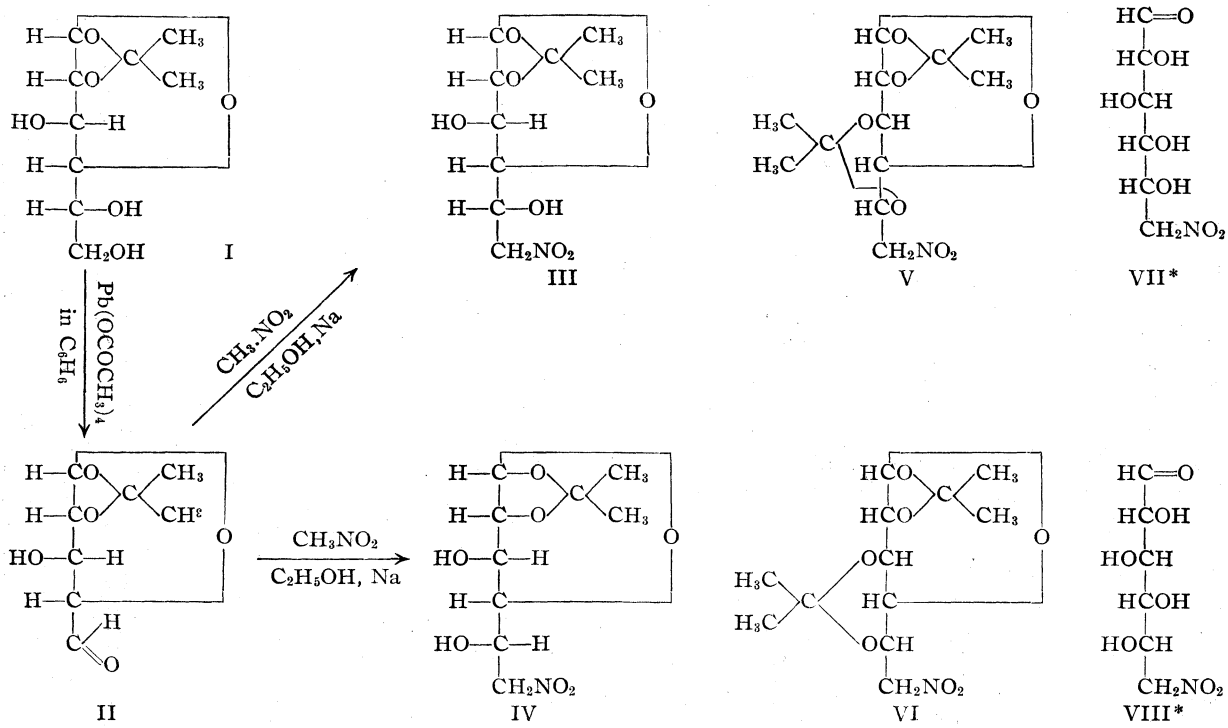
(5) Preparation according to Hixon, *ibid.*, **51**, 523 (1929).

(6) Koichi Iwadare, *Bull. Chem. Soc., Japan*, **16**, 40 (1941); *C. A.*, **35**, 4740 (1941).

(7) C. S. Hudson, THIS JOURNAL, **31**, 66 (1909).

(8) H. Ohle and L. v. Vargha, *Ber.*, **61**, 1206 (1928).

(9) H. Ohle and L. v. Vargha, *ibid.*, **62**, 2432 (1929).



* No ring form has been assigned

was then reduced with a few drops of ethylene glycol and, after cooling to room temperature, the precipitated lead diacetate was filtered off and washed with a little benzene. The combined filtrates, about 2 liters, were quickly extracted four or five times with 25 cc. of ice-water, until no more lead diacetate could be traced in the last aqueous extract, and the benzene solution was cleared from suspended water by filtration. On removal of the benzene under reduced pressure, about one-third of the amount of aldehyde formed remained as a viscous sirup. The optical rotation of this sirup was $[\alpha]^{25}D$ +50 ± 2° (c = 5) in ethanol. The combined aqueous extracts, about 125 cc., were kept at 0° and extracted quickly six to eight times with 25 cc. of chloroform. Thus the remaining aldehyde was almost entirely extracted from the aqueous solution, containing lead diacetate and acetic acid, and was obtained as a viscous sirup after drying and evaporating the chloroform under reduced pressure. The optical rotation of this sirup was $[\alpha]^{25}D$ +40 ± 2° (c = 5) in ethanol. The lower optical rotation of the product recovered from the chloroform solution, as compared with that recovered from the benzene solution, may be due to polymerization or to a partial desacetonation, resulting in an admixture of the optically inactive xylo-trihydroxyglutaric dialdehyde. However, both sirups, which may still contain small amounts of formaldehyde, gave the same mono-phenylhydrazone, m. p. 140.5–141°, $[\alpha]^{25}D$ −42° (c = 5.0) in chloroform, as described by Koichi Iwadare.[6] Over-all yield of the sirupy material was approximately 80%. For all further experiments these sirups were dissolved in ethanol and used together.

One hundred grams of the above 1,2-acetone-D-xylo-trihydroxyglutaric dialdehyde was dissolved in a mixture of 400 cc. of 95% ethanol and 200 cc. of nitromethane. The solution was made alkaline to litmus by the addition of 2 N sodium methoxide. An excess of 20 cc. of 2 N sodium methoxide was then added and the solution left at room temperature for eighteen hours. The solution was then concentrated *in vacuo* to about one-fifth of its volume, and, after addition of about 500 cc. of chloroform, it was extracted five to six times with about 20 cc. of water. The condensation products were then obtained as a viscous residue on evaporation of the organic solvents *in vacuo*. On addition of an equal amount of absolute ether to this residue and stirring until a homogeneous mixture was obtained, crystallization of the condensation products was soon induced and the crystals were filtered with suction and washed twice with absolute ether. The mother liquor and ether washings, containing an appreciable amount of condensation products, were collected and evaporated and the residue treated as above. This crystalline mixture of 1,2-acetone-6-nitro-6-desoxy-D-glucose and 1,2-acetone-6-nitro-6-desoxy-L-idose could be crystallized from dibutyl ether (25 parts), chloroform and ether–petroleum ether (b. p. 40–60°), but no appreciable separation of the isomers took place. The mixture melted between 105 and 120° and showed a specific optical rotation of between −21° and −25°. The yield of this mixture A of colorless crystalline nitrodesoxysugars was about 50% of the theoretical.

(2) **1,2-Acetone-6-nitro-6-desoxy-D-glucose.**—One hundred grams of mixture A, as under (1), was dissolved in 2 liters of absolute acetone, containing 10.0 cc. of concentrated sulfuric acid, and kept at room temperature for four days. The sulfuric acid was then just neutralized with concentrated ammonia (an excess of ammonia being avoided), the ammonium sulfate was centrifuged off, and the solution was concentrated *in vacuo* to about 200 cc. The residue was taken up in 2 liter of ether and extracted twice with 50 cc. and twice with 25 cc. of water and filtered clear. The ether was distilled off, leaving a crystalline sludge from which the remaining solvent was distilled off *in vacuo* at about 60°. The resulting crystalline mass was dissolved in about 150 cc. of hot ethanol and the solution was slowly diluted with 600 cc. of water. Most of the diacetone products crystallized out immediately, and, after standing overnight in the ice-box, the crystals (B) (about 40 g.) were filtered with suction and washed with a little water. The mother liquor was concentrated *in vacuo* to half its volume, heated shortly to 80° with a little charcoal, and filtered. On complete evaporation of the solvents *in vacuo* the unchanged 1,2-acetone-6-nitro-6-desoxy-D-glucose crystallized out and was recrystallized first from benzene and then from

dibutyl ether (1 g. in 25 cc.). In this way 40 g. of the almost pure isomer, m. p. 123–125°, $[\alpha]^{25}D$ −18 to −20°, was obtained. On repeating with this substance the entire acetonation and crystallization procedure as above, the purest isomer we could prepare, m. p. 126–127° and $[\alpha]^{24}D$ −16.8° in water (c = 4.2), was obtained. *Anal.* Calcd. for $C_9H_{15}O_7N$ (249): C, 43.3; H, 6.02; N, 5.62; acetone, 23.3. Found: C, 43.4; H, 6.17; N, 5.64; acetone, 23.1.

(3) **1,2-Acetone-6-nitro-6-desoxy-L-idose.**—On extraction of 5 g. of mixture A, as under (1), with absolute ether in a Soxhlet apparatus, about 0.5 g. of impure 1,2-acetone-6-nitro-6-desoxy-L-idose, m. p. 135–142°, remained undissolved. After three crystallizations from dibutyl ether this substance had a m. p. of 161–162° and $[\alpha]^{24}D$ −39.0° in water (c = 3.32) and no change of these constants was observed on recrystallization. *Anal.* Calcd. for $C_9H_{15}O_7N$ (249): C, 43.3; H, 6.02; N, 5.62; acetone, 23.3. Found: C, 43.6; H, 5.93; N, 5.55; acetone, 23.6.

(4) **1,2,3,5-Diacetone-6-nitro-6-desoxy-D-glucose.**—This was obtained on acetonation of our purest 1,2-acetone-6-nitro-6-desoxy-D-glucose, as under (2) and crystallization from ethanol, and subsequently from 50% aqueous methanol, in a yield of 25%, while 60% of the unchanged starting material was recovered; m. p. 106–107°, $[\alpha]^{23}D$ +18.8° in pyridine (c = 3.56). *Anal.* Calcd. for $C_{12}H_{19}O_7N$ (289): C, 49.8; H, 6.58; N, 4.84; acetone, 40.1. Found: C, 50.0; H, 6.49; N, 4.87; acetone 40.3.

(5) **1,2,3,5-Diacetone-6-nitro-6-desoxy-L-idose.**—On crystallizing the mixture B (40 g. as under (2)), once from 80% ethanol and three times from methanol, 20 g. of diacetone-6-nitro-6-desoxy-L-idose, m. p. 150–151° and $[\alpha]^{25}D$ −30.1° in pyridine (c = 2.80), was obtained. After five recrystallizations from methanol or ethanol the melting point was one-half degree higher, but the optical rotation was unchanged. *Anal.* Calcd. for $C_{12}H_{19}O_7N$ (289): C, 49.8; H, 6.58; N, 4.84; acetone, 40.1. Found: C, 49.7; H, 6.78; N, 4.75; acetone, 40.3. The mother liquors were combined and concentrated *in vacuo*, leaving a crystalline sludge, consisting mainly of the diacetone-glucose derivative. Fractional crystallization of this mixture from ethanol and water yielded further amounts of the diacetone-idose derivative. The main portion of about 15 g., however, could not be separated completely from its isomer and melted from about 95 to 105°.

Acetonation of 1,2-acetone-6-nitro-6-desoxy-L-idose, as under (2), yielded about 90% of diacetone-6-nitro-6-desoxy-L-idose.

(6) **6-Nitro-6-desoxy-D-glucose.**—The 1,2-acetone-6-nitro-6-desoxy-D-glucose (m. p. 124° and higher), was dissolved in five times its weight of 0.1 N sulfuric acid and kept for about seventy-five minutes in a water-bath at 75–80°. The diacetone-6-nitro-6-desoxy-D-glucose was treated in the same manner, except for the addition of about 20% of ethanol to facilitate its solution. The solutions were then freed from the sulfuric acid by careful addition, with stirring, of 80% of the theoretical amount of barium hydroxide solution and balanced out exactly with a 0.1 N solution of barium acetate. This solution should at no time become even slightly alkaline on account of the extreme sensitivity of the free nitrodesoxysugar. The barium sulfate was removed by centrifuging or filtering. On evaporation *in vacuo* of the water, the free sugar was obtained as a white powder, m. p. 152–154°, with an initial optical rotation of $[\alpha]^{23}D$ +40 ± 2° within five minutes after dissolution in water. Ten grams of this substance was dissolved in a boiling mixture of 500 cc. of n-butanol and 500 cc. of n-dibutyl ether and the solution seeded at about 100° with crystalline nitrodesoxyglucose. (Seeds were obtained by dissolving a sample of the nitrodesoxysugar in a mixture of the solvents as above, and letting stand overnight.) Approximately 5 g. of material crystallized in small white needles on slow cooling to 50° within six hours. On further cooling, the remaining substance came out as an amorphous precipitate from the mother liquor, and could be recovered completely by evaporation of the solvents *in vacuo*.

The crystalline 6-nitro-6-desoxy-D-glucose melts at 156–157° and shows the mutarotation (±0.5°).

Time	$[\alpha]^{23}D$ in H_2O (c = 2.90)	$[\alpha]^{23}D$ in 0.1 N H_2SO_4 (c = 2.81)
5 min.	+45° ± 0.5°	+44.6° ± 0.5°
10 min.	44.6°	44.0°
30 min.	43.6°	42.8°
60 min.	43.0°	40.9°
2 hours	41.0°	39.2°
3 hours	39.0°	37.9°
4 hours	37.8°	37.4°
5 hours	37.0°	37.0°
6 hours	36.7°	36.9°
12 hours	36.7°	36.8°
2 days	35.6°	36.8°
5 days	32.6°	36.8°
12 days	29.1°	..
18 days	24.9°	..

The end rotation was thus reached within six to seven hours in water and dilute acid. A very much slower change of the optical rotation was observed after that time in water, indicating that a secondary reaction took place. This was probably due to the slight alkalinity of the glass with which the solution came in contact, since no such change was observed in dilute acid. *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.6; H, 5.23; N, 6.94.

(7) **6-Nitro-6-desoxy-L-idose** was prepared from its diacetone derivative, as under (6). So far, it has not been obtained in a crystalline state, but only as a resinous, slightly colored mass. We have been unable, therefore, as yet, to determine accurately the optical properties of this compound, especially since sharp drying in high vacuum over phosphorus pentoxide resulted in a brittle, glassy mass with a very much smaller mutarotation than material dried to a viscous consistency. A representative experiment can be given as follows: 1.503 g. of diacetone-6-nitro-6-desoxy-L-idose, m. p. 150–151°, was dissolved in 20 cc. of boiling ethanol and kept at 75–80° for one hour after the addition of 10.0 cc. of N sulfuric acid; then 15 cc. of warm water was added and the solution kept at the same temperature for an additional hour. After cooling to room temperature and adjusting the volume of the solution to 50.0 cc. with water, the optical rotation was $[\alpha]^{20}D$ −13.8°. After removal of the sulfuric acid and the solvents, as under (6), and drying the residue to a viscous consistency, the initial optical rotation was $[\alpha]^{23}D$ −16.6° in water (c = 3.15), $[\alpha]^{23}D$ −12.3° in 0.1 N sulfuric acid (c = 2.63), and the rotation seven days later $[\alpha]^{23}D$ −20.9° in water, $[\alpha]^{23}D$ −26.0° in 0.1 N sulfuric acid. After drying the same sample to a brittle, glassy mass, which was crushed to a powder, the initial optical rotation was $[\alpha]^{23}D$ −10.4° in water (c = 4.36), $[\alpha]^{21}D$ −12.2° in 0.1 N sulfuric acid, and the rotation forty-eight hours later $[\alpha]^{22}D$ −12.9° in water, $[\alpha]^{22}D$ −14.0° in 0.1 N sulfuric acid.

(8) **1,2-Acetone-6-amino-6-desoxy-D-glucose *p*-Toluenesulfonate.**—1,2-Acetone-6-nitro-6-desoxy-D-glucose (1.01 g., m. p. 126°) was dissolved in 30 cc. of water and reduced with hydrogen at ordinary temperature and pressure in the presence of 8 g. of freshly prepared Raney nickel catalyst. Within the first ten minutes 250 cc. of hydrogen was absorbed and 55 cc. within the next fifty minutes (calcd., 307 cc. at 23° and 753 mm.). (This reduction was also carried out at room temperature and a hydrogen pressure of 20–30 atm. and was then complete in five minutes.) The catalyst was then centrifuged off and the solution neutralized with 0.5 N *p*-toluenesulfonic acid and evaporated to dryness *in vacuo*. The amorphous residue was dissolved in about 6–8 cc. of absolute ethanol and filtered. On gradual addition of about 300 cc. of absolute ether, in portions, 1.2 g. (85%) of the crystalline compound was obtained, m. p. 176–177°, $[\alpha]^{26}D$ −7.0°

in water (c = 3.7). These constants agree with those reported by Ohle[8] for the same compound (m. p. 176–177°, $[\alpha]^{20}D$ −7.02° in water, (c = 5.01)).

(9) **1,2,3,5-Diacetone-6-amino-6-desoxy-D-glucose *p*-Toluenesulfonate.**—An amount of 1.05 g. 1,2,3,5-diacetone-6-nitro-6-desoxy-D-glucose (m. p. 106–107°) was dissolved in 60 cc. of dioxane and reduced as under (8). The reduction was complete within forty-five minutes and the free amine was obtained as a viscous sirup after centrifuging off the catalyst and evaporating the dioxane *in vacuo* at 40°. This sirup was dissolved in 20 cc. of water, neutralized exactly with 0.5 *N* *p*-toluenesulfonic acid and filtered. On evaporating the water *in vacuo*, 1.3 g. (83%) of the salt was obtained and was crystallized once from benzene and once from dry ethyl acetate. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.9; H, 6.62; N, 3.12; acetone, 26.7.

Since the melting point found for this substance did not entirely agree with that reported by Ohle, the physical constants of the salt were thoroughly examined by Mr. D. L. MacDonald of this Laboratory, who reports as follows:

"The melting point of this compound varied considerably with the rate of heating, and melting was accompanied by decomposition; as these characteristics were not reported by Ohle and v. Vargha, the compound was also prepared according to their method from 6-tosyl-1,2-monoacetone-D-glucose *via* 6-tosyl-1,2,3,5-diacetone-D-glucose.[9,10] The amine salt prepared by the two different methods was found to be identical as regards melting point (with decomposition), solubilities in various solvents, crystal form, optical rotation and dependence of melting point on rate of heating, as shown in the table. From the data, it can be concluded that the compound under consideration is identical with Ohle and v. Vargha's

	Prepared according to: Ohle and v. Vargha	Grosheintz and Fischer	Mixed melting point, °C.
From dry ethyl acetate:			
(1) Standing in bath for 20 minutes at	160°	160°	
(2) Heating at 1°/minute	172–172.5°	171.5–172°	171.5–172°
(3) Heating at 10°/minute	177–179°	176–179°	
(4) $[\alpha]D$ (1 dm. tube, H_2O)	+30.5° (c = 5.4, t = 25°)	+29.1 (c = 4.0, t = 24°)	

(10) H. Ohle and E. Dickhäuser, *Ber.*, **58**, 2602 (1925); H. Ohle and L. v. Vargha, *ibid.*, **61**, 1208 (1928).

1,2,3,5-diacetone-6-amino-6-desoxy-D-glucose *p*-toluenesulfonate. The slightly low rotation may indicate the presence of a small amount of the corresponding L-idose compound."

(10) **1,2,3,5-Diacetone-6-amino-6-desoxy-L-idose *p*-Toluenesulfonate.**—An amount of 2.35 g. of 1,2,3,5-diacetone-6-nitro-6-desoxy-L-idose (m. p. 150–151°) was dissolved in 100 cc. of dioxane, reduced, and the resulting amine was neutralized with *p*-toluenesulfonic acid as under (9). The crude salt was dissolved in a little warm methanol, treated with charcoal, and filtered. On addition of about 5 volumes of absolute ether to this solution 2.8 g. (80%) of substance crystallized immediately in long fine needles, m. p. 198–200° (dec.), $[\alpha]^{25}D$ +5.8° in 0.1 *N* NaOH (c = 3.8), $[\alpha]^{26}D$ +0.84° in absolute ethanol (c = 3.5), $[\alpha]^{26}D$ −7.0° in dry pyridine (c = 5.3). No optical rotation could be observed in water. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.7; H, 6.55; N, 3.24; acetone, 26.8.

Acknowledgment.—We are pleased to acknowledge gratefully the generous support of a section of this work by the Nutrition Foundation, Inc.

Summary

The preparation of a new type of sugar derivative is described. 1,2-Acetone-D-*xylo*-trihydroxyglutaric dialdehyde was condensed with nitromethane to yield a mixture of 1,2-acetone-6-nitro-6-desoxy-D-glucose and 1,2-acetone-6-nitro-6-desoxy-L-idose. Separation of the two diastereoisomers could be effected. The free nitrodesoxysugars were obtained on desacetonation with dilute sulfuric acid.

The constitution and configuration of the glucose derivatives were established by the reduction of the mono- and diacetone-6-nitro-6-desoxy-D-glucose to the known 1,2-acetone-6-amino-6-desoxy-D-glucose and to 1,2,3,5-diacetone-6-amino-6-desoxy-D-glucose and subsequent isolation of their *p*-toluenesulfonates.

This leaves for the other isomer the L-idose configuration.

TORONTO, CANADA RECEIVED NOVEMBER 10, 1947

[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Cyclization of 6-Nitrodesoxyaldohexoses to Nitrodesoxyinositols

BY J. M. GROSHEINTZ AND HERMANN O. L. FISCHER

When an aldose, in which the primary hydroxyl group is replaced by a nitro group, is exposed to a mild alkali, condensation of the aldehyde group into the $—CH_2NO_2$ group may be expected[1] forming the group $—CH(NO_2)—CH(OH)—$ with two new asymmetric carbon atom centers. Such a reaction, reminiscent of an aldol condensation, could produce either straight-chain or cyclic polymers or produce cyclic monoisomers. In the latter case the aldehyde group would condense with the nitromethylene group of the same molecule. It was with this reaction in mind that we synthesized 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose,[2] since we expected intramolecular condensation, *i. e.*, cyclization of these nitrodesoxysugars to a number of nitrodesoxyinositol stereoisomers. We found our expectations confirmed and we were able to isolate some of these nitrodesoxyinositols under certain controlled conditions.

Evidence for the cyclohexane ring structure of our condensation products is shown by the quantitative transformation of these compounds to a known aromatic compound. Thus, on dissolving a pentaacetylnitrodesoxyinositol in warm pyridine

(1) L. Henry, *Compt. rend.*, **120**, 1265 (1895).

(2) Grosheintz and Fischer, THIS JOURNAL, **70**, 1476 (1948).

it is immediately and quantitatively transformed to diacetyl-5-nitroresorcinol. Similarly, on dissolving any of the nitrodesoxy inositols in warm pyridine and acetic anhydride the diacetyl-5-nitroresorcinol is immediately formed in a quantitative yield. This transformation is in principle the same as that of inosose and its pentaacetate to the tetraacetate of 1,2,3,5-tetrahydroxybenzene as described by Posternak.[3] On ring closure the aldehyde group disappears with the formation of a new hydroxyl group. This was evidenced by the preparation of pentasubstituted nitrodesoxyinositol derivatives and by the absence of any carbonyl reaction. Thus, after reduction of the nitro group to an amino group, the amino sugars give a strong Fehling test, whereas the amino inositols give none whatever. Also characteristic for our condensation products is the absence of any optical activity. This property points to the formation of symmetrically built molecules, or the presence of equal amounts of enantiomorphs.

The cyclization process, which was followed polarimetrically, is induced by very small amounts of alkali, as was already observed during the investigation of the mutarotation of 6-nitro-6-desoxy-D-glucose.[2] It takes place, in water, *via* the nitronium salts, as evidenced by an initial (numerical) increase in the optical rotation, and it can be arrested at any stage by acidification of the reaction solution or by precipitation of the nitronium salts; on restoring the initial *p*H of the solution or on redissolving the precipitated salts in water the cyclization continues where it had been interrupted, until the optical activity had disappeared. The rate of cyclization and the end-products are dependent, within limits, on the alkalinity to which the nitrodesoxysugars are exposed.

For one series of experiments the nitrodesoxysugars were dissolved in the calculated amount of 0.1 to 0.16 *N* barium hydroxide. Approximately half of the theoretical amount of barium salts of the cyclic compounds would crystallize overnight and the other half could be precipitated by the addition of ethanol. A slight excess of barium hydroxide solution did not affect the reaction, but tends to discoloration of the barium salts, whereas a great excess and especially greater concentration of the alkali induces strong discoloration and subsequent lower yields of the free nitrodesoxyinositols. On dissolving the barium salts in acetic acid and eliminating the barium in the usual manner, a mixture of the crystalline isomers was obtained in excellent yield. Thus from the cyclization of crystalline nitrodesoxy-D-glucose two individual substances could be isolated in approximately equal amounts. The separation could be effected due to the fact that one isomer, which we shall call **Nitrodesoxyinositol I,** crystallized from pure 1,4-dioxane with one half mole of solvent, was practically insoluble in acetone and could not be acetonated under the usual conditions, whereas the other isomer, which we shall call **Nitrodesoxyinositol II,** crystallized only in very small amounts, when pure, from dioxane, and was very easily acetonated to a diacetone derivative. In a similar manner, but in somewhat smaller yields, two nitrodesoxyinositols could be isolated from the mixture of stereoisomers obtained from the cyclization of amorphous nitrodesoxy-L-idose. These two isomers proved to be identical with those obtained from the cyclization of nitrodesoxyglucose.

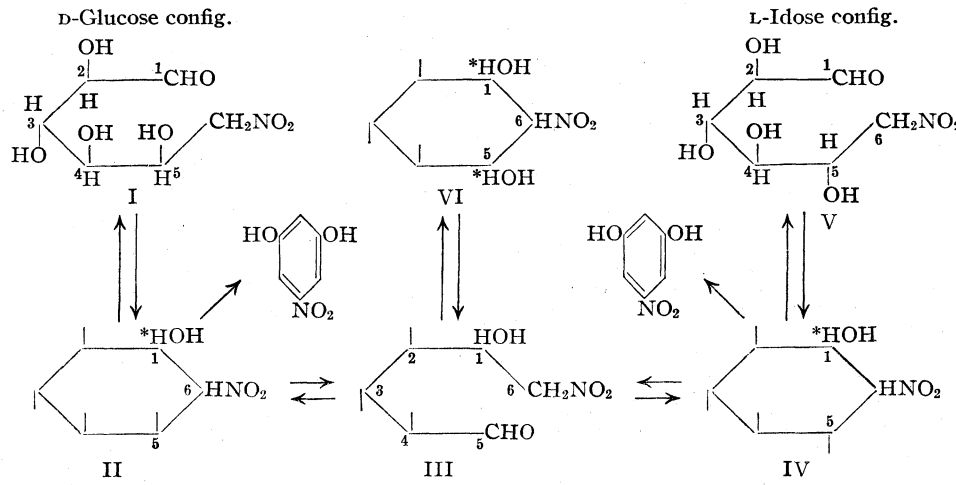
An altogether different mixture of nitrodesoxyinositols was obtained when a molar solution of nitro glucose was made alkaline with one-third of the calculated amount of normal sodium hydroxide. The cyclization proceeded slowly and a main product, which we will call **Nitrodesoxyinositol III,** was obtained in a yield of about 65% of the theoretical. This material did not represent a pure isomer, since products of slightly differing melting points were isolated on fractional crystallization, but no clear separation of individual compounds could be effected. It did not form acetone derivatives under the usual conditions. Moreover, the reaction mixture contained some nitrodesoxyinositol II, which could be isolated due to its ready formation of a diacetone derivative, and we believe, therefore, that it also contained smaller amounts of nitrodesoxyinositol I.

These results lead to the following considerations with regard to the steric configuration of our compounds: on ring closure of 6-nitro-6-desoxy-D-glucose four isomers may be formed theoretically, of which two would possess symmetrical and two asymmetrical molecular structure; the same is the case for 6-nitro-6-desoxy-L-idose. The isomers with asymmetrical molecular structure which would be thus obtained by cyclization of one of the sugars are the enantiomorphs of those to be expected by cyclization of the other sugar, whereas all the expected isomers with symmetrical molecular structure would have a different steric configuration from one another. Therefore, having obtained two nitrodesoxyinositols from one of the sugars under certain experimental conditions, one should expect two different nitrodesoxyinositols from the other sugar under the same experimental conditions, while the absence of optical activity would, in general, indicate the absence of asymmetrical structure in these compounds. Since we obtained only two different compounds in all, under similar experimental conditions, we conclude that, in alkaline medium, an equilibrium is established between the cyclic and open-chain forms of the nitrodesoxysugar derivatives (Table I) resulting in a transformation of these derivatives, whether originally of the D-glucose or L-idose configuration, to an identical mixture of nitrodesoxyinositol isomers.[4] This would therefore not ex-

(3) Th. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

(4) This, of course, does not exclude other reaction mechanisms in the alkaline medium, *e. g.*, cleavage of the nitrohexoses into nitromethane and D-xylo-trihydroxyglutaric dialdehyde, and the recondensation to nitrohexoses and/or nitroinositols.

TABLE I



clude the formation of racemates and one may not rule out any of the eight possible steric configurations on the grounds of optical inactivity. We believe that in the case of cyclization experiments with mild and dilute alkali, such as one-tenth normal barium hydroxide, the reaction indicated in the table is the main reaction. Thus, the conversion into one another of the two nitrodesoxyinositols I and II was easily effected under the same conditions as their preparation from the nitrodesoxysugars. This conversion may, of course, simply indicate an isomerization due to the intermediate formation of a nitronium salt, but we are more inclined to believe that a symmetrical arrangement of the hydroxyl groups is achieved prior to the precipitation of the salts and that upon reconversion of the salts to the free nitro compounds the nitro group is guided into the *trans* position with regard to the neighboring hydroxyl groups. Such an arrangement would agree with all observed reactions as well as with previous experience.[5] In the case of the cyclization experiments which led to the formation of nitrodesoxyinositol III, a much greater concentration of alkali prevailed. Therefore, one cannot dismiss completely the possibility of far reaching enolization such as the sugars are known to undergo in alkaline solution as evidenced in the reduction of glucose at ordinary temperature and *p*H 10–13.[6]

Such a reaction would leave the way open to all theoretically possible steric rearrangements. The non-occurrence of isomers is not surprising in such a labile system where certain molecular structures would naturally be preferred.

From the aforesaid it is evident that for the preparation of these cyclic compounds one need not start from the individual 6-nitro-6-desoxy-D-glucose or 6-nitro-6-desoxy-L-idose, but may use their equimolecular mixture, which is readily available by desacetonation of "mixture A," as described in our previous publication.[2]

All cyclic nitro compounds were reduced and in most cases the corresponding amino compounds could be isolated. The desamination of the amino compounds to the inosityls and the transformation of the nitro compounds to inososes by means of the Nef reaction[7] has not yet been realized.

We wish to stress the fact that the significance of our observations lies not so much in the purity or final identification of individual isomers, but rather in the ease with which ring closure is effected[8] under mild conditions. We feel that such a model experiment gives validity to the belief that inositol is formed in nature through cyclization of glucose.[9] The easy transformation of a sugar *via* an inositol derivative to an aromatic compound as demonstrated by us in the laboratory might well have its counterpart in an enzymatic process in nature.

Experimental

A. Cyclization of 6-Nitro-6-desoxy-D-glucose. (1) **Barium Salts of Nitrodesoxyinositols.**—To a solution of 12.0 g. of nitrodesoxy-D-glucose (m. p. 154–156°)[2] in 100 cc. of water was added 352 cc. of 0.163 *N* barium hydroxide. Crystallization of barium nitrodesoxyinositol started within a few minutes; 8.7 g. or 55% of the theoretical of the salts separated within twelve hours and 7.2 g. or 45% of the theoretical of crystalline salts precipitated on addition, in portions, of 600 cc. of ethanol within the next thirty-six hours. The first crystals formed were colorless, whereas those formed later were usually light brown. *Anal.* Calcd. for $C_{12}H_{20}O_{14}N_2Ba$ (553): Ba, 24.77. Found: Ba, 24.6.

(2) **Nitrodesoxyinositols.**—An amount of 8.65 g. of the above barium salts was dissolved in 40 cc. of 2 *N* acetic acid by shaking at room temperature. The resulting solution was freed from the barium by addition of 95% of the theoretical amount of *N* sulfuric acid and balanced

(5) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **19**, 519 (1936).

(6) M. L. Wolfrom, B. W. Lew and R. Max Goepp, Jr., THIS JOURNAL, **68**, 1443 (1946), and preceding papers.

(7) Nef reaction: J. U. Nef, *Ann.*, **280**, 263–291 (1894); *cf.* also J. C. Sowden and H. O. L. Fischer, THIS JOURNAL, **69**, 1963 (1947).

(8) For literature on attempted ring closure by chemical means *cf.* F. Micheel, *Ann.*, **496**, 77 (1932); "Chemie der Zucker und Polysaccharide," Leipzig, 1939, p. 329.

(9) For further support of this contention *cf.* H. O. L. Fischer, Harvey Lectures, Series XL, 1944–1945, pp. 156–178.

out exactly with 0.1 *N* sulfuric acid. On evaporation, *in vacuo*, of the filtered solution a mixture of isomeric nitrodesoxyinositols was obtained as a partly crystalline mass. After drying this mixture over phosphorus pentoxide and sodium hydroxide and dissolving it in 50 cc. of boiling 1,4-dioxane, 3.7 g. or 47% of the theoretical of substance (**Nitrodesoxyinositol I**) crystallized with one-half mole of dioxane on cooling to room temperature. Twice recrystallized from the same solvent, this substance melted at 147–148°. *Anal.* Calcd. for $(C_6H_{11}O_7N)_2 \cdot C_4H_8O_2$ (506): C, 37.94; H, 5.93; N, 5.53. Found: C, 38.10; H, 5.97; N, 5.55.

The mother liquors were collected and evaporated *in vacuo* and the residue was dissolved in a little hot methanol. On partial evaporation of the solvent over phosphorus pentoxide 3.0 g. or 46% of the theoretical of crystalline substance (**Nitrodesoxyinositol II**) was obtained. Crystallized from absolute ethanol with addition, in portions, of about 20% of absolute ether this substance melted at 185–186° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.5; H, 5.26; N, 6.72.

(3) Nitrodesoxyinositol I.—This substance, as obtained under (2), contained some isomers which could not be eliminated satisfactorily by repeated crystallization. However, separation was partially effected due to the fact that this substance could not be acetonated under standard conditions, whereas the contaminating isomers were easily acetonated. Thus 2 g. of this powdered substance was shaken for five hours in 50 cc. of absolute acetone containing 0.5% of concentrated sulfuric acid, whereupon the undissolved material was filtered off, washed with a few drops of absolute acetone and crystallized from dry 1,4-dioxane. This operation was repeated (3–5 times) until the substance showed a constant melting point. After filtration from the acetonation solution it melted at 182–183° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.6; H, 5.23; N, 6.82. After crystallization from 1,4-dioxane the nitrodesoxyinositol I contained one half mole of dioxane and melted at 162–163°. *Anal.* Calcd. for $(C_6H_{11}O_7N)_2 \cdot C_4H_8O_2$ (506): C, 37.94; H, 5.93; N, 5.53. Found: C, 38.10; H, 5.81; N, 5.52. The acetone mother liquor contained some diacetone-nitrodesoxyinositol II, as described under (6), and small amounts of not acetonated nitrodesoxyinositols, which were not further investigated.

(4) Aminodesoxyinositol I Hydrochloride.—An amount of 1.02 g. of nitrodesoxyinositol I, as obtained under (2), was dissolved in 50 cc. of distilled water and reduced with hydrogen at 26° and 752 mm. pressure in the presence of 2 g. of freshly prepared Raney nickel. Within the first ten minutes 250 cc. of hydrogen was absorbed, and 15 cc. within the next fifty minutes (calcd. 263 cc.). The catalyst was centrifuged off and the solution was neutralized with 0.5 *N* hydrochloric acid, and concentrated to about 25 cc., filtered with a little charcoal, and further concentrated to about 10 cc. On addition of about 80 cc. of acetone the solution turned slightly turbid and the hydrochloride crystallized within thirty minutes in long needles with one mole of water in a yield of about 75%. *Anal.* Calcd. for $C_6H_{14}O_5 \cdot HCl \cdot H_2O$ (233.5): C, 30.9; H, 6.85; N, 6.01. Found: C, 31.3; H, 6.80; N, 6.00. This compound sintered at 211° and slowly fused under decomposition on further heating to 230°. It did not reduce Fehling solution, which is a characteristic difference between the aminoinositols and the aminosugars, nitrosugars or nitroinositols.

(5) Nitrodesoxyinositol II.—This substance, as obtained under (2), appeared to be free of isomers, since its melting point did not change on repeated crystallization from ethanol or methanol and ether. Moreover, this procedure is wasteful. Pure substance in best yields is obtained by acetonation of the crude mixture of isomers and subsequent desacetonation, as described under (6).

(6) Diacetone-nitrodesoxyinositol II.—An amount of 2.4 g. of nitrodesoxyinositol II was added to 50 cc. of dry acetone containing 0.25 cc. of concentrated sulfuric acid, in which it dissolved on shaking, within thirty minutes. The solution was kept at room temperature overnight and was then neutralized with the calculated amount of concentrated ammonium hydroxide; the precipitate of ammonium sulfate was centrifuged off and the solution was evaporated, *in vacuo*, to about 5 cc. Then 100 cc. of ether was added and the ethereal solution was washed and dried and the ether was evaporated. Crystallization from *n*-butanol gave 2.8 g. or 85% of the theoretical of the diacetone compound, which showed a constant melting point of 186–186.5° after one more crystallization from the same solvent. *Anal.* Calcd. for $C_{12}H_{19}O_7N$ (289): C, 49.8; H, 6.58; N, 4.84; acetone, 40.1. Found: C, 49.7; H, 6.62; N, 4.74; acetone, 40.4.

Desacetonation of this substance by dissolving 2.0 g. of it in 20 cc. of boiling ethanol, refluxing for one hour with 20 cc. of *N* sulfuric acid, eliminating the sulfuric acid with the exact amount of barium acetate, evaporating the solvent *in vacuo* and crystallizing the residue from ethanol and ether, gave the nitrodesoxyinositol II, m. p. 185–186° (dec.), in a yield of 83% of the theoretical.

(7) Monoacetyl-diacetone-nitrodesoxyinositol II.—This was obtained by acetylating 0.5 g. of diacetone-nitrodesoxyinositol II in a mixture of 2 cc. of pyridine and 2 cc. of acetic anhydride and keeping the reaction mixture at room temperature for two hours, then evaporating the solvents *in vacuo* and crystallizing the residue twice from ethanol; m. p. 226°; yield about 87% of the theoretical. *Anal.* Calcd. for $C_{14}H_{21}O_8N$ (331): C, 50.7; H, 6.35; N, 4.23; acetone, 35.0. Found: C, 50.6; H, 6.35; N, 4.24; acetone, 34.9.

(8) Diacetone-aminodesoxyinositol II *p*-Toluenesulfonate.—An amount of 0.929 g. of diacetone-nitrodesoxyinositol II was dissolved in 25 cc. of 1,4-dioxane and reduced with hydrogen at 28° and 756 mm. pressure in the presence of 1 g. of freshly prepared Raney nickel. Within the first ten minutes 210 cc. of hydrogen was absorbed and 40 cc. within the next twenty minutes (calcd. 248 cc.). The catalyst was centrifuged off, the dioxane was evaporated *in vacuo* to about 5 cc. and 20 cc. of water was added, whereupon the solution was neutralized with 0.5 *N* *p*-toluenesulfonic acid, filtered with a little charcoal and evaporated to dryness *in vacuo*. On dissolving the residue in a little cold absolute ethanol and adding about five times the amount of absolute ether, long colorless needles of the salt formed immediately in a yield of 82% of the theoretical; decomposition point 225°. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.8; H, 6.64; N, 3.22; acetone, 26.9.

(9) Nitrodesoxyinositol III.—To a solution of 12.3 g. of nitrodesoxy-D-glucose in 90 cc. of water was added 30.0 cc. of 1.003 *N* sodium hydroxide. This reaction mixture was kept at room temperature until the optical rotation had disappeared (forty-eight hours), and was then acidified with 32 cc. of *N* acetic acid. After the addition of 1.030 *N* sulfuric acid the solution was evaporated to dryness *in vacuo*. The dry, crystalline residue was extracted three times with 100 cc. of absolute ethanol. On cooling the alcoholic extract, 4.0 g. of nitrodesoxyinositol III, m. p. 215° (dec.) crystallized. From the mother liquor an additional 4.1 g. of the same substance was collected on evaporation of the solvent and boiling the residue in a little dioxane. On dissolving this substance in boiling ethanol only 20% of it crystallized on cooling, m. p. 212–213° (dec.); still less was obtained on using dioxane, from which it crystallized with a m. p. of 218–219° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.8; H, 5.14; N, 6.84. This compound did not form acetone derivatives under standard conditions, but some diacetone-nitrodesoxyinositol II, m. p. 184–185°, was isolated on acetonation of the mother liquor residues, as under (6).

(10) Aminodesoxyinositol III.—An amount of 1.04 g. of nitrodesoxyinositol III was dissolved in 50 cc. of distilled water and reduced with hydrogen at 24° and 760 mm. pressure in the presence of freshly prepared Raney nickel; 265 cc. of hydrogen or 71% of the theoretical were absorbed within two and one-half hours. The

catalyst was then centrifuged off and the solution filtered with a little charcoal, and evaporated to about 10 cc. *in vacuo*, whereupon crystallization of the amine began; yield 69% of the theoretical. *Anal.* Calcd. for $C_6H_{13}O_5N$ (179): C, 40.2; H, 7.26; N, 7.82. Found: C, 40.1; H, 7.09; N, 7.74. This substance started decomposing at about 255° and melted under decomposition at 280–285°.

(11) **Pentaacetyl-nitrodesoxyinositol III.**—This was obtained by mixing 0.5 g. of nitrodesoxyinositol III with 10 cc. of acetic anhydride containing one drop of concentrated sulfuric acid and keeping the mixture at 20–22°; the nitrodesoxyinositol went quickly into solution and the pentaacetate crystallized immediately. After standing for two hours the crystals were filtered with suction and washed with water, yielding 90% of the theoretical. After crystallization from dioxane this substance melted at 258–259° (dec.). *Anal.* Calcd. for $C_{16}H_{21}O_{12}N$ (419): C, 45.7; H, 5.01; N, 3.34. Found: C, 45.7; H, 4.88; N, 3.63.

(12) **Sodium Salts of Nitrodesoxyinositols.**—These were isolated in an almost quantitative yield by dissolving 2.0 g. of nitrodesoxyinositol I or nitrodesoxyinositol II in 7 cc. of water and adding the theoretical amount of 2 *N* sodium hydroxide. Small colorless needles formed quickly; 30 cc. of ethanol was added, in portions, and the crystals were filtered with suction and washed with a little ethanol and ether. These salts could be recrystallized from water alone, or better by dissolving 1 g. in 25 cc. of warm water and adding 50 cc. of acetone in portions. *Anal.* Calcd. for $C_6H_{10}O_7NNa$ (231): Na, 9.95. Found: 9.78. From a concentrated aqueous solution of these sodium salts the barium nitrodesoxyinositols could be precipitated quantitatively by a molar solution of the calculated amount of barium chloride.

(13) **Conversion of Nitrodesoxyinositol I into Nitrodesoxyinositol II.**—To a solution of 0.010 mole (2.09 g.) of pure nitrodesoxyinositol I, as obtained under (3), in 64 cc. of water, was added 0.0050 mole of barium hydroxide dissolved in 36 cc. of water. Crystals appeared within two minutes; 2.66 g. of barium nitrodesoxyinositol was isolated after fifteen hours and 0.10 g. from the mother liquor, on addition of 200 cc. of ethanol, or a total of 99.7% of the theoretical. On treating this salt as described under (2), (5) and (6), the diacetonenitrodesoxyinositol II was isolated in a yield of 58% of the theoretical.

(14) **Conversion of Nitrodesoxyinositol II into Nitrodesoxyinositol I.**—On repeating as under (12) with nitrodesoxyinositol II, barium nitrodesoxyinositol was isolated in a nearly quantitative yield. On treating this salt as under (2), nitrodesoxyinositol I was isolated in a yield of 43% of the theoretical.

B. Cyclization of 6-Nitro-6-desoxy-L-idose.—(15) To a solution of 9.2 g. of nitrodesoxy-D-idose[2] in 100 cc. of water was added 188 cc. of 0.235 *N* barium hydroxide. The solution was kept at room temperature for sixteen hours, during which time only a very small precipitate formed.[10] On addition, in portions, of 700 cc. of ethanol, 8.5 g. or 70% of the theoretical of finely precipitated barium nitrodesoxyinositol was obtained. On eliminating the barium, as described under (2), a mixture of nitrodesoxyinositols was obtained in a yield of 83% of the theoretical. From this mixture identical compounds were isolated as described under (2)–(8).

(16) **Change of the Optical Rotation during Cyclization.**—This was observed on the following solutions—**Solution A**: 104.5 mg. crystalline nitrodesoxy-D-glucose, m. p. 156°, dissolved in 5.0 cc. of 0.126 *N* sodium hydroxide. **Solution B**: 2.50 cc. of an 0.20 molar solution of the same sample of nitrodesoxy-D-glucose, prepared twenty hours in advance and made alkaline with 2.50 cc. of 0.252 *N* sodium hydroxide. **Solution C**: 68.7 mg. of crystalline nitrodesoxy-D-glucose dissolved in 0.4 *N* sodium hydroxide. **Solution D**: 5.00 cc. of a solution of nitrodesoxy-L-idose, prepared by deacetonation of 3.563 g. of diacetone-6-nitro-6-desoxy-L-idose with 8.00 cc. of *N* sulfuric acid, as described previously (2), made up to 100.0 cc., made alkaline with 1.00 cc. of 1.20 *N* sodium hydroxide. The following changes in rotation were observed:

TABLE II

Time	Soln. A. $[\alpha]^{24}D$	Soln. B. $[\alpha]^{24}D$	Soln. C. $[\alpha]^{25}D$	Soln. D. $[\alpha]^{25}D$
Before addition of NaOH	(+45.5)	+36.4	(+44.3)	−27.3
After addition of NaOH				
2 minutes	+56.1	....	+57.8	−60.7
3 minutes	+56.3	+56.3	....	....
4 minutes	+56.8	+56.8	....	....
5 minutes	+56.1	+56.3	+49.8	−56.3
6 minutes	+55.5	+56.0	....	....
7 minutes	+54.7	....	....	....
8 minutes	+53.5	+54.7	....	....
9 minutes	+52.5	....	....	....
10 minutes	....	+53.0	+44.1	−50.7
11 minutes	+51.3	....	....	....
15 minutes	+49.0	+48.5	....	....
20 minutes	....	+45.4	+36.8	−44.6
25 minutes	+40.6	+40.6	....	....
48 minutes	+27.9	....	....	....
50 minutes	....	+25.2	....	....
60 minutes	....	....	....	−19.7
1.5 hours	....	....	+11.6	−14.2
2 hours	+10.1	+10.3	....	....
2.5 hours	+ 2.9	+ 2.5	0	− 8.8
3 hours	+ 1.2	+ 1.2		....
3.5 hours	0	0		....
5.5 hours				− 3.9
8 hours				0

C. Cyclization Products Obtained from "Mixture A."[11]—(17) An amount of 50 g. of "Mixture A" was dissolved in 300 cc. of 0.1 *N* sulfuric acid and kept for about seventy-five minutes at 75–80°. The warm solution was then freed from the sulfuric acid by addition of the exact amount of barium acetate; the precipitate was centrifuged off and the solution was concentrated to dryness *in vacuo*. The residue was dissolved in 100 cc. of water and 2100 cc. of 0.1 *N* barium hydroxide was added. Crystallization of barium nitrodesoxyinositols started within a few hours and the optical activity of the supernatant solution disappeared after twenty hours. The solution was acidified with glacial acetic acid and stirred until all crystals had dissolved. On processing this solution, as described under (2), a crystalline mass was obtained from which 25 g. of nitrodesoxyinositol I (50% of the theoretical) was obtained on crystallization from dioxane, and 18 g. of diacetone nitrodesoxyinositol II (31% of the theoretical) was obtained on acetonation of the dioxane soluble material, as described under (5) and (6).

D. Aromatization of the Nitrodesoxyinositols.—(18) Acetylation of any of the foregoing nitrodesoxyinositols by dissolving 0.5 g. of these substances in a mixture of 2 cc. of pyridine and 2 cc. of acetic anhydride and warming the solution to 70° for one minute, then evaporating the solvents *in vacuo* and crystallizing the residue twice from ethanol, gave **diacetyl-5-nitroresorcinol**, m. p. 105°, in an almost quantitative yield. *Anal.* Calcd. for $C_{10}H_9O_6N$

(10) The failure of the barium salts to precipitate directly from the aqueous solution, as in the case of the cyclization of the 6-nitro-6-desoxy-D-glucose, may be due to the fact that the starting material was amorphous and perhaps less pure. This is also indicated by the considerably lower yield in which the mixture of nitrodesoxyinositols was obtained.

(11) This "mixture A" represents the crude mixture of 1,2-acetone-6-nitro-6-desoxy-D-glucose and 1,2-acetone-6-nitro-6-desoxy-L-idose as described in our preceding publication.[2]

(239): C, 50.2; H, 3.76; N, 5.85; CH_3CO-, 36.0. Found: C, 50.1; H, 3.72; N, 5.81; CH_3CO-, 36.9. Propionylation of the nitroinositols gave in a similar manner, the **dipropionyl-5-nitroresorcinol**, m. p. 115°, from 70% ethanol. *Anal.* Calcd. for $C_{12}H_{13}O_6N$ (267): C, 53.9; H, 4.86; N, 5.24. Found: C, 53.7; H, 4.90; N, 5.20. On hydrolysis of the two above substances with 50% alcoholic 0.5 *N* potassium hydroxide, the known 5-nitro resorcinol, m. p. 157–159°, was isolated in the usual manner and gave, on methylation, the known 3,5-methoxynitrobenzene, m. p. 89.5°.

On dissolving 0.5 g. of pentaacetyl-nitrodesoxyinositol III, as described under (11), in 5 cc. of hot pyridine, it was transformed almost quantitatively into diacetyl-5-nitroresorcinol.

Acknowledgment.—The authors wish to express their gratitude to the Nutrition Foundation, Inc., for the support of this work.

Summary

The cyclization of 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose to a mixture of nitrodesoxyinositols is described. Starting from either of the nitrodesoxy hexoses, the same mixture of nitrodesoxyinositols was obtained. A reaction mechanism for the cyclization is proposed.

TORONTO, CANADA RECEIVED NOVEMBER 10, 1947

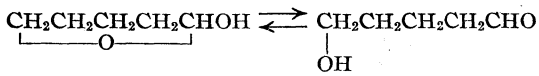
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Hydroxylation of 2,3-Dihydropyran and the Application of Desoxyaldopentoses in the Browning Reaction[1]

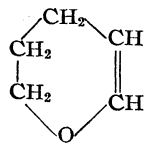
BY CHARLES D. HURD AND CHARLES D. KELSO

The reaction of reducing sugars with amino acids, leading to the evolution of carbon dioxide and the development of an intense brown color was studied by Maillard.[2] This general subject of the "browning reaction" has been one of considerable interest in recent years, since it seems to be intimately associated with the color changes observed in many foodstuffs during processing or storage.

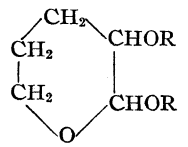
To extend our knowledge of the fundamentals of this reaction, two model aldoses were synthesized for test purposes. One was tetrahydropyran-2-ol, made by hydration of dihydropyran (I), following the directions[3] of Schniepp and Geller. This is stated to exist in equilibrium (95:5) with 5-hydroxypentanal



This material may be regarded as a 2,3,4-tridesoxyaldopentose. The substance is similar to



I



II (R = H)
III (R = Ac)

4-hydroxypentanal, $CH_2CHOHCH_2CH_2CHO$, which was synthesized by Helferich[4] and shown to exist primarily in the cyclic modification

The second model sugar was tetrahydropyran-2,3-diol (II). This substance is new. It may be regarded as a 3,4-didesoxyaldopentose, thereby providing an aldose molecule with inert beta and gamma positions. In solution the cyclic alpha and beta forms of II should be in equilibrium with the open-chain structure, $HOCH_2CH_2CH_2CHOHCHO$, just as the alpha and beta forms of a glycose are in equilibrium with the glyconaldehyde.

Synthesis of II was readily accomplished from I by use of hydrogen peroxide in *t*-butyl alcohol using osmium tetroxide as catalyst. This follows the type of synthesis devised by Milas and co-workers[5] for such syntheses as these: isobutylene glycol from isobutylene, ethylene glycol from ethylene, racemic acid from fumaric acid, glycerol from allyl alcohol, glycolaldehyde from vinyl acetate or vinyl ether, etc. Glycals, according to Hockett and co-workers,[6] behave analogously.

Although hydroxylation of double bonds by hydrogen peroxide ordinarily produces *cis* glycols,[5] it seems reasonable to think that both *cis* and *trans* hydroxyls are present in II because of the equilibration reaction mentioned above. Besides II, the reaction product also contained a considerable C_{10}-fraction revealing both non-reducing and reducing isomers. The non-reducing compound was shown to be 3,4-didesoxyaldopentosyl 3,4-didesoxyaldopentoside (IV). Products II and IV accounted for half of the I used. An additional 10–15% was accounted for by reducing disaccharide and 6% by a fraction, some of which is reducing, which may contain trisaccharide.

(1) The subject matter of this paper has been undertaken in coöperation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces under a contract with Northwestern University. The opinions and conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or endorsement of the War Department.

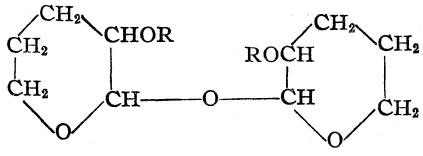
(2) Maillard, *Compt. rend.*, **154**, 66 (1912); *Ann. chim.*, [9] **5**, 258 (1916).

(3) Schniepp and Geller, THIS JOURNAL, **68**, 1646 (1946).

(4) Helferich, *Ber.*, **52**, 1128, 1802 (1919).

(5) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2345 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939); Milas and Maloney, *ibid.*, **62**, 1842 (1940).

(6) Hockett, Sapp and Millman, *ibid.*, **63**, 2051 (1941); Hockett and Millman, *ibid.*, **63**, 2587 (1941).



IV (R = H)
V (R = Ac)

Structures II and IV are apparent from the following evidence: (1) correct carbon and hydrogen analyses; (2) II reduces Benedict solution, while IV is non-reducing; (3) IV is quantitatively converted to II by dilute hydrochloric acid at 70°. This is proven by the identity of the 2,4-dinitrophenylosazones formed from II and from the hydrolysis product of IV and by the fact that the hydrolysis product reduces Benedict solution; (4) II and IV yield bis-3,5-dinitrobenzoic esters on treatment with 3,5-dinitrobenzoyl chloride in pyridine. Similarly, on acetylation, II gives rise to 2,3-diacetoxytetrahydropyran (III) and IV yields 2-acetyl-3,4-didesoxyaldopentosyl 2-acetyl-3,4-didesoxyaldopentoside (V). II has been obtained only as a thick oil, whereas IV is crystalline (m. p. 142.5–143°).

The crystalline nature of IV suggests that it may be a D,L pair or one *meso* form. Out of four possible D,L pairs and two *meso* forms for IV, only one D,L pair and one *meso* form would be expected if IV was related only to the *cis* forms of II.

In the browning studies it was demonstrated that 2,3,4-tridesoxyaldopentose or tetrahydropyran-2-ol underwent only a slight discoloration when heated with glycine solution, whereas 3,4-didesoxyaldopentose browned more readily even than D-glucose itself. Evidently, therefore, a δ-hydroxy aldehyde does not undergo the browning reaction, whereas an α,δ-dihydroxy aldehyde does do so. It seems that the α-hydroxy group is required for this reaction. Results are shown in Table I. In these experiments the solutions in question were heated at 90–95° under reflux condensers for four hours. Carbon dioxide was evolved from solutions 1 and 3. Initial and final absorptions at 4900 Å. were observed, using a Beckman spectrophotometer. The *p*H was that of the natural, unadjusted solutions. The four-hour samples of solutions 1, 2, and 3 were also taken for absorption spectra measurements between 3300–2550 Å. Solutions 1 and 3 revealed a definite maximum at 2950 Å., whereas solution 2 showed no such maximum.

TABLE I

PER CENT. ABSORPTION AT 4900 Å.

Hours	0		4	
Solution	*p*H	% abs.	*p*H	% abs.
1	5.2	11	4.1	98
2	4.5	8	4.0	11
3	5.6	1	5.2	57.5
4	5.95	3.2	5.5	7.5
5	6.6	0	5.5	0

Solution 1. Equal volumes of 1.0 *M* 3,4-didesoxyaldopentose and 1.0 *M* glycine
2. 1.0 *M* 3,4-didesoxyaldopentose alone
3. Equal volumes of 1.0 *M* D-glucose and 1.0 *M* glycine
4. Equal volumes of 1.0 *M* 2,3,4-tridesoxyaldopentose and 1.0 *M* glycine
5. 1.0 *M* 2,3,4-tridesoxyaldopentose alone

Experimental

Hydroxylation of 2,3-Dihydropyran.—2,3-Dihydropyran (196 g., 2.3 moles), obtained from the du Pont Company, and 5 ml. of osmium tetroxide catalyst (0.5 g. OsO_4 in 100 ml. of *t*-butyl alcohol) were placed in a 2-liter, 3-neck flask and 1320 ml. of hydrogen peroxide solution (6% H_2O_2 in *t*-butyl alcohol[5]) was added dropwise with stirring at −10 to +5° over a period of four hours. Additional catalyst solution (3 ml.) was added after two hours and after all of the peroxide solution had been added. The reaction is highly exothermic and care must be exercised not to add the peroxide at too fast a rate. The solution was allowed to stand overnight. The solvent was removed under reduced pressure at a bath temperature of 60° or below. The residue (255 g.) was acetylated by dissolving it in 500 ml. of pyridine and adding 750 ml. of acetic anhydride at 10°. The solution was allowed to warm to room temperature and stand overnight. After destruction of the unused acetic anhydride by addition of excess 75% ethyl alcohol, the solvent was removed at reduced pressure. The residue (335 g.) was allowed to stand overnight, whereupon some crystallization was noted, leading to 53 g. of V, which was collected on a filter. The solid was recrystallized from methyl alcohol: m. p. 132–133°. It sublimes at a pressure of 1 mm. of mercury.

Anal. Calcd. for $C_{14}H_{22}O_7$: C, 55.61; H, 7.34. Found: C, 55.78; H, 7.38.

The filtrate, after separation of V, was distilled at 1 mm., yielding 135 g. of crude 2,3-diacetoxytetrahydropyran (III) (b. p. 96–115°). Redistillation of this material gave 115 g. of product collected at 108–120° and 2–5 mm.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.43; H, 7.74.

The residue (120 g.) after removal of V and III was dissolved in 100 ml. of methanol and cooled to 0°. Another 12 g. of crude V separated and was collected on a filter. Methanol was distilled from the filtrate and the residue was distilled at low pressure[7] into two fractions, VI and VII. At a bath temperature of 150–170° and a pressure of 10^{-6} to 10^{-3} mm., there was collected 48.4 g. of VI, a mixture of V and its isomers (the diacetate of the "disaccharide" portion). At a bath temperature of 170–200° and the same pressure was collected the acetate of the higher-boiling portion (VII); yield, 19.7 g.

The over-all yield data for utilization of 2,3-dihydropyran are as follows: 135 g. or 28.6% of III, 65 g. or 18.5% of V, 48.4 g. or 13.5% of a mixture of V and a diacetate of a reducing disaccharide, 19.7 g. or 6.3% of an acetate of a higher-boiling fraction.

Hydroxylation, Second Method.—The products of another comparable run were processed without the acetylation procedure. In this experiment 70 ml. of dihydropyran was taken and other reagents were used proportionately. After the solvent had been removed under reduced pressure, the resulting sirupy product was subjected to continuous extraction with cyclohexane (100 ml.). Sixteen grams of the product was insoluble in the hot hydrocarbon, whereas 41 g. was extracted. Of this 41-g. portion, 33.6 g. (A) was a sirup soluble in ether, and 7.4 g. (B) was a white solid insoluble in ether. Fraction A was essentially II (37% yield), and fraction B was proved by analysis (Found: C, 55.50; H, 8.76) and m. p. 141° to be IV (8% yield).

Deacetylation of 2,3-Diacetoxytetrahydropyran (III).—Twelve grams of III was dissolved in 100 ml. of absolute

(7) Hurd, Liggett and Gordon, THIS JOURNAL, **63**, 2656 (1941).

methanol and 8 ml. of 0.4 *N* barium methoxide solution was added. After forty-eight hours at 0°, the solution was carbonated by addition of Dry Ice, and the methyl alcohol was evaporated off at room temperature. Treatment of the residue with dry ether resulted in formation of a white amorphous precipitate (barium salts). After filtration and distillation of the solvent, finally at 52° (10 mm.), there remained 6.0 g. (85% yield) of water white, thick liquid. In other runs, yields of II have been 95–97%.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.88; H, 8.54. Found: C, 51.63; H, 8.54.

This material is soluble in water, ether and most other organic solvents except hexane. It reduces Benedict solution at once at 90° and reacts with phenylhydrazine to give a red oil.

3,4-Didesoxypentose 2,4-Dinitrophenylosazone.—Tetrahydropyran-2,3-diol (0.5 g.) was dissolved in 200 ml. of absolute ethanol and 2.5 g. of 2,4-dinitrophenylhydrazine was added. The reaction mixture was refluxed several minutes. Then 5 ml. of concd. hydrochloric acid was added and the refluxing was resumed, whereupon the color changed to dark brown. After fifteen minutes of refluxing, the reaction mixture was cooled and filtered (yield, 1.1 g.). Three recrystallizations from acetone led to a red-orange, crystalline solid of m. p. 242°.

Anal. Calcd. for $C_{17}H_{16}N_8O_9$: N, 23.52. Found: N, 23.35.

Tetrahydropyran-2,3-diol Bis-3,5-dinitrobenzoate.—One gram of II was dissolved in 10 ml. of pyridine. Three grams of 3,5-dinitrobenzoyl chloride was added. The reaction mixture was allowed to stand overnight at room temperature and was then treated with water and 5% aqueous sodium carbonate. The gummy product weighed 3 g. Three recrystallizations from a 3:1 mixture of ethanol and ethyl acetate led to a crystalline product melting at 174.5–175.5°.

Anal. Calcd. for $C_{19}H_{14}N_4O_{13}$: N, 11.06. Found: N, 10.95.

Deacetylation of 2-Acetyl-3,4-didesoxyaldopentosyl 2-Acetyl-3,4-didesoxyaldopentoside (V) into (IV).—The V (8.5 g., m. p. 132–133°), which had been recrystallized twice from methanol, was dissolved in 200 ml. of absolute methanol and deacetylated as above (dilute sulfuric acid instead of carbon dioxide was used to destroy the barium methoxide). It was necessary to allow the reaction to proceed for six days because of the limited solubility of IV in cold methanol. The product was worked up as above except that the residue was extracted with ethyl acetate instead of ether. The yield was 5.7 g. or 92%. The product was crystallized twice from ethyl acetate and sublimed before analysis (m. p. 141.5–142°).

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.42; H, 8.35.

This material (IV) is water soluble, is non-reducing to Benedict solution, and does not react with phenylhydrazine. A dinitrobenzoyl derivative of this material may be prepared as above (m. p. 245–246° after three recrystallizations from a 3:1 mixture of ethyl acetate and acetic anhydride).

Anal. Calcd. for $C_{24}H_{22}N_4O_{15}$: N, 9.24. Found: N, 9.35.

Hydrolysis of IV into II.—Acid hydrolysis of IV was carried out by dissolving 1 g. of the solid in 25 ml. of water, adding 1.5 ml. of concd. hydrochloric acid, and heating to 70–80° for thirty minutes. The solution was cooled, neutralized to phenolphthalein with 10% sodium hydroxide solution, and one drop of concd. hydrochloric acid added. This solution reduced Benedict solution, whereas the solution before treatment with acid was non-reducing. The solution was evaporated to dryness at room temperature with the aid of an air jet. The residue was treated with ether and the ether solution decanted from sodium chloride and evaporated, leading to 1 g. of clear sirup. This was placed in reaction with 2,4-dinitrophenylhydrazine as above The product melted at 242–243° after two recrystallizations from acetone and showed no m. p. depression when mixed with the 2,4-dinitrophenylosazone of II described above.

Deacetylation of Fractions VI and VII from High Vacuum Distillation.—These water insoluble acetates were deacetylated as above Fraction VI was first dissolved in methyl alcohol and crystallization was allowed to take place to remove the bulk of V present. The filtrate after removal of the solid was evaporated leaving an oily residue which showed no tendency to crystallize. This residue (8.5 g.) was deacetylated in 90.5% yield (5.8 g.). The product is water soluble and reduces Benedict solution strongly. Attempts to prepare pure derivatives of this material have failed.

Fraction VII showed no tendency to crystallize and was deacetylated in 80% yield to a water soluble, reducing material.

Acknowledgments.—Combustion analyses (C, H, N) were performed by P. Craig, M. M. Ledyard, and N. Mold.

Summary

Mono- and disaccharide-like compounds have been obtained by hydroxylation of 2,3-dihydropyran, using hydrogen peroxide in *t*-butyl alcohol and osmium tetroxide. The implications of the fact that tetrahydropyran-2,3-diol may be regarded as 3,4-didesoxyaldopentose are expounded. This compound gives rise to a strong brown coloration in its reaction with glycine, whereas 2,3,4-tridesoxyaldopentose (tetrahydropyran-2-ol) does not, thereby demonstrating the importance of the α-hydroxy aldehyde function in this reaction.

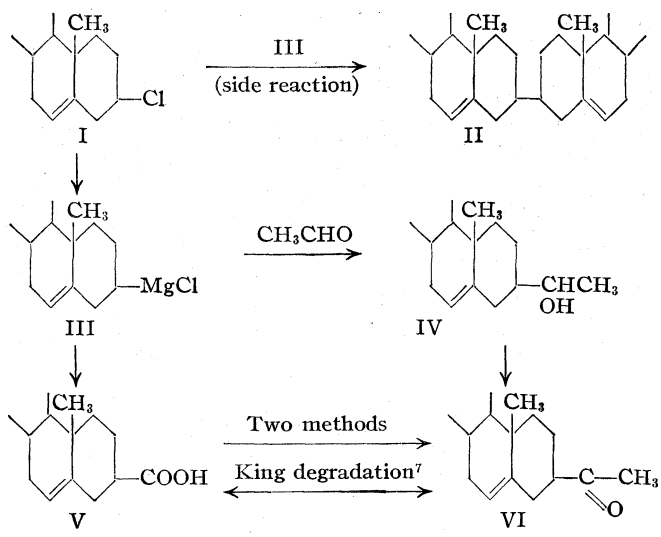
EVANSTON, ILLINOIS RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Derived Steroids. I. Cholesteryl Ketones[1]

BY ROBERT H. BAKER AND EDWARD N. SQUIRE[2]

As a model for the preparation of 3-acylsteroids, we have made a study of various methods for preparing methyl cholesteryl ketone, VI. All of the successful methods make use of cholesteryl Grignard reagents. This reagent may be converted into an impure methyl carbinol, IV, which is then oxidized to the ketone or it may be converted into the acid and to the acid chloride which with methyl Grignard or dimethylcadmium yields the ketone.



The preparation of cholesterylmagnesium chloride has been described briefly by Marker.[3] The reaction is carried out in the presence of ethylmagnesium bromide and is very slow in refluxing ethyl ether. Even though the cholesteryl chloride is added slowly over a period of six hours, there is always formed the coupling product, 3-cholesteryl-5-cholestene (biocholesteryl), II. This compound is almost insoluble in ether, and, although it must have been encountered previously, it has not been characterized.[4] We have isolated the compound in yields as high as 12% and have characterized it by physical constants and molecular weight determination. Cholesteryl bromide forms the Grignard reagent more rapidly than does the chloride but offers no advantage as a means of diminishing the production of bicholesteryl.

The reactions of cholesteryl Grignard are quite slow and although it is possible to carbonate it in almost quantitative yield, those reagents which are condensable undergo reaction with the production of large quantities of cholestene.[5] Table I summarizes the Grignard reactions. Cholestene was formed in all of these runs in yields of approximately 50%. In spite of the fact that acetaldehyde probably condenses more rapidly than do the other reagents used, it also reacts more rapidly in the desired way. The products of the acetaldehyde reactions do not crystallize, probably due to the presence of steroisomeric carbinols. The product of the Oppenauer[6] oxidation of the crude carbinol also is difficult to crystallize, but after purification by way of the semicarbazone it crystallizes very well.

Another approach, through the reaction of methylmagnesium bromide or dimethylcadmium on cholesteryl-3-carboxylic acid chloride, has proven to be the best route to the ketone. Although these methods, involving two Grignard reactions, would seem to be longer than the first ones discussed they are actually economical of time since the ketone is produced without an oxidation step and its purity is sufficiently high to allow crystallization without purification by the semicarbazone. An approximately 40% yield of crystalline ketone may be obtained by use of the magnesium or 82% by use of the cadmium reagents.

Diethylcadmium furnishes the ethyl ketone to about the same extent. In early experiments with the cadmium alkyls the reaction was carried out over long periods of time at comparatively low temperature and there resulted high-melting by-products. One of these has been identified as dimethylcholesterylcarbinol by comparison with a sample synthesized from 3-carbomethoxy-5-cholestene and methylmagnesium iodide. Since the color test for methylmagnesium bromide was negative it appears that a large excess of organocadmium reagent is capable of production of tertiary alcohols.

The various methods have thus far produced only one crystalline form of the methyl ketone, m. p. 104–105°; $[\alpha]^{27}D$ − 11°. The assignment of structure is based not only on its method of synthesis but also upon the fact that it has been de-

(1) Presented under the the title "Methyl Cholesteryl Ketone" at the Atlantic City Meeting of the American Chemical Society, April, 1947.

(2) Junior Fellow of the National Institute of Health.

(3) Marker, Oakwood and Crooks, THIS JOURNAL, **58**, 481 (1936); Marker, Kamm, Oakwood and Laucius, *ibid.*, **58**, 1948 (1936).

(4) The white solid (ref. 3) which was removed by filtration and rejected probably was bicholesteryl. The compound obtained by Galinovsky and Bretschneider (*Monatsh.*, **72**, 190 (1938) by the catalytic reduction of cholestenone pinacol may have been it though no physical constants were given.

(5) Carbonization and oxidation (ref. 3) are the only previously studied reactions of this Grignard reagent.

(6) Oppenauer, *Rec. trav. chem.*, **56**, 137 (1937).

TABLE I

Organometallic	Reagent	%Products[a] Ketone	%Products[a] 3-Cholesteryl-5-cholestene, II
RMgCl[b]	CH_3CHO	16.3	7
RMgBr	CH_3CHO	12.8	12
RMgBr	CH_3COCl	0.34	
RMgCl	CH_3CN	0	
RMgCl	$CH_3COCOCH_3$	0	3
CH_3MgBr	RCOCl	40	
$(CH_3)_2Cd$	RCOCl	82	
$(C_2H_5)_2Cd$	RCOCl	75	

[a] Cholestene accounts for approximately 50% of each yield except the last three. [b] R is 3-cholesteryl.

graded to cholesteryl-3-carboxylic acid. The degradation was accomplished according to the excellent method discovered by Professor Carroll King of these Laboratories.[7] When heated with iodine and pyridine the ketone was converted into the crude pyridinium iodide in 75% yield and this upon cleavage by alkali gave Marker's acid[3] in 86% yield.

The success experienced recently in the replacement of the *p*-toluenesulfonoxy group through the use of sodiomalonic ester[8] led to attempts to effect similar replacements with potassium cyanide. Such a cyanide would probably yield the methyl ketone by reaction with methyl Grignard. The replacement has not been accomplished, but this reaction is of interest because it produces 3,5-cholestadiene in good yield. Suspensions of equimolar mixtures of cholesteryl tosylate and potassium cyanide in xylene do not react at 80° or 100° during twenty-four hours, but refluxing (139°) for eighteen hours produced the easily isolated diene in 70% yield. The diene is also formed (81%) by fusion of cuprous cyanide and cholesteryl bromide at 130° for four hours, but the product is more difficult to purify.

Experimental[9]

Cholesteryl Chloride, I.—This was prepared according to Diels[10] with the exceptions that enough thionyl chloride was used to take all the cholesterol into solution and the reaction product was poured into water. A quantitative yield of crude product was obtained and this was reduced to 63% by crystallization from four times its weight of acetone, m. p. 96–97°. A quantitative yield of crude product, m. p. 84–92°, was also obtained from the reaction of equal weights of cholesterol and phosphorus oxychloride for eighteen hours at room temperature but the product is difficult to purify.

It is necessary that the cholesteryl chloride used in the preparation of cholesterylmagnesium chloride be very pure; the melting point should be as high as 95–96°. The purification has been accomplished by chromatographic adsorption. A solution of 10 g. of crude cholesteryl chloride, m. p. 85–93°, in 100 ml. of petroleum ether (80–100°) was passed through a column containing 18 × 100 mm. of 80–200 mesh activated alumina and 18 × 50 mm. of Norit. The petroleum ether was evaporated off under vacuum and the cholesteryl chloride crystallized from acetone, m. p. 95–96°. The purified compound was then crystallized from absolute ether at −50° and dried *in vacuo* at 78° for four hours.

Cholesteryl-3-carboxylic Acid, V.—This was prepared in 85% yield, m. p. 210–220°, by a modification of Marker's method[3] in which the Grignard solution made from 12 g. of chloride was poured into a flask containing crushed Dry Ice in absolute ether and allowed to stand overnight before working up. One crystallization from benzene gave 90% of the material, m. p. 222–223°, and 10%, m. p. 225–227°.

Cholesterylmagnesium Chloride and Bromide.—To 0.73 g. (0.03 mole) of powdered magnesium there was added 0.7 g. (0.0064 mole) of ethyl bromide in 10 ml. of absolute ether. When this reaction was complete a solution of 9.2 g. (0.023 mole) of pure cholesteryl chloride in 50 ml. of dry ether was added over a period of three hours, gentle reflux being maintained throughout the addition time and for an additional thirty to thirty-five hours. The volume of the solution was maintained at 50–60 ml. by occasional addition of dry ether. Stirring was not used.

The preparation of the bromo Grignard was similarly carried out with the exception of a shorter refluxing period, fifteen to twenty hours.

3-Cholesteryl-5-cholestene, II.—This was isolated from the early experiments by filtration of the ether extracts of acidified reaction mixtures. The suspended material collects at the interface between the aqueous and ether phases, but is re-suspended upon shaking. In later experiments it was removed from the Grignard preparation by filtration prior to addition of the reactant. It was separated from any unreacted magnesium by extraction with hot benzene in which it is only slightly soluble. It crystallizes from benzene in small colorless plates which melt at 267–269° to a cloudy melt with decomposition, $[\alpha]^{24.5}D$ +30° (6.8 mg. made up to 5 ml. with benzene, α + 0.07°; *l*, 2 dm.).

Anal. Calcd. for $C_{54}H_{90}$: C, 87.73; H, 12.27; mol. wt., 739. Found: C, 87.90; H, 12.39; mol. wt. (Rast), 751.

Methyl Cholesteryl Ketone Semicarbazone.—To the Grignard solution prepared from 0.7 g. (0.006 mole) of ethyl bromide and 9.2 g. (0.023 mole) of cholesteryl chloride in 50 ml. of ether was added 50 ml. of an absolute ether solution of dry acetaldehyde (0.077 mole). The addition was made at 0° over a period of two hours and the mixture was allowed to stand, finally reaching room temperature over a period of four hours. The mixture was then hydrolyzed with 5% hydrochloric acid and extracted with ether. The crude bicholesteryl, 1.2 g., was separated by filtration and then the ether solution was evaporated to an oil which was dried *in vacuo* at 100°.

The oil was oxidized by refluxing for fourteen hours in a mixture of 75 ml. of dry acetone and 150 ml. of benzene containing 10 g. of aluminum *t*-butoxide. Upon working up the product there was obtained about 5 g. of a yellow oil which was heated *in vacuo* at 100° for three hours in order to remove the simple condensation products of acetone.

The resulting ketonic oil was refluxed for one hour with 0.9 g. of semicarbazide hydrochloride and 2 ml. of pyridine in 20 ml. of ethanol. The solvent and pyridine were removed by evaporation and the solid was washed with ether and collected on a filter. It was then boiled with 20 ml. of water and filtered hot to remove biurea. The dried **semicarbazone** weighed 1.74 g., (16.3%), m. p. 215–225°. Crystallized from benzene twice the m. p. is 229–231°, dec.

Anal. Calcd. for $C_{30}H_{51}ON_3$: C, 76.70; H, 10.94; N, 8.95. Found: C, 76.87; H, 10.98; N, 9.02.

Methyl Cholesteryl Ketone, VI.—To 194 mg. of the semicarbazone and 20 ml. of 95% ethanol there was added 1 ml. of concentrated sulfuric acid and the mixture heated under reflux. The suspension became homogeneous and when concentrated to 10 ml. after two hours of heating

(7) King, THIS JOURNAL, **66**, 894, 1612 (1944).

(8) Kaiser and Svarz, *ibid.*, **67**, 1309 (1945).

(9) Microanalyses by Margaret Ledyard and Patricia Craig.

(10) Diels and Blumberg, *Ber.*, **44**, 2847 (1911); Diels and Abderhalden, *ibid.*, **37**, 3102 (1904).

and cooled to 0° the ketone crystallized. This was taken up in ether and washed with potassium carbonate solution then water and the ketone was recovered. Crystallization from 5 ml. of 95% ethanol gave 51 mg. (29.8%) of colorless needles, m. p. 104–105°, $[\alpha]^{27}D$ −11° (67 mg. made up to 2.0 ml. with chloroform, α −0.37; l, 1 dm.).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.44; H, 11.76.

Methyl Cholesteryl Ketone (second method).—3-Cholesterylcarboxylic acid, 2.84 g. (0.0069 mole), m. p. 210–220°, was dried for one hour *in vacuo* at 100°. It was then mixed with 2.0 g. (0.0096 mole) of phosphorus pentachloride and the mixture heated *in vacuo* at 100° for an hour. The dark reaction mixture was allowed to stand at room temperature for eighteen hours at the end of which time it was taken up in dry ether and filtered to remove the insoluble residue. The ether solution was then cooled to −10° and to it was added a solution of methylmagnesium iodide prepared from 1.24 ml. (0.02 mole) of methyl iodide and 0.5 g. of magnesium in 10 ml. of ether. The mixture was allowed to stand at −10° for thirty-six hours during which time an oil had settled out. The mixture was then poured into 50 ml. of ice water containing 10 ml. of 10% sulfuric acid. The organic material was then taken up in ether which was dried, filtered, and evaporated to a gum, 0.74 g. The gum was then dissolved in acetone, filtered and crystallized to yield two fractions; 0.138 g., m. p. 107–112°, and 0.280 g., m. p. 98–103°. The latter fraction was recrystallized from acetone to give a product, m. p. 100–103°, which with methylcholesteryl ketone, previously prepared, m. p. 104–105°, gave a mixed m. p. 103–105°.

Methyl Cholesteryl Ketone (third method).—Thionyl chloride was a more suitable reagent than phosphorus pentachloride for the preparation of 3-cholesterylcarboxylic acid chloride. The acid, 1.2 g., was refluxed with 1 ml. of thionyl chloride in 10 ml. of benzene for four hours and allowed to stand overnight. The solvent and excess reagent were then removed *in vacuo* at 100° leaving the crude acid chloride, 96% yield, m. p. 118–120°.

The acid chloride, 0.50 g. (1.15×10^{-3} mole), in 3 ml. of ether was added to 2×10^{-3} mole of dimethylcadmium contained in 5 ml. of ether at 0°. The mixture was refluxed for forty-five minutes and then decomposed by ice water. The product was extracted with ether and washed with 10% hydrochloric acid, saturated sodium bisulfite, 10% potassium hydroxide and then water. Acidification of the alkaline wash afforded 0.10 g. of crude 3-cholesteryl carboxylic acid. The ether solution was dried over sodium sulfate and evaporated to yield 0.39 g. of ketone, m. p. 103–105°, 82% yield.

Variation of this procedure by refluxing the reactants in benzene for two hours[11] led to a product more difficult to purify in 40% yield.

Ethyl Cholesteryl Ketone.—In a manner similar to the third method described above diethylcadmium gave the ethyl ketone, m. p. 133–134°; $[\alpha]^{27}D$ −14 (25.9 mg. made up to 3.61 ml. with chloroform, α −0.10, l, 1 dm.).

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.82. Found: C, 84.31; H, 11.77.

The **semicarbazone** of ethyl cholesteryl ketone was prepared in order to determine the amount of ketone in an impure fraction of material prepared as above. By use of the pyridine method previously described, 1.45 g. of ketonic material gave 0.58 g. of semicarbazone, m. p. 224–225°, from benzene–ethanol.

Anal. Calcd. for $C_{31}H_{53}N_3O$: C, 76.93; H, 11.03; N, 8.73. Found: C, 77.24; H, 11.08; N, 8.41.

Degradation of Methyl Cholesteryl Ketone.[7]—Methyl cholesteryl ketone, 65 mg. (1.58×10^{-4} mole) was heated with 1 ml. (1.24×10^{-2} mole) of pyridine and 25 mg. (1×10^{-4} mole) of iodine at 100° for twenty-two hours. The pyridine was then removed *in vacuo* at 100° and the product was extracted with three 1-ml. portions of absolute ether which yielded 26 mg. of starting material. The ether insoluble material was then extracted with three 2-ml. portions of warm methanol. By fractional crystallization of the methanol solution there was obtained 43 mg. of the crude pyridinium iodide of methyl cholesteryl ketone, m. p. 190–192° with prior softening (75% yield based on recovered ketone).

The pyridinium iodide, 20 mg. (3.2×10^{-5} mole) in 5 ml. of ethanol containing 0.2 ml. of 10% potassium hydroxide was then refluxed three hours. The reaction mixture was then poured into water and extracted with ether. The aqueous layer upon acidification with sulfuric acid gave a yellow coagulum, which, after cooling to 0° and filtering, yielded 11.5 mg. (86%) of crude acid. Crystallized from benzene the acid melted at 223–225° and showed no depression with mixtures of 3-cholesteryl carboxylic acid.

3-Carbomethoxy-5-cholestene.—Following the method of Marker,[3] 550 mg. (1.3×10^{-3} mole) of 3-cholesterylcarboxylic acid, V, was converted into 559 mg. of the methyl ester, m. p. 93–103°. One crystallization from methanol or chromatographing a cyclohexane solution on alumina followed by elution with benzene yielded crystals, m. p. 100–101°, $[\alpha]^{27}D$ −16 (53 mg. made up to 2 ml. with chloroform, α −0.42, l, 1 dm.). The purified product amounted to 64% of the total ester. The benzene eluate, 33%, melted at 86–90° and this indicates that the 101.5°-melting form of Marker is probably entirely of one configuration.

Dimethylcholesterylcarbinol.—This compound was isolated in about 4% yield from reactions of five-fold excess cadmiumdimethyl (prepared from methyl bromide) with the acid chloride in benzene at 25° for eighteen hours. It was isolated in two ways. Upon adding petroleum ether solutions of the reaction product to ethanol there was obtained as many as three fractions melting variously between 143 and 160°. The filtrate from the third fraction upon evaporation yielded the ketone. When the whole reaction product was absorbed from petroleum ether solution on alumina and eluted with methanol, the ketone was removed first and the carbinol melted as low as 128°. Air-dried crystals from methanol melt about 128° and prolonged drying *in vacuo* at 100° (72 hours) is required to obtain an analytically pure sample, m. p. 159–160°; $[\alpha]^{28}D$ −26 (47.0 mg. made up to 2.0 ml. with chloroform, α −0.62; l, 1 dm.).

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.96; H, 12.02.

The melting point was not depressed by mixtures with a sample synthesized as follows:

Methylmagnesium iodide was prepared in the usual way from 0.5 g. (2.06×10^{-2} mole) of magnesium powder and 2.28 g. (1.6×10^{-2} mole) of methyl iodide in 8 ml. of ether. To the Grignard solution, 200 mg. of 3-carbomethoxy-5-cholestene in 2 ml. of ether was added. The reaction mixture was allowed to reflux twenty-four hours with stirring under 800 mm. nitrogen pressure. The ether was evaporated and the residue cooled to 0°. This was hydrolyzed by slow addition of 13 ml. of 10% ammonium chloride solution and the mixture was allowed to stand eighteen hours. The solution was transferred to a separatory funnel, and following acidification with sulfuric acid it was extracted twice with ether. The ether extracts were washed once with water, once with saturated sodium bisulfite, and then four times with water; the ether was then dried over anhydrous sodium sulfate for eighteen hours, filtered and evaporated to dryness *in vacuo* yielding crystals; 200 mg., m. p. 129–130°.

Upon drying *in vacuo* at 100° for seventy-two hours a different form of the carbinol results, m. p. 159–160°.

3,5-Cholestadiene.—Cholesteryl-*p*-toluenesulfonate,[12] 5 g. (0.0093 mole), and 1.2 g. of potassium cyanide (0.0185 mole) were dried and suspended in 20 ml. of xylene. The mixture was refluxed for eighteen hours at which time a heavy white precipitate is obtained. The suspension was cooled and extracted by filtration with 200

(11) Cason, THIS JOURNAL, **68**, 2078 (1946).

(12) Wallis, Fernholz and Gephart, *ibid.*, **59**, 137 (1937).

ml. of dry ether. The clear filtrate was evaporated in a dry air stream at 100° and the product crystallized from 100 ml. of acetone to produce 2.4 g. (70%) of 3,5-cholestadiene, m. p. 73–74°. Crystallization from acetone then absolute ethanol raised the m. p. to 76–77°, $[\alpha]^{22.5}D$ −96.5 (109.8 mg. made up to 5 ml. with chloroform, α, −4.24°; l, 2 dm.); γ_{max} (obs.) 236. These values are in agreement with those of the literature, m. p. 78–79°,[13] $[\alpha]^{20}D$ −97.5,[13] γ_{max} (obs.) mμ 235.[14] The diene gives a 20° depression in m. p. when mixed with *i*-cholestadiene[15] and its ultraviolet spectrum is clearly different from that of the *i*-diene.[16]

Isolation of 5-Cholestene.—Separate experiments generally were made to determine the extent of cholestene formation. The product resulting from the reaction of 0.026 mole of diacetyl with a mixture of 0.024 mole of cholesterylmagnesium chloride was treated so as to remove bicholesteryl. Of the remaining 8.3 g. of oil, 2 g. was dissolved in 50 ml. of petroleum ether (30–60°) and passed through a 17 by 1 cm. column packed with Brockman alumina. The eluate, 45 ml., and the first 15 ml. fraction of petroleum ether washings gave upon evaporation 1.26 g. of product, m. p. 80–84°. Crystallized once from acetone the m. p. was 85–87°, $[\alpha]^{24.5}D$ −53.5°. The literature[17] values are 89–90° and −56.3°.

(13) Stavely and Bergmann, *J. Org. Chem.*, **1**, 567 (1937).

(14) Woodward, THIS JOURNAL, **64**, 74 (1942).

(15) Kindly furnished by Professor Byron Riegel.

(16) We are indebted to Professor I. M. Klotz and his associates for determining this spectrum, *cf.* Klotz, *ibid.*, **66**, 88 (1944).

(17) Mauthner, *Monatsh.*, **28**, 1113 (1907).

Acknowledgment.—We are grateful to Professor Byron Riegel for help and encouragement during the course of this work.

Summary

1. Methyl cholesteryl ketone has been prepared by the reaction of cholesteryl Grignard reagents with acetaldehyde followed by oxidation of the impure carbinol and by Grignard alkylation of cholesteryl-3-carboxylic acid chloride. Its semicarbazone is described.

2. The ketone has been degraded back to cholesteryl-3-carboxylic acid.

3. 3-Cholesteryl-5-cholestene has been identified as a by-product of the formation of cholesteryl Grignard reagents.

4. 5-Cholestene is formed in large quantity in the reaction of cholesteryl Grignard reagents with a variety of compounds.

5. 3,5-Cholestadiene is conveniently prepared by the reaction of cholesteryl *p*-toluenesulfonate with potassium cyanide.

6. Ethyl cholesteryl ketone, its semicarbazone, and dimethylcholesterylcarbinol have also been prepared.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 1, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Cleavage of Benzyl Ethers with Hydrogen

BY ROBERT H. BAKER, KATHRYN HEROLD CORNELL AND MARTIN J. CRON

Recently it has been shown that vinyl ethers and amines which are so substituted as to activate the alkyloxy or alkylamino group may be cleaved by hydrogen prior to saturation of the double bond which carries the activating effect.[1] It was hoped that the remarkable promoting effects of perchloric and sulfuric acids[2] might allow preferential cleavage of unsaturated benzyl ethers, but the results, Table I, were not promising.

Cyclic ethers bearing phenyl groups on the α carbon atom have been found to undergo hydrogenolysis. 2-Phenyltetrahydropyran[3] yields 5-phenylpentanol and since the starting materials are easily available, a convenient synthesis for 5-arylpentanols is indicated. Phenyldioxane and 2,3-diphenyldioxane[4] reacted, respectively, with one and two moles of hydrogen. The 2-(2-phenylethoxy)-ethanol produced from the former of these demonstrated that the ether linkage β to a phenyl group is quite stable under the conditions which will completely cleave a similar group in the α position.

(1) Baker and Weiss, THIS JOURNAL, **66**, 343 (1944); Baker and Schlesinger, *ibid.*, **68**, 2009 (1946).

(2) Karg and Marcus, *Ber.*, **75**, 1850 (1942); Kindler and Kwok, *Ann.*, **554**, 9 (1943).

(3) Paul, *Compt. rend.*, **198**, 1246 (1934).

(4) The aryldioxanes were furnished by Prof. R. K. Summerbell, *cf.* Summerbell and Bauer, THIS JOURNAL, **57**, 2364 (1935).

Two isomeric compounds, m. p. 122 and 174°, to which the structure of *cis* and *trans* 2,5-diphenyldioxane have been tentatively assigned failed to behave in the expected manner.[5] Over palladium–charcoal they showed no reduction in acetic acid; with added hydrochloric acid the reduction was very slow and with added perchloric or sulfuric acids they took up three moles of hydrogen with no diminution of the rate at two moles. This can hardly be due to cleavage of 2-phenylethanol followed by its reduction to ethylbenzene because this would require four moles of hydrogen and repeated values of three would be unexpected. Further evidence against this explanation is seen in the behavior of phenethyl benzyl ether and in the fact that 2-phenylethanol takes up only 4% of one mole of hydrogen in the time and under the conditions required for complete cleavage of the phenyldioxanes.

A liquid described as 2,6-diphenyldioxane was

(5) These compounds were prepared by Aldro Bryan, Ph.D. Thesis, Northwestern University, 1945, by reaction of 2,5-dichlorodioxane with a phenyl Grignard. They were believed to contain no acetal or ketal linkage on the basis of stability to acid hydrolytic conditions. Dibromination followed by hydrolysis and treatment with phenylhydrazine produced the osazone of phenylglyoxal in poor yield. The compound referred to as 2,5-diphenyl-1,4-dioxane, m. p. 147–152°, by Smedley, U. S. Patent 2,414,982; *C. A.*, **41**, 2755 (1947), is in fact the source of these isomers.

TABLE I

HYDROGENATIONS WITH PALLADIUM–CHARCOAL

Compound	Run	Millimoles	Cat., mg.	Solvent[a]	Moles H_2	Time, min.	% Products isolated
Benzyl allyl ether	1	1	35	AcOH	2	100	
	2	1	35	Ac–P	2	40	
	3	1	35	EtOH	1	60	
Benzyl methallyl ether	4	1	35	AcOH	2	60	
	5	1	35	Ac–P	2	50	
	6	1	35	EtOH	1	80	
Benzyl 2-phenylethyl ether	7	100	500	Ac–S	1	90	86 $C_6H_5CH_2CH_2OH$
2-Phenyltetrahydropyran	8	56	1000	Ac–P	1	35	72 $C_6H_5(CH_2)_5OH$
Phenyldioxane[4]	9	1	35	Ac–S	1	120	75 $C_6H_5CH_2CH_2OCH_2CH_2OH$
2,3-Diphenyldioxane[4]	10	1	35	Ac–P	1	180	83 $C_6H_5CH_2CH_2C_6H_5$
122°-Isomer[5]	11	1	35	Ac–S	2[b]	36	[c]
	12[d]	1	100	Ac–S	3	45	40–48 $C_6H_5CH_2CH_2OH$
	13	1	35	Ac–P	3	48	[c]
	14	1	35	Ac–HCl	2[b]	140	31 Starting cpd.
174°-Isomer[5]	15	1	35	Ac–S	2[b]	42	[c]
Liquid isomer[6]	16	12	500	Ac–S	1.8[b]	195	10 $C_6H_5CH_2CH_2OH$
Benzoin diethylacetal[7]	17	1	100	Ac–P	3	30	.. $C_6H_5CH_2CH_2C_6H_5$

[a] Ac–P and –S refer to acetic acid containing 2.5% of 60% aqueous perchloric or 2% sulfuric acid, respectively. The millimolar runs employed 4 ml. and the 0.1 molar 40 ml. of solvent. [b] These runs were stopped short of completion. [c] The unmistakable odor of 2-phenylethanol was observed but no derivatives were obtained. [d] Average values of three identical runs.

kindly furnished by Dr. W. S. Emerson.[6] Two middle fractions of it, b. p. 158–162° and 162–163° (2 mm.), $n^{20}D$ 1.5602, were combined and subjected to incomplete hydrogenation. No product corresponding to the expected diphenethyl ether could be isolated by 3-plate fractionation. The lowest boiling fraction, 75° at 2 mm., $n^{20}D$ 1.5109, was shown to contain 2-phenylethanol.

Benzoin diethylacetal was studied because of its similarity of structure to some of the other compounds in Table I. The compound is very difficult to obtain by the published method,[7] and is obtained only when very dry reagents are used and the reaction mixture is allowed to stand in the cold for twenty-one days. The oil which is obtained slowly produces crystals from petroleum ether, b. p. 60–80°, and after two more crystallizations gives the acetal, m. p. 67–68° in 3% yield. The compound could not be hydrogenated over palladium on charcoal in ethanol even at 70°.

Experimental

Preparation of Compounds.—Benzyl allyl ether has been described previously.[8] It was prepared in 65% yield by reaction of 2.1 moles of benzyl chloride with 2.1 moles of sodium allyloxide in excess allyl alcohol, b. p. 204–205°; $n^{20}D$ 1.5090; d^{25}_4 0.959.

Benzyl methallyl ether was made in a similar manner from 5.4 moles of dry methallyl alcohol, 1.56 moles of sodium and 1.56 moles of benzyl chloride. The crude ether, b. p. 110–118° at 13 mm., was subjected to 10-plate fractionation to give 33% yield, b. p. 113–114° at 12 mm.; $n^{20}D$ 1.5095; d^{25}_4 0.958; M_D calcd., 50.57, found 50.59.

Benzyl 2-phenylethyl ether was similarly prepared but from sodium 2-phenylethyloxide in toluene, b. p. 175–178° at 13 mm., $n^{20}D$ 1.5545.[9]

2-Phenyltetrahydropyran was prepared from dihydropyran according to the method of Paul.[3] The crude product, b. p. 110–114° at 12 mm., from the first distillation was distilled again to duplicate the published physical properties. The sources of other materials are noted in Table I.

Hydrogenations.—The millimolar reactions were carried out at one atmosphere pressure in a shaking vessel of 8-ml. capacity attached to a hydrogen buret. Palladium on charcoal (5%) obtained from Wilkens-Anderson Company, Chicago, was used in all the runs. In the small runs the catalyst was shaken with hydrogen to constant volume before dropping the sample, contained in a thimble, into the reaction mixture. Larger runs were carried out in standard size apparatus at 3 atmospheres. The data are summarized in Table I.

Isolation and Identification of Products.—No attempts to isolate products from the allyl and methallyl ethers were made. The reaction mixtures which were expected to contain alcohols were poured into 10% sodium hydroxide–ice mixtures and were refluxed for thirty minutes to saponify acetate esters which often form in the presence of noble metal catalysts. The neutral materials were extracted from the alkaline saponification mixtures with ether or tetrachloroethane. It was proved independently that tetrachloroethane could be distilled from 2-phenylethanol without loss of the latter.

An analytical procedure was used to determine the quantity of 2-phenylethanol resulting from Run 12 in dry tetrachloroethane, the procedure being standardized with known samples of the alcohol.[10] From other runs similar to 12 the alcohol was identified as its 1-naphthylcarbamate, m. p. 116–117° (lit.[11] 119°). This alcohol was otherwise identified from Run 7 by physical constants, and from Run 16 by its allophanate, m. p. 184–185°, (lit.[12] 186°).

2-(2-Phenylethoxy)-ethanol from Run 9 was also identified as its allophanate, m. p. 148–149° (from toluene), lit.[13] 150°. 1,2-Diphenylethane was purified by sublimation *in vacuo*, m. p. and mixed m. p. with an authentic sample, 51.5–52°, lit.[14] 52°.

(6) Emerson, THIS JOURNAL, **67**, 516 (1945).
(7) Ward, *J. Chem. Soc.*, 1541 (1929).
(8) v. Braun, *Ber.*, **43**, 1350 (1910).
(9) This preparation will be the subject of a future publication.
(10) Adkins, Frank and Bloom, THIS JOURNAL, **63**, 554 (1941).
(11) McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 195.
(12) Béhal, *Bull. soc. chim.*, [4] **25**, 473 (1919).
(13) Halasz, *ibid.*, [5] **8**, 170 (1941).
(14) Ref. 11, p. 237.

5-Phenylpentanol from Run 8, b. p. 142–148° at 10 mm., d^{26}_4 0.9857, had the characteristic odor of lemons and compared favorably with the product as previously described, b. p. 140–142° at 16 mm., d^{26}_4 0.9651.[15] Since no direct derivatives were found, the alcohol was converted into crude 5-phenylpentyl bromide by refluxing with hydrobromic acid containing a trace of sulfuric acid. The bromide was refluxed in ethanol with an equivalent of ammonium dithiocarbamate[16] to produce an oil which upon crystallization from ether–petroleum ether gave 5-phenylpentyl dithiocarbamate, m. p. 72–74°, lit.[17] 75°.

(15) v. Braun, Anton and Weissbach, *Ber.*, **63**, 2847 (1930); v. Braun, *ibid.*, **44**, 2867 (1911).

(16) Mulder, *Ann.*, **168**, 228 (1873).

(17) v. Braun, *Ber.*, **45**, 1563 (1912).

Summary

1. In acid solution it is not practical to selectively hydrogenate allyl or methallylbenzyl ethers over palladium–charcoal.
2. The structures of certain aryldioxanes have been proved by hydrogenation.
3. Some compounds isomeric with 2,3-diphenyldioxane do not react with hydrogen in ways consistent with their suspected structures.
4. A convenient synthesis of 5-phenylpentanol has been described.

EVANSTON, ILLINOIS RECEIVED DECEMBER 11, 1947

[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

3-Nitrofluorenone

BY FRANCIS EARL RAY AND JAMES G. BARRICK

Mononitration of fluorene yields only 2-nitrofluorene. As this is easily oxidized to 2-nitrofluorenone the properties of both compounds are well known.[1]

4-Nitrofluorenone also seems to be well known, having first been prepared by Schmidt and Baur,[2] from the known 4-nitrophenanthraquinone by means of the benzilic acid rearrangement followed by oxidation and decarboxylation. Courtot[3] and Bell[4] have confirmed this work.

1-Nitrofluorenone has not been prepared.

3-Nitrofluorenone was first reported by Schmidt and Soll[5] who obtained it by the simultaneous nitration and oxidation of 9,10-diaminophenanthrene to 3-nitrophenanthraquinone. A benzilic acid rearrangement, followed by oxidation and decarboxylation gave a compound melting at 209–210° which was described as 3-nitrofluorenone. Its oxime melted at 240°. As the structure of 3-nitrophenanthraquinone had been proved conclusively by J. Schmidt[6] seven years previously, there seemed no reason to question the identity of Schmidt and Soll's compound. Especially was this true after the appearance of the paper by Eckert and Langecker[7] in 1928.

Using a different method, the simultaneous nitration and oxidation of 2-acetylaminofluorene to 3-nitro-2-amino-fluorenone followed by removal of the 2-amino group, Eckert and Langecker obtained identical melting points, Table I. Eckert and Langecker proved the position of the nitro group by converting their compound to the known 3-hydroxyfluorenone.[8]

(1) "Organic Syntheses," Coll. Vol. II, 447 (1943); Barbier, *Ann. chim. phys.*, [5] **7**, 479 (1876); Ullmann and Mallett, *Ber.*, **31**, 1694 (1898).

(2) Schmidt and Baur, *Ber.*, **38**, 3737 (1905).

(3) Courtot, *Ann. chim.*, [10] **14**, 5 (1930).

(4) Bell, *J. Chem. Soc.*, 1990 (1928).

(5) Schmidt and Soll, *Ber.*, **41**, 3691 (1908).

(6) J. Schmidt, *ibid.*, **34**, 3531 (1901).

(7) Eckert and Langecker, *J. prakt. Chem.*, **118**, 263 (1298).

(8) Ullmann and Bleier, *Ber.*, **35**, 4279 (1902); Errera and La Spada, *Gass. chim. ital.*, **35**, 539 (1905).

Better evidence for the identity of 3-nitrofluorenone could hardly be desired. Nevertheless, in 1931 Bardout[9] reported that his preparation of this compound by essentially Eckert and Langecker's method yielded 3-nitrofluorenone melting, not at 210°, but at 239°. The oxime instead of melting at 240°, as previously reported, melted at 221°, cor. Bardout also converted his compound to the known 3-hydroxyfluorenone as well as to the known 3-bromofluorenone.[10]

In the course of his synthesis Bardout also obtained 3-nitrofluorene melting at 105°. Hayashi and Nakayama[11] repeated the synthesis of 3-nitrofluorene and found the same melting point as Bardout. They did not, however, oxidize it to the fluorenone.

With a view to resolving this difficulty, Scheer[12] attempted to repeat Bardout's synthesis but found great difficulty in isolating pure compounds. Repeating Schmidt and Soll's work, he obtained, supposedly, 3-nitrofluorenone which melted considerably higher than Schmidt and Soll's and Eckert and Langecker's compound but not quite as high as Bardout's. From the two degree range in melting point Scheer concluded that his material was still impure. The significant part remains that even the impure material melted considerably higher than the first investigators reported. A summary of these results will be found in Table I.

It seemed of interest, therefore, to attempt an entirely *new* synthesis of 3-nitrofluorenone in the hope of settling the controversy.

Our starting material was the readily available 2-aminobiphenyl. This was treated with toluenesulfonyl chloride and the product nitrated accord-

(9) Bardout, *Anales asoc. quim. argentina*, **19**, 117 (1931); **22**, 123 (1934).

(10) Montagne, *Rec. trav. chim.*, **28**, 449 (1909); Montagne and van Charenti, *ibid.*, **32**, 164 (1913).

(11) Hayashi and Nakayama, *J. Soc. Chem. Ind. Japan*, **36**, 1278 (1933).

(12) Scheer, Master's Thesis, University of Cincinnati, 1942.

TABLE I

PROPERTIES OF 3-NITROFLUORENONE AND DERIVATIVES

Worker	Melting points, °C. Ketone	Oxime	3-Amino-fluorenone	Acetyl deriv.
S and S[5]	209–210	240		
E and L[7]	210	240	158–159	215
Bardout[9]	232 (239 cor.)	217 (221 cor.)		
Scheer[12]	225–227	214		
Authors	235–236 (239–240 cor.)	224–225	157–158	215–216

ing to the method of Bell[13] and of Jones and Braker[14] to give on hydrolysis 2-amino-5-nitrobiphenyl. The use of the acetyl derivative gives inferior results in nitration.[15] 2-Cyano-5-nitrobiphenyl was obtained in the usual manner. On hydrolysis, 5-nitrobiphenyl-2-carboxylic acid was obtained.

The structure of this compound rests on Sako's[16] proof of structure for 2-amino-5-nitrobiphenyl. Reduction gave the diaminobiphenyl and by conversion to a Lauth's violet, the amino groups were shown to be *para* to each other. An isomeric diamine was shown to be 2,3-diaminobiphenyl by treating it with phenanthraquinone to form the quinoxaline. The 2-amino-4-nitro isomer would yield the well known 2-nitrofluorenone.

5-Nitrobiphenyl-2-carboxylic acid was converted to 3-nitrofluorenone by heating with concentrated sulfuric acid, a method widely used in the preparation of fluorenones[17] as well as other cyclic ketones.[18] The crude 3-nitrofluorenone was obtained on pouring the sulfuric acid solution onto ice. The oxime was prepared by Bardout's method. It melted somewhat higher than Bardout's value but not nearly as high as the value reported by Schmidt and Soll, and by Eckert and Langecker, Table I.

It is possible that the differences in the melting point of the oximes may be due to *cis–trans* isomerism. It is not so easy, however, to explain the low melting point for 3-nitrofluorenone reported by the earlier investigators. If only a single paper were involved one might be tempted to suggest that the melting point values for the ketone and the oxime were interchanged.

In the hope of obtaining further data we reduced our 3-nitrofluorenone to 3-aminofluorenone and prepared the acetyl derivative. Much to our surprise we found the melting points to agree almost exactly with those reported by Eckert and Langecker. We must conclude that the impurities in their 3-nitrofluorenone were eliminated when it was converted into 3-aminofluorenone. These values are also given in Table I.

(13) Bell, *J. Chem. Soc.*, 2770 (1928).

(14) Jones and Braker, U. S. Patent, 1,922,265, August 15, 1933, 1,976,940, October 16, 1934.

(15) Barrick, Master's Thesis, University of Cincinnati, 1947.

(16) Sako, *Bull. Chem. Soc. Japan*, **9**, 55 (1933).

(17) Huntress, Pfister, 3rd, and Pfister, THIS JOURNAL, **64**, 2845 (1942); Atkinson, *et al.*, *ibid.*, **67**, 1513 (1945).

(18) Johnson, "Organic Reactions," Vol. II, 115 (1944).

Experimental

2-Aminobiphenyl.—This dark pink material was Eastman Kodak Co. practical grade and melted at 47–49°. Distillation under reduced pressure removed the color but did not raise the melting point above 49°.

2-*p*-Toluenesulfonamidobiphenyl.—This compound was best prepared by condensing *p*-toluenesulfonyl chloride and 2-aminobiphenyl in the presence of pyridine. From 85 g. of 2-aminobiphenyl, 100 g. of *p*-toluenesulfonyl chloride and 200 cc. of pure pyridine there was obtained 135 g. (84%) of 2-*p*-toluenesulfonamidobiphenyl melting at 98–99°.[14]

5-Nitro-2-*p*-toluenesulfonamidobiphenyl.—Bell's method[13] gave largely the unchanged starting material. It was modified as follows. Sixty grams of 2-*p*-toluenesulfonamidobiphenyl was dissolved in 120 cc. of warm glacial acetic acid, nitric acid (15 cc., sp. g. 1.5) was added slowly and the mixture was heated on the steam-bath to 90°. When the temperature started to rise rapidly, the beaker was removed from the heat and the reaction allowed to continue for three minutes. It was poured into cold water and a red oil precipitated which quickly solidified. When recrystallized from 400 cc. of hot ethyl alcohol, yellow needles were obtained melting at 168–169°; yield 55 g. (80%). When recrystallized a second time the compound melted sharply at 169°.

5-Nitro-2-aminobiphenyl.—A solution of 25 g. of 5-nitro-2-*p*-toluenesulfonamidobiphenyl in 50 cc. of concentrated sulfuric acid was allowed to stand for one hour at room temperature. It was then added dropwise to 200 cc. of an ice slurry. The yellow amine weighed 16 g. (yield quantitative) and was recrystallized twice from alcohol, m. p. 125°.[13]

5-Nitro-2-cyanobiphenyl.—A solution of 16 g. of 5-nitro-2-aminobiphenyl in 100 cc. of concentrated hydrochloric acid was diazotized at 0° with 5.2 g. of sodium nitrite in 50 cc. of water. After one hour urea was added and the solution filtered. This solution was slowly added to a solution of potassium cuprocyanide, prepared from 25 g. of copper sulfate and 28 g. of potassium cyanide and containing 15 g. of sodium carbonate, at 10°. After half of the diazonium solution had been added a further 15 g. of sodium carbonate was added in 50 cc. of water. After one hour the light tan precipitate was removed. It weighed 12 g.; yield, 72%. On recrystallization it melted at 134–135°.[13]

5-Nitrobiphenyl-2-carboxylic Acid.—Twelve grams of 5-nitro-2-cyanobiphenyl was hydrolyzed by boiling with 70 cc. of concentrated sulfuric acid in 100 cc. of water for six hours. After several hours the solid changed to an oil and finally became semisolid. The crude material (10 g.) was dissolved in 100 cc. of 10% sodium hydroxide, 1 g. of Darco added, the mixture boiled for fifteen minutes, filtered and acidified. White platelets weighing 6 g., yield 50%, were obtained melting at 179–180°. Recrystallization from alcohol gave a m. p. of 180°. No m. p. is given by Jones and Braker.[14]

Anal. Calcd. for $C_{13}H_9NO_4$: eq. wt., 243. Found: eq. wt., 244.

3-Nitrofluorenone.—Two grams of 5-nitrobiphenyl-2-carboxylic acid in 10 cc. of concd. sulfuric acid was heated in an oil-bath to 120° and held at this temperature for ten minutes. After cooling this blood red solution to room temperature it was poured into a slurry of ice yielding a yellow precipitate weighing 2 g. It was recrystallized from glacial acetic acid with Darco, then from ethyl alcohol and melted constantly at 235–236° (239–240°, cor.). The same melting point was obtained when samples were recrystallized from benzene and pyridine.

Anal. Calcd. for $C_{13}H_7NO_3$: N, 6.22. Found: N, 6.45.

3-Nitrofluorenone Oxime.—A 0.5-g. sample of 3-nitrofluorenone was heated with 0.25 g. of hydroxylamine in 15 cc. of alcohol and 0.3 g. of oxime was obtained which on recrystallization from alcohol melted at 224–225°, Table I.

3-Aminofluorenone.—Five grams of sodium sulfide was added over a period of two hours to 100 cc. of boiling alcohol containing 1 g. of 3-nitrofluorenone and 2 g. of ammonium chloride. After refluxing for an additional hour it was poured into cold water and extracted with ether. The ether was extracted with dilute hydrochloric acid and on neutralization a deep yellow precipitate was obtained. It was not possible to get a better melting point than 142–146°. Following the procedure of Eckert and Langecker,[7] who encountered similar difficulties, the amine was acetylated. Recrystallization from alcohol gave 3-acetylaminofluorenone.

3-Acetylaminofluorenone was hydrolyzed by boiling with 20% hydrochloric acid. It yielded 3-aminofluorenone, Table I.

Summary

A new synthesis of 3-nitrofluorenone has been described and Bardout's characterization of this compound has been substantially confirmed.

The following melting points, uncorrected unless otherwise stated, have been found for 3-nitrofluorenone and related compounds:

	M. p., °C.
3-Nitrofluorenone	235–236 (239–240, cor.)
3-Nitrofluorenone oxime	224–225
3-Aminofluorenone	157–158
3-Acetylaminofluorenone	215–216

The values of the latter two compounds given by Eckert and Langecker have been confirmed but their values for 3-nitrofluorenone and 3-nitrofluorenone oxime as well as those of Schmidt and Soll are shown to be in error.

CINCINNATI 21, OHIO RECEIVED DECEMBER 3, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Synthesis and Spectrum of 2-Cyclopropylpyridine*

BY RAYMOND P. MARIELLA, LOWELL F. A. PETERSON[1] AND ROBERT C. FERRIS[2]

Some recent work by Klotz[3] has shown that the cyclopropane ring, when adjacent to an olefinic or carbonyl group, produced spectra which could be interpreted in terms of resonance due to hyperconjugation. This effect had also been observed by Carr and Burt,[4] who examined the spectra of compounds in which the cyclopropane ring was in "conjugation" with both a carbonyl group and the benzene ring. From these spectra it was not possible to secure information regarding the extent of conjugation of the cyclopropane grouping alone with the aromatic nucleus.

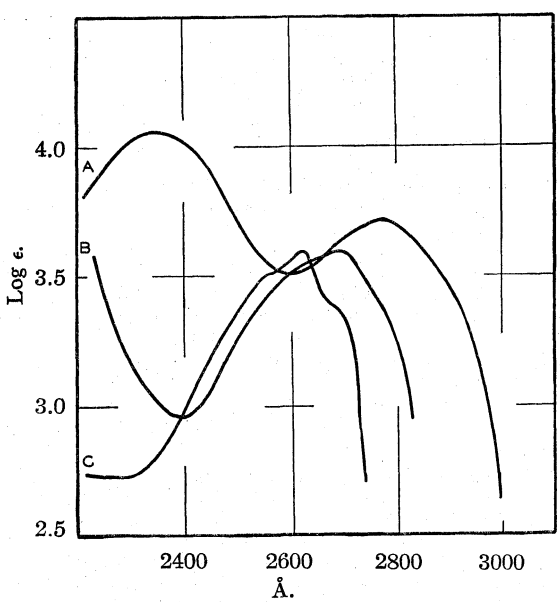


Fig. 1.—Absorption spectra of 2-vinylpyridine, A; 2-cyclopropylpyridine, B; and 2-*n*-propylpyridine, C.

In the present work, 2-cyclopropylpyridine (IX) was synthesized. This compound has the cyclopropane ring alone in conjugation with a highly aromatic nucleus.[5] A comparison of its absorption spectrum with those of 2-*n*-propylpyridine (VIII) and 2-vinylpyridine (X) (Fig. 1), showed the cyclopropane compound to have a maximum (2690 Å.) between that of the similarly conjugated (2775 Å.) and non-conjugated (2620 Å.) system.

Since the maximum for pyridine itself is at 2530 Å.,[6] the presence of an alkyl or alicylic group in the α position causes a shift of the maximum to longer wave lengths. This effect appears greater with the cyclopropyl group than with the *n*-propyl group, and confirms chemical evidence long known[7] that the cyclopropane ring possesses a certain degree of unsaturation. The phenomenon no doubt occurs because the electrons of cyclopropane are rendered especially polarizable by the unusual angle between the bonds.

If the shift to longer wave lengths is to be interpreted as a "hyperconjugation" effect, then in the case of 2-cyclopropylpyridine we can postulate that certain ionic structures exist, which in addi-

* Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, April 22, 1948.

(1) Present address: Northwestern University Medical School, Chicago, Illinois.

(2) Present address: University of Utah, Department of Chemistry, Salt Lake City, Utah.

(3) Klotz, THIS JOURNAL, **66**, 88 (1944).

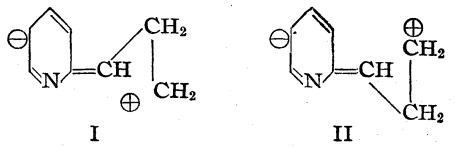
(4) Carr and Burt, *ibid.*, **40**, 1590 (1918).

(5) After the initial submission of this manuscript a paper appeared (Rogers, *ibid.*, **69**, 2544 (1947)), in which the absorption spectrum of cyclopropylbenzene was given. This compound also showed a shift in the maximum toward longer wave lengths when compared with propylbenzene, which was interpreted as a hyperconjugation effect.

(6) Fischer and Steiner, *Compt. rend.*, **175**, 882 (1922).

(7) Kohler and Conant, THIS JOURNAL, **39**, 1404, 1699 (1917).

tion to the usually written hyperconjugation forms, contribute to the excited structure. Two of the twelve possible additional forms are listed below (I and II).



I II

Since the three-membered ring is not necessarily coplanar with the pyridine ring these resonance forms probably do not contribute as much as expected, causing the shift from *n*-propyl to cyclopropyl to be small but still measurable.

The maximum due to the cyclopropane ring itself, probably about 2100 Å., was beyond the range of the instrument used.

The flow sheet for the synthesis of 2-cyclopropylpyridine and related compounds is shown in Fig. 2.

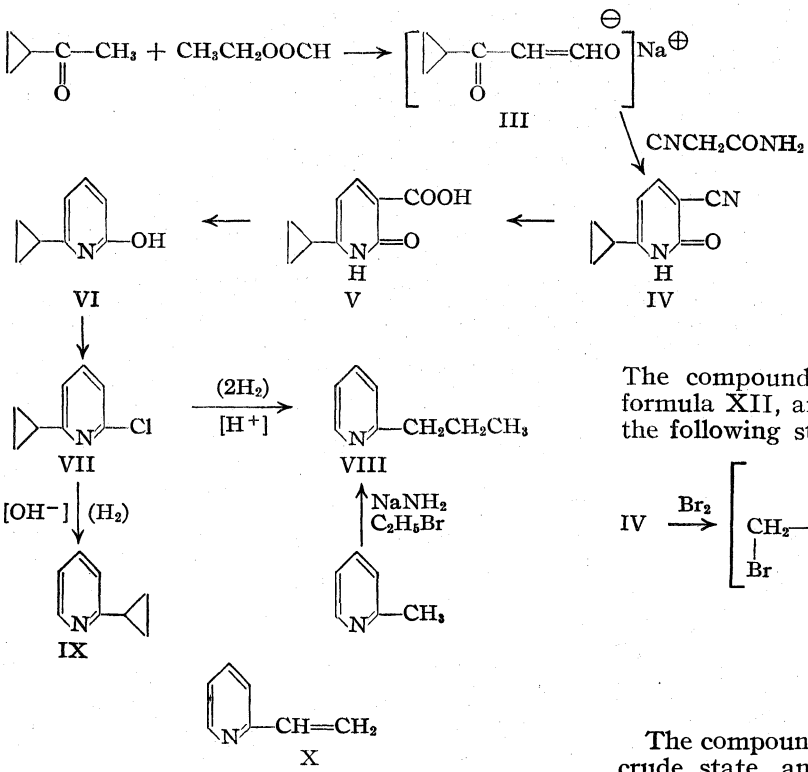
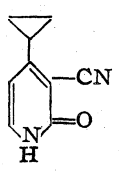


Fig. 2.

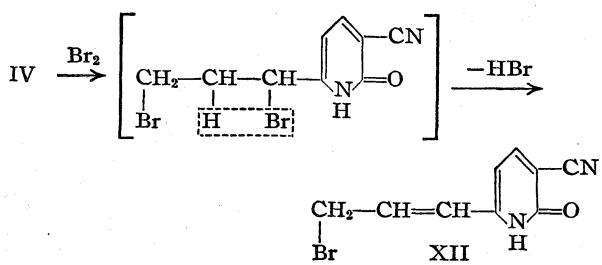
The sodium salt (III) was reported recently,[8]



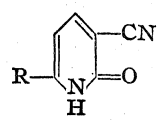
XI

but no yield was given. The condensation of III with cyanoacetamide could have yielded XI instead of IV, but this possibility was eliminated by the isolation of the known compound (VIII), in the acidic reduction of VII. In all steps, the yields were lower than in similar reactions of compounds[9,10] in which the cyclopropyl ring was replaced by a simple alkyl group. In many of the reactions, there was evidence of considerable decomposition and tar formation. This was particularly noticeable in the decarboxylation of V to VI, which succeeded only in small runs of one and a half grams each.

The cyclopropane ring remained fairly stable to reagents such as concentrated hydrochloric acid and phosphorus pentachloride, as evidenced by the isolation of V and VII, which still possessed the alicyclic ring intact. Treatment with bromine, however, immediately destroyed the cyclopropane ring in IV to give a compound containing only *one atom* of bromine, instead of two. The compound, $C_9H_7BrN_2O$, probably has the formula XII, and its formation is postulated by the following steps.



The compound (XII) was quite unstable in the crude state, and purification by crystallization was very difficult. Bromination was assumed to attack the cyclopropane ring because compounds having the general formula XIII, where R is a simple aliphatic group, do not react with bromine in glacial acetic acid.[11]



XIII

The 2-*n*-propylpyridine (VIII) (conyrine) was made by a method similar to that of Chichibabin,[12] and the 2-vinylpyridine was a product obtained from the Reilly Tar and Chemical Corporation.

The authors acknowledge a grant from the

(8) Chelintsev, *J. Gen. Chem. U. S. S. R.*, **14**, 1070 (1944); *cf. C. A.*, **41**, 101 (1947).

(9) Perez-Medina, Mariella and McElvain, THIS JOURNAL, **69**, 2574 (1947).

(10) Mariella, *ibid.*, **69**, 2670 (1947).

(11) Mariella, unpublished work.

(12) Chichibabin, *Bull. soc. chim.*, [5] **3**, 1607 (1936).

Graduate School, which made some of the work possible.

Experimental[13]

Sodium Salt of Hydroxymethylene Methyl Cyclopropyl Ketone (III).—To 58 g. of sodium metal ribbon in one liter of absolute ether was added a mixture of 185 g. of ethyl formate[14] and 210 g. of methyl cyclopropyl ketone,[15] dropwise over a period of two hours. The reaction mixture was protected from moisture, cooled in an ice-bath, and stirred during the addition. When about one-fourth of the addition mixture had been added, the tan-colored precipitate first appeared, and increased in amount as the addition continued. Stirring was continued for one-half hour after the addition was completed. The cooling bath was then removed, and stirring continued, at room temperature, for an hour and a half. The brown solid was then filtered and dried in a vacuum desiccator. Additional product was obtained by filtering the solid which developed in the filtrate. The combined solids weighed 219 g. (65% yield).

3-Cyano-6-cyclopropylpyridone-2 (IV).—A solution of 115 g. of the sodium salt (III), 84 g. of cyanoacetamide, and piperidine acetate catalyst in 250 ml. of water was refluxed for two hours. (The catalyst was prepared by adding piperidine to a solution of 9 ml. of glacial acetic acid in 25 ml. of water until basic to litmus.) The solution was then diluted with 250 ml. of water, acidified with glacial acetic acid, and cooled in an ice-bath for an hour. The yellow solid, which had formed, was filtered and dried, 73 g. (53% yield). Purification by a carbon treatment and several recrystallizations from alcohol gave a white powder, m. p. 239–240° (dec.).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.04; N, 17.5. Found: C, 67.39; H, 5.06; N, 17.2.

Bromination of 3-Cyano-6-cyclopropylpyridone-2.—A solution of 0.50 g. of IV in 10 ml. of glacial acetic acid heated to 60° was treated with a solution of 0.3 ml. of bromine in 5 ml. of glacial acetic acid. A copious evolution of hydrogen bromide gas ensued, as the solution was kept at 60° for ten minutes. The solution was then poured on 50 g. of cracked ice, and the yellow solid, which immediately formed, was filtered and dried, 0.69 g. (93% yield). The crude material soon developed a green color and finally turned black. A pure sample was obtained by treating the yellow solid with Norit in alcohol, followed by five recrystallizations from alcohol and six recrystallizations from benzene. The white solid, so obtained, remained colorless, m. p. 221–222°.

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; N, 11.7. Found: C, 45.09; H, 3.04; N, 12.0.

6-Cyclopropane-2-oxo-3-pyridine Carboxylic Acid (V).—A solution of 73 g. of IV in 250 ml. of concentrated hydrochloric acid was refluxed for four hours. The solution was then poured into 250 ml. of water, cooled in an ice-bath for an hour, and the gray solid filtered and dried, 44 g. (54% yield). After a carbon treatment and seven recrystallizations from 3:1 water–glacial acetic acid, the pure white solid was obtained, m. p. 248–250° (dec.). The compound was only slightly soluble in cold water and gave a negative ferric chloride test.

Anal. Calcd. for $C_9H_9NO_3$: N, 7.8. Found: N, 7.8.

2-Cyclopropyl-6-pyridol (VI).—A test-tube containing powdered V was heated to 290°. The solid melted and decomposed as carbon dioxide was evolved. A cold finger was then inserted in the test-tube to collect the product which sublimed in the form of white plates. The yields varied, depending upon the amount and purity of the starting material. A maximum of 70% yield was obtained when 1.5 g. of V, purified by two crystallizations from alcohol, was used. The yields fell off sharply if more material was used in the decarboxylation. Additional purification was achieved by a vacuum sublimation at 0.05 mm. and at a temperature of 110–120°, m. p. 165–166°. The white solid gave a deep red ferric chloride test.

Anal. Calcd. for C_8H_9NO: N, 10.4. Found: N, 10.4.

2-Cyclopropyl-6-chloropyridine (VII).—To a solution of 10.5 g. of VI in 16 ml. of phosphorus oxychloride heated to refluxing was added 20 g. of phosphorus pentachloride, in small portions, over a period of one-half hour. The oil-bath temperature was then raised to 165° and kept there for one hour. The phosphorus oxychloride was removed under reduced pressure, 50 g. of ice then added, and the mixture made strongly basic by adding a concentrated potassium hydroxide solution. When this was steam distilled, a colorless heavy oil was obtained, which was separated by two extractions with 100-ml. portions of ether. The ether was dried and removed, and the residue distilled, giving a colorless oil, 4.0 g. (34% yield), b. p. 107–108° (16 mm.), $n^{25}D$ 1.5512. The liquid darkened very slowly when exposed to light.

Anal. Calcd. for C_8H_8ClN: N, 9.1. Found: N, 9.1.

Reduction of VII in Acidic Solution.—To a solution of 0.193 g. of VII in 15 ml. of absolute alcohol were added a solution of 100 mg. of palladium chloride in one ml. of concentrated hydrochloric acid, one ml. of 15% hydrogen chloride in absolute alcohol, 0.50 g. of Norit and hydrogen. The reduction proceeded at room temperature and atmospheric pressure and stopped in fifty minutes, at which time two moles of hydrogen had been absorbed. There was no distinct break in the hydrogenation curve during the reduction. The mixture was filtered and the liquid filtrate concentrated to a colorless oil. The chloroplatinate of this material did not depress the m. p. 163° of an authentic sample of the chloroplatinate of 2-*n*-propylpyridine.

Reduction of VII in Basic Solution: 2-Cyclopropylpyridine (IX).—To a solution of 1.26 g. of VII in 25 ml. of 3% alcoholic potassium hydroxide was added 4.0 g. of 5% palladium on charcoal. The hydrogenation proceeded at room temperature and atmospheric pressure and was complete in thirty minutes, at which time 0.90 mole of hydrogen had been absorbed. The mixture was filtered, made faintly acid with hydrochloric acid and concentrated. The addition of concentrated potassium hydroxide liberated the free base, which was taken up in ether. The solution was dried, ether removed *in vacuo*, leaving an oil, which on distillation gave 0.65 g. (67% yield), b. p. (750 mm.) 174–175°, $n^{25}D$ 1.5110, d^{29}_4 0.956. The material possessed the characteristic alkyl pyridine odor. It was observed that the liquid caused a temporary numbing effect when brought in contact with the skin.

The picrate was isolated as pale yellow needles, m. p. 115–117°.

Anal. Calcd. for $C_{14}H_{12}N_4O_7$: C, 48.28; H, 3.47. Found: C, 48.19; H, 3.48.

The chloroaurate was prepared as a yellow powder, m. p. 111–113°.

Anal. Calcd. for $C_8H_{10}Cl_4NAu$: Au, 43.0. Found: Au, 43.0.

The chloroplatinate came down very slowly when a solution of chloroplatinic acid was added to the 2-cyclopropylpyridine hydrochloride in water. The orange solid melted at 159–160°. The mixed m. p. with the chloroplatinate of 2-*n*-propylpyridine was depressed to 140°.

Anal. Calcd. for $C_{16}H_{20}Cl_6N_2Pt$: Pt, 30.1. Found: Pt, 30.1.

2-*n*-Propylpyridine (Conyrine) (VIII).—To 300 ml. of liquid ammonia containing 0.3 g. of ferric nitrate, was added 35 g. of sodium metal. The excess ammonia was allowed to escape and 83 g. of α-picoline (b. p. 128°) was

(13) Analyses by Miss Patricia Craig and Mrs. Nelda Mold.

(14) Purified according to "Org. Syntheses," Coll. Vol. II, p. 180, b. p. 53.5–54.5°.

(15) A U. S. Industrial Chemicals product. The sample used in this work had a b. p. 110–111°.

added. To this mixture, with stirring, was added 120 g. of ethyl bromide, over a period of four hours. After standing two days, the excess sodamide was decomposed by the addition of 200 ml. of water. The mixture was extracted with ether, the ether solution dried, and the ether removed on a steam-bath. The residue was distilled, giving 8.0 g. (7% yield), b. p. 165–166° (755 mm.),[16] $n^{25}D$ 1.4897, d^{26}_4 0.9121.

The picrate was easily isolated as small yellow needles, m. p. 64°.[16]

Anal. Calcd. for $C_{14}H_{14}N_4O_7$: C, 48.00; H, 4.03; N, 16.0. Found: C, 47.89; H, 4.01; N, 15.8.

The chloroplatinate formed very quickly, and resulted in orange plates, m. p. 163–164°.[17]

Anal. Calcd. for $C_{16}H_{24}Cl_6N_2Pt$: Pt, 29.9. Found: Pt, 30.2.

The chloroaurate came down as a yellow powder, m. p. 77°.

Anal. Calcd. for $C_8H_{12}Cl_4NAu$: Au, 42.7. Found: Au, 42.5.

2-Vinylpyridine (X).—A sample from the Reilly Tar and Chemical Corporation was fractionated, and the constant boiling cut, b. p. 60° (17 mm.), used in this work,[18] $n^{31}D$ 1.5442, d^{31}_4 0.9661.

The picrate was isolated as a yellow powder, m. p. 152–154°.

Anal. Calcd. for $C_{13}H_{10}N_4O_7$: C, 46.71; H, 3.02. Found: C, 46.73; H, 3.01.

(16) Chichibain, ref. 12, reports a b. p. 173° and a m. p. 76° for the picrate.

(17) Ladenburg, *Ann.*, **247**, 21 (1888), reports a m. p. of 159–160°.

(18) Ladenburg, *Ber.*, **22**, 2585 (1889), reports a b. p. 79–82° (29 mm.).

The chloroplatinate melted at 174–175°, and the chloroaurate melted at 143°.[19]

Spectra.—The ultraviolet absorption spectra were obtained with a Beckmann quartz spectrophotometer. All physical constant measurements of the above alkyl pyridines were performed immediately after their isolation. Solutions of known concentrations were made by dissolving weighed quantities of compound in absolute alcohol in a volumetric flask. Dilutions were made volumetrically to give suitable density readings. The solutions were poured into one of two matched silica absorption cells and the second cell was filled with the solvent. Extinction coefficients were calculated from the equation

$$\epsilon = d/cl$$

where c is the concentration of the solute, in moles per liter, l is the thickness of the cell, in centimeters, and $d = \log_{10}(I_0/I)$. I_0 is the intensity of light passing through the solvent, and I is the intensity of light passing through the solution.

Summary

2-Cyclopropylpyridine was prepared and its ultraviolet absorption spectrum compared with those of 2-*n*-propylpyridine and 2-vinylpyridine. The maximum of 2-cyclopropylpyridine falls in a position between the two comparison compounds. This effect can be interpreted in terms of additional resonance due to hyperconjugation.

(19) Ladenburg, *ibid.*, reported the chloroplatinate m. p. 174°, and the chloroaurate, m. p. 144°.

EVANSTON, ILLINOIS RECEIVED OCTOBER 6, 1947

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 1157]

An Electron Diffraction Investigation of the Structure of Adamantane

BY WERNER NOWACKI AND KENNETH W. HEDBERG

The crystal structure of adamantane ($C_{10}H_{16}$, see Fig. 1) has been investigated by Nowacki,[1] who found a C–C bond distance of 1.54 ± 0.02 Å. on assumption of tetrahedral bond angles, and by Giacomello and Illuminati,[2] who obtained similar results by Fourier methods. A significant difference has been found between C–N distances in the crystal[3] and vapor[4] of hexamethylenetetramine, a molecule whose configuration is closely similar to that of adamantane, and although no such difference would be expected in adamantane, it seemed worth while to study it by electron diffraction in the vapor phase.

The photographs obtained show twelve maxima and shelves extending to q values of about 90 ($q = (40/\lambda) \sin \varphi/2 = (10/\pi)s$).

Experimental

The sample of adamantane, which had been synthesized by Prelog and Seiwerth,[5] was vaporized by use of a high temperature nozzle[6] in the apparatus described by Brockway.[7] The camera distance was about 11 cm. and the electron wave length[8] about 0.06 Å. Corrections were made for film expansion.

Radial Distribution Curve

The radial distribution curve (Fig. 2) was calculated from the equation[9,10] by use of punched

$$rD(r) = \sum_{q=1,2\ldots}^{q\ max} I(q) \exp.(-aq^2) \sin\left(\frac{\pi}{10} q\, r\right)$$

cards[10,11]; the quantities $I(q)$ were taken from the visual curve (Fig. 2) drawn to represent the

(1) W. Nowacki, *Helv. Chim. Acta*, **28**, 1233 (1945).

(2) G. Giacomello and G. Illuminati, *Ricerca Sci.*, **15**, 559 (1945).

(3) P. A. Shaffer, Jr., THIS JOURNAL, **69**, 1557 (1947).

(4) V. Schomaker and P. A. Shaffer, Jr., *ibid.*, **69**, 1555 (1947).

(5) V. Prelog and R. Seiwerth, *Ber.*, **74**, 1644, 1769 (1941).

(6) L. O. Brockway and K. J. Palmer, THIS JOURNAL, **59**, 2181 (1937).

(7) L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

(8) For wave length calibration see C. S. Lu and E. W. Malmberg, *Rev. Sci. Instruments*, **14**, 271 (1943); the lattice constants of zinc oxide given by Lu and Malmberg in kx units were converted to Ångström units.

(9) R. Spurr and V. Schomaker, THIS JOURNAL, **64**, 2693 (1942).

(10) P. A. Shaffer, Jr., V. Schomaker and L. Pauling, *J. Chem. Phys.*, **14**, 659 (1946).

(11) P. A. Shaffer, Jr., V. Schomaker and L. Pauling, *ibid.*, **14**, 648 (1946).

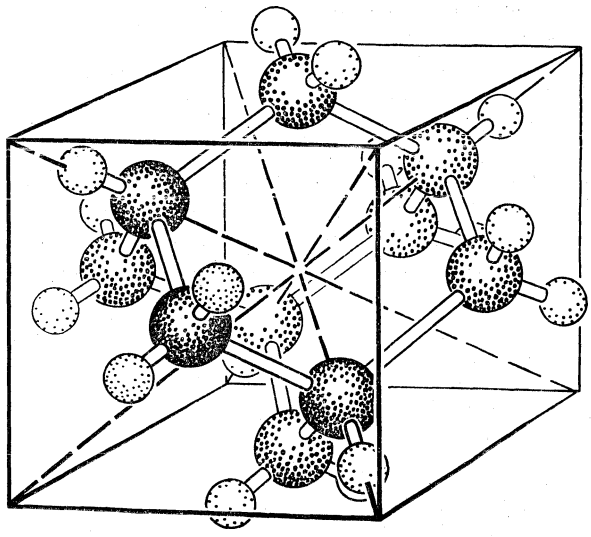


Fig. 1.—Adamantane.

appearance of the photographs, and the constant a was chosen to give exp $(-aq^2) = 1/10$ at $q = 90$. The resulting curve shows major peaks at 1.53 and 2.52 Å. which correspond to the bonded and to the shortest non-bonded C···C distances in a model such as C with tetrahedral bond angles; in model C these distances are 1.540 and 2.515 Å. There are additional peaks at 1.00, 2.92 and 3.46 Å., and a broad feature at 2.20 Å. With the exception of the first none of these is sufficiently well resolved for a determination of interatomic distances, though they agree well with our final model, as shown by the vertical lines. The heavy lines denote the C···C distances and the light, the C···H; the lengths of the lines indicate the relative weights of the distances.

The deviation of the peak at 1.00 Å. from the value 1.09 Å. normally obtained from bonded C···H interactions closely parallels the result obtained by Schomaker and Shaffer[4] in their study of hexamethylenetetramine.[12]

Correlation of Visual and Intensity Curves

Intensity curves were calculated[10,11] from the

$$I(q) = \sum_{i,j}{}' \frac{Z_i Z_j}{r_{i,j}} \exp.\ (-a_{i,j}q^3) \sin\left(\frac{10}{\pi} qr\right)$$

equation[9] for a model of symmetry $T_d - \bar{4}3m$ assuming C–C = 1.54 Å. throughout, C–H = 1.09 Å. except for model G, and ∠HCH 109°28′ except for model H. In models A to F the $C_2C_3C_2$ bond angle is varied from 106°28′ to 112°28′. Models G and H, which have tetrahedral C–C–C angles, are characterized by a shortened C–H distance (1.05 Å.) and an increased H–C–H angle (114°28′), respectively. Terms representing all bonded and non-bonded atomic interactions except H···H were included in the calculations. An effective value of $Z = 1.2$ was employed for hydrogen in order to approximate better its scattering power relative to carbon for small q. The coefficient $a_{i,j}$ was given the value 0.00016 for bonded C–H, 0.00030 for all non-bonded C···H interactions,[13] and zero otherwise.

TABLE I

ELECTRON DIFFRACTION DATA FOR ADAMANTANE

Max.	Min.	$q_{obsd.}$	$q_{calcd.}$ (Model C)	$q_{calcd.}/q_{obsd.}$[a]
	1	6.5	5.3	(0.815)
1		9.6	8.5	(0.885)
	2	13.3	12.6	(0.947)
2		17.8	17.8	1.000
	A	21.9	22.2	1.014
A		25.1	25.5	(1.016)
	3	27.8	27.2	(0.798)
3		30.3	29.3	(0.967)
	4	32.8	33.7	[1.027]
4		35.7	35.3	[0.989]
	5	38.7	38.1	0.984
5		42.2	42.0	0.995
	6	45.8	46.2	1.009
6		49.3	49.8	1.010
	7	53.3	53.2	0.998
7		57.4	57.0	0.993
	8	61.4	61.2	0.997
8		66.0	67.3	(1.020)
	9	70.6	72.3	[1.024]
9		74.2	75.2	[1.013]
	10	77.7	78.1	1.005
10		81.7	82.2	1.006
	11	85.5	86.7	1.014
11		90.1	90.5	1.004
			Average	1.004
			Average deviation	0.008

[a] Parenthesized values were omitted in evaluation of averages, bracketted values were given half weight.

Comparison of the calculated curves with the visual curve shows model A to be unacceptable; minimum 8 appears in the calculated curve as far too broad and the relative depths of minima 9 and 10 are inverted. Curve B is somewhat better than A but the disagreement in the relative depths of minima 9 and 10 is still present. Curve C is generally satisfactory.[14] Curve D is acceptable

(12) The visual curve for adamantane was drawn without previous knowledge of the appearance of the hexamethylenetetramine photographs or of the corresponding intensity curves, although subsequently the photographs of the two substances were carefully compared and found to be closely similar. The errors in the two visual curves which correspond to the errors at 1.0 Å. in the two radial distribution functions are evidently nearly alike. Perhaps this is because they represent errors of interpretation which are in some way peculiar to the types of features shown by hexamethylenetetramine and adamantane.

(13) Because of the relative rigidity of the carbon skeleton of adamantane we believe the value 0.00030 for $a_{i,j}$ to be a reasonable one for all the non-bonded C···H interactions.

(14) The main points of disagreement in the correlation of model C with the observed intensity distribution are seen to involve (1) the relative depths of minima 1 and 2, (2) the strength of shelf A, (3) the shape of maximum 8, and (4) the relative depths of minima 5 and 6. The first two items do not appear to be serious; estimates of the depth of the first minimum are subject to considerable error, and a

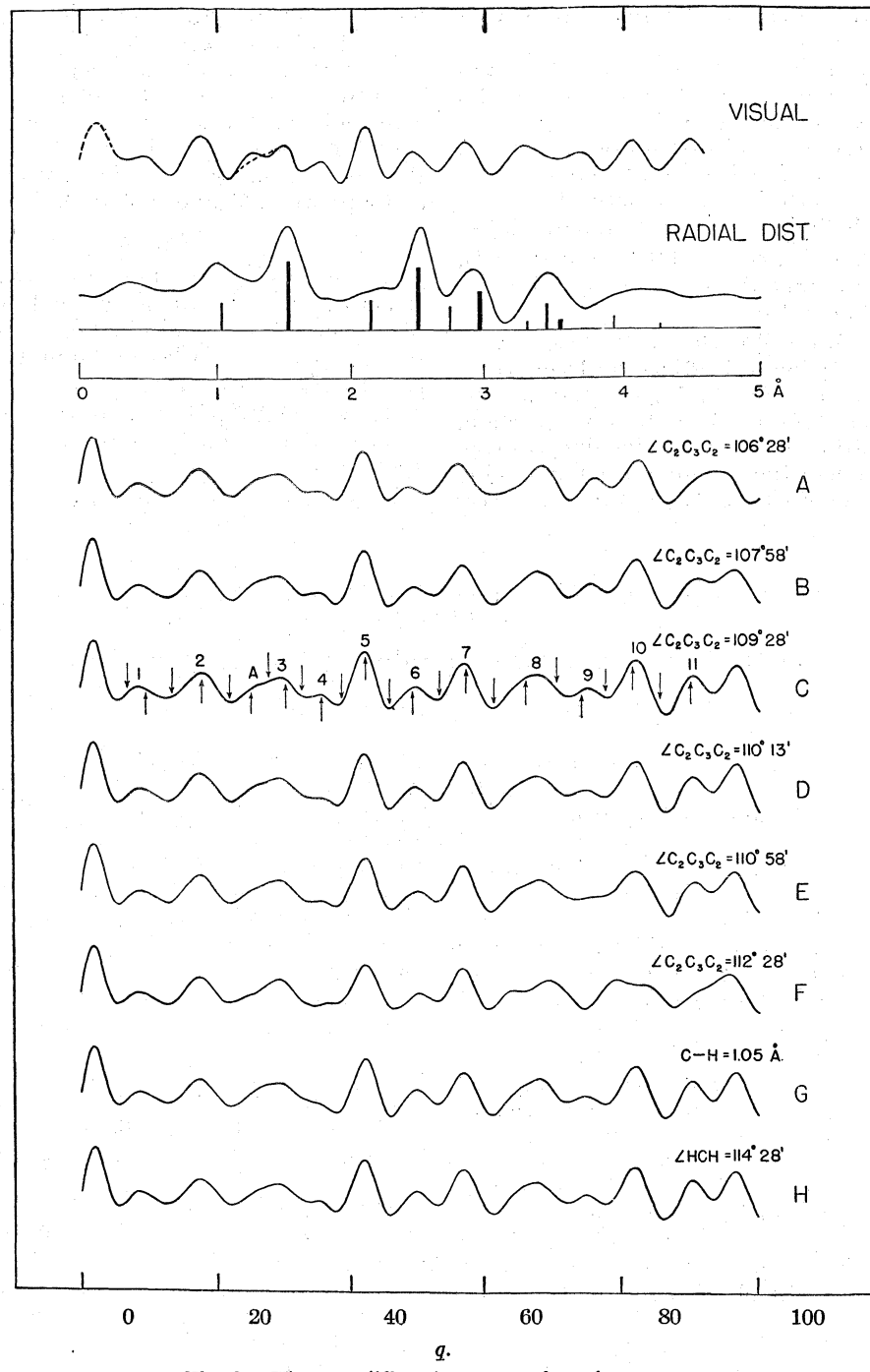


Fig. 2.—Electron diffraction curves for adamantane.

reexamination of the photographs indicates the exaggeration of shelf A to be a simple misinterpretation (the dotted line is felt to be a more accurate representation of this feature). Item (3) also arises from errors of interpretation, as shown by comparing photographs of adamantane and hexamethylenetetramine; the appearance of maximum 8 is closely similar and was satisfactorily represented by Schomaker and Shaffer[4] in their visual intensity curve for hexamethylenetetramine. It is difficult to explain the reversal of minima 5 and 6 (item (4)). Perhaps the trouble is due to a tendency to compensate incorrectly for the background intensity, which is difficult to estimate in patterns as complicated as that of adamantane.

although maximum 4 is a poorer representation of the appearance of the photographs than the same maximum in C. Curves E and F are unsatisfactory. Curves G and H are both acceptable although G is not as satisfactory as C in the region of maximum 4. We conclude that in the adamantane molecule in the gas phase $\angle C_2C_3C_2 = 109.5 \pm 1.5°$, the upper limit of this determination being especially conservative. The ∠HCH and C–H/

C–C determinations cannot be made to within sizable limits of error.

A comparison (Table I) of the observed q values with those calculated for model C (all bond angles tetrahedral, C–C = 1.54 Å., C–H = 1.09 Å.), a consideration of the radial distribution function, and comparisons of visual and calculated intensity curves lead to the following structural parameters and probable limits of error: symmetry $T_d - \bar{4}3m$ (assumed), $\angle$HCH = 109°28′ (assumed), C–H = 1.09 Å. (assumed), C–C = 1.54 ± 0.01 Å., $\angle C_2C_3C_2$ = 109.5 ± 1.5°.

Acknowledgment.—We thank Professor Verner Schomaker for helpful advice and constructive criticism, Professor V. Prelog (Zürich) for the sample of adamantane used in the investigation, and the International Business Machines Corporation for the loan of the machines used in making calculations. One of us (W. N.) wishes to express his gratitude to Professor Linus Pauling for the many kindnesses extended him; he is also indebted to the American-Swiss Foundation for Scientific Exchange (Montclair, N. J.), to the Stiftung zur Förderung der wissenschaftlichen Forschung an der Bernischen Hochschule, and to the Government of the Canton of Berne for financial support and leave of absence.

Summary

An electron diffraction investigation of the structure of the adamantane molecule in the gas phase has led to values for the structural parameters in agreement with those found in the crystal. On the assumption of symmetry $T_d - \bar{4}3m$, of C–H = 1.09 Å., and of $\angle$HCH = 109.5°, the results are C–C = 1.54 ± 0.01 Å., and $\angle C_2C_3C_2$ = 109.5 ± 1.5°.

PASADENA 4, CALIFORNIA RECEIVED NOVEMBER 18, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

The System Cesium Fluoride–Hydrogen Fluoride

BY R. VIRGINIA WINSOR AND GEORGE H. CADY

Mathers and Stroup[1] have shown that solutions made by melting acid fluorides of cesium may be used at approximately room temperature as electrolytes for the preparation of fluorine. They found that the acid fluorides of cesium have lower melting points than the corresponding salts of potassium, but in their work identified only the previously known compound, CsF·HF. A more thorough study of the system comprises the subject matter of the present article.

Experimental

A 36.0-g. sample of cesium fluoride was prepared from pulverized pollucite following a procedure based upon work of Wells[2] and recommended by Geo. McPhail Smith. The mineral was digested with an equal weight of 6 N hydrochloric acid at about 95° for approximately three days. Solid remaining undissolved was separated by filtration and the filtrate was evaporated to dryness. The product was then dissolved in four times its weight of 4 N hydrochloric acid and, after filtering, one gram atom of iodine was added for each mole of cesium chloride present. The liquid was then heated while an excess of chlorine was passed. As the resulting solution was allowed to cool, the compound $CsICl_2$ crystallized. This salt was purified by three recrystallizations in the presence of a little ICl in solution. Cesium chloride was produced by the thermal decomposition of $CsICl_2$. The chloride was converted to the nitrate which was fused with oxalic acid to form the carbonate. Aqueous hydrofluoric acid was allowed to react with the carbonate and the resulting solution was poured into the silver vessel shown in Fig. 1. Evaporation of the solution left the fluoride. Hydrogen fluoride was then added. The vessel was heated and hydrogen fluoride was removed by vacuum distillation. This process of adding and then removing hydrogen fluoride was repeated a few times with the result that the vessel plus the cesium fluoride came to constant weight.

Hydrogen fluoride was obtained as the vapor by distillation from a cylinder of the commercial anhydrous acid. About half of the material originally present in the cylinder had been removed by evaporation before starting the work on the system.

Cooling or warming curves were determined using the apparatus shown in Fig. 1. This comprised a silver cylinder, A, of 105 ml. capacity equipped with a thermocouple well, B, and a monel metal tube, C, through which materials were added or removed. The composition of the charge was determined by weighing the vessel and its contents. Temperatures were measured with a calibrated copper–constantan thermocouple connected to a potentiometer. Each cooling curve was established by first heating the vessel and then allowing it to cool slowly while being held firmly in a Dewar flask or other well-insulated vessel which was moved rapidly back and forth in a mechanical shaker. Temperatures below that of the room were reached by placing solid carbon dioxide in the Dewar vessel in such a location that the

(1) F. C. Mathers and P. T. Stroup, *Trans. Am. Electrochem. Soc.*, **66**, 245 (1934).

(2) H. L. Wells, *Am. Chem. J.*, **26**, 265 (1901).

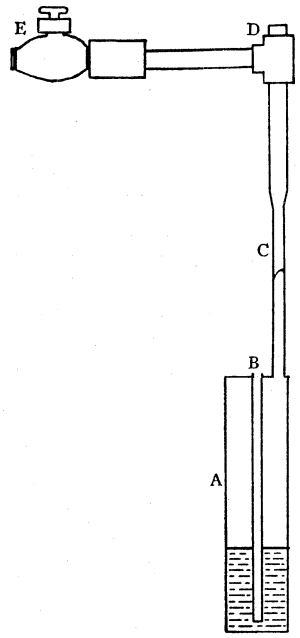


Fig. 1.

refrigerant did not touch the silver cylinder. In a number of cases, both cooling and warming curves were determined.

The temperatures of the observed significant breaks in the curves are shown in Fig. 2. From this diagram the data presented in Table I were selected.

Discussion

The data indicate the existence of four acid fluorides: CsF·HF, CsF·2HF, CsF·3HF and CsF·6HF. The first of these exists in two or perhaps three forms within the temperature range 30° to the melting point 176°. Several attempts were made to determine the number of forms and the transition temperatures, but the experiments gave ambiguous results.

TABLE I

SYSTEM CsF–HF

Mole fraction of HF in solution	Temp., °C.	Type of point	Solid phases present
0.500	176.0	Freezing	CsF·HF
.667	50.2	Freezing	CsF·2HF
.750	32.6	Freezing	CsF·3HF
.857	−42.3	Freezing	CsF·6HF
.453	151.5	Eutectic	CsF·HF and CsF
.639	38.3	Eutectic	CsF·HF and CsF·2HF
.709	16.9	Eutectic	CsF·2HF and Cs·F3HF
.828	−49.5	Eutectic	CsF·3HF and CsF·6HF
< .61	34.4 to 58.8	One or two transition points	Two or perhaps three forms of CsF·HF

In general, an abrupt change in slope in the cooling curve for a sample containing solid CsF·HF occurred at about 56.5°. The corresponding break in the warming curve usually occurred at about 42°. The proximity of the latter temperature to the eutectic point, 38.3°, for CsF·HF and CsF·2HF added to the difficulty of interpreting the experimental observations.

It is almost certain that no additional acid fluorides of cesium will be discovered by extending the study of the system beyond the concentration limits used in this research. In the case of mixtures rich in cesium fluoride, the thermal effect resulting from the freezing of CsF·HF and another solid, probably cesium fluoride, was still readily detected at a mole fraction of hydrogen fluoride of 0.205. It is also the case that the thermal decomposition of molten CsF·HF leaves

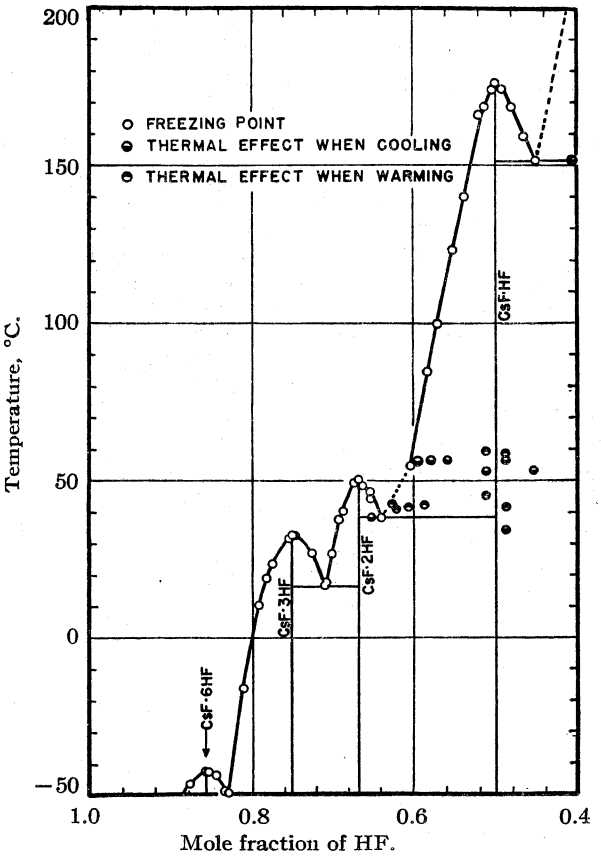


Fig. 2.—The system CsF–HF.

solid cesium fluoride rather than an acid fluoride. These two facts strongly suggest that no acid fluorides exist which are richer in cesium fluoride than the salt CsF·HF. Since the most dilute solution studied (mole fraction of hydrogen fluoride equal to 0.876) showed no thermal effect due to eutectic freezing down to temperatures as low as −83° and since no other acid fluorides containing over six moles of hydrogen fluoride per mole of metal fluoride are known, it is unlikely that additional compounds exist in this part of the system.

A comparison of the acid fluorides of the alkali metals reveals the following trends with increasing atomic number of the metal: (1) The melting points of corresponding compounds decrease. (2) The corresponding compounds become more stable. (3) The maximum number of moles of hydrogen fluoride capable of combining with one mole of metal fluoride apparently increases. Item (1) is illustrated by the fact that NaF·HF melts at some as yet undetermined temperature above 278°,[3] while the corresponding acid fluorides of potassium,[4] rubidium[5] and cesium melt congruently at 239.0, 205 and 176.0°, respectively. This trend is comparable with that existing for the

(3) Froning, Richards, Stricklin and Turnbull, *Ind. Eng. Chem.*, **39**, 275 (1947).

(4) G. H. Cady, THIS JOURNAL, **56**, 1431 (1934).

(5) E. B. R. Prideaux and K. R. Webb, *J. Chem. Soc.*, 1 (1937).

normal fluorides whose freezing points are reported to be: lithium fluoride, 870°; sodium fluoride, 980–997°; potassium fluoride, 880°; rubidium fluoride, 760°; cesium fluoride, 684°. Item (2) is illustrated by the heats of formation of the acid fluorides of the type MF·HF from the solid fluorides of the type MF·HF from the solid fluoride of the metal and gaseous hydrogen fluoride. Values given by de Forcrand[6] for the salts progressing from that of sodium to that of cesium are in calories per mole: 17.10, 21.56, 22.58, 23.57. Further evidence for increasing stability is furnished by the temperatures at which the MF·HF compounds decompose to give solid MF and hydrogen fluoride vapor at one atmosphere pressure. The lithium and sodium salts decompose without melting at "below 200°"[7] and at 278°,[3] respectively. Potassium acid fluoride, KF·HF, melts, and the liquid must be heated to about 400°,[4,8] to cause the vapor pressure of hydrogen fluoride to be one atmosphere. The corresponding salts of rubidium and cesium require still higher, but at present unknown, temperatures. Item (3) is illustrated by the formulas for the highest known acid fluorides: LiF·HF, NaF·HF, KF·4HF, RbF·3HF (others may yet be found), CsF·6HF.

Both KF·HF and CsF·HF undergo transitions involving large heat effects. In the case of the former, the heat of transition is larger than the heat of fusion and the modification existing above the transition point is much softer than the low temperature form. The cause of the transition is not known, but it may possibly involve rotation of the HF_2^- ion.

(6) M. de Forcrand, *Compt. rend.*, **152**, 1557 (1911).

(7) H. V. Wartenberg and O. Bosse, *Z. Elektrochem.*, **28**, 386 (1922).

(8) Fredenhagen and Cadenback, *Z. anorg. allgem. Chem.*, **178**, 289 (1928).

Summary

Cesium fluoride and hydrogen fluoride form the compounds: CsF·HF, CsF·2HF, CsF·3HF and CsF·6HF.

SEATTLE 5, WASHINGTON RECEIVED AUGUST 8, 1947

[CONTRIBUTION NO. 9 FROM THE THERMODYNAMICS LABORATORY, PETROLEUM EXPERIMENT STATION, BUREAU OF MINES]

The Heat Capacity, Heat of Fusion and Entropy of Benzene[1]

BY GEORGE D. OLIVER, MARGARET EATON AND HUGH M. HUFFMAN

Because of the importance of benzene in organic chemistry and in industry the Bureau of Mines has considered it desirable to include this material in its research program involving determination of the thermodynamic properties of hydrocarbons and their derivatives.

Low-temperature measurements have been made on benzene by several investigators. Nernst[2] made measurements over the temperature range 20 to 80°K. Huffman, Parks and Daniels[3] made measurements over the temperature range 92 to 300°K. More recently Ahlberg, Blanchard and Lundberg[4] made measurements from 4 to 93°K. These authors used their data, combined with those of Huffman, Parks and Daniels,[3] to calculate the entropy of liquid benzene at 298.1°K. Hence the best experimental value of the entropy of benzene is the resultant of measurements made in different laboratories. It seemed desirable to obtain the value of the entropy from a single set of precise data in order to make a reliable comparison with the entropy calculated from spectroscopic and molecular data.

The Apparatus.—The measurements were made in the apparatus described by Ruehrwein and Huffman.[5] Very briefly, the method is as follows: About 0.6 mole of the material under investigation was contained in a sealed copper calorimeter, which was mounted in the adiabatic calorimetric system. A measured amount of electrical energy was supplied to the calorimeter, and at all times the temperature of the environment was maintained at that of the calorimeter to prevent heat interchange. The initial and final temperatures of the calorimeter were measured by means of a platinum resistance thermometer. The electrical measurements required for determination of the resistance of the thermometer and for electrical energy were made on a "White" double potentiometer in conjunction with a high-sensitivity galvanometer and accurately calibrated resistances. The potential was in terms of a bank of six saturated cadmium cells which had been certified by the National Bureau of Standards. Time measurements were made with an electric stop clock driven by alternating current, the frequency of which was controlled to about 0.001%. The precision of the measurements was in general better than 0.1%, and above 30°K. it is believed that the accuracy uncertainty should not be greater than 0.2%. The energy measurements were made in terms of the NBS international joule and were converted to calories by dividing by 4.1833.

Experimental

The Material.—The benzene used in this investigation was purified at the Laramie station of the Bureau of Mines[6] and supplied to this Laboratory for a check of its purity by a calorimetric melting point determination.

In July, 1944, a melting point study was made on this material but heat capacity measurements were not made at that time, since the laboratory hydrogen liquefier was not yet in operation. The material was left in the sealed calorimeter from July, 1944, until June, 1947, when the measurement of the heat capacity was undertaken. Due to a change in calorimetric technique it was necessary to

(1) Published by permission of the Director, Bureau of Mines, U. S. Dept. of the Interior. Article not copyrighted.

(2) W. Nernst, *Ann. Physik*, **36**, 395 (1911).

(3) H. M. Huffman, G. S. Parks and A. C. Daniels, THIS JOURNAL, **52**, 1547 (1930).

(4) J. E. Ahlberg, E. R. Blanchard and W. O. Lundberg, *J. Chem. Phys.*, **5**, 539 (1937).

(5) Ruehrwein and Huffman, THIS JOURNAL, **65**, 1620 (1943).

(6) H. M. Thorne, W. Murphy and J. S. Ball, *Anal. Chem.*, **19**, 481 (1945).

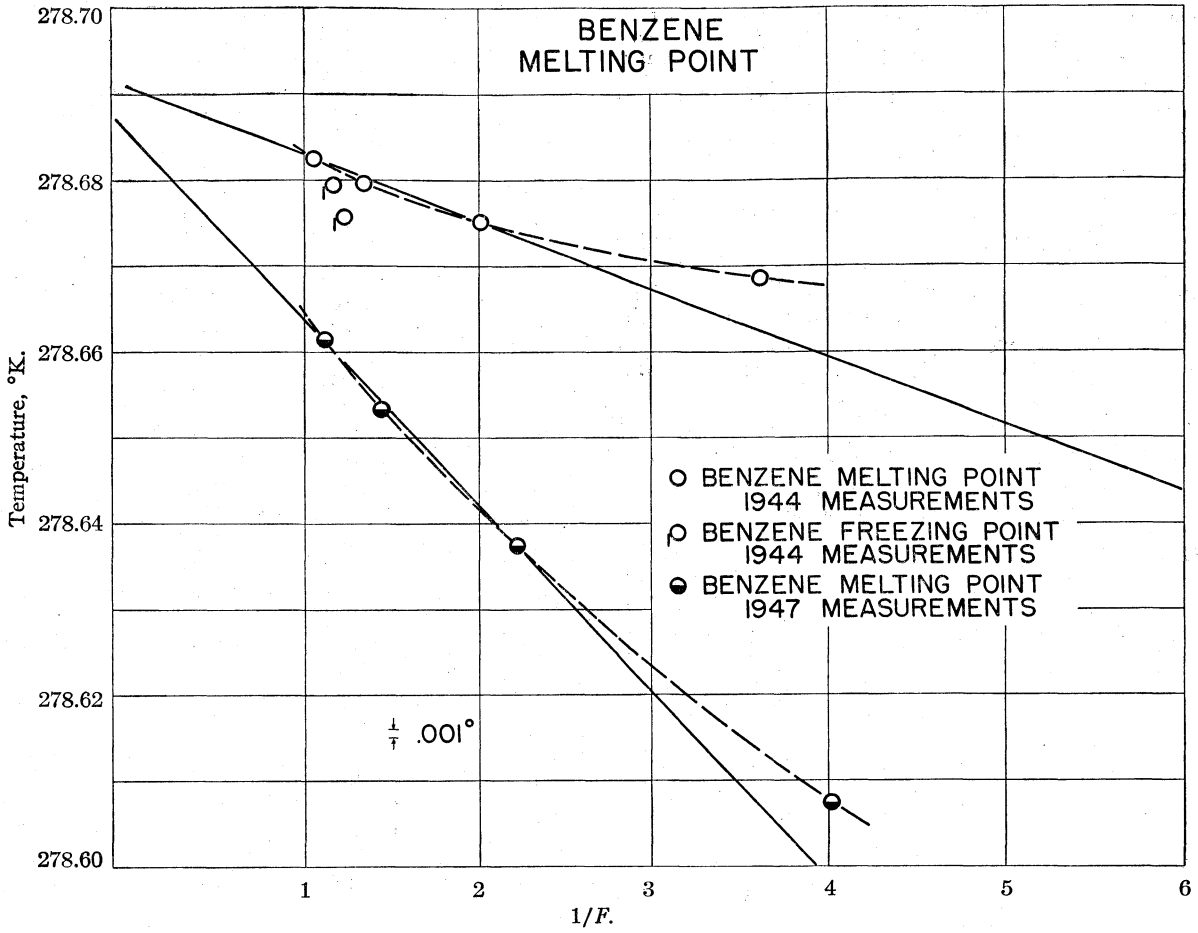


Fig. 1.—Benzene melting point.

transfer the benzene to another calorimeter. The transfer was made by distillation at room temperature in an air-free glass system.

During the heat capacity measurements, a second study of the melting point was made, and the amount of impurity found was approximately three times as great as in the original investigation. This finding suggests that benzene stored in copper is not stable, although it is possible that the benzene may have been contaminated in the transfer process.

TABLE I

BENZENE MELTING POINT SUMMARY

$0°C. = 273.16°K.$ $N_2/F = 0.0153\Delta T$

1944 Expt.			1947 Expt.		
% Melted	T, °K. Obsd.	Calcd.	% Melted	T, °K. Obsd.	Calcd.
5.3	278.5882	278.5436	24.9	278.6067	278.5974
27.6	.6686	.6626	45.1[a]	.6367	.6367
49.7[a]	.6751	.6751	69.3	.6526	.6537
74.4	.6796	.6804	89.5[a]	.6606	.6606
81.0[b]	.6757	.6812	100%		.6633
85.3[b]	.6794	.6817	Pure		.6850
94.1[a]	.6825	.6825			
100%		.6830			
Pure		.6908			
Triple point = 278.691 ± 0.010			Triple point = 278.685 ± 0.010		
Impurity = 0.012 mole %			Impurity = 0.033 mole %		

[a] These points used to obtain calculated values. [b] These points obtained from freezing expt.

The melting point studies were made in the way described by Todd, Oliver and Huffman.[7] The results of the investigations are summarized in Table I. As discussed in the above reference,[7] a plot of the melting point against the reciprocal of the fraction melted should yield a straight line if Raoult's law is obeyed. The data are plotted in Fig. 1, and it is apparent that the observed points do not follow the theoretical linear relationship. It may be argued that the departure from linearity is due to experimental error. This is quite possible, but it is believed that it is not due to the thermometry, as in general the thermometry is precise to a few ten thousandths of a degree. The fact that the departure from linearity is qualitatively the same in both sets of measurements is a substantial argument in favor of the observations being characteristic of the benzene solution. If the observed curvature is not characteristic of the benzene solution under equilibrium conditions, it is a resultant of the combination of benzene, the calorimetric system, and the method employed. This latter statement is made because, in similar studies of other compounds using the same calorimetric system, a linear relation, within the thermometric error, has been found.

The data have been used in the usual way to obtain the melting point of the pure material by an extrapolation of the straight line, through the points at approximately 90 and 50% melted, to $1/F$ equals zero. The slope of this line times the cryoscopic constant gives the mole fraction of impurity.

It is obvious that, in this case, the above procedure is

(7) S. S. Todd, G. D. Oliver and H. M. Huffman, THIS JOURNAL, **69**, 1519 (1947).

arbitrary, since the data do not show conclusively that Raoult's law is obeyed. These observations will emphasize the conclusion of Todd, Oliver and Huffman[7] that the interpretation of melting point data obtained in the ordinary specific heat calorimeter should be made with caution.

Results

In Table II are given the results of the experimental heat capacities and in Table III are listed the values of the molal heat capacity at integral temperatures as selected from a smooth curve drawn through the experimental data. The smoothed heat capacity data of Ahlberg, Blanchard and Lundberg[4] and of Huffman, Parks and Daniels[3] have also been listed in Table III for comparison.

TABLE II

THE MOLAL HEAT CAPACITY OF BENZENE

0°C. = 273.16°K., mol. wt. 78.108

0.60020 mole in calorimeter

T, °K.	ΔT	$C_{satd.}$ cal./deg.	T, °K.	ΔT	$C_{satd.}$ cal./deg.
12.97	1.502	0.687	156.08	8.996	15.943
14.25	1.765	.870	157.46	8.151	16.045
14.77	2.142	.957	164.90	8.645	16.646
16.52	2.802	1.270	173.39	8.323	17.393
16.95	2.259	1.350	181.56	8.018	18.154
19.64	3.142	1.913	189.92	8.694	18.979
19.93	4.037	1.981	198.90	9.281	19.895
23.04	3.666	2.689	207.99	8.903	20.916
23.67	3.463	2.837	216.73	8.560	21.921
26.77	3.794	3.570	225.53	9.048	23.002
27.47	4.141	3.717	234.19	8.268	24.072
30.59	3.841	4.427	235.10	10.145	24.200
31.77	4.466	4.698	242.79	8.945	25.285
36.51	5.026	5.691	245.02	9.691	25.583
41.68	5.318	6.631	252.03	9.529	26.583
47.09	5.498	7.482	254.51	9.282	26.948
52.68	5.673	8.232	261.36	9.129	27.972
54.07	4.743	8.404	261.41	8.192	27.896
58.09	5.151	8.860	263.16	8.029	28.249
59.33	5.780	8.999	269.42	7.834	29.427
65.52	6.616	9.607	270.28	8.709	29.592
71.72	5.762	10.100	270.61	6.862	29.612
78.20	7.196	10.602		Liquid	
85.58	7.569	11.151	286.90	8.108	31.930
93.35	7.943	11.646	289.37	8.124	32.063
101.65	8.682	12.151	294.96	8.012	32.343
110.12	8.257	12.681	300.41	9.389	32.629
118.19	7.885	13.194	309.73	9.255	33.104
125.92	7.572	13.712	318.92	9.119	33.614
133.80	8.188	14.262	327.97	8.986	34.160
141.84	7.887	14.835	336.89	8.856	34.670
149.59	7.603	15.425			

Two measurements of the heat of fusion were made. The values found were 2357.6 and 2358.6 calories per mole, mean 2358.1 ± 0.5 calories per mole. The uncertainty given is the precision uncertainty; the accuracy uncertainty may be considerably greater than this due to lack of knowledge of the exact amount of premelting, of the exact composition, and of the behavior of the impurity when the material was crystallized.

TABLE III

MOLAL HEAT CAPACITY OF BENZENE AT INTEGRAL TEMPERATURES

T, °K.	This research	$C_{satd.}$ cal./degree A, B & L	H, P & D
13	0.685		
14	.830		
15	.995	0.920	
20	2.000	1.84	
25	3.145	3.00	
30	4.300	4.24	
35	5.385		
40	6.340	6.47	
45	7.165		
50	7.885	8.14	
55	8.505		
60	9.065	9.32	
65	9.540		
70	9.975	10.16	
75	10.375		
80	10.750	10.85	
85	11.105		
90	11.430	11.44	11.40
95	11.745		11.70
100	12.050	11.99	12.01
110	12.670		12.65
120	13.310		13.34
130	14.000		14.07
140	14.700		14.80
150	15.450		15.56
160	16.230		16.34
170	17.090		17.16
180	18.020		18.06
190	18.980		19.03
200	20.010		20.06
210	21.140		21.17
220	22.320		22.32
230	23.550		23.55
240	24.880		24.83
250	26.300		26.21
260	27.760		27.77
270	29.310		
278.69	30.760		
.....	.....		
278.69	31.52		
280	31.59		31.46
290	32.10		31.87
298.16	32.52		32.22
300	32.62		32.30
310	33.16		
320	33.69		
330	34.26		
340	34.87		
350	35.50		
353.26	35.70		

The heat capacity data have been utilized to calculate the entropy of benzene. The results of these calculations are summarized in Table IV.

Discussion

Heat capacity measurements on liquid benzene were made to within about 12° of the normal boil-

TABLE IV

ENTROPY OF BENZENE IN CAL./DEG./MOLE

$S_{13°}$ (Debye, 4.5° freedom, θ = 130.5)	= 0.228
$\Delta S_{13-278.69}$ (graphical)	= 30.560
$\Delta S_{278.69}$ (2358.1/278.69)	= 8.461
$\Delta S_{278.69-298.16}$ (graphical)	= 2.162
$S_{298.16}$[a] liquid	= 41.411 ± 0.08
$\Delta S_{vap.,\ 298.16}$ (8090[12]/298.16)	= 27.133
$\Delta S_{compression}$, (R ln 95.13[13]/760)	= −4.129
$\Delta S_{gas\ imperfection}$[b]	= 0.042
S^0, ideal gas at 1 atm.	= 64.457 ± 0.12
$\Delta S_{278.69-353.26}$ (liq.) graphical	= 7.928
$S_{liq.\ 353.26}$[a]	= 47.177
$\Delta S_{vap.,\ 353.26}$ (7349[14]/353.26)	= 20.803
$\Delta S_{gas\ imperfection}$[b]	= 0.145
S, ideal gas at b. p. 353.26	= 68.125 ± 0.12

[a] Entropy of saturated liquid. [b] From equation of state of reference.[11]

ing point. Hence it should be noted that the values listed in the tables are for the saturated liquid. The difference between C_p and $C_{satd.}$ may become barely significant at the higher temperatures.

The heat capacity measurements of Ahlberg, Blanchard and Lundberg[4] showed no regular deviation from those of this research but were both lower and higher in the temperature range 15 to 90°K. The differences ranged from −8.7 to +3.2%. They calculated a value of 10.89 cal./degree for the molal entropy at 90° compared with 10.82 cal./degree obtained in this research.

The entropy of gaseous benzene has been calculated by Taylor, Wagman, Williams, Pitzer and Rossini,[8] who used the vibrational assignment of Pitzer and Scott.[9] They calculated $S_{gas\ 298.16°}$ = 64.34 and $S_{gas\ 353.26°}$ = 67.98 cal./degree/mole. A similar calculation using the more recent vibrational assignment of Herzfeld, Ingold and Poole[10] and the same values for the moments of inertia and fundamental constants used by Taylor, *et al.*,[8] gives values of 64.33 and 67.97 cal./degree/mole. The vapor heat-capacity data of Scott, Waddington, Smith and Huffman[11] indicate significant anharmonicity in the vibrations of the benzene molecule. The correction for anharmonicity increases the calculated entropy by 0.02 and 0.04 cal./degree/mole at 298.16° and 353.26°K., respectively. These calculated values are shown in Table V. The agreement between the experimental and calculated values is within the estimated experimental error.

TABLE V

COMPARISON OF CALCULATED AND EXPERIMENTAL ENTROPIES OF BENZENE GAS

	298.16°K.	353.26°K.
S^0, ideal gas at 1 atm. (calcd.)[a]	64.33	67.97
Correction for anharmonicity[b]	0.02	0.04
S^0, ideal gas at 1 atm. (exptl.)	64.46 ± 0.12	68.12 ± 0.12

[a] Harmonic oscillator–rigid rotator approximation, using vibrational assignment of Herzfeld, Ingold and Poole.[10] [b] See ref. 11.

Summary

The heat capacity of benzene has been measured over the temperature range 12 to 341°K. From these and other data the entropy of the liquid and vapor at 298.16 and 353.26°K. were calculated. The experimental values of the entropy were found to be in good agreement with those calculated from spectroscopic and molecular data.

BARTLESVILLE, OKLA. RECEIVED DECEMBER 5, 1947

(8) Taylor, Wagman, Williams, Pitzer and Rossini, *J. Research, Natl. Bur. Standards*, **37**, 95 (1946).

(9) K. S. Pitzer and D. W. Scott, THIS JOURNAL, **65**, 817 (1943).

(10) Herzfeld, Ingold and Poole, *J. Chem. Soc.*, 316 (1946).

(11) Scott, Waddington, Smith and Huffman, *J. Chem. Phys.*, **15**, 565 (1947).

(12) Osborne and Ginnings, *J. Research Natl. Bur. Standards*, **39**, 453 (1947).

(13) American Petroleum Institute Research Project 44 at the National Bureau of Standards, Selected Values of Properties of Hydrocarbons, Table No. 5k (Part 1).

(14) Waddington and Douslin, THIS JOURNAL, **69**, 2275 (1947).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Entropy of Ethyl Chloride. Heat Capacity from 13 to 287°K. Vapor Pressure. Heats of Fusion and Vaporization

BY JOSEPH GORDON AND W. F. GIAUQUE

This paper presents the results of a low temperature calorimetric investigation on ethyl chloride. Linnett[1] has calculated the entropy of the gas for several assumed atomic distances and the cases of completely free and completely restricted internal angular motion about the carbon–carbon bond. In the absence of more complete molecular data these calculations leave an uncertainty of the order of one or two cal. deg.$^{-1}$ mole^{-1} in the entropy.

Ethyl Chloride.—Ethyl chloride, C_2H_5Cl, was obtained from the Eastman Company in five 100 g. ampoules. The material was purified by the following procedure: Two fractional crystallizations were carried out in a bulb equipped with a side arm. The resulting material was pumped to remove air and then dried by condensing it in a bulb of phosphorus pentoxide. Following this the material was alternately solidified and melted several times and a vacuum of 10^{-6} mm. was pumped on the solid after each such crystallization to insure the removal of air or any other volatile material. The ethyl chloride was then distilled in two lots in a silvered, vacuum-jacketed column about 1.3 cm. i.d., which was packed for a length of 50 cm. with small glass helices. A reflux ratio of the order of 30:1 was used. The rate of removal was controlled by means of a system of capillaries which led to a receiving vessel where the product was obtained as a solid by condensation in liquid air. As usual the glass receiving vessel was protected from the liquid air by means of a metal sheath in case of breakage. The condenser of the fractionating column was cooled by ice. The two middle fractions were combined to give about 100 cc. of the final product.

The small amount of heat due to premelting observed in connection with heat capacity measurements just below the melting point was used to estimate the liquid-soluble solid-insoluble impurity as of the order of 0.02 mole per cent.

Method and Apparatus.—The measurements were made in a calorimeter which has been described previously[2,3,4] and given the laboratory designation Gold Calorimeter II. The most detailed description of this type of calorimeter has been given by Giauque and Egan.[5] An accident to the apparatus necessitated winding a new gold resistance thermometer-heater which was practically the same as had been used previously. A small platinum well was fused to the bottom of the gold calorimeter and filled with Rose's metal to facilitate contact with the junction of the standard thermocouple.

The standard thermocouple which has the laboratory designation W was, as usual, compared with the triple and boiling points of hydrogen and the vapor pressure of liquid oxygen by liquefying these substances in the calorimeter. The comparison served to emphasize the importance of considering a standard thermocouple and the potentiometer used to measure its e. m. f. as a unit to be calibrated together. The potentiometer had been returned to the manufacturer for reconditioning prior to its use in this research. In terms of temperature the comparison using the reconditioned potentiometer indicated that the thermocouple read high by 0.70° at the triple point of hydrogen, 13.95°K., and 0.45° high at the boiling point of hydrogen 20.37°K. Since two other standard thermocouples compared under similar conditions showed almost identical deviations it was clearly evident that the absolute reading of the potentiometer had been altered. At 72°K. the apparent change was 0.04° high and at 78°K., 0.05° high. As nearly as the change could be allocated between thermocouple and potentiometer it appeared that the actual change of the thermocouple was in the direction to read about 0.1° low at liquid hydrogen temperatures if the potentiometer had not been altered. It was of course not necessary to allocate the change in using the thermocouple to determine temperature.

Vapor Pressure of Ethyl Chloride.—The vapor pressure was measured by means of a mercury manometer with an inside diameter of 1.6 cm., and a standard meter bar suspended between the manometer tubes. A Société Génévoise cathetometer with a precision of 0.002 cm. was used as a comparison instrument.

The manometer line was connected to the calorimeter which provided almost ideal temperature control. The data of Cawood and Patterson[6] were used to correct for capillary depression. The data were corrected to international cm. by means of the thermal expansion of mercury as given in the "I.C.T."[7] and the acceleration of gravity[8] which was taken as 979.973 cm. sec.$^{-2}$ for this location. The standard acceleration used was 980.665 cm. sec.$^{-2}$.

The vapor pressure data covering the range 217 to 286°K. are represented by the equation

(1) Linnett, *Trans. Faraday Soc.*, **36**, 527 (1940).
(2) Giauque and Wiebe, THIS JOURNAL, **50**, 101 (1928).
(3) Giauque and Johnston, *ibid.*, **51**, 2300 (1929).
(4) Blue and Giauque, *ibid.*, **57**, 991 (1935).
(5) Giauque and Egan, *J. Chem. Phys.*, **5**, 45 (1937).
(6) Cawood and Patterson, *Trans. Faraday Soc.*, **29**, 522 (1933).
(7) "International Critical Tables," Vol. I, McGraw-Hill Book Co., New York, N. Y., 1926.
(8) Landolt, Bornstein and Roth, "Physikalisch-chemische Tabellen," Verlag Julius Springer, Berlin, 1923.

$$\log_{10} P \text{ (int. cm. Hg)} = (-1777.378/T) - 0.0115789T + 1.06734 \times 10^{-5}T^2 + 10.54417$$

The observations are compared with the above equation in Table I. The temperatures are given to thousandths of a degree to permit the calculation of accurate derivatives from the precise remometer data although the absolute temperatures may be in error by as much as 0.05°.

The equation gives the value of the boiling point as 285.37°K.

TABLE I

VAPOR PRESSURES OF ETHYL CHLORIDE

(0°C. = 273.10°K.)

T, °K.	P obsd. (int. cm. Hg)	P obsd. − P calcd.	T obsd. − T calcd.
217.223	2.245	+0.005	−0.031
229.456	5.045	− .004	+ .013
237.659	8.245	− .006	+ .012
245.015	12.413	+ .003	− .005
253.106	18.841	+ .006	− .007
259.621	25.786	− .002	+ .002
265.464	33.661	− .006	+ .004
271.222	43.219	+ .002	− .001
276.548	53.899	+ .031	− .014
279.591	60.830	+ .002	− .001
283.590	71.037	+ .001	.000
285.611	76.683	− .002	+ .001

dP/dT = 2.8591 cm./degree at 1 atm.

TABLE II

MELTING POINT OF ETHYL CHLORIDE

0°C. = 273.10°K.

Per cent. melted	T, °K. thermocouple	T, °K. resistance thermometer
10	134.69	134.702
30	134.84	134.803
60	134.80	134.804
80	134.81	134.808
Accepted value	134.80 ± 0.05°K.	

TABLE III

COMPARISON OF MELTING AND BOILING POINT DATA OF ETHYL CHLORIDE

0°C. = 273.10°K.

Melting point, °K.	Boiling point, °K.	Observer
....	285.28	Linnemann[9] (1871)
....	285.43	Schacherl[10] (1880)
....	285.6	Jenkin and Shorthose[11] (1923)
133.7	285.30	Kanolt[12] (1926)
....	285.50	Fuchs[13] (1930)
134.4	....	Timmermans and Hennaut-Roland[14] (1937)
134.80	285.37	This research

(9) Linnemann, *Ann.*, **160**, 214 (1871).
(10) Schacherl, *ibid.*, **206**, 68 (1880).
(11) Jenkin and Shorthose, *Dept. of Sci. and Ind. Red.*, No. 14, (1923).
(12) Kanolt, *Bur. of Standards Sci. Paper* **520**, 619 (1926).
(13) Fuchs, *Z. Physik*, **63**, 838 (1930).
(14) Timmermans and Hennaut-Roland, *J. chim. phys.*, **34**, (1937).

Melting Point of Ethyl Chloride.—As usual the melting temperature was observed with various fractions of the material, in the calorim-

TABLE IV

MOLAL HEAT CAPACITY OF ETHYL CHLORIDE

0°C. = 273.10°K. Molecular weight, 64.517. 1.3946 moles in calorimeter

T, °K.	Approx. ΔT	C_P Cal. deg.$^{-1}$ mole^{-1}	Series
14.55	2.4	1.20	
17.08	2.4	1.93	
19.99	3.3	2.73	
23.62	3.6	3.61	
27.43	3.9	4.51	
31.40	4.0	5.37	
35.33	3.9	6.18	
39.03	3.5	6.97	
42.71	3.8	7.58	
46.61	4.0	8.21	
50.87	4.5	8.79	
55.55	4.7	9.54	I
60.34	4.9	10.20	
65.15	4.4	10.78	
69.78	4.9	11.34	
74.70	5.0	11.92	
79.96	5.5	12.58	
85.67	5.3	12.95	
91.50	6.1	13.32	
97.49	5.8	13.95	
103.74	6.5	14.78	
110.19	5.903	15.68	
115.90	5.351	16.68	
121.08	4.868	17.83[a]	
126.82	6.427	19.70[a]	
134.80		Melting point	
139.82	6.0	23.16	I
145.83	5.8	23.07	
151.09	5.4	23.00	
156.55	5.2	22.99	
162.39	5.9	22.91	
168.30	5.7	22.84	
174.10	5.5	22.84	
179.75	5.3	22.90	
185.14	5.2	22.87	
190.62	5.7	22.90	
199.72	5.4	22.83	II
205.44	5.3	22.89	
210.87	5.1	22.92	
216.72	5.7	23.06	
222.68	5.5	23.08	
228.54	5.3	23.22	
234.25	5.2	23.26	
239.77	5.0	23.35	
244.51	4.9	23.46	III
250.29	5.3	23.62	
255.97	5.2	23.78	
261.68	5.1	23.86	
267.74	5.0	24.03	
273.67	4.8	24.24	
279.47	4.7	24.41	
284.47	4.1	24.49	

[a] Premelting.

eter, melted. The data are given in Table II. Each of the temperatures given was obtained by waiting a long period for equilibrium after each addition of heat to alter the fraction melted. The observations extended over a period of 35 hours.

The melting and boiling point observations of other observers are given in Table III for comparison with those found in the present research.

Heat Capacity of Ethyl Chloride.—The heat capacity from 13°K. to the boiling point was measured in the same manner as has been used in many similar researches[3] in this Laboratory.

The value 4.1833 international joules was taken equal to one calorie. The amount of ethyl chloride in the calorimeter was 89.978 g., equivalent to 1.3946 moles, using 64.517 as the molecular weight. Correction was applied for the small amount of heat used in vaporization into the gas space above the liquid in the calorimeter.

Values of the heat capacity read at even values of the temperature from a smooth curve through the observations are given in Table V. It is estimated that the smooth curve represents the heat capacity to within 0.2% above 35°K., within 1% at 20°K. and within 3% at 15°K. due to the low temperature coefficient of the resistance thermometer.

TABLE V

HEAT CAPACITY OF ETHYL CHLORIDE

Smooth curve through observations

(0°C. = 273.10°K.; molecular weight, 64.517)

T, °K.	C_P cal. deg.$^{-1}$ mole^{-1}	T, °K.	C_P cal. deg.$^{-1}$ mole^{-1}
15	1.35	140	23.15
20	2.73	150	23.04
25	3.95	160	22.95
30	5.07	170	22.90
35	6.10	180	22.86
40	7.08	190	22.86
45	7.96	200	22.89
50	8.73	210	22.94
60	10.15	220	23.04
70	11.36	230	23.19
80	12.58	240	23.37
90	13.20	250	23.60
100	14.26	260	23.85
110	15.65	270	24.12
120	17.58	280	24.40
130	20.22	290	24.69
134.80	21.71 (solid)		
Melting point			
134.80	23.23 (liquid)		

Heat of Fusion of Ethyl Chloride.—Three determinations of the heat of fusion of ethyl chloride were made in the usual way. Heat input started somewhat below the melting point and ended at a temperature somewhat above. A correction was made for the small amount of premelting which had occurred below the starting temperature. The results are summarized in Table VI.

TABLE VI

HEAT OF FUSION OF ETHYL CHLORIDE

Melting point 134.80°K.; molecular weight 64.517

Temperature interval, °K.	Total heat added cal. mole^{-1}	Pre-melting cal. mole^{-1}	$\int C_p\,dT$ cal. mole^{-1}	ΔH fusion cal. mole^{-1}
130.109–135.698	1181.6	1.5	119.0	1064.1
131.837–138.162	1203.1	2.4	141.0	1064.5
132.242–136.095	1145.1	2.7	84.6	1063.2
			Average	1064 ± 1

Heat of Vaporization of Ethyl Chloride.—The heat of vaporization was measured by vaporizing the material from the calorimeter into a bulb where it was condensed by means of liquid air. The pressure was maintained constant during vaporization at approximately 1 atmosphere by means of a system of capillary tubes, which could be used in various combinations, between the calorimeter line and the condensation bulb. Only the heater on the lower half of the calorimeter was used in these measurements and only liquid in the upper half of the calorimeter was evaporated. This avoided possible superheating of the gas following vaporization.

The temperature of vaporization was obtained by observing the vapor pressure during the heat input. The rate of vaporization used in such measurements in this Laboratory is kept low enough so that vaporization occurs quietly at the surface with no bubble formation Since some superheat occurs toward the bottom of the liquid the final temperature after heating and condensation is ended will be somewhat different than the initial temperature or the vaporization temperature. Accordingly correction was applied for the heat capacity, heat leak and vaporization into the known gas volume, including the volume previously occupied by the liquid. A small correction was applied to correct the values of the heat of vaporization to the exact temperature 285.37°K., the normal boiling point of ethyl chloride.

The experimental observations are given in Table VII. The value calculated from the vapor pressure equation and the assumption that the gas volume may be calculated by assuming a Berthelot gas is in excellent agreement but is given no weight in comparison with the direct observations.

TABLE VII

HEAT OF VAPORIZATION OF ETHYL CHLORIDE

Boiling point, 285.37°K.

Run	Moles evaporated	Time of energy input, minutes	ΔH vaporization cal. mole^{-1}
1	0.15210	40	5894
2	.14240	40	5898
3	.13736	40	5897
4	.13379	40	5891
5	.17709	45	5886
6	.17732	45	5885
			Average 5892 ± 6

Value calculated from vapor pressure equation 5875 cal. mole^{-1}.

The Entropy of Ethyl Chloride.—The calculation of the entropy of ethyl chloride from the calorimetric data is summarized in Table VIII.

TABLE VIII

CALCULATION OF THE ENTROPY OF ETHYL CHLORIDE

	Cal. deg.$^{-1}$, mole^{-1}
0–15°K., Debye extrapolation	0.50
15–134.80°K., graphical	18.725
Fusion, 1064/134.80	7.893
134.80–285.37°K., graphical	17.401
Vaporization, 5892/285.37	20.647
Entropy of actual gas at boiling point	65.17 ± 0.10
Correction for gas imperfection	0.14
Entropy of ideal gas at boiling point	65.31

The correction for gas imperfection given in Table VIII was calculated by assuming that Berthelot's equation of state represented the gas imperfection. For this case the equation $(\partial S/\partial P)_T = -(\partial V/\partial T)_P$ gives

$$S_{\text{ideal}} - S_{\text{actual}} = (27RT_c^3P)/(32T^3P_c)$$
$$= 0.14 \text{ cal. deg.}^{-1} \text{ mole}^{-1}$$

The values $T_c = 460.3$°K. and $P_c = 52$ atm. were taken from the "International Critical Tables."

Entropy Calculations Based on Molecular Data.—Since the potential barrier for internal rotation of ethyl chloride has not been observed spectroscopically the entropy could not be completely calculated from molecular data. However, the data are otherwise sufficiently complete so that the entropy due to internal rotation may be evaluated by difference. "I.C.T." values of natural constants were used in the calculations.

The following distances were adopted as a basis for the calculation C–C, 1.54 Å.; C–H, 1.09 Å.; C–Cl, 1.75 Å. Tetrahedral angles were assumed in the absence of definite information since the error due to this assumption should not have much effect on the entropy calculation. The vibrational assignment given by Linnett[1] was adopted except that we accepted a suggestion of Professor K. S. Pitzer to delete the values 1000 and 1120 cm.$^{-1}$, and add 1319 and 1385 cm.$^{-1}$ although the change has little effect on the vibrational entropy at the boiling point since this is principally due to the lower frequencies. The assignment used is 337, 655, 790, 970, 1050, 1070, 1290, 1319, 1385, 1400, 1450(2), 3000(5).

The principal moments of inertia were calculated to be $I_1 = 30.20 \times 10^{-40}$, $I_2 = 159.7 \times 10^{-40}$ and $I_3 = 178.5 \times 10^{-40}$ g. cm^2., where I_3 is perpendicular to the plane of symmetry. The angle between the C–C direction and the principal axis of I_1 was found to be $45°48' = \theta$. The reduced moment of inertia was calculated from the formula

$$I_{\text{red.}} = I_{CH_3}\left[1 - I_{CH_3}\left(\frac{\cos^2\theta}{I_1} + \frac{\sin^2\theta}{I_2}\right)\right]$$

given as Formula (1a) by Pitzer and Gwinn.[15] $I_{\text{red.}}$ was found to be 4.73×10^{-40} g. sq. cm.$^{-2}$.

The entropy calculation for the gas at the boiling point is summarized in Table IX.

TABLE IX

CALCULATION OF THE ENTROPY OF ETHYL CHLORIDE GAS FROM MOLECULAR DATA AT ITS BOILING POINT, 285.37°K.

	Calories degree^{-1} mole^{-1}
Translation	38.20
Rotation (rigid molecule)	23.58
Vibration	1.98
	63.76
Total entropy, measured	65.31
Entropy due to internal rotation	1.55

The potential barrier may be evaluated from the tables prepared by Pitzer and Gwinn.[15] If the internal rotation were completely free the entropy corresponding to the reduced moment of inertia given above would be 3.46 cal. deg.$^{-1}$ mole^{-1} at 285.37°K. $S_{\text{free}} - S_{\text{restricted}} = 3.46 - 1.55 = 1.91$ cal. deg.$^{-1}$ mole^{-1}. In the present case there are three potential minima per revolution and the potential barrier corresponding to the suppression of internal rotation by 1.91 cal. deg.$^{-1}$ mole^{-1} is found to be 4700 cal. mole^{-1}.

A summary of the entropy calculation for 298.1°K. is given in Table X.

TABLE X

ENTROPY OF ETHYL CHLORIDE GAS AT 298.1°K.

	Calories degree^{-1} mole^{-1}
Translation	38.42
Rotation (rigid molecule)	23.70
Vibration	2.19
Internal rotation	1.60
	65.91

The entropy value 65.91 cal. deg.$^{-1}$ mole^{-1} does not include the effects of isotopes and nuclear spin since these effects should be ignored in ordinary thermodynamic calculations.

We thank Dr. W. M. Jones for assistance with some of the experimental measurements.

Summary

The heat capacity of ethyl chloride has been measured from 13 to 287°K.

The melting and boiling points were found to be 134.80 and 285.37°K., respectively.

The heat of fusion was determined to be 1064 cal. mole^{-1} and the heat of vaporization 5892 cal. mole^{-1}.

The vapor pressure was measured and represented by the equation $\log_{10} P(\text{inter. cm. Hg}) = (-1777.378/T - 0.0115789T + 1.06734 \times 10^{-5}T^2 + 10.54417$ which applies over the range 217 to 286°K.

The entropy of the gas at the boiling point was found to be 65.31 cal. deg.$^{-1}$ mole^{-1} of which 1.55

(15) Pitzer and Gwinn, *J. Chem. Phys.*, **10**, 428 (1942).

cal. deg.$^{-1}$ mole^{-1} was shown to be due to internal rotation, corresponding to a potential barrier of 4700 cal. mole^{-1}.

The entropy at 298.1° K. and 1 atmosphere was found to be 65.91 cal. deg.$^{-1}$ mole^{-1}.

BERKELEY, CALIFORNIA RECEIVED NOVEMBER 6, 1947

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, INSTITUTE OF TECHNOLOGY, UNIVERSITY OF MINNESOTA]

The Chlorophyll-sensitized Photooxidation of Phenylhydrazine by Methyl Red. II. Reactivity of the Several Forms of Methyl Red[1]

BY ROBERT LIVINGSTON AND RUDOLPH PARISER

In a previous study[2] of this reaction a mechanism was suggested which led to the prediction that the quantum yield should increase with increasing concentration of phenylhydrazine. Direct measurements, in the range from 0.01 to 0.20 *M* phenylhydrazine, showed a definite although small decrease in the yield with increasing concentrations. Since it was noticed that the color of methyl red was also affected by this change in concentration, a series of measurements using varying mixtures of phenylhydrazine and phenylhydrazine hydrochloride were made. Both the concentration of a "red" form of the methyl red and the yield of the reaction increased with increasing acidity of the solution, the yield approaching a limiting value of about 0.5. Since methyl red has three colored forms,[3] it was necessary to determine the absorption spectra of each of these forms, before it was possible to analyze the solutions spectrophotometrically. Using this method of analysis, it was found that only the intermediate form of methyl red reacted in the solutions used. Making allowance for the variation of quantum yield with dye concentration, it can be shown that the yield is also a (symbatic) function of the phenylhydrazine concentration. The yield appears to be independent of intensity. A relatively simple reaction mechanism is consistent with these observations.

Part I. Spectrophotometric Analysis of Methyl Red

Experimental Methods and Materials

Materials.—The methanol was purified by treating synthetic methanol with an amount of sodium estimated to be three times as much as was required to react with the water present, refluxing with an excess of methyl phthalate,[4] and then distilling through an efficient packed column. The purification of the methyl red has been described.[2] Alcoholic hydrochloric acid was prepared by bubbling dry hydrogen chloride into methanol. Sodium methylate solutions were prepared by allowing weighed quantities of clean sodium to react completely with methanol. The concentrations of the acid and base solutions were checked by titration with aqueous standard solutions.

The several solutions were made from stock solutions of methyl red and of either sodium methylate or alcoholic hydrochloric acid. All measurements were made with 2×10^{-5} *M* methyl red. As only ordinary precautions were taken to keep the solutions out of contact with laboratory air, it is probable that the sodium methylate solutions contained some carbonate and hydroxide.

Methods.—The photometric measurements were made with a Beckmann spectrophotometer at room temperature (24 to 27°). Measurements were made at 100 Å. intervals in the range from γ 3600 to 6000 Å. Duplicate preparations and measurements were made for each solution studied.

Experimental Results

The solutions studied were made up to contain, in addition to 2×10^{-5} *M* methyl red, the following added substances: (1) 0.40 *M* HCl, (2) 10^{-3} *M* HCl, (3) 10^{-4} *M* HCl, (4) 10^{-5} *M* HCl, (5) 10^{-6} *M* $NaOCH_3$, (6) 10^{-5} *M* $NaOCH_3$, (7) 2×10^{-5} *M* $NaOCH_3$, (8) 5×10^{-5} *M* $NaOCH_3$, and (9) 10^{-3} *M* $NaOCH_3$.

Further increase of the hydrochloric acid concentration above 0.40 *M* did not affect the extinction curve. At the other end of the range, use of concentrated sodium methylate results in a fading of the yellow color. This fading is reversible. It is not complete even in very basic solutions. The extinction coefficients at wave lengths near the maximum decrease about 30% as the concentration of methylate is increased from 10^{-3} to 1 *M*. The absorption spectrum of the dye is practically unchanged in the range from 2×10^{-4} to 5×10^{-3} *M* $NaOCH_3$.

The extinction curves for solutions 1, 3, 6, 7, and 9 are plotted in Fig. 1. The curves corresponding to solutions 4, 5 and 8 have been omitted from the plot to simplify it. They belong to the same family of curves as those plotted. It should be noted that the curves intersect at one of two points, corresponding to either λ 4360 or 4800 Å. One curve, number II, passes through both points of intersection.

It is apparent that the dye can exist in three different colored forms. From the variation of the absorption curves with the acidity of the solutions, it may be safely assumed that curves 9 and 7 correspond, respectively, to the pure forms I and III.[5] It is impossible to calculate exactly the extinc-

(1) This work was supported jointly by the Graduate School of the University of Minnesota and by the Office of Naval Research (Contract N6ori-212, T. O. I) to whom the authors are indebted.

(2) R. Livingston, D. Sickle and A. Uchiyama, *J. Phys. Colloid Chem.*, **51**, 775 (1947).

(3) A. Thiel, A. Dassler and F. Wülfkin, *Fortsch. Chem. Physik. physik. Chem.*, **18**, no. 3 (1924).

(4) We are indebted to Dr. R. Arnold of the Organic Division of this department for suggesting this method.

(5) It is possible that solution 9 contains a trace of the colorless form. However, the practical independence of the curve from the methylate concentrations over a wide range is evidence that the percentage of the dye present in the colorless form is small.

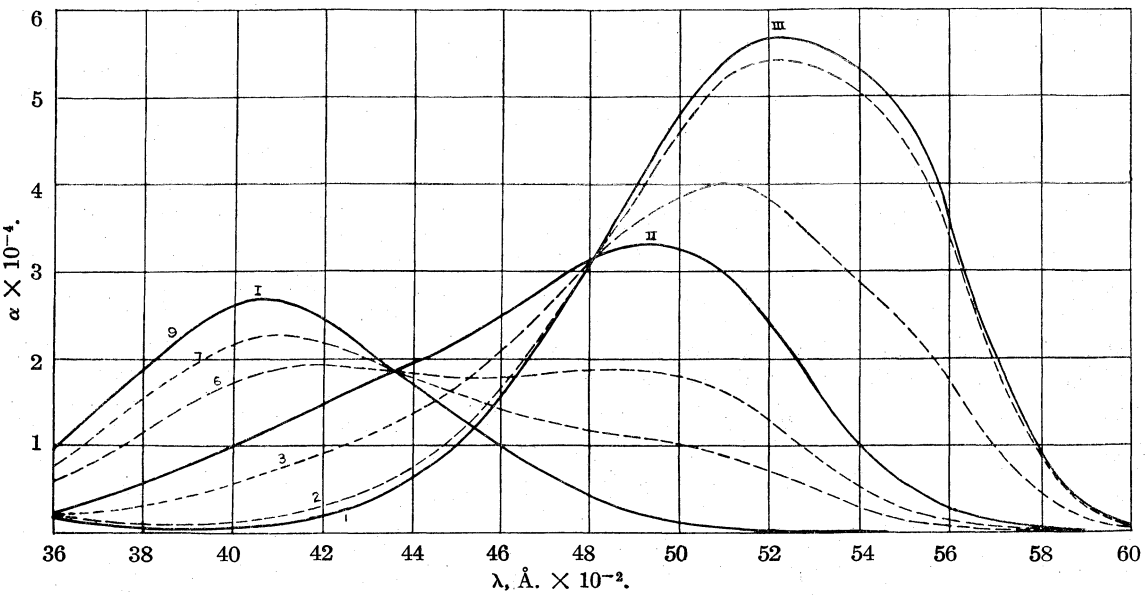


Fig. 1.—Extinction coefficients of methyl red dissolved in methanol containing acid or base.

tion curve of the third form from the curves for the two pure forms and from any number of curves for mixtures.[6] However, a reasonably precise numerical approximation, to the curve of form II, may be readily obtained.[3,6] The curves which pass through the point at 4360 Å. correspond to solutions which are free from form III; and those which cross at 4800 Å. represent solutions free from form I. The analysis of the data was simplified by the fact that one curve (for solution number 4) which is not shown on Fig. 1 passes very close to both points of intersection. Accordingly this solution must contain chiefly form II of the dye. For those solutions whose curves cross at 4360 Å. the observed extinction coefficient β_i equals

$$\beta_{i,\lambda} = \alpha_{1,\lambda}C_1 + \alpha_{2,\lambda}C_2$$

when C_1 and C_2 are the concentrations of form I and II in the ith solution and $\alpha_{1,\lambda}$ and $\alpha_{2,\lambda}$ are the extinction coefficients of the pure form I and II at the wave length λ. Similarly for curves crossing at 4800 Å.

$$\beta_{i,\lambda} = \alpha_{2,\lambda}C_2 + \alpha_{3,\lambda}C_3$$

Approximately the values of $\beta_{4,\lambda}$ are equal to those of $\alpha_{2,\lambda}$. Curve II has been obtained from the values of solution No. 4 by a process of successive approximations, as follows. Minor adjustments were made in these approximate values of $\alpha_{2\lambda}$ until all of the mixture curves (2, 3, 5, 6, 7 and 8) could be fitted in terms of the preceding two equations and a series of values of $\alpha_{1,\lambda}$, $\alpha_{2,\lambda}$ and $\alpha_{3,\lambda}$. It is assumed that these values are close approximations to the true values for the extinction coefficients of the three pure forms of the dye. The three solid curves of Fig. 1 are plots of these values which are listed in Table I.

(6) Compare E. Q. Adams and L. Rosenstein, THIS JOURNAL, 36, 1452 (1914).

TABLE I

EXTINCTION COEFFICIENTS OF THE COLORED FORMS OF METHYL RED

λ, Å.	$\alpha_1 \times 10^{-4}$ (lit./mole)[a]	$\alpha_2 \times 10^{-4}$ (lit./mole)[a]	$\alpha_3 \times 10^{-4}$ (lit./mole)[a]
3600	0.99	0.243	0.187
3700	1.44	.40	.117
3800	1.91	.55	.075
3900	2.32	.79	.057
4000	2.64	1.00	.065
4060	2.71[b]		
4100	2.67	1.26	.112
4200	2.45	1.50	.212
4300	2.07	1.75	.39
4400	1.72	1.97	.66
4500	1.37	2.22	1.05
4600	1.01	2.53	1.61
4700	0.70	2.87	2.32
4800	.44	3.18	3.13
4900	.262	3.33	3.94
4910		3.34[b]	
5000	.138	3.27	4.78
5100	.085	2.99	5.42
5200	.038	2.44	5.70
5210			5.71[b]
5300	.020	1.72	5.60
5400	.010	1.04	5.35
5500	.005	0.57	4.79
5600	.005	.270	3.56
5700	.005	.130	2.02
5800	.000	.075	0.89
5900	.000	.025	.295
6000	.000	.000	.082

[a] The values of the extinction coefficients are in terms of common logarithms. [b] The maximum value of the extinction coefficient.

It is interesting to compare these results with those obtained by Thiel, Dassler and Wülfkin (ref. 3, Fig. 13) for aqueous solutions of methyl

red. The data of Table II[7] suggest that, while two of the colored forms are chemically identical in methanol and in water, the remaining forms differ.

TABLE II

COMPARISON OF MAXIMUM ABSORPTION IN AQUEOUS AND METHANOL SOLUTIONS

Solution	Aqueous solutions λ, Å.	Aqueous solutions $\alpha \times 10^{-4}$	Methanol solutions λ, Å.	Methanol solutions $\alpha \times 10^{-4}$
Basic	4470	2.08	4060	2.71
Intermediate	5300	5.33	4910	3.34
Acidic	5170	5.25	5210	5.71

Part II. Photochemical Measurements

Experimental Methods and Materials

The reagents used were similar to those described by Livingston, Sickle and Uchiyama.[2] The method of purifying methanol is described in the first part of the paper. The apparatus, described by them,[2] was slightly improved mechanically and by the use of a voltage stabilizer with the light source. Cylindrical reaction vessels, 12 mm. in length, were used in all of the present experiments.

Except for the analytical method, the experimental procedure and the routine computations were similar to those previously described.[2] All solutions were analyzed for methyl red concentration, before and after illumination, with the Beckmann spectrophotometer. Two or more wave lengths were used and the measured values were corrected for the (small) absorption due to chlorophyll. Control experiments showed that this method of analysis did not produce any change in the concentration and that it gave results consistent with the analytical method used in the earlier measurements.[2]

The results of a number of determinations of the quantum yield, in terms of the disappearance of methyl red, are presented in Table III. Chlorophyll A at a concentration of 5×10^{-6} M was used in all experiments. The solvent was methanol. The experiments were performed at room temperature, which varied between 25 and 28°. The actinic light was a red band, having a maximum at 6200 Å., cutting off sharply at 6000 Å., and tailing off gradually to about 7300 Å. The special symbols used in the table have the following significance: I, number of quanta absorbed per second in the reaction cell, (Ph), molarity of phenylhydrazine, (PhHCl), molarity of phenylhydrazine hydrochloride, $(D)_0$, initial molarity of the total methyl red, and $(D'')_0$, initial molarity of the intermediate form of methyl red. The quantum yield, $\bar{\varphi}$, is the average value and is defined by the equation

$$\bar{\varphi} = \frac{[(D_0) - (D)_{final}](\text{moles/liter})}{I\ (\text{quanta/sec.})\ [T_0 - T_{final}]\ (\text{sec.})}\ V(l) \times N\ (\text{molecules/mole})$$

The significance of the values tabulated in the last three columns is discussed in a later section of the paper.

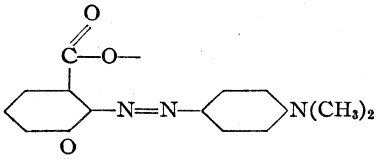
The average value of the quantum yield, $\bar{\varphi}$, corresponding to those solutions in which there was no phenylhydrazine hydrochloride, is 0.14. This is in reasonable agreement with the value of 0.12 obtained by Livingston, Sickle and Uchiyama.[2] The statement by these latter authors, that the yield is independent of the methyl red concentration, was based upon preliminary unpublished experiments and appears to be in error.

Attempts to make quantum yield measurements in more acid solutions were unsatisfactory, due partly to the instability of chlorophyll in acid solutions, and partly to a dark reaction between phenylhydrazine and methyl red, which becomes appreciable as the phenylhydrazine is completely neutralized with hydrogen chloride.[8] A few experiments were performed with solutions which contained 0.10 M phenylhydrazine hydrochloride but no free base. In these solutions, the dye was partly in form II and partly in form III. The quantum yields obtained were lower than in less acid solutions, and suggest that form III (like form I) of methyl red is incapable of undergoing a photosensitized reaction with phenylhydrazine.

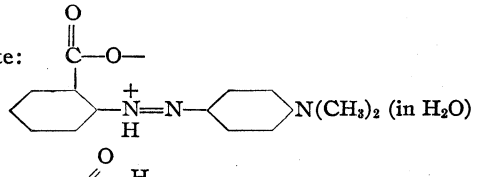
When purified methylaniline is substituted for phenylhydrazine no detectable reaction occurs.

(7) As was pointed out by Thiel in 1924,[3] the probable structures of methyl red in aqueous solutions are as follows.

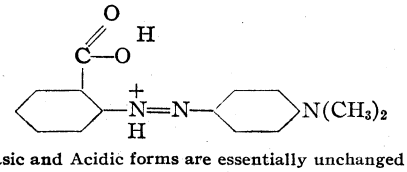
Basic:



Intermediate:

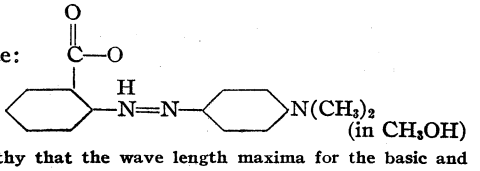


Acidic:



While the Basic and Acidic forms are essentially unchanged in going from aqueous to alcoholic solution, the zwitterion form of the intermediate is probably replaced by an uncharged molecule which is stabilized by an internal hydrogen bond.

Intermediate:



It is noteworthy that the wave length maxima for the basic and intermediate forms are shifted strongly to the violet when the solvent is changed from water to methanol. In both of these cases the principal resonance of the excited states involves a separation of charges. In the acid form where a similar resonance can occur without a separation of charge, the effect of the solvent upon the wave length of the extinction maximum is slight. As a result of these shifts, the maximum of the Acidic form lies between the maxima of the Basic and intermediate forms in aqueous solution, but to the red side of that of the Intermediate form in alcoholic solution.

(8) Ghosh and Sen Gupta, *J. Ind. Chem. Soc.*, **11**, 69 (1934).

TABLE III

SUMMARY OF THE EXPERIMENTAL MEASUREMENTS

No.	$I \times 10^{-15}$	(Ph)	(PhHCl)	$(D)_0 \times 10^4$	$(D'')_0 \times 10^4$	$\bar{\varphi}$	$\bar{\varphi}'$	$(\bar{D}) \times 10^4$	Φ
45	8.3	0.100	[a]	1.22	0.089	0.11	0.12	0.065	0.49
44	7.5	.050	[a]	1.19	.110	.10	.10	.072	.44
9	4.7	.100	0	1.19	.107	.13	.14	.074	.52
4	3.9	.200	0	1.19	.109	.12	.13	.081	.43
3	3.9	.100	0	1.19	.125	.13	.14	.096	.44
8	4.7	.100	0	1.19	.135	.13	.15	.100	.44
214	5.5	.050	0	1.09	.134	.11	.14	.105	.40
211	6.6	.050	0	1.10	.137	.18	.22	.106	.63
213	5.9	.050	0	1.10	.141	.16	.19	.109	.54
206	1.0	.050	0	1.09	.140	.13	.16	.109	.44
14	5.3	.050	0	1.19	.165	.15	.18	.116	.50
5	3.4	.200	0	1.19	.147	.12	.12	.117	.34
119	1.1	.050	0	1.12	.141	.14	.17	.119	.38
2	3.8	.050	0	1.12	.162	.14	.16	.132	.41
1	4.8	.050	0	1.17	.181	.16	.19	.137	.48
23	1.6	.500	0.250	0.24	.208	.21	.21	.142	.52
6	3.7	.025	0	1.19	.304	.15	.22	.195	.43
7	3.9	.020	0	1.19	.359	.14	.22	.222	.41
37	3.1	.250	0.750	0.61	.610	.31	.32	.348	.50
38	2.4	.250	.750	0.61	.610	.34	.35	.357	.54
29	2.5	.100	.200	1.19	0.87	.29	.30	.438	.43
24	2.4	.050	.250	1.19	1.05	.32	.33	.468	.46
33	2.4	.100	.005	1.19	0.81	.23	.25	.468	.35
30	3.0	.500	.100	1.23	1.03	.31	.31	.478	.44
34	2.8	.100	.005	1.22	0.85	.27	.30	.498	.42
31	2.5	.100	.010	1.19	.91	.26	.28	.543	.38
32	2.9	.500	.005	1.23	0.97	.28	.28	.578	.38
25	2.5	.500	.250	1.19	1.05	.29	.29	.605	.39
26	2.4	.250	.750	1.19	1.14	.35	.36	.690	.46
28	2.4	.250	.750	1.19	1.19	.34	.34	.735	.43
42	1.4	.250	.750	6.10	6.10	.45	.45	2.49	.49
36	2.5	.250	.750	5.95	5.95	.41	.42	2.54	.45
35	2.2	.250	.750	5.95	5.95	.49	.49	2.68	.53
39	7.9	.250	.750	6.10	6.10	.45	.46	3.12	.48

[a] Contained 10^{-4} M $NaOCH_3$.

Two experiments were performed with solutions containing 5×10^{-6} M chlorophyll A, 2×10^{-5} M methyl red, and 0.050 M methylaniline. If any reduction of methyl red occurred its quantum yield was less than 0.005. In contrast to this result, hydrazobenzene undergoes a reaction comparable to that obtained with phenylhydrazine. Quantum yields of 0.17 and 0.19 were obtained with solutions containing 5×10^{-6} M chlorophyll A, 1×10^{-4} M methyl red, and 0.050 M hydrazobenzene. In these (four) experiments the solvent was methanol, and the light intensity and temperature were comparable to those reported in Table III.

Discussions and Computations

The data presented in Table III are consistent with any of several different mechanisms. The following series of steps has been adopted for purposes of discussion. It is as simple as any and has the further advantage that it is in agreement with the interpretation of the reversible bleaching of chlorophyll which was recently suggested by McBrady and Livingston.[9,10] The special symbols used have the following significance: GH, chlorophyll, HG, long-lived activated chlorophyll, D″, methyl red in form II, and DH_2, reduced methyl red. Making the usual assumption that a

$$GH + h\nu \longrightarrow GH^* \quad (1)$$

$$GH^* \longrightarrow GH + h\nu_f \quad (2)$$

$$GH^* \longrightarrow HG \quad (3)$$

$$HG \longrightarrow GH \quad (4)$$

$$D'' + HG \longrightarrow HGD \quad (5)$$

$$HGD \longrightarrow GH + D'' \quad (6)$$

$$C_6H_5N_2H_3 + HGD \longrightarrow GH + DH + C_6H_5N_2H_2 \quad (7)$$

$$2DH \longrightarrow D'' + DH_2 \quad (8)$$

$$2C_6H_5N_2H_2 \longrightarrow (C_6H_5N_2H_2)_2 \quad (9)$$

steady state exists, an equation for the steady-

(9) J. McBrady and R. Livingston, *J. Phys. Colloid Chem.*, **52**, in press (1948).

(10) Unpublished results on the quenching of fluorescence, obtained recently in this Laboratory by Dr. W. Watson, indicate that the photochemical properties of chlorophyll are modified by methyl red due to the formation of an addition compound. If this postulate is confirmed, the present mechanism can be modified to conform to it.

state can be obtained[11]

$$\varphi_{-D} = \frac{1}{2} \times \frac{k_3}{k_2 + k_3} \times \frac{k_7\,(C_6H_5N_2H)}{k_6 + k_7\,(C_6H_5N_2H_3)} \times \frac{k_5\,(D'')}{k_4 + k_5\,(D'')} \quad (1)$$

For the concentrations used in the present experiments, the factor involving the concentrations of phenylhydrazine as well as the ratio of (D″) to (D) remain sensibly constant during each run, and therefore we write

$$\varphi_{-D} = -\frac{1}{I'} \times \frac{d(D)}{dt} = -\frac{1}{I'} \times \frac{(D)_0}{(D'')_0} \times \frac{d(D'')}{dt} \quad (2)$$

and

$$-\frac{d(D'')}{dt} = \frac{(D'')_0}{(D)_0} I'A \frac{(k_5/k_4)(D'')}{1 + (k_5/k_4)(D'')} \quad (3)$$

where I' is the intensity of the absorbed light expressed in Einsteins per liter per second and

$$A = \frac{k_7(C_6H_5N_2H_3)}{k_6 + k_7(C_6H_5N_2H_3)}$$

The definite integral corresponding to equation (3) is

$$\frac{k_4}{k_5} \ln \frac{(D'')_0}{(D'')} + (D'')_0 - (D'') = \frac{(D'')_0}{(D)} AI't \quad (4)$$

Introducing the experimentally determined average value for the quantum yield

$$\bar{\varphi} = \frac{(D)_0 - (D)}{I't} = \frac{(D)_0}{(D'')_0} \frac{(D'')_0 - (D'')}{I't} \quad (5)$$

we obtain

$$\frac{k_4}{k_5} \frac{\ln (D'')_0 - \ln (D'')}{(D'')_0 - (D'')} + 1 = \frac{A}{\bar{\varphi}}$$

Rearranging and introducing the symbol $(\bar{D}'')$ for the logarithmic mean[12]

$$\frac{(D'')_0 - (D'')}{\ln (D)_0/(D'')}$$

we obtain equation (5) for the mean quantities, which has the same form as equation (1) relating to the instantaneous values.

$$\bar{\varphi} = \frac{1}{2} \times \frac{k_3}{k_2 + k_3} \times \frac{k_7/k_6(C_6H_5N_2H_3)}{1 + k_7/k_6(C_6H_5N_2H_3)} \times \frac{k_5/k_4\,(\bar{D}'')}{1 + k_5/k_4\,(\bar{D}'')} \quad (6)$$

Assuming the validity of this equation, we may compute $\bar{\varphi}'$, the values which $\bar{\varphi}$ would approach at high concentrations of phenylhydrazine.

$$\bar{\varphi}' = \bar{\varphi}\left[1 + \frac{k_6}{k_7} \times \frac{1}{(C_6H_5N_2H_3)}\right] \quad (7)$$

The values of $\bar{\varphi}'$, listed in the eighth column of Table III, were computed in this way, using an empirical value of k_7/k_6 of 1.0×10^2 (liter/mole). In making this correction, the total concentration of phenylhydrazine, rather than the concentration of the free base, was used. While this procedure seems to be in better agreement with the data, they are not sufficiently precise to prove that it is correct.

Figure 2 is a plot of $1/\bar{\varphi}'$ against $1/(\bar{D}'')$. While the points show considerable scatter, they unmistakably conform to the expected linear relation. The values of the constants, corresponding to the line drawn in the figure, are $k_5/k_4 = 5.0 \times 10^4$ (liter/mole) and $\Phi = 1/2 \times k_3/k_2 + k_3) = 0.46$ (molecules/quantum). The latter quantity is the maximum value for the quantum yield and corresponds to a value of $k_3/(k_2 + k_3)$ of 0.92. If the electronically excited chlorophyll, GH*, is incapable of directly sensitizing the reaction (as is assumed in the mechanism), this value is in close agreement with the commonly quoted value of 0.08 for the fluorescence efficiency of chlorophyll in solution.

The values of Φ, listed in the last column of Table III, were computed from the corresponding values of $\bar{\varphi}'$ and of $(\bar{D}'')$ by means of equation (8).

$$\Phi = \varphi'\left[1 + \frac{k_4}{k_5} \frac{1}{(\bar{D}'')}\right] \quad (8)$$

The mean of the tabulated values of Φ is 0.45, with a standard deviation of the mean of 0.06. The several values of Φ show no significant correlation with any of the experimental variables (concentrations or intensity). In other words equation (6) fits the data within the limit of their random variation. It was not found possible to fit to the data any *simple* equation which contained, in place of (D″), the total concentration of the dye, the concentration of its basic form or the concentration of its acidic form. Accordingly, we are forced to the conclusion that only the intermediate form of the dye enters, directly, into the reaction. This result, which was unexpected, is probably related to the relative stabilities of the semiquinones of the several forms of the dye.

The mechanism proposed here is based as much upon the reversible bleaching data (5) as it is upon the kinetics results. Therefore, the values of the rate constants of the individual reaction steps must be consistent with both sets of data. The mean life of the activated state, HG, was determined[13] from the reversible bleaching measurements to be equal to or less than 4×10^{-5} seconds. Combining this with the present value for k_5/k_4, we obtain

$$k_5 \lesssim 10^9 \text{ (liter/moles) per sec.}$$

In terms of the simple collision theory, the value for k_5 corresponds to a collision efficiency of about 1%. In other words, step 5 would require little or no heat of activation, and its rate would be practically independent of temperature.

(11) It is interesting to note that the preceding mechanism and the derived equation for the quantum yield are formally similar to those presented by Ghosh and Sen Gupta.[8] The chief differences are the nature of the activated chlorophyll molecule, the restriction of the reaction to the intermediate form of the dye, and the postulated final products. The latter differences lead to a limiting quantum yield of one-half in the present case and of unity in the earlier paper.

(12) We are indebted to Dr. B. Crawford, Jr., for pointing out that the function $(x_1 - x_2)/\ln x_1/x_2$ is known as the *logarithmic* mean and is commonly used in engineering problems.

(13) R. Livingston, *J. Phys. Chem.*, **45**, 1312 (1941).

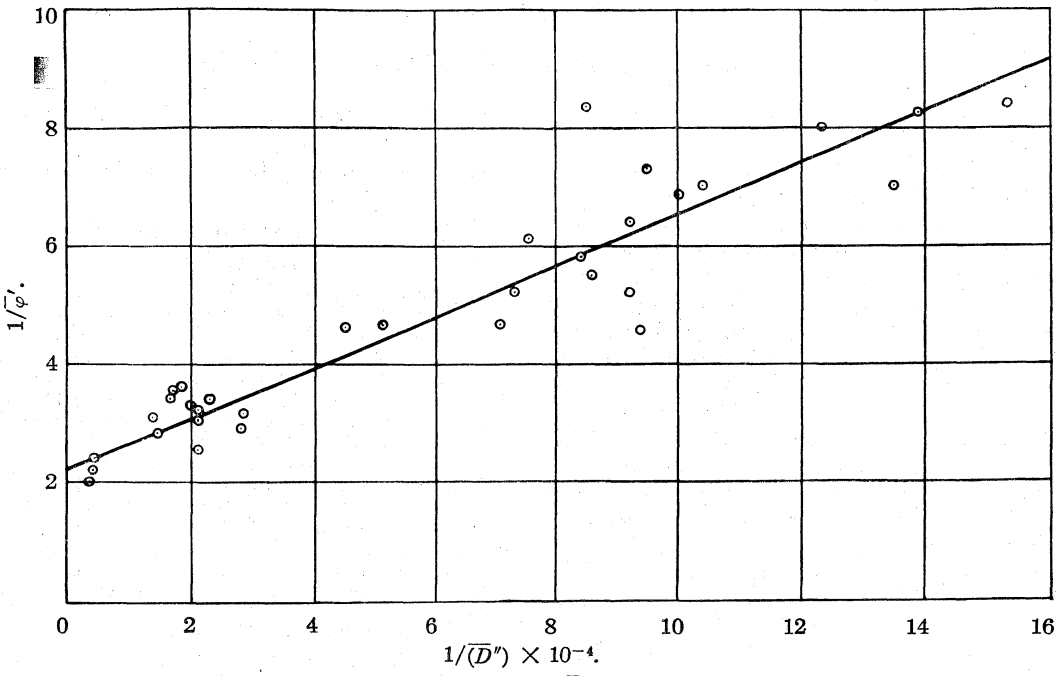


Fig. 2.—The reciprocal of the (corrected) average quantum yield, $\bar{\varphi}'$, plotted as a function of the reciprocal of the logarithmic mean, $\bar{D}''$, of the dye concentration.

The mean life of the complex, HGD, was not determined[9] at all precisely, but is approximately 1 second. If we identify HGD with the bleached form of chlorophyll in solutions containing methyl red and further assume[9] that its disappearance is due to a monomolecular reaction (step 6), we may conclude that $k_6 \simeq 1$ sec.$^{-1}$. The corresponding value of k_7 is apparently 10^2 (liter/mole) per second. Since this is smaller than the maximum value for a second order rate constant, it indicates that step 7 must require a considerable energy of activation. It is to be expected, therefore, that the reaction should exhibit a marked dependency upon temperature when the phenylhydrazine concentration is low, but not when it is high.

The simple form of equation (1) or (2) is a direct consequence of the use of the analytically determined concentration of the intermediate form of methyl red. An equation containing the stoichiometric concentration of methyl red would be of much more complex form. It would contain a function of the concentration of phenylhydrazine hydrochloride as well as of the free base.

The present case is the first chlorophyll-sensitized photoöxidation which has been studied quantitatively over a wide range of experimental conditions. It is, therefore, particularly gratifying that it can be represented by a relatively simple empirical relation. The available facts do not determine a mechanism uniquely, but they do constitute a definite step in that direction and suggest that further measurements of this type may be of real aid to our understanding of the "inner mechanism" of photosynthesis.

Summary

Methyl red can exist in three colored forms in methanol. The relative concentration of these forms depends upon the acidity of the solution. The absorption coefficients for each of these pure forms has been determined in the range λ3600 to 6000 Å.

In the chlorophyll-sensitized photoöxidation of phenylhydrazine, only the intermediate form of methyl red reacts.

The maximum quantum yield for the reaction is about 0.5.

The quantum yield, φ, is an empirical function of the stoichiometric concentration of phenylhydrazine, (Ph), and of the concentration of the intermediate form of methyl red, (D″)

$$\varphi = 0.46 \frac{10^2(\mathrm{Ph})}{1 + 10^2(\mathrm{Ph})} \times \frac{5 \times 10^4(\mathrm{D}'')}{1 + 5 \times 10^4(\mathrm{D}'')}$$

Over a fairly wide range, φ is independent of the light intensity and of the concentration of chlorophyll.

A relatively simple mechanism is proposed which is consistent with the preceding facts and with recently published results[9] on the reversible photobleaching of chlorophyll.

MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 12, 1947

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF UNION OIL COMPANY OF CALIFORNIA]

Photochemical Decomposition of *t*-Butyl Nitrite

BY CLARENCE S. COE AND THOMAS F. DOUMANI

The photochemical decomposition of *t*-butyl nitrite has been studied in the vapor phase using a quartz mercury vapor lamp as a source of ultraviolet radiation. Some of the experimental technique and methods of analysis employed in these laboratories for the study of the determination of the primary products from the thermal cracking of hydrocarbons have been applied to this photochemical decomposition. This study involves distinguishing between the initial and the secondary reaction products by determining the composition of the products formed when only small percentages of the compound studied are decomposed at relatively low pressures. The mass spectrometer pattern for the gaseous decomposition products free of undecomposed *t*-butyl nitrite was obtained by subtracting the mass number contributions of the latter compound from the total pattern of the decomposition products. To determine which decomposition products were present, the mass spectrometer patterns for a large number of possible compounds were examined. Chemical tests were made on the residue in the quartz flask after each experiment and, where possible, solid derivatives were prepared for identification.

The initial photochemical decomposition products are acetone and nitrosomethane. During the decomposition this latter compound is constantly removed from the gas phase forming colorless long needles of m. p. 122° in dimeric form on the surface of the quartz reaction flask. Nitrosomethane and its dimer are believed to be new compounds. The initial reaction in the photochemical decomposition of *t*-butyl nitrite appears to be as follows

$$(CH_3)_3CONO \longrightarrow (CH_3)_2CO + CH_3NO$$

Dimerization of nitrosomethane appears to occur rapidly

$$2CH_3NO \longrightarrow (CH_3NO)_2$$

The progress of this decomposition was followed by mass spectrometer analysis and manometrically by determining the total gas pressure in the irradiation quartz flask after various reaction times.

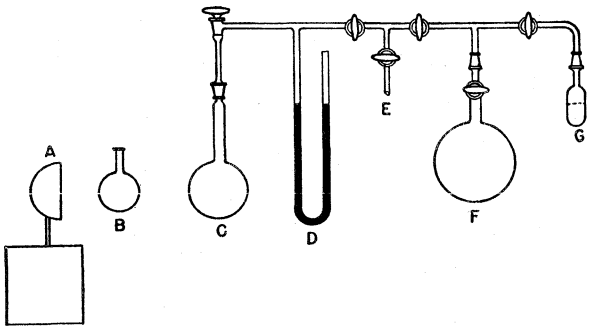


Fig. 1.—Diagram of apparatus.

Experimental

Materials Used

t-Butyl Nitrite.—Technical *t*-butanol was purified by fractional distillation followed by fractional crystallization. Five moles (370.6 grams) of *t*-butanol, m. p. 25.0–25.1°, was mixed with a solution of 5.5 moles (379.5 g.) of sodium nitrite dissolved in 1500 ml. of distilled water. Three moles (667 ml.) of 35% sulfuric acid was added during two hours to the bottom of the previous solution at 0° with stirring. The oil layer which was less dense than the aqueous layer was washed with water, aqueous sodium bicarbonate solution (5%), again with water, and finally dried with anhydrous sodium sulfate. The crude *t*-butyl nitrite (400 g.) was fractionated *in vacuo* in a packed column of about 10 theoretical plates. The composited fractions used in the irradiation studies had a b. p. of 34.0° (250 mm.), $n^{20}D$ 1.3687 and sp. gr. $^{20}_{4}$ 0.867_1.

Acetone.—J. T. Baker analyzed, C. P. was used.

Nitromethane.—The product from Commercial Solvents Corporation was fractionated, b. p. 101–102°, $n^{20}D$ 1.3821.

Nitrogen Dioxide and Nitrous Oxide.—These gases were obtained in cylinders from the Matheson Company in 98% purity.

Nitric Oxide.—The method of Johnson and Giauque[1] was used.

Irradiation

The apparatus (Fig. 1) used for the irradiation experiments was assembled in a dark room which could be maintained at 25 ± 1°. The radiation from a quartz mercury vapor lamp[2] (A) was passed through a quartz flask (B) containing distilled water and then into the quartz flask (C) of 350 ml. capacity filled with vapors of *t*-butyl nitrite. The quartz flask containing distilled water served to filter out infrared wave lengths and helped to focus the ultraviolet beam on the sample. The distance from "Uviarc" to focusing flask was 21.7 cm. and from the center of the latter to the center of the sample flask was 16.1 cm. The quartz flask (C) was connected to a mercury manometer (D) which was used to determine the total pressure therein. To introduce the *t*-butyl nitrite into the flask (C) the entire system was evacuated with a mercury diffusion pump through stopcock (E) in the presence of a few ml. of liquid *t*-butyl nitrite which was surrounded by liquid nitrogen in (G). The nitrite was then allowed to warm until the desired pressure was reached in the system. Gas samples were taken after varying irradiation times directly into evacuated 2-liter glass bulbs (F) which were covered with black tape to eliminate photochemical decomposition due to daylight. All samples were analyzed in a mass spectrometer within eight hours after collection.

In following the pressure change in the system during the photochemical decomposition the mercury manometer was replaced by a more sensitive combination mercury–oil manometer.

To prepare sufficient amounts of dimeric nitrosomethane for a determination of some of its properties the following procedure was found effective. About one milliliter of liquid *t*-butyl nitrite was condensed into the bottom of the

(1) H. L. Johnson and W. F. Giauque, THIS JOURNAL, **51**, 3195 (1929).

(2) "Uviarc," 360 watt, 6 inch (General Electric Company). The principal lines are reported to lie between 2345 and 5790 Å.

TABLE I[a]

PHOTOCHEMICAL DECOMPOSITION OF *t*-BUTYL NITRITE

Experiment	Reaction time, min.	Pressure, mm. Initial	Pressure, mm. Final	Analysis of gaseous reaction product, mole % t-C_4H_9ONO	$(CH_3)_2CO$	t-C_4H_9OH	CH_3NO_2, NO_2, NO, CH_3NO, etc.
P-9692	30	154.9	160.1	91.1	4.5	1.6	2.8
P-9693-2	5	159.7	160.3	96.4	1.0	0.2	2.4
P-9696-1	5	48.0	48.2	97.0	2.0	0.4	0.6
Q-2310-2	7.5	46.4	47.2	95.1	3.3	0.6	1.0
Q-2306-5	10	46.4	46.6	93.9	4.4	0.7	1.0
Q-2312-6	20	46.5	48.6	88.0	9.0	0.0	3.0
Q-2328-3	40	46.4	48.4	77.0	17.0	1.0	5.0
Q-2328-5	60	46.6	48.8	74.0	25.0	1.0	0.0
Q-2329-2	120	46.9	50.1	50.0	50.0	3.0	4.0
Q-2333-2	290	34.4	39.7	5.5	71.7	7.3	15.5
Q-2333-3	386	35.0	48.0	1.8	57.9	7.4	32.9

[a] Detailed data for the spectrometer analyses may be obtained from the authors on request.

evacuated quartz flask. The reaction vessel was then irradiated with the "Uviarc," shielding the liquid from direct radiation. The liquid *t*-butyl nitrite served as a reservoir for the production of the gaseous nitrite. The crystals were deposited in much larger quantities in the quartz flask than when the homogeneous nitrite vapors were irradiated.

Results

Data on the photochemical decomposition of *t*-butyl nitrite vapor at various pressures and irradiation times are given in Table I. A plot showing the decrease in the *t*-butyl nitrite and the increase in the acetone percentages with time is given in Fig. 2.

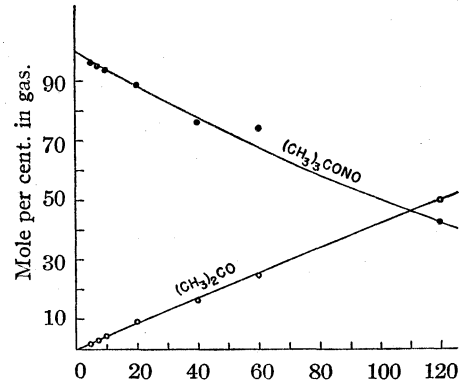


Fig. 2.—Effect of irradiation time.

A pressure–time curve for the photochemical decomposition of *t*-butyl nitrite is shown in Fig. 3. This first irradiation period of about 200 minutes is characterized by the production of predominantly initial decomposition products. Secondary decomposition products are principally formed during the second reaction period from 200 to about 320 minutes. The practically constant pressure state is finally reached after about 400 minutes when compounds substantially stable to the ultraviolet light are present. For this experiment small crystals of nitrosomethane dimer were noticeable with the naked eye after about 120 minutes of irradiation. These crystals grew to well-defined needles until after about 290 minutes they commenced to be transformed to an amorphous deposit of trimeric formaldoxime. Continued irradiation caused a practically complete conversion of the dimeric nitrosomethane to the latter compound after about 420 minutes. A photograph of some crystals of nitrosomethane dimer in the quartz irradiation flask is shown in Fig. 4.

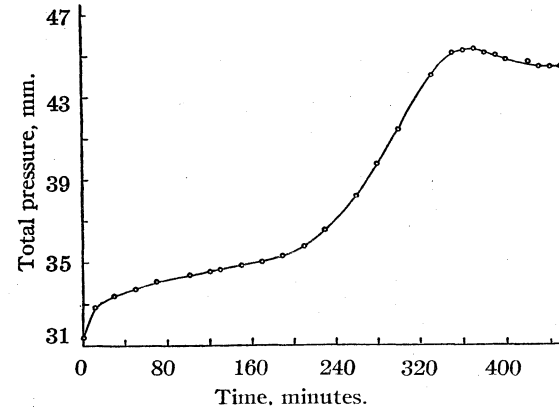


Fig. 3.—Total pressure–time plot.

The irradiated vapors of *t*-butyl nitrite in the quartz flask was shaken with an aqueous solution of 2,4-dinitrophenylhydrazine hydrochloride forming the hydrazone of m. p. 125.6° (cor.). Mixed m. p. with pure acetone 2,4-dinitrophenylhydrazone was the same.

Anal. Calcd. for $C_9H_{10}N_4O_4$; C, 45.38; H, 4.23. Found: C, 45.41; H, 4.50.

Some Properties of Dimeric Nitrosomethane.—Several grams of crystals was collected from a series of the irradiation experiments and crystallized from ethanol as colorless needles, m. p. 122.0–122.2° (cor.). This compound is very soluble in ethanol, moderately soluble in water or acetone, slightly soluble in ethyl ether, benzene or carbon tetrachloride, and insoluble in pentane.

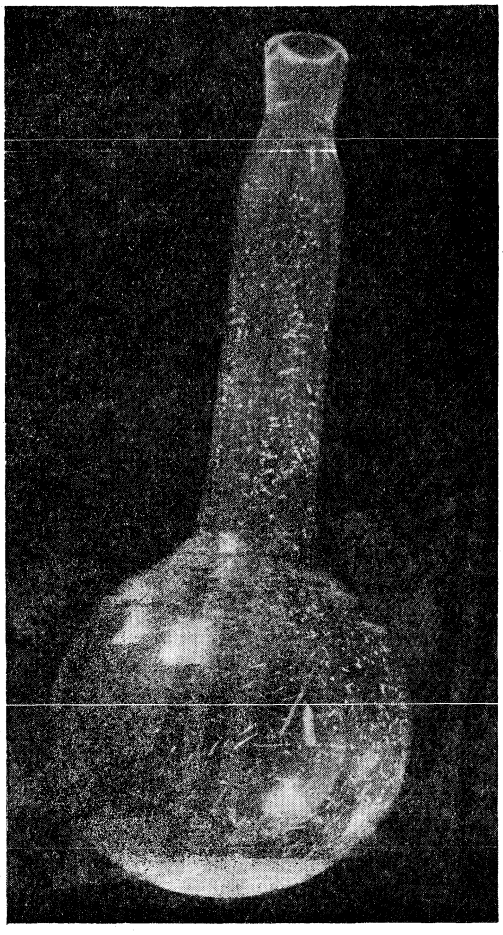


Fig. 4.—Crystals of dimeric nitrosomethane in quartz reaction flask.

Anal.[3] Calcd. for $(CH_3NO)_2$: C, 26.66; H, 6.71; N, 31.10; mol. weight, 90.1. Found: C, 26.94; H, 7.01; N, 31.15; mol. weight, 93.4 (benzophenone as solvent).

The mass spectrometer numbers for this dimer were obtained by admitting vapors from the finely crushed powder at room temperature into the head of the mass spectrometer at low pressure. The mass numbers 90, 75, 60, 45, 30, and 15 were obtained.

When nitrosomethane dimer is heated above its melting point a blue color is noticeable, especially in the vapor. Likewise, when this dimer is heated in organic solvents, such as toluene, a blue color is produced. The colorless solution is restored by cooling. This reversible color change may be represented by the equation

$$(CH_3NO)_2 \rightleftharpoons 2CH_3NO$$

Colorless Blue

Prolonged heating of dimeric nitrosomethane above its melting point converts it to trimeric formaldoxime, insoluble in ethanol

$$3(CH_3NO)_2 \longrightarrow 2(CH_2NOH)_3$$

Nitrosomethane dimer forms a blue color when tested with diphenylamine in concentrated sulfuric acid.

Discussion

Both the experimental data and the proposed mechanism for the photochemical decomposition of *t*-butyl nitrite of Thompson and Dainton[4] are at variance with the results of the present investigation. Their mechanism involving the formation of hyponitrous acid does not explain the formation of nitrosomethane or acetone. None of the products propylene, formaldehyde, ethane or ethylene required by their mechanism could be found in the gaseous decomposition products.

The complete absence of ethane in the decomposition products seems to indicate that the nitrosomethane is probably formed intramolecularly. If the nitrosomethane were formed by the combination of free methyl radicals with nitric oxide the formation of at least some ethane might be expected.

The mass spectrometer pattern for nitrosomethane dimer serves as further evidence for its constitution. Loss of a methyl radical of mass 15 from dimeric nitrosomethane of mass 90 leaves a mass of 75. Removal of a second methyl radical leaves 60, whereas depolymerization of the dimer produces two molecules of monomeric nitrosomethane of molecular weight 45. Removal of a methyl radical from the monomer produces the 30 mass.

Previous workers[5] have postulated the existence of nitrosomethane in explaining the inhibition of some chain reactions by nitric oxide. Isolation of this compound serves to substantiate some of these mechanisms.

The development of alternative methods for the synthesis of nitrosomethane dimer is being considered as well as its isomerization to trimeric formaldoxime. The photochemical decomposition of some other organic nitrites is being checked to determine whether nitroso compounds are involved.

Acknowledgment.—We wish to thank the management of the Union Oil Company of California for permission to publish this paper. We are especially grateful to our analytical department for their generous assistance.

Summary

1. The photochemical decomposition of *t*-butyl nitrite has been studied in the vapor phase at 25° and at pressures of about 50 mm. using a quartz mercury vapor lamp.

(3) Low N values are obtained by the usual micro-Dumas or micro-Kjeldahl methods. Friederich's micro-Kjeldahl method with hydriodic acid was used (Pregl-Grant, "Quantitative Organic Microanalysis," The Blakiston Co., Philadelphia, Pa., 1946, p. 82).

(4) H. W. Thompson and F. S. Dainton, *Trans. Faraday Soc.*, **33**, 1551 (1937).

(5) H. A. Taylor and H. Bender, *J. Chem. Phys.*, **9**, 761 (1941).

2. Acetone and nitrosomethane were found to be initial products of the decomposition. The latter new compound was identified as the hitherto unknown crystalline dimer.

3 Some of the properties of nitrosomethane and its dimer have been determined.

WILMINGTON, CALIFORNIA
RECEIVED SEPTEMBER 26, 1947

[CONTRIBUTION NO. 66 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. IV. Effects of Temperature and Solvents on Monomer Reactivity Ratios

BY FREDERICK M. LEWIS, CHEVES WALLING, WILLIAM CUMMINGS,[1] EMORENE R. BRIGGS[2] AND FRANK R. MAYO

Previous papers from this Laboratory and elsewhere[3] have shown that the behavior of monomers in free radical type copolymerizations may be described accurately by the copolymerization equation[3a,4,5]

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]\,r_1[M_1] + [M_2]}{[M_2]\,r_2[M_2] + [M_1]} \qquad (1)$$

where $[M_1]$ and $[M_2]$ are concentrations of unreacted monomers, r_1 is the ratio of the rate constants for the reaction of an M_1-type radical with M_1 and M_2, respectively, and r_2 is the ratio for reaction of an M_2-type radical with M_2 and M_1, respectively. The quantities r_1 and r_2 have been designated *monomer reactivity ratios*, and it should be noted[3b] that a comparison of the *reciprocals* of a series of monomer reactivity ratios for a particular radical with a number of monomers yields the *relative reactivities* of the monomers toward that radical. If such series for all radicals were the same, *i. e.*, if, in general, $r_1r_2 = 1$, Equation (1) would reduce to the simpler form earlier proposed by Wall.[6] However, a striking feature of free radical copolymerizations is that, in many pairs, each monomer prefers to react with the opposite type radical. This "alternating effect," which can be discussed qualitatively in terms of r_1r_2 products (r_1r_2 being zero for complete alternation), appears to be an additional effect superimposed upon a fundamental order of monomer reactivity,[3b] and Price[7] has suggested, on the basis of the data available at the time, that it arises from polar interaction between radical and monomer. The present series of nine papers increases five-fold the number of monomer pairs for which monomer reactivity ratios are available. The results give partial support to Price's suggestion and permit a much more detailed discussion of copolymerization phenomena than has hitherto been possible.

The present paper discusses refinements in techniques and in the treatment of data which have been developed in this Laboratory during the past three years and presents measurements of the temperature coefficients of monomer reactivity ratios for five monomer pairs. It also reports more precise measurements of the effects of solvents on the monomer reactivity ratios for styrene and methyl methacrylate.

The next three papers, V–VII, describe new experiments on twenty-nine monomer pairs. In VIII, all of these data are reviewed and the theoretical implications discussed in terms of monomer activity and polarity series. Copolymerization IX presents and discusses experiments on the relative reactivities in copolymerization of *cis* and *trans* isomers. The last three papers, X–XII, are a study of the effect of nuclear substitution on the reactivity of styrene in copolymerization. Here, measurements on thirty-six systems throw further light on the nature of the "alternating effect" in copolymerization.

Experimental

Materials.—Diethyl maleate and diethyl fumarate were Eastman Kodak Co. materials, melting points −12 to −11 and 0 to 1°, respectively. They were used without further purification. Styrene, methyl methacrylate and methyl acrylate were commercial materials, fractionally distilled and stored in the ice-box until used. *p*-Chlorostyrene was prepared by the decarboxylation of *p*-chlorocinnamic acid. Its preparation and physical properties are described elsewhere.[8]

Polymerization Technique.—Polymerizations were carried out in duplicate or triplicate on 1:4 and 4:1 molar ratios of monomers in sealed tubes in absence of air, essentially as described in previous papers in this series.[3a] At 60°, 0.1 mole % benzoyl peroxide was used as catalyst, at 131°, no catalyst except for the styrene–methyl methacrylate system where 0.1% acetone peroxide was added. All polymers were soluble in benzene and were isolated by the frozen benzene technique.[9] Results of all experiments reported here are listed in Tables I and II.

Experimental Errors.—Extensive experience in this laboratory has shown that, although any set of experiments may give a very small intersection in the graphical

(1) Present address, Department of Chemistry, University of Minnesota, Minneapolis, Minn.

(2) Present address, R. F. D. 2, Guilford, Conn.

(3) (a) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944); (b) Lewis, Mayo and Hulse, *ibid.*, **67**, 1701 (1945); (c) Bartlett and Nozaki, *ibid.*, **68**, 1495 (1946); (d) Alfrey, Goldberg and Hohenstein, *ibid.*, 2464; (e) Fordyce and Chapin, *ibid.*, **69**, 581 (1947). Further references will be found in these papers.

(4) (a) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944); (b) Wall, THIS JOURNAL, **66**, 2050 (1944).

(5) Hereafter in this series the new nomenclature for copolymerization constants, *cf.* Alfrey, Mayo and Wall, *J. Polymer Sci.*, **1**, 581 (1946), is used. Thus, M_1, M_2, r_1 and r_2 correspond to S, M σ and μ in previous papers.

(6) Wall, *ibid.*, **63**, 1862 (1941).

(7) Price, *J. Polymer Sci.*, **1**, 83 (1946).

(8) Walling and Wolfstirn, THIS JOURNAL, **69**, 852 (1947).

(9) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

TABLE I

COPOLYMERIZATION EXPERIMENTS AT TWO TEMPERATURES

$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_1]$[a]	$[M_2]$[a]	Time, hr.	% C in polymer		
Styrene (M_1)–Methyl Methacrylate (M_2) at 60°[b]							
63.21	16.03	58.80	14.43	5.0	83.66	83.77	83.94
39.77	39.67	36.24	36.27	5.0	76.52	76.61	
16.04	63.42	14.46	59.41	2.68	69.13	69.11	
63.24	15.81	58.76	14.24	89[c]	83.98	84.00	
39.62	39.37	35.88	35.78	89[c]	76.70	76.53	
15.75	63.97	12.83	56.39	68.5[c]	68.90	69.07	
Same at 131°							
63.0	16.19	46.3[d]	10.73[d]	1.0	84.45	84.34	
39.50	39.64	29.56	29.99	1.0	76.59	76.42	
15.95	6.45	12.38	54.4	0.83	68.39	68.41	
Styrene (M_1)–Methyl Acrylate (M_2) at 60°							
17.67	78.65	14.28	73.30	2.8	71.55	71.49	71.59
19.24	80.88	15.66	75.25	3.7	71.55	71.67	71.68
19.15	80.98	15.37	74.98	3.7	71.59	71.61	71.73
79.85	20.21	74.12	18.68	3.7	85.68	85.63	85.69
79.78	20.18	74.72	18.85	3.7	85.79	85.72	85.62
80.28	21.03	75.62	19.74	3.7	85.48	85.39	85.46
Same at 131°							
19.65	80.92	16.38	75.28	.67	70.69	70.77	70.84
19.64	80.85	16.13	74.86	.67	70.94	70.93	70.88
22.32	81.20	18.42	75.00	.67	71.67	71.68	71.65
79.80	20.17	68.10	17.24	.67	86.03	85.99	86.04
80.30	20.00	68.80	17.17	.67	86.09	86.18	86.11
78.80	20.81	67.60	17.94	.67	85.92	85.87	85.90
Styrene (M_1)–Diethyl Maleate (M_2) at 60°							
63.51	15.68	37.79[e]	14.54	36	89.81	89.71	
64.05	15.62	38.77	14.48	36	89.63	89.76	
16.13	62.77	7.985	59.12	100	76.75	76.74	
16.05	62.69	8.030	59.31	100	76.60	76.57	
Same at 131°							
63.88	15.87	6.056	10.59	66	87.50	87.42	
63.53	15.95	12.31	12.45	18	88.62	88.47	
65.68	15.85	11.94	11.89	18	88.22	88.35	
Styrene (M_1)–Diethyl Fumarate (M_2) at 60°							
15.93	63.48	2.979	49.90	62.6	69.27	69.03	
15.72	63.61	3.191	50.13	62.6	68.89	68.96	
15.88	63.28	3.096	49.45	62.6	69.00	68.82	
64.99	16.94	4.936	9.83	23	76.42	76.79	
63.83	16.03	4.790	9.34	23	77.22	77.39	
Same at 131°							
16.12	64.22	3.307	45.22	219.3	66.30	66.43	
16.61	63.81	3.574	44.81	219.3	66.50	66.59	
63.80	16.34	53.13	12.16	2.0	78.02	78.07	
63.85	16.10	52.33	11.76	2.0	78.20	78.30	
Styrene (M_1)–*p*-Chlorostyrene (M_2) at 60°							
9.615	32.27	6.825	22.10	14	21.18[f]	21.18	
40.09	10.06	31.33	7.32	14	7.48[f]	7.51	
39.57	10.96	29.97	7.77	12	7.87[f]	7.78	
10.14	41.61	7.555	30.47	12	21.70[f]	21.78	
Same at 131°							
39.70	10.34	24.73	5.86	1.75	7.21[f]	7.41	
10.07	39.90	5.78	21.80	1.25	21.66[f]	21.71	
10.09	39.55	6.34	23.90	1.25	21.63[f]	21.74	
40.00	10.15	19.29	4.30	1.50	6.90[f]	7.08	
10.21	39.90	3.80	13.37	1.0	21.56[f]	21.68	

[a] Millimoles of unreacted monomers; zero subscripts indicate initial quantities. [b] Data taken from Mayo and Lewis, ref. 3, experiments 4B, 4C, 4D, 5A, 5B, 5C listed in that order but recalculated using empirical analyses on blanks (4A and 4E) for calculating polymer composition (see text). [c] Calculated using 92.24 as % C in styrene (see text). [d] Calculated using same blanks as 60° experiments. [e] Thermal polymerization, no catalyst added. [f] Per cent. Cl in polymer.

TABLE II

EFFECT OF SOLVENTS ON MONOMER REACTIVITY RATIOS OF STYRENE (M_1) AND METHYL METHACRYLATE (M_2) AT 60°

$[M_1]_0$	$[M_2]_0$	$[M_1]$	$[M_2]$	Time, hr.	% C in polymer		
Benzene (9 vol.)[a]							
63.7	16.01	51.7	11.91	72	84.40	84.39	84.10
39.8	40.02	29.9	30.6	72	77.11	76.75	76.96
16.03	63.79	8.37	43.79	72	69.13	69.34	69.20
Acetonitrile (8 vol.)[a]							
63.06	17.07	55.74	14.27	72	83.74	83.43	
46.12	39.84	32.87	32.77	72	76.61	76.69	
16.13	71.70	9.55	52.47	72	68.49	68.45	
Methanol (2 vol.)[a]							
63.44	19.07	55.98	16.13	24	83.30	83.43	
40.60	39.54	32.33	32.12	24	77.31	77.29	
16.03	66.11	7.09	42.45	24	69.14	69.05	

[a] Per volume total monomers.

solution of the copolymerization equation, these intersections shift appreciably from set to set. In early work many of these shifts proved to be due to inadequate techniques of polymer isolation. With more refined methods, they now appear to be usually the result of small systematic errors in polymer analysis. The temperature coefficients of monomer reactivity ratios discussed in this paper represent, at best, small differences between experimentally measured quantities. Accordingly, the highest attainable accuracy in determination of monomer reactivity ratios is important. Further, since the desired quantities are *differences*, the presence of a small systematic error (so long as it is the same for the experiments at both temperatures) causes no trouble.

In order to "freeze" this error as nearly as possible, each set of experiments at two temperatures reported here was carried out and worked up by the same operator at the same time and using the same techniques. The relative experimental error at each temperature was then calculated as the standard deviation of duplicate experiments, and the errors in heats and entropies of activation were determined by the usual formulas for propagation of error. In the most fortunate cases, for example, styrene–methyl acrylate, the relative experimental error in monomer reactivity ratios determined in this way is considerably smaller than the probable *absolute* error. However, for the reasons outlined above, we consider it the proper one to use in the subsequent calculations. The styrene–methyl methacrylate system was studied before this procedure was adopted. The experimental error in this case was taken as that arising from a 0.1% error in carbon analysis (see below). An idea of the agreement obtained between experiments and the magnitude of the change in monomer reactivity ratios arising from a 70° change in temperature may be gotten from Fig. 1 in which the graphical solutions of the copolymerization equation for the styrene–methyl acrylate system are illustrated.

In the case of the styrene–diethyl maleate system, the monomer reactivity ratio for the maleate-type radical is indistinguishable from zero. Accordingly, only 4:1 styrene–maleate experiments were carried out at 131°, and the heats and entropies of activation differences for the reaction of the styrene type radical calculated from the shift of the intersection of the high styrene experiments with the zero axis.

It is of course important to have an idea, as well, of the magnitude of the *absolute* experimental error in the measurement of monomer reactivity ratios. Since, with suitable technique in polymer isolation, this error arises chiefly from errors in polymer analysis, we have adopted the following technique for its estimation, based upon the observation that blank carbon analyses run in

our analytical laboratory on known samples deviate from calculated results by over 0.2% less than one time in five. For a given monomer pair two representative experiments, one at 1:4 and the other at 4:1 monomer ratios are chosen and $[M_1]$ and $[M_2]$ recalculated assuming +0.2% and −0.2% errors in analysis. The results are then replotted on a r_1 *vs.* r_2 plot, yielding a parallelogram about the former intersection. This parallelogram is now shifted so that its center coincides with the best value of r_1 and r_2 determined by the whole set of experiments carried out on the given monomer pair, and the absolute experimental error is taken as the range of values of r_1 and r_2 lying within the parallelogram. The best justification for the method, aside from the arguments just outlined, is that with sufficient care sets of experiments can generally be obtained in which all of the lines corresponding to the individual experiments pass through the parallelogram. In the case that they do not, and it does not appear feasible to run additional polymerizations, the standard deviation is taken as the absolute experimental error. However, this difficulty has not arisen with any of the monomer pairs reported here. In the cases where $[M_1]$ and $[M_2]$ are determined by nitrogen or chlorine analysis, calculations are based upon a 0.1% experimental error. In the case of the system styrene–methyl methacrylate, blanks of pure polymeric styrene and methyl methacrylate were analyzed simultaneously with the copolymers and the empirical carbon contents used in calculating copolymer compositions. Although the experiments are those described in the first paper of this series,[3a] this changes the values of the momomer reactivity ratios slightly from the values previously reported.[10] For styrene–diethyl maleate, polymer compositions lay very close to pure polystyrene. Accordingly, a sample of pure polystyrene to which diethyl maleate monomer had been added was worked up together with the copolymers and analyzed. The result (92.24% C) was used in calculations and served as a check both on the isolation procedure and the accuracy of carbon analysis (calcd. 92.26%). In view of the employment of these precautions, the use of 0.1% error in carbon seemed justified in calculating the experimental errors in this system.

Results and Discussion

Measurements at Two Temperatures.—Previous measurements of monomer reactivity ratios in copolymerizations have been limited to a single temperature. Measurement at two temperatures are of obvious practical interest. Further, since a monomer reactivity ratio represents the ratio of two rate constants which may be expressed in the form

$$r_1 = e^{\frac{\Delta S_{11}^{\ddagger} - \Delta S_{12}^{\ddagger}}{R} - \frac{\Delta H_{11}^{\ddagger} - \Delta H_{12}^{\ddagger}}{RT}} \qquad (2)$$

where $\Delta S_{11}^{\ddagger}$, $\Delta H_{11}^{\ddagger}$, $\Delta S_{12}^{\ddagger}$, and $\Delta H_{12}^{\ddagger}$ are, respectively, the entropies and heats of activation for the reaction of M_1 type radical with M_1 and M_2, measurement of r_1 at two temperatures permits the calculation of the differences in the heats and entropies of activation for the two reactions of the radical. These differences, for the monomer pairs of Table I, are listed in Table III. Since $(\Delta S_{11}^{\ddagger} - \Delta S_{12}^{\ddagger})/R = \ln (P_{11}Z_{11}/P_{12}Z_{12})$ in the Arrhenius treatment, and since this ratio perhaps provides a simpler way of visualizing the magnitude of a "steric" effect, it has been calculated as well, and is included in Table III.

(10) Although blanks were run indicating slightly low (0.1–0.3%) carbon analyses, the original calculations were based on theoretical carbon analyses. We have since frequently based calculations on actual instead of theoretical analyses and this procedure is now extended to our earlier work; *cf.* Nozaki, ref. 11.

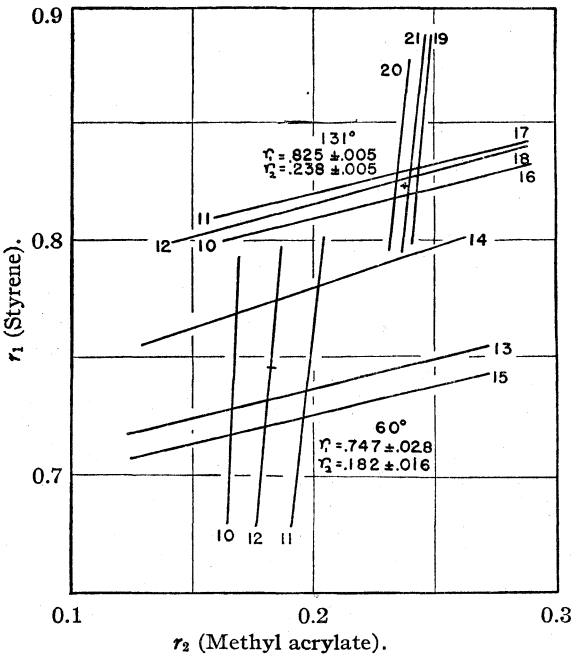


Fig. 1.—Copolymerization of styrene and methyl acrylate at 60° and 131°. Numbers of lines correspond to order of experiments in Table I.

Two conclusions may be safely drawn from the data of Table III. The first is that, despite the care with which the experiments were carried out, the resulting uncertainties in heat and entropy of activation differences are still quite large. The second is that, for most of the pairs, entropy of activation differences do not differ significantly from zero, and the major source of the differences in reactivity of monomers in polymerization lies in heats of activation. Accordingly, the practice of discussing these differences as due to resonance stabilization of complexes, polar interaction, etc., is in general justified. The only case where the entropy difference clearly differs from zero is that of the reaction of the fumarate type radical with styrene and diethyl fumarate. Although the reason for the difference, corresponding to a threefold difference in PZ factors, cannot be stated unequivocally, it lies in the direction which would be expected if the second carboethoxy group of diethyl fumarate offered steric hindrance toward the attack of the radical on the double bond. If this were the case, a similar difference should be anticipated for the styrene radical in the same copolymerization and in the system styrene–diethyl maleate. Although in both cases the entropy difference does lie in the right direction, it is smaller and, in the first, within experimental error of zero.

Another result of these measurements is that in general the temperature coefficients of the monomer reactivity ratios are rather small. This

TABLE III

HEAT AND ENTROPY OF ACTIVATION DIFFERENCES IN THE COPOLYMERIZATION OF SOME MONOMER PAIRS

Radical type[a]	r_1 60°	r_1 131°	$\pm\pm\Delta H_{11} - \Delta H_{12}$	$\pm\pm\Delta S_{11} - \Delta S_{12}$	$P_{11}Z_{11}/P_{12}Z_{12}$
Styrene	0.520 ± 0.026	0.590 ± 0.026	480 ± 250	0.12 ± 0.68	1.06 ± 0.30
Methyl methacrylate	.460 ± .026	.536 ± .026	580 ± 280	.19 ± .76	1.10 ± .34
Styrene	.747 ± .028	.825 ± .005	380 ± 140	.54 ± .36	1.31 ± .16
Methyl acrylate	.182 ± .016	.238 ± .005	1020 ± 340	.66 ± .86	1.39 ± .49
Styrene	6.52 ± .05	5.48 ± .56	−660 ± 480	1.87 ± 1.36	2.55 ± 1.26
Diethyl maleate	< .01	.....	.....	.....	.....
Styrene	.301 ± .024	.400 ± .014	1070 ± 320	.82 ± .82	1.50 ± .50
Diethyl fumarate	.0697 ± .0041	.0905 ± .0008	990 ± 290	−2.35 ± .73	0.31 ± .14
Styrene	.742 ± .030	.816 ± .015	360 ± 170	.48 ± .43	1.27 ± .24
p-Chlorostyrene	1.032 ± .030	1.042 ± .015	35 ± 120	.40 ± .32	1.22 ± .18

[a] Each monomer of the pair being considered as M_1 in turn.

is, indeed, a necessary consequence from the observed small differences in entropies of activation, and may be generalized to the statement that the composition of the copolymer obtained from systems in which neither monomer reactivity ratio differs greatly from unity will be quite insensitive to temperature. This conclusion is of some practical importance.

Absolute Values of Monomer Reactivity Ratios.—Using the procedure described in the Experimental Part, absolute experimental errors for monomer reactivity ratios for the monomer pairs studied here have been calculated, and results are summarized in Table IV, together with the results of other workers on the same systems. The agreement between work in this Laboratory and elsewhere will be seen to be quite satisfactory.

TABLE IV

MONOMER REACTIVITY RATIOS AT 60° WITH CALCULATED EXPERIMENTAL ERRORS

Radical type	Error assumed, %	Monomer reactivity ratios This paper	Other workers
Styrene	0.2 C	0.520 ± 0.026	(60°) 0.65 ± 0.08[a]
Methyl methacrylate	.2 C	.460 ± .026	(60°) .51 ± .10[a]
Styrene	.2 C	.75 ± .07	(70°) .75 (±0.1)[b]
Methyl acrylate	.2 C	.18 ± .02	(70°) .2 (±0.05)[b]
Styrene	.1 C	6.52 ± .50	(70°) 5 (±1.5)[b]
Diethyl maleate	.1 C	.005 ± .01	(70°) 0 (±0.1)[b]
Styrene	.2 C	.30 ± .02	...
Diethyl fumarate	.2 C	.070 ± .007	...
Styrene	.1 Cl	.74 ± .03	[c]
p-Chlorostyrene	.1 Cl	1.025 ± .05	[c]

[a] Nozaki, *J. Polymer Sci.*, **1**, 455 (1946). Results of two sets of experiments have been averaged. [b] Alfrey, Merz and Mark, *ibid.*, p. 37. The experimental errors have been estimated by plotting their data on a r_1 *vs.* r_2 plot and by taking the axes of the smallest ellipses through which all the lines corresponding to their experiments would pass. [c] Marvel and Schertz, THIS JOURNAL, 65, 2054 (1943), prepared and analyzed samples of this copolymer but monomer compositions were not varied sufficiently for a calculation of monomer reactivity ratios.

Effect of Solvents.—Copolymerizations of styrene with methyl methacrylate in benzene and acetonitrile (solvents of low and high dielectric constant, respectively) and in methanol (a solvent from which the polymer precipitates) are listed in Table II and the graphical solutions illustrated in Fig. 2. Since experiments were carried out using better techniques than in the first paper, intersections are smaller and render more certain the conclusion[3a,11] that solvents have no detectable effect on monomer reactivity ratios. This conclusion is also in agreement with the results of other workers who have found identical monomer reactivity ratios for the systems styrene–methyl methacrylate[12] and styrene–acrylonitrile[3e] studied under homogeneous conditions and in emulsion.

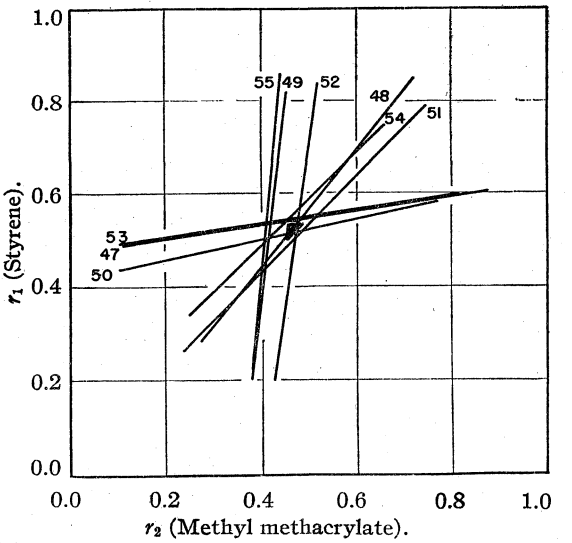


Fig. 2.—Constancy of monomer reactivity ratios for styrene–methyl methacrylate in various solvents at 60°: 47–49, benzene; 50–52 acetonitrile; 53–55, methanol. Numbers of line correspond to order of experiments in Table II. Black triangle represents intersection in absence of solvent.

Acknowledgment.—The inception of work on copolymerization in these laboratories is largely due to the early decision by Dr. Robert T.

(11) Nozaki, *J. Polymer Sci.*, **1**, 455 (1946).
(12) Smith, THIS JOURNAL, **68**, 2069 (1946).

Armstrong that a study of copolymerization would be one of the best approaches to a fundamental understanding of polymerization as a whole, a decision which we feel has been amply justified. We are also indebted to Dr. Oscar W. Lundstedt who was in charge of analytical work while most of the work in this series of papers was in progress. The consistency of analytical results discussed in this paper is largely the result of his efforts. Finally, we wish to acknowledge the considerable contributions of Mrs. Charles J. Pennino and Miss Lucille Librizzi, who have carried out much of the actual experimental work described in this series.

Summary

1. By carrying out copolymerizations at 60 and 131°, heat and entropy of activation differences for the reaction of each radical with the two monomers have been determined for the systems styrene–methyl methacrylate, styrene–methyl acrylate, styrene–diethyl maleate, styrene–diethyl fumarate and styrene–*p*-chlorostyrene.

2. In every case the difference in reactivity of the two monomers is found to be due, primarily, to differences in heat of activation. Only in the reaction of the diethyl fumarate radical with styrene does the difference in entropies of activation clearly differ from zero by more than experimental error.

3. Further data are presented showing that solvents (benzene, acetonitrile or methanol) are without effect on the monomer reactivity ratios of the system styrene–methyl methacrylate.

PASSAIC, NEW JERSEY RECEIVED JULY 17, 1947

[CONTRIBUTION NO. 67 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. V.[1] Some Copolymerizations of Vinyl Acetate

BY FRANK R. MAYO, CHEVES WALLING, FREDERICK M. LEWIS AND W. F. HULSE[2]

This paper presents experiments on the copolymerization of vinyl acetate with eight representative monomers. The double bond of vinyl acetate proves to be one of the least reactive of any common monomers toward free radical attack.

Experimental

Materials.—Vinyl bromide was prepared from ethylene bromide by the action of alcoholic sodium hydroxide. After washing with water and drying with potassium carbonate, the fraction used boiled at 15.5–16.0° at 761 mm. Vinyl chloride, obtained from the Dow Chemical Co., was used without purification. The other monomers were commercial materials fractionally distilled before use and stored in a refrigerator.

Procedure.—With the exceptions noted below, reaction mixtures were prepared as described previously[1] and products were isolated by the frozen benzene technique.[3] In the trichloroethylene experiments (5.00 g. of total monomers and 6.1 mg. of benzoyl peroxide) air was displaced from the reaction tubes by flushing with nitrogen and the polymers obtained by distilling off the monomers and heating the residue for sixteen hours at 90–100° and 2 mm. pressure. The acrylonitrile runs were carried out in the presence of 5 cc. of acetonitrile. The low nitrile runs remained homogeneous. These polymers were precipitated twice from acetone solution with petroleum ether and were then pressed out into thin sheets and dried for twenty hours at 60° and 1 mm. pressure. The high acrylonitrile runs gave a very fine suspension of polymer which at first gave no indications of coagulating or settling. As soon as these indications appeared, heating was stopped. The mixtures were diluted with benzene and petroleum ether; the polymer was collected on a filter as a white powder, washed with the latter solvent and dried for twenty hours at 60° and 1 mm. pressure.

The vinyl halides were measured out approximately by volume; their exact weights were determined by difference from the weights of the total contents of the reaction tubes. Copolymers containing large proportions of vinyl halide were insoluble in the reaction mixture (except when chlorobenzene was used as solvent) and in benzene. The excess vinyl halide was allowed to escape and the polymers were precipitated twice from chloroform (bromide) or a chloroform–acetone mixture (chloride) and petroleum ether. The chloride polymers were broken up and heated for about twenty-four hours at 60° and 1 mm. pressure. Solvent was removed from the bromide polymers by twenty-four hours of evacuation at 0° and 1 mm. pressure. They were finally warmed cautiously for a few minutes in warm water. Longer or stronger heating led to very rapid discoloration.

Analyses for acetic acid[4] were carried out by determining hydrolyzable acetoxy groups as acetic acid. The polymer sample (0.3–0.8 g.) was weighed into a flask, dissolved in 30 ml. of benzene, and treated for forty-eight hours at room temperature with 50 ml. of 0.5 *N* alcoholic sodium hydroxide. Benzene and alcohol were then removed by steam distillation, adjusting heat and steam input to maintain about the same volume of solution. The mixture was next acidified with 15 ml. of phosphoric acid and 500 ml. of steam distillate collected. The steam distillate was gently aerated for twelve minutes to remove carbon dioxide and titrated to phenolphthalein end-point using decinormal sodium hydroxide. A blank correction (~0.3 ml.) was applied and the results calculated as per cent. acetic acid in the original polymer sample.

Data on experiments are summarized in Table I. In the copolymerization with vinyl ethyl ether, the monomer reactivity ratio for the ether was assumed to be zero and the vinyl acetate monomer reactivity ratio calculated from two duplicate experiments.

Discussion

Monomer reactivity ratios obtained from the data of Table I are summarized in Table II. Since data on the eight systems were gathered at scattered times over four years, during which analytical precision has varied, the standard deviation

(1) For the preceding paper in this series, see Lewis, Walling, Cummings, Briggs and Mayo, THIS JOURNAL, **70**, 1519 (1948).

(2) Present address, Department of Geology, Bureau of Mineral Research, Rutgers University, New Brunswick, N. J.

(3) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

(4) The authors are indebted to Dr. Ellen Bevilacqua for the development of the analytical method described, and also for most of the analyses reported here.

TABLE I

PEROXIDE-CATALYZED POLYMERIZATIONS OF VINYL ACETATE (M_2) AT 60°

$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_1]$[a]	$[M_2]$[a]	Reaction time, hr.	Polymer analysis			
	M_1 = styrene				% C			
16.20	66.45	5.35	65.60	120	89.69	89.80		
10.86	62.70	3.22	61.55	168	87.46	87.30		
39.50	35.99	6.13	34.95	168	91.24	91.13		
39.20	36.38	5.96	34.92	168	90.76	90.90		
	M_1 = methyl methacrylate				% AcOH			
41.98	158.43	29.77	157.5	5.3	7.80	7.89		
40.61	159.80	29.84	158.9		7.43	7.52		
41.33	158.70	28.23	157.7		8.02	7.59		
161.02	42.58	133.83	40.3	2.7	0.76	0.56		
159.20	40.56	131.97	38.28		0.69	0.81		
158.62	35.78	131.6	33.51		0.68	0.8		
	M_1 = methyl acrylate				% AcOH			
17.36	63.89	11.80	61.31	.25	22.06	22.08		
41.69	40.53	32.26	39.62	.11	6.21	6.11		
65.45	17.16	28.33	15.13	.07	3.64	3.60		
	M_1 = acrylonitrile; each run contained 5 cc. acetonitrile				% N (Dumas)[d]			
16.45	63.04	5.97	54.65	15.75	11.45	11.27	11.31	
16.42	62.88	5.95	54.93		11.73	11.62		
63.75	15.91	56.72	15.504	2	23.51	24.04		
63.93	16.03	56.70	15.556		23.69	23.40		
	Vinyl bromide = M_1				% Br[b]			
15.70	63.28	6.32	47.95	3	32.16	32.33		
17.64	64.65	7.86	51.59		35.96	35.97		
69.70	16.14	47.71	14.44		70.38			
63.54	16.08	40.69	14.79		71.22	71.69		
47.61	16.22	37.03	15.35		70.09			
	Vinyl chloride = M_1 (12 mg. Bz_2O_2)				% Cl			
23.39	78.70	12.76	64.17	4.5	19.66	19.71		
25.60	78.35	14.62	64.46		20.62	20.76		
65.08	19.88	53.81	18.25	3.5	47.23	47.41		
64.42	19.70	56.06	18.24		45.87	45.63		
	Following runs contained 5.00 cc. chlorobenzene, 10 mg. Bz_2O_2							
92.80	16.67	84.40	15.84	6	49.02	49.86	50.95[c]	
88.16	16.50	78.10	15.39		49.09	49.52	49.22	49.03[c]
	Vinyl ethyl ether = M_1				% AcOH			
16.06	62.85	12.43	25.26	19.76	63.75	63.65		
15.60	63.30	11.79	24.03		63.70	63.50		
	Trichloroethylene = M_1				% Cl			
7.61	46.46	3.42	25.27	24	18.80	18.81		
15.23	34.96	12.35	27.84		31.54	31.61		
19.04	29.04	14.96	21.12		35.64	35.65		
23.98	23.35	21.26	17.98		38.56	38.59		

[a] Millimoles of unreacted monomers; zero subscripts indicate initial quantities. [b] Analyzed by combustion in stream of oxygen, as described by Gregg and Mayo,[c] after unsuccessful attempts to obtain reasonable and reproducible results by other methods. [c] Heterogeneity of sample may be responsible for poor checks. All sample used in analyses and all results averaged. [d] Calculations based on experimental value of 26.06% N in polyacrylonitrile. In press.

of separate experiments is taken as the experimental error.[1] The outstanding feature of the results is the low reactivity toward free radicals of vinyl acetate as compared with other monomers: except for vinyl ethyl ether, the vinyl acetate radical prefers to react with the other monomer of the pair. A similar conclusion, based on α-values[5] derived from single experiments, has been reached by Nozaki.[6] Although the unconjugated monomers (unsaturated halides) have the same order of

(5) Wall, THIS JOURNAL, **63**, 1862 (1941).

(6) Nozaki, *J. Polymer Sci.*, **1**, 455 (1946).

reactivity as vinyl acetate, the monomers with conjugated phenyl, ester, or nitrile groups are so much more reactive than vinyl acetate that the monomer reactivity ratios for the vinyl acetate radical are indistinguishable from zero and it is therefore impossible to compare the reactivities of these monomers.

TABLE II

SUMMARY OF MONOMER REACTIVITY RATIOS IN COPOLYMERIZATIONS OF VINYL ACETATE (M_2)

M_1	r_1	r_2
Styrene	55 ± 10	0.01 ± 0.01
Methyl methacrylate	20 ± 3	.015 ± .015
Methyl acrylate	9 ± 2.5	.1 ± .1
Acrylonitrile	4.05 ± .3	.061 ± .013
Vinyl bromide	4.5 ± 1.2	.35 ± .09
Vinyl chloride	1.68 ± .08	.23 ± .02
Vinyl ethyl ether	0	3.0 ± .1
Trichloroethylene	.01 ± .01	0.66 ± .04

Vinyl ethyl ether not only is less reactive than vinyl acetate with both the latter and with styrene, it retards the polymerization of vinyl acetate. Thus a 4:1 ether–acetate feed gives <3% polymer in two-hundred fifty-eight hours. This retardation may be due to the formation of a less reactive α-vinyloxyethyl radical by chain transfer, the α-hydrogen of the ethyl group being easily susceptible to free radical attack, or to as rapid decomposition and inefficient utilization of the catalyst.[7]

Experiments on the vinyl chloride–vinyl acetate system indicate a possible effect of precipitation of the polymer on its composition. The polymers from the high vinyl chloride feeds precipitated as they formed, yielding a highly swollen but fairly stiff gel. Such experiments failed to give reproducible results, although the homogeneous runs gave good checks. The monomer reactivity ratios here obtained are consistent with the observation of Staudinger and Schneiders[8] that fractionation of a 1:1 copolymer gave fractions containing as much as three chlorine atoms per acetate group. The difficulty encountered by Marvel and coworkers[9] in obtaining consistent α-values with these monomers may have been partly due to precipitation of polymer.

The vinyl bromide results are subject to considerable uncertainty because of analytical difficulties. The lowest values of the monomer reactivity ratios are the most probable because otherwise the product of the ratios exceeds unity by an unexpected margin. Even so, the results indicate that, in comparison with a chlorine atom, a bromine atom gives much less tendency to alternate with vinyl acetate, but a considerably higher average activity.

A comparison of the reactivity of several chloroethylenes with vinyl acetate[10] and a discussion of rate phenomena in the styrene–vinyl acetate system[11] will be given in later papers in this series.

Summary

Copolymerizations of eight monomers with vinyl acetate have been examined. The data show that, in comparison with monomers with conjugated substituents, the double bond in vinyl acetate is unreactive.

(7) See, *e. g.*, Cass, THIS JOURNAL, **69**, 500 (1947).

(8) Staudinger and Schneiders, *Ann.*, **541**, 193 (1939).

(9) Marvel, Jones, Mastin and Schertz, THIS JOURNAL, **64**, 2356 (1942). Plotting these data with the integrated copolymerization equation gives erratic results, the monomer reactivity ratios for the chloride and acetate radicals ranging from 1.0 to 2.8 and from 0.2 to 1.3, respectively.

(10) Doak, THIS JOURNAL, **70**, 1525 (1948).

(11) Mayo, Lewis and Walling, *ibid.*, **70**, 1529 (1948).

PASSAIC, NEW JERSEY RECEIVED JULY 17, 1947

[CONTRIBUTION NO. 68 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. VI.[1] The Copolymerization of Chloroethylenes with other Monomers

BY KENNETH W. DOAK

This paper presents a comparison of the reactivities of all the chlorinated ethylenes with each of two or more other radicals. Some data have been taken from other papers in this series; the new data include the systems vinyl chloride and trichloroethylene with styrene, tetrachloroethylene with styrene, vinyl acetate and acrylonitrile, and vinylidene chloride with vinyl acetate and diethyl fumarate. More precise data for the system styrene and vinylidene chloride have been obtained.

The relative reactivities of 1,1- and 1,2-dichloroethylenes with some other monomers have been reported by Nozaki[2] on the basis of single experiments, but strong alternation tendencies[3] involved in some of the systems make the present method more reliable.

The monomers were commercial samples which had been carefully refractionated. Except as indicated, the experimental procedure was similar to that of Mayo and Lewis.[3a] The copolymers of acrylonitrile and tetrachloroethylene and of vinylidene chloride (80 mole % in reaction mixture)

(1) For the preceding paper in the series, see Mayo, Walling, Lewis and Hulse, THIS JOURNAL, **70**, 1523 (1948).

(2) Nozaki, *J. Polymer Sci.*, **1**, 455 (1946).

(3) (a) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944); (b) Lewis, Mayo and Hulse, *ibid.*, **67**, 1701 (1945); (c) Bartlett and Nozaki, *ibid.*, **68**, 1495 (1946).

with vinyl acetate and diethyl fumarate precipitated from the reaction mixtures as finely divided powders which were washed with ethanol and dried at 65° and 1 mm. All other copolymers were purified by the frozen benzene technique of Lewis and Mayo.[4]

The monomer reactivity ratios were determined graphically from the data in Table I. For the systems containing tetrachloroethylene, it was assumed that the reactivity ratio for the tetrachloroethylene radical is zero, since this monomer did not homopolymerize under the experimental conditions. The other reactivity ratio was considered to be the intersection of the calculated lines with the r_1 axis. Monomer reactivity ratios, together with literature data necessary for the discussion, are given in Table II.

TABLE I

COPOLYMERIZATIONS WITH 0.1 MOLE PER CENT. BENZOYL PEROXIDE AT 60°

$[M_1]_0$[a]	$[M_1]$[a]	$[M_2]_0$[a]	$[M_2]$[a]	Time, hr.	Polymer analysis (% Cl)	
Vinyl Acetate		Tetrachloroethylene				
160.3	63.7	40.6	35.9	9	7.20	7.45
80.84	25.52	19.73	16.80	18	7.96	7.87
80.50	25.86	19.92	17.00	18	8.00	7.96
Acrylonitrile		Tetrachloroethylene				
94.1	36.0	94.0	93.8	1?	0.79	0.90
Styrene		Tetrachloroethylene				
48.00	16.10	94.02	93.50	168	2.12	2.17
49.87	41.09	49.85	49.80	25	0.88	0.78
Vinylidene Chloride		Vinyl Acetate				
78.58	74.40	21.64	21.33	3	26.72	26.63[b]
79.09	73.31	22.62	22.17	3	26.69	26.91[b]
19.14	9.45	78.70	72.86	8	35.43	35.71[b]
19.16	9.05	78.28	72.36	8	35.50	35.37[b]
Vinylidene Chloride		Diethyl Fumarate				
77.31	59.11	21.06	20.62	6	26.04	26.09[b]
76.56	59.14	21.18	20.72	6	26.07	26.24[b]
18.40	6.62	83.60	77.86	24	39.17[b]	
19.34	7.15	83.83	78.34	24	38.57[b]	
Styrene		Vinyl Chloride				
80.82	51.64	53.59	52.32	39	1.43	1.45
20.75	5.60	101.53	95.50	130	10.93	10.95
79.91	56.61	29.82	29.08	29	0.85	0.89
Styrene		Vinylidene Chloride				
76.03	65.86	20.02	18.67	13	8.06	
75.45	66.36	20.88	19.63	13	8.28	
34.48	29.84	63.16	60.40	15	26.05	
34.42	29.79	62.71	59.95	15	26.08	
Styrene		Trichloroethylene				
68.83	55.20	29.97	29.59	20	2.76	
68.68	55.22	30.35	29.93	20	3.06	
20.20	16.62	79.16	78.41	68	16.95	

[a] Millimoles of unreacted monomers; zero subscripts indicate initial quantities. [b] % C.

(4) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

Results and Discussion

Relative reactivities of the chloroethylenes with four radicals were determined from the reciprocals[3,5] of r_1, and are recorded in Table III. The values for vinyl chloride are taken as unity.

The relative reactivities of the chloroethylenes depend upon the reference radical, presumably because of the alternating tendency, although qualitatively the general order, with one possible exception, is the same for different radicals. As shown qualitatively by Nozaki,[2] unsymmetrical substitution of a second chlorine increases the reactivity, since extra resonance forms are possible. These data show the increase to vary from a factor of 3.6 to 10.5 or greater. Symmetrical substitution of the second chlorine decreases the reactivity, presumably because of steric interference with the approaching radical. The difference in the *cis*- and *trans*-dichloroethylenes is discussed by Lewis and Mayo in a later paper in this series.[6] Trichloroethylene, in which the effects are opposed, has a reactivity intermediate between that of the symmetrical and unsymmetrical dichloroethylenes. Tetrachloroethylene offers additional steric hindrance, and is much less reactive than trichloroethylene.

A comparison of the r_1r_2 products[5] in Table II shows that vinyl chloride alternates better than vinylidene chloride with the electron acceptors diethyl fumarate and acrylonitrile but less readily with the electron donors vinyl acetate and styrene. With vinyl acetate, all the dichloroethylenes alternate better than vinyl chloride. All these results are consistent with the idea that dichloroethylenes should be better electron acceptors[7] than vinyl chloride. Trichloroethylene, tetrachloroethylene, and the 1,2-dichloroethylenes, in comparison with vinyl chloride, are about three times as reactive toward the styrene radical as toward the vinyl acetate radical. If this result were wholly due to donor–acceptor effects, it would mean that styrene is a better donor than vinyl acetate, a conclusion which seems to be contradicted by the weight of other evidence.[7c]

Acknowledgment.—The author wishes to express his appreciation to Dr. Frank R. Mayo for

(5) Lewis, Walling, Cummings, Briggs and Mayo, THIS JOURNAL, **70**, 1519 (1948).

(6) Lewis and Mayo, THIS JOURNAL, **70**, 1533 (1948).

(7) (a) Price, *J. Polymer Sci.*, **1**, 83 (1946); (b) Alfrey and Price, *ibid.*, **2**, 101 (1947); (c) Mayo, Lewis, and Walling, THIS JOURNAL, **70**, 1529 (1948).

TABLE II

MONOMER REACTIVITY RATIOS

Monomer	r_1	Monomer	r_2	r_1r_2
Vinyl acetate	6.8 ± 0.5	Tetrachloroethylene	(0)	
Acrylonitrile	470 ± ?	Tetrachloroethylene	(0)	
Styrene	185 ± 20	Tetrachloroethylene	(0)	
Vinyl acetate[a]	0.66 ± 0.04	Trichloroethylene	0.01 ± 0.01	0.007
Styrene	16 ± 2	Trichloroethylene	0.0 ± ?	
Styrene[b]	1.85 ± 0.05	Vinylidene chloride	0.085 ± 0.010	0.16
Acrylonitrile[c]	0.91 ± 0.1	Vinylidene chloride	0.37 ± 0.1	0.34
Vinyl acetate	0.0 ± 0.03	Vinylidene chloride	3.6 ± 0.5	< .1
Diethyl fumarate	0.046 ± 0.015	Vinylidene chloride	12.2 ± 2.0	.56
Styrene	17 ± 3	Vinyl chloride	0.02 ± ?	.34
Vinyl acetate[a]	0.23 ± 0.02	Vinyl chloride	1.68 ± 0.08	.38
Acrylonitrile[d]	3.28 ± 0.06	Vinyl chloride	0.02 ± 0.02	.07
Diethyl fumarate[e]	0.47 ± 0.05	Vinyl chloride	0.12 ± 0.01	.056
Vinyl acetate[e]	6.3 ± 0.2	*cis*-Dichloroethylene	0.018 ± 0.003	.11
Vinyl acetate[c]	0.99 ± 0.02	*trans*-Dichloroethylene	0.086 ± 0.010	.085

[a] Ref. 1. [b] Lewis, Mayo and Hulse[3b] reported 2.0 ± 0.1 and 0.14 ± 0.05. [c] Ref. 3b. [d] Lewis, Walling, Cummings, Briggs and Wenisch, THIS JOURNAL, **70**, 1527 (1948). [e] Ref. 6.

helpful discussions during the course of this work.

TABLE III

RELATIVE REACTIVITIES OF CHLOROETHYLENES WITH DIFFERENT RADICALS

Monomer radical type	Vinyl acetate	Styrene	Acrylonitrile	Diethyl fumarate
Vinylidene chloride	>7.5	9.2	3.6	10.5
Vinyl chloride	1.00	1.00	1.00	1.00
Trichloroethylene	0.34	1.06		
trans-Dichloroethylene[a]	.12	0.27[b]		
cis-Dichloroethylene[a]	.018	.039[b]		
Tetrachloroethylene[a]	.017	.046	0.0035	

[a] The values for the symmetrical monomers have been divided by two, since there are two equivalent ways in which they can add to a radical. [b] Ref. 6.

Summary

Monomer reactivity ratios have been determined for several new systems of chloroethylenes with other monomers. The data are correlated with other available data to give the following reactivity series: vinylidene chloride > vinyl chloride > trichloroethylene > *trans*-dichloroethylene > *cis*-dichloroethylene and tetrachloroethylene. This series can be accounted for qualitatively by a consideration of steric effects and of the ease of formation of di- and trisubstituted radicals. Differences in alternating tendencies in various systems are consistent with existing theories of alternation.

PASSAIC, NEW JERSEY RECEIVED JULY 17, 1947

[CONTRIBUTION NO. 69 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. VII.[1] Copolymerizations of Some Further Monomer Pairs

BY FREDERICK M. LEWIS, CHEVES WALLING, WILLIAM CUMMINGS,[2] EMORENE R. BRIGGS[3] AND W. J. WENISCH[4]

This paper presents experimental data on the copolymerization of eight monomer pairs needed to supplement our series of relative reactivities of monomers with radicals. The monomer reactivity ratios calculated from these data are summarized in Table I. Since the data were gathered over an interval of four years, the standard deviations of the separate experiments rather than any established analytical error[5] have usually been used to determine the stated experimental errors. Also included in this paper are some less reliable mono-

TABLE I

MONOMER REACTIVITY RATIOS AT 60°[a]

M_1	r_1	M_2	r_2
Styrene	0.78 ± 0.01	Butadiene	1.39 ± 0.03
Styrene	.54 ± .01	β-Chloroethyl acrylate	0.10 ± .01
Styrene	.30 ± .10	Methacrylonitrile	0.16 ± .06
Styrene[b]	.29 ± .04	Methyl vinyl ketone	0.35 ± .02
Acrylonitrile[c]	.61 ± .04	Methyl vinyl ketone	1.78 ± .22
Acrylonitrile	3.28 ± .06	Vinyl chloride	0.02 ± .02
Methyl methacrylate	0.67 ± .10	Methacrylonitrile	0.65 ± .06
Isobutylene	0.08 ± .10	Vinyl chloride	2.05 ± .3

[a] M's and *r*'s in each line correspond to the particular monomer pair indicated. [b] Experimental error from 0.2% error in carbon analysis. [c] Experimental error from 0.1% error in nitrogen analysis.

(1) For the preceding paper in this series see Doak, THIS JOURNAL, **70**, 1525 (1948).

(2) Present address, Department of Chemistry, University of Minnesota, Minneapolis, Minn.

(3) Present address, R. F. D. 2, Guilford, Conn.

(4) Present address, Department of Chemistry, New York University, New York, N. Y.

(5) Lewis, Walling, Cummings, Briggs and Mayo, THIS JOURNAL, **70**, 1519 (1948).

mer reactivity ratios for six additional pairs (Table II). Most of the experiments were carried out in the course of preliminary studies using three experiments at 4:1, 1:1, and 1:4 mole ratios of the two monomers, but the lower accuracy obtained (*cf.* experimental errors in Table II) does not appear to justify detailed presentation.

Table II

Additional Monomer Reactivity Ratios at 60°

M_1	r_1	M_2	r_2
Vinyl acetate[a]	0.60 ± 0.15	Allyl acetate	0.45 ± 0.15
Styrene	90 ± 20	Vinyl ethyl ether	0
Methyl methacrylate[a,b]	0.25 ± 0.03	Butadiene	0.75 ± 0.05
β-Chloroethyl acrylate	5.5 ± 1	Allyl acetate	0
β-Chloroethyl acrylate	4 ± 1	Methallyl acetate	0
β-Chloroethyl acrylate[c]	0.9 ± 0.1	Methyl acrylate	0.9 ± .1

[a] Experiment by Mr. R. H. Snyder. [b] At 90°. [c] Experiment by Dr. K. W. Doak.

Correlation and discussion of the results of Table I and II will be given in a subsequent paper in this series.[6]

Experimental

Materials.—**Isobutylene** and **butadiene** were obtained from the Matheson Company and used without purification other than drying. **Methacrylonitrile,** from the Shell Chemical Company, was fractionated just prior to use; $n^{20}D$ 1.4003. **β-Chloroethyl acrylate** was prepared by acid-catalyzed ester interchange from methyl acrylate and ethylene chlorohydrin in the presence of an inhibitor. The crude product was fractionated *in vacuo* under nitrogen; b. p. 94.1–95 at 18.5 mm.; $n^{20}D$ 1.4490. **Methyl vinyl ketone** was obtained from E. I. du Pont de Nemours and Co. as an azeotrope with water containing 85% ketone. Upon saturating with potassium carbonate and distilling through a packed column the pure ketone was collected as a fraction boiling at 80.5–81.0° at one atmosphere. Since it was unstable and polymerized readily, it was stored in the ice-box and used as soon as possible. Other monomers, usually fractionated commercial materials, were those described in previous papers in this series.

Polymerizations.—Except as noted, experiments were carried out and polymers isolated as described in previous papers. Results are tabulated in Table III.

In styrene–butadiene experiments, styrene charges were first weighed accurately into tubes, then butadiene was added in approximate amounts to the chilled tube. The exact weights of butadiene used were then determined from the weights of the charged and sealed, and empty reaction tube.

Since both isobutylene and vinyl chloride are low boiling monomers, a manifold was constructed with stopcocks leading to a vacuum line, to a standard taper joint and to two graduated tubes for measuring the monomers. Tubes containing pure monomer were attached by the standard taper joint and the monomers were degassed and distilled into the respective graduated tubes. By suitable manipulation of the stopcocks the monomers could then be separately distilled *in vacuo* into the reaction tube attached to the ground joint. The graduated tubes were adjusted to approximately −50° for volume readings, the exact temperature noted, and the corresponding density read from graphs. Weights of single monomers measured from this apparatus showed that their densities were a linear function of temperature, varying from 0.949 g./ml. at 0° to 1.018 at −48° for vinyl chloride; and from 0.619 at 0° to 0.664 at −40° for isobutylene.

(6) Mayo, Lewis and Walling, This Journal, **70**, 1529 (1948).

Table III

Experimental Data on Copolymerizations at 60°

$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_1]$[a]	$[M_2]$[a]	Time, hr.	Polymer analysis	
Styrene (M_1)–Butadiene (M_2)					$n^{20}D$	
69.45	12.40	40.60	6.24	72	1.5860	
39.80	23.40	15.33	6.64	117	1.5730	
16.00	36.80	13.43	29.03	239	1.5461	
Styrene (M_1)–β-Chloroethyl Acrylate (M_2)					% Cl	
57.70	17.32	49.15	14.19	5.3	8.5	
41.00	42.70	33.32	37.25	3.5	12.8	
16.31	68.60	9.85	59.60	2.5	17.0	
Styrene (M_1)–Methacrylonitrile (M_2)					% N	
63.58	18.88	42.65	8.21	62	4.63	4.67
39.68	39.20	24.30	25.56	62	7.56	7.52
15.87	63.05	8.00	47.84	62	11.58	11.57
Styrene (M_1)–Methyl Vinyl Ketone (M_2)					% C	
64.28	16.11	50.71	9.45	11.3	86.28	86.44
63.80	16.39	49.63	10.02	11.3	86.85	86.64
16.62	64.34	10.74	50.72	2.7	77.92	77.65
16.66	64.34	11.86	53.34	2.7	77.79	77.71
Acrylonitrile (M_1)–Methyl Vinyl Ketone (M_2)					% N	
15.61	64.25	14.10	53.53	0.84	2.53	
15.63	64.10	14.40	54.92	0.84	2.42	
16.47	63.30	14.66	52.75	1.00	3.03	3.01
64.90	16.14	55.34	12.44	0.67	17.46	17.49
64.78	16.07	52.50	11.07	0.67	17.16	17.20
64.08	16.17	58.12	13.64	4.25	16.94	
Acrylonitrile (M_1)–Vinyl Chloride (M_2)					% N	
23.72	39.49	4.87	30.87	9.5	16.94	17.37
64.55	24.34	36.98	21.02	1.1	23.02	23.29
62.80	17.60	31.11	14.42	1.1	23.48	23.71
24.21	38.44	5.13	29.31	9.5	16.77	16.98
Methyl Methacrylate (M_1)–Methacrylonitrile (M_2)					% N	
79.06	19.88	61.58	14.35	15.5	3.65	
79.61	19.93	63.02	14.78	15.5	3.61	
19.95	87.24	14.79	68.78	49.5	14.38	
20.12	87.77	14.55	69.39	49.5	14.29	
Isobutylene (M_1)–Vinyl Chloride (M_2)					% Cl	
64.5	21.0	61.4	16.5	56	35.65	35.57
43.0	43.3	36.4	27.6	56	41.70	41.91
17.0	59.0	13.17	31.5	56	50.53	50.79

[a] Millimoles of unreacted monomer; zero subscripts indicate initial quantities.

Isobutylene–vinyl chloride polymers were precipitated from acetone solution with methanol. Nitrile polymers were dissolved in dimethylformamide or acetonitrile, precipitated with petroleum ether or methanol, and dried for several days at 60° *in vacuo*.

Polymer compositions were determined by standard analytical methods except for styrene–butadiene systems. Several attempts to determine the monomer reactivity ratios for this pair by combustion analysis or by separation and analysis of the unreacted monomer mixture were unsatisfactory. The data given in Table I are based on polymer analysis by index of refraction. Since, for emulsion copolymers of styrene and butadiene, other

factors being constant, the index of refraction of the copolymers is a linear function of composition,[7] the same relation has been assumed here for oil-phase copolymers, using for the pure polymers of styrene and butadiene, made under the same conditions as the copolymers, $n^{20}D$ 1.5935 and 1.5160, respectively. The high-styrene polymer was quite hard and an optical surface was generated by pressing the polymer against a hot glass plate and allowing it to cool in contact. Optical contact of the resulting surface with the prism of an Abbe refractometer was made with a saturated aqueous solution of cadmium borotungstate and the refractive index was measured by reflected light. The intermediate-styrene polymer was soft enough to make optical contact with the prism directly under pressure, allowing measurement by reflected light. The low-styrene polymer was soft enough to squeeze between the two prisms of the refractometer for measurement by transmitted light. All readings were reproducible to ±0.0002.

(7) "Analyses by Refractive Index," Lundstedt and Hampton, Akron Copolymer Research Group Meeting, June 12–13, 1944.

Summary

1. Copolymerization data and monomer reactivity ratios at 60° are given for eight new monomer pairs.

2. Monomer reactivity ratios of lower precision are given for six additional pairs.

PASSAIC, NEW JERSEY RECEIVED JULY 17, 1947

[CONTRIBUTION NO. 70 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. VIII. The Relation Between Structure and Reactivity of Monomers in Copolymerization[1]

BY FRANK R. MAYO, FREDERICK M. LEWIS AND CHEVES WALLING

The first papers in this series[2] showed that series of copolymerizations make possible the determination of the relative reactivities of monomers toward certain radicals, and that such relative reactivities are independent of the feed composition, conversion, solvents, regulators, sources of free radicals used and rates of polymerization. On the other hand, such relative reactivities do appear to depend upon the particular attacking radical, and the results indicate a general order of monomer reactivity toward radicals on which is superimposed a tendency of certain monomers to alternate in copolymerization. In some monomer pairs this alternating effect appears to be negligible; relative reactivities of the monomers are the same toward both types of radicals and the monomer reactivity ratio product, r_1r_2, $\cong$ 1. Such systems, of which styrene–butadiene is an example (r_1r_2 = 1.08) have been termed "ideal" by Wall.[3] In other systems the "alternating effect" appears dominant, $r_1r_2 \cong 0$, and the initial copolymer from any feed consists of regularly alternating units of the two monomers (*e. g.*, styrene–maleic anhydride $r_1r_2 \leq 0.001$).[4] In the great majority of copolymerizations, however, both effects appear of importance and monomer reactivity ratios have intermediate values: styrene–methyl methacrylate, r_1r_2 = 0.26; acrylonitrile–methyl methacrylate, r_1r_2 = 0.24.

The purpose of the present paper is to discuss these phenomena in more detail using the extensive experimental data recently presented from this Laboratory,[5] and also making reference to additional material to appear in subsequent papers in this series.[6]

The Alternation Tendency in Copolymerization.—An earlier paper[2b] stated that the alternating effect "seems sometimes to be due to steric effects, at other times to dipole effects or specific interactions (compound formation) between monomers." This section will amplify this statement in the light of the work cited above.[5,6] Price[7] has proposed that substitutents in a radical or monomer may withdraw or supply electrons from the site of reaction, resulting in effective charges on the trivalent or doubly bound carbon atoms. The alternating effect then arises from an attraction between a negative double bond and a positive radical, or *vice versa*. Alfrey and Price[8] have since attempted to place this suggestion on a general and quantitative basis, describing the reactivity of each monomer in terms of two parameters, referring to the "general monomer reactivity" (Q) and "polarity factor" (e). Bartlett and Nozaki[9] have mentioned the possibility that electron transfer from a donor radical to an acceptor monomer, or *vice versa*, in the activated complex may account for alternation tendencies, and we have developed and discussed this concept further in later papers in this series.[10]

(1) This paper is based on papers presented at the Atlantic City Meeting of the American Chemical Society, April 9, 1946 (Symposium on the Physical Chemistry of Copolymers and Copolymerization) and at the Gibson Island Conference on High Polymers, July 1, 1946.

(2) (a) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944); (b) Lewis, Mayo and Hulse, *ibid.*, **67**, 1701 (1945).

(3) Wall, *ibid.*, **66**, 2050 (1944). This theoretical paper shows clearly how copolymer compositions depend on feed for representative monomer reactivity ratios. Some special cases were considered earlier by Jenckel, *Z. physik. Chem.*, **190A**, 24 (1942).

(4) Alfrey and Lavin, *ibid.*, **67**, 2044 (1945).

(5) (a) Lewis, Walling, Cummings, Briggs and Mayo, *ibid.*, **70**, 1519 (1947); (b) Mayo, Walling, Lewis and Hulse, *ibid.*, **70**, 1523 (1948); (c) Doak, *ibid.*, **70**, 1525 (1948); (d) Lewis, Walling, Cummings, Briggs and Wenisch, *ibid.*, **70**, 1527 (1948).

(6) (a) Lewis and Mayo, *ibid.*, **70**, 1533 (1948); (b) Walling, Briggs and Wolfstirn, *ibid.*, **70**, 1543 (1948).

(7) Price, *J. Polymer Sci.*, **1**, 83 (1946).

(8) Alfrey and Price, *ibid.*, **2**, 101 (1947); Alfrey, paper presented at Atlantic City Meeting, April, 1946.[1]

(9) Bartlett and Nozaki, THIS JOURNAL, **68**, 1495 (1946).

(10) (a) Walling, Briggs, Wolfstirn and Mayo, *ibid.*, **70**, 1537 (1948); (b) Walling, Seymour and Wolfstirn, *ibid.*, **70**, 1544 (1948).

TABLE I

PRODUCTS OF MONOMER REACTIVITY RATIOS IN COPOLYMERIZATIONS AT 60°

Vinyl acetate							
	Butadiene						
	1.08	Styrene					
0.3			Allyl acetate				
.39		0.34		Vinyl chloride			
<.3	0.19	.26			Methyl methacrylate		
<.1		.16			0.61	Vinylidene chloride	
		.14					Methyl acrylate
		.10					Methyl vinyl ketone
		.054	<.3			.8	β-Chloroethyl acrylate
		.05			.43		Methacrylonitrile
.25		.02		.07	.24	.34	1.1 Acrylonitrile
.004		.02		.06		.56	Diethyl fumarate

Both of these schemes lead to the prediction that the larger the *difference* in polarity or donor-acceptor properties between two monomers, the greater will be the alternation tendency, a conclusion which is given qualitative support by Table I. In this table, monomers have been arranged approximately in order of their increasing tendency to alternate with styrene, as measured by the decreasing products of monomer reactivity ratios. The monomers are then seen to be arranged approximately in order of the tendency of the substituents to accept electrons from the double bonds (*i. e.*, decrease the rate of substitution in the benzene ring). The acetoxy, vinyl and phenyl groups seem to be the best donors and poorest acceptors, followed by substituted alkyl, chlorine, carbalkoxy, carbonyl and nitrile groups. The effects of substituents are roughly additive. Considering the rather large experimental errors in some of the products, Table I is surprisingly consistent and gives strong support to the qualitative notion: in each horizontal row, the monomer reactivity ratio products tend to increase from a minimum value at the left margin to unity at the right end, and the products in each column tend to decrease from unity at the top to a minimum value at the bottom.

On the other hand, there are enough inconsistencies in Table II to suggest that such a scheme will not work quantitatively. For example, using the Q and e values of Alfrey and Price[8] for styrene, methyl methacrylate and acrylonitrile, Q and e values for methyl vinyl ketone and methacrylonitrile[5d] were each calculated from two independent sets of data. Styrene data give for methyl vinyl ketone, $Q = 0.75$ and $e = 0.51$, while the acrylonitrile data give $Q = 0.59$, $e = 1.00$. For methacrylonitrile, our styrene data give $Q = 0.59$, $e = 0.74$ while our methacrylate data give $Q = 0.95$, $e = 0.914$. Clearly some other factors must be considered. One of these is the existence of specific resonance interactions between certain radicals and monomers, often large, and perhaps involving actual electron transfer.[9,10] Another is the effect of differences in entropies of activation, or steric effects, most striking in the case of copolymerization of a 1- or 1,1-substituted ethylene with a 1,2-substituted derivative (as with styrene–diethyl fumarate[5a]), where alternation results (in half the steps) in more crowding of substituents. Such an effect may account for the abnormally low alternation tendency (large r_1r_2) in the diethyl fumarate-vinylidene chloride system (Table I) and for the high alternation tendency in the vinyl acetate–trichloroethylene system.[5b] In the latter case, polyvinyl acetate and the copolymer may be constructed from Fisher–Hirschfelder models while polytrichloroethylene cannot: an alternation tendency should be expected in general when a radical from a small monomer prefers to react with a more highly substituted monomer which cannot polymerize with itself. Further, comparison of *cis* and *trans* isomers in copolymerizations shows that even configurations of substituents in the activated complex are important in determining reactivity.[6a] While the above examples are all concerned with 1,2-substituted ethylenes, where steric effects were anticipated by Alfrey and Price,[8] there is good evidence of steric hindrance in the polymerization of 1,1-disubstituted ethylenes where these workers neglect steric effects: heats of polymerization of 1,1-substituted ethylenes (methyl methacrylate, 11.6 kcal./mole, isobutylene, 12.8 kcal./mole)[11] are significantly lower than for 1-substituted ethylenes (styrene, 16.1 kcal./mole,[12] acrylic acid, 18.3 kcal./mole[11]).

Average Activities of Monomers in Copolymerization.—The reciprocals of a series of monomer reactivity ratios for a reference radical with a number of monomers are the relative reactivities of the monomers toward the reference radical.[2] Table II summarizes data on monomers which have been tested in enough combinations to be of interest. The first column of figures gives the relative reactivity of monomers toward the vinyl acetate-type radical, taking the relative reactivity of vinyl acetate as one. Similarly, the second column gives the relative reactivity of monomers toward the styrene-type radical, taking the relative reactivity of styrene as one, *etc.* Since

(11) Evans and Polanyi, *Nature*, **152**, 738 (1943).

(12) Tong and Kenyon, THIS JOURNAL, **69**, 1402 (1947).

TABLE II

RELATIVE REACTIVITIES OF MONOMERS WITH VARIOUS RADICALS AT 60°[a]

Radical Monomer	Vinyl acetate	Styrene	Allyl acetate	Vinyl chloride	Methyl methacrylate	Vinylidene chloride	Methyl acrylate	β-Chloroethyl acrylate	Acrylonitrile	Diethyl fumarate
α-Vinylpyridine		1.82			2.54					
o-Chlorostyrene		1.78			2.0					
Styrene	>50	1.00	>50	50	2.2	12	5.5	10	25	14
Methyl methacrylate	70	1.9	>50		1.00	4.0			5.5	
Methyl vinyl ketone		3.5							1.6	
Methacrylonitrile		3.3			1.5					
Acrylonitrile	16	2.5		50	0.75	2.7			1.00	
β-Chloroethyl acrylate		1.9	>50				1.1	1.00		
Methyl acrylate	10	1.34			*1.0**	1.00	1.00	1.1		
Vinylidene chloride	>30	0.54		*3.2**	.40	1.00	*1.0**		1.1	22
Methallyl chloride	8[c]	*.05*		3.2[d]	*.13*	0.9				
Methallyl acetate		.014[g]			*.1*	*.42*		0.25		
Vinyl chloride	4.3	.06		1.00	*.08*	*.31*	*0.2*		0.30	2.1
Vinyl acetate	1.00	.02	2.2	0.60	.05	.28	.11		.25	2.3
Isobutylene				.49		*.65*				*0.3**
Vinyl ethyl ether	0.33	.01				*.31*	*.3*		*.2*	
Allyl chloride		.03[b]			*.02*	*.22*			*.18*	
Allyl acetate	1.7	.011[g]	1.00	.86[e]	.043[g]	*.15*	*.2*	.18		
Maleic anhydride	>50		>130[f]			.11	*.4**		*.17*	
Diethyl fumarate	90	3.3		8.3		.08			*.12*	1.00
Diethyl maleate	6	.15		1.3	*.05**	*.08*			*.08*	
Trichloroethylene	1.5	.06			*.01*		*.03**		*.015*	
trans-Dichloroethylene	1.0	.03								
cis-Dichloroethylene	.16	.005								
Tetrachloroethylene	.15	.005					.005		.007	

[a] Italic values have been calculated from α-values obtained from single experiments in a preliminary survey carried out largely by Mr. W. F. Hulse. The results have not been reported elsewhere, but, except when starred, are probably accurate within a factor of two. [b] Alfrey and Harrison, THIS JOURNAL, **68**, 299 (1946) (70°). [c,d,e] Calculated from Moffett and Smith, U. S. Patent 2,356,871. Reactions at 80°, 45°, 40°, respectively. [f] Ref. (9), 35°. [g] Doak and Walling, unpublished work.

the reactivities in various columns are related by the ratios of the rate constants for chain growth of the standard monomers, relations between columns must await determinations of these constants.

The radicals at the top of Table II are arranged in order of decreasing electron-donor tendencies, increasing electron-acceptor tendencies, as listed in Table I. Except that 1,2-disubstituted ethylenes have been arbitrarily grouped at the bottom for later discussion, the order of the monomers in the first column is a compromise arranged so that the reactivities decrease in each column. The decrease in each column is sufficiently uniform, within the often considerable experimental error, that the order approximates the average activities of the monomers. The lack of uniformity can be correlated qualitatively with the alternating tendency. For example, the monomers immediately below styrene are more reactive toward the styrene-type radical for this reason. Similarly, the relative reactivities of vinyl chloride and vinyl acetate change as the electron-accepting properties of the attacking radical increase. Quantitative changes in relative reactivities, without change in order, in other addition reactions of double bonds suggest that the order of stability of radicals is tertiary > secondary > primary.[13] Thus, those addition reactions to double bonds are preferred where the new radical formed is the most stabilized by resonance. However, the conjugation and hyperconjugation which stabilize the radicals should also stabilize the double bonds (but to a lesser extent since there will be a greater energy difference between the main and resonating structures), making the double bonds less reactive. Since the conjugated double bonds are actually more reactive, the conjugation must stabilize the activated complex more than the monomer, a conclusion consistent with the expectation that the resonance stabilization in the activated complex should be intermediate between the initial and final states. In other words, direct attachment of a vinyl, phenyl, carbonyl, carboxyl, nitrile or alkyl group to a double bond reduces the activation energy required for formation of the activated complex when any radical approaches. This conclusion is consistent with the proposal to be developed later[10] relating alternation effects to resonance contributions to the activated complex.

It follows from the above conclusions about

(13) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 238; Mayo and Walling, *Chem. Rev.*, **27**, 373 (1940).

resonance stabilization in monomers and radicals that, in general, the most reactive monomers are converted, in polymerization, to the least reactive radicals and the least reactive monomers yield the most reactive radicals.

Effects of Substituents.—The conclusions of the last two sections on the copolymerization of the 1- and 1,1-substituted ethylenes are summarized in Table III. The "average activity series," based on Table III, shows the effects of substituents on the ease with which an ethylene derivative reacts with an average radical and on stabilizing the radical which will be formed. The electron "donor-acceptor series," based on Table I, is a measure of the abilities of the substituents to serve as donors or acceptors in radical monomer interactions. The effects of a second α-substituent are roughly additive in both series.[14]

TABLE III

THE EFFECTS OF SUBSTITUENTS ON THE COPOLYMERIZATION OF MONOSUBSTITUTED ETHYLENES, R'—CH=CH$_2$

Average activity series	Donor–acceptor series
Increasing activity ↑	Increasing acceptor ability ↓
C_6H_5—	R—O—
H_2C=CH—[a]	H_2C=CH—
R—CO—	C_6H_5—
N≡C—	R—CH_2—
R—O—CO—	H—(?)
Cl—	Cl
R—O— }	R—CO— }
R—CH_2— }	R—O—CO— }
H—(?)	N≡C—
	Decreasing donor ability ↓

[a] As pointed out to us by Dr. T. Alfrey, although butadiene is about four-thirds as reactive as styrene, it contains two vinyl groups, each of which must be two-thirds as reactive as the vinyl group in styrene.

When two monomers lie close together in the donor–acceptor series then the copolymer will be the "ideal" or random type. If the monomers are also close together in the average activity series (example, styrene–butadiene),[5d] the composition of the copolymer will approximate the composition of the feed. The greater the separation of the monomers in the average activity series, the greater will be the tendency of the more reactive monomer to predominate in the copolymer; the less reactive monomer may be practically excluded (example, styrene–vinyl acetate[5b]).

When two monomers are well-separated in the donor-acceptor series, then they will have a marked tendency to alternate in copolymerization. If neither monomer polymerizes easily by itself (*e. g.*, stilbene–maleic anhydride),[6a] or if they lie close together in the average activity series (*e.g.*, styrene–acrylonitrile)[2b] then the products will approximate a 1:1 copolymer as long as the feed permits. These are the conditions under which a system is most likely to form an azeotropic copolymer, the only requirement being that both monomer reactivity ratios be less than unity.[3] On the other hand, if the monomers are well separated in both series, then the more reactive monomer will predominate to an extent such that the alternating effect will be apparent only from the monomer reactivity ratios or their product (example, acrylonitrile–vinyl acetate).[5b]

Copolymerization of 1,2-Disubstituted Ethylenes.—Toward the styrene-type radical, diethyl fumarate is 2.5 times as reactive as methyl acrylate[5a] and fumaronitrile[6a] is twice as reactive as acrylonitrile, but these bifunctional monomers have two equally probable sites of reaction. The fumaric ester is about ten times as reactive as the acrylic ester toward the vinyl acetate-type radical. Toward the radicals which are poorer donors, however, the acrylate seems more reactive than the fumarate. These results show that a 2-carbethoxy group enhances the reactivity of ethyl acrylate toward donor monomers but decreases activity toward acceptor monomers. However, results in the polychlorinated ethylenes[5c] reveal only a retarding effect of 2-substituents.

Rates of Polymerization and Copolymerization.—Comparison of some over-all rates of polymerization of single monomers has yielded the following order of decreasing rates with 0.1 mole % of benzoyl peroxide at 60°: methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate, vinyl chloride, vinylidene chloride, styrene, α-methacrylonitrile, allyl chloride, allyl acetate, isobutylene, vinyl ethyl ether.[15] This order has no relation to the order of activity of these monomers in copolymerization, or to conjugation, since over-all rates are determined primarily by the competition between chain growth and chain termination reactions and since they involve the rate of reaction of a different radical with each monomer, not the relative reactivities of monomers toward a common radical. Over-all rates in copolymerization are even more complex, and can be discussed quantitatively only if absolute rate constants are known.[16] Although such a discussion will be presented shortly from this Laboratory, some qualitative generalizations are worth mention here. First, copolymerization of two monomers far apart on the polarity series will frequently lead to much higher rates than are obtained for either monomer alone. This effect is observed in most copolymerizations of maleic anhydride with donor monomers[9] and arises because the rate of the chief growth step for each radical is greatly increased. Second, addition of a small amount of a reactive monomer may markedly inhibit the polymerization of an unreactive monomer close to it in the polarity series, as in the inhibition by styrene of the polymerization of vinyl acetate. A series

(14) An interesting observation is that even rather remote substitution may change monomer reactivity ratios appreciably. Thus values for styrene–methyl acrylate, 0.75 and 0.18,[5a] are changed to 0.54 and 0.10, respectively, for styrene–β-chloroethylacrylate.[5d]

(15) Experiments in this Laboratory by R. Van Meter and D. M. Alderman.

(16) Melville, Noble and Watson, *J. Polymer Sci.*, **2**, 229 (1947).

of experiments[17] showed that the inhibition depended on the catalyst concentration. Below about 0.4 mole % of styrene, one molecule of catalyst per molecule of styrene would permit the formation of a hard polymer in twenty-four hours at 70° while less catalyst (although ample to polymerize vinyl acetate alone) gave little polymer. At higher styrene concentrations, a higher ratio of catalyst to styrene was required unless much longer reaction times and addition of fresh catalyst were allowed. The result was then a mixed polymer. Copolymerization data show that styrene is at least fifty times as reactive as vinyl acetate toward both radicals. Hence with about 0.1% styrene in vinyl acetate, although the vinyl acetate radicals can add rapidly to vinyl acetate, they have a strong preference for styrene and are rapidly converted to styrene-type radicals. While these styrene radicals can add readily enough to styrene, this monomer is present only in very low concentration and the vinyl acetate is unreactive, acting like a rather inert diluent. As a result, relatively little chain growths occurs before two radicals meet and destroy each other, but if enough catalyst is supplied to sweep out the last traces of styrene, then the vinyl acetate can polymerize normally.

(17) Unpublished results by Drs. R. T. Armstrong and D. W. Sherwood, obtained in these laboratories in 1942.

Summary

Survey of the extensive new data from this laboratory is shown to support the conclusion that the reactivities of monomers in copolymerization are determined by an order of average monomer activity on which is superimposed a tendency toward alternation. The average activity of monomers depends largely on conjugation, *i. e.*, on the possibilities of resonance stabilization of the activated complex and resulting radical. The alternation tendency seems to result from several factors which are roughly summarized as the ability of one monomer (or radical) of a pair to donate electrons to the other radical (or monomer) of the pair. Tables show the effects of substituents on both the average activity and electron-donating ability of monomers.

Limited data on symmetrically substituted ethylenes show that the behavior of these monomers is more complicated than that of the 1- and 1,1-substituted monomers.

The qualitative relations between reactivity in copolymerization and over-all polymerization rates are discussed.

PASSAIC, N. J. RECEIVED JULY 17, 1947

[CONTRIBUTION NO. 71 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. IX. A Comparison of Some *cis* and *trans* Isomers[1,2]

BY FREDERICK M. LEWIS AND FRANK R. MAYO

As a study of the principles governing copolymerization was getting under way in this Laboratory, the paper by Marvel and Schertz[3] called our attention to the fact that dimethyl fumarate had a greater tendency than dimethyl maleate to enter a copolymer with *p*-chlorostyrene. Since any general scheme of copolymerization must account for such differences, we have compared the behavior of six pairs of geometrical isomers with a total of four other monomers. The results support our previous conclusion[1] that the possibilities of resonance stabilization of the activated complex is a critical factor determining the activity of a monomer toward a free radical.

Experimental

Materials.—Stilbene, maleic anhydride and methyl fumarate and maleate esters were Eastman Kodak Co. materials used without purification. The half esters were prepared according to the directions of Shields.[4] Eastman Kodak Co. mixed dichloroethylenes were separated by fractional distillation through a packed column: *trans*, b. p. 48.0 at 752 mm., $n^{20}D$ 1.4454; *cis*, b. p. 60.6 at 772 mm., $n^{20}D$ 1.4486. Wood and Dickinson[5] give: *trans*, b. p. 47.2° at 745 mm.; *cis*, b. p. 59.6 at 745 mm. Isostilbene was prepared by Mr. R. W. Strassburg by the partial hydrogenation of tolane. It distilled at 82.5° at 0.5 mm. and melted at −28 to −26°, although the melt was slightly cloudy up to 0°. This clearing point indicates that the product contains less than 3% *trans*-stilbene.[6]

Fumaronitrile was prepared from fumaramide and phosphorus pentoxide.[7] The nitrile was then partially isomerized to maleonitrile with hydrogen chloride in ether.[8] From 24 g. of crude product were obtained, by fractional distillation and crystallization, 12.6 g. fumaronitrile (m. p. 96–97°), 3.1 g. maleonitrile (m. p. 23–27°) and 2.10 g. chlorosuccinonitriles. These yields are in fair agreement with determinations of equilibrium mixtures. Mommaerts[9] isomerized the *cis* isomer thermally to a 50% *cis-trans* mixture in 1180 hours at 105–110° but apparently did not reach equilibrium. We have heated the *trans* isomer in a sealed, evacuated tube at 140° for seventy

(1) For the preceding paper in this series, see Mayo, Lewis and Walling, THIS JOURNAL, **70**, 1529 (1948).

(2) The conclusions of this paper were presented at the Symposium on the Physical Chemistry of Copolymers and Copolymerization at the Atlantic City Meeting of the American Chemical Society, April 9, 1946, and at the Gibson Island Conference on High Polymers, July 1, 1946.

(3) Marvel and Schertz, THIS JOURNAL, **65**, 2054 (1943).

(4) Shields, *J. Chem. Soc.*, **59**, 736 (1891).

(5) Wood and Dickinson, THIS JOURNAL, **61**, 3259 (1939). Extrapolation of their data indicates that the equilibrium mixture of the isomers contains 22% *trans* at 60°. Equilibria in the vapor phase are not greatly different: *cf.*, Olson and Maroney, *ibid.*, **56**, 1320 (1934).

(6) Taylor and Murray, *J. Chem. Soc.*, 2078 (1938).

(7) de Wolfe and van de Straete, *Bull. soc. chim. Belg.*, **44**, 288 (1935).

(8) Mommaerts, *Bull. Acad. Roy. Belg.*, **27**, 579 (1941).

(9) Mommaerts, *Bull. soc. chim. Belg.*, **52**, 79 (1943).

hours with a trace of iodine and apparently obtained an equilibrium mixture containing 76% fumaronitrile as determined from the melting point phase diagram.

Other materials have been described in previous papers.

Procedure.—Except as indicated, experiments were put up and polymers isolated as described previously. When a polymer was of low molecular weight, the solution above the precipitate was concentrated and examined for polymer, which was combined with the main lot when found in appreciable quantities. This procedure permitted distillation of the monomer from a small fraction of the polymer instead of from the whole product.

Results are summarized in Tables I and II.

TABLE I

RATES OF COPOLYMERIZATION OF EQUIMOLECULAR MIXTURES OF MALEIC ANHYDRIDE AND STILBENE AT 60°

Moles of each monomer	Stilbene isomer	Chloroform, cc.	Reaction time, hr.	Yield, wt. %
0.0250	*trans*	7.00	15.3	61.0[a]
.0250	*cis*	7.00	15.3	35.6[b]
.0100	*trans*	2.80	3	21.9[c]
.0100	*cis*	2.80	3	13.3[c]

[a] Stiff polymer cut into thin slices, extracted twice with boiling methyl ethyl ketone, washed with petroleum ether, dried, ground, and heated to 100° at 1 mm. pressure for two to three hours. [b] Soft polymer broken up and soaked in methyl ethyl ketone for three days, washed on filter with petroleum ether and dried as in *a*. [c] Reaction products heated slowly at 3 mm. pressure up to 175°. Residue taken as polymer.

TABLE II

COPOLYMERIZATION OF REFERENCE MONOMERS (M_1) WITH *cis* AND *trans* ISOMERS (M_2) WITH 0.2 MOLE % BENZOYL PEROXIDE AT 60°

$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_1]$[a]	$[M_2]$[a]	Reaction time, hr.	Polymer analyses	
Styrene–Dimethyl Fumarate					% C	
64.00	16.68	47.38	8.46	32.0	75.28	75.06
40.40	39.53	25.46	26.80	35.1	70.02	79.86
16.10	62.60	3.16	49.25	30.2	67.33	67.31
Styrene–Dimethyl Maleate					% C	
63.90	17.42	28.50	15.85	42.7	88.91	89.72
40.00	42.18	22.40	39.76	21.1	85.75	85.45
16.07	67.80	79.15	63.45	11.4	77.54	77.39
Styrene–Monoethyl Fumarate					% C	
69.80	21.75	60.10	16.08	5.0	73.24	73.34
39.50	32.60	29.40	32.30	3.2	67.34	67.58
20.05	44.30	11.45	32.80	2.2	64.78	64.93
Styrene–Monoethyl Maleate					% C	
72.70	61.85	23.35	16.04	2.1	71.85	71.87
40.00	34.91	48.68	43.90	3.0	68.03	
16.05	35.78	78.00	62.85	2.1	65.77	65.74
Styrene–Fumaronitrile					% N	
80.10	21.55	54.45	7.42	8.5[c]	10.06	
79.10	20.00	50.60	6.09	8.5[c]	9.63	
19.95	79.20	5.01	65.70	3[e]	14.50	
19.80	79.82	4.20	66.85	3[e]	14.31	
78.70	19.86	73.229	16.997	2[d]	10.00	10.23
Styrene–Maleonitrile					% N	
19.89	4.62	16.30	2.818	8.5[d]	9.81	
6.795	28.10	3.507	25.30	32.5[e]	13.90	
78.60	19.43	74.324	17.083	2[c]	10.48	10.45
Styrene–*trans*-Dichloroethylene					% Cl	
78.89	19.18	54.29	19.00	24	0.43	0.55
79.06	19.57	54.96	19.38		0.54	0.54
Styrene–*cis*-Dichloroethylene					% Cl	
77.83	20.47	59.12	20.44	24	0.09	0.12
78.18	20.35	51.48	20.31		0.07	0.12
Vinyl Chloride–Diethyl Fumarate					% Cl	
16.48	78.65	11.02	59.07	26	5.13	5.31
17.40	79.32	11.96	62.82	25	6.05	6.41
					5.51	5.90
95.19	21.65	78.94	11.03	5.6	20.26	20.27
100.50	21.75	86.69	12.68	5.6	20.17	20.20
Vinyl Chloride–Diethyl Maleate					% Cl	
28.85	64.96	12.56	51.78	53	17.56	17.60
32.48	64.40	12.99	49.06	51	17.84	17.99
87.74	10.32	63.63	7.096	15.25[b]	41.52	41.44
84.89	10.13	60.01	6.925	15.25[b]	41.77	42.01
Vinyl Acetate–Diethyl Fumarate					% AcOH[f]	
15.90	62.90	11.75	51.13	8	10.45	
15.82	63.34	11.95	52.38	8	10.48	
58.30	11.79	51.56	5.03	1.25	23.20	
59.07	12.14	51.68	4.75	1.25	23.24	
Vinyl Acetate–Diethyl Maleate					% AcOH[f]	
15.63	66.55	9.56	59.50	9	21.00	
16.07	64.33	9.82	56.98	9	20.80	
57.72	13.47	49.33	8.73	2.5	32.76	
58.68	13.69	50.29	9.11	2.5	33.37	
Vinyl Acetate–*trans*-Dichloroethylene					% Cl	
78.15	18.86	33.97	9.81	7.5	13.74	13.70
78.40	20.26	34.88	10.65	7.5	14.51	14.59
19.46	79.25	1.09	49.50	121	47.19	47.33
18.91	76.95	0.41	46.44	136	47.59	47.53
Vinyl Acetate–*cis*-Dichloroethylene					% Cl	
78.30	20.51	17.15	16.37	7.5	5.22	5.11
78.40	20.46	15.71	16.22	7.5	5.18	5.13
19.00	81.25	0.35	65.87	121	35.07	35.22
19.61	79.75	.19	64.57	121	34.12	34.15

[a] Millimoles of unreacted monomers; zero subscripts indicate initial concentrations. [b] Contained 5.00 cc. chlorobenzene. [c,d,e] Contained 10,[c] 2.5,[d] or 3.75[e] cc. of chloroform, respectively. [f] The % acetic acid was determined by the method described by Mayo, Walling, Lewis and Hulse, THIS JOURNAL, 70, 1523 (1948), corrected empirically from the error in the nearest known sample: copolymers of diethyl fumarate and vinyl acetate, known to contain 10.97, 21.06 and 28.24% acetic acid, analyzed for 11.45, 20.90 and 27.95% acetic acid.

Vinyl acetate runs containing a high proportion of dichloroethylene were not precipitated at all but were heated slowly at 1 mm. pressure to remove monomer, finally for a minute or two at 150–175°. These residues were then analyzed directly.

The high vinyl chloride runs with diethyl maleate gave a precipitate of polymer and chlorobenzene was therefore added to some to keep them homogeneous. In low vinyl chloride runs, monomer reactivity ratios for the maleate radical varied with the isolation procedure although checks were obtained with each procedure: (a) simply distilling off the monomer from the soft liquid polymer at 150–200° and 2 mm. pressure gave 0.10; (b) precipitating the polymer three times, concentrating the liquors at reduced pressure and combining this residue with the polymer gave 0.05; (c) distilling off the bulk of the unreacted diethyl maleate first, then treating as in (b) with repeated washings of precipitated polymer with petroleum ether gave 0.009, the recorded results. The high vinyl chloride runs showed little difference between procedures (b) and (c), the polymers being harder and less readily soluble.

Chloroform was used as a solvent for all the dinitrile runs because fumaronitrile was immiscible with styrene. The polymers precipitated from solution as highly swollen gels; they were precipitated three times from methyl ethyl ketone with methanol and were then swollen in benzene

TABLE III

COMPARISON OF *Cis* AND *Trans* ISOMERS IN COPOLYMERIZATION

Reference monomer (M_1)	r_1	*cis–trans* isomer (M_2)	r_2	More reactive isomer	Less stable isomer	Planar *cis* form hindered
Styrene	0.30 ± 0.02[a]	Diethyl fumarate	0.070 ± 0.007[a]	*trans*	*cis*	+
	6.52 ± .50[a]	Diethyl maleate	< .01[a]	(21)[f]		
Styrene	0.21 ± .02	Dimethyl fumarate	.025 ± .015	*trans*	*cis*	+
	8.5 ± .2	Dimethyl maleate	.03 ± .01	(40)		
Styrene	0.18 ± .10	Monoethyl fumarate	.25 ± .10	no significant difference	*cis*	–
	.13 ± .01	Monoethyl maleate	.035 ± .01			
Styrene	.19 ± .03	Fumaronitrile	.0		*cis*	–
	.19 ± .01	Maleonitrile	.0			
Styrene	37 ± 3	*trans*-Dichloroethylene	.0	*trans*	*trans*	–
	210 ± 15	*cis*-Dichloroethylene	.0	(6)		
Vinyl chloride	.12 ± .01	Diethyl fumarate	.47 ± .05	*trans*	*cis*	+
	.77 ± .03	Diethyl maleate	.009 ± .003	(6.5)		
Vinyl acetate	.011 ± .001	Diethyl fumarate	.444 ± .003	*trans*	*cis*	+
	.17 ± .01	Diethyl maleate	.043 ± .005	(15)		
Vinyl acetate	.99 ± .02	*trans*-Dichloroethylene	.086 ± .01	*trans*	*trans*	–
	6.3 ± .2	*cis*-Dichloroethylene	.018 ± .003	(6.5)		
Maleic anhydride	0.03 ± .03	Stilbene	.03 ± .03	*trans*	*cis*	+
	.08 ± .08	Isostilbene	.07 ± .07	(1.5–2.0)[b]		
Diethyl maleate or fumarate		Diethyl fumarate		*trans*	*cis*	+
		Diethyl maleate		(52,[c] 10[d], >7[e])		
Dichloroethylene		*trans*-Dichloroethylene		*trans*	*trans*	–
		cis-Dichloroethylene		(4.8)[d]		

[a] Experimental errors for ethyl esters are based on a possible 0.1 or 0.2% error in carbon analyses.[10] Experimental errors in other instances represent the areas of the intersections obtained in graphical solutions of the copolymerization equation. [b] From rates of polymerization, Table I. [c,d,e] From copolymerizations with vinyl chloride, vinyl acetate, and styrene, respectively. [f] Ratio of reactivities of two isomers toward reference radical.

and subjected to the freezing procedure, or dried in powder form when obtainable.

The copolymers formed from all maleic anhydride–stilbene feeds were 1:1 copolymers within experimental error. The *rates* of copolymerization of the two isomers were therefore compared. Even in chloroform the polymers formed a gel, including all the reaction mixture and becoming stiffer as the reaction progressed. Data are summarized in Table I.

Discussion

Results of comparisons of *cis* and *trans* isomers are summarized in Table III. The experimental errors given were, in general, obtained from the standard deviation of individual experiments.[10] In the cases of some of the maleic and fumaric esters, however, the low volatility of these monomers and their high solubility in the polymer made their complete removal difficult and actual errors may be larger. This is especially likely for the vinyl acetate–maleate and fumarate and styrene–methyl maleate and fumarate systems with which special precautions[10] (see Experimental part, also ref. 10) were not taken.

The addition of a free radical to either a *cis* or *trans* isomer presumably results in the formation of the same free radical with the three attached substituents in the same plane[11] or with a pyramidal configuration which is easily reversible. Accordingly, addition to the isomer which is less stable thermodynamically might be expected to require less activation energy, so that this isomer should be the more reactive. However, the data show that dialkyl fumarates are 6–20 times as reactive as the maleates toward the styrene, vinyl chloride, and vinyl acetate radicals. Our previous conclusion that the possibilities of resonance in the activated complex[1] is a major factor governing the reactivity of double bonds toward free radicals suggests a probable explanation for such results. When a radical adds to these monomers, the activated complex can be stabilized by resonance between forms I–III only if the oxygen of the carbonyl group involved lies in the same plane as the other atoms attached to the doubly-bound carbon atoms.

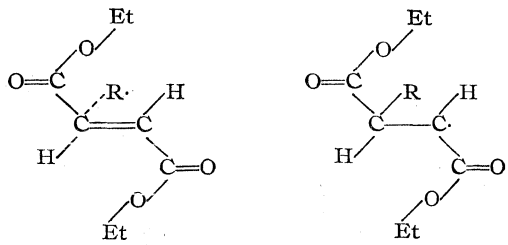
Consideration of models shows that the two ester groups in maleic esters cannot be coplanar simultaneously and interference between them is such that a coplanar configuration for either is not very probable. On the other hand, in the fumaric esters either or both ester groups may be coplanar. Such an interpretation also suggests a reason for the high reactivity of the double bond of maleic anhydride[1] in which both carbonyl groups are constrained to a coplanar configuration by the five-membered ring. Price[12] has proposed that purely steric effects can account for the observed differences without considering resonance.

Similarly, in *cis*-stilbene, both rings cannot be

(10) Lewis, Walling, Cummings, Briggs and Mayo, THIS JOURNAL, **70**, 1519 (1948).

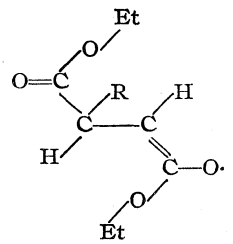
(11) An unsuccessful search for differences in the free radicals from the *sym*-dichloroethylenes was made by K. E. Wilzbach in this Laboratory.

(12) Price, *J. Polymer Sci.*, **1**, 83 (1946).



I

II



III

simultaneously coplanar and the possibilities of activation of the double bond by the phenyl groups are less favorable than in *trans*-stilbene. The rate data show that the *trans* form is 1.5–2 times as reactive as the *cis* form toward the maleic anhydride radical.[13] The half esters of maleic and fumaric esters did not differ significantly. Here the smaller size of the substituent and the possibilities (at least) of hydrogen bonding and ring formation in the *cis* form reduce the difference found between the normal esters.

In the cases of the dichloroethylenes and the dinitriles, no steric inhibition of resonance can be involved. Although the ratio of *cis* to *trans* forms in the equilibrium mixture of the dichloroethylenes is about 3.5, the *trans* form reacts 6–7 times as fast with both the styrene and vinyl acetate radicals. Thus the difference in free energy of activation is greater than the free energy difference in the monomers. The equilibrium *trans*:*cis* ratio in the dinitriles is about 3.0, but there is no difference in reactivity. Here the difference in rate of reaction is less than would be anticipated. These results show that the isomer pairs do not yield the same activated complex (whether or not they are eventually converted to the same radical) and that there is no consistent relation between the free energies of the isolated monomers and their free energies of activation. The results further suggest that the dipole and resonance effects and energy levels which determine the relative stabilities of the pure monomers lead to larger differences in the stabilities of the activated complexes.

Our data show that coplanarity of conjugated groups is an important factor determining the relative reactivities of *cis–trans* isomers in copolymerization. The general principle that the less stable isomer should be more reactive is only a qualitative guide in other cases, showing that other factors must be considered. Factors such as general availability of electrons in the double bonds[14] or dipole moment have not led to useful correlations in these compounds. The present work suggests also that the steric inhibition of resonance should be important in the copolymerization of 1,1-disubstituted ethylenes: vinylidene chloride is considerably more reactive than vinyl chloride and 1,1-dicyanoethylene should be much more reactive than acrylonitrile, but because of interference between the 1-substituents, considerably less difference should be expected between 1,1-diphenylethylene and styrene, or between methylenemalonic esters and acrylic esters.

(13) This comparison of rates assumes that the rate of chain initiation is the same in both monomer mixtures, and that both isomers yield the same free radical, so that the rates of reaction of this radical with maleic anhydride and the rates of chain termination are the same in both experiments.

Summary

The relative reactivities of the *cis* and *trans* forms of six pairs of isomers have been compared with radicals from a total of four monomers. The order of decreasing activity, maleic anhydride, fumaric esters, maleic esters, parallels the decreasing ability of these monomers to assume a planar configuration and thus to stabilize the activated complex by resonance with the carbonyl groups. Similarly, the inability of both phenyl groups in isostilbene to resonate with the double bond accounts for the higher reactivity of stilbene.

Of the 1,2-dichloroethylenes, the less stable *trans* form is more reactive, while maleonitrile and fumaronitrile are equally reactive. Thus, steric inhibition of resonance, when it occurs, seems to determine the relative reactivities of geometrical isomers, and the relative stabilities of the isomers has only a qualitative relation to reactivity in other cases.

PASSAIC, NEW JERSEY RECEIVED JULY 17, 1947

(14) Price and Alfrey, *J. Polymer Sci.*, **2**, 101 (1947).

[CONTRIBUTION NO. 72 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. X. The Effect of *meta*- and *para*-Substitution on the Reactivity of the Styrene Double Bond

BY CHEVES WALLING, EMORENE R. BRIGGS,[1a] KATHERINE B. WOLFSTIRN[1b] AND FRANK R. MAYO

Although previous work has established the validity of the copolymerization equation[2] as a description of the free radical copolymerization of a large number of systems,[3] interpretation of the monomer reactivity ratios observed has been neither simple nor unequivocal. Thus, the reactivities of monomers in copolymerization depend both upon a general order of reactivity, apparently independent of the attacking radical and related to the resonance stabilization of the radical resulting from reaction, and a specific tendency of certain monomers to alternate in copolymerization. This "alternating tendency" has proved to be of particular interest, and polar interaction,[4,5] electron donor–acceptor properties[6] and actual compound formation,[4] have been suggested as possible causes. Still further factors appear to be involved in the interpretation of the relative reactivities of *cis-trans* isomers,[7] and in some systems, where monomer reactivity ratios appear to depend upon differences in both heats and entropies of activation[8] the situation is still further complicated.

Since any attempt to identify or evaluate all of these factors in the copolymerization of the usual monomers appeared to us a formidable undertaking, we have looked for a simpler system. We have chosen the *meta* and *para*-substituted styrenes since the effect of *meta* and *para* substitution on the rates and equilibria of (polar) side-chain reactions of benzene appear to be particularly simple and well understood. Thus, Hammett, who has surveyed available data on a wide variety of such side-chain reactions of benzene,[9] has found that, in general, the effect of *meta*- or *para*-substituents can be expressed by the relation $\log K_0/K = \sigma\rho$, where K_0 and K are the rate or equilibrium constants for the reaction of the unsubstituted and substituted compound, σ a parameter having a single value for each substituent and ρ a constant for any particular reaction. The parameters σ and ρ are probably best interpreted as measures, respectively, of the ability of the substituent to withdraw electrons or make them available at the site of reaction and the effect of such electron-availability on the reaction considered.

If a given monomer (M_1) is copolymerized in turn with a series of substituted styrenes (M_2's), the reciprocals of the monomer reactivity ratios for the radical corresponding to that monomer ($1/r_1$'s) are the relative reactivities of the substituted styrenes with that radical. Such series, obtained with several radicals, might permit the assigning of a value to each substituent analogous to Hammett's σ value, but applying now to *radical* reactions rather than to ones proceeding through "polar" intermediates. In particular, it was hoped that such a series might throw light on the nature and magnitude of the "alternating effect" in copolymerization.

Experimental

Materials.—Styrene and methyl methacrylate were commercial materials, distilled before use and stored in the ice-box. *p*-Methoxy, *p*-chloro, *m*-chloro-, *o*-chloro- and *m*-bromostyrene were prepared by the decarboxylation of the corresponding cinnamic acids. Their preparation and properties are described elsewhere,[10] as are the preparation and properties of the samples of *p*-iodo, *p*-nitro and *p*-dimethylaminostyrene.[11] *p*-Bromostyrene was prepared by the aluminum isopropoxide reduction of *p*-bromoacetophenone followed by dehydration over potassium bisulfate essentially as described by Brooks.[12] An over-all yield of 32.8% of product was obtained, b. p. 49.5–50.0° (2.5 mm.), $n^{20}D$ 1.5952 (lit. gives b. p. 83.5–84.5 (11 mm.), $n^{20}D$ 1.5961).[13] By similar procedures were prepared *p*-methylstyrene in over-all yield of 34.7%, b. p. 59.3–59.5° (15.5 mm.), $n^{20}D$ 1.5425 (lit. gives b. p. 65–66 (18 mm.), $n^{25}D$ 1.5402[14]), and *p*-cyanostyrene in over-all yield of 15.2%, b. p. 69–71 (2 mm.), $n^{20}D$ 1.5795 (lit. gives b. p. 102–4 (9 mm.), $n^{20}D$ 1.5781[15]). *m*-Methylstyrene was a sample supplied by Dr. Schoene of the Naugatuck Chemical Co. Refractionated here, it had an index of refraction $n^{20}D$ of 1.5402 (lit. $n^{20}D$ 1.5410[16]).

Copolymerization Technique.—Polymerizations were carried out at 60° in sealed evacuated tubes essentially as described in the first paper in this series,[2b] using 0.05 to 0.10 mole total monomers and 0.1 mole % benzoyl peroxide in each experiment. In general two experiments each at 1:4 and 4:1 molar ratios were carried out on each

(1a) Present address, R. F. D. 2, Guilford, Conn.

(1b) Present address, Bell Telephone Laboratories Summit, N. J.

(2) (a) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1944); (b) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944); Wall, *ibid.*, 2050.

(3) For a recent summary and references, see Mayo, Lewis and Walling, *ibid.*, **70**, 1529 (1948).

(4) Mayo, Lewis and Hulse, THIS JOURNAL, **67**, 1701 (1945).

(5) (a) Price, *J. Polymer Sci.*, **1**, 83 (1946); (b) Alfrey and Price, *ibid.*, **2**, 101 (1947).

(6) Bartlett and Nozaki, THIS JOURNAL, **68**, 1495 (1946).

(7) Lewis and Mayo, *ibid.*, **70**, 1533 (1948).

(8) Lewis, Walling, Cummings, Briggs and Mayo, *ibid.*, **70**, 1519 (1948).

(9) Hammett "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Ch. VII.

(10) Walling and Wolfstirn, THIS JOURNAL, **69**, 852 (1947).

(11) Strassburg, Gregg and Walling, *ibid.*, **66**, 2141 (1947). The authors are also indebted to Mr. Strassburg for the preparation of the styrenes described below.

(12) Brooks, *ibid.*, **66**, 1295 (1944).

(13) Ziegler and Tiemann, *Ber.*, **55**, 3414 (1922).

(14) Mowry, Renoll and Huber, THIS JOURNAL, **68**, 1105 (1946).

(15) Marvel and Overberger, *ibid.*, **67**, 2250 (1945).

(16) Marvel, Overberger, Allen and Saunders, *ibid.*, **68**, 736 (1946). The sample from Dr. Schoene was obtained by the steam distillation of unreacted monomers from a butadiene-*m*-methylstyrene copolymer and is believed to have come originally from the University of Illinois.

monomer pair, as this provides a better check on experimental error than several experiments each with different monomer compositions. Polymers, whenever possible, were worked up by the frozen benzene technique.[17a] *p*-Cyanostyrene copolymers made from high *p*-cyanostyrene feeds and all *p*-nitrostyrene copolymers however, were insoluble in benzene. *p*-Nitrostyrene copolymers from high *p*-nitrostyrene feeds were insoluble in all solvents tried and were freed from monomer as well as possible by repeated swelling in chloroform and shrinking in petroleum ether, followed by drying for a week at 70° *in vacuo*. The other benzene-insoluble polymers were repeatedly dissolved in chloroform and precipitated with petroleum ether, followed by vacuum drying at 70°. Polymer compositions were determined by elementary analysis and the quantities of unreacted monomers then calculated by difference. Experimental data for four typical systems are given in Table I.[17b]

Calculation of Results and Experimental Errors.—Monomer reactivity ratios were determined graphically[2b] for each monomer pair, the results for the four pairs for which data are listed in Table I being illustrated in Fig. 1. Results for all of the systems are tabulated in Tables II, III and IV, together with a number of derived quantities. Experimental errors were calculated as described previously[8] using the assumed analytical errors listed in the tables. In all but four cases all lines corresponding to individual experiments passed through the calculated parallelograms (*cf.* Fig. 1.). In the four showing a larger scatter, the standard deviation of duplicate experiments was taken as the experimental error.[8]

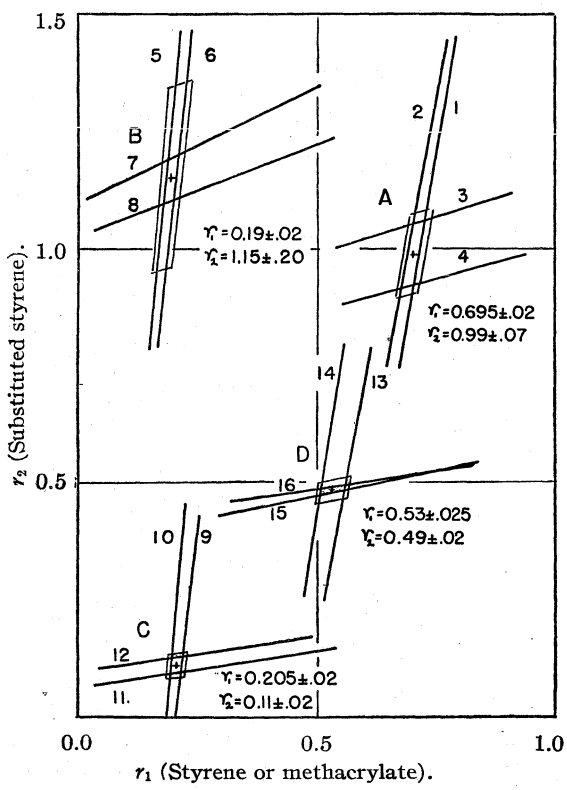


Fig. 1.—Graphical solutions of copolymerization equation for representative systems listed in Table I: A, styrene–*p*-bromostyrene; B, styrene–*p*-nitrostyrene; C, methacrylate–*p*-dimethylaminostyrene; D, methacrylate–*m*-methylstyrene. Numbers of lines correspond to experiments in table.

TABLE I

REPRESENTATIVE COPOLYMERIZATIONS OF STYRENE AND METHYL METHACRYLATE WITH SUBSTITUTED STYRENES AT 60°

Expt.	$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_1]$[b]	$[M_2]$[b]	Time, hr.	Polymer analyses	
	Styrene $[M_1]$–*p*-Bromostyrene $[M_2]$					% Br	
1	66.0	15.76	50.6	11.18	15.5	14.91	15.06
2	64.6	15.52	49.2	10.80	15.5	15.49	15.02
3	9.90	38.28	7.13	26.70	14	38.37	38.18
4	10.30	38.21	7.34	27.17	14	37.49	37.75
	Styrene $[M_1]$–*p*-Nitrostyrene $[M_2]$					% N	
5	39.58	10.80	35.37	7.67	96	4.83	4.85
6	39.65	10.35	35.70	7.66	96	4.60	4.67
7	10.18	31.33	8.17	22.80	31	7.98	8.13
8	9.84	30.55	7.71	22.13	31	8.38	7.73
						8.10	7.84
						7.87	
	Methyl Methacrylate $[M_1]$–*p*-Dimethylaminostyrene $[M_2]$					% N	
9	41.160	10.410	39.275	9.367	261	4.31	4.25
10	40.050	10.100	38.514	9.228	329	4.35	4.32
11	10.110	29.270	9.896	29.014	329	6.07	
12	10.070	29.408	9.860	29.142	329	6.23	
	Methyl Methacrylate $[M_1]$–*m*-Methylstyrene $[M_2]$					% C	
13	47.69	17.28	38.42	12.84	11	71.31	71.36
14	48.69	11.89	36.58	7.78	11	68.96	69.10
15	12.88	49.10	6.49	31.74	32	83.97	83.92
16	11.60	48.80	5.78	31.35	32	84.53	84.56

[a] Millimoles of initial monomers. [b] Millimoles of unreacted monomers.

The median % of the measured values of r_1 for the errors in r_1's listed in Tables II and III is 7%. For r_2's, it is larger, 11.6%, and could probably be improved somewhat by using lower than 4:1 feeds in the high substituted styrene experiments since analyses in these runs usually involved determining small amounts of M_1 in the polymer by difference. The main subject of this paper, however, is concerned with the consideration of r_1 values, and their accuracy appears to lie close to the limits of our experimental techniques.

Experiments on Complexes.—Absorption coefficients for violet light for maleic anhydride-substituted styrene complexes were measured using a Cenco photelometer with a Corning #511 filter. Chloroform solutions giving 30–70% transmission (approximately 3 molar in styrene and 2 molar in maleic anhydride for most of the styrenes) were employed and $\log_{10} I_0/I$ calculated for a solution 1 molar in each component, assuming a highly dissociated 1:1 complex following the law $\log I_0/I = K$ [styrene][maleic anhydride]. The high dissociation and obedience to the above law was established for styrene–maleic anhydride

(17a) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

(17b) A tabulation of all of the experimental data obtained in this investigation may be obtained by requesting Document 2497 from American Documentation Institute, 1719 N Street, Washington 6. D. C., remitting 50¢ for microfilm or 70¢ for photoprints.

TABLE II

MONOMER REACTIVITY RATIOS AND DERIVED QUANTITIES FOR THE COPOLYMERIZATION OF STYRENE (M_1) WITH SUBSTITUTED STYRENES (M_2)

Substituent	Assumed[a] error, %	r_1	r_2	r_1r_2	Log rel. reactivity[b]	Hammett σ value
p-OCH_3	0.1 C[c]	1.16 ± 0.09	0.82 ± 0.07	0.95 ± 0.11	−0.065 ± 0.034	−0.268
p-$N(CH_3)_2$	.1 N	1.015 ± .06	0.84 ± .05	0.85 ± .07	− .006 ± .027	− .205
None	.....	1.00	1.00	1.00	.000	.000
p-Cl	.1 Cl	0.74 ± .03	1.025 ± .05	0.76 ± .05	.132 ± .018	.227
p-Br	.2 Br	.695 ± .02	0.99 ± .07	.69 ± .05	.158 ± .013	.232
p-I	.5 I	.62 ± .05	1.25 ± .30	.76 ± .20	.208 ± .035	.276
m-Cl	Std. dev.[c]	.64 ± .05	1.09 ± .23	.70 ± .16	.193 ± .034	.373
m-Br	Std. dev.[c]	.55 ± .03	1.05 ± .21	.58 ± .13	.260 ± .024	.391
p-CN	0.1 N	.28 ± .025	1.16 ± .13	.325 ± .047	.553 ± .039	1.000[d]
p-NO_2	.1 N	.19 ± .02	1.15 ± .20	.218 ± .045	.722 ± .046	1.27[d]

[a] Analytical error assumed in calculating errors in subsequent columns. [b] *I. e.*, $-\log_{10} r_1$. [c] See text. [d] Value for reaction with phenols and amines (the only one available for *p*-CN). [e] Small experimental error achieved through use of simultaneous blanks in analysis. Unusual accuracy was required in this case because of small difference in carbon analysis between monomers.

TABLE III

MONOMER REACTIVITY RATIOS AND DERIVED QUANTITIES FOR THE COPOLYMERIZATION OF METHYL METHACRYLATE (M_1) WITH SUBSTITUTED STYRENES (M_2)

Substituent	Assumed[a] error, %	r_1	r_2	r_1r_2	Log rel. reactivity[g]	Hammett σ value
p-OCH_3	0.1 C	0.29 ± 0.03	0.32 ± 0.05	0.093 ± 0.017	0.230 ± 0.045	−0.268
p-$N(CH_3)_2$	.1 N	.205 ± .02	.11 ± .02	.023 ± .005	.351 ± .042	− .205
p-CH_3	.2 C	.405 ± .025	.44 ± .02	.178 ± .014	.056 ± .027	− .170
m-CH_3	.2 C	.53 ± .025	.49 ± .02	.26 ± .02	−.062 ± .021	− .069
None[f]	.2 C	.46 ± .026	.52 ± .026	.24 ± .02	.000	.000
p-Cl	.1 Cl	.415 ± .02	.89 ± .05	.37 ± .03	.046 ± .021	.227
p-Br	.2 Br	.395 ± .02	1.10 ± .25	.44 ± .10	.067 ± .022	.232
p-I	.5 I	.36 ± .03	0.95 ± .20	.34 ± .08	.107 ± .036	.276
m-Cl	Std. dev.[c]	.47 ± .075	0.91 ± .11	.43 ± .09	−.009 ± .070	.373
m-Br	0.2 Br	.48 ± .02	1.17 ± .25	.56 ± .12	−.018 ± .018	.391
p-CN	0.1 N	.22 ± .02	1.41 ± .13	.31 ± .04	.321 ± .040	1.000[d]

[f] From data of ref. (2b) recalculated in ref. (8). [g] Compared with styrene, *i. e.*, log 0.46 − log r_1. Other footnotes have same significance as in Table II.

TABLE IV

MONOMER REACTIVITY RATIOS FOR COPOLYMERIZATIONS OF SOME ADDITIONAL VINYL AROMATICS

M_1	M_2	Assumed error	r_1	r_2
p-Chloro-styrene	*p*-Methyl-styrene	0.1% Cl	1.15 ± 0.05	0.61 ± 0.03
p-Chloro-styrene	*p*-Methoxy-styrene	0.1% Cl	0.86 ± .08	.58 ± .03
p-Chloro-styrene	*p*-Nitro-styrene	Std. dev.	0.70 ± .08	.91 ± .37

by Dr. F. M. Lewis in another study in this Laboratory.

Complexes with chloranil were much more stable and showed appreciable color in concentrations ranging from 0.008 *M* chloranil in 0.35 *M* styrene for the styrene–chloranil complex to 0.000003 *M* chloranil in 0.05 *M* *p*-dimethylaminostyrene for the *p*-dimethylaminostyrene complex.

Trinitrobenzene complexes were prepared by dissolving 1,3,5-trinitrobenzene in the styrenes and appeared to show intermediate intensity of color.

Results and Discussion

Relative Reactivities toward Styrene-type Radicals.—Monomer reactivity ratios and some derived quantities for the copolymerizations described in Table I are listed in Table II. In Figure 2 the logarithms of the relative reactivities of the substituted styrenes toward the unsubstituted styrene radical are plotted against Ham-

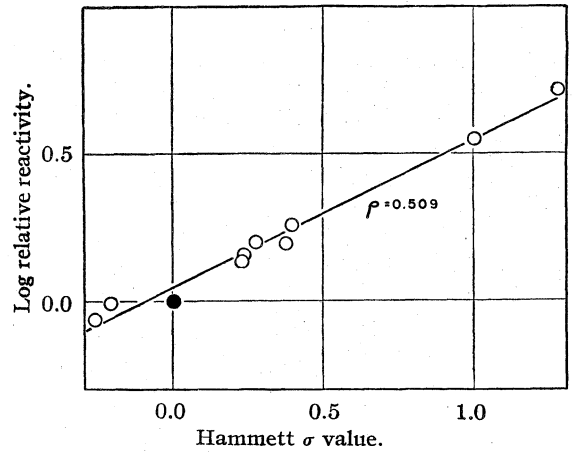


Fig. 2.—Plot of log relative reactivity toward the styrene type radical *vs.* Hammett σ value of substituent for various substituted styrenes.

mett's σ values for the same substituents. Strikingly, excellent correspondence is observed between the relative reactivities and Hammett's σ values. The median deviation of points from the best straight line (drawn by the method of least squares) is only 0.024 log unit, less than the average experimental error, and better than all but six of the 52 polar reactions originally investigated by Hammett.[9] In short, this radical reaction behaves like an ordinary polar reaction with a ρ value (the slope of the line in Fig. 1) of 0.509, approximately the same as that for the ionization of phenylacetic acids.[9,18]

If the Hammett σ values may be interpreted as measures of electron density at the site of reaction (here the substituted styrene double bond) this result suggests that polar interaction between reactants, perhaps of the sort suggested by Price and Alfrey,[5] may be of primary importance in determining reactivity in this series. Further, since ρ is positive and dipole measurements[19] show the styrene double bond to possess an absolute negative charge, the styrene-type *radical* must possess an effective negative charge as well as it approaches the monomer.[20]

If such a polar interaction were here the primary factor in determining relative reactivity, it would be predicted that substituting the styrene radical with negative (electron-attracting) groups should decrease the magnitude and possibly even change the sign of its charge. As a result, the reactions of styrenes with negatively substituted styrene radicals should have decreasing and perhaps even negative ρ values. In Fig. 3 are plotted relative reactivities taken from the more reliable data of Tables II and IV *vs.* σ values for the reactions of some substituted styrene radicals with substituted styrenes. Although the prediction is realized, the ρ values seem to fall into two sharp classes, positive and roughly equal for styrene and positively substituted styrenes, and close to zero for those with negative substituents.

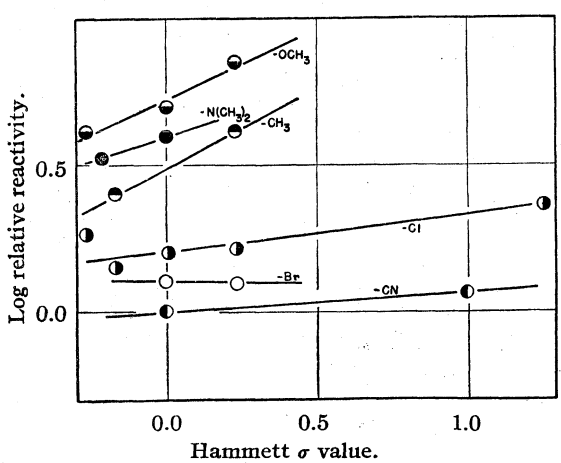


Fig. 3.—Plot of log relative reactivities toward indicated *para*-substituted styrene radicals *vs.* Hammett σ values for various substituted styrenes. Height of ordinate scale is arbitrary.

The interpretation given above fails to take into account any contribution from the differing resonance stabilizations of the resulting substituted styrene radicals to the reactivities of the substituted styrenes.[3,4,5,21] On the other hand, if the results illustrated in Fig. 3 are to be ascribed entirely to such differential stabilization, the close agreement with the Hammett series must be partly coincidental, and the decreased reactivities of the *p*-methoxy- and *p*-dimethylaminostyrenes (for which plausible additional resonance forms can be drawn) are surprising. Furthermore, there then seems to be no simple way of accounting for the observed reactivities toward substituted styrene radicals (*cf.* Fig. 3).

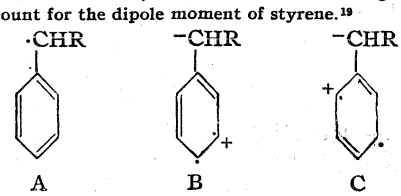
That resonance stabilization of the resulting radicals may, however, play some role in the observed reactivities is suggested by a closer inspection of Fig. 2, where it will be noted that the (black) point corresponding to styrene lies appreciably below the best square line. Since all other points were determined by comparison with styrene, purely random scatter would be expected to put the styrene point on the line. On the other hand, such a result may be due to increased reactivity of all the substituted styrenes due to additional resonance stabilization of their resulting radicals above that arising from polar interaction. It is likely that both factors are involved to some degree, but a determination of their relative magnitudes is not as yet possible.

Relative Reactivities toward the Methyl Methacrylate Radical.—Monomer reactivity ratios for the reaction of methyl methacrylate with eleven substituted styrenes are listed in Table III, and, in Fig. 4, logarithms of relative reactivities are plotted against the Hammett σ values for the substituents. It can be immediately seen that, unlike the case for reaction with the styrene radical, no simple linear relation is evident and no generally applicable value of ρ can be selected. In short, in the case of this radical, derived from the class of carbonyl-conjugated monomers which tend to alternate in copolymerization with sty-

(18) Kindler, *Ann.*, **452**, 90 (1927).

(19) Styrene has a dipole moment of 0.37 debye unit, opposite in direction to toluene, Otto and Wenzke, THIS JOURNAL, **57**, 294 (1935).

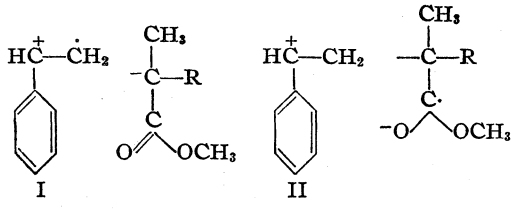
(20) Since both reactants would possess like charges, this could hardly represent an induced polarization, but must correspond to either a general inductive effect of the ring or contributions from structures such as B and C, similar to those which might be called upon to account for the dipole moment of styrene.[19]



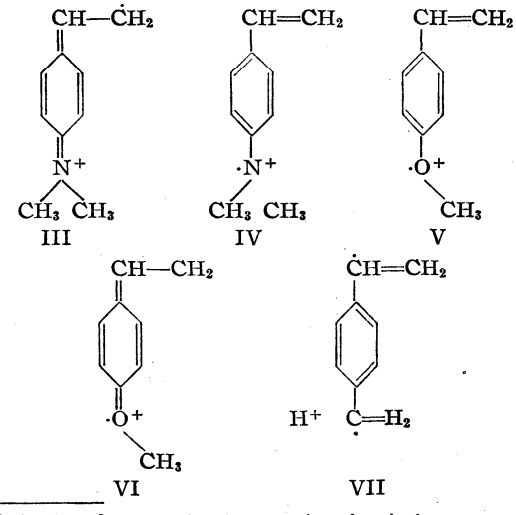
(21) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, Chap. 8.

rene,[2b,3] some additional factor besides those considered in the preceding section must be at work determining the effect of substituents on reactivity.

Other cases of deviation from the usual Hammett series can sometimes be accounted for by special resonance forms available to one of the reactants in the transition state.[22] Here, since the respective electron accepting and donating properties of carbonyl-conjugated and aromatic systems are well recognized, it seems reasonable to consider the possible contributions of non-bonded and bonded structures such as I and II.[23] Since transfer of an electron to give the non-bonded structure I transforms the methacrylate radical to the relatively stable enolate ion, while the styrene radical carbonium ion may resonate through some twenty-six more or less equivalent forms, structure I appears to have considerable plausibility. Similarly, the energy difference gained in forming a C–C bond while opening a carbonyl group and by the shifting of a negative charge to oxygen suggests that contributions from II might also be important. Inspection of Fig. 4, however, indicates that the chief problem in this discussion lies in accounting for the high reactivities of *p*-dimethylamino-, *p*-methoxy- and, to a lesser degree, *p*-methylstyrene. By this interpretation, there should be available to them additional forms not possessed by the styrene radical carbonium ion. A number of such structures can be drawn, of which III–VII are examples.



I II



III IV V VI VII

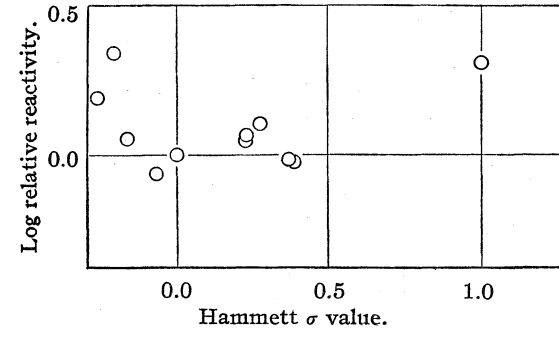
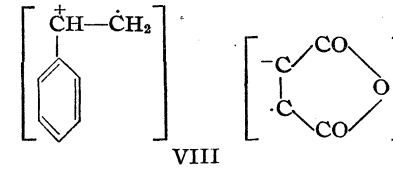


Fig. 4.—Plot of log relative reactivity toward the methyl methacrylate type radical *vs.* Hammett σ value of substituent for various substituted styrenes.

An interesting property of unsaturated carbonyl compounds and similar materials (maleic anhydride, quinones, polynitrobenzenes, etc.) is that they form colored molecular complexes with styrenes and other aromatic compounds. A suggested structure of these materials is one consisting of pairs of radical ions in which the aromatic compound has donated an electron to the conjugated carbonyl system,[24] for styrene–maleic anhydride, the hybrid resulting from the resonance between various forms of VIII.



VIII

Inspection of VIII shows the styrene portion to be identical with I. It is thus evident that, if the unbonded resonance forms are important, a relation should exist between the complex forming tendency of substituted styrenes and their tendency to copolymerize with acceptor radicals.[25] Some observations on such complexes are listed in Table V in which the nature of light absorption of complexes of substituted styrenes with maleic anhydride, 1,3,5-trinitrobenzene, and chloranil is compared with their reactivity toward the methacrylate radical. Maleic anhydride yields rather unstable complexes, highly dissociated in solution and, since all are yellow in dilute solution, their relative absorption of violet light has been com-

(22) Thus, for example, the necessity of assigning two σ values to the *p*-nitro group, one for the reactions of amines and phenols, in all probability arises from the heightened resonance possibilities between nitro and —OH or —NH_2 groups. Physical evidence of such interaction has long been available from dipole moments, increased color, etc.

(23) The possibility of the importance of special resonance structures in the transition state as a means of interpreting alternation in coplymerization was first made to us by Prof. Saul Winstein of the University of California at Los Angeles, and we are indebted to him for several discussions which have been most helpful in formulating the viewpoint expressed here.

(24) Weiss, *J. Chem. Soc.*, 245 (1942).

(25) A relation between the complex forming and copolymerizing tendencies of maleic anhydride has been suggested by Bartlett and Nozaki, ref. 6. Also Woodward, THIS JOURNAL, **64**, 3058 (1942), has postulated the existence of structures similar to VIII in the transition state of the Diels–Alder reaction.

pared. Chloranil complexes are more stable (preliminary measurements indicate dissociation constants of 1–5 and heats of dissociation of 0 to −1500 cal./mole) and have absorption maxima in the visible spectrum, while trinitrobenzene complexes have intermediate properties. Examination of the data of Table V shows a very reasonable correlation between increasing depth of color (shade or intensity) and reactivity, and lends strong support, in general, to the idea of a relation between the complex forming tendency of styrenes and their ease of copolymerization with radicals conjugated with a carbonyl system, and in particular, to the idea of the importance of special forms in the transition state of such copolymerizations.

TABLE V

COMPLEXES OF SUBSTITUTED STYRENES

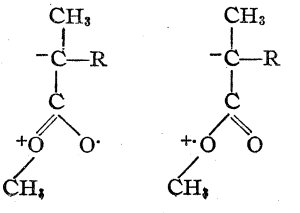
Substituent	Rel. reactivity	Maleic color	anhydride intensity[a]	Trinitrobenzene color	Chloranil color
p-OCH_3	1.59	Yellow	3.95	Orange	Red-violet
p-$N(CH_3)_2$	2.24	Red[b]	20.5	Deep violet	Sky blue
p-CH_3	1.14	Yellow	0.202	Deep yellow	Orange
m-CH_3	0.87	Yellow	.080	Yellow	.....
None	1.00	Yellow	.027	Yellow	Yellow
p-Cl	1.11	Yellow	.046	Yellow	Yellow
m-Cl	0.98	Yellow	.019	Pale yellow	.....

[a] Log I_0/I for a 10-mm. cell containing 1 *M* styrene and 1 *M* maleic anhydride in chloroform viewed with a Corning 511 (violet) filter. [b] Yellow in dilute solution.

Even though special resonance forms are of primary importance in determining the reactivities of styrenes toward the methacrylate radical, some contribution might still be expected from the resonance structures of the resulting radical and (unless the methacrylate radical is just electrically neutral) polar interactions. Some evidence for such contribution is gained from Fig. 4, for, if the points for *p*-methyl-, *p*-dimethylamino-, and *p*-methoxystyrenes (the monomers showing the highest complex-forming tendencies) are omitted, a line can be drawn through the remaining points corresponding to a ρ value of 0.33 with the reasonable median deviation of 0.04 log unit. Differences in reactivities of these styrenes may thus be due to the same factors as govern reactivity toward the styrene radical.[26] Consideration of these factors also aids in interpreting the r_2 values in Table III. Thus, negatively substituted styrene radicals show little preference in reaction with their own monomers or methacrylate, paralleling their behavior toward styrene. On the other hand, the styrene radicals with electron-supplying groups show heightened reactivity toward methacrylate, as might be anticipated since structures analogous to I–VII can be drawn in which an electron has been donated from the styrene radical to the methacrylate double bond.

The necessity of considering special resonance forms related to those involved in molecular complex formation in interpreting the copolymerization of styrenes with even such a weakly alternating monomer as methyl methacrylate (r_1r_2 = 0.24) makes it appear likely that they, rather than some sort of simple electrostatic interaction, are primarily responsible for the "alternating effect" in copolymerization. Accordingly, it seems doubtful to us that the equation of Alfrey and Price[5b] has any real theoretical justification.[27] The determination of the relative reactivities of styrenes with a more strongly electron accepting radical is described in Paper XII of this series, and will be the subject of future communications.

(26) The same difficulties arise, however, in assessing the importance of differences in the resonance stabilization of the resulting radical. If such differences are minor, incidentally, and the effects primarily polar, we are led to the conclusion that the methacrylate radical possesses a partial negative charge. Since the ester group would usually be expected to attract rather than donate electrons, this conclusion is surprising and suggests the possibility of resonance forms such as



Summary

1. Copolymerizations of methyl methacrylate and styrene with eleven *meta* and *para* substituted styrenes have been carried out and the monomer reactivity ratios calculated.

2. The relative reactivities of the substituted styrene radical closely follow the order found by Hammett for "polar" side-chain reactions of benzene, with a ρ value of 0.509. Negatively substituted styrene radicals show lower ρ values. These results are interpreted as being due to the effect of substituents on the polar interaction between the styrene and the radical as they approach the transition state and on the resonance stabilization of the resulting radicals.

3. Relative reactivities of substituted styrenes toward the methyl methacrylate type radical fail to follow a Hammett series. These results are interpreted as being due to the effect of contributions of non-bonded resonance forms to the transition state in which the radical has accepted an electron, superimposed upon factors similar to those involved in reaction with the styrene radical.

4. Molecular complexes between substituted styrenes and maleic anhydride, trinitrobenzene and chloranil have been investigated and a relation between complex forming tendency and abnormal reactivity toward the methacrylate radical noted and interpreted on the basis of the importance of non-bonded resonance structures.

PASSAIC, NEW JERSEY RECEIVED JULY 22, 1947

(27) Attempts to calculate *Q*'s and *e*'s by Alfrey and Price's equation for the systems reported here have not given very satisfactory agreement with experiment and have fallen down particularly in the cases where strong alternation occurs.

[CONTRIBUTION NO. 73 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. XI. Copolymerizations Involving α-Vinylpyridine, α-Vinylthiophene, o-Chlorostyrene and α-Methylstyrene

BY CHEVES WALLING, EMORENE R. BRIGGS[1a] AND KATHERINE B. WOLFSTIRN[1b]

In the preceding paper of this series,[2] the copolymerization of styrene and methyl methacrylate with a series of *meta* and *para*-substituted styrenes was reported. At the same time it appeared of interest to investigate the copolymerization of these same two monomers with some other vinyl aromatics which were available.

This paper describes the copolymerization of styrene with α-vinylpyridine, α-vinylthiophene, and *o*-chlorostyrene and of methyl methacrylate with α-vinylpyridine, *o*-chlorostyrene, and α-methylstyrene. The series is not complete since it did not appear possible to analyze a styrene–α-methylstyrene copolymer accurately, and insufficient α-vinylthiophene was available for further experiments.

Due to space limitations, the ultimate experimental data on the systems have been omitted, but are available from the American Documentation Institute.[3] An idea of the accuracy of the work can, however, be gained from the graphical solutions of the copolymerization equation[4] illustrated in Figs. 1 and 2. Experimental errors (represented by the parallelograms around each intersection in the Figs.) have been calculated assuming analytical errors of 0.2% C, 0.1% N and 0.1% Cl as described previously.[5] Since all the lines corresponding to individual experiments pass through the parallelograms, the precision of the experiments may be seen to be appreciably greater than their assumed accuracy.

In Table I the relative reactivities towards the styrene and methyl methacrylate type radicals of the monomers are listed compared with styrene,[6]

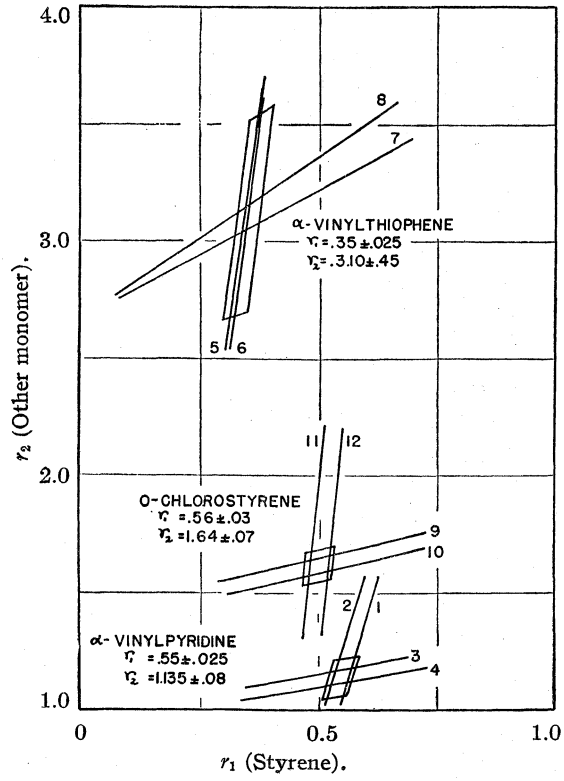


Fig. 1.—Determination of monomer reactivity ratios for some copolymerizations of styrene.

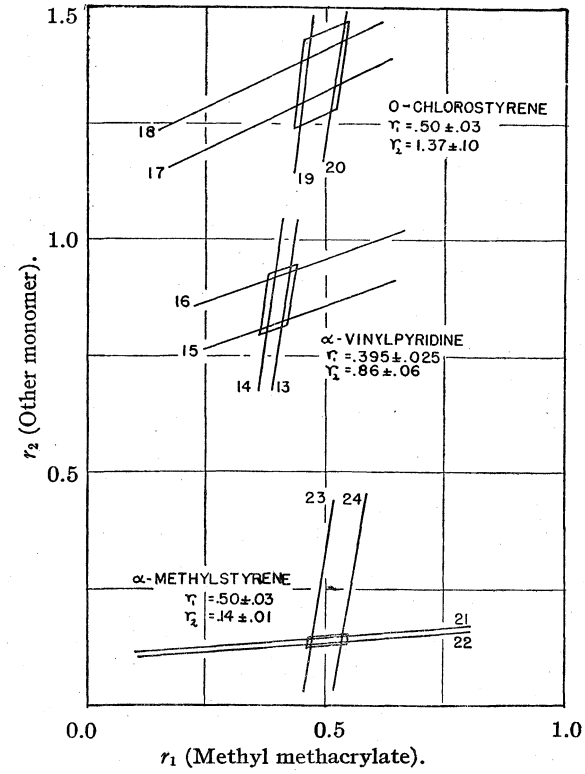


Fig. 2.—Determination of monomer reactivity ratios for some copolymerizations of methyl methacrylate.

(1a) Present address, R. F. D. 2, Guilford, Conn.

(1b) Present address, Bell Telephone Laboratories, Summit, N. J.

(2) Walling, Briggs, Wolfstirn and Mayo, THIS JOURNAL, **70**, 1537 (1948).

(3) Remit 50¢ for microfilm or 70¢ for photoprints of Document 2497 to American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C.

(4) Mayo and Lewis, *ibid.*, **66**, 1594 (1944).

(5) Lewis, Walling, Cummings, Briggs and Mayo, *ibid.*, **70**, 1527 (1948).

(6) *i. e.*, $1/r_1$'s for the styrene radical and $0.46/r_1$'s for the methacrylate radical, since the best value for the monomer reactivity ratio for styrene with the methacrylate radical has been found to be 0.46.[4,5]

TABLE I

RELATIVE REACTIVITIES AND MONOMER REACTIVITY RATIO PRODUCTS (r_1r_2)

Monomer	Relative reactivities toward Styrene radical	Relative reactivities toward Methacrylate radical	(r_1r_2) With styrene	(r_1r_2) With methacrylate
Styrene	1.00	1.00	1.00	0.24 ± 0.01
α-Vinylpyridine	1.82 ± 0.08	1.17 ± 0.08	0.625 ± 0.052	.340 ± .035
α-Vinylthiophene	2.86 ± .20	.....	1.09 ± .18	.....
o-Chlorostyrene	1.78 ± .06	.97 ± .06	.919 ± .063	.685 ± .065
α-Methylstyrene	.....	.97 ± .06	.....	.070 ± .007

and also the monomer reactivity ratio products (r_1r_2's) which serve as qualitative measures of the tendencies of the two monomers to alternate in copolymerization.

It may be seen from Table I that the monomers are all more reactive toward the styrene-type radical, than styrene and lie in the order styrene < o-chlorostyrene < α-vinylpyridine < α-vinylthiophene. Further, only α-vinylpyridine shows an appreciable tendency to alternate with a r_1r_2 value significantly smaller than unity. It is of interest that, of the three chlorostyrenes, the o-chloro is the most reactive, reactivities[2] lying in the order p-Cl (1.35) < m-Cl (1.56) < o-Cl (1.78). In reactivity toward the methacrylate radical, the three styrenes are indistinguishable and α-vinylpyridine is slightly more reactive. Apparently, the greater reactivity of α-vinylpyridine and o-chlorostyrene (as shown in copolymerization with styrene) is counteracted by a lesser tendency to alternate in copolymerization with methacrylate (larger r_1r_2 values) than is shown by styrene. The very small r_1r_2 value for α-methylstyrene is probably due to its reluctance to polymerize alone (a 1:4 methacrylate-α-methylstyrene mixture yields only 7–10% polymer in six hundred hours) rather than to an unusually high reactivity toward the methyl methacrylate type radical.

Experimental

Styrene, methyl methacrylate, α-methylstyrene and α-vinylpyridine were commercial materials, distilled *in vacuo* and stored in the ice-box before use. The preparation and properties of the samples of o-chlorostyrene[7] and α-vinylthiophene[8] are described elsewhere.

Polymerizations were carried out at 60° in sealed tubes in absence of air, using, usually, 0.08 mole total monomers and 0.5 mole % benzoyl peroxide. All polymers were benzene soluble, and were worked up by the frozen benzene technique[9] using petroleum ether as a precipitant.

Summary

1. Monomer reactivity ratios have been determined for the copolymerization at 60° of styrene with α-vinylpyridine, α-vinylthiophene, and o-chlorostyrene and of methyl methacrylate with α-vinylpyridine, o-chlorostyrene and α-methylstyrene, and the results are discussed.

(7) Walling and Wolfstirn, *ibid.*, **69**, 852 (1947).
(8) Strassburg, Gregg, and Walling, *ibid.*, **69**, 2141 (1947).
(9) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

PASSAIC, NEW JERSEY RECEIVED JULY 22, 1947

[CONTRIBUTION NO. 74 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Copolymerization. XII. The Effect of m- and p-Substitution on the Reactivity of α-Methylstyrene toward the Maleic Anhydride Type Radical

BY CHEVES WALLING, DEXTER SEYMOUR AND KATHERINE B. WOLFSTIRN[1]

A study[1a] of the copolymerization of methyl methacrylate with a series of m- and p-substituted styrenes has shown that, for most of the styrenes studied, relative reactivities toward the methyl methacrylate type radical followed quite well the order found by Hammett[2] for ionic-type side-chain reactions with a small positive rho value, *i. e.*, increasing reactivity with the introduction of increasingly electron withdrawing groups. However, anomalously high reactivities were observed (in increasing order) for p-methyl-, p-methoxy- and p-dimethylaminostyrenes.

These enhanced reactivities were shown to parallel the increased tendencies of these styrenes to form colored complexes with molecules such as maleic anhydride and chloranil, and it was suggested that they were due to the availability of additional resonance forms in the transition state of the copolymerization reaction in which an electron had been transferred from the styrene to the attacking carbonyl-conjugated radical. Existence of similar forms in the complexes in which an electron has been transferred to the conjugated carbonyl system has already been proposed by Weiss.[3]

Since these observations throw valuable light on the nature of the "alternating tendency" in

(1) Present address, Bell Telephone Laboratories, Summit, N. J.
(1a) Walling, Briggs, Wolfstirn and Mayo, THIS JOURNAL, **70**, 1537 (1948).
(2) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII.
(3) Weiss, *J. Chem. Soc.*, 245 (1942).

copolymerization[4,5,6] it seemed desirable to carry out further studies with a monomer showing a greater tendency to alternate with styrene, in which such resonance forms might be even more important. This paper reports such a study, using substituted α-methylstyrenes and maleic anhydride, probably the extreme type of such a monomer.[6,7,8]

Due to the high tendency of styrenes and maleic anhydride to alternate in copolymerization, both monomer reactivity ratios are essentially zero. Accordingly, it is not possible to investigate relative reactivities by simple copolymerization experiments, and recourse must be had to competitive reactions in three-component systems composed of two styrenes and maleic anhydride. In such a system, since four of the six monomer reactivity ratios are very small, the polymer consists of chains in which maleic anhydride residues alternate regularly with one or the other styrene and the complex terpolymerization equation[9] can be greatly simplified.[10] Under such conditions virtually the only[11] reaction which consumes either styrene is attack by the maleic anhydride type radical. Designating the two styrenes as M_1 and M_2 and the rate constants for their respective reactions with maleic anhydride as k_1 and k_2, this condition leads to the simple differential equation

$$\frac{d[M_1]}{d[M_2]} = \frac{k_1[M_1]}{k_2[M_2]} \qquad (1)$$

which on integration yields

$$\log [M_1]_0/[M_1] = k_1/k_2 \log [M_2]_0/[M_2] \qquad (2)$$

with zero subscripts indicating initial concentrations. Carrying out such a polymerization to partial conversion, determining $[M_1]$ and $[M_2]$ by analysis of either the polymer, or, as proves more convenient in these systems, the unreacted styrenes, and substituting these values into (2) permits a calculation of k_1/k_2, the desired ratio of reactivities of the two styrenes toward the maleic anhydride type radical. By comparing a series of substituted α-methylstyrenes with one selected as a standard, the relative reactivities of the whole series toward the maleic anhydride type radical may thus be determined.

(4) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944).

(5) (a) Price, *J. Polymer Sci.*, **1**, 83 (1946); (b) Alfrey and Price, *ibid.*, **2**, 101 (1947).

(6) Mayo, Lewis and Walling, THIS JOURNAL, **70**, 1529 (1948).

(7) Wagner-Jauregg, *Ber.*, **63**, 2313 (1930).

(8) Bartlett and Nozaki, THIS JOURNAL, **68**, 1495 (1946).

(9) (a) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 322 (1944); (b) Walling and Briggs, THIS JOURNAL, **67**, 1774 (1945).

(10) The simplification arising when one or two monomer reactivity ratios are zero has been already discussed by Alfrey and Goldfinger, *J. Chem. Phys.*, **14**, 115 (1946).

(11) When this project was undertaken preliminary measurements on the system styrene–maleic anhydride had indicated a monomer reactivity ratio for the styrene radical of 0.15, too small for the comparison of ordinary copolymerizations, but enough to introduce errors into the kinetics described above. Accordingly, a series of α-methylstyrenes were employed since the α-methylstyrene radical shows very little tendency to add to its own monomer (*cf.* Walling, Briggs and Wolfstirn, THIS JOURNAL, **70**, 1543 (1948). Subsequent work[6] has shown that the monomer reactivity ratio is actually less than 0.01, making the precaution unnecessary.

Experimental

Materials

Maleic anhydride was Eastman Kodak Co. material, m. p. 54.0–57.0°, used without further purification.

α-Methylstyrene was purified by fractionating commercial material through a 14-cm. column packed with glass helices. The fraction used had the following constants: b. p. 69.0–69.2° at 27 mm., $n^{20}D$ 1.5383. The material was always used shortly after distillation since it tended to oxidize to acetophenone and formaldehyde even when stored in a stoppered bottle in the refrigerator.

α-*p*-Dimethylstyrene was purified by fractionating commercial material through a 45-cm. helices-packed column. The fraction used had b. p. 72–3° at 11.5 mm. $n^{20}D$ 1.5334.

Substituted α-Methylstyrenes.—The syntheses and properties of the other α-methylstyrenes are described elsewhere.[12]

Polymerizations and Analyses

Polymerizations were carried out by heating mixtures of two α-methylstyrenes and maleic anhydride in sealed tubes at 60° in the presence of benzoyl peroxide and absence of air.[4] In general 0.1 mole of mixed styrenes (in 1:2, 1:1, or 2:1 molar ratios), 0.05 to 0.1 mole maleic anhydride, and 0.16–0.18 millimole of benzoyl peroxide were used in each experiment, and heating times were adjusted to consume 50–90% of the maleic anhydride. As might be expected, the products under these conditions yielded viscous solutions and had the properties of high polymers rather than Diels–Alder adducts.[13]

Although reactivities were ultimately related to α-methylstyrene, most reactions were actually run on mixtures of α-methylstyrenes with α,*p*-dimethylstyrene, since this compound proved to be more stable to storage than our sample of α-methylstyrene. Due to its high reactivity, it was found necessary to compare *p*-dimethylamino-α-methylstyrene with *p*-methoxy-α-methylstyrene and also to dilute the reaction mixture with 15 cc. of acetic anhydride to moderate the reaction.

Analyses were carried out by determining the amount and composition of the unreacted styrenes. After removal from the 60° bath, tubes were frozen in liquid nitrogen, wrapped in cellophane, crushed, and dropped into a one l. flask containing 200 cc. of 1 *N* sodium hydroxide solution and 0.5 g. hydroquinone. After shaking for an hour at room temperature, during which time the polymer usually dissolved, the residual styrenes were steam distilled into a graduated water separator (Dean and Stark trap) modified so that liquids either lighter or heavier than water could be separated. When distillation was complete, the volume of styrenes was noted and they were separated from the water layer, dried over anhydrous potassium carbonate, and analyzed. In the case of the systems containing *p*-cyano-α-methylstyrene, sodium bicarbonate was substituted for sodium hydroxide to minimize hydrolysis of the nitrile. For the system *p*-dimethylamino-α-methylstyrene–*p*-methoxy-α-methylstyrene, the unreacted monomers were steam-distilled into a 500-cc. flask which was next attached to a liquid–liquid extractor and the styrenes extracted for twenty-four hours with ether containing a little *t*-butylcatechol. Following removal of the ether (first at atmospheric pressure and then by freezing the mixture at −5° and pumping for five hours at 2 mm.) the styrenes were analyzed for nitrogen.

Compositions of the unreacted styrene mixtures containing chlorine, bromine or nitrogen were determined by

(12) Seymour and Wolfstirn, THIS JOURNAL, **70**, 1177 (1948).

(13) Tomayo-Viguera, *Anales fis. chim.*, **38**, 184 (1942). By heating maleic anhydride and α,*p*-dimethylstyrene in the presence of 1% trinitrobenzene as a polymerization inhibitor, we were able to isolate, besides considerable dioxane-soluble polymer, a small amount of a high-melting (>230°) material relatively insoluble in dioxane and giving solutions of low viscosity ($[\eta] = 0.07$). This may represent the Diels–Alder type product.

elementary analysis. Mixtures of α,p-dimethylstyrene with p-fluoro- or p-methoxy-α-methylstyrene were analyzed by index of refraction, the linear relation between index and volume fraction having been established from known mixtures.

α-Methylstyrene and α,p-dimethylstyrene differ too little in index of refraction for accurate analysis and so mixture compositions were determined by melting point using a melting-point curve constructed from the data of Table I.

TABLE I

MELTING POINTS OF KNOWN α-METHYLSTYRENE–α,p-DIMETHYLSTYRENE MIXTURES

Vol. % dimethylstyrene	M. p., °C.	Vol. % dimethylstyrene	M. p., °C.
0.0	−24.5	55.6	−52.0
16.6	−31.8	62.5	−47.7
28.6	−36.8	71.4	−43.0
37.5	−42.4	83.2	−36.6
44.5	−49.5	100.0	−28.0
50.0	−52.8		

All melting points were taken as the "flats" observed in the warming curve of styrene mixtures measured with a Leeds and Northrup potentiometer using a copper–constantan thermocouple with a melting ice reference junction. This combination gives readings to ±0.2°.

Calculation of Experimental Errors.—The accuracies of the analytical methods were tested for the systems α-methylstyrene–p-chloro-α-methylstyrene and α-methylstyrene–α,p-dimethylstyrene by putting up tubes similar to those used in the polymerizations, but working them up without heating. Results are listed in Table II.

TABLE II

BLANK EXPERIMENTS ON α-METHYLSTYRENE MIXTURES

Total monomer volume, cc. Calcd.	Found	Vol. % α-Methylstyrene Calcd.	Found
With α,p-Dimethylstyrene			
13.6	13.4	46.8	45.0
13.6	13.4	47.2	52.5
13.8	13.8	46.8	44.5
With p-Chloro-α-methylstyrene			
11.9	11.7	47.6	47.2
11.6	11.5	48.0	49.0
12.0	11.9	48.9	49.4

Results of actual terpolymerization experiments are listed in Table III. Relative reactivities were calculated from each experiment by Equation (2) and averaged for each pair. Experimental error was taken as the standard deviation of the separate experiments for each pair from this mean. Results, all referred to α-methylstyrene as standard,[14] are listed in Table IV. The given experimental errors, in general, correspond to 1–5% errors in monomer isolation and analysis, in reasonable agreement with the blank runs of Table II. In the case of the p-cyano-α-methylstyrene system, however, errors were definitely larger. Whether the difficulty was due to the analytical method or other causes was not determined before the sample of p-cyano-α-methylstyrene was exhausted.[15] The high reactivity of p-dimethylamino-α-methylstyrene, and the rather complex isolation technique which was necessary permit only the assignment of a minimum value for its relative reactivity.

TABLE III

REACTION OF MIXED α-METHYLSTYRENES (M_1 AND M_2) WITH MALEIC ANHYDRIDE (M_3) AT 60°

$[M_1]_0$[a]	$[M_2]_0$[a]	$[M_3]_0$[a]	Time, hr.	$[M_1]$[a]	$[M_2]$[a]
α-Methylstyrene (M_1)–α,p-dimethylstyrene (M_2)					
49.4	49.5	49.9	20	31.8	24.3
49.1	49.5	49.9	35	30.9	20.3
32.1	64.8	100.4	7.5	23.0	12.3
64.6	32.4	100.0	7.5	20.1	4.63
α-Methylstyrene (M_1)–p-chloro-α-methylstyrene (M_2)					
49.6	49.7	50.0	22	31.0	34.8
65.4	32.4	100.3	20	17.17	11.05
32.5	65.4	99.9	16	13.06	31.6
α,p-Dimethylstyrene (M_1)–p-fluoro-α-methylstyrene[b] (M_2)					
49.8	49.9	49.9	16.3	31.1	35.1
65.8	32.7	100.0	4.75	10.77	13.68
31.7	65.9	99.9	6.83	4.12	30.8
α,p-Dimethylstyrene (M_1)–p-bromo-α-methylstyrene (M_2)					
50.0	50.0	50.1	2.33	24.9	38.2
66.0	33.0	100.0	5.75	10.37	17.20
32.8	65.2	99.9	3.66	6.19	29.7
32.9	65.8	100.0	1.50	11.08	37.2
α,p-Dimethylstyrene (M_1)–m-bromo-α-methylstyrene (M_2)					
49.7	51.5	50.0	23.25	16.68	26.0
66.9	33.6	100.0	5.25	12.24	12.82
33.1	65.9	100.0	9.20	4.55	24.8
α,p-Dimethylstyrene (M_1)–p-cyano-α-methylstyrene (M_2)					
50.3	45.1	49.9	11.0	27.2	25.5
67.0	28.0	99.9	6.25	21.9	12.23
57.6	32.0	99.9	8.5	23.4	16.50
33.4	65.0	100.0	24.25	1.85	27.4
α,p-Dimethylstyrene (M_1)–p-methoxy-α-methylstyrene (M_2)					
48.4	49.3	50.0	[c]	45.7	29.0
48.5	49.0	50.0	1.5	42.6	13.43
31.6	64.6	99.4	1.17	23.6	0.98
p-Methoxy-α-methylstyrene (M_1)–p-dimethylamino-α-methylstyrene (M_2)					
66.5	58.9	100.0	0.33	62.7	16.10
32.3	26.6	99.9	0.17	32.3	7.71

[a] In millimoles. [b] Monomer contained 2 wt. % p-fluorobromobenzene, and results have been corrected accordingly. [c] Experiment was intended as blank, but polymerization occurred on standing at room temperature.

Discussion

In Table IV are listed relative reactivities of the eight α-methylstyrenes toward the maleic anhydride type radical compared with the relative reactivities of the corresponding styrenes toward the methyl methacrylate and styrene type radicals reported previously.

The striking feature of Table IV is the high reactivity of the first three styrenes, which paral-

(14) In the case that the original comparison was not with α-methylstyrene, the experimental errors in both of the ratios involved were taken into account, using the usual formulas for the propagation of error.

(15) If the difficulty is analytical, it most probably results from failure to recover all of the unreacted p-cyano-α-methylstyrene. In this case the apparent reactivity of this monomer is too high and the true value may be near the lower limit indicated in Table IV.

TABLE IV

RELATIVE REACTIVITIES OF STYRENES AND α-METHYLSTYRENES TOWARD VARIOUS RADICALS IN COPOLYMERIZATION

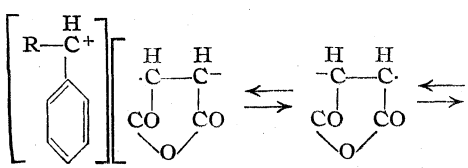
Substituent[a]	Attacking radical: Maleic anhydride	Methyl methacrylate	Styrene
p-$N(CH_3)_2$	>300	2.44	0.98
p-OCH_3	18.5 ± 4	1.72	0.86
p-CH_3	1.72 ± 0.12	1.23	..
None	1.00	1.00	1.00
p-F	0.72 ± .10	..	..
p-Cl	.79 ± .02	1.20	1.35
p-Br	.73 ± .15	1.27	1.44
m-Br	.96 ± .14	1.04	1.82
p-CN	.96 ± .57	2.27	3.57

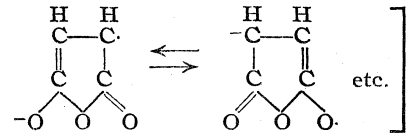
[a] On α-methylstyrene in second column, on styrene in third and fourth.

lels, but is much larger than, that noted previously in connection with reactivity toward the methacrylate radical.[1a] Thus, this increased reactivity, which parallels the tendencies of these styrenes to form colored molecular complexes with carbonyl conjugated systems, appears to be general for carbonyl-conjugated radicals and to increase with the "alternating tendency" of the monomer from which the attacking radical is derived.

This lends much support to the suggestion made earlier[1a] that the driving force for "alternation" arises from the presence of resonance structures in the transition state similar to those of molecular compounds.

Possible structures of such forms, in which an electron has been transferred from styrene monomer to attacking radical, were suggested previously,[1a] but it should be pointed out that similar structures may be drawn to explain as well the great reactivity of carbonyl conjugated double bonds with styrene type radicals, and thus to account for both "halves" of the alternating copolymerization reaction.





Further, it should be noted that relative reactivities of all α-methylstyrenes toward the maleic anhydride type radical now show little relation to the Hammett sigma values of the substituents, again indicating the dominant importance of special resonance forms in the transition state of this reaction, rather than some general property of electron density or availability at the double bond, as required by any "electrostatic" interpretation.[5]

The parallel drawn between the transition state of polymerization and molecular compound formation again brings up the possibility that alternation in copolymerization may actually involve attack of a radical on a molecular complex, particularly in a pair such as styrene–maleic anhydride where appreciable concentrations of actual colored complex exist. It should be pointed out, however, that by the interpretation given above the transition from a weakly alternating system such as styrene–methyl methacrylate where participation of such a complex can be excluded[16,17] to a strongly alternating system where its role is equivocal[16] becomes one in degree, not in kind. Thus, while participation of an actual complex in the reaction would still be of importance in the over-all reaction kinetics, it would not be in our understanding of the nature of the reaction.

Summary

1. The relative reactivity of eight *meta-* and *para-* substituted α-methylstyrenes toward the maleic anhydride type radical have been determined.

2. Further evidence has been obtained that the major driving force leading to alternation in copolymerization is the presence in the transition state of polar resonance forms resembling those in the colored "molecular complexes."

PASSAIC, NEW JERSEY RECEIVED JULY 22, 1947

(16) Nozaki, *J. Polymer Sci.*, **1**, 445 (1946).

(17) Lewis, unpublished work in this Laboratory.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Difluoromalonic Derivatives from Difluoropentane

BY ALBERT L. HENNE AND EARL G. DEWITT

To prepare a fluorinated compound containing an oxygenated function, we have consistently introduced the fluorine atoms in a non-oxygenated compound first, then created the oxygenated function afterwards. In so doing, we have frequently been able to take advantage of the directing power of the fluorinated cluster. The syntheses of CF_3CO_2H, and of $HO_2C(CF_2)_nCO_2H$, are examples of this procedure.[1,2]

We have now prepared difluoromalonic acid and some of its derivatives by the following sequence. Diethyl ketone was transformed into 3,3-difluoropentane; due to the directing effect of the CF_2 group away from the alpha hydrogen atoms,[3] moderate chlorination gave preferentially the 1,5-dichloro derivative $CH_2ClCH_2CF_2CH_2CH_2Cl$. Aided by the stronger acidity of the hydrogen atoms in 2 and 4 positions, the removal of two molecules of hydrogen chloride proved quite easy and yielded a diene $CH_2{=}CHCF_2CH{=}CH_2$. Alkaline permanganate oxidation of the diene gave difluoromalonic acid which, although fairly stable, was nevertheless handled as its di-ester and characterized as its crystalline diamide.

In the process of chlorinating 3,3-difluoropentane, the various mono- and di-chloro derivatives were isolated and characterized; their relative abundances were determined, and agreed with the expectations based on the directing influence of the CF_2 group. All chlorides beyond the dichlorinated stage were further treated for complete transformation into the perchlorinated form $C_2Cl_5CF_2C_2Cl_5$, a well crystallized product. From this, the non-conjugated pentadiene $CCl_2{=}CCl\text{-}CF_2CCl{=}CCl_2$ was prepared, and its formula demonstrated by oxidation to difluoromalonic acid. It is proposed to use this diene as an intermediate toward $CF_2{=}CFCF_2CF{=}CF_2$, a perfluorinated non-conjugated diene, the polymerization of which may offer new characteristics.

Experimental

Synthesis of $C_2H_5CF_2C_2H_5$.—Diethyl ketone was treated with phosphorus pentachloride to obtain a mixture of $C_2H_5CCl_2C_2H_5$ and $C_2H_5CCl{=}CHCH_3$. Since the latter is more advantageous for the subsequent treatment with hydrogen fluoride, operations were adjusted to obtain as favorable a ratio as possible. In a five-liter, three-necked flask maintained at 12 to 14° by a water-bath was placed 1342 g. (6.45 moles) of phosphorus pentachloride; this was agitated by a Hershberg stirrer driven by a motor strong enough to plow through the dry material. From a dropping funnel, 500 g. (5.8 moles) of diethyl ketone was fed over a period of two to two and one-half hours; the mixture was stirred overnight, then progressively brought to boiling under constant stirring, and maintained at the boiling point for forty-five minutes. After cooling, the reaction mixture was delivered dropwise into vigorously boiling water, held in a five-liter, three-necked flask. Superheated steam was supplied continuously to the bottom through one neck, and the vapors were led from the other neck to a condensing system adequately cooled. The organic material steamed over was decanted, neutralized, and dried to yield 582 g. of product. Distillation gave 439 g. b. 87–95° ($CH_3CH_2\text{-}CCl{=}CHCH_3$) and 110 g. b. 127–135° ($C_2H_5CCl_2C_2H_5$). The average yield was 73% of chloropentene, and 14% of dichloropentane or 88% of usable material. The dichloride was transformed into more chloro-olefin by treating its boiling alcoholic solution (2.4 moles in 600 cc.) with a solution of 2.6 moles of potassium hydroxide in 700 cc. of alcohol; this treatment gave a 36% conversion and a 55% recovery of unreacted dichloride, which was treated again.

The chloro-olefin was treated with hydrogen fluoride in a manner which would minimize the formation of the mere addition product ($C_2H_5CClFC_2H_5$) in favor of the desired $C_2H_5CF_2C_2H_5$. In a 1500-ml. steel vessel were placed 700 g. (6.7 moles) of chloro-olefin cooled to −80°, then 660 g. (33 moles) of liquefied hydrogen fluoride also cooled to −80°. A 45-cm. length of pipe bearing the customary thermometer well, pressure gage, and releasing needle valve was screwed on; the pipe was cooled by means of a sleeve through which cold water was passed. Warming to room temperature caused the pressure to rise rapidly to 12 atmospheres, due to formation of hydrogen chloride. This was reduced to 8 atmospheres by slow release of the gases through a wash train. The temperature was progressively raised to 60° and held there as long as the pressure could be kept around 8 atmospheres while slowly bleeding off the hydrogen chloride formed in the reaction. After cooling, the remaining pressure was released, then the contents of the vessel were poured into a slurry of 30% sodium hydroxide–ice, washed three times by siphoning, steam-distilled and dried, giving 579 g. of organic material. Distillation gave 524 g. (4.85 moles) b. 55–65° ($C_2H_5CF_2C_2H_5$); 5 g. b. 65–85°; 12 g. b. 85–95° (recovered $C_2H_5CCl{:}C_2H_4$); 15 g. b. 95–105° ($C_2H_5CFClC_2H_5$) and 18 g. of residue. Average yields were similarly between 67 and 73%, an appreciable improvement over those in the literature.[4,5]

Monochlorination of $C_2H_5CF_2C_2H_5$.—Chlorine was led into liquid difluoropentane floating over water, in a Pyrex flask equipped with a reflux condenser, until the increase in weight corresponded to about 70% of monochlorination. A 480 g. batch (4.6 moles) took about ten hours to reach this stage (585 g.). Distillation gave 160 g., b. 54–67° (recovered $C_2H_5CF_2C_2H_5$); 7 g., b. 67–97°; 91 g., b. 97–101° ($C_2H_5CF_2CHClCH_3$); 13 g., b. 101–114°; 198 g., b. 114–119° ($C_2H_5CF_2CH_2CH_2Cl$) and 115 g. of higher chlorides. The average of several such operations gave a ratio $C_2H_5CF_2CH_2CH_2Cl/C_2H_5CF_2CHClCH_3$ of about 2. The formula of the two monochlorides was derived from chlorine analysis, differences of boiling points similar to those observed in the butane series[3,6] and reactions with alcoholic potassium hydroxide, which was much stronger for the higher boiling isomer.[3,6]

Dehydrochlorination of $C_2H_5CF_2CH_2CH_2Cl$ was performed by dripping into its hot alcoholic solution a very concentrated alcoholic solution of potassium hydroxide, and adjusting the reflux in such a way as to allow only the olefin $C_2H_5CF_2CH{=}CH_2$, b. 51° to distil out of the reaction mixture. This olefin was used successfully to

(1) Henne and Trott, THIS JOURNAL, **69**, 1820 (1947).
(2) Henne and Zimmerschied, *ibid.*, **69**, 281 (1947).
(3) Henne and Hinkamp, *ibid.*, **67**, 1194 (1945).
(4) Renoll, *ibid.*, **64**, 1115 (1942).
(5) Henne and Plueddeman, *ibid.*, **65**, 1271 (1943).
(6) Henne and Hinkamp, *ibid.*, **67**, 1197 (1945).

PHYSICAL PROPERTIES OF NEW COMPOUNDS

	F. p., °C.	B. p., °C., 760 mm.	$n^{20}D$	d^{20}_4	MR	AR_F
$C_2H_5CF_2CHClCH_3$		99.4 ± 0.1	1.3788	1.1085	29.7	0.9
$C_2H_5CF_2CH_2CH_2Cl$		117.9 ± 0.2	1.3859	1.1278	29.7	.9
$CH_3CH_2CF_2CHClCH_2Cl$		146.7 ± 0.1	1.4140	1.2840	34.5	.8
$CH_2ClCH_2CF_2CHClCH_3$		154.8	1.4179	1.2899	34.6	.9
$CH_2ClCH_2CF_2CH_2CH_2Cl$	− 24.9 ± 0.2	176.3 ± 0.1	1.4261	1.3179	34.4	.8
$CH_2{=}CHCF_2CH{=}CH_2$	−135.3 ± 0.2	46.8	1.3552	0.9368	24.2	1.0
$CCl_2{=}CClCF_2CCl{=}CCl_2$	− 40.8 ± 0.2	101–102 (13 mm.)	1.5171	1.7480	53.8	1.2
$C_2Cl_5CF_2C_2Cl_5$	89.6 ± 0.2					
$CF_2(CO_2CH_3)_2$	about − 35°	58–59 (9 mm.)	1.3721	1.3059	29.2	1.4
$CF_2(CONH_2)_2$	206.4 ± 0.2					

synthesize $C_2H_5CF_2CHClCH_2Cl$, needed for contrast with other dichlorides, and also $C_2H_5CF_2CO_2H$ to test its response to oxidation.[2]

Chlorination of $C_2H_5CF_2CH_2CH_2Cl$.—Chlorination was carried out to 60% of the next stage in the same manner as above. Fractionation of 598 g. of reaction product gave 91 g., b. up to 140°; 48 g., b. 140–148°, $C_2H_5CF_2CHClCH_2Cl$, calcd. Cl, 40.4, found, Cl, 39.3; 12 g., b. 148–150°; 91 g., b. 150–155°, $CH_2ClCH_2CF_2CHClCH_3$, calcd. Cl, 40.4, found, Cl, 40.4; 34 g., b. 155–170°; 220 g., b. 170–173°, $CH_2ClCH_2CF_2CH_2CH_2Cl$, calcd. Cl, 40.4, found Cl, 41.0; 20 g., b. 173–179°, and 78 g. of residue (higher chlorides). By averaging, the following proportion of the possible dichlorides was found to be: $C_2H_5CF_2CH_2CHCl_2$ / $C_2H_5CF_2CHClCH_2Cl$ / $CH_3CHClCF_2CH_2CH_2Cl$ / $CH_2ClCH_2CF_2CH_2CH_2Cl$ 0/1/4/10. The tendency to affect the hydrogen *beta* to the CF_2 group is thus evident.

Chlorination of $C_2H_5CF_2CHClCH_3$.—Carried out in the same manner as above the results were, for 353 g. of chlorinated material: 70 g., b. up to 118°; 19 g., b. 118–122° ($CH_3CHClCF_2CHClCH_3$ or $C_2H_5CF_2CCl_2CH_3$); 26 g., b. 122–149°; 165 g., b. 149–154° ($CH_2ClCH_2CF_2CHClCH_3$); 10 g., b. 154–166°; 35 g., b. 166–171° (a trichloride isomer); 6 g., b. 171–174°; and 20 g. of residue. Chlorination of $C_2H_5CF_2CHClCH_3$ proceeds almost exclusively to $CH_2ClCH_2CF_2CHClCH_3$, by preferred action on the hydrogen beta to the CF_2 group.

The identity of $CH_2ClCH_2CF_2CHClCH_3$ is derived from the facts that (1) it is obtained from both possible monochlorides, and (2) it differs from $C_2H_5CF_2CHClCH_2Cl$ obtained by chlorine addition to the olefin.

Perchlorination.—Perchlorination was performed with a source of ultraviolet light immersed in the organic material, as shown before.[7] The chlorinator was, however, redesigned to permit its use at varied temperatures without risk of breakage due to the different coefficients of expansion of quartz and Pyrex glass (Fig. 1). The operation was carried out around 60°. Chlorination was pushed as fast as the consumption of the chlorine would permit. It was noted that after a period of continued chlorination the rate of absorption dropped very markedly. When this happened, the material solidified at room temperature. The crystals were separated from the oil by suction, and a sample, after repeated crystallization from alcohol, melted sharply at 62.3–62.8°, and analyzed for 72.6% chlorine. This is midway between $C_5F_2H_2Cl_8$ and $C_5F_2H_3Cl_7$. The formula was not further investigated. With alcoholic KOH, removal of two moles of hydrogen chloride occurred without loss of fluorine. The reaction product, b. 95–100° at 2 mm., d^4_{20} 1.7751, $n^{20}D$ 1.5162, was presumed to be mostly $CCl_2{=}CClCF_2CCl{=}CCl_2$, and on this basis the computed value for AR_F was 0.9, an acceptable value. Chlorine addition was performed at 70–80° and quantitatively yielded a solid material, which after recrystallization from absolute alcohol melted at 89.4–89.8° and analyzed for 78.6% chlorine; calculated for $C_5F_2Cl_{10}$, 78.4%.

Synthesis of $CH_2{=}CHCF_2CH{=}CH_2$.—An alcoholic solution of $CH_2ClCH_2CF_2CH_2CH_2Cl$ (277 g. or 1.56 moles in 450 ml. absolute alcohol) was treated with a solution of 3.42 moles of potassium hydroxide in one liter of alcohol, the addition and reflux being controlled in such a way as to permit only the diene to distil off. The distillate, after washing off alcohol and drying, amounted to 148 g. of which 110 g. was good diene, 30 g. was $CH_2ClCH_2CF_2CH{=}CH_2$ and the remainder unreacted dichloride. This is a conversion of 63% and a recovery of 83%. *Anal.* Calcd.: F, 36.4. Found: F, 35.0.

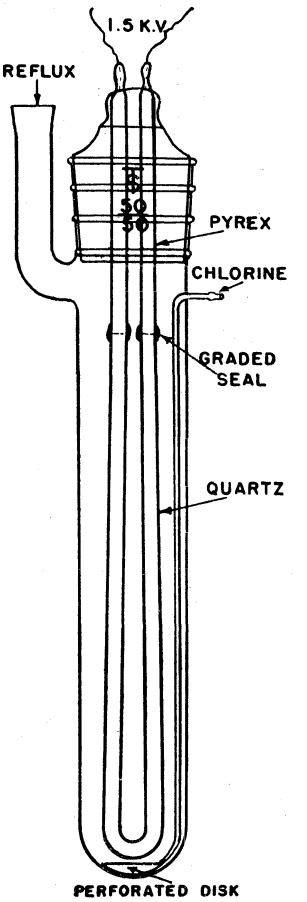


Fig. 1.—Ultra-violet light chlorinator.

Synthesis of $CCl_2{=}CClCF_2CCl{=}CCl_2$.—The treatment of an alcoholic solution of $C_2Cl_5CF_2C_2Cl_5$ with zinc is too vigorous. However, if methylene chloride is added, its refluxing keeps the reaction at a temperature no higher than 40°, and the desired removal of four chlorine atoms takes place efficiently (91%). The reaction product boils at 101–102° under 13 mm., and analyzes for 68.3% chlorine, while theoretical for $C_5F_2Cl_6$ is 68.4%.

Difluoromalonic Acid and Derivatives.—In a small preliminary run, $CH_2{=}CH{-}CF_2{-}CH{=}CH_2$ was oxidized with alkaline permanganate in our conventional way.[1,2] Ether extraction gave a few grams of mushy material, from which filtration gave grayish crystals with a neutral equivalent of 77, while the mother liquid had an equivalent of 90; the calculated value for difluoromalonic acid is 70 and for difluoroacetic acid is 96. On standing the crystals became liquid; this was interpreted as a slow decarboxylation of difluoromalonic acid to difluoroacetic acid, and in further tests the free acid was avoided.

The oxidation of the diene (21 g. or 0.2 mole) was exceedingly vigorous and exothermic, necessitating cooling of the oxidation mixture during addition to maintain the temperature at 60°. Within fifteen minutes after completion of the addition, oxidation was complete. Treatment of the reaction mixture with sulfur dioxide followed the conventional practice, and so did the ether extraction. However, at this point, the free acid was esterified by dripping its ether solution into an ether solution of diazomethane. Fractional distillation under reduced pressure gave 7 g. of a lighter boiling material, presumed to be

(7) Henne and Zimmerschied, THIS JOURNAL, **67**, 1235 (1945).

methyl difluoroacetate, and 24 g. of dimethyl difluoromalonate (*Anal.* Calcd.: F, 22.6. Found: F, 22.5), a 67% yield. A solution of 2 g. of this ester in 8 g. of ethyl ether was treated at 0° with anhydrous ammonia. White crystals formed at once, and 1.6 g. of amide, m. 206.5–206.7°, was collected, the theoretical yield. Nitrogen analysis indicated 20.1% (calculated, 20.3%).

The same amide (as determined by mixed melting point) was also obtained by oxidation of CCl_2=$CClCF_2CCl$=CCl_2 but this oxidation was slow; it required long heating, and the yield was poor. Better operating conditions were not worked out.

Summary

Diethyl ketone was transformed into 3,3-difluoropentane and the latter subjected to chlorination. The directing effect of the CF_2 group upon the first two chlorine atoms entering the organic molecule was ascertained, before perchlorination was allowed to proceed. From saturated derivatives, two non-conjugated dienes were prepared, CH_2=$CHCF_2CH$=CH_2 and CCl_2=$CClCF_2CCl$=CCl_2, both of which were oxidized to difluoromalonic acid. The latter was transformed into its dimethyl ester by means of diazomethane, and characterized as its crystalline diamide.

COLUMBUS, OHIO RECEIVED NOVEMBER 22, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Polyfluoro Alkyl Ethers and their Preparation

BY J. D. PARK, D. K. VAIL, K. R. LEA AND J. R. LACHER

Alkyl ethers containing fluorine were previously prepared by Swartz[1-3] by the action of alcoholic caustic or metallic carbonate on polyfluorohaloethanes. This procedure was later modified by Gowland.[4] Aryloxy alkanes containing fluorine also were prepared by McBee and Bolt[5] by a similar reaction. In the present work, alkoxy-2-chloro-1,1,2-trifluoroethanes were prepared by the base-catalyzed addition of alcohol to chlorotrifluoroethylene carried out at room temperature and atmospheric pressure. This type of addition to fluoroölefins was first carried out by Hanford and Rigby[6] under autogenous pressure and at elevated temperatures in the presence of sodium alkoxide as a catalyst.

Starting Materials.—The various alcohols and chemicals used in this study were of technical grade. When deemed necessary they were purified by distilling before using. The compound, CF_2ClCCl_2F, used as an intermediate in the preparation of chlorotrifluoroethylene was of "refrigerant-grade" furnished us through the courtesy of Mr. R. J. Thompson of the Kinetic Chemicals, Inc. Chlorotrifluoroethylene was obtained by dehalogenation of CF_2ClCCl_2F with ethanolic zinc according to a known method.[7]

Fractionation of the product showed the pure olefin to boil at −34 to −35° at 630 mm. pressure.

Preparation of Ethers.—The general reaction involved is

$$ROH + CF_2{=}CFCl \longrightarrow ROCF_2CHFCl \quad (1)$$

According to Pauling's[8] bond energies, the vapor phase reaction should be exothermic to the extent of 5.7 kcal. The entropy change is not known but may be estimated by analogy with similar reactions,[9-12] to be around −28 e. u. The free energy change at 298°K. is +2.6 kcal. and becomes zero at 200°K. It is apparent, therefore, that an equilibrium would be favored by low temperatures and high pressures. Since the reaction was quite rapid at room temperature and slightly above, it was not necessary to employ high pressures. An excess of alcohol was used in all cases.

In the experimental arrangement finally chosen, the olefin, CF_2=$CFCl$, from a cylinder was bubbled through a dispersion disk at the bottom of a long vertical tube filled with a potassium hydroxide saturated solution of the alcohol. The outlet end of the tube was connected to an upright water condenser. The unreacted olefin escaping through the condenser was led into a second potassium hydroxide–alcohol solution. The flow of organic through the disk was so regulated that most of the reaction took place in the first reactor. The reaction was quite slow at first. However, as soon as some ether was formed, the rate increased quite rapidly with a resultant rise in temperature. After the necessary amount of olefin had reacted with the alcohol, the reaction mixture was poured into water. The excess alcohol was completely removed by washing with water and the heavier ether layer separated. The ether was then dried over "Drierite" and fractionated in a laboratory precision column.

The addition of alcohols to chlorotrifluoroethylene may proceed to give the product listed in equation I or the structure may be $ROCClFCHF_2$. It is believed that the structure containing the —CHFCl group is the more probable. This is indicated by the formation of CHFCl-COOH in the catalytic hydrolysis of the ethyl ether in the presence of silica gel.[6] The second structure is not consistent with the relative stabilities of the ethers (with the possibile exception of the isopropyl derivative). This structure would permit the elimination of hydrochloric acid quite easily with the formation of $ROCF{=}CF_2$. Such a compound was not isolated under our reaction conditions. If the addition of alcohols to chlorotrifluoroethylene leads to the thermodynamically most stable product, then considerably more heat must be liberated when the isomer containing the —CHFCl group is formed, in which case tables of bonding energies will not be sufficiently precise to determine the course of the reaction.

(1) F. Swartz, *Bull. acad. roy. Belg.*, [3] **37**, 357–383 (1899).

(2) F. Swartz, *ibid.*, 563–589 (1911).

(3) F. Swartz, *Mem. Courones Acad. roy. Belg.*, **61**, 94 (1901); *Chem. Zentr.*, **74**, I, 12–14 (1903).

(4) T. B. Gowland (to Imperial Chem. Ind.), Brit. Patent 523,449 (July 15, 1940).

(5) E. T. McBee and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 412 (1947).

(6) W. E. Hanford and G. W. Rigby (to du Pont), U. S. Patent, 2,409,274 (Oct. 15, 1946).

(7) E. G. Locke, W. R. Brode and A. L. Henne, THIS JOURNAL, **56**, 1726 (1934).

(8) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1944.

(9) J. G. Aston, *Ind. Eng. Chem.*, **34**, 514 (1942).

(10) G. R. Cuthbertson and G. B. Kistiakowsky, *J. Chem. Phys.*, **3**, 631 (1935).

(11) K. K. Kelley, Bureau of Mines, Bulletin 434.

(12) H. A. Smith and W. E. Vaughan, *J. Chem. Phys.*, **8**, 341 (1935).

TABLE I

PHYSICAL PROPERTIES OF POLYFLUORO ALKYL ETHERS

Formula	B. p., °C. 630 mm.	d^{20}_4	$n^{20}D^a$	MR^b	$AR_F{}^c$	Fluorine analyses, % Calcd.	Found
CH_3OCF_2CHFCl[d]	64.4	1.3632	1.33381	22.460	1.063	38.4	38.2
$C_2H_5OCF_2CHFCl$	82.0	1.2726	1.34787	27.163	1.094	35.0	34.8
n-$C_3H_7OCF_2CHFCl$	102.3	1.2173	1.35751	31.814	1.105	32.3	32.1
Iso-$C_3H_7OCF_2CHFCl$	94.0	1.2010	1.35211	31.800	1.100	..	..
n-$C_4H_9OCF_2CHFCl$	124.5	1.1779	1.36796	36.448	1.100	29.9	29.8

[a] Determinations made with a Pulfrich refractometer. [b] MR denotes molecular refraction calculated by the Lorentz–Lorenz formula. [c] AR_F denotes the atomic refraction for fluorine obtained from MR by subtracting the customary increments for C, H, Cl, O, and the ether linkage. [d] This compound has also been prepared by Miller, *et al.*, THIS JOURNAL, **70**, 432 (1948).

The fact that the ethers were obtained in yields between 70 and 85% indicates that the heat of reaction is greater than that calculated.

Physical Properties.—Some physical properties of the ethers are listed in Table I. The boiling points, densities, and refractive indices are in line with what one might expect for an homologous series. The atomic refraction for fluorine is reasonable for compounds of this type.

The absorption spectra of the ethers were measured using a Beckman quartz spectrophotometer model DU. Pure cyclohexane was used as a reference liquid and the experiments were carried out in a 10-mm. quartz cell. The ethers were transparent from 9000 to about 3600 Å. Below this wave length they absorb strongly. The curves in the ultraviolet region are given in Figs. 1 and 2. In order to bring out the details of the curves, the logarithm of the extinction coefficient, log E, is given as a function of wave length in Ångstrom units.

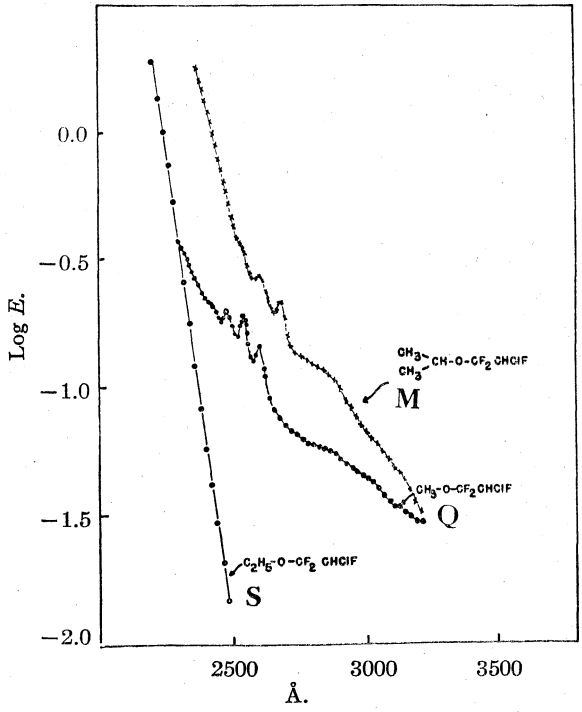


Fig. 1.—Ultraviolet absorption spectra of some alkyl fluoroethers. Logarithm of the extinction coefficient against wave length in Ångström units.

In case of the ethyl ether, absorption sets in sharply below 2500 Å. The logarithm of the extinction coefficient as a function of the wave length is a straight line and no structure is evident. Both the methyl and isopropyl ethers show vibrational fine structure. In case of the methyl compound the peaks occur at 2420, 2480, 2540 and 2600 Å. giving separations between them of 1000, 950 and 900 cm.$^{-1}$, respectively. The isopropyl ether shows peaks of 2535, 2605, and 2685 Å. with separations of 1050 and 1150 cm.$^{-1}$. These frequencies may be reliable to ±10% and could correspond either to a C–F or C–C stretching vibration.[13] It is also possible for a bending motion in the molecule to have a frequency in this range.

The isopropyl compound shows a slight shoulder between 2800 and 2900 Å., which, in case of the n-propyl derivative, is a distinct broad band. The n-butyl ether gives only a shoulder. Absorption in this region may be due to unresolvable fine structure or to the presence of small amounts of the isomer formed by the reverse addition of the alcohol to chlorotrifluoroethylene. We plan to extend absorption studies to longer wave lengths using our infrared spectrometer.

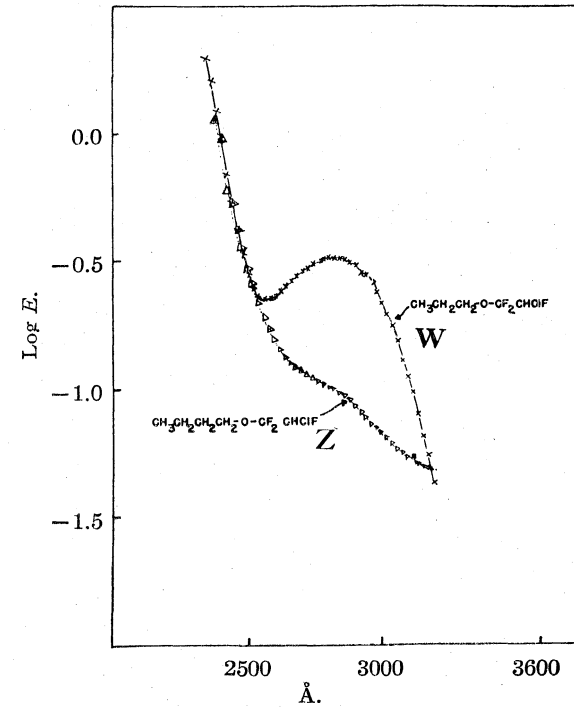


Fig. 2.—Ultraviolet absorption spectra of some alkyl fluoroethers. Logarithm of the extinction coefficient plotted against wave length in Ångström units.

Summary

This paper reports the base-catalyzed addition

(13) G. Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., New York, N. Y., 1945.

of alcohols to chlorotrifluoroethylene resulting in the formation of ethers of the type $ROCF_2CFClH$, which in general are quite stable. The reaction is carried out at room temperature and atmospheric pressure. Some of the physical properties of the ethers, along with their ultraviolet absorption spectra are discussed.

BOULDER, COLORADO RECEIVED NOVEMBER 21, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOUSTON REFINERY, SHELL OIL COMPANY, INCORPORATED]

Alkylation of Thiophene with Olefins[1]

BY W. G. APPLEBY, A. F. SARTOR, S. H. LEE, JR.,[2] AND S. W. KAPRANOS[3]

In connection with other work in these laboratories, it was necessary to prepare several alkyl thiophenes. When the experimental work was started in 1943, no method of preparation of the desired compounds which would meet our needs was found in the literature. It seemed worthwhile, consequently, to investigate the possibility of the direct alkylation of thiophene with appropriate olefins. This paper presents the results of our investigation of the alkylation of thiophene with propylene and isobutylene.

In the intervening time, the direct alkylation of thiophene by olefins and alcohols was reported by Kutz and Corson.[4] These authors reported the results of two experiments on the direct alkylation of thiophene with propylene and isobutylene under conditions considerably removed from those to be presented here. It is remarkable that in these experiments no evidence was presented for the formation of 3-isopropyl- and 3-*t*-butylthiophene, whereas in the experiments described below a considerable reaction to the 3-isomer was observed with each olefin. An explanation of the discrepancy will be presented in following sections of this paper.

Experimental

Purity of Chemicals.—The catalyst was phosphoric acid on kieselguhr (50–60%) manufactured by Universal Oil Products Company. The commercial 1/4-inch pellets were cut into 1/8-inch pellets. A fresh sample of catalyst was used for each experiment.

Synthetic thiophene was obtained from the Eastman Kodak Company. Satisfactory purity of the sample was indicated by a comparison of its properties with those reported in the literature: our sample, $n^{20}D$ 1.5287, d^{20}_4 1.0646; literature,[5] $n^{20}D$ 1.5286, d^{20}_4 1.0642.

Technical isobutylene from the Phillips Petroleum Corporation and propylene from the Ohio Chemical Company were used. The propylene had a purity of 98%, and the isobutylene contained a maximum of 4% isobutane as the only impurity.

Apparatus.—The alkylation reactions were carried out under continuous flow conditions in an 18–8 stainless steel reactor with a one-inch diameter. The unit was pressured with nitrogen prior to the introduction of thiophene and the olefin. For experiments in which 1:1 thiophene to olefin mole ratios were used, the liquids were charged from separate cylinders of a dual displacement pump. Higher thiophene to olefin ratios were obtained by dissolving the liquid olefin in the thiophene and maintaining the mixture at a low temperature until it was charged to the pump.

Alkylation of Thiophene with Propylene.—The alkylation of thiophene with propylene was carried out at 288°, 21.5 atmospheres, 1.1 thiophene to propylene mole ratio, and a flow rate of 3.6 g. of liquid charge per gram of catalyst per hour (WHSV). Under these conditions 70% of the thiophene and 50% of the propylene reacted to give an 80% by weight yield of liquid product which contained 40% mono-isopropylthiophene and significant amounts of di-isopropylthiophenes. This was equivalent to 30–35% conversion of propylene to the mono-isopropylthiophene. The amount of mono-isopropylthiophene recovered in each experiment was too small for analysis. The combined monoalkylate fractions from several experiments were therefore distilled and then hydrogenated over a catalyst of mixed tungsten and nickel sulfides[6] at 288°, 33 atmospheres pressure, 0.1 WHSV and a hydrogen/alkylate molal ratio of 15. The resulting paraffin hydrocarbons, as determined by physical properties and infrared spectra, consisted by weight of 38% 2,3-dimethylpentane, 54% 2-methylhexane and 8% of lower boiling hydrocarbons (perhaps from the propylene polymerization reaction). These values correspond to a relative distribution by weight of the mono-isopropylthiophenes in the liquid product of 41% 3-isopropylthiophene and 59% 2-isopropylthiophene.

Although the isopropylthiophenes were not purified as efficiently as the *t*-butylthiophenes (see below), the physical properties of selected distillation cuts were as follows: 2-isopropylthiophene,[7] b. p. 152.0°, $n^{20}D$ 1.5037, d^{20}_4 0.9673; 3-isopropylthiophene,[7] b. p. 155.5°, $n^{20}D$ 1.5060, d^{20}_4 0.9722.

Infrared analysis of the C_{10} hydrocarbons resulting from the hydrogenation of the di-isopropylthiophenes showed that the principal product was 2,7-dimethyloctane (from 2,5-di-isopropylthiophene). The presence of the other three possible decanes (2,3,4,5-tetramethylhexane, 2,3,6-trimethylheptane, and 2,5-dimethyl, 3-ethylhexane) was also indicated.

Alkylation of Thiophene with Isobutylene.—No physical properties were available in the literature for *t*-butylthiophene. Consequently, in order to have this information for identification of the products in later experiments, it was necessary to prepare pure samples of these compounds for such determinations. The liquid product for this purpose was prepared by alkylating thiophene with isobutylene (1:1 mole ratio) at 21.5 atmospheres, 270°, and a WHSV of 4.3.

The liquid product from this experiment was distilled in a column having nine theoretical plates at total reflux. This distillation separated the product roughly into three fractions: (1) unreacted thiophene, (2) mono-alkylthio-

(1) Presented before the Organic Division at the September, 1947, meeting of the American Chemical Society at New York City.

(2) Present address: Department of Chemistry, University of Texas, Austin, Texas.

(3) Present address: Corn Products Company, Chicago, Illinois.

(4) Kutz and Corson, THIS JOURNAL, **68**, 1477 (1946).

(5) Haines, Wanger, Helm and Ball, U. S. Bur. Mines, R. I. 4060 (1946).

(6) Appleby, Lovell and Love, U. S. Patent 2,429,575 (1947).

(7) Haines, *et al.*, ref. 5, reported for the 2-isomer, b. p. 153°, $n^{20}D$ 1.503, d^{20}_4 0.967; for the 3-isomer, b. p. 157°, $n^{20}D$ 1.505, d^{20}_4 0.973.

TABLE I

PROPERTIES AND ANALYSES OF ALKYLATION PRODUCTS

Compound	Density d^{20}_4	Refractive index $n^{20}D$	$n^{20}C$	$n^{20}F$	B. p., °C.	M. p., °C.	Sulfur, % Calcd.	Sulfur, % Found	Mol. weight Calcd.	Mol. weight Found
2-*t*-Butylthiophene	0.9514	1.49788	1.49395	1.50755	163.9	−59.2	22.8	22.4	140	141
3-*t*-Butylthiophene	.9574	1.50149	1.49755	1.51113	168.9	−54.8	22.8	22.5	140	141
Di-*t*-butylthiophene[a]	.9192	1.49312	1.48951	1.50205	223.5	....	16.3	16.3	196	196
Di-*t*-butyl-isomer A[b]	.9192	1.4923	1.4885	1.5008	221	....	..	..	...	...
Di-*t*-butyl-isomer B[b]	.9230	1.4935	1.4897	1.5022	224	....	..	..	...	...
Residue	....	....	....	....	...	....	..	21.7	...	253

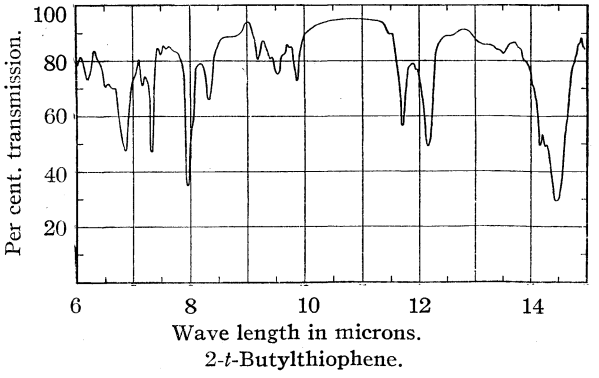
[a] Mixture of di-*t*-butylthiophenes. [b] Partially separated di-*t*-butylthiophenes.

phene, and (3) di-alkylthiophene and heavier. The last fraction was vacuum distilled to separate the di-alkylthiophene from the heavier residue.

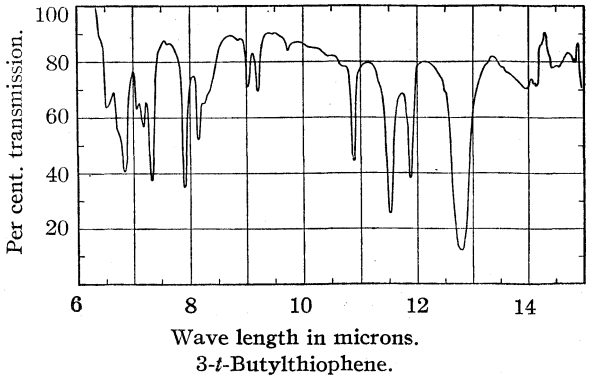
The isomeric mono-*t*-butylthiophenes were separated and purified by a series of precision distillations which were carried out at a 49:1 reflux ratio in a Stedman column having 60 theoretical plates at total reflux.

As a final check of the purity of the two isomers, time *versus* temperature freezing curves were obtained by a method similar to that of the Bureau of Standards.[8] These curves indicated a minimum purity for each isomer of 97%.

Hydrogenation of the higher boiling *t*-butylthiophene yielded principally 2,2,3-trimethylpentane, thus establishing the identity of that isomer as 3-*t*-butylthiophene. The lower boiling isomer was shown to be 2-*t*-butylthiophene by the formation of 2,2-dimethylhexane upon hydrogenation. These designations are analogous to those of other substituted thiophenes and the picolines; *i. e.*, the 3-isomers have the higher boiling points and densities. The paraffins resulting from the hydrogenation of the pure *t*-butylthiophenes were identified by determination of their infrared spectra.



2-*t*-Butylthiophene.



3-*t*-Butylthiophene.

Fig. 1.—Infrared absorption spectra.

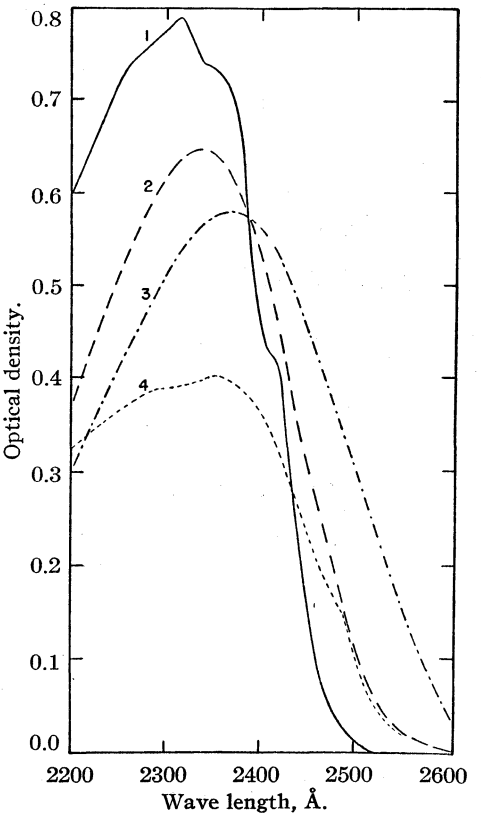
(8) Glasgow, Streiff and Rossini, *J. Research Nat. Bur. Standards*, **35**, 355 (1945).

The di-*t*-butylthiophene, which was separated from the heavy residue, was pure only as regards the removal of the residue and mono-*t*-butylthiophene. Actually, at least two isomers were present. These were partially separated by precision distillation, but not enough of either of the isomers was available for further identification.

A summary of the physical properties and analytical values which were determined on the pure compounds and fractions discussed above is presented in Table I.

The residue left after removal of the di-*t*-butylthiophene showed, in addition to the analytical data of Table I, values of % C and % H of 70.3 and 7.6, respectively. These values correspond closely to the calculated values for a mixture containing about 70% di-*t*-butyldithienyl and 30% di-*t*-butylthiophene.

A very small amount of material boiling below thio-



1—Eastman thiophene
2—2-*t*-Butylthiophene
3—Mixed di-*t*-butylthiophenes
4—3-*t*-Butylthiophene

Fig. 2.—Ultraviolet absorption spectra—dilution 1:100,000 in cyclohexane.

phene and a small amount boiling between thiophene and the monoalkylate and possessing lower refractive indexes were indicated in the distillation of the liquid product. This material could have been formed in the course of a small amount of isobutylene polymerization followed by polymer disproportionation.

There was also noted a small amount of material with a high refractive index boiling between the monoalkylate and dialkylate. A substituted thiophene with a double bond in the side chain could have these properties, but it is not clear how a compound of that type could be formed under the conditions investigated here.

From the foregoing distillation and analytical data, the following approximate liquid product composition by weight can be written—37% 2-*t*-butylthiophene, 23% 3-*t*-butylthiophene, 33% di-*t*-butylthiophenes, 5% di-*t*-butyl-dithienyl and 2% unidentified.

Infrared and ultraviolet absorption spectra of several of the compounds of Table I are shown in Figs. 1 and 2. The marked differences between the spectra of the 2- and 3-*t*-butylthiophenes support the freezing point purity data mentioned above.

Thermal Alkylation.—Thiophene and isobutylene (1.2/1 mole ratio) were passed over glass beads at 267°, 21.5 atmospheres, and 4.4 WHSV. Distillation of the product from this experiment gave an overhead material which was thiophene. Since the sulfur content of the distillation residue was lower than that of thiophene, the residue may have contained two or more of the following products: thiophene, alkythiophenes, isobutylene polymer and polythienyls. If it is assumed that only thiophene and monoalkyl thiophenes were present, the maximum amount of thermal alkylation possible at these conditions is approximately 5%. A small amount of thiophene thermal decomposition was indicated by the presence of hydrogen sulfide in the product.

Catalytic Decomposition of Thiophene.—The catalytic decomposition of thiophene, as determined by passing thiophene over the phosphoric acid catalyst at 281°, 21.5 atmospheres, and 2.8 WHSV, amounted to 6.7%. In addition to the decomposition reaction, indicated by the amount of hydrogen sulfide formed, there was evidence of a considerable amount of some other reaction to form heavier compounds, possibly dithienyl. Distillation of the liquid product was stopped at 76.3% by volume overhead because of excessive kettle temperature. The overhead product was thiophene, but the remainder of the product solidified upon cooling to room temperature. Since 2,2′-dithienyl and 3,3′-dithienyl melt at 33° and 132°, respectively, it is possible that these materials constituted a major part of the residue.

Discussion

The results of the experiments above indicate that the reactions of major importance in the alkylation of thiophene with isobutylene over phosphoric acid are

(I) Thiophene ⟶ H_2S + carbonaceous material
(II) Thiophene ⟶ dithienyl
(III) Thiophene + isobutylene ⟶ 2- and 3-*t*-butylthiophene
(IV) *t*-Butylthiophene + isobutylene ⟶ di-*t*-butylthiophene
(V) *t*-Butylthiophene ⟶ di-*t*-butyldithienyl
(VI) Isobutylene ⟶ polymer
(VII) Disproportionation of the isobutylene polymer

On the basis of the liquid product compositions and the ratios of moles of isobutylene reacted/moles of thiophene reacted, it was possible to deduce the effects of the reaction variables on the above reactions.

Increase of the pressure in the range 7.8 to 21.5 atmospheres caused increases in the amounts of all reactions, particularly reactions I, II, III and IV. The relative amounts of 2- and 3-*t*-butylthiophenes were not affected appreciably by changes in operating pressure.

In the range of 235 to 302°, increases in the reaction temperature caused increases in the amounts of reactions I, II, IV, V, VI and VII. Although less monoalkylate was produced at the higher temperature, the ratio of the 3-isomer to the 2-isomer was greater than at the lower temperature.

Increase of the thiophene/isobutylene mole ratio in the range 1.2 to 6.1 caused decrease of the amounts of all reactions except I and II, and also a decrease of the ratio of 3-*t*-butylthiophene to the 2-isomer. Reaction I was not markedly affected by the change in mole ratio. The composition of the residue indicated that the amount of reaction II increased, relative to reaction V, at the higher mole ratio.

Increase of the weight space velocity from 2.9 to 9.9 caused decreases in the amounts of all reactions except III. The amount of reaction III increased, but the relative amounts of the 2- and 3-isomers remained approximately constant. Part of the differences in product composition and yields between our results and those of Kutz and Corson can undoubtedly be attributed to the differences in experimental conditions and the physical states of the catalysts used. It does not seem reasonable, however, that no 3-*t*-butylthiophene was formed in their work. An examination of their data on the physical properties of mono-*t*-butylthiophene (assumed by them to be the 2-isomer) reveals that the refractive index and density are intermediate between the values listed in Table I for the 2- and 3-isomers, suggesting that some 3-*t*-butylthiophene was formed in their work. A rough value of the amount may be estimated from these properties to be 21% of the monoalkylate fraction on the basis of the density and 22% on the basis of the refractive index, assuming a linear blending relation in these properties for the isomers. These values are to be compared to a value of 38% from our data reported above.

In the homogeneous reactions of thiophene it has been established[9] that substitution occurs almost entirely in the 2-position. The production of relatively high yields of 3-isopropyl- and 3-*t*-butylthiophenes in the heterogeneous reactions described above must, therefore, be attributed either to (1) some effect of the catalyst on the "normal" orientation influence of the sulfur atom or to (2) isomerization of the 2- to the 3-isomer. If the latter explanation is correct, both the temperature and the space velocity would be expected to have considerable influence on the relative yields of the two isomers. The influence of space velocity was shown to be negligible in the range 3–10 The 3-/2-*t*-butylthiophene ratio varied over a re-

(9) Steinkopf, "Die Chemie des Thiophenes," Theodor Steinkopf, Dresden and Leipzig, 1941; Edwards Brothers, Inc., Ann Arbor, Michigan, 1944.

markably small range in all of the experiments and was below about 0.6 only in the experiments involving lower temperature and low yields of mono-alkylate. This suggests that an isomerization equilibrium between the two isomers was established under all of the conditions except those under which the low concentration of mono-alkylate prevented the attainment of equilibrium at the space velocities used.

The possibility that the catalyst influences the "normal" action of the sulfur atom in controlling the point of substitution should not be overlooked, however, since our data show that appreciable thiophene decomposition (evolution of hydrogen sulfide) occurred in all experiments. This suggests that the thiophene molecule, during the heterogeneous reaction, is not in the state corresponding to that of the aforementioned homogeneous reactions and, therefore, is not subject to the orientation rules of the homogeneous reactions. A study of the activity of the phosphoric acid catalyst for isomerization of the 2- to the 3-isomer should show which of the above two hypotheses is correct.

The complicated array of simultaneous and consecutive reactions which appear to be involved in the over-all reaction make it impossible to obtain an adequate theoretical treatment of the reaction kinetics which can be tested by the experimental data herein presented.

Acknowledgments.—We wish to express our thanks to the following people for their contributions to the work: Messrs. M. P. L. Love and L. L. Lovell at whose suggestion the larger project, of which this work was a part, was carried out; Mr. W. K. Meerbott who carried out the hydrogenation of the alkylates; and Dr. R. A. Friedel for his interpretation of the infrared spectra of the decanes.

Summary

Alkylthiophenes were prepared by direct alkylation of thiophene with isobutylene and propylene over a phosphoric acid polymerization catalyst. Alkylation was predominantly in the 2-position, although remarkably high yields of the 3-isomer were obtained. The physical properties and absorption spectra of several of the alkylthiophenes were determined. A study was made of the influence of several reaction variables on the alkylation with isobutylene.

HOUSTON, TEXAS RECEIVED JULY 7, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. I

BY E. CAMPAIGNE AND WILLIAM M. LESUER[1]

A great deal of work has been reported in the recent literature on the preparation and pharmacological evaluation of thiophene compounds.[2-5] Due to the fact that 3-substituted thiophene derivatives have not been available in the desired quantities, this work has been limited, by necessity, to thiophene compounds substituted in the 2-position.

It has been shown repeatedly that replacement of the 2-thienyl radical for the benzene nucleus in pharmacologically active compounds leads to products of similar activity.[3,4,6] In some cases the thiophene analog has been toxic to a lesser degree.[7] It therefore seemed of interest to prepare some 3-substituted thiophene compounds in order that their pharmacological properties might be compared with those of the 2-substituted derivatives and the benzene analogs. The work described in this paper deals with the synthesis of intermediate compounds required in the preparation of some 3-substituted thiophene derivatives with possible pharmacological activity.

The synthesis of 3-thenaldehyde (V)[8] has been previously carried out in poor yield in a reaction utilizing the difficultly obtainable 3-iodothiophene.[9] 3-Thenoic acid (VII) has been prepared in small amounts by numerous methods: oxidation of 3-methylthiophene (I)[10,11]; chlorination of I followed by hydrolysis, oxidation and finally reduction[12]; treatment of 3-iodothiophene with potassium cyanide and water in a sealed tube[13];

(1) Taken from part of a thesis to be submitted by William M. LeSuer in partial fulfilment of the requirements for the degree of Doctor of Philosophy at Indiana University.

(2) Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942).

(3) Chen and Abreu, *Fed. Proc.*, **6**, 316 (1947).

(4) Dann and Moller, *Ber.*, **80**, 23 (1947).

(5) Johnson, Green and Pauli, *J. Biol. Chem.*, **153**, 37 (1944).

(6) Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941).

(7) Steinkopf and Ohse, *Ann.*, **448**, 205 (1926).

(8) The recent literature contains various names for the same thiophene compound. For instance, thiophenecarboxylic acid, 2-thienoic acid, 2-thiophenoic acid, and thenoic acid are all used to designate the same compound. We have used the system which seems simplest, based on the analogy between thiophene and benzene compounds. In this system the prefix "then" corresponds to the prefix "benz"; *i. e.*, "benzyl chloride," "2-thenyl chloride," "benzaldehyde," "3-thenaldehyde," "benzoic acid," "3-thenoic acid," "2-thenoyl chloride," etc. The prefix "thienyl" corresponds to "phenyl" and we have "2-thienylacetic acid," "3-acetothienone," etc. This system fits into the framework of the large group of useful trivial names which has been established in the benzene series, and saves much space. Thus 1-hydroxy-2-keto-1,2-di-(3-thienyl)-ethane becomes 3,3'-thenoin, and thiophene-3-aldehyde becomes 3-thenaldehyde.

(9) Steinkopf and Schmitt, *Ann.*, **533**, 264 (1938).

(10) Muhlert, *Ber.*, **18**, 3003 (1885).

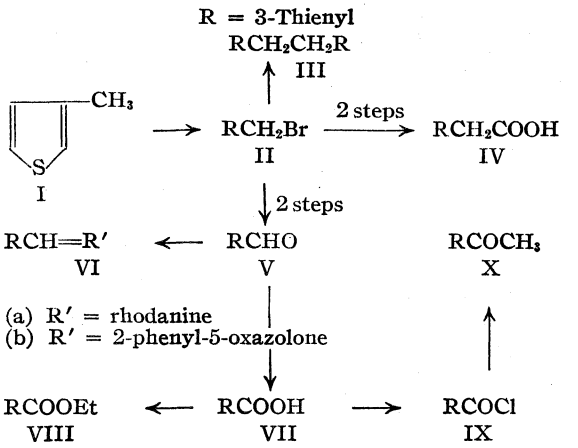
(11) Damsky, *ibid.*, **19**, 3282 (1886).

(12) Voerman, *Rec. trav. chim.*, **26**, 293 (1907).

(13) Rinkes, *ibid.*, **55**, 991 (1936).

and by the Grignard reaction with carbon dioxide on 3-iodothiophene.[9]

We have used N-bromosuccinimide as a bromination agent in the preparation of 3-thenyl bromide (II) from 3-methylthiophene. Buu-Hoi and Lecocq[14] described the preparation of α-bromomethylnaphthalene by the action of N-bromosuccinimide on α-methylnaphthalene, but Buu-Hoi[15] was unable to prepare benzyl bromide



from toluene by the same procedure. Schmid and Karrer[16] reported that the latter reaction yielded benzyl bromide in 64% yield in the presence of small amounts of benzoyl peroxide. In the absence of the peroxide catalyst we have obtained only nuclear substitution in the reaction of N-bromosuccinimide with 3-methylthiophene, but when benzoyl peroxide was added to the reaction mixture side chain bromination predominates, yielding mainly II along with a small amount of nuclear substituted material. The latter material is probably 2-bromo-3-methylthiophene. Some difficulty has been experienced in the separation of the side chain and nuclear substituted products. 3-Thenyl bromide decomposes on distillation at atmospheric pressure and a sharp separation of the two isomers could not be effected by distillation under reduced pressure. The presence of the nuclear substituted material caused no trouble as it was removed in the next step in the sequence of reactions leading to the aldehyde. The aldehyde was prepared from II by the method of Sommelet.[17] The mixture of bromides was treated with hexamethylenetetramine in chloroform and the salt formed with II separated from solution while the nuclear substituted material remained in solution. Steam-distillation of a water solution of the salt yields V in 30–40% yield.

The aldehyde was converted to 3-thenoic acid (VII) in nearly quantitative yield by silver oxide oxidation, but only to the extent of 40–60% by alkaline permanganate. The aldehyde undergoes the usual aromatic aldehyde reactions. Treatment with sodium cyanide in alcoholic solution yielded the benzoin analog, 3,3′-thenoin. Normal condensation products were obtained with hippuric acid and rhodanine, namely, 2-phenyl-4-(3-thenal)-5-oxazolone and 3-thenalrhodanine, respectively.

The acid was converted to several esters for characterization. From the acid chloride[9] we have prepared 3-acetothienone (X) employing cadmium methyl, by the method of Gilman and Nelson.[18]

An attempt was made to prepare 3-thienylacetic acid (IV) from II through the Grignard reaction with carbon dioxide. In this preparation the same difficulty reported by Blicke and Burckhalter[2] in a Grignard reaction on 2-thenyl chloride was encountered. Coupling occurred giving rise to the formation of a dithienylethane, in our case *sym*-di-3-thienylethane (III). 3-Methyl-2-thenoic acid[19] was also isolated from this reaction. This may have been formed from a small amount of 2-bromo-3-methylthiophene which contaminated the starting material. The yield of 3-methyl-2-thenoic acid was somewhat higher than expected, considering the purity of the starting material as calculated from the yield of hexamethylenetetramine salt. It is not impossible that some rearrangement has occurred giving rise to the formation of 3-methyl-2-thenoic acid. Such a rearrangement does not occur in the benzene series when benzylmagnesium bromide is treated with carbon dioxide,[20] but the high activity of the alpha position in the thiophene nucleus must be considered in dealing with thiophene compounds substituted in the beta position such as II. Further work is being carried out on the possibility of rearrangement in this reaction.[21]

3-Thienylacetic acid was prepared by conversion of II to the nitrile and hydrolysis of the latter product.

Experimental[22]

N-Bromosuccinimide.—This compound was prepared by the method of Ziegler, *et al.*[23] A good grade of succinimide should be employed in this preparation; that described by Clarke and Behr[24] being satisfactory. Some commercial materials give a poor product which reacts unsatisfactorily in brominations. The product should be thoroughly washed with water to remove any excess bromine. It was found that storing the material open to the air, allowing traces of bromine to escape, gives the most active brominating agent.

3-Thenyl Bromide (II).—To a solution of 55 g. (0.56 mole) of 3-methylthiophene in 150 ml. of carbon tetra-

(14) Buu-Hoi and Lecocq, *J. Chem. Soc.*, 830 (1946).
(15) Buu-Hoi, *Ann.*, **556**, 1 (1944).
(16) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).
(17) Sommelet, *Compt. rend.*, **157**, 852 (1913).
(18) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).
(19) Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).
(20) Gilman and Kirby, THIS JOURNAL, **54**, 345 (1932).
(21) Since this paper was submitted, Lecocq and Buu-Hoi [*Compt. rend.*, **224**, 658 (1947)] have shown that allylic rearrangement of this type does occur in 5-methyl-2-bromomethylthiophene, yielding 3-substituted-2,5-dimethylthiophenes.
(22) All melting points are uncorrected.
(23) Ziegler, Spath, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).
(24) Clarke and Behr, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 562.

chloride was added 88.5 g. (0.50 mole) of N-bromosuccinimide and 0.2 g. of benzoyl peroxide. The mixture was shaken vigorously and then heated. During the first ten minutes an additional 0.2 g. of benzoyl peroxide was added. The flask and contents were shaken vigorously at frequent intervals during the first hour, then refluxed for five additional hours. After cooling in an ice-bath the succinimide was removed by filtration and washed with 50 ml. of carbon tetrachloride. The solutions from two identical experiments were combined at this point and the carbon tetrachloride removed at reduced pressure. The remaining highly lachrymatory oil was distilled in vacuum and 114 g. of faintly tan material was collected at 70–100° (2 mm.). This material was unstable and darkened slowly. The best sample contaminated by a small amount of 2-bromo-3-methylthiophene was collected at 75–78° (1 mm.); d^{20}_4 1.635, $n^{20}D$ 1.604.

Hexamethylenetetramine Salt of 3-Thenyl Bromide.—Hexamethylenetetramine (90 g.) was added to a solution of 114 g. of 3-thenyl bromide in 200 ml. of chloroform. The mixture was refluxed for one hour, cooled, and the salt filtered. Distillation of the chloroform filtrate yielded a small amount of 2-bromo-3-methylthiophene, b. p. 173–175° (745 mm.). The salt was washed with 100 ml. of ether; yield, 150 g. This material may be purified by crystallization from absolute ethanol, yielding white needles. It softens at 120°, becomes brown and melts completely at 150°. *Anal.* Calcd. for $C_{11}H_{17}N_4SBr$: S, 10.10. Found: S, 9.80.

3-Thenaldehyde (V).—The hexamethylenetetramine salt (150 g.) was dissolved in 500 ml. of hot water and rapidly steam-distilled, one liter of distillate being collected. The distillate was acidified with hydrochloric acid and extracted with three 100-ml. portions of ether. The ether solution was dried over drierite and the ether removed on a steam-bath. Distillation of the residue at atmospheric pressure yielded 35.8 g. (32%, based on N-bromosuccinimide) of 3-thenaldehyde, b. p. 195–199° (744 mm.); d^{24}_4 1.2800, $n^{20}D$ 1.5860.

The phenylhydrazone,[25] previously reported,[7] melted at 136–137° after recrystallization from dilute alcohol.

The **2,4-dinitrophenylhydrazone** crystallized as deep orange needles from nitromethane, m. p. 236–237°.

Anal. Calcd. for $C_{11}H_8O_4N_4S$: S, 10.97. Found: S, 11.09.

The **semicarbazone** crystallized from a water–ethanol solution as white leaflets, m. p. 233–234°.

Anal. Calcd. for $C_6H_7N_3OS$: S, 18.95. Found: S, 19.25.

3-Thenoic Acid (VII).—To the brown silver oxide, formed from 150 g. of silver nitrate and 70 g. of sodium hydroxide in 600 ml. of water, was added 47.5 g. (0.424 mole) of 3-thenaldehyde in small portions with cooling. The addition was completed in twenty minutes and the oxidation was completed in thirty minutes as evidenced by the disappearance of the characteristic aldehyde odor. The silver was removed and washed with 200 ml. of water. The solution was acidified with concentrated hydrochloric acid and cooled for twelve hours; yield 49.3 g.; m. p. 136–137°. Concentration of the mother liquors to 50 ml. yielded an additional 3.2 g. of acid; total yield, 52.5 g. (97%); m. p. 137–138° after recrystallization from water.

The ***p*-bromophenacyl ester** was crystallized from ethanol; m. p. 129–130°.

Anal. Calcd. for $C_{13}H_9O_3SBr$: S, 9.86. Found: S, 9.99.

The **amide**[9] was recrystallized from water; m. p. 179–180°.

3-Thenoyl Chloride (IX).[9]—This material was prepared from VII, employing thionyl chloride, in 88% yield; b. p. 203–204° (748 mm.), 110–111° (36 mm.); m. p. 51–52°.

Ethyl-3-thenoate (VIII).—The ester was prepared from IX in 76.7 yield; b. p. 207–208° (736 mm.); d^{27}_4 1.1799, $n^{20}D$ 1.5230.

Anal. Calcd. for $C_7H_8O_2S$: S, 20.53. Found: S, 20.77.

3-Acetothienone (X).—The procedure of Gilman and Nelson,[18] used in the preparation of *p*-methoxyacetophenone, was employed in this preparation; yield 81%; b. p. 208–210° (748 mm.). After recrystallization from petroleum ether (30–60°) this material melted at 57°.

Anal. Calcd. for C_6H_6OS: S, 25.41. Found: S, 26.08.

The **2,4-dinitrophenylhydrazone** crystallized as red needles from chloroform, m. p. 265°.

Anal. Calcd. for $C_{12}H_{10}O_4N_4S$: S, 10.47. Found: S, 10.80.

The **semicarbazone** crystallized from water as white leaflets, m. p. 174–175°.

Anal. Calcd. for $C_7H_9N_3OS$: S, 17.50. Found: S, 17.27.

***sym*-Di-3-thienylethane** (III).—To a mixture of 200 ml. of anhydrous ether and 12.2 g. (0.5 mole) of magnesium was added dropwise with stirring 30 g. of the bromide mixture (3-thenyl bromide and 2-bromo-3-methylthiophene) in 75 ml. of ether. After the addition was complete and refluxing had subsided the mixture was stirred at room temperature for one-half hour and was then poured into a beaker containing 200 g. of crushed Dry Ice. The mixture was stirred vigorously and a stiff mass resulted which finally solidified. Water, followed by concentrated hydrochloric acid, was added with stirring. When all the solid material had dissolved the ether solution was removed, washed with water, and extracted twice with sodium bicarbonate solution. Acidification of the bicarbonate solution yielded 3 g. (12.5%) of 3-methyl-2-thenoic acid[19]; m. p. 144–145° after recrystallization from water.

Anal. Calcd. for $C_6H_6O_2S$: neut. equiv., 142.17. Found: neut. equiv., 142.20.

The ether solution was dried and the ether removed on a steam-bath. Vacuum distillation of the oil yielded 8 g. (48%) of *sym*-3,3′-dithienylethane; b. p. 120–130° (2 mm.); m. p. 64–65° after recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{10}S_2$: S, 33.00. Found: S, 33.31.

3-Thienylacetic Acid (IV).—A mixture of 100 ml. of water, 100 ml. of ethanol and 15 g. (0.3 mole) of sodium cyanide was stirred and refluxed while a solution of 54 g. of the mixture of bromides dissolved in 50 ml. of ethanol was added dropwise. After refluxing for three hours, the sodium bromide was removed by filtration. To the alcoholic filtrate was added 30 g. of potassium hydroxide and the solution was refluxed for fifteen hours. The alcohol was then removed by distillation. The basic solution was extracted with ether and the aqueous layer acidified with concentrated hydrochloric acid. The acid separated as an oil which was extracted with ether, dried and the ether removed on a steam-bath. The crystalline acid was recrystallized from petroleum ether (90–130°); m. p. 79–80°; yield 9.7 g. (25%).

Anal. Calcd. for $C_6H_6O_2S$: S, 22.54; neut. equiv., 142.17. Found: S, 23.10; neut. equiv., 142.00.

3,3′-Thenoin.—A solution of 50 ml. of ethanol containing 2 g. of sodium cyanide and 3 g. of 3-thenaldehyde was refluxed for one hour. The reaction mixture was poured into 150 ml. of water, the mixture thoroughly shaken, and cooled overnight; yield 1 g. (33%) after recrystallization from water; m. p. 116–117°.

Anal. Calcd. for $C_{10}H_8O_2S$: S, 28.59. Found: S, 28.59.

3-Thenalrhodanine (VIa).—This compound was prepared following the procedure of Julian and Sturgis[26]

(25) All derivatives were prepared by the methods described by Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940.

(26) Julian and Sturgis, THIS JOURNAL, **57**, 1126 (1935).

for veratralrhodanine, in a yield of 98%. Yellow needles were obtained from a water–acetone mixture, m. p. 212–213°.

Anal. Calcd. for $C_8H_5ONS_3$: S, 42.31. Found: S, 42.27.

2-Phenyl-4-(3-thenal)-5-oxazolone (VIb).—This material was prepared, following the procedure described by Gillespie and Snyder[27] for the preparation of 2-phenyl-4-benzal-5-oxazolone, in a yield of 63.5%. Yellow needles were obtained on crystallization from benzene, m. p. 188–190°.

Anal. Calcd. for $C_{14}H_9O_2NS$: S, 12.56. Found: S, 12.62.

Acknowledgment.—The authors wish to thank Dr. George A. Harrington of the Socony Vacuum Oil Company for the generous gift of 3-methylthiophene used in this investigation.

(27) Gillespie and Snyder, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 490.

Summary

A synthesis, based on the side-chain bromination of 3-methylthiophene with N-bromosuccinimide, has been described for a number of 3-substituted thiophenes.

New compounds which have been prepared in this investigation are 3-thenyl bromide, 3-thienylacetic acid, 3-acetothienone, *sym*-di-3-thienylethane, 3-thenalrhodanine, 2-phenyl-4-(3-thenal)-5-oxazolone, 3,3′-thenoin, and some esters of 3-thenoic acid.

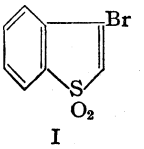
BLOOMINGTON, INDIANA RECEIVED AUGUST 21, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Studies in the Thianaphthene Series. I. Reactivity of the Bromine Atom in 3-Bromothianaphthene-1-dioxide

BY F. G. BORDWELL AND C. J. ALBISETTI, JR.[1]

Komppa[2] found that the bromine atom in 3-bromothianaphthene was inert to boiling alcoholic alkali and 30% aqueous alkali. In contrast, 3-bromothianaphthene-1-dioxide (I) liberates bromide ion rapidly when treated with hot alkaline



I

solutions, and several reactions in which the bromine atom of I was replaced with other groups were found to occur readily. By oxidation of 3-bromothianaphthene[2] with 30% hydrogen peroxide in acetic acid–acetic anhydride solution I was obtained in good yields.

The reaction of I with piperidine in refluxing alcoholic solution was rapid, a 96% yield of 3-(1-piperidino)-thianaphthene-1-dioxide being obtained within thirty minutes. In a similar manner excellent yields of 3-butylaminothianaphthene-1-dioxide and 3-diethylaminothianaphthene-1-dioxide were obtained. When I was dissolved in liquid ammonia no reaction occurred at −38°, but heating the reaction mixture at 110° for one and one-half hours in a pressure vessel gave 3-aminothianaphthene-1-dioxide. Aqueous ammonia at 110° gave only highly colored non-crystalline material. Less basic amines including aniline, 2-aminopyridine and 2-aminopyrimidine did not react with I in refluxing alcoholic solution.[3] Refluxing I with 2-aminopyridine in phenol also failed to effect the desired replacement; instead a small quantity of 3-phenoxythianaphthene-1-dioxide was obtained.

The hydrolytic behavior of 3-diethylaminothianaphthene-1-dioxide was tested in a few experiments. In refluxing solution hydrolysis to 3-hydroxythianaphthene-1-dioxide occurred within ten minutes in the presence of 10% sulfuric acid. 3-Aminothianaphthene-1-dioxide was also hydrolyzed rapidly in acidic solutions. In neutral or basic solutions 3-diethylaminothianaphthene-1-dioxide was more stable to hydrolysis.

It seems probable that the bromine atom in I can be replaced by reaction with nucleophilic reagents other than aliphatic amines. Thus far, the reaction with only one other class of reagents has been investigated. By refluxing I in methanol solution in the presence of an equimolar quantity of potassium hydroxide an excellent yield of 3-methoxythianaphthene-1-dioxide was obtained. When phenol was included in the reaction mixture 3-phenoxythianaphthene-1-dioxide was isolated. Refluxing a methanol solution of I for thirty minutes with an equimolar portion of sodium cyanide also gave 3-methoxythianaphthene-1-dioxide.

To test quantitatively the activity of the bromine atom, I was refluxed in benzene solution with excess piperidine as described by Spitzer and Wheland[4] for the determination of the activity of the bromine atoms in *p*- and *o*-nitrobromobenzenes

(1) Du Pont Fellow, 1946–1947. Present address: Du Pont Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Abstracted from the Ph.D. dissertation of C. J. Albisetti, Jr.

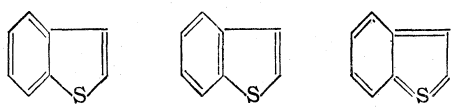
(2) Komppa, *J. prakt. Chem.*, **122**, 319 (1929).

(3) The bromine atom in I is less active than that in 3-bromoindone, since Schlossberg, *Ber.*, **33**, 2426 (1900), found that the latter reacts readily in alcoholic solution with aniline to give 3-anilinoindone.

(4) Spitzer and Wheland, THIS JOURNAL, **62**, 2995 (1940).

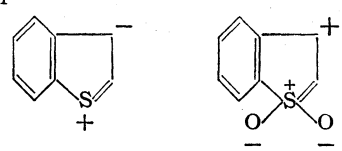
and related compounds. The authors[4] report the reaction of *p*-nitrobromobenzene to be about 52% complete in eight hours, whereas with *o*-nitrobromobenzene the reaction was about 82% complete in one hour. With I, the reaction was found to be essentially complete under these conditions even when the reaction time was shortened to one-quarter hour.[5] It is impossible from these data to calculate a rate constant to compare with those given,[4] but the bromine atom in I must be at least four times as reactive as that in *o*-nitrobromobenzene. Since Todd and Shriner[6] found that an *o*-methylsulfonyl group is only about one-fifteenth as effective as an *o*-nitro group in activating an aryl halogen atom in a similar type of reaction, the bromine atom in I must be much more easily replaced than that in *o*-methylsulfonylbromobenzene.

For thianaphthene, resonance structures, II, III and IV, may be written, comparable to those



II III IV

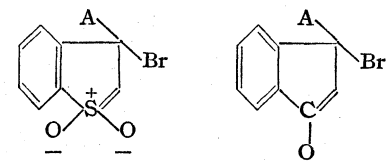
for naphthalene. In view of the lower aromaticity of thianaphthene[7a] it is probable, however, that IV contributes less to the structure of the molecule than does II or III.[7b] For thianaphthene-1-dioxide no structure comparable to IV may be written, since the sulfur atom has no unshared electrons. Charge separation structures such as V and VI,



V VI

may be written for thianaphthene and its 1-dioxide, but in structures for the latter the sulfur atom must again be given ten electrons. It seems likely, therefore, that the hetero ring in the dioxide has less aromatic character than that in thianaphthene. The chemical evidence indicates that the 2–3 bond in thianaphthene-1-dioxide is olefinic in type, since it will add bromine,[8a,b] ethyl alcohol[8b] and hydrogen[8b] under conditions similar to those used for α-β-unsaturated sulfones.

The relative inertness of aryl halides in replacement reactions initiated by nucleophilic reagents has been ascribed[9] to the inability of the reagent to approach the carbon atom holding the halogen atom in such a way as to give a reasonable transition state, unless the Kekulé-type resonance is disrupted in the process. The activation of the halogen of aryl halides by substitution of *meta*-directing groups in *o*- and/or *p*-positions, is accounted for by increased resonance stabilization in the transition state. The fact that 2,4-dinitro-1-chloronaphthalene reacts about twenty times as rapidly with methoxide ion as does 2,4-dinitrochlorobenzene[10] is understandable since more structures can be written for the transition state in the naphthyl halide. The effective activation of the bromine atom in I and in 3-bromoindone has a similar explanation, since resonance structures of the type VII and VIII can be



VII VIII

written for the transition state of a displacement reaction involving the attack of the anion, A^-. The higher order of activity of the bromine atom in 3-bromoindone,[3] despite the greater electron attracting power of a sulfonyl group, can be accounted for by a smaller amount of resonance stabilization by structures such as VII due to the ten electrons around the sulfur atom.

Acknowledgment.—The authors wish to thank Professor Ralph Pearson for helpful suggestions.

Experimental[11]

3-Bromothianaphthene-1-dioxide (I).—A mixture of 8.0 g. (0.037 mole) of 3-bromothianaphthene,[2,12] 50 ml. of acetic anhydride and 50 ml. each of acetic acid and hydrogen peroxide (30%) was brought carefully to reflux temperature. The initial ebullition was very vigorous. The mixture was refluxed for one hour, 200 ml. of water was added, and the solution thoroughly cooled. By filtration there was obtained 6.5 g. (70.6%) of 3-bromothianaphthene-1-dioxide, m. p. 180–182°. The compound crystallized as short white needles from alcohol; m. p. 183.5–184°.

Anal. Calcd. for $C_8H_5O_2SBr$: C, 39.20; H, 2.06. Found: C, 39.07; H, 1.85.

3-(1-Piperidino)-thianaphthene-1-dioxide.—A mixture of 1.2 g. (0.005 mole) of I, 25 ml. of 85% alcohol and 1.3 g. (0.015 mole) of piperidine was refluxed for thirty minutes and cooled. There separated 1.20 g. (96%) of a yellow crystalline solid, m. p. (dec.) 223–227°. After three crystallizations from alcohol the material decomposed at 246° with gas evolution.

Anal. Calcd. for $C_{13}H_{15}O_2NS$: C, 62.23; H, 6.07. Found: C, 62.04; H, 5.85.

A similar reaction of I with diethylamine gave a 67% yield of **3-diethylaminothianaphthene-1-dioxide.** Crystallization from alcohol and twice from ethyl acetate gave long yellow needles, m. p. 186.5–187°.

(5) We wish to thank Mr. W. H. McKellin for carrying out this determination.

(6) Todd and Shriner, THIS JOURNAL, **56**, 1382 (1934).

(7) (a) Fieser and Kennelly, *ibid.*, **57**, 1611 (1935); (b) Schomaker and Pauling, *ibid.*, **61**, 1769 (1939), estimate that structures for thiophene in which the sulfur atom is given ten electrons are important, but less so than structures in which sulfur has eight electrons.

(8) (a) Lanfry, *Compt. rend.*, **154**, 519 (1912); (b) unpublished results of W. H. McKellin of this Laboratory.

(9) Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, 1941, p. 447.

(10) Talen, *Rec. trav. chim.*, **47**, 329 (1928).

(11) The microanalyses reported were by Mrs. Margaret Ledyard, Mrs. Nelda Mold and Miss Patricia Craig.

(12) We wish to thank the Texas Company, Beacon, New York, for a generous supply of thianaphthene.

Anal. Calcd. for $C_{12}H_{15}O_2NS$: C, 60.73; H, 6.37. Found: C, 60.58; H, 6.46.

The reaction of I with butylamine gave 83% of **3-butylaminothianaphthene-1-dioxide**, which was obtained as fine white needles, m. p. 145°, after crystallization from methanol–water and twice from ethyl acetate.

Anal. Calcd. for $C_{12}H_{15}O_2NS$: C, 60.73; H, 6.37. Found: C, 60.91; H, 6.47.

The kinetic experiments[5] were run essentially by the method described by Spitzer and Wheland,[4] except that silver bromide was determined gravimetrically. In one hour 99% of the bromine was liberated from I and in one-fourth hour 97% of the theoretical amount of silver bromide was obtained.

Attempted Preparation of 3-(2-Pyridylamino)-thianaphthene-1-dioxide.—After refluxing an alcoholic solution of I and 2-aminopyridine for eighteen hours I was recovered unchanged. No reaction occurred when an alcoholic solution of I and aniline was refluxed for thirty minutes or when an alcoholic solution of I and 2-aminopyrimidine was refluxed for eighteen hours.

Refluxing a solution of I and 2-aminopyridine in phenol for three hours gave a very small amount of 3-phenoxythianaphthene-1-dioxide (properties reported below).

3-Aminothianaphthene-1-dioxide.—A mixture of 3.7 g. (0.015 mole) of I and 25 ml. of liquid ammonia was heated at 110° for one and one-half hours in a glass liner in a pressure vessel. After evaporation of the ammonia the product was washed from the liner with absolute ethanol. There was obtained 1.5 g. (53%) of a yellow powder which melted at 200–205° with the evolution of gas. The gas evolved by heating a small amount of the material in a shallow tube turned litmus paper blue. Purified from absolute ethanol, the material melted at 211–213°.

Anal. Calcd. for $C_8H_7O_2NS$: C, 53.03; H, 3.90; N, 7.73. Found: C, 53.22: H, 4.13; N, 7.25.

Hydrolysis of 3-Diethylaminothianaphthene-1-dioxide.—A mixture of 0.1 g. of 3-diethylaminothianaphthene-1-dioxide and 10 ml. of 10% sulfuric acid was refluxed for ten minutes. On cooling there separated 0.05 g. of 3-hydroxythianaphthene-1-dioxide, m. p. 132–133°. The most recent reference to this compound[13] gives the melting point as 133.5–134°. From a similar experiment with 10% potassium hydroxide the starting material was recovered almost quantitatively.

(13) Weston and Suter, THIS JOURNAL, **31**, 389 (1939).

3-Methoxythianaphthene-1-dioxide.—A solution of 2.45 g. (0.01 mole) of I and 0.56 g. (0.01) mole of potassium hydroxide in 30 ml. of dry methanol was refluxed one hour and cooled. By filtration there was obtained 1.5 g. (77%) of small white crystals, m. p. 208–210°. Several purifications from boiling ethanol gave large white flat blades, m. p. 220°.[14]

Anal. Calcd. for $C_9H_8O_3S$: C, 55.10; H, 4.11. Found: C, 55.11; H, 4.27.

An 84% yield of 3-methoxythianaphthene-1-dioxide was obtained in a somewhat less pure state by substituting sodium cyanide for potassium hydroxide in the above experiment.

3-Phenoxythianaphthene-1-dioxide.—A mixture of 2.45 g. (0.01 mole) of I, 1.0 g. (0.01 mole) of phenol and 0.56 g. (0.01 mole) of potassium hydroxide was dissolved in 20 ml. of absolute ethanol and the solution refluxed for one hour and cooled. The crude material melted at 110–124°. Several purifications from ethanol gave a small quantity of clear plates, m. p. 137°. The yield could undoubtedly be improved.

Anal. Calcd. for $C_{14}H_{10}O_3S$: C, 65.00; H, 3.87. Found: C, 64.80; H, 3.98.

Summary

1. Excellent yields of 3-alkylamino-, 3-amino- and 3-methoxythianaphthene-1-dioxides were readily obtained by the reaction of 3-bromothianaphthene-1-dioxide (I), respectively, with primary and secondary amines, anhydrous ammonia, and methanol in the presence of potassium hydroxide. Aryl amines did not react with I under comparable conditions.

2. The bromine atom in I was displaced at least four times as rapidly as that in *o*-nitrobromobenzene in the reaction with excess piperidine in benzene solution.

3. The reactivity of the bromine atom in I and related compounds is discussed on the basis of current theory.

(14) Arndt and Martius, *Ann.*, **499**, 282 (1932), report a m. p. of 215°.

EVANSTON, ILLINOIS RECEIVED OCTOBER 3, 1947

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Preparation and Polymerization of *m*-Cyanostyrene

BY RICHARD H. WILEY AND NEWTON R. SMITH

Many substituted styrenes, including *p*-cyanostyrene[1,2] and *o*-cyanostyrene[2] have been described in a number of recent papers[3] but no mention has been made of *m*-cyanostyrene. We have prepared *m*-cyanostyrene by the decarboxylation of *m*-cyanocinnamic acid. Poly-*m*-cyanostyrene resembles poly-*p*-cyanostyrene in that both are insoluble in aromatic hydrocarbons and are soluble in nitromethane. The principle of vinylogy which by reference to polyacrylonitrile predicts the insolubility of poly-*p*-cyanostyrene does not apply to the meta isomer. The relative insolubility of each is undoubtedly caused by the polarity of the cyano group but it is not possible, with the meta isomer, to relate this effect vinylogously to the behavior of the polyacrylonitrile.

(1) (a) Overberger and Allen, THIS JOURNAL, **68**, 722 (1947); (b) Marvel and Overberger, *ibid.*, **67**, 2250 (1945); (c) Mowry, Renoll and Huber, *ibid.*, **68**, 1105 (1946).

(2) Wingfoot Corp., British Patent 571,829; *C. A.*, **41**, 3323 (1947).

(3) (a) Marvel, *et al.*, THIS JOURNAL, **68**, 1088 (1947); (b) Emerson, *et al.*, *ibid.*, **69**, 1905 (1947); (c) Bachman, *et al.*, *ibid.*, **69**, 2022 (1947); (d) Strassburg, Gregg and Walling, *ibid.*, **69**, 2141 (1947); (e) Inskeep and Deanin, *ibid.*, **69**, 2237 (1947); (f) Frank, *et al.*, *ibid.*, **68**, 1365 (1946); (g) Renoll, *et al.*, *ibid.*, **68**, 1159 (1946).

Experimental

***m*-Cyanobenzaldehyde.**—*m*-Tolunitrile (Eastman Kodak Co.) was converted to the aldehyde by the procedure used in "Organic Syntheses" for the preparation of *p*-

bromobenzaldehyde.[4] Eight to ten hours were required to complete the bromination of the nitrile. The dibromide was hydrolyzed with calcium carbonate. The aldehyde was separated by steam distillation and, after cooling, was collected on a filter. The yield of dried *m*-cyanobenzaldehyde was 45%, m. p. 76–77°.[5]

m-Cyanocinnamic Acid.—The procedure of Walling and Wolfstirn[6] was followed. A solution of 48.0 g. (0.37 mole) of crude *m*-cyanobenzaldehyde and 42.5 g. (0.41 mole) of malonic acid (E.K. Co.) in 5 ml. of pyridine and 50 ml. of 95% alcohol was heated for ten hours on a steam-bath. The precipitate was collected and recrystallized from alcohol to give 45.3 g., 71.4% of the theoretical amount, of *m*-cyanocinnamic acid, m. p. 247° cor.

Anal. Calcd. for $C_{10}H_7NO_2$: eq. wt., 173.2; N, 8.08. Found: eq. wt., 174.5; N, 8.04, 8.09.

m-Cyanostyrene.—*m*-Cyanocinnamic acid was decarboxylated by the method of Walling and Wolfstirn.[6] To 125 g. of boiling quinoline and 2 g. of copper powder in a 250-ml. Claisen flask was added 40 g. of *m*-cyanocinnamic acid in 10-g. portions. Twenty five ml. of distillate was collected after each addition. The distillate was taken up in ether, extracted with 3 *N* hydrochloric acid, and dried over anhydrous sodium sulfate. After removing ether from the dried solution, the residue was fractionated to give 16.2 g., 51% of the theoretical amount, of *m*-cyanostyrene, b. p. 81–5° (3.5 mm.). Refractionation of 22 g. of crude styrene gave 19.6 g. of purified *m*-cyanostyrene, b. p. 83° (3.5 mm.), $n^{20}D$ 1.5630.

Anal. Calcd. for C_9H_7N: N, 10.85. Found: N, 11.03, 11.05.

The dibromide was prepared by adding bromine to a solution of *m*-cyanostyrene in carbon tetrachloride. The crystals obtained on evaporation of the carbon tetrachloride were recrystallized from alcohol, m. p. 71–72°.

Anal. Calcd. for $C_9H_7NBr_2$: N, 4.96. Found: N, 5.01.

Polymerization of m-Cyanostyrene.—A solution of 0.002 g. (*ca.* 0.1% by weight) of benzoyl peroxide in 1.71 g. of purified monomer was prepared in a test-tube, stoppered, and heated with protection from the air for twenty-four hours at 80° to form a hard, brittle, transparent, slightly yellow solid. A control without benzoyl peroxide did not polymerize. The polymer softens at 100°, sticks at 135°, and turns into a thick gum at 190°. It is soluble in nitromethane and acetone and swells in hot toluene and benzene. Relative viscosity 1.270 for concentration of 0.400 g. in 100 ml. of nitromethane; 2.835 for 2.000 g. in 100 ml. of nitromethane.

(4) Coleman and Honeywell, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, p. 89.

(5) P. Reinglass, *Ber.*, **24**, 2421 (1891), gives m. p. 79–81°.

(6) C. Walling and K. B. Wolfstirn, THIS JOURNAL, **69**, 825 (1947).

Summary

m-Cyanostyrene has been prepared from *m*-cyanobenzaldehyde through *m*-cyanocinnamic acid and polymerized to a brittle, transparent polymer.

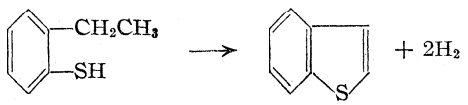
CHAPEL HILL, NORTH CAROLINA
RECEIVED DECEMBER 18, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, POMONA COLLEGE]

The Vapor Phase Catalytic Synthesis of Thianaphthenes

BY CORWIN HANSCH AND WILLIAM A. BLONDON

The synthesis of thianaphthenes from *o*-alkylbenzenethiols was undertaken in this Laboratory as a part of a general investigation of the vapor phase catalytic synthesis of hetrocyclic compounds. Preparation of thianaphthene itself was taken as the model reaction on which the catalysts and apparatus were developed. The following equation gives the over-all reaction.



The arylthiols used in this work were prepared from the corresponding hydrocarbons (ethylbenzene, *n*-propylbenzene, isopropylbenzene) by treating them with chlorosulfonic acid and reducing the resulting sulfonyl chloride with sulfuric acid and zinc dust. The pure sulfonylchlorides were not isolated, in fact the propylbenzenesulfonyl chlorides were found to be quite unstable to heat. Attempts to distill these compounds, even under reduced pressure, resulted in explosive decompositions.

The apparatus used in this work was similar to that described by Hoog, Verheus and Zuiderweg.[1]

(1) Hoog, Verheus and Zuiderweg, *Trans. Faraday Soc.*, **35**, 995 (1939).

Experimental

Catalyst Preparations. I. Chromium on Aluminum Oxide.—To a boiling solution of 36.4 g. of chromic anhydride in 400 ml. of distilled water, was added 200 g. of ALORCO alumina,[2] H-40 Grade R2200, 8–14 mesh. The solution was allowed to stand for two minutes and filtered, then the product was dried at 100°.

II. **Molybdenum Sulfide.**—One hundred grams of alumina was added to a boiling solution of 60 g. of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 200 ml. of distilled water. The mixture was allowed to stand for a few minutes and then a rapid stream of hydrogen sulfide was passed into the catalyst for twenty minutes. The catalyst was filtered, washed repeatedly with water and dried at 100°.

III. **Platinum on Charcoal.**—To 75 ml. of distilled water was added 5 g. of chloroplatinic acid containing 40% platinum. The solution was heated to boiling and 12 g. of activated charcoal[3] was added. This mixture was boiled for five minutes and then the catalyst was filtered and dried at 100°.

Preparation of Ethylbenzenethiol.—To 2300 g. of chlorosulfonic acid, cooled to 0° in an efficient ice-bath, 652 g. of ethylbenzene was added, with stirring. The temperature of the mixture was held at 0° during the addition, after which the reaction mixture was stored in a refrigerator at 0° for eighteen hours. After this period of standing, the product was poured, with vigorous stirring, onto 6 liters of crushed ice. The lower oily layer was then separated and divided into three equal portions to facilitate reduction.

(2) This type of alumina was used exclusively in this research.

(3) The activated charcoal used in this work was Type B15P, 6–8 mesh, obtained from the Pittsburgh Coke & Chemical Co.

Three 5-liter round-bottom flasks were fitted with efficient stirrers and surrounded with ice–salt mixtures. Into each flask was placed 4 liters of crushed ice and 1300 g. of concd. sulfuric acid. When the temperature of this mixture had reached 0°, the sulfonyl chloride was allowed to drop into the mixture, with rapid stirring. After the addition of the sulfonyl chloride, 650 g. of zinc dust was added to each flask in small portions so that the temperature never rose above 5°. When all of the zinc had been added, the flasks were fitted with reflux condensers and permitted to come to room temperature slowly. After the initial evolution of hydrogen had ceased, the reaction mixtures were boiled for six hours. The upper oily layer was then separated, washed and dried. Distillation gave 621 g. (68%) of *o*-ethylbenzenethiol, b. p. 207–209° (730 mm.).

o-Propylbenzenethiols.—*o,n*-Propylbenzenethiol and *o*-isopropylbenzenethiol were synthesized by the above procedure, giving 76% yield of the former, b. p. 219–221° (730 mm.) and 70% yield of the latter, b. p. 225–227° (730 mm.).

	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
Ethylbenzenethiol	69.50	7.25	69.50	7.59
n-Propylbenzenethiol	71.05	7.89	70.96	7.97
Isopropylbenzenethiol	71.05	7.89	71.03	7.89

α-(o-Carboxyphenylmercapto)-propionic Acid.—In 300 ml. of boiling water were dissolved 10 g. of anhydrous sodium carbonate and 20 g. of *o,o'*-dithiodibenzoic acid.[4] When all of the acid had dissolved, 30 g. of sodium hydrosulfite was added slowly, with stirring. The reactants were refluxed for fifteen minutes and then cooled to room temperature. To this cooled solution was added 49 g. of α-bromopropionic acid (previously neutralized with sodium bicarbonate) in 150 ml. of water. This mixture was boiled for fifteen minutes and then acidified to congo red paper while hot. On cooling, the α-(*o*-carboxyphenylmercapto)-propionic acid crystallized and was filtered and dried; yield 20 g. Recrystallization from 700 cc. of boiling water gave 15 g. of product, m. p. 192–194° (dec.).

2-Methylthianaphthene.—Ten grams of α-(*o*-carboxyphenylmercapto)-propionic acid, 5 g. of anhydrous sodium acetate and 25 ml. of acetic anhydride were placed in a round-bottom flask and slowly warmed to 75°, at which temperature the evolution of carbon dioxide began. After the gas evolution had subsided somewhat, the temperature was raised to 140° and held there for twenty minutes. Excess 50% sodium hydroxide was then added and the solution refluxed for one hour. It was then acidified with phosphoric acid and steam-distilled, giving a yellow oil: 2-methyl-3-thianaphthenol. Five grams of this oil was dissolved in 50 ml. of acetic acid, the resulting mixture being refluxed for two hours with 10 g. of zinc dust, then made basic with sodium hydroxide and steam-distilled. About 1 g. of a water-white oil distilled and solidified on cooling; m. p. 42–47°. Recrystallization from an alcohol–water mixture gave a product which melted at 51–52°.

Anal. Calcd. for C_9H_8S: C, 72.96; H, 5.41. Found: C, 72.73; H, 5.90.

2-Methylthianaphthene, formed by catalytic dehydrogenation of *o*-isopropylbenzenethiol, possessed the same melting point. A mixed melting point of the two substances showed no depression. Both preparations yielded picrates; m. p. 108–109°.

Anal. Calcd. for $C_{15}H_{11}N_3O_7S$: C, 47.75; H, 2.92. Found: C, 47.90; H, 3.28.

Catalytic Preparation of Thianaphthene.—The following is an example of a typical dehydrogenation run made in this research, using *o*-ethylbenzenethiol and chromium on alumina (I) catalyst. Ten milliliters of catalyst (I) was reduced *in situ* with a slow stream of hydrogen at a temperature of 400° for one hour, after which the catalytic tube was swept free of hydrogen with a stream of nitrogen. Then, 82 g. of *o*-ethylbenzenethiol was passed over the catalyst during a period of two hours. The temperature of the catalyst was held at 475 ± 3° during this reaction. The condensate (72 g.) was extracted with dilute sodium hydroxide, and by this means 4.5 g. of unchanged mercaptan was recovered. The alkali insoluble portion was distilled through a 1.5 ft. column using a variable take-off head with a reflux ratio of 5 to 1. Twenty-six grams boiled at 132–140° and was identified as mainly ethylbenzene. The 5 g. distilling at 140–210° was ethylbenzene with some thianaphthene. Twenty-two grams, which distilled between 210–230°, solidified on cooling; m. p. 22–24°. Crystallization from alcohol gave a product, m. p. 31–32°, the temperature at which thianaphthene melts.

Catalytic Preparation of 2-Methylthianaphthene.—2-Methylthianaphthene was prepared in the same manner, using 10 ml. of chromium oxide catalyst. Thirty grams of *o,n*-propylbenzenethiol was processed at 450° during a one-hour period, yielding 8 g. of oil insoluble in dilute sodium hydroxide. Fourteen grams of unchanged mercaptan was recovered. Distillation of the alkali insoluble fraction gave 3 g., b. p. 220–265°. This fraction was heated under reflux with 0.5 g. of sulfur for four hours to dehydrogenate any dihydromethylthianaphthene, then steam-distilled from an alkaline solution. The white solid collected was crystallized from alcohol; yield 1.6 g., m. p. 51–52°.

Attempted Catalytic Preparation of 3-Methylthianaphthene.—*o*-Isopropylbenzenethiol (65 g.), processed over 10 ml. of catalyst (I) at a temperature of 425° during a ninety-minute period, yielded 16 g. of isopropylbenzene and 7.5 g. of a substance which distilled at 235–250°. Fifteen grams of unchanged thiol was recovered. Considerable decomposition occurred on the catalyst. Attempts to purify the material boiling at 235–250°, by crystallization of its picrate, were unsuccessful. A sharp melting point could not be obtained with the picrate in spite of repeated crystallizations from various solvents. Attempts to crystallize the thianaphthene itself were also unsuccessful.

Discussion

It should be pointed out that although over fifty runs were made (mostly with *o*-ethylbenzenethiol) using various catalysts and conditions, the authors feel that by continued study the yield of thianaphthenes could be improved. It has been shown recently,[5] however, that thianaphthene may be made in good yield by the vapor phase catalytic reaction of styrene and hydrogen sulfide. Preliminary work in this Laboratory has shown that ethylbenzene and hydrogen sulfide may be catalytically converted into thianaphthene. At present, work is in progress to develop a general method of synthesis from alkylbenzenes and hydrogen sulfide.

The catalysts employed in this work which were at all effective were: chromium oxide on alumina (I), molybdenum sulfide on alumina (II), platinum on charcoal (III), and type J-2 dehydrogenation catalyst obtained from Universal Oil Products. Of the above catalysts, the platinum was the least effective because of rather rapid poisoning. The molybdenum sulfide, although effective in cyclization and resistant to poisoning, was not practical because of its great tendency to desulfurize the thiols to the corresponding hydro-

(4) Allen and MacKay, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 580.

(5) Moore and Greensfelder, THIS JOURNAL, **69**, 2008 (1947).

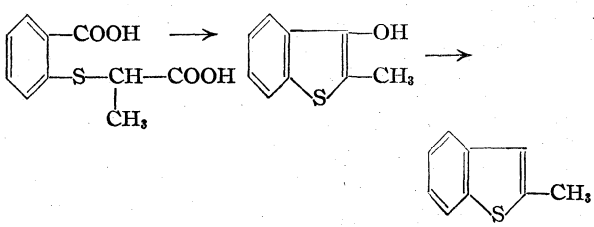
carbons. Apparently, hydrogen, formed during the dehydrogenation, reacted with the thiols to convert them to hydrocarbons and hydrogen sulfide. This side reaction occurred with all catalysts used but was most pronounced with molybdenum sulfide. The best catalyst found in this work was chromium oxide (I), although the J-2 catalyst from Universal Oil Products was almost as active.

Table I summarizes below the results of a series of comparable runs, and shows the effect of temperature and space velocity on the dehydrogenation of *o*-ethylbenzenethiol, using chromium on alumina catalyst (I).

TABLE I

Temp., °C.	Space vel., ml./ml. cat./hr.	% Conversion to thianaphthene
350	600	10
400	600	32
450	800	42
500	600	35
450	1500	28
450	900	40
450	800	42
450	200	42

In an attempt to extend the reaction to other alkylbenzene thiols, several runs were made using *o,n*-propylbenzenethiol. Conversions of 10–12% of 2-methylthianaphthene were obtained. Since its synthesis had not been reported previously, this compound was prepared by a known procedure[6] to check its identity.



The 2-methylthianaphthene prepared catalytically was identical with that made by the method illustrated.

The ultraviolet absorption spectrum determined for 2-methylthianaphthene followed closely that of thianaphthene (Fig. 1), with maxima at 288.5 and 297 mμ, and a minimum at 299 mμ. The absorption spectrum for thianaphthene was in close agreement with that previously reported,[7] with maxima at 288 and 297.5 mμ, and a minimum at 295 mμ. All of the absorption measurements were made with methanol solutions at dilutions of 1/100,000, by means of a Beckman quartz spectrophotometer.

An attempt to prepare 3-methylthianaphthene was not completely successful. A liquid was obtained which had the expected boiling point, but attempts to purify it by distillation or crystallization of the picrate were unsuccessful. It is interesting to note that this substance possessed an absorption spectrum (Fig. 1) closely resembling that of thianaphthene and 2-methylthianaphthene.

(6) Hansch and Lindwall, *J. Org. Chem.*, **10**, 381 (1945).
(7) Charlampowicz and Marchlewski, *C. A.*, **25**, 5097 (1931).

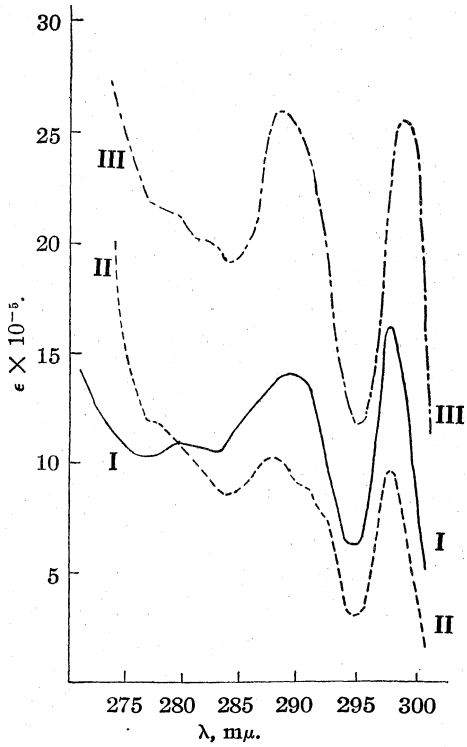
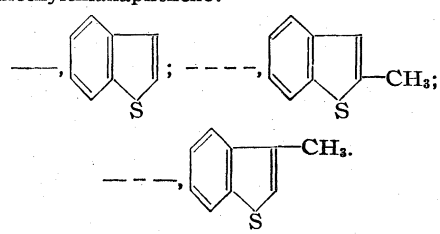


Fig. 1.—Ultraviolet absorption spectra of thianaphthene and 2-methylthianaphthene:



Acknowledgment.—The authors are very much indebted to the Research Corporation for a Frederick Gardner Cottrell grant-in-aid which supported this research. We also wish to acknowledge a generous gift from the Signal Oil Company which made possible the purchase of the Beckman spectrophotometer used in this work.

Summary

1. The preparation of two new alkylbenzenethiols is described.

2. A study of the cyclodehydrogenation of the thiols to the corresponding thianaphthenes is discussed.

3. The ultraviolet absorption spectra are reported for the thianaphthenes.

4. A special synthesis for 2-methylthianaphthene is reported.

CLAREMONT, CALIF. RECEIVED NOVEMBER 12, 1947

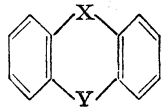
[CONTRIBUTION FROM THE DYSON PERRINS LABORATORY, OXFORD, ENGLAND, AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Use of Fluoro Compounds in the Determination of Valency Angles by Electric Dipole Moment Measurements

BY NELSON J. LEONARD AND LESLIE E. SUTTON

Our initial aim in this investigation was to determine bond angles from electric dipole substitution, using methods previously developed[1,2,3,4] but using fluorine as the substituent atom. Evaluations of the interaction moments between halogens and the NH_2- or CH_3O- grouping indicated that these are least with fluorine,[5] and therefore that this cause of error in bond angle determinations should be least if fluorine is used. Our results caused us to investigate more thoroughly the magnitudes of such interaction moments in fluorine compounds, and to compare them with those for other halogens.

We applied information so obtained about bond angles in the discussion of the configuration of molecules of the type I, when X and Y are divalent atoms or groups, *e. g.*, O, S, Se, NH, and we augmented the dipole moment data for such compounds by measuring phenoxthine and phenthiazine.



I

Experimental

Preparation and Purification of Materials.—Benzene (British Drug Houses "AnalaR") was purified by freezing three times, boiling under reflux over phosphorus pentoxide, and finally distilling in a dry air stream. It was stored under dry air until used.[2] Diphenylamine (B. D. H.) was recrystallized four times from dry petroleum ether (b. p. 40–60°), m. p. 53°. Di-*p*-tolylamine (B. D. H.) was recrystallized twice from dry petroleum ether, m. p. 79°.

The following compounds were prepared by methods previously described: fluorobenzene,[6] *p*-fluoroaniline,[7] *p*-fluoroanisole,[8] *p*-fluorobenzaldehyde,[9] *p*-fluorobromobenzene,[10] *p*-fluoronitrobenzene,[11] *p*-fluorobenzophenone,[13] *p*-fluorophenol,[12] *p*-fluorotoluene,[11] *p,p'*-difluorobenzophenone,[13] phenyl-*p*-tolylamine,[14] phenyl-*p*-tolylnitrosamine, m. p. 82°,[15] di-*p*-tolylnitrosamine, m. p. 100–101°,[15] phenoxthine,[16] phenthiazine,[17] and triphenylamine.[18]

The compounds described below are, with one exception, new compounds, prepared specifically for the presently described dipole moment investigation.

***p*-Fluorodimethylaniline.**—This compound had previously been prepared by Schiemann and Pillarsky[19] from *p*-aminodimethylaniline, but a better yield was obtained by methylation of *p*-fluoroaniline. A mixture of 20 g. of dimethyl sulfate and 17 g. of *p*-fluoroaniline was sealed in a pressure tube and heated at 200° for one hour. The oily product was treated with aqueous sodium hydroxide and the resultant mixture was extracted with ether. After drying the ethereal solution, the ether was removed and the residue was distilled *in vacuo*, b. p. 86–87° (18 mm.), 79.5° (16 mm.); yield, 15 g. (71.5%).

***p*-Fluorodiphenyl Ether.**—A method similar to that used for *p*-tolyl- and di-*o*-tolyl ether by Reilly, Drumm and Barrett[20] was employed. A mixture of 12 g. of potassium *p*-fluorophenoxide, 12 g. of bromobenzene, and 0.5 g. of copper–bronze was heated at 200° for four hours under an air condenser. The product was subjected to steam distillation and the distillate was extracted with ether. The ethereal solution was dried and the ether was removed. The liquid residue was fractionated at atmospheric pressure. The portion boiling above 200° was retained and twice fractionated. Seven grams (47%) of colorless liquid, b. p. 247–249° (760 mm.), was finally collected.

Anal. Calcd. for $C_{12}H_9FO$: C, 76.59; H, 4.79. Found: C, 76.25; H, 4.82.

***p,p'*-Difluorodiphenyl Ether.**—Twelve grams of potassium *p*-fluorophenoxide, 15 g. of *p*-fluorobromobenzene, and 0.5 g. of copper–bronze were mixed and the mixture was heated under reflux for six hours at 200°. The product was isolated by the same method as employed for *p*-fluorodiphenyl ether. The colorless liquid boiled at 239–240° (743 mm.); yield, 9.0 g. (56%).

Anal. Calcd. for $C_{12}H_8F_2O$: C, 69.88; H, 4.01. Found: C, 70.08; H, 3.94.

***p*-Fluorodiphenyl Sulfide.**—A method similar to that used by Mauthner[21] for analogous sulfides was employed. Fourteen grams of potassium thiophenoxide, 29 g. of *p*-fluoroiodobenzene, and 0.5 g. of copper–bronze were heated together under reflux at 235–240° for four hours. The reaction product was treated with warm ethanol and acidified with dilute sulfuric acid. After the addition of zinc dust, the mixture was steam-distilled. The distillate was extracted with ether, the ethereal solution was dried and the ether was removed. The colorless product was distilled once with fractionation at atmospheric pressure, then twice at reduced pressure, b. p. 147–148° (15 mm.), 141–142° (11 mm.); yield, 18 g. (66%).

Anal. Calcd. for $C_{12}H_9FS$: C, 70.58; H, 4.44. Found: C, 70.25; H, 4.35.

***p,p'*-Difluorodiphenyl Sulfoxide.**—This compound was prepared successfully by the method which Colby and McLoughlin[22] used for diphenyl sulfoxide. Sixty grams of fluorobenzene and 16 g. of thionyl chloride were mixed in

(1) Hampson and Sutton, *Proc. Roy. Soc.* (*London*), **140A**, 562 (1933).
(2) Hampson, Farmer and Sutton, *ibid.*, **143A**, 147 (1933).
(3) Sutton and Hampson, *Trans. Faraday Soc.*, **31**, 945 (1935).
(4) Coop and Sutton, *J. Chem. Soc.*, 1869 (1938).
(5) Marsden and Sutton, *ibid.*, 599 (1936).
(6) "Organic Syntheses," **13**, 46 (1933).
(7) Schiemann and Pillarsky, *Ber.*, **62**, 3035 (1929).
(8) Bergmann and Tschudnowsky, *Z. physik. Chem.*, **17B**, 107 (1932).
(9) Schiemann, *ibid.*, **156A**, 397 (1931).
(10) Schiemann and Pillarsky, *Ber.*, **64**, 1340 (1931).
(11) Balz and Schiemann, *ibid.*, **60**, 1186 (1927).
(12) Bennett, Brooks and Glasstone, *J. Chem. Soc.*, 1821 (1935).
(13) Dunlop and Gardner, THIS JOURNAL, **55**, 1665 (1933).
(14) Chapman, *J. Chem. Soc.*, 569 (1929).
(15) Lachman, *Ber.*, **33**, 1022 (1900).
(16) "Organic Syntheses," **18**, 64 (1938).
(17) Kehrmann and Dardel, *Ber.*, **55**, 2346 (1922).
(18) "Organic Syntheses," **8**, 116 (1928).
(19) Schiemann and Pillarsky, *Ber.*, **66**, 727 (1933).
(20) Reilly, Drumm and Barrett, *J. Chem. Soc.*, 67 (1927).
(21) Mauthner, *Ber.*, **39**, 3593 (1906).
(22) Colby and McLoughlin, *ibid.*, **20**, 195 (1887).

an ice-cooled flask to which a reflux condenser was attached. Anhydrous aluminum chloride was added in small portions; hydrogen chloride ceased to be evolved after 40 g. had been added. The mixture was heated on a water-bath for thirty minutes, after which it was cooled and poured into ice-water. The thick oil which separated on the surface was washed with water and was then heated to remove excess fluorobenzene. A yellow, wax-like solid remained which was recrystallized three times from petroleum ether (b. p. 40–60°). A yield of 23 g. (72%) of colorless crystals, m. p. 50.5°, was obtained.

Anal. Calcd. for $C_{12}H_8F_2OS$: C, 60.47; H, 3.39. Found: C, 60.26; H, 3.55.

p,p'-Difluorodiphenyl Sulfide.—This compound was prepared by a method analogous to that of Gazdar and Smiles[23] for di-*p*-cresol sulfide. *p,p'*-Difluorodiphenyl sulfoxide (17 g.) was boiled for four hours under reflux with 6 g. of powdered zinc in glacial acetic acid. When the filtered solution was diluted with water, the sulfide separated as a colorless oil, which was twice fractionally distilled *in vacuo*, b. p. 136–137° (9 mm.); yield, 15 g. (90%).

Anal. Calcd. for $C_{12}H_8F_2S$: C, 64.83; H, 3.63. Found: C, 64.71; H, 3.51.

p,p'-Difluorodiphenyl Sulfone.—*p,p'*-Difluorodiphenyl sulfide (5 g.) was dissolved in a ten-fold quantity of glacial acetic acid and oxidized with 3 g. of potassium permanganate. After dilution of the reaction mixture with water, the precipitate was twice recrystallized from ethanol as colorless needles, m. p. 98–98.5°; yield, 4 g. (80%).

Anal. Calcd. for $C_{12}H_8F_2O_2S$: C, 56.67; H, 3.17. Found: C, 56.34; H, 3.18.

p-Fluorodiphenyl Sulfone.—This compound was prepared in the same manner, using 8.5 g. of *p*-fluorodiphenyl sulfide, 80 g. of glacial acetic acid, and 6 g. of potassium permanganate. After dilution of the reaction mixture with water, the precipitate was twice recrystallized from ethanol as colorless needles, m. p. 109.5–110°; yield, 6 g. (70%).

Anal. Calcd. for $C_{12}H_9FO_2S$: C, 60.98; H, 3.84. Found: C, 60.97; H, 3.76.

p-Fluorodiphenylamine.—This compound, b. p. 164–166° (17 mm.), m. p. 34°, was made from *p*-fluoroacetanilide and bromobenzene essentially by the method of Goldberg,[24] which is general for the preparation of diarylamines.

Anal. Calcd. for $C_{12}H_{10}FN$: C, 76.99; H, 5.38. Found: C, 76.89; H, 5.32.

p,p'-Difluorodiphenylamine.—This compound, b. p. 165–166.5° (17 mm.), m. p. 37.5°, was likewise prepared from *p*-fluoroacetanilide and *p*-fluorobromobenzene by the general method of Goldberg.[24]

Anal. Calcd. for $C_{12}H_9F_2N$: C, 70.24; H, 4.40. Found: C, 70.37; H, 4.46.

p-Fluorotriphenylamine.—A method similar to that for triphenylamine[18] was employed. A mixture of 8 g. of diphenylamine, 13 g. of *p*-fluoroiodobenzene, 8 g. of potassium carbonate, and 2 g. of copper–bronze in 50 ml. of nitrobenzene was boiled under reflux for ten hours. The nitrobenzene was removed by steam distillation and the residue was extracted with benzene. The benzene extract was dried by partial distillation of benzene, saturated with dry hydrogen chloride gas in the cold, and allowed to stand for three hours. The precipitated diphenylamine hydrochloride was removed by filtration and the benzene by distillation. The residue was distilled under reduced pressure, b. p. 187–189° (8 mm.), when the distillate solidified. Three recrystallizations from ethanol, followed by centrifuging and drying, gave 7 g. (60%) of colorless needles, m. p. 98–98.5°.

Anal. Calcd. for $C_{18}H_{14}FN$: C, 82.09; H, 5.32. Found: C, 82.22; H, 5.31.

(23) Gazdar and Smiles, *J. Chem. Soc.*, **97**, 2248 (1910).

(24) Godberg, *Ber.*, **40**, 4541 (1907).

Physical Measurements.—Electric dipole moments were determined from measurements of the dielectric constant, refractive index and density of benzene solutions of varying concentration at the same temperature. Dielectric constants were determined by a heterodyne beat method using an apparatus and a technique essentially the same as described before.[2,25] The solution condenser was similar to that described by Jenkins and Sutton.[26]

Densities were determined with a 10-ml. Sprengel–Ostwald pyknometer.

Refractive indices were measured relative to the solvent with a Pulfrich refractometer fitted with a divided cell; the mercury green line (5461 Å.) was used for illumination. For three of the compounds (fluorobenzene, *p*-fluorodiphenyl sulfide, and *p*-fluorotriphenylamine) it was not possible to obtain the molecular refractivities experimentally, due to temporary instrumental disorder, but they were calculated from the most acceptable values for the refractivities of the constituent atoms.

The dielectric constant of pure dry benzene was taken to be 2.2727 at 25°, that of dry air 1.0000. The square of the refractive index of pure dry benzene at 25° was taken to be 2.25714.

Atom polarizations, for the moments recorded in Table I, were allowed by adding 5% to the electron polarization.

Results

All measurements are in benzene solution at 25°. Moments are expressed in Debye units (1 D = 10^{-18} e. s. u.).

TABLE I

DIPOLE MOMENTS IN BENZENE AT 25°

Compound	$_AP = 0$	$_AP = 5\%_EP$
Fluorobenzene	1.45	1.53
p-Fluoroaniline	2.48	2.46
p-Fluoroanisole	2.06	2.04
p-Fluorobenzaldehyde	1.98	1.96
p-Fluorobromobenzene	0.22	0.0
p-Fluorodimethylaniline	2.69	2.67
p-Fluoronitrobenzene	2.64	2.62
p-Fluorophenol	2.10	2.08
p-Fluorotoluene	1.71	1.68
Diphenyl ether	1.16[2]	1.11
p-Fluorodiphenyl ether	1.39	1.35
p,p'-Difluorodiphenyl ether	0.62	0.51
Diphenyl sulfide	1.50[2]	1.45
p-Fluorodiphenyl sulfide	1.42	1.37
p,p'-Difluorodiphenyl sulfide	0.61	0.48
Diphenyl sulfoxide	3.99[2]	3.97
p,p'-Difluorodiphenyl sulfoxide	2.67	2.64
Di-*p*-tolyl sulfoxide	4.40[2]	4.38
Diphenyl sulfone	5.05[32]	5.04
p-Fluorodiphenyl sulfone	4.28	4.26
p,p'-Difluorodiphenyl sulfone	3.31	3.28
Benzophenone	2.96[33]	2.93
p-Fluorobenzophenone	2.67	2.63
p,p'-Difluorobenzophenone	1.78	1.74
Diphenylamine	1.04	0.99
p-Fluorodiphenylamine	1.89	1.86
p,p'-Difluorodiphenylamine	2.12	2.09

(25) Sutton, *Proc. Roy. Soc.* (*London*), **133A**, 668 (1931).

(26) Jenkins and Sutton, *J. Chem. Soc.*, 609 (1935).

(27) Calculated from the atomic refractivities.

(28) Audsley and Goss (*J. Chem. Soc.*, 497 (1942)) reported 1.44; Bergmann, Engel and Sandor (*Z. physik. Chem.*, **10B**, 106 (1930)), 1.45.

TABLE I (*Continued*)

Compound	$_AP=0$	$_AP=5\%_EP$
Phenyl-*p*-tolylamine	1.12	1.01
Di-*p*-tolylamine	1.05	0.93
Diphenylnitrosamine	3.39[34]	3.35
Phenyl-*p*-tolylnitrosamine	3.59	3.54
Di-*p*-tolylnitrosamine	3.83	3.79
Triphenylamine	0.71[35]	0.55
p-Fluorotriphenylamine	1.47	1.40
Phenoxthine	1.00	0.92
Phenthiazine	2.16	2.13

Fluorobenzene

f_2	d^{25}_4	ϵ	n^2	P_2	$_EP_2$
0.00541	0.8742	2.2883	....	70.76	
.01161	.8751	2.3064	....	70.47	
.02099	.8765	2.3824	....	69.50	26.2[27]
.03142	.8880	2.3618	....	69.22	

$_\infty P_2 = 71.0$; $_EP_2 = 26.2$; $_oP_2 = 44.8$ cc.; $\mu = 1.46 \pm 0.02\ D$[28]

p-Fluoroaniline

0.00631	0.8756	2.3285	2.2581	155.5	29.4
.01459	.8784	2.4025	2.2591	154.4	29.3
.02232	.8810	2.4728	2.2605	153.4	29.5
.03456	.8853	2.5854	2.2624	151.3	29.4

$_\infty P_2 = 156.7$; $_EP_2 = 29.4$; $_oP_2 = 127.3$ cc.; $\mu = 2.48 \pm 0.01\ D$[29]

p-Fluoroanisole

0.00439	0.8746	2.2991	2.2575	122.1	35.4
.00911	.8759	2.3276	2.2577	122.3	35.3
.01411	.8773	2.3577	2.2578	121.7	35.0
.02225	.8795	2.4067	2.2583	120.9	35.1

$_\infty P_2 = 123.2$; $_EP_2 = 35.2$; $_oP_2 = 88.0$ cc.; $\mu = 2.06 \pm 0.01\ D$[8]

p-Fluorobenzaldehyde (in atmosphere of nitrogen)

0.00680	0.8759	2.3109	2.2576	113.5	32.4
.00844	.8765	2.3194	2.2577	112.2	32.5
.01385	.8784	2.3495	2.2579	112.0	32.4
.01782	.8797	2.3717	2.2580	111.8	32.3

$_\infty P_2 = 113.7$; $_EP_2 = 32.4$; $_oP_2 = 81.3$ cc.; $\mu = 1.98 \pm 0.01D$

p-Fluorobromobenzene

0.00753	0.8799	2.2742	2.2580	35.37	33.9
.01528	.8868	2.2757	....	35.21	..
.02771	.8973	2.2778	2.2598	35.70	34.1

$_\infty P_2 = 35.0$; $_EP_2 = 34.0$; $_oP_2 = 1.0$ cc.; $\mu = 0$–$0.22\ D$

p-Fluorodimethylaniline

0.00473	0.8749	2.3217	2.2579	188.0	39.3
.01073	.8769	2.3846	2.2587	187.0	38.9
.02149	.8803	2.4993	2.2598	185.9	39.0
.03067	.8834	2.5958	2.2607	183.0	38.7

$_\infty P_2 = 188.7$; $_EP_2 = 39.0$; $_oP_2 = 149.7$ cc.; $\mu = 2.69 \pm 0.01D$

(29) Bergmann and Tschudnowsky (*Z. physik. Chem.*, **17B**, 100 (1932)) reported 2.75.

p-Fluoronitrobenzene

f_2	d^{25}_4	ϵ	n^2	P_2	$_EP_2$
0.00484	0.8759	2.3206	....	175.0	..
.00956	.8787	2.3671	2.2581	172.5	31.6
.01912	.8837	2.4589	2.2588	168.8	32.3
.02546	.8876	2.5226	2.2595	167.6	31.9

$_\infty P_2 = 176.3$; $_EP_2 = 31.9$; $_oP_2 = 144.4$ cc.; $\mu = 2.64 \pm 0.01D$[30]

p-Fluorophenol

0.00621	0.8757	2.3117	2.2577	119.2	29.1
.01255	.8781	2.3517	2.2580	118.1	28.2
.02242	.8811	2.4138	2.2584	117.6	28.6
.03611	.8860	2.5001	....	115.6	..

$_\infty P_2 = 119.9$; $_EP_2 = 28.6$; $_oP_2 = 91.3$ cc.; $\mu = 2.10 \pm 0.01D$

p-Fluorotoluene

0.00684	0.8742	2.3016	2.2580	95.02	34.9
.01346	.8751	2.3295	2.2588	94.68	35.0
.01817	.8757	2.3496	2.2595	94.69	35.0
.03312	.8777	2.4128	2.2616	94.04	35.1

$_\infty P_2 = 95.3$; $_EP_2 = 35.0$; $_oP_2 = 60.3$ cc.; $\mu = 1.71 \pm 0.01D$

p-Fluorodiphenyl Ether

0.00470	0.8758	2.2870	2.2587	92.36	52.5
.00725	.8771	2.2946	....	92.59	..
.01571	.8815	2.3197	2.2621	92.13	52.4
.03146	.8896	2.3657	2.2676	91.50	52.6

$_\infty P_2 = 92.8$; $_EP_2 = 52.5$; $_oP_2 = 40.3$ cc.; $\mu = 1.39 \pm 0.01D$

p,p'-Difluorodiphenyl Ether

0.00430	0.8762	2.2758	....	60.83	..
.00790	.8786	2.2782	2.2587	60.49	52.8
.01334	.8822	2.2824	2.2599	60.55	52.5
.02016	.8864	2.2758	2.2614	60.73	53.0

$_\infty P_2 = 60.7$; $_EP_2 = 52.7$; $_oP_2 = 8.0$ cc.; $\mu = 0.62 \pm 0.02D$

p-Fluorodiphenyl Sulfide

0.00401	0.8758	2.2867	....	102.6	
.01014	.8798	2.3087	....	102.6	61.1[27]
.01848	.8848	2.3364	....	101.6	
.02629	.8895	2.3624	....	101.1	

$_\infty P_2 = 102.9$; $_EP_2 = 61.1$; $_oP_2 = 41.8$ cc.; $\mu = 1.42 \pm 0.01D$

p,p'-Difluorodiphenyl Sulfide

0.00372	0.8762	2.2769	2.2593	68.88	60.5
.00686	.8785	2.2801	....	68.86	..
.01083	.8815	2.2844	2.2640	68.56	59.6
.02586	.8928	2.3012	2.2704	68.75	61.7

$_\infty P_2 = 68.7$; $_EP_2 = 60.9$; $_oP_2 = 7.8$ cc.; $\mu = 0.61 \pm 0.03D$

p,p'-Difluorodiphenyl Sulfoxide

0.00480	0.8779	2.3238	....	207.6	..
.00961	.8824	2.3742	....	205.2	..

(30) Bergmann, Engel and Sandor (*Z. physik. Chem.*, **10B**, 397 (1930)) reported 2.63.

TABLE I (*Continued*)

f_2	d^{25}_4	ϵ	n^2	P_2	$_ED_2$
.01658	.8887	2.4474	2.2662	203.6	60.3
.02252	.8943	2.5092	2.2696	201.7	60.3

$_\infty P_2 = 209.0$; $_ED_2 = 60.3$; $_oP_2 = 148.7$ cc.; $\mu = 2.67 \pm 0.01D$

p-Fluorodiphenyl Sulfone

0.00316	0.8763	2.2563	2.2589	434.5	60.4
.00670	.8795	2.4502	2.2609	428.5	60.6
.00994	.8823	2.5355	2.2628	422.6	61.1
.01420	.8862	2.6484	2.2649	414.8	60.5

$_\infty P_2 = 440.6$; $_ED_2 = 60.6$; $_oP_2 = 380.0$ cc.; $\mu = 4.28 \pm 0.02D$

p,p'-Difluorodiphenyl Sulfone

0.00264	0.8760	2.3142	2.2483	285.0	61.4
.00409	.8776	2.3365	2.2589	281.0	60.6
.00506	.8787	2.3516	2.2593	279.8	59.8
.01025	.8840	2.4303	2.2615	274.6	60.4

$_\infty P_2 = 287.0$; $_ED_2 = 60.5$; $_oP_2 = 226.5$ cc.; $\mu = 3.31 \pm 0.02D$

p-Fluorobenzophenone

0.00364	0.8754	2.3108	2.2589	203.3	57.1
.00940	.8791	2.3721	2.2623	202.5	57.3
.01724	.8838	2.4526	2.2662	198.7	56.9
.02640	.8891	2.5462	2.2708	195.9	57.0

$_\infty P_2 = 205.3$; $_ED_2 = 57.1$; $_oP_2 = 148.2$ cc.; $\mu = 2.67 \pm 0.02D$

p,p'-Difluorobenzophenone

0.00338	0.8757	2.2890	....	123.0	..
.00735	.8787	2.3087	2.2603	123.0	57.8
.01139	.8817	2.3281	2.2619	122.8	57.4
.01695	.8860	2.3556	2.2642	122.6	57.0

$_\infty P_2 = 123.2$; $_ED_2 = 57.4$; $_oP_2 = 65.8$ cc.; $\mu = 1.78 \pm 0.02D$

Diphenylamine

0.00543	0.8755	2.2844	2.2618	77.56	57.8
.01100	.8775	2.2983	....	79.99	..
.01741	.8801	2.3130	2.2716	79.59	57.6
.03164	.8856	2.3486	2.2810	80.92	56.4

$_\infty P_2 = 79.8$; $_ED_2 = 57.3$; $_oP_2 = 22.5$ cc.; $\mu = 1.04 \pm 0.01D$

p-Fluorodiphenylamine

0.00465	0.8758	2.2986	....	128.4	..
.00456	.8756	....	2.2597	...	55.2
.00990	.8786	2.3269	....	126.8	..
.01502	.8815	2.3532	2.2673	124.9	56.5

$_\infty P_2 = 130.0$; $_ED_2 = 55.8$; $_oP_2 = 74.2$ cc.; $\mu = 1.89 \pm 0.01D$

p,p'-Difluorodiphenylamine

0.00429	0.8763	2.3017	....	146.9	..
.00663	.8779	2.3177	2.2606	147.5	55.6
.01164	.8814	2.3494	2.2631	144.3	55.6

$_\infty P_2 = 148.8$; $_ED_2 = 55.6$; $_oP_2 = 93.2$ cc.; $\mu = 2.12 \pm 0.01D$

(31) Higasi (*Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **38**, 331 (1941)) reported 1.09.

Phenyl-*p*-tolylamine

0.00468	0.8748	2.2846	2.2610	88.04	62.6
.00642	.8754	2.2885	....	87.00	..
.01138	.8773	2.3017	2.2664	88.37	62.5
.01649	.8792	2.3158	....	89.42	..
.02096	.8809	2.3265	2.2748	88.75	63.0
.02800	.8834	2.3447	....	88.90	..

$_\infty P_2 = 88.7$; $_ED_2 = 62.7$; $_oP_2 = 26.0$ cc.; $\mu = 1.12 \pm 0.01D$

Di-*p*-tolylamine

0.00562	0.8754	....	2.2609	....	64.8
.00583	.8754	2.2848	....	86.11	..
.01003	.8772	2.2942	2.2636	86.58	64.0
.01748	.8797	2.3090	....	86.47	..
.02782	.8839	2.3267	2.2740	84.12	63.9

$_\infty P_2 = 87.0$; $_ED_2 = 64.2$; $_oP_2 = 22.8$ cc.; $\mu = 1.05 \pm 0.01D$

Phenyl-*p*-tolylnitrosamine

0.00566	0.8767	2.3799	2.2614	328.1	65.6
.01385	.8809	2.5352	2.2663	321.8	65.1
.02023	.8844	2.6571	2.2715	317.1	65.8

$_\infty P_2 = 332.4$; $_ED_2 = 65.5$; $_oP_2 = 266.9$ cc.; $\mu = 3.59 \pm 0.01D$

Di-*p*-tolylnitrosamine

0.00616	0.8767	2.4054	2.2614	369.5	70.1
.01365	.8806	2.5702	2.2670	364.8	70.7
.02114	.8846	2.7336	2.2728	357.1	71.1

$_\infty P_2 = 375.2$; $_ED_2 = 70.6$; $_oP_2 = 304.6$ cc.; $\mu = 3.83 \pm 0.01D$

p-Fluorotriphenylamine

0.00311	0.8756	2.2858	2.2609	129.8	85.4
.00601	.8779	2.2980	....	128.8	
.00836	.8796	2.3076	....	128.4	85.5[27]
.00993	.8807	2.3137	....	127.8	

$_\infty P_2 = 130.6$; $_ED_2 = 85.5$; $_oP_2 = 45.1$ cc.; $\mu = 1.47 \pm 0.02D$

Phenoxthine

0.00351	0.8759	2.2809	2.2605	80.93	60.4
.00739	.8787	2.2900	2.2641	80.67	60.1
.01026	.8807	2.2967	2.2670	80.68	60.2
.01717	.8857	2.3129	2.2736	80.65	60.1

$_\infty P_2 = 80.8$; $_ED_2 = 60.2$; $_oP_2 = 20.6$ cc.; $\mu = 1.00 \pm 0.01$[31]

Phenthiazine

0.00222	0.8751	2.2901	....	161.1	..
.00461	.8768	2.3088	2.2634	160.3	65.4
.00659	.8783	2.3246	2.2658	160.4	64.8
.00890	.8799	2.3419	2.2687	158.7	64.7

$_\infty P_2 = 162.2$; $_ED_2 = 65.0$; $_oP_2 = 97.2$ cc.; $\mu = 2.16 \pm 0.02D$

In Table I all the dipole moment data used in the discussion are collected together.

(32) deVries and Rodebush, THIS JOURNAL, **53**, 2888 (1931).
(33) Kadesch and Weller, *ibid.*, **63**, 1310 (1941).
(34) Cowley and Partington, *J. Chem. Soc.*, 1252 (1933).
(35) A. H. Warburton, private communication.

TABLE II

C–X–C ANGLES, INTERACTION MOMENTS NEGLECTED

	μ_0	μ_s	μ_T	X	θ[a]
I	Diphenyl ether	Fluorobenzene	*p*-Fluorodiphenyl ether	O	125°
	Diphenyl ether	Fluorobenzene	*p,p'*-Difluorodiphenyl ether	O	112°
II	Diphenyl sulfide	Fluorobenzene	*p*-Fluorodiphenyl sulfide	S	114°
	Diphenyl sulfide	Fluorobenzene	*p,p'*-Difluorodiphenyl sulfide	S	95°
III	Diphenyl sulfoxide	Fluorobenzene Toluene	*p,p'*-Difluorodiphenyl sulfoxide Di-*p*-tolyl sulfoxide	SO	(90°)[b]
IV	Diphenyl sulfone	Fluorobenzene	*p*-Fluorodiphenyl sulfone	SO_2	100°
	Diphenyl sulfone	Fluorobenzene	*p,p'*-Difluorodiphenyl sulfone	SO_2	104°
V	Benzophenone	Fluorobenzene	*p*-Fluorobenzophenone	CO	129°
	Benzophenone	Fluorobenzene	*p,p'*-Difluorobenzophenone	CO	131°
VI	Diphenylamine	Fluorobenzene	*p*-Fluorodiphenylamine *p,p'*-Difluorodiphenylamine	NH	113°[c]
VII	Triphenylamine	Fluorobenzene	*p*-Fluorotriphenylamine	NC_6H_5	114°[d]

[a] The values of θ are derived from dipole moments based on an allowance for ${}_AP = 5\%_EP$. [b] Very sensitive to changes in the value of μ_0; 3.97 used for this calculation. [c] The angle ω, between the unsubstituted moment μ_0 and the perpendicular to the plane of the benzene rings,[1] is 16°. [d] The angle between the N-phenyl bond and the axis of symmetry in triphenylamine is $\phi = \cos^{-1}(\mu_T^2 - \mu_0^2 - \mu_s^2)/2\mu_0\mu_s$; $\sin\theta/2 = \sqrt{3/2}\sin\phi$, where θ is the C–N–C angle.

Discussion

From the preceding data, we evaluated the valence angles in diphenyl ether, sulfide, sulfoxide, sulfone, ketone, amine and in triphenylamine. In Table II are given the results when interactions between the central group and the substituent group or groups are ignored. In Table III are the angle values corrected for these, together with the interaction moments themselves. These will be discussed *seriatim*.

TABLE III

C–X–C ANGLES, CORRECTED FOR INTERACTION MOMENTS

		$d_1\mu_s = d_2\mu_s$		$d_1\mu_s = 2d_2\mu_s$	
${}_AP = 5\%_EP$	X	θ	$d_2\mu_s$	θ	$d_2\mu_s$
Diphenyl ether	O	117°	0.11	115°	0.07
Diphenyl sulfide	S	106°	.17	103°	.12
Diphenyl sulfone	SO_2	93°	− .16	106°	.08
Benzophenone	CO	128°	− .06	132°	.04

The value of 115–117° calculated for ∠C–O–C in diphenyl ether is lower than the value 124 ± 5° obtained by Coop and Sutton[4] from measurements on bromo derivatives in the gas-phase, but agrees well with the value of 118 ± 3° ascribed by Maxwell, Hendricks and Mosley[36] from an electron diffraction investigation. The probable range may be given as 115–124°. This is distinctly greater than the values for ∠C–O–C in aliphatic compounds, *viz.*, 111 ± 4° in dimethyl ether[37] and 108° in 1,4-dioxane.[38] The earlier differentiation[3] between the aromatic and the aliphatic ethers is therefore confirmed and its explanation in terms of resonance may still be regarded as valid.

The value of 103–106° found for ∠C–S–C in diphenyl sulfide is also lower than the earlier value, 113 ± 3° from the dipole moments of the *p*-chloro- and *p*-methyl-derivatives.[3] Toussaint,[39] from an X-ray investigation of the *p,p'*-dibromo-derivative, has obtained a value 109.5 ± 0.5°. In aliphatic compounds, the values reported for ∠C–S–C are, in dimethyl sulfide 100°[40] and 100–110°,[41] in 1,4-dithian 100°,[38] in *sym*-trithian 106.5°,[38] and in α- and β-trithioacetaldehyde also 106.5°.[38] The angles in this case are not, therefore, clearly different in the aromatic and aliphatic compounds, so there is no conclusive evidence from this source for resonance between the normal structure for diphenyl sulfide and others with positive, tricovalent sulfur. Toussaint[39] reports, however, that the C–S distance is 1.75 Å., *i. e.*, that it is shorter than the sum of the covalent radii (1.81 Å.) and that it therefore indicates some resonance of the type mentioned.

The value for ∠C–S–C in diphenyl sulfoxide (Table II) cannot be regarded as accurate since it is very sensitive to the moment value taken for diphenyl sulfoxide itself.

That in diphenyl sulfone, of 93–106°, or more probably 100–104°, is in good agreement with the 100° reported by Toussaint[39] from an X-ray diffraction examination of the *p,p'*-dibromo-derivative, though less than the 109° reported by Bergmann and Tschudnowsky.[42] Toussaint's value for the C–S distance is 1.84 Å., which should be compared with that of 1.90 Å. found by Lister and Sutton[43] in dimethyl sulfone. There is, therefore, some evidence of conjugation between the phenyl groups and the SO_2-group. Toussaint observes that the benzene rings are turned into planes at right angles to the C–S–C plane, but Koch[44] has

(36) Maxwell, Hendricks and Mosley, *J. Chem. Phys.*, **3**, 699 (1935).

(37) Sutton and Brockway, THIS JOURNAL, **57**, 473 (1935).

(38) Hassel and Viervoll, *Acta Chemica Scandinavica*, **1**, 149 (1947).

(39) Toussaint, *Bull. soc. chim. Belg.*, **54**, 319 (1945).

(40) Pai, *Indian J. Phys.*, **9**, 121 (1934).

(41) Brockway and Jenkins, THIS JOURNAL, **58**, 2036 (1936).

(42) Bergmann and Tschudnowsky, *Ber.*, **65**, 457 (1932).

(43) Lister and Sutton, *Trans. Faraday Soc.*, **35**, 495 (1939).

(44) Koch, private communication.

TABLE IVa

CALCULATED ANGLE AND MOMENT VALUES FOR COMPOUNDS OF TYPE I

	α		0°	5	10	15	20	25	30	35
	180–2α		180°	170	160	150	140	130	120	110
	β		120°	119	117	113.5	109	103.5	97	90.5
	ω		0°	8.5	17	24	30.5	36	41	45
	X	*Y*								
$\mu_{calcd.}$	O	O	0	0.32	0.65	0.90	1.13	1.30	1.44	1.56
	O	S	0.34	0.53	0.83	1.10	1.35	1.54	1.70	1.83
	S	S	0	0.46	0.87	1.19	1.49	1.71	1.92	2.10
	S	NH	1.75	1.86	2.00	2.08	2.15	2.20	2.24	2.28
	Se	Se	0	0.42	0.80	1.12	1.39	1.60	1.82	1.92
	Te	Te	0	0.33	0.66	0.94	1.17	1.35	1.50	1.61

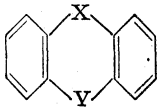
suggested that this need not necessarily preclude resonance between them and the SO_2-group.

The large angle, 128–132°, calculated in benzophenone agrees with that of 131–133° derived by Sutton and Hampson[3] (*cf.*, however, Coomber and Partington,[45] who consider 125 ± 3° to be more accurate, from considerations of interaction), and with the 135° reported by Banerjee and Jaque.[46] It is a clear indication that there is resonance involving structures with double bonds between the benzene rings and the carbonyl group.

The value of 113° for ∠C–N–C found in diphenylamine and that of 114° in triphenylamine are probably real, and they are larger than the value observed in trimethylamine, 108 ± 4°, by Brockway and Jenkins.[41] The inference is that, in accordance with the expectations of current theory, there is resonance involving structures with the grouping $\overset{+}{\diagdown\!\!\diagup}\!\!\mathrm{N}\!\!\diagdown$, but that neither molecule is coplanar.

Some moment values for N-nitrosodiphenylamino compounds were determined (Table I) in the hope that this group might be sufficiently rigid for the treatment applicable to diphenylamine to be suitable. The C–N–C angle calculated is, however, unreal, so the configuration of the N-nitroso group is evidently not simple. It is interesting to note that phenyl-*p*-tolylnitrosamine has a moment 3.59 D nearly equal to that of N-nitrosomethylaniline (3.62 *D*).[34]

The moments of molecules of type I have been measured by various authors and have been dis-



I

cussed in relation to the folding of the molecule along the X-Y line.[3,31,42,47,48,49,50] It is possible to show that the moments calculated when X = Y

(45) Coomber and Partington, *J. Chem. Soc.*, 1444 (1938).
(46) Banerjee and Jaque, *Indian J. Phys.*, **12**, 87 (1938).
(47) Campbell, LeFèvre, LeFèvre and Turner, *J. Chem. Soc.*, 404 (1938).
(48) Higasi and Uyeo, *J. Chem. Soc. Japan*, **62**, 396 (1941).
(49) Higasi and Uyeo, *ibid.*, **62**, 400 (1941).
(50) Higasi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **38**, 331 (1941).

TABLE IVb

OBSERVED MOMENT VALUES IN COMPOUNDS OF TYPE I

X	*Y*	$\mu_{obs.}$			
O	O	0.64[50]	0[51]		
O	S	0.92[52]	1.09[50]		
S	S	1.68[42]	1.41[53]	1.54[54]	1.57[47]
S	NH	2.13[52]			
Se	Se	1.41[47]			
Te	Te	...			

are close to those observed if it be assumed that the angle C–X–C is approximately the same in these compounds as in C_6H_5–X–C_6H_5, that the moments of the C–X–C segments are likewise equal to those of the diphenyl compound, and that the valences of carbon in the benzene rings are all coplanar and at 120° to each other.[47,50] This treatment may be extended to the case where X ≠ Y by taking a common mean value for both angles.

In Table IVa, β is the angle C–X–C or C–Y–C in the tricyclic compound, 2α is the supplement of the angle between the benzene ring planes, ω is the angle between the C–X–C (or C–Y–C) segment and the X–Y line; $\mu_{calcd.}$ is the moment evaluated on the preceding assumptions for various values of β. For the particular case of phenthiazine, we assumed that ω is 90° for the C–NH–C segment. In Table IVb, the observed values ($\mu_{obs.}$) are given.

By comparison of these two tables, we see that agreement between calculated and observed values of the moments is obtained for the following values of β:

TABLE V

X	*Y*	β	180–2α
O	O	117–120°	160–180°
O	S	113–116°	150–160°
S	S	107–109°	135–140°
S	NH	109–113°	140–150°
Se	Se	107–109°	135–140°

Exact agreement between these β values and the valency angles in Table III would not be ex-

(51) Bennett, Earp and Glasstone, *J. Chem. Soc.*, 1179 (1934).
(52) This paper.
(53) Smyth and Walls, *J. Chem. Phys.*, **1**, 337 (1933).
(54) Bennett and Glasstone, *J. Chem. Soc.*, 128 (1934).

TABLE VI

INTERACTION MOMENTS[a]

p-Substituted	F	Cl	Br	I	NO_2
Toluenes	−0.14	−0.01	+0.04	+0.01	+0.07
Phenols	− .17	− .03	− .09	....	+0.71
Anisoles	− .06	+ .04	+ .15	+ .16	+0.37
Anilines[b]	− .17	+ .22	+ .20	+ .36	+1.26
Dimethylanilines	− .17	+ .34	+ .46	+ .69	+1.86
Nitrobenzenes	− .14	+ .05	− .02	+ .02	....
Benzaldehydes[45]	(− .27	− .25			+0.16)
Diphenyl ethers[c]	0.07 to 0.11	....	0.43 to 0.50[4]	....	0.70 to 0.76[3]
Diphenyl sulfides[c]	.12 to .17	0.10 to 0.16[3] +0.25[39]	+0.35[39]	....	....

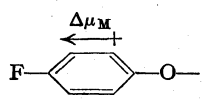
[a] Calculated by the method of Marsden and Sutton.[5] A negative value is one with its negative end away from the halogen atom. Moment values derived from the "Table of Dipole Moments" of Sidgwick and collaborators (*Trans. Faraday Soc.*, 30, 1934) are: for toluene, 0.40; phenol, 1.61; aniline ($\theta_2 = 56°$), 1.53; anisole ($\theta_2 = 76°$), 1.23; dimethylaniline ($\theta_2 = 38°$), 1.58; nitrobenzene, 3.95; chlorobenzene, 1.56; bromobenzene, 1.52; iodobenzene, 1.30. [b] Series of Marsden and Sutton[5] recalculated. [c] Calculated simultaneously with bond angles.

pected, because the conditions which determine them are somewhat different in the two cases. The value which we derive for 180-2α in thianthrene, *ca.* 140°, is the same as that reported by Wood and Crackston,[55] from X-ray investigations. We find that 180-2α in selenanthrene also is *ca.* 140°, a value which agrees with the earlier one of Wood and Crackston, but which is higher than the revised one of 127° given by Wood and Williams.[56]

The phase-rule investigations made by Cullinane and Plummer[57] agree with there being a marked difference of configuration between diphenylene dioxide on the one hand and either thianthrene or selenanthrene on the other; likewise, Cullinane and Rees[58] find evidence of a difference between diphenylene dioxide and phenoxthine and a similarity between phenoxthine and phenthiazine.

The interaction moments between the substituent atoms and the central atoms in the ether and sulfides are perhaps less when fluorine is used (Table III) than when chlorine is used (Table VI), and, as expected, they are certainly less than with bromine. The sign of the interactions is such as to indicate that when fluorine is substituted *para* to the phenoxy group, the mesomeric moment of the former is diminished (see diagram II). According to the sign convention adopted (see Table VI) this is termed a positive change.

Examination of the interaction moments of halogens with other groups in *para* positions shows that they are less positive (using the preceding

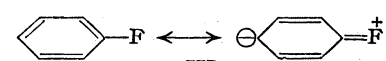


II

convention) the less polarizable the halogen, and are actually negative for fluorine. Therefore, although there is a difference between the actual sign for the interaction moments in the fluoro-substituted diphenyl ethers or sulfides and those in the other fluoro compounds listed, the algebraic changes in these moments, as the polarizability of the halogen increases, are the same.

Groves and Sugden[59] showed that the mesomeric effect of the fluorine atom is such that it drives electrons into the benzene ring and that it does this to a greater extent than does any other halogen. Our results show that fluorine has unique power to suppress the mesomeric effect of groups *para* to it if they conflict with its own.

This mesomeric effect of fluorine with benzene has been attributed to resonance between the structure with neutral monovalent fluorine and others with positive divalent fluorine (III) (*vide, e. g.*, Kenner[60]). In view of the great electronegativity of fluorine and its unwillingness to form single dative bonds, some doubts have been ex-



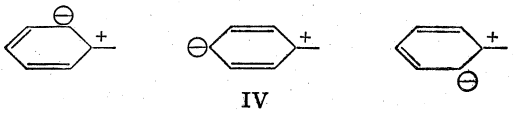
III

pressed about the validity of this explanation.[61] We suggest that an alternative should be considered, in which it is not necessary to postulate a change in multiplicity of the C–F bond, nor a positive charge on fluorine. The general problem is to discover the most stable state possible for the whole molecule, and this means discovering the most favorable electron distribution. It seems improbable that this will involve a considerable reduction in electron density around the fluorine atom; rather the reverse. Now, if we suppose that the key to the problem is that the electron density around the fluorine atom shall be increased, it is possible to propose a means by which this may happen, by which the C–F bond may be shortened and strengthened, and by which electrons may be driven into the benzene ring.

The carbon and fluorine atoms have some permitted range of atomic orbitals available for bond

(55) Wood and Crackston, *Phil. Mag.*, **31**, 62 (1941).
(56) Wood and Williams, *Nature*, **150**, 321 (1942).
(57) Cullinane and Plummer, *J. Chem. Soc.*, 63 (1938).
(58) Cullinane and Rees, *Trans. Faraday Soc.*, **36**, 507 (1940).
(59) Groves and Sugden, *J. Chem. Soc.*, 1992 (1937).
(60) Kenner, *Proc. Roy. Soc.* (*London*), **185A**, 119 (1946).
(61) Bennet, *J. Chem. Soc.*, 1112 (1933).

formation. These would vary in the degree of overlap which they would give in the bond, and therefore in the concentration of the negative cloud charge which they would give between the nuclei. At large internuclear distances, the orbitals giving greatest overlap would be least favored because they would require the removal of the negative centroid somewhat from each nucleus. If, however, either or both the atoms have high electronegativities, the high axial concentration resulting from these orbitals would increase stability, because the positive nuclei would be better shielded from each other, *i. e.*, the nuclei would be better "cemented" together, so they could approach more closely, the electrostatic potential energy of the system would be reduced, and accordingly, the total energy would also be lowered. There might, in fact, be opposing tendencies: on the one hand, for the electrons to remain held in the configurations which are best in the fields of the separate nuclei, and on the other hand, for them to move from these into others that are most favorable in the joint, binuclear field. We think it possible that in the C–F link a considerable degree of such redistribution might occur, with the results indicated, *viz.*, a shortening and strengthening of the C–F bond and a reduction in its dipole moment. Furthermore, if the bond shortens, the density of electronic charge on the carbon atom might actually increase, with the result that electronic distributions in the neighborhood might be repelled; *i. e.*, driven into the nucleus. If this field effect occurs by resonance with polar structures (IV) (as has previously been postulated[62]) the appearance of *o,p*-direction in fluorobenzene might be expected.



IV

Summary

The valence angles (C–X–C) in diphenyl ether, sulfide, sulfone, ketone, amine and in triphenylamine have been determined from the dipole moments in benzene solution of the unsubstituted and the *p*-fluoro-substituted compounds. They are, in the same order: 116 ± 4°, 106 ± 4°, 102 ± 4°, 130 ± 4°, 113 ± 3° and 114 ± 3°. The relation of these to other reported values, and their significance, have been discussed.

The moments of phenoxthine and phenthiazine have also been measured. They are 0.92 and 2.13 *D*, respectively. These agree with angles of 155 ± 5° and 145 ± 5° between the planes of the benzene rings, the molecules being folded along the OS and NS lines.

The moments resulting from the interaction between fluorine atoms substituted on benzene, with other groups *para* to them, show that fluorine has unique power to suppress mesomeric effects which conflict with its own.

The origin of the mesomeric effect in fluorobenzene has been discussed.

(62) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1939, p. 141.

URBANA, ILLINOIS RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA]

Search for Elements 94 and 93 in Nature. Presence of 94^{239} in Pitchblende[1]

BY GLENN T. SEABORG AND MORRIS L. PERLMAN[1a]

The discovery[2] of a rather easily prepared form of radioactive element 94 and the subsequent determination of the chemical properties[3] of 94 with the help of this isotope as tracer make it possible to conduct a search for 94 in natural minerals. It is convenient to search for 93, whose chemical properties[3,4] are also known, at the same time. The hope would be to discover a very long-lived 94 or 93 and that this be present in an amount large enough so that useful quantities should be extracted from the minerals. Alpha and beta radioactivity is to be tested for in the final very thin sample which, in view of the chemical procedure, would contain the 94 or 93. In case the 94 or 93 is not alpha or beta active, a test for fissions with neutrons should be made since it appears likely that any isotopes of these elements will undergo fission either with slow or with fast neutrons. The presence of an amount of the order of one microgram can be established by the neutron tests; therefore, starting with about 1 lb. of the pitchblende, the sensitivity for the detection of these elements can be about 1 part in 10^8 or 10^9.

This report describes a careful search for elements 94 and 93 in a sample of pitchblende concentrate obtained from the Great Bear Lakes region of Canada. Since this pitchblende, which is

(1a) Now at the Research Laboratory of the General Electric Company at Schenectady, New York.

(1) This article was mailed, as a secret report, from Berkeley, California, to the "Uranium Committee" in Washington, D. C., on April 13, 1942. The experimental work was done during 1941 and the early part of 1942. The report is unchanged from its original form except for slight editing to make it conform to JOURNAL standards.

(2) G. T. Seaborg, E. M. McMillan, J. W. Kennedy and A. C. Wahl, *Phys. Rev.*, **69**, 366 (1946) (submitted January 28, 1941); G. T. Seaborg, A. C. Wahl and J. W. Kennedy, *Phys. Rev.*, **69**, 367 (1946) (submitted March 7, 1941).

(3) G. T. Seaborg and A. C. Wahl, THIS JOURNAL, **70**, 1128 (1948).

(4) E. M. McMillan and P. H. Abelson, *Phys. Rev.*, **57**, 1185 (1940).

said to contain some 40 different elements, seems to offer more hope to contain 94 and 93 than does any other mineral, it was decided to make an extremely careful search in this mineral. Great care was taken to be sure that all the material was dissolved, even down to the last few milligrams, and the most sensitive means of detection for 94 and 93 in the final fraction, including tests for alpha and beta radioactivity and neutron induced fissions, were employed.

Another reason that seemed to make it definitely worth while to extend the sensitivity of the method to the limit was the possibility of establishing the presence of the 30,000-year 94^{239} [5] in this material. From the spontaneous fission rate of uranium, one can calculate the amount of 94^{239} which might be formed as a result of the absorption by U^{238} of the neutrons emitted in the spontaneous fission process. In an amount of pitchblende of the order of one pound, there might be expected to be present an amount of 94^{239}, formed from spontaneous fission neutrons, corresponding to an alpha counting rate of several thousand counts per hour, provided an appreciable fraction of these neutrons were absorbed by U^{238} ultimately forming 94^{239}. Even if only a small percentage of the neutrons leads to the formation of 94^{239} from U^{238} in this manner, it still should be possible to detect the 94^{239}, since alpha counting rates of the order of a few counts per hour are readily determinable. Our experiments indicate that we have discovered the presence of 94^{239} in pitchblende.

Experimental

Four hundred grams of the pitchblende concentrate was treated successively with a number of reagents, and after each treatment the solution which was obtained was set aside and the residue was subjected to the action of the next reagent. The reagents, in the order in which they were used, were (1) boiling concentrated hydrochloric acid followed by boiling aqua regia, (2) hot 6 *N* sodium hydroxide, (3) hot aqua regia, (4) boiling 6 *N* hydrochloric acid, (5) boiling 27 *N* hydrofluoric acid followed by nitric acid extraction, (6) fuming hot sulfuric acid followed by water extraction, (7) sodium hydroxide fusion followed by dilute sodium hydroxide extraction, (8) boiling 6 *N* hydrochloric acid, and (9) hydrofluoric acid solution followed by sulfuric acid, sodium carbonate and nitric acid solutions. After this series of treatments the final undissolved matter was entirely negligible, perhaps of the order of a few milligrams in weight.

The acidity of each of these solutions was adjusted to the range from 1 to 6 *N*, sulfur dioxide was added, and hydrofluoric acid was added to each in order to remove a fluoride precipitate. When necessary, lanthanum and cerium carrier material was added before the addition of the hydrofluoric acid.

(5) J. W. Kennedy, G. T. Seaborg, E. Segrè and A. C. Wahl, *Phys. Rev.*, **70**, 555 (1946) (submitted May 29, 1941).

The various fluoride precipitates were all combined and dissolved in concentrated sulfuric acid, and after dilution with water and the addition of dilute nitric acid (to oxidize any uranous uranium to the uranyl form) the rare earth fluorides were again precipitated by the addition of hydrofluoric acid. This rare earth and thorium fluoride precipitate, which amounted to about 20 g. and which would contain, in their reduced forms, any 94 or 93 which might have been present in the original pitchblende, was dissolved in sulfuric acid and reprecipitated as the fluoride. It was now necessary to go through a chemical procedure designed to isolate any such 94 or 93 into a very thin layer (0.3 mg./sq. cm.) of rare earth carrier material, special care being taken to eliminate all the elements in the uranium, thorium and actinium radioactive series which would interfere with the detection of the 94 or 93 in the final sample.

This rare earth and thorium fluoride precipitate was dissolved in sulfuric acid and after the addition of a few grams of potassium peroxydisulfate, $K_2S_2O_8$, and a few tenths of a gram of silver nitrate, hydrofluoric acid was again added to precipitate the rare earth and thorium fluoride. In this procedure, the 94 and 93 remain in solution, present in their higher oxidation states. This solution, after the removal of the fluoride preicpitate by centrifugation, was boiled in order to remove the hydrofluoric acid and decompose the peroxydisulfate and it was then treated with sulfur dioxide to reduce the 94 and 93 to their lower (fluoride-insoluble) oxidation states. About 120 mg. of lanthanum and cerium carrier was then added and the fluoride precipitated by the addition of hydrofluoric acid.

This 120 mg. fluoride precipitate was then dissolved in sulfuric acid and taken through another identical cycle in which the amount of rare earth was reduced to about 5 mg. The 5 mg. of rare earth, which would contain the 94 or 93, was then dissolved in sulfuric acid and, after the addition of peroxydisulfate and silver ion, the rare earths were removed from solution by precipitation as the fluoride. The hydrofluoric acid was removed by boiling the solution until the white fumes of sulfur trioxide appeared and after dilution another 0.2 mg. of rare earth carrier was added. After treatment with peroxydisulfate and silver ion, this 0.2 mg. of rare earth was precipitated as fluoride. The purpose of this last precipitation, which was made just before the final isolation of the material which would contain the 94 and 93 was to establish that there was a negligible amount of isotopes of thorium (UX_1, Io) present in the solution at this stage. This 0.2 mg. of precipitate showed no detectable beta activity, above the background of the Geiger–Müller counter, and an alpha counting rate of about 45 per hour when placed on one electrode of an ionization chamber in which the calibrated counting efficiency amounted to about 45 per cent.

The hydrofluoric acid was removed from the solution by boiling until the dense white fumes of sulfur trioxide appeared, and after dilution and reduction with sulfur dioxide, another 0.2 mg. of rare earth was added. This was precipitated as fluoride by the addition of hydrofluoric acid, and centrifuged onto a platinum disk for final measurements. This sample would contain any 94 or 93 which was present in the original pitchblende. (Calibration experiments, starting with 20 g. of rare earth and ending with 0.2 mg. of rare earth fluoride in an identical chemical procedure, in which the 50-year alpha-emitting 94 was added as tracer to the original 20 g., proved that the yield of 94 in this rather lengthy chemical procedure amounted to about 80 per cent.) Previous careful counting experiments had proved that the rare earth carrier material and the platinum, upon which the final sample was mounted, were free from alpha-emitting contamination.

Results

This final sample showed no detectable beta-activity, above the background of the Geiger–Müller counter. It showed an alpha counting rate of about 90 per hour when placed on one electrode of an ionization chamber in which the calibrated counting efficiency was about 45 per cent. Since it is likely that any isotopes of 94 or 93 would undergo fission with slow or fast neutrons, a test for fissions with neutrons was made by placing the final sample on one electrode of an ionization chamber connected to a linear amplifier and recording system adjusted to record the impulses due to fissions. When slow neutrons were used, from a 300-mg. radium-beryllium source with paraffin between the chamber and neutron source and around the chamber and neutron source, there was recorded zero fissions in seven hours of counting. When the sample was replaced by a "standard" 200-microgram uranium sample, containing therefore 1.4 microgram of U^{235}, the fission counting rate due to slow neutrons amounted to about 15 counts per hour. Therefore, assuming that the slow neutron fission cross section of the 94 or 93 would be of the same order of magnitude as that of U^{235}, there was present in the final sample no more than a small fraction of a microgram of any isotope of 94 or 93 capable of undergoing fission with slow neutrons. So far as fast neutrons are concerned our experiments place an upper limit of the order of a microgram on the amount of any isotope of 94 or 93 which was present and capable of undergoing fission with fast neutrons; therefore, we can say that there was not present in this pitchblende as much as one part in 10^8 or 10^9 of 94 or 93.

On the other hand, the alpha counting rate might very well be due to the presence of 94^{239} in view of the expectation that some of this isotope would be present as the end-product formed as the result of absorption of spontaneous fission neutrons by U^{238}. The chemical procedure is very stringent and specific for the isolation of 94 (and 93). A counting rate of about 90 per hour, amounting to some 10^{-6} microcuries, would correspond to the order of 10^{-5} microgram of 30,000-year 94^{239}. This would correspond to something like one part in 10^{14} of 94^{239} in the original pitchblende concentrate. This amounts to only a few per cent. of the amount to be expected if a large proportion of the spontaneous fission neutrons were absorbed by the U^{238}, but this is not surprising in view of the number of other neutron absorbing materials which might be present in the pitchblende.

Summary[6]

A chemical method for separating and concentrating elements 94 and 93 from uranium and thorium has been applied to a sample of pitchblende concentrate from the Great Bear Lakes region of Canada. A final fraction of 94 and 93 precipitated with rare earth carrier has been counted for fissions with slow and with fast neutrons, and an upper limit of 1 part in 10^8 to 10^9 has been set for the amount of these elements in the sample. Based on the number of alpha-particle counts in the sample, 1 part in 10^{14} is estimated as the amount of 30,000-year 94^{239} in the original pitchblende concentrate.

BERKELEY 4, CALIFORNIA RECEIVED FEBRUARY 18, 1948

(6) Summary was written at time of publication, since the original report contained no summary.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

A Study of the Distribution of Arsine in Impregnated Charcoal by Means of Radioactive Tracers

BY JOSEPH W. HICKEY[1] AND EDWIN O. WIIG

The object of the present work, which formed part of an investigation of the mechanism of arsine removal by impregnated charcoals, was to study the distribution of arsine in beds of charcoal using a radioactive tracer. The various experiments were carried out in the light of certain facts that had already been ascertained concerning arsine removal. Of chief interest were the effects of the time of exposure to the toxic gas, the water content both of the charcoal and of the air stream, the concentration of arsine in the air stream, and the nature of the absorbent. In conjunction with the arsine distribution, the distribution of water was also determined in an attempt to find some correlation with the effect of water in the removal process.

Experimental Details

Absorbent.—The absorbent, supplied by Edgewood Arsenal, was a 12–16 mesh (U. S. Standard Sieve Series), activated coconut shell charcoal which had been impregnated to contain cupric oxide. It was dried by heating for three hours at 150°. In some experiments the charcoal was previously equilibrated to a definite relative humidity.

Radioactive Arsine.—The radioactive arsenic employed was obtained by bombarding Ge^{73} with deuterons in a cyclotron to give As^{74} with a half-life of seventeen days.

Since the radioactive material was obtained from a germanium dioxide target, it was necessary to separate arsenic from germanium and also from copper from the bombardment chamber. Treatment of the radioactive material with aqua regia followed by a sodium carbonate fusion of the residue rendered the sample soluble. After addition of pure sodium arsenite as a carrier, a large part of the germanium was removed as volatile germanium chloride by evaporating the solution nearly to dryness twice with hydrochloric acid. Removal of copper was effected by precipitation with hydrogen sulfide and subsequent treatment with polysulfide reagent. After this separation the arsenic was fairly pure except for a small amount of germanium which might conceivably form germane during the reduction of the arsenic to arsine. The separation of the remaining germanium was carried out after the method of Abrahams and Müller,[2] using a double precipitation of arsenic sulfide to ensure complete removal of germanium. The pure radioactive arsenic sulfide was dissolved in aqua regia, evaporated with a small amount of sulfuric acid and diluted in a volumetric flask. Both procedures for the removal of germanium chloride by boiling and the separation of arsenic from germanium by precipitation of the sulfide were checked using samples of radio-arsenic and radio-germanium. It was found that practically all of the germanium was lost by boiling with a hydrochloric–nitric acid mixture while the arsenic stayed in the solution. Also, it was shown that no appreciable amount of germanium came down in the second precipitation of arsenic sulfide while the arsenic was obtained in good yield.

Radio-arsine was prepared by reaction of metallic zinc with a solution of dilute sulfuric acid and sodium arsenate to which some of the radio-arsenic solution had been added. The arsine and hydrogen evolved were passed through anhydrous calcium sulfate and a dry ice–ether trap to remove water vapor. Thence the gases were led through two liquid air traps to freeze out arsine and the non-condensable gases removed with a Hyvac pump. The pure arsine was later allowed to expand into a storage bottle.

Absorption Apparatus.—The set-up used to expose the absorbent bed consisted essentially of an apparatus for obtaining an air–arsine stream of known concentration, temperature and humidity, at a constant flow rate of 500 cm. per minute through the empty absorption tube. The main air stream was split into two streams, one of which flowed through two bottles of distilled water and a glass wool trap and thence to a mixing chamber while the second passed through concentrated sulfuric acid, a glass wool trap and into the wet air stream. Any desired relative humidity could be obtained by varying the ratio of the two streams. The entire humidifying system was placed in a thermostat at 25.0° to insure constant humidity. The humidified air passed on through a calibrated wet and dry bulb psychrometer enclosed in an insulated box, the pressure being kept constant by a small overflow in a hydrostatic regulator. The air stream was then mixed with arsine in a mixing chamber.

Arsine was forced out of the storage vessel at a constant rate by allowing sodium chloride solution to run slowly into the vessel under a constant head. The amount introduced into the air stream was determined by passing the arsine through a flowmeter before entering the mixing vessel. The flowmeter was calibrated by actual chemical analysis of the air–arsine stream and the proper flowmeter setting checked by analysis at the beginning of each run. From the mixing vessel the air–arsine stream passed through a second flowmeter, kept constant to insure a constant arsine concentration, and into the manifold. A small excess flow was allowed to escape through a stopcock into the hood.

Attached to the manifold were six absorption tubes, each preceded by its own flowmeter and constant temperature coil. Water jackets, through which a rapid flow of water at 25° was maintained, surrounded both the coil and the absorption tube. A three-way stopcock inserted after the flowmeter permitted diversion of the flow either to a waste line or an analysis train. The analysis for arsine was carried out by allowing a known flow, as measured by the tube flowmeter, to pass for a measured length of time, through two bubbler tubes containing a mercuric chloride–gum arabic solution. The latter quantitatively absorbs arsine, which was then determined by the method of Cassil.[3]

The absorption tube, shown in detail in Fig. 1, was a uniform Pyrex tube of internal diameter 19.0 ± 0.1 mm. with a semi-ball joint at each end. In order that the absorption tube might be attached and detached without using rubber connections, a U-tube with a ground glass joint at each end was placed between the bottom of the absorption tube and the rest of the system. About half way up the absorption tube on the inside and held by a ring seal was a glass ring with a ground surface. This ring served as a seat for a perforated porcelain disk which in turn was the support for the charcoal bed. The disk (of the type used as small filtering plates) had about sixty-three regularly spaced holes, and its diameter was such that it could be just slipped in and out of the tube. The

(1) From a thesis submitted in 1942 to the Graduate School of the University of Rochester in partial fulfillment of the requirements for the degree Doctor of Philosophy. Present address: Atlantic Refining Co., Philadelphia, Pennsylvania.

(2) Abrahams and Müller, THIS JOURNAL, **54**, 86 (1932).

(3) Cassil, *J. Assoc. Official Agr. Chem.*, **24**, 196 (1941).

sealed-in ring support decreased channeling of the gas stream at the periphery of the disk. This design of the absorption tube was necessary so that the entire bed (5.0 ± 0.1 cm. in depth and introduced by the standard Chemical Corps procedure) could be pushed up the tube as a unit after exposure to arsine. The absorbent could then be progressively removed in layers of known size at the top of the tube. To carry this out, the tube was removed from the system, the joints carefully cleaned with ether to remove the grease and the tube mounted vertically. The bed was raised up the tube by means of a rod pressing against the bottom of the supporting porcelain disk. This rod was moved by a screw shown at the bottom in the diagram. When the top of the bed was exactly level with the top of the tube, a millimeter scale attached to the rod was read. The rod was then moved up gradually for a measured distance (usually 3 mm.). The absorbent thus forced up beyond the top of the tube was removed, collected in a rubber mat surrounding the tube and placed in a small corked tube. The procedure was repeated until the entire bed had been sectioned. No mixing or appreciable contraction of the bed was ever noticed in using this method of layer separation. This was checked by coloring some of the charcoal particles.

The breakpoint indicator apparatus followed the absorption tube. A three-way stopcock was used in order that the flow might be changed instantly to either of two bubbler tubes. The absorbent was considered "broken" to arsine when a faint brown color appeared in a 2% silver nitrate solution in three minutes. This corresponds to 0.02% transmission of arsine by the absorbent for an initial arsine concentration of 4.15 mg. per liter.

Geiger Counter Assembly.—The separated layers of charcoal were weighed and, in most cases, dried to determine their moisture content after the run. It was found experimentally that the drying procedure had no effect on the counting rate of the sample. Then a 0.350-g. portion of each layer was placed evenly in a circular brass counting cup and covered with thin aluminum foil. This size sample proved satisfactory for the absorbent used and for the counter tube.

The Geiger–Müller tube, the quenching circuit and the assembly for holding the counting cup in place were enclosed in a grounded brass housing. The counting cup was placed in a fixed position on a support that could be moved up and down directly beneath the window of the counting tube. With the cup raised to a fixed distance from the window the average counting rate of the sample was determined. One sample was kept and counted from time to time during a set of experiments in order to measure the rate of decay of the radioactivity. Using the decay data, the counting rates of the various samples were calculated back to the time of starting the experiments.

The counting tube, with a thin mica window sealed on the bottom, was filled to a pressure of 8 cm. with a mixture of 90% argon and 10% ethanol and had a background of about thirty counts per minute. The counter itself consisted of a Neher–Harper type quenching circuit, a high voltage supply, a counting rate meter circuit capable of counting up to 20,000 counts per minute and a Cenco mechanical counter for low counting rates. The counting rate meter circuit was calibrated frequently by means of a standard pulse generator. In actual operation the rate meter was used for all the samples except those with counting rates less than 100 counts per minute.

Calculations.—The counting rates measured were for a 0.350-g. (or 0.300-g. in some cases) portion of the layer. The total counting rate per layer was found by simple weight proportion. It was observed by actual experiment that the counting rate was proportional to the weight of a given sample over the range used. Since the layers of absorbent obtained by the sectioning method were small and sometimes different in size, the data were expressed as weight of arsine absorbed per gram of dry absorbent at a given depth. It was assumed that the dried layers contained only the dried absorbent and arsenic trioxide. The latter has been found[4] present by X-ray analysis of similar absorbents exposed to a dry air–arsine stream. Also, Pierce[5] observed in some experiments on the change in weight of the same type of absorbents on exposure to arsine that this oxide was a strong possibility.

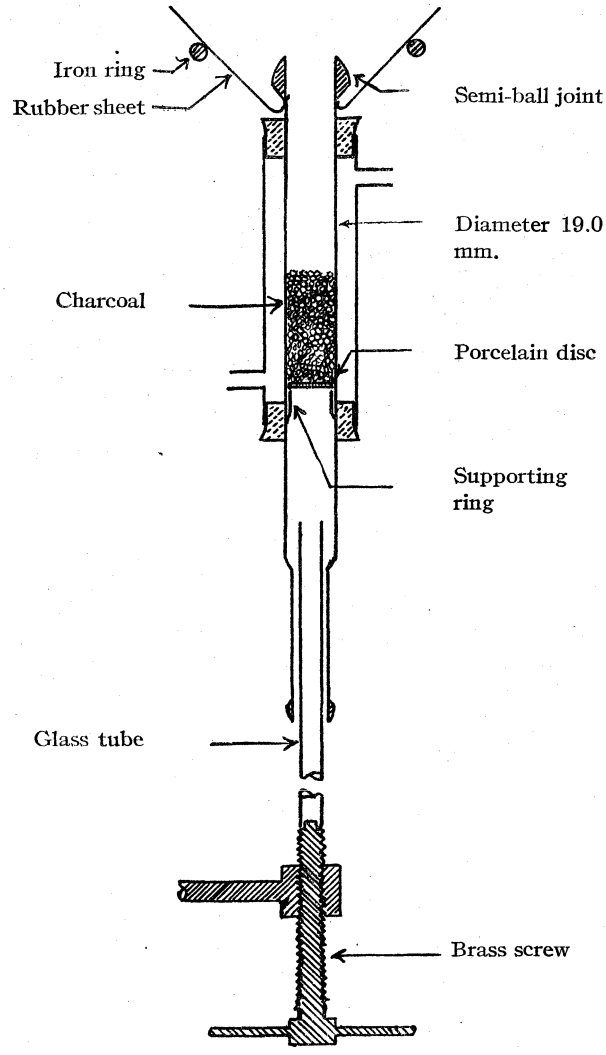


Fig. 1.—Apparatus for sectioning.

In order to obtain the amount of arsine absorbed in any layer, it was necessary to know the counting rate per unit weight of arsenic trioxide. The total number of counts in an entire bed was found by adding together the counting rates of all the layers. This total count divided by the weight of arsenic trioxide in the whole bed, calculated from the known amount of arsine absorbed during the run, gave the desired ratio. In actual practice the value used was an average for all the samples exposed to the same batch of radioactive arsine and not run beyond the breakpoint. Using this factor, the weight of arsenic oxide in each layer was obtained. The amount of dry absorbent in each layer was found by subtracting the weight of arsenic trioxide from the total weight of the dried layer. This method of finding the amount of absorbent in each layer was verified by adding together the weights of all the layers of a given sample and comparing with the weight of absorbent as calculated from the apparent density and the volume of the char used. These two values agreed to within 1–4%, including several samples

(4) H. F. Johnstone, NDRC Informal Report, 1941.

(5) W. C. Pierce, NDRC Formal Report, 1941.

that had absorbed almost 2 g. of arsine. Finally, the weight of arsine originally absorbed per gram of dry absorbent in each layer was calculated and plotted against the bed depth (the distance from the influent end to the center of the layer).

As a matter of allied interest, the weight of water (equal to the loss in weight on drying) per unit weight of dry absorbent was calculated for the various layers and plotted as a function of bed depth.

Results and Discussion

A study of the distribution curves in Figs. 2–6 shows the marked influence of water on arsine removal. With dry absorbent as much arsine is removed by the very first layers in ninety-three

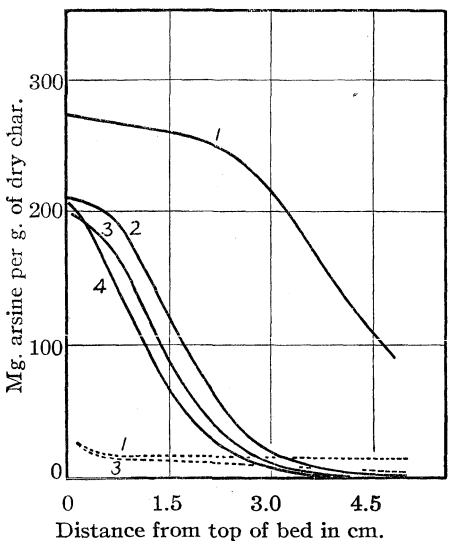


Fig. 2.—Variation of the distribution of arsine with time using dry char and dry air. 1–300 min., 2–100 min., 3–78 min., 4–60 min. Dotted curves represent water distribution.

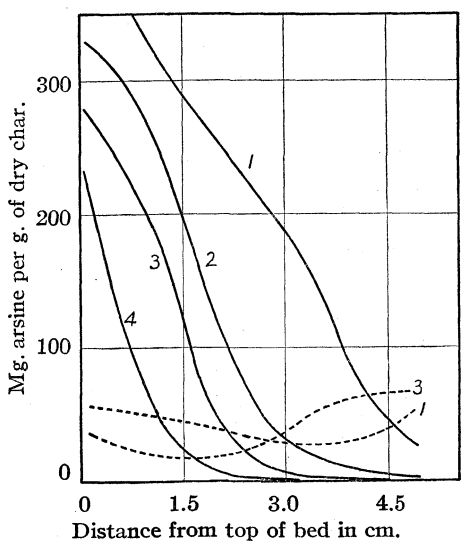


Fig. 3.—Variation of arsine distribution with time using dry char and air at 50% relative humidity. 1–300 min., 2–150 min., 3–93 min., 4–40 min. Dotted curves represent water distribution.

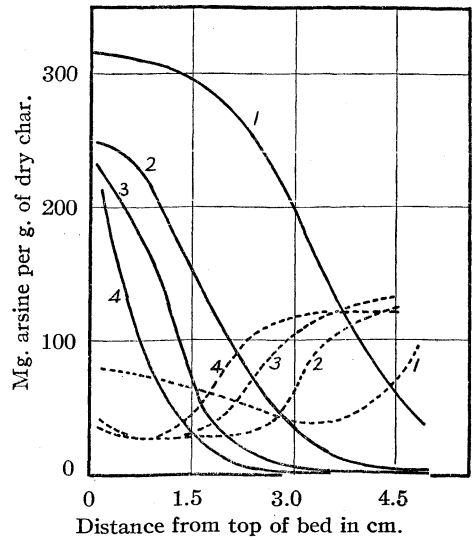


Fig. 4.—Variation of arsine distribution with time using char equilibrated to 50% relative humidity and air at 50% relative humidity. 1–300 min., 2–130 min., 3–80 min., 4–48 min. Dotted curves represent water distribution. Original water content about 100 mg. per g. of dry char.

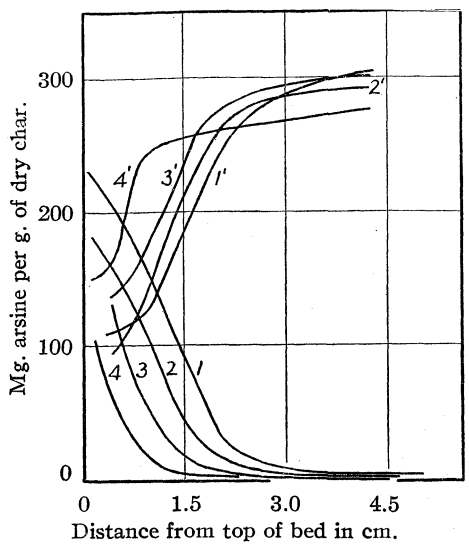


Fig. 5.—Variation of arsine distribution with time using char equilibrated to 70% relative humidity and air at 70% relative humidity. 1–80 min., 2–60 min., 3–40 min., 4–20 min. Upper primed curves represent water distribution. Original water content = 325 mg. per g. of dry char.

minutes from 50% relative humidity air as is taken up in three hundred minutes from dry air. Water vapor in the air stream is obviously accelerating the removal. In the former case, however, the amount of arsine drops sharply through the bed whereas with dry air it falls more slowly. This indicates that water also inhibits the removal of arsine. Water vapor, which is incompletely absorbed by charcoal, moves ahead of the arsine wave and poisons the more active centers.

This inhibiting effect of water is seen in comparing Figs. 3, 4 and 5. Using 50% relative humidity air more arsine is removed at the influent end in ninety-three minutes by dry char than is absorbed in one hundred thirty minutes by char equilibrated to 50% relative humidity. The inhibiting effect is very marked in experiments with air at 70% relative humidity and absorbent equilibrated to this humidity. In the latter case the amount of arsine removed at the influent end still remains greater than for dry char and dry air, as may be seen in Fig. 6. The rate of removal of arsine at lower concentrations as it passses through the bed is evidently less for the equilibrated char as indicated by the appreciable amount at the effluent end.

From the longest runs it appears that the arsine saturation value depends upon the amount of water present in the gas stream and on the charcoal. The highest value obtained for the dry absorbent using dry air was about 270 mg. of arsine per gram of char while values of over 400 mg. were found using dry charcoal and air at 50% relative humidity. The highest value for the absorbent equilibrated to 50% relative humidity and run at this humidity was intermediate at about 315 mg. of arsine per gram of dry charcoal. Since the apparent density of the absorbent was 0.50, the value obtained with dry air corresponds to 135 mg. of arsine per cc. of charcoal. This latter value agrees quite well with values of about 130 mg. per cc. reported by Pierce[5] from the results of his experiments on the change in weight of the same absorbent on absorption of arsine. Yost,[6] using a different base charcoal impregnated with copper oxide, found 120 mg. of arsine absorbed per cc. of absorbent by a radioactive method similar to the one used here. The difference in the saturation values with dry absorbent using in one case dry air and in the other air at 50% relative humidity may be correlated with the observation[7] that the breaktime for arsine using dry absorbent varies with the relative humidity of the air stream, gradually rising to a maximum at about 30% humidity and then falling off to low values at very high humidities.

The rate of approach toward a saturation value in the first layers of a bed varies considerably with conditions and presumably with the gas being absorbed. In the case of the inorganic gas cited by Klotz[8] (which was done in this Laboratory) the approach toward a saturation value proceeds at a slowly decreasing rate. The behavior of arsine with 70% relative humidity char and air stream (Fig. 5) or with dry char and 50% relative humidity air (Fig. 3) is somewhat similar. With 50% relative humidity char and air stream (Fig. 4) or dry char and dry air (Fig. 2), however, practically the same large amount of arsine is removed

(6) D. M. Yost, NDRC Formal Report, 1941.
(7) Scoville and Wiig, forthcoming publication.
(8) Klotz, *Chem. Rev.*, **39**, 241–268 (1946).

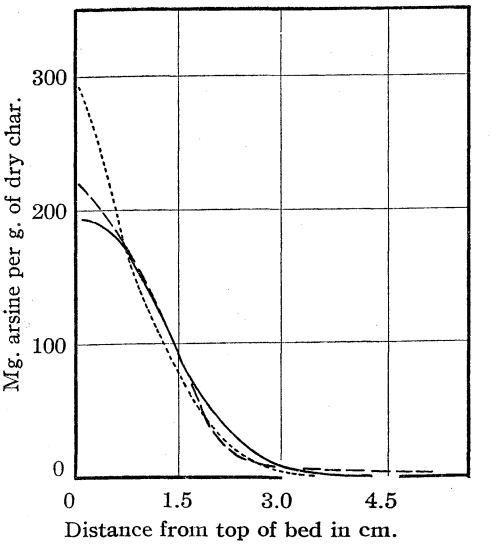


Fig. 6.—Arsine distribution under different humidity conditions with the same total amount of arsine passed through the char (80 min.). Dotted curve --- is dry char, 50% relative humidity air. Dashed curve – – is char equilibrated to 70% relative humidity, air 70% relative humidity. Full curve — is dry char, dry air.

by the influent end of the bed for exposures of fifty to one hundred thirty minutes and then the amount removed increases very slowly.

The reaction of arsine with oxygen is known to be highly exothermic (arsine is endothermic to the extent of 43.5 kcal.). The effect of the heat liberated can be readily traced by a study of the water distribution curves in Figs. 2–5. As arsine is removed at the influent end, the heat generated results in local desorption of water and an increase further down the bed. There is a distinct minimum in the water curves in most cases at a point corresponding roughly to the steep part of the arsine distribution curve where most of the adsorption was taking place. On continued exposure as the rate of accumulation of arsine at the influent end and the heat effects decrease, the amount of water present increases again. Experiments with and without water jackets on the absorption tube (Fig. 7) show that this heat also results in a displacement of the arsine distribution. As the air stream is warmed by the heat of reaction at the influent end evidently the rate of removal (oxidation of arsine) is increased a short distance down the bed.

Three runs with dry char and dry air at different concentrations of arsine for such lengths of time that the total amount of arsine passed through was the same in each case gave distribution curves similar to those in Fig. 2. The distributions at 4.15 and 7.18 mg. of arsine per liter were identical within experimental error, but at 1.67 mg. per liter the arsine was spread more throughout the bed. These observations can be correlated with the product of the breaktime and

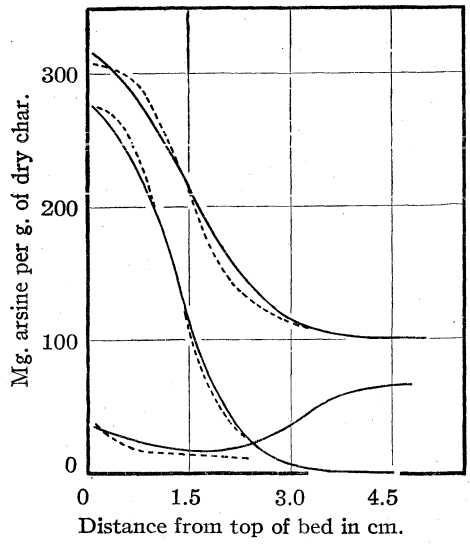


Fig. 7.—Effect on the arsine distribution of water cooling the absorption tube. Full curves — shows water jacket. Dotted curves --- have no water jacket. Top two curves with dry char and dry air have been displaced upward 100 mg. Other four curves are for dry char and 50% relative humidity air. Lowest two curves represent corresponding water distribution.

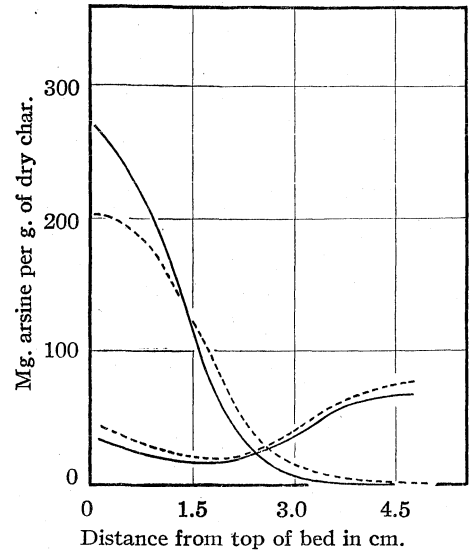


Fig. 8.—Arsine distribution in two different base chars impregnated with copper oxide using dry char and 50% relative humidity air. Full curve — shows coconut shell char. Dotted curve --- is $ZnCl_2$ activated wood char. Two lower curves represent corresponding water distribution.

initial concentration (C_0T) that have been found at these concentrations:

C_0 (mg./liter)	1.67	4.15	7.18
C_0T	2.82	3.28	3.38

It would seem that only the more active catalyst centers are effective at low concentrations, and of course this is also shown by the tailing off of all the distribution curves. It suggests that if this charcoal were exposed to a very low concentration of arsine for some time to use up the more active centers throughout the bed, the breaktime toward a higher concentration would be much less than expected.

No attempt was made in this investigation to make a complete study of the distribution of arsine in various absorbents. One experiment was performed with an activated, zinc chloride-treated, wood charcoal impregnated with cupric oxide. This absorbent had a breaktime of fifty minutes as compared to ninety minutes for the other, using dry char and air at 50% relative humidity. A comparison of the two absorbents run for the same time at the same concentration (Fig. 8) shows that the coconut char apparently had a higher saturation value. The water distributions were similar except that the amount absorbed by the wood char was greater, in agreement with the observation that the latter also absorbed more water, 13% compared to 10%, when equilibrated to 50% relative humidity.

The actual mechanism of arsine removal cannot be assumed on the basis of this investigation, but it does involve the oxidation of arsine mainly to arsenic trioxide and water with copper oxide as a catalyst. It is necessary to have both charcoal and copper oxide present since copper oxide alone will not remove arsine, and unimpregnated charcoal removes it for only a very short time. Furthermore, it is evident from the highest values obtained for the amount of arsine accumulated in the top layer that arsine is not removed by reacting directly with copper oxide since there is only 58 mg. of copper present per gram of absorbent. It seems quite probable that the first step in the removal is adsorption of arsine followed by the oxidation reaction. The role that small amounts of water play is not at all certain, but it might be mentioned that even in the gas phase arsine and oxygen undergo practically no reaction in the absence of water.[9] The presence of large amounts of water on the charcoal and covering the copper oxide may decrease the initial adsorption of arsine to such an extent that little arsine is removed until some of this water is driven off by the heat of a small amount of reaction.

Acknowledgment.—The authors wish to express their thanks to the National Defense Research Committee of the OSRD who sponsored this research, to the Edgewood Arsenal Laboratories for their coöperation and to Drs. John H. Raley and Herbert Scoville, Jr., for their assistance with some of the experimental work.

Summary

The distribution of arsine on a charcoal bed has been followed as a function of the humidity of the air stream and the absorbent, concentration of ar-

(9) W. C. Johnson, private communication.

sine, time of exposure and cooling, by the use of radioactive arsenic. The distribution curves show a marked accelerating effect of small amounts of water and an inhibiting effect of larger amounts. A constant saturation value for arsine at the influent end of the bed is apparently not reached even after long exposure.

ROCHESTER 3, NEW YORK RECEIVED JULY 10, 1947

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

Determination of the Product of the Constants for the Overlapping Dissociation of Weak Acids by Electromotive Force Methods

BY ROGER G. BATES

The exact determination of the thermodynamic dissociation constants of many weak dibasic and tribasic acids is complicated by the "overlapping" of the successive ionization steps. When the ratio of the thermodynamic constants for the primary and secondary steps, K_1/K_2, is less than 500 to 1000, as it is for most of the common aliphatic dicarboxylic acids[1] and many substituted benzoic acids,[2] the ionic and molecular concentrations cannot be established with sufficient accuracy by consideration of a single equilibrium. Hence, a determination of the constants often requires laborious arithmetical approximations.[3,4,5,6]

The constant for the second overlapping step in the dissociation of a dibasic acid can often be determined by the thermodynamic method of Harned and Ehlers[7] from measurements of cells without liquid junction. The determination is facilitated through choice of buffer solutions on the alkaline side of the midpoint of the neutralization curve for the second group, with a decrease in the correction for the first dissociation equilibrium. A buffer ratio of 5:1 appears not to be excessive.[8] However, the advantage of a similar procedure is sometimes offset in the evaluation of the first constant by the enhanced correction for hydrogen ion, the concentration of which must be established by successive approximations or, at a sacrifice of accuracy, derived from a pH measurement.[9]

When conditions cannot readily be chosen to isolate each of the individual equilibria in turn, solutions of the acid salt, where overlapping of the two equilibria is at a maximum, can be used to advantage in establishing the product of the constants for two overlapping equilibria. A thermodynamic method for the determination of this product from measurements of the electromotive force of cells without liquid junction is described. If one dissociation constant of an overlapping pair is known, this procedure usually permits the other to be determined accurately.

Method

The electromotive force, E, of the cell

$$\text{Pt; } H_2\text{, acid salt } (m)\text{, MCl } (m_2)\text{, AgCl; Ag} \qquad \text{I}$$

where M represents an alkali metal and the acid salt is of one of the three types: MHA, MH_2A, or M_2HA, is given by

$$\frac{F(E - E^0)}{2.3026\ RT} + \log m_{Cl} = -\log (f_H f_{Cl} m_H) \equiv pwH \qquad (1)$$

For convenience, this experimental quantity will be termed pwH. In equation (1), f is an activity coefficient on the scale of molality (m), F is the faraday, and the other symbols have their usual significance. The hydrogen-ion concentration, m_H, is readily expressed in terms of dissociation constants, molalities, and activity coefficients. The product of the thermodynamic constants for the two overlapping steps is obtained by extrapolation of an appropriate function of E, with the aid of the Debye–Hückel formula,[10] to infinite dilution, where the estimated activity coefficients are exact. To simplify the treatment, the following discussion is restricted to solutions of acid salts with pH < 8, in which the concentration of hydroxyl ion can be ignored.

Case I. Acid Salt of a Dibasic Acid, $K_1/K_2 < 500$.—The molecular and ionic species participating in the equilibria are H^+, H_2A, HA^-, and $A^=$. The concentration of hydrogen ion, m_H, in solutions of the acid salt is given by

$$m_H^2 = \frac{K_1 K_2 m_{H_2A}}{m_A} \times \frac{f_{H_2A}}{f_H^2 f_A} \qquad (2)$$

Inasmuch as

$$m_A = m_{H_2A} + m_H \qquad (3)$$

we obtain, by combination of equations (1) and (2)

(1) R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

(2) W. R. Maxwell and J. R. Partington, *Trans. Faraday Soc.*, **33**, 670 (1937).

(3) F. Auerbach and E. Smolczyk, *Z. physik. Chem.*, **110**, 65 (1924); H. T. S. Britton, *J. Chem. Soc.*, 1896 (1925); N. Bjerrum and A. Unmack, *Kgl. Danske Videnskab. Selskab., Math.-fys. Medd.*, **9**, No. 1 (1929).

(4) H. S. Simms, THIS JOURNAL, **48**, 1239 (1926).

(5) W. J. Hamer and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 381 (1945).

(6) W. J. Hamer, G. D. Pinching and S. F. Acree, *ibid.*, **35**, 539 (1945).

(7) H. S. Harned and R. W. Ehlers, THIS JOURNAL, **54**, 1350 (1932).

(8) G. D. Pinching and R. G. Bates, *J. Research Natl. Bur. Standards*, in press (data for oxalic acid).

(9) The simultaneous evaluation of overlapping K_1 and K_2 from pH-titration data obtained from cells with liquid junction has been described by J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

(10) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

$$-\frac{1}{2}\log(K_1K_2) = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_2A}} + m_{\mathrm{H}}}{m_{\mathrm{H_2A}}} - \frac{1}{2}\log\frac{f_{\mathrm{A}}}{f_{\mathrm{H_2A}}f_{\mathrm{Cl}}^2} \quad (4)$$

To aid in the extrapolation, the Debye–Hückel equation may be employed for the ionic activity coefficients and unity assumed for the activity coefficient of the uncharged molecule. In this way an expression for the "apparent" value of the product of K_1 and K_2, namely $(K_1K_2)'$, is obtained

$$-\frac{1}{2}\log(K_1K_2)' = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_2A}} + m_{\mathrm{H}}}{m_{\mathrm{H_2A}}} + \frac{A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (5)$$

where A and B are constants of the Debye–Hückel theory,[11] μ is the ionic strength, and a^* is the so-called ion-size parameter. The limiting value of $(K_1K_2)'$ at zero ionic strength is K_1K_2.

Case II. Primary Acid Salt of a Tribasic Acid, $K_1/K_2 < 500$, $K_2/K_3 > 1000$.—The ionic and molecular species concerned are H^+, H_3A, H_2A^-, and $HA^=$. The molality of hydrogen ion is given by

$$m_{\mathrm{H}}^2 = \frac{K_1K_2m_{\mathrm{H_3A}}}{m_{\mathrm{HA}}} \times \frac{f_{\mathrm{H_3A}}}{f_{\mathrm{H}}^2 f_{\mathrm{HA}}} \quad (6)$$

Inasmuch as the third dissociation step need not be considered

$$m_{\mathrm{HA}} = m_{\mathrm{H_3A}} + m_{\mathrm{H}} \quad (7)$$

By combination of equations (1), (6) and (7), an expression is obtained that differs from equation (4) only in substitution of H_3A for H_2A and of HA for A in the subscripts of m and f. This expression can be written in a form suitable for extrapolation as follows

$$-\frac{1}{2}\log(K_1K_2)' = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_3A}} + m_{\mathrm{H}}}{m_{\mathrm{H_3A}}} + \frac{A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (8)$$

Case III. Secondary Acid Salt of a Tribasic Acid, $K_1/K_2 > 1000$, $K_2/K_3 < 500$.—The ionic species are H^+, H_2A^-, $HA^=$, and $A^{\equiv}$. The square of the concentration of hydrogen ion is

$$m_{\mathrm{H}}^2 = \frac{K_2K_3m_{\mathrm{H_2A}}}{m_{\mathrm{A}}} \times \frac{f_{\mathrm{H_2A}}}{f_{\mathrm{H}}^2 f_{\mathrm{A}}} \quad (9)$$

Equations (3) and (4) are valid for Case III as well as for Case I, with the substitution of the product K_2K_3 for K_1K_2. The charges of H_2A and A are, of course, now -1 and -3 instead of 0 and -2 as in Case I. By combination with the Debye–Hückel equation, an expression suitable for extrapolation is obtained

$$-\frac{1}{2}\log(K_2K_3)' = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_2A^-}} + m_{\mathrm{H}}}{m_{\mathrm{H_2A^-}}} + \frac{3A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (10)$$

(11) G. G. Manov, R. G. Bates, W. J. Hamer and S. F. Acree, THIS JOURNAL, **65**, 1765 (1943).

Case IV. Primary Acid Salt of a Tribasic Acid, $K_1/K_2 < 500$ and $K_2/K_3 < 500$.[12]—The ionic and molecular species of concern in Case IV are H^+, H_3A, H_2A^-, $HA^=$, and $A^{\equiv}$. All three steps in the dissociation of the acid must be considered, and

$$m_{\mathrm{HA}} = m_{\mathrm{H_3A}} + m_{\mathrm{H}} - m_{\mathrm{A}} \quad (11)$$

Formula (6) applies here, and equation (8) of Case II accordingly takes the form

$$-\frac{1}{2}\log(K_1K_2)' = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_3A}} + m_{\mathrm{H}} - m_{\mathrm{A^{\equiv}}}}{m_{\mathrm{H_3A}}} + \frac{A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (12)$$

Case V. Secondary Acid Salt of a Tribasic Acid, $K_1/K_2 < 500$ and $K_2/K_3 < 500$.—The molalities of the molecular acid and of the primary and tertiary ions in a solution of the secondary salt are related by

$$m_{\mathrm{A}} = m_{\mathrm{H_2A}} + m_{\mathrm{H}} + 2m_{\mathrm{H_3A}} \quad (13)$$

The hydrogen-ion concentration is given by equation (9). Hence, an expression analogous to equation (10) is obtained:

$$-\frac{1}{2}\log(K_2K_3)' = pw\mathrm{H} - \frac{1}{2}\log\frac{m_{\mathrm{H_2A^-}} + m_{\mathrm{H}} + 2m_{\mathrm{H_3A}}}{m_{\mathrm{H_2A^-}}} + \frac{3A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (14)$$

Compositions of the Solutions

Only two overlapping dissociation steps are involved in Cases I, II and III. The evaluation of the second terms on the right of equations (5), (8) and (10) requires that the concentration of only one ionic or molecular species in addition to that of hydrogen ion be established. In equations (12) and (14) of Cases IV and V, the concentration of a second species, fortunately considerably smaller than that of the first, must be estimated. In each instance the hydrogen-ion concentration, m_{H}, can be computed from the equation

$$-\log m_{\mathrm{H}} = pw\mathrm{H} + \log f_{\mathrm{H}}f_{\mathrm{Cl}} = pw\mathrm{H} - \frac{2A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (15)$$

In the following discussion of the exact and approximate methods of computing these concentration terms, it will be convenient to employ the classical dissociation constants, k_n, for the three steps. For a weak tribasic acid

$$k_1m_{\mathrm{H_3A}} = m_{\mathrm{H}}m_{\mathrm{H_2A}};\ k_2m_{\mathrm{H_2A}} = m_{\mathrm{H}}m_{\mathrm{HA}};\ k_3m_{\mathrm{HA}} = m_{\mathrm{H}}m_{\mathrm{A}} \quad (16)$$

If, further, it is assumed that each activity coefficient is given by the Debye–Hückel equation, we may write

$$k_n = \bar{K}_n / f^{2n} \quad (17)$$

(12) The formulas of Cases IV and V have been applied successfully to the resolution of the three overlapping constants of citric acid by Miss Gladys D. Pinching and the author (unpublished work). For citric acid, each ratio is about 44, and K_1/K_2 is about 1900. If K_1/K_2 were less than 1000, the separation would doubtless be more difficult.

where

$$-\log f^n = nA\sqrt{\mu}/(1 + Ba^*\sqrt{\mu}) \qquad (18)$$

and n is 1, 2, or 3. The symbol K_n represents the thermodynamic dissociation constant.

Complete or Exact Treatment, Cases I, II, and III.—When the acid salt of a dibasic acid with overlapping constants (Case I) is dissolved in water the interaction

$$2HA^- \rightleftarrows H_2A + A^= \qquad (19)$$

may proceed rather extensively. This reaction is usually considerably more important than the normal acidic dissociation of the intermediate ion. When K_1/K_2 is 4 (the theoretical lower limit for a symmetrical dibasic acid[13]), as much as half of the acid anion may be converted into H_2A and $A^=$.[13,14]

From the mass law and equations (3), (17) and (19) we have

$$\frac{k_2}{k_1} = \frac{K_2}{K_1 f^2} = \frac{m_{H_2A}(m_{H_2A} + m_H)}{(m - m_H - 2m_{H_2A})^2} \qquad (20)$$

Even though m_H is obtained by equation (15) and the ratio of constants is known, equation (20) cannot readily be solved for m_{H_2A}. The desired quantity can, however, be obtained graphically or by trial.

Two features of this method are noteworthy. First, the second terms on the right of equations (5), (8), (10), (12) and (14) are of the form $^1/_2 \log [(a + b)/a]$, where a is large relative to b. Hence, the values of these terms are rather insensitive to small changes in a. The higher the pH of the solution of the acid salt the smaller is b, and the larger is the permissible error in a. Secondly, although the evaluation of both m_H and k_2/k_1 rests upon an assumed value of a^*, the ion-size parameter, the second terms on the right of these five extrapolation formulas are but little influenced by the choice of a^*, when the same value is used in both equation (15) and equation (18). This point will be illustrated later in this paper. The value of a^* used in the extrapolation equations themselves is immaterial, so long as the plots of $^{-1}/_2 \log (K_1K_2)'$ as a function of ionic strength display the convergence at infinite dilution demanded by theory.

The treatment of Cases II and III is entirely analogous to Case I. For Case II the principal equilibrium is

$$2H_2A^- \rightleftarrows H_3A + HA^= \qquad (21)$$

In equation (20), m_{H_2A} is replaced by m_{H_3A}. The extrapolation is performed with the aid of formula (8) instead of with (5). For Case III the principal ionic equilibrium is

$$2HA^= \rightleftarrows H_2A^- + A^{\equiv} \qquad (22)$$

Hence, equation (20) becomes

$$\frac{k_3}{k_2} = \frac{K_3}{K_2 f^2} = \frac{m_{H_2A^-}(m_{H_2A^-} + m_H)}{(m - m_H - 2m_{H_2A^-})^2} \qquad (23)$$

(13) R. Wegscheider, *Monatsh.*, **16**, 153 (1895); E. Q. Adams, THIS JOURNAL, **38**, 1503 (1916); N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

(14) C. W. Davies, *J. Chem. Soc.*, 1850 (1939).

The extrapolation is made, of course, with equation (10)

Complete Treatment, Cases IV and V.—Formula (21) represents the principal equilibrium in solutions of the primary salt of a tribasic acid with three overlapping constants (Case IV). The secondary anion, $HA^=$, formed in this reaction is capable of further acidic dissociation, as is the primary anion. Contrary to the situation in Case II, where K_3 was too small to require consideration, three equilibria are involved here. Inasmuch as

$$m_{H_2A} = m - m_{H_3A} - m_{HA} - m_A \qquad (24)$$

we have, from equation (11) and the mass-law expression for equilibrium (21)

$$\frac{k_2}{k_1} = \frac{m_{H_3A}(m_{H_3A} + m_H - m_A)}{(m - m_H - 2m_{H_3A})^2} \qquad (20a)$$

The analogy with equation (20) is evident. The molality of $A^{\equiv}$ appearing in the numerator of (20a) is small (slightly less than 1% of m_{H_3A} in solutions of potassium dihydrogen citrate[12]). It is readily computed with an accuracy exceeding the experimental error in the electromotive force by

$$m_A = k_3 m_{HA}/m_H = K_3 m_{HA}/(m_H f^6) \qquad (25)$$

from a first estimate of m_{HA} and a value of pK_3 accurate to ± 0.1. Otherwise, the evaluation of K_1K_2 parallels Case I.

The principal equilibrium in solutions of the secondary salt of a tribasic acid with three overlapping constants (Case V) is (22). Acidic dissociation of the secondary anion must be considered as well as the reaction of the primary anion formed in (22) with a part of the hydrogen ion liberated by dissociation of $HA^=$

$$H_2A^- + H^+ \rightleftarrows H_3A \qquad (26)$$

From equations (13), (24), and the mass law

$$\frac{k_3}{k_2} = \frac{m_{H_2A}(m_{H_2A} + m_H + 2m_{H_3A})}{(m - m_H - 2m_{H_2A} - 3m_{H_3A})^2} \qquad (23a)$$

The molality of H_3A, like m_A in Case IV, is a correction of secondary importance. It is obtained with sufficient accuracy from the approximate K_1 and m_{H_2A} by

$$m_{H_3A} = m_H m_{H_2A}/k_1 = m_H m_{H_2A} f^2/K_1 \qquad (27)$$

Approximate Treatment.—If the pH of the solution of acid salt is higher than 3.5 to 4.0, m_H is usually small with respect to m_{H_2A} and m_{H_3A} in equations (5), (8), (10), (12) and (14), and the treatment can be simplified. Fortunately, the acid salts of most dicarboxylic acids with overlapping fall in this category.

If m_H in equation (3) approaches zero, it is easy to show that the molality of molecular acid produced by reaction (19) is approximately

$$m_{H_2A} \approx \frac{1}{2}(mx - m_H) \qquad (28)$$

where

$$x \equiv \frac{2(k_2/k_1)^{1/2}}{1 + 2(k_2/k_1)^{1/2}} \qquad (29)$$

Hence, the concentration term of equation (5) is readily obtained and, by a similar procedure, also that of equation (8)

Cases I and II.—

$$\frac{m_{H_2A} + m_H}{m_{H_2A}} \approx \frac{mx + m_H}{mx - m_H}$$
$$\frac{m_{H_3A} + m_H}{m_{H_3A}} \approx \frac{mx + m_H}{mx - m_H} \quad (30)$$

Similarly, from equation (23), we have

$$m_{H_2A^-} \approx \frac{1}{2}(my - m_H) \quad (31)$$

where

$$y \equiv \frac{2(k_3/k_2)^{1/2}}{1 + 2(k_3/k_2)^{1/2}} \quad (32)$$

Hence, the concentration term of formula (10) is given by

Case III.—

$$\frac{m_{H_2A^-} + m_H}{m_{H_2A^-}} \approx \frac{my + m_H}{my - m_H} \quad (33)$$

By the same reasoning, the second term on the right of formula (12) can be expressed in terms of x

Case IV.—

$$\frac{m_{H_3A} + m_H - m_{A^{\equiv}}}{m_{H_3A}} \approx \frac{mx + m_H - 2m_A}{mx - m_H} \quad (34)$$

In Case V the situation is slightly different, for a part of the primary anion, H_2A^-, produced by (22) is converted into H_3A. Hence

$$m_{H_2A} \approx \frac{1}{2}(my - m_H) - m_{H_3A} \quad (35)$$

The second term on the right of equation (14) is thus given by

Case V.—

$$\frac{m_{H_2A^-} + m_H + 2m_{H_3A}}{m_{H_2A^-}} \approx \frac{my + m_H + 2m_{H_3A}}{my - m_H - 2m_{H_3A}} \quad (36)$$

Ionic Strength.—Whether the complete or approximate treatment is used, sufficiently accurate values of the ionic strength can ordinarily be obtained with the aid of x and y

Case	Mixture	Ionic Strength	
I	MHA (m), MCl (m_2)	$m\,(1 + 0.5x) + 1.5m_H + m_2$	(37a)
II	MH_2A (m), MCl (m_2)	$m\,(1 + 0.5x) + 1.5m_H + m_2$	(37b)
III	M_2HA (m), MCl (m_2)	$m\,(3 + 0.5y) + 2.5m_H + m_2$	(37c)
IV	MH_2A (m), MCl (m_2)	$m\,(1 + 0.5x) + 1.5m_H + 2.5m_A + m_2$	(37d)
V	M_2HA (m), MCl (m_2)	$m\,(3 + 0.5y) + 2.5m_H + 2m_{H_3A} + m_2$	(37e)

Evaluation of K_1K_2 and K_2K_3

The determination of K_1K_2 for a dibasic acid is made as follows. Values of x are computed by equation (29) from a reasonable estimate of k_2/k_1, and a first estimate of the ionic strength is obtained by equation (37a). The hydrogen-ion concentration can be ignored or estimated from the approximate pH of the solution. Equation (15) yields a value of m_H when the ionic strength has been estimated, and the second term on the right of equation (5) is computed with the aid of equation (20) or the approximation, equation (28). It is suggested that a value of 4.0 be assigned to a^* in equations (15) and (18). A first approximation of K_1K_2 is obtained by extrapolation of the right-hand side of equation (5) to infinite dilution. The plots of $-{}^1/_2 \log (K_1K_2)'$ as a function of ionic strength will dictate the value of a^* in equation (5) necessary to provide an accurate extrapolation, although 4.0 is a reasonable first choice.

A value of K_2/K_1 results from combining K_1K_2 with K_1 or K_2, whichever is available from independent determinations, and a new k_2/k_1 is obtained with the assistance of equations (17) and (18). The process is then repeated. Inasmuch as m_{H_2A} need not be known accurately, a third approximation is usually unnecessary.

For the solution of Cases IV and V an approximate value of m_A or m_{H_3A} is calculated as described in an earlier section. In other respects, K_1K_2 and K_2K_3 are evaluated in Cases II, III, IV, and V exactly as is K_1K_2 in Case I.

The extrapolation of the right side of equations (12) and (14) to infinite dilution is illustrated in Fig. 1 with data for the acid salts of citric acid. The two sets of curves were computed from the electromotive force of cells of type I. The upper lines represent mixtures of secondary potassium citrate and potassium chloride, whereas the lower set was derived from studies of mixtures of primary potassium citrate and potassium chloride.[12,15] The approximate formulas (34) and (36) were used in evaluating the second terms on the right of equations (12) and (14). Curves a, b, c, d, e, and f were computed with a^* values of 5.0, 5.5, 6.0, 2.0, 3.0 and 4.0, respectively. As mentioned earlier, altering a^* in formulas (15) and (18) has little effect on the plotted points.

Limitations of the Approximation.—In Figure 2, the differences between the true ${}^1/_2 \log [(m_{H_2A} + m_H)/m_{H_2A}]$ of formula (5) and approximate values computed by equation (30) are plotted as a function of the molality of the acid salt. To enhance the accuracy of the determination of the constants for the overlapping steps, the concentration of acid salt should preferably not be lower than 0.01 molal. The lower limit of $-\log m_H$ (pcH), below which the error of the approximation exceeds 0.0005 in ${}^1/_2 \log (K_1K_2)'$ (0.03 mv. in the electromotive force), is a function of the magnitude of k_1/k_2, that is, of the extent of overlapping. The approximate treatment is adequate above pcH 3.25 when k_1/k_2 is 10, above 3.70 when k_1/k_2 is 100, and above 3.95 when k_1/k_2 is 215.

K_1K_2 for *o*-Phthalic Acid

The two dissociation constants of *o*-phthalic acid have been determined accurately by electromotive-force methods.[5,6] These constants can be employed to illustrate the application of the equa-

(15) These curves were plotted from preliminary data. They serve, nevertheless, to illustrate the nature of the extrapolation.

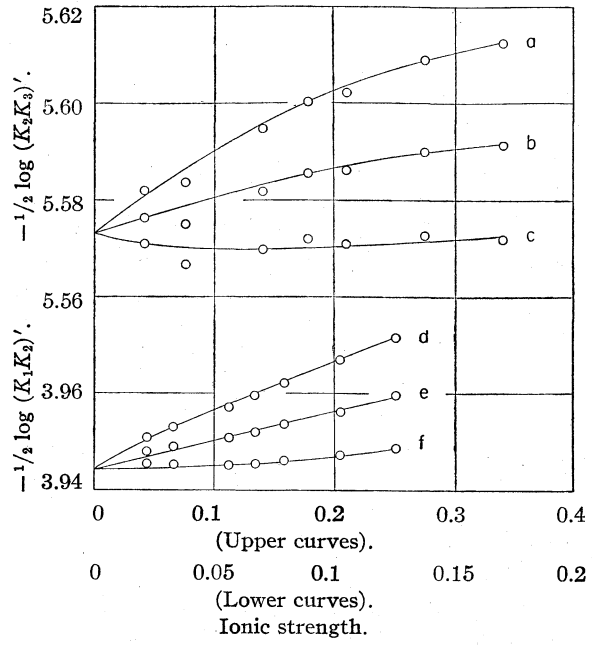


Fig. 1.—Determination of K_1K_2 and K_2K_3 for citric acid from the electromotive force of cell I at 25°.

tions of the foregoing sections and to test this method of determining K_1K_2.

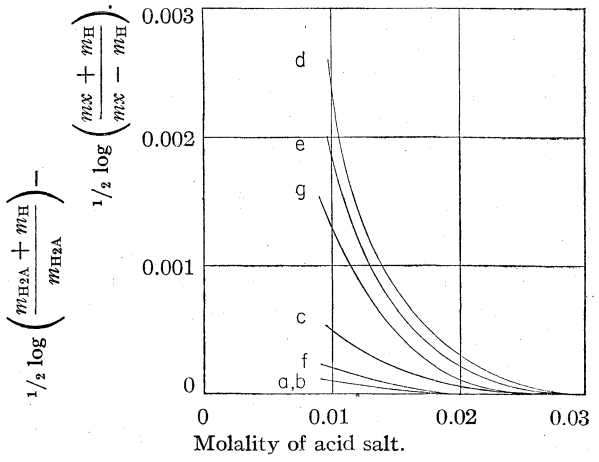


Fig. 2.—Error of the approximation plotted as a function of the molality of the acid salt:

Curve	k_1/k_2	$-\log m_H$
a	7	3.43
b	10	3.50
c	10	3.25
d	10	3.00
e	20	3.15
f	100	3.80
g	100	3.50

The electromotive force of 19 cells of type I was measured at 25° with mixtures of acid potassium phthalate[16] and potassium chloride (m_2 = 0.01). Palladium electrodes were substituted for platinum.[17] The molality of acid salt varied from 0.01 to 0.07. The electromotive force in int. v. appeared to be a linear function of log m in this range

$$E_{25} = 0.57662 - 0.00476 \log m \qquad (38)$$

The reproducibility and stability of the cells with 0.01 m to 0.02 m acid potassium phthalate were not good, and an uncertainty of nearly 0.2 mv. must be assigned to the electromotive force at 0.01 m. The uncertainty is indicated in Fig. 3 by the varying sizes of the circles which represent the values of $-1/2 \log (K_1K_2)'$. The approximate treatment was employed throughout. The error of the approximation is only 0.0002 in $-1/2 \log (K_1K_2)'$ for the 0.01 m solution, the most dilute studied.

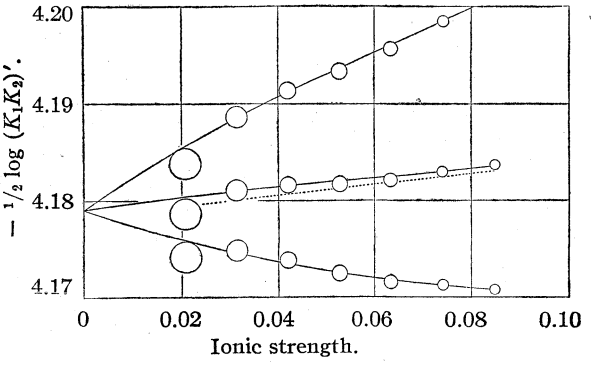


Fig. 3.—Determination of K_1K_2 for phthalic acid from the electromotive force of cell I at 25°: from top to bottom, the lines represent a^* values of 2.0, 4.0, and 6.0, equation (5). The curves are drawn to intersect at 4.179, the known value of $-1/2 \log (K_1K_2)$.[5,6]

From top to bottom of Fig. 3, the three lines represent a^* values of 2.0, 4.0, and 6.0 in the last term of formula (5). In each instance, 4.0 was used for a^* in equations (15) and (18). When a^* was set equal to zero in these two equations, the middle curve in Fig. 3 took the position indicated by the dotted line. It is evident, therefore, that the final result is altered by only 0.001 if the Debye–Hückel limiting law ($a^* = 0$) is used in these two formulas. The three lines are drawn to intersect at 4.179, the value of $-1/2 \log (K_1K_2)$ at 25°.[5,6]

It should be noted that the electromotive force of cell I containing a solution of primary or secondary acid salt is rather sensitive to variations in the composition of the salt. For example, the change in the electromotive force of the cell containing 0.05 m acid potassium phthalate and 0.01 m potassium chloride that results from a change of 0.1% in the titration value of the acid salt is about 0.17 mv. For phthalic acid, K_1/K_2 is 288.[5,6] The electromotive force is somewhat less sensitive to the purity of the salt when the extent of overlapping is greater. A change of 0.03 mv. in

(16) National Bureau of Standards Standard Samples 84a and 84c.

(17) W. J. Hamer and S. F. Acree, *J. Research Natl. Bur. Standards*, **33**, 87 (1944).

E corresponds to 0.001 in $pK_1 + pK_2$. Hence, the uncertainty in pK caused by experimental errors is twice that of the conventional method where a single dissociation step is involved.

Summary

The use of electromotive-force measurements of hydrogen–silver chloride cells without liquid junction in resolving the constants for the overlapping dissociation steps of weak dibasic and tribasic acids is discussed. When one constant of an overlapping pair is known, the second can be derived from studies of solutions of the appropriate primary or secondary acid salt with added alkali chloride. The equations for the five possible cases of overlapping have been developed. A simple means of estimating the molalities needed in the computation is described. The method has been applied to a determination of the product of the constants of phthalic acid at 25°. The result is consistent with earlier determinations of the two constants.

WASHINGTON, D. C. RECEIVED OCTOBER 31, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. IV. The Application of the Darzens Reaction to β-Ionone[1a]

BY NICHOLAS A. MILAS, S. WARREN LEE,[2] EMILE SAKAL,[3] HERBERT C. WOHLERS,[4] NORMAN S. MACDONALD,[5] FRANK X. GROSSI[6] AND HERBERT F. WRIGHT[7]

One of the key intermediates in the synthesis of several biologically active vitamin A products[8] was produced by the application of the Darzens synthesis to β-ionone.[9] The structure of this product presented a special problem in view of the anomalous results obtained in the early stages of our investigation. When β-ionone was condensed with ethyl chloroacetate at low temperatures (−30 to −60°) in anhydrous ether or toluene using alcohol-free sodium ethoxide or methoxide as the condensing agents, the glycidic ester I was produced which upon hydrolysis presumably gave a glycidic acid of similar structure. When the crude glycidic ester was hydrolyzed and the crude glycidic acid decarboxylated in the presence or absence of powdered glass or by passing it under a reduced pressure downwards through a hot tube (140–160°) packed with freshly reduced copper powder on pumice, the decarboxylation product had slightly different properties from that obtained by the decarboxylation of the pyridine salt of the same glycidic acid. Furthermore, decarboxylation under similar conditions of the two glycidic acids, one crystalline and the other highly viscous liquid both derived from pure glycidic ester, yielded products still different in physical and chemical properties. Table I shows the main fractions of decarboxylation products obtained by various methods from crude as well as from crystalline glycidic acids. Upon careful fractionation of a large sample of the decarboxylation product obtained from the crude glycidic acid using a four-foot packed fractionation column, three fractions were obtained: a small low-boiling fraction with a high index of refraction; a large fraction with an intermediate b. p. and an index of refraction ranging from 1.5133 (20°) to 1.5155 (25°); and a small high-boiling fraction with a high index of refraction. It may be seen from the table that the low-boiling fraction resembles in properties the main product obtained from the decarboxylation of the crystalline glycidic acid. The high-boiling fraction, on the other hand, has several properties in common with the main product resulting from the crude glycidic acid, except that it exhibits a secondary absorption maximum at 3000 Å.

The results shown in Table I raise the question whether the purified glycidic ester and the glycidic acids derived from it have the same structure as the corresponding crude compounds. The purified glycidic ester was found to have one active hydrogen (Zer.), while the crystalline glycidic acid showed the presence of two active hydrogens. Both the ester and the acid gave a strong ferric chloride reaction, and upon catalytic hydrogenation showed the presence of approximately three double bonds. Furthermore, the ultraviolet spec-

(1) (a) Since this and other work related to the synthesis of vitamin A was under confidential classification during the War, we wish to point out for purposes of priority the existence of two documents deposited in the Office of the Committee on Medical Research of the O. S. R. D. and describing the synthesis of biologically active vitamin A products using the Darzens aldehyde made from β-ionone as the key intermediate. These documents were dated March 6, 1942; (b) Paper No. 3, *Science*, **103**, 581 (1946). For paper No. 2, THIS JOURNAL, **63**, 752 (1941). First presented in part before the North Jersey Section of the A. C. S., April 9, 1945.

(2) Research Associate, 1939–1940. Present address: American Cyanamid Co., Bound Brook, N. J.

(3) Research Associate, 1941–1943. Present address: Warner Institute for Therapeutic Research, New York, N. Y.

(4) Research Assistant, 1941–1942. Present address: Michigan Chemical Company, St. Louis, Michigan.

(5) Research Associate, 1942–1943. Present address: Occidental College, Los Angeles, California.

(6) Research Assistant, 1942–1945. Present address: Royal Bond, Inc., St. Louis 2, Missouri.

(7) Research Associate, 1945–1946. Present address: Tufts College, Medford, Massachusetts.

(8) Milas, U. S. Patents 2,369,156–2,369,168, inclusive, excepting 2,369,158, Feb. 13 (1945); 2,382,085–086, Aug. 14 (1945).

(9) (a) Ishikawa and Matsuura, *Sci. Rep. Tokyo Bunrika Daigaku*, **3A**, 173 (1937); (b) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942); Cymerman, Heilbron, Jones and Lacey, *ibid.*, 500 (1946).

TABLE I

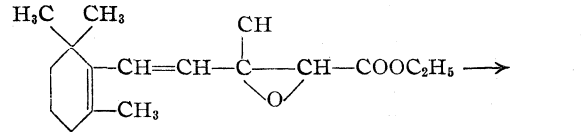
COMPARISON OF PROPERTIES OF FRACTIONS OBTAINED IN THE DECARBOXYLATION OF "β-GLYCIDIC ACIDS"

Decarboxylation product	B. p., °C.	Mm.	n_D	°C.	$\lambda_{max.}$, Å.	$E^{1\%}_{1\ cm.}$	Fuchsin-aldehyde test	M. p. of 2,4-dinitrophenylhydrazone, °C.
Main fraction from crystalline glycidic acid[a]	91–98	2–3	1.5450	25	2380 3150	978 856	Faint (2–3 hr.)	Fails to form
Main fraction from liquid glycidic acid[a]	98–105 49–53	2–3 10^{-4}	1.5320	25	2350	741	Fair (1–2 hr.)	.....
Main fraction from crystalline glycidic acid[b]	106–120	3–4	1.5486	25	2380 3150[d]	661 221	Faint (2–3 hr.)	Fails to form
Main fraction from crude glycidic acid[c]	96–101	2	1.5134	20	2320	996	Strong (0.25–1 hr.)	169–170
Low boiling fraction from crude glycidic acid[c]	79–82	2	1.5450	26	2380 3150	923 645	Faint (2–3 hr.)	Fails to form
High boiling fraction from crude glycidic acid[c]	55–60	10^{-4}–10^{-5}	1.5202	25	2310 3000	737 402	Fair (1–2 hr.)[d]	160.5–162

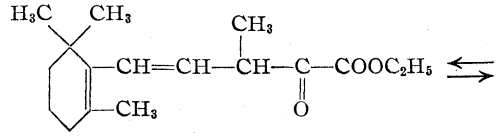
[a] From purified glycidic ester. Decarboxylation was accomplished via the pyridine salt. [b] Same as in (a) except that decarboxylation was accomplished in the presence of copper chips. [c] From crude glycidic acid derived from the condensation without first isolating the pure glycidic ester. [d] Inflection.

trum of both the ester and the acid ($\lambda_{max.}$, 2860 Å.) indicates the presence of three double bonds in conjugation with the ester or carboxyl groups.[10] That spectroscopically the epoxide group is not equivalent to a double bond as Heilbron, *et al.*,[9b] assumed is shown by the spectra of several epoxides (*cf.* structure V)[11] which exhibit maxima in the neighborhood of 2300 Å. In view of these facts we feel that the crude reaction product should be represented by structures I, II and III. The crude glycidic ester and the acids derived from it may be represented mainly by structures I and II while that of the pure glycidic ester and its acids may be represented by structure III. Structure III accounts for all the observed facts for the "crystalline glycidic acid" as well as the large amount of resin produced during its decarboxylation.

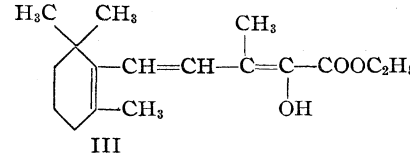
These views are in accord with the original assumption of Darzens[12] who found that under certain conditions even the simple glycidic esters rearrange into the α-ketoesters.



I



II



III

The only product used in the synthesis of biologically active vitamin A substances[13] was that represented by the main fraction from a fractionation of the decarboxylation product of the crude glycidic acid, as it was felt that this, being the largest portion, represented the main product of the reaction. It was therefore essential that the structure of this key intermediate be established with some degree of certainty in order to assign structures to products synthesized in the subsequent steps. The structure of this substance is not very easy to establish since it can be represented by four possible isomeric structures (IVa, IVb, IVc and IVd). Of these, structures IVd can be eliminated since a substance represented by this structure should absorb in the region of 2600–2900 Å.,[14] and no maximum was observed in this region. The fact that our substance responds slowly to the fuchsin aldehyde test and forms phenylhydrazones should place it in the aldehyde class, although isomeric compounds having structures similar to IVa or even isobutylene oxide were found to respond similarly to these reactions. Even the spectrum of IVa, IVb and IVc might conceivably be similar, although that of IVc should have, in addition to a band in the region of 2300 Å., a second or even a third band of higher wave lengths and of lower intensity as observed in the spectra of the known α,β-unsaturated aldehydes.[15] No such a band was found in the purified decarboxylation product which was used in our synthetic experiments, although a small high boiling fraction with an abnormally high index of refraction was found to have an additional band

(10) For an analogous structure of ethyl β-ionylidene acetate, see Young and Linden, THIS JOURNAL, **69**, 2042 (1947).

(11) Milas, MacDonald and Black, THIS JOURNAL, **70**, in press (1948).

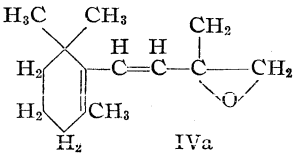
(12) Darzens, *Compt. rend.*, **152**, 443 (1911).

(13) See THIS JOURNAL, **70**, 1591, 1597 (1948).

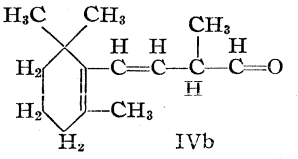
(14) Braude, *Ann. Reports*, **42**, 115 (1945), gives 2630 Å. for sorbaldehyde, which is closely related to structure IVd.

(15) Henri, "International Critical Tables," Vol. V, 1929, p. 372.

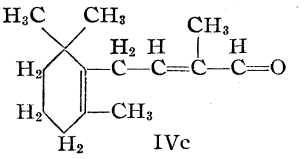
at 3000 Å. It is this fraction which may have structure IVc.



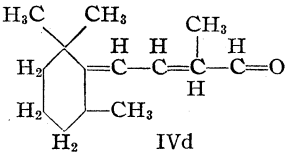
IVa



IVb



IVc



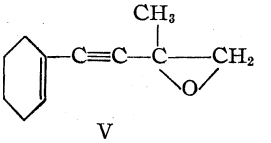
IVd

If our decarboxylation product had structure IVc, as proposed by Heilbron, *et al.*,[9b] it should yield on ozonization 3,3-dimethyloctanedione-2,7, or if the reaction of Böeseken and Jacobs[16] operates in this case, 2,2-dimethyl 6-heptanol-1, both of which are neutral products. No such products were found, but instead, geronic acid was obtained in a yield of about 40%. Since the intermediate product formed upon hydrolysis of the ozonization product should theoretically be a derivative of acetoacetic acid which may oxidize[17] under the conditions of our hydrolytic reaction using small amounts of 30% hydrogen peroxide, we determined the stability of both acetoacetic ester and ethanol under these conditions by measuring the hydrogen peroxide consumed. We have found that the amount of hydrogen peroxide consumed is very small to account for the production of geronic acid from the theoretically possible acetoacetic acid derivative. Furthermore, alcohols are not oxidized rapidly with hydrogen peroxide in the absence of catalysts, and even in the presence of catalysts, glycols have been isolated in good yields.[18] Therefore, if we assume that ozonolysis is a reliable method for determining the structure of organic compounds, we are forced to the conclusion that our main decarboxylation product must have either structure IVa or IVb.

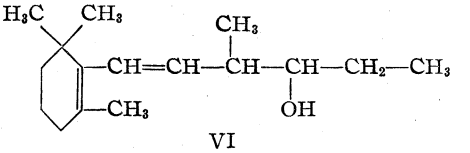
In order to obtain more reliable information concerning the structure of our product, it was necessary to stabilize its functional group by some simple reactions, thereby preventing a possible rearrangement during ozonization. For example, if our product had structure IVc, the addition of lithium acetylide or that of ethylmagnesium bromide should destroy the conjugation, and the ultraviolet absorption spectrum of the resulting carbinols should be that of two isolated double bonds acting individually. Furthermore, both carbinols should yield on ozonolysis 3,3-dimethyloctanedione-2,7 or 2,2-dimethyl-6-heptanol-1 rather than geronic acid. Actually, both carbinols exhibited absorption maxima in the neighborhood of 2260 Å., which indicates the preservation of conjugation. On ozonolysis, both carbinols yielded geronic acid rather than the neutral products mentioned. Again we are forced to the conclusion that the substance from which the carbinols were made must have either structure IVa or IVb.

To decide between structures IVa and IVb, two methods were employed. The synthesis of the epoxide V structurally analogous to IVa was first undertaken.[11] This was found to have similar but not identical properties with those of our key intermediate. It exhibited an absorption maximum at 2320 Å., indicating the presence of a triple and a double bond in conjugation. It responded to the fuchsin-aldehyde test in the same manner but was more reluctant to form a 2,4-dinitrophenylhydrazone than the decarboxylation product. Several attempts to prepare a semicarbazone of the epoxide were entirely unsuccessful. In spite of the fact that some properties of the epoxide resemble those of the decarboxylation product, the evidence is not convincing that the latter has the epoxy structure.

The oxidation of the carbinols derived from the decarboxylation product by the Oppenauer reagent[19] would establish the nature of the hydroxyl group in these carbinols as well as in the vitamin A intermediates.[13] If the carbinols were secondary, ketones would be formed while if they were tertiary no oxidation would be expected to occur. When the unsaturated carbinol VI and its perhydro derivative were actually oxidized with a large excess of aluminum *t*-butoxide, the corresponding ketones were obtained in yields of 79 and 70%, respectively. These results, together with the ozonolysis, seem to establish the structure of the carbinol VI and that of its perhydro derivative.



V



VI

If the decarboxylation product had structure IVb, the acetylene carbinol VII should also be a secondary carbinol and form easily an acid phthalate.[20] Actually, only a small amount could be converted into the acid phthalate, the bulk of the product either remained unchanged or dehydrated into the polyvinylacetylene VIII. Similarly, when 3-nitrophthalic anhydride was used, only a small amount of the acid 3-nitrophthalate was obtained; the remaining product had two bands in

(16) Böeseken and Jacobs, *Rec. trav. chim.*, **55**, 804 (1936).

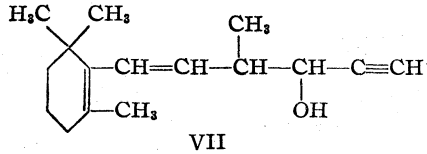
(17) Schaffer and Friedmann [*J. Biol. Chem.*, **61**, 585 (1925)] report that "free acetoacetic acid" resists oxidation with hydrogen peroxide.

(18) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2545 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939).

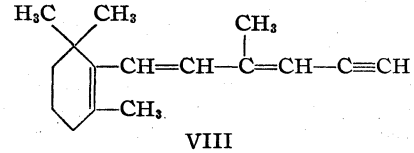
(19) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(20) McGrew and Adams, THIS JOURNAL, **59**, 1497 (1937).

the ultraviolet, one at 2860 Å. and the other at 2260 Å. Even the crude preparation of the acetylene carbinol showed two bands, the 2260 Å. band attributed to the acetylene itself and a band of low intensity at 2860 Å. with an $E^{1\%}_{1\text{ cm.}}$ value of 18–78 attributed to the polyvinylacetylene. The ease with which the acetylene carbinol dehydrates suggests the possibility of the hydroxyl group being tertiary. However, in accordance with the



VII



VIII

Saytzev rule[21] the same polyvinylacetylene will result by the dehydration of either the acetylene VII or its isomer which is derived from the epoxy IVa. Direct dehydration of the acetylene carbinol using various dehydrating agents produced the polyvinylacetylene mixed with isomeric products which were difficult to remove. Dehydrohalogenation of the acetylene halide using quinoline to remove the hydrogen halide failed to remove all of the halogen, indicating that a small portion of the latter was probably attached to the double bond through an allylic shift to the acetylene bond. The pure polyvinylacetylene was obtained only when the chloroacetylene was treated with alcoholic potash and the acetylene hydrocarbon subsequently purified through its silver derivative. The polyvinylacetylene had an $E^{1\%}_{1\text{ cm.}}$ value at 2860 Å. of 760 and showed normal hydrogenation and other properties.

Some of the properties of the acetylene carbinol, however, are not consistent with those expected of a secondary carbinol. For example, when its perhydro derivative was treated with acetyl bromide, it was partly converted into a bromide, indicating the presence of a loosely bound hydroxyl group. Although this derivative resembled in physical properties the perhydro carbinol prepared from the carbinol VI, its chemical properties were somewhat different. When it was treated with excess aluminum *t*-butoxide or with chromic acid in acetic acid solution, a product was obtained which failed to form a solid semicarbazone, phenylthiosemicarbazone, or 2,4-dinitrophenylhydrazone. In spite of the fact that the product underwent a change in some of its properties, such as reduction of active hydrogen, increase of unsaturation (with aluminum *t*-butoxide), it was difficult to isolate any pure component from it other than recovering the original product. Therefore, the perhydroacetylene carbinol seems to show properties which cannot be entirely reconciled with the view that the hydroxyl group in this derivative is a secondary hydroxyl, in spite of the fact that the original acetylene carbinol formed a 3-nitrophthalate, which is not usually formed by tertiary carbinols under the conditions employed. At present we cannot explain this anomaly.

Heretofore, the decarboxylation of glycidic acids in general has always led to the production of aldehydes or ketones; the epoxy intermediates which are theoretically possible have never been isolated.[22] Furthermore, authentic epoxides[11] related to structure IVa have been found to have somewhat different properties than those shown by the main decarboxylation product. Therefore, we feel strongly at present that of all the structures considered, structure IVb seems to account best for the properties of our main decarboxylation product, although on standing for long periods of time, it may slowly rearrange to the structure IVc.

Table II summarizes the spectroscopic data of the important substances mentioned in this investigation.

TABLE II

SUMMARY OF ULTRAVIOLET ABSORPTION SPECTRA DATA (IN ALCOHOL)

Compound	$\lambda_{max.}$, Å.	$E^{1\%}_{1\text{ cm.}}$	log $\epsilon_{mol.}$
Hydroxy ester III	2860	793	4.34
Hydroxy acid (crystals) from III	2860	1363	4.53
Main decarboxylation product IV from crude glycidic ester	2320	996	4.31
Semicarbazone of IV	2660	1375	4.56
2,4-Dinitrophenylhydrazone of IV	3800	859	4.52
	2560	550	4.33
Product IV (high boiling fraction)	2310	737	4.18
	3000	402	3.92
2,4-Dinitrophenylhydrazone of high boiling fraction	3800	853	4.52
	2560	506	4.28
Epoxy V	2320	1281	4.32
Carbinol VI	2260	264	3.79
Acetylene carbinol VII	2260	407	3.98
3-Nitroacidphthalate of VII	2260	746	4.50
Ketone from VI	2340	469	4.05
Semicarbazone of ketone from VI	2660	1019	4.40
Polyvinylacetylene VIII	2860	760	4.21
	3050[a]	404	3.94

[a] Inflection.

Experimental

β-Ionone.—Three different methods have been used in this Laboratory for the purification of β-ionone. Although the bisulfite and semicarbazone methods were used for small quantities, fractionation under reduced pressure was resorted to for the purification of larger quantities. The commercial grade (Maywood) of β-ionone (n^{25}D 1.5155–1.5162) was fractionated in quantities

(21) Saytzev, *Ann.*, **179**, 300 (1875); Thoms and Mannich, *Ber.*, **36**, 2544 (1903).

(22) Bodforss, "Sammlung Chemische-technischer Vortrage," Vol. XXVI, 1922, p. 145.

of 1–2 kg. under a constant reduced pressure maintained between 10 and 18 mm. through a four-foot packed fractionating column of about 25 theoretical plates using a reflux ratio of about 5:1. The purity was followed by measuring the index of refraction of every fraction. Those between 1.5168–1.5180 (25°) were collected and refractionated and the fractions boiling 124–126° (10 mm.), or 133–134° (13 mm.), or 135–137° (15 mm.), or 142–143° (18 mm.), collected. These had $n^{25}D$ between 1.15172 and 1.5182 and d^{20}_4 of 0.944 and 0.9442 and $\epsilon_{mol.}$ (2950 Å.) between 10,500–11,000. In the majority of our syntheses, the β-ionone used had an $n^{25}D$ >1.5175. Recently through the courtesy of the du Pont Company we received a generous sample with an $n^{25}D$ 1.5185.[23]

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methyl-4-hydroxypentadien-1,3-oic Ethyl Ester-5 (I, II, III).—This compound was prepared over fifty times under a variety of conditions by several members of our group. A representative procedure embodying our latest modifications follows: A mixture of 184 g. (1.5 moles) of ethyl chloroacetate (b. p. 142–143° at 750 mm.), 96 g. (0.5 mole) of β-ionone and 135 g. of dry thiophene-free toluene was cooled between −50 and −60° in a three-necked flask supplied with a stirrer, a dropping funnel, a thermometer, a nitrogen inlet and a long Gooch tube attached to a flask containing 56.7 g. (1.05 moles) of alcohol-free sodium methoxide.[24] A little over one-half of the sodium methoxide was slowly added with vigorous stirring in the course of one-half hour, then an additional 96 g. (0.5 mole) of β-ionone was added dropwise in the course of one-half hour alternately with the remainder of the sodium methoxide. The mixture was then packed at −50° and allowed to stir gently overnight at the same time warming up slowly to room temperature. The mixture was then heated in nitrogen on the water-bath for four hours, then cooled quickly to −5° and maintained at this temperature while the aqueous solution of 500 cc. of tartaric acid containing 90 g. of the latter was added to it. The toluene layer was separated, washed with water, dried, and the toluene and excess ethyl chloroacetate removed on the water-bath under reduced pressure. The brown residue was fractionated in nitrogen and the fraction (190 g.) boiling at 152–157° (2 mm.) refractionated and the final fraction (178 g.) boiling at 154–156° (2 mm.) collected; $n^{25}D$ 1.5293; $E^{1\%}_{1\ cm.}$ (2860Å.), 793; log $\epsilon_{mol.}$ 4.34.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.18; H, 9.39; unsaturation, 3 ⌐¬; active hydrogen (Zer.), 1. Found: C, 73.5, 73.3; H, 8.80, 9.61; unsaturation, 3.19 ⌐¬ (Pt); active hydrogen (Zer.), 1.08.

In alcoholic solution, the ester gives an immediate green color with ferric chloride, indicating the presence of an enol form.

Crystalline Hydroxy Acid from Ester (III).—The pure hydroxy ester (158 g.) was hydrolyzed in the usual manner with alcoholic potash, then the mixture diluted with two volumes of water and extracted several times with petroleum ether to remove non-saponifiable materials. The water layer was then neutralized with dilute phosphoric acid and extracted with ether. Since the ester is strongly enolic, it can be retained by the alkali in the aqueous layer. The ethereal solution was therefore extracted with excess sodium bicarbonate solution, and the hydroxy acid recovered by acidification with dilute phosphoric acid. The crude acid thus obtained was dissolved in the least volume of ether and to the solution was added enough petroleum ether until a cloudiness resulted. The mixture was allowed to stand at 0° for several days, whereby a solid acid separated out. By repeating the process several times and recrystallizing the solid each time from similar solvent mixtures, a total of 44 g. of crystalline acid m. p. 150–150.2° (dec.),[25] and 78 g. (combined total of 86% yield) of liquid acid from which no more crystals could be obtained by any means tried. The crystalline acid is also strongly enolic; it gives a greenish coloration with ferric chloride and has two (1.99, 2.09, 2.15) active hydrogen atoms (Zer.), and an unsaturation of 2.74 double bonds. It also has an $E^{1\%}_{1\ cm.}$ (2850 Å.) value of 1363; log $\epsilon_{mol.}$ 4.53. Calcd. N. Eq. for $C_{15}H_{22}O_3$, 250. Found: 255, 256.

The liquid acid showed similar properties.

Decarboxylation of the Crystalline Acid (Pyridine Method).—In a Claisen flask attached to a 6 inch Vigreux was placed 50 g. of crystalline glycidic acid and to it was added 60 cc. of pure anhydrous pyridine. Some of the excess pyridine was removed by distillation under reduced pressure, then decarboxylation was allowed to proceed in nitrogen and under ordinary pressures at 130–135° for about one to two hours. The mixture was then subjected to a vacuum distillation and the product distilling at 80–125° (2 mm.) collected. A large amount of resin was also formed. The crude distillate was washed in petroleum ether several times with sodium bicarbonate solution, then fractionated under reduced pressure and the fraction boiling at 91–98° (2–3 mm.) collected; $n^{25}D$ 1.5450. This product failed to give the fuchsin-aldehyde test except on long (two to three hours) standing when a faint purplish color developed. It slowly reduced ammoniacal silver nitrate solution, and gave no solid semicarbazones or phenylhydrazones. It gave a negligible (0.12) active hydrogen (Zer.) and showed an unsaturation of 4.1 double bonds. The ultraviolet absorption spectrum showed two bands; one at 2380 Å., $E^{1\%}_{1\ cm.}$ .978, and one at 3150 Å., $E^{1\%}_{1\ cm.}$ 856.

A less pure product was obtained when 10 g. of the crystalline acid was decarboxylated in the presence of clean copper chips. This product had exactly the same properties as the one above except its $E^{1\%}_{1\ cm.}$ value at 2380 Å. was 661 and at 3150 Å., 221.

Decarboxylation of the Liquid Acid.—The liquid acid (124 g.) separated from the crystalline acid was mixed with 150 cc. of pyridine and after removal of the excess pyridine, decarboxylation was effected at 130 to 135°. When decarboxylation was over, the mixture was distilled in nitrogen at 76–135° (2–3 mm.). The crude product was shaken several times with sodium bicarbonate solution, and, after drying, fractionated twice using a 6-inch Vigreux column and a fraction boiling at 98–105° (2–3 mm.) or 49–53° (10^{-4} mm.) collected. This product had the following properties: $n^{25}D$ 1.5320, negligible active hydrogen (0.07) and an unsaturation of 2.32 double bonds. It gave a fair fuchsin-aldehyde test and reduced ammoniacal silver nitrate solution. It showed a band in the ultraviolet at 2350 Å. with an $E^{1\%}_{1\ cm.}$ value of 741.

Decarboxylation without Isolation of the Glycidic Ester (Commonly used in the Various Syntheses).—In the preparation of the glycidic acid, the crude ester prior to its fractionation was dissolved in 10% alcoholic potash and the mixture allowed to stand in nitrogen overnight, then heated on the water-bath for two hours under slightly reduced pressure to remove about one-third of the alcohol. The mixture was then cooled and diluted with three volumes of water and extracted several times either with ether or petroleum ether[26] to remove unsaponifiable matter. The aqueous layer was then acidified with 10% phosphoric acid and extracted several times with ether. The ether extracts were dried and the ether removed under reduced pressure. The crude glycidic acid was then mixed with excess pyridine (2 moles per mole of glycidic acid) and decarboxylated at 130–135°

(23) Determined in our Laboratory.

(24) Best results were obtained when the residual methanol in sodium methoxide was removed under reduced pressure at about 70–80°. Sodium ethoxide treated the same way gives identical results. Sodamide gives much lower yields of the final product.

(25) The decomposition point was determined by the method of Cocker and Lapworth, *J. Chem. Soc.*, 1398 (1931).

(26) β-Ionone dissolves in alkali to give red solutions, but it can be extracted to the extent of 98% with petroleum ether or ethyl ether.

in the usual manner. When decarboxylation was over, the resulting mixture was fractionated under reduced pressure and the fraction boiling up to 135° (2–3 mm.) collected and treated several times with sodium bicarbonate; yield of crude product, 40–60%, a variation of several experiments. The crude product was refractionated twice using a 6-inch Vigreux and the largest fraction with an acceptable index of refraction was used for synthetic purposes. The results of a representative final fractionation are given in Table III.

TABLE III

FINAL FRACTIONATION OF THE DECARBOXYLATION PRODUCT FROM THE CRUDE GLYCIDIC ACID

Wt., g.	B. p. (≤ 1 mm.) °C.	$n^{24}D$
32	<86	1.5330
74	86–89	1.5144
7	90–137	1.5234

The middle fraction was used for synthetic and analytical purposes. Yields of the pure product varied from 19–30% not including products obtained from refractionations of the low and high boiling fractions. The specific fraction given above had a d^{25}_{25} 0.956, and an $E^{1\%}_{1\ cm.}$ (2320 Å.) value of 967.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; unsaturation, 2.0 ⌐; active hydrogen (Zer.), 0.0. Found: C, 81.90, 81.49; H, 11.2, 10.75; unsaturation, 3.38, 3.01, 3.43 (Pt), 1.91 (Pd) ⌐; active hydrogen (Zer.), 0.12, 0.07.

This product gave a strong fuchsin-aldehyde test only after fifteen minutes to one hour of standing, and reduced alcoholic ammoniacal silver nitrate solution. The semicarbazone, m. p., 149.5–150.5° (from 50% alcohol), $E^{1\%}_{1\ cm.}$ (2660 Å.), 1375; the thiosemicarbazone, m. p., 156–159° (from alcohol); and the 2,4-dinitrophenylhydrazone, m. p., 169–170° (from alcohol), $E^{1\%}_{1\ cm.}$ (2560 Å.), 550, $E^{1\%}_{1\ cm.}$ (3800 Å.), 859 were prepared from this product. In all cases the production of these derivatives was slow and the yields were low.

When appreciable quantities of the low and high boiling fractions were collected, they were fractionated several times and the main fractions separated. They had the following properties.

Low Boiling Fraction.—B. p., 79–82° (2 mm.); $n^{26}D$ 1.5450; $E^{1\%}_{1\ cm.}$ (2380 Å.), 923, $E^{1\%}_{1\ cm.}$ (3150 Å.), 645. It gave a negative fuchsin-aldehyde test (faint purple color developed after two to three hours). After long standing it reduced alcoholic ammoniacal silver nitrate solution. It failed to form solid semicarbazone and nitrophenylhydrazones. This product was not investigated further.

High Boiling Fraction.—B. p. 113–115° (1.5 mm.), 55–60° (10^{-4}–10^{-5} mm.), $n^{25}D$ 1.5202; $E^{1\%}_{1\ cm.}$ (2310 Å.), 737, $E^{1\%}_{1\ cm.}$ (3000 Å.), 402. It gave a positive fuchsin-aldehyde test (one to two hours) and reduced alcoholic ammoniacal silver nitrate solution. 2,4-Dinitrophenylhydrazone, m. p. 161–162° (from alcohol); mixed m. p. with 2,4-dinitrophenylhydrazone of the main fraction, 160.5–166°. Like the 2,4-dinitrophenylhydrazone of the normal decarboxylation product, this derivative showed two maxima in the ultraviolet with values of $E^{1\%}_{1\ cm.}$ (2560 Å.), 506 and $E^{1\%}_{1\ cm.}$ (3800 Å.) 853, respectively. The parent product gave the following analyses:

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; unsaturation, 2.0 ⌐; active hydrogen (Zer.), 0.0. Found: C, 81.2, 81.3; H, 10.4, 10.4; unsaturation, 2.27 ⌐; active hydrogen (Zer.), 0.12.

Ozonization of Aldehyde (main product IV).—About 4 g. of aldehyde IV was ozonized following the method of Strain[27] and the 2,4-dinitrophenylhydrazone precipitated. The precipitate was almost completely soluble in sodium bicarbonate solution from which the crude 2,4-dinitrophenylhydrazone of geronic acid was precipitated by the addition of 20% potassium bisulfate. A yield of about 40% calculated as geronic acid was obtained at this stage, having a m. p. of 115–120°. This was recrystallized several times from aqueous acetic acid, from aqueous methanol and finally from cyclohexane; m. p. 131–132.5° (cor.). A mixed m. p. with an authentic sample of the geronic acid derivative gave a m. p. of 132–133.5° (cor.).

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexen-1-ol-4 (VI).—A Grignard was prepared from 5.8 g. of ethyl bromide and 1.3 g. of magnesium in about 150 cc. of anhydrous ether. To this was added 10 g. of the normal decarboxylation product ($n^{24}D$ 1.5144). When the Grignard reaction mixture was hydrolyzed and the product fractionated under a reduced pressure using a 6-inch Vigreux, a carbinol (8 g.) was obtained which boiled at 66–68° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.5020; $E^{1\%}_{1\ cm.}$ (2260 Å.) 264.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.29; H, 11.94; unsaturation, 2.0 ⌐; active hydrogen (Zer.), 1.0. Found: C, 81.00, 81.30; H, 11.80, 12.00; unsaturation, 2.3, 2.4 ⌐; active hydrogen (Zer.), 0.90, 0.95, 0.97.

Ozonization of Carbinol VI.—About 2.8 g. of carbinol VI was ozonized as before and the 2,4-dinitrophenylhydrazone precipitated, extracted with sodium bicarbonate and reprecipitated; yield of the crude bicarbonate soluble product, about 35%. This was purified as in the previous case, m. p. 133.5–134.5° (cor.). A mixed m. p. with an authentic sample of the geronic acid derivative showed no significant depression.

Oxidation of Carbinol VI with Aluminum *t*-Butoxide.—The carbinol (2.8 g.) was oxidized in a mixture of 70 cc. of anhydrous, thiophene-free benzene and 40 cc. of pure, freshly distilled acetone with 4 g. (large excess) aluminum *t*-butoxide[16] by refluxing the mixture on the water-bath in an atmosphere of nitrogen for fourteen hours. The crude product was isolated in the usual manner and distilled at a pressure of 10^{-4} mm. in a molecular still of the falling film type using a heating liquid (mixture of ethanol and carbon tetrachloride) which boiled at 65.2°. The largest fraction (79%) obtained had the properties: $n^{25}D$ 1.5033; $E^{1\%}_{1\ cm.}$ (2340 Å.), 469; active hydrogen (Zer.), 0.19, 0.22. A semicarbazone was prepared from it, m. p. 167.5–169° (from 50% alcohol); $E^{1\%}_{1\ cm.}$ (2660 Å.), 1019.

Anal. Calcd. for $C_{17}H_{29}ON_3$: C, 70.06; H, 10.03. Found: C, 70.11; H, 10.05.

Reduction of Carbinol VI to the Perhydrocarbinol.—To avoid hydrogenolysis with platinum oxide as catalyst, the carbinol (8 g.) was first reduced in alcohol using Raney nickel (0.16 g.) for sixteen hours under a hydrogen pressure of 7–12 pounds. Complete hydrogenation was effected in the same solvent (minimum hydrogenolysis is known to occur in alcohol) for several days using platinum oxide as catalyst. The product was finally recovered and fractionated using a 6-inch Vigreux and the fraction boiling at 58–59° (10^{-4}–10^{-5} mm.) collected; $n^{25}D$ 1.4838; active hydrogen (Zer.), 0.96.

Oxidation of the Perhydrocarbinol with Aluminum *t*-Butoxide.—When this carbinol was oxidized with excess aluminum *t*-butoxide using the same procedure as above, a product was obtained boiling at 44–50° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.4855; active hydrogen (Zer.), 0.25; semicarbazone, m. p. 165–166° (from 75% ethanol, 25% water); 2,4-dinitrophenylhydrazone, m. p. 111–114° (from alcohol).

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methyl-4-hydroxyhexen-1-yne-5 (VII).—After a number of trials using calcium and sodium acetylide in liquid ammonia, and sodamide in ether, it was found that lithium acetylide gave the best yields of the acetylene carbinol VII. Into a 3-necked, round-bottomed flask provided with a stirrer, a dropping funnel and an inlet tube and externally cooled

(27) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

to −60°, was condensed 1.5 liters of ammonia. The liquid ammonia was then saturated with dry acetylene and, while stirring and the latter passing through the solution, 3.1 g. of small pieces of metallic lithium was added in the course of two hours. When the color of the mixture turned gray, the latter was cooled to −70° and to it was added dropwise in the course of one hour 80 g. of the aldehyde IV in 80 cc. of dry ether while acetylene was still passing through the solution. Stirring and cooling to −70° was continued overnight then the cold-bath was removed, the ammonia slowly expelled and the mixture allowed to warm up to 0°. At this temperature 500 cc. of dry ether was added and the mixture acidified with 80 g. of tartaric acid in 120 cc. of water. The ether layer was then separated, washed with a 10% salt solution, dried and the ether removed. The residue was fractionated twice under reduced pressure using a 3-inch Vigreux and the fraction (67 g., 83.8% yield) boiling at 69–72° (10^{-4} mm.) collected; $n^{25}D$ 1.5122; d^{25}_{25} 0.9538; M_D (calcd.), 72.48; found, 73.02; $E^{1\%}_{1\ cm.}$ (2260 Å.), 407. Crude samples of the acetylene carbinol had an additional band of low intensity with a maximum at 2860 Å.; $E^{1\%}_{1\ cm.}$, 18–78.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41; unsaturation, 4.0 ⌐; active hydrogen (Zer.), 2.0. Found: C, 82.28; H, 10.30; unsaturation, 4.01, 4.07, 4.39 ⌐ (Pt), 3.83, 3.95 ⌐ (Pd); active hydrogen (Zer.), 2.01, 2.06, 1.91, 1.99.

The acetylene carbinol formed a silver derivative which exploded on rubbing and on the hot plate. This derivative was purified from benzene by precipitation with methanol.

Anal. Calcd. for $C_{16}H_{23}OAg$: Ag, 31.8. Found: Ag, 31.5.

The acetylene carbinol also formed a solid acid 3-nitrophthalate[17] in low yields (7–10%); m. p. 149.5–150° (methanol); $E^{1\%}_{1\ cm.}$ (2260 Å.), 746.

Anal. Calcd. for $C_{24}H_{27}O_6N$: C, 67.76; H, 6.40; unsaturation (including benzene ring and nitro group), 9.0 ⌐. Found: C, 68.14; H, 6.61; unsaturation, 9.24 ⌐ (Pt).

The recovered product from this reaction had a spectrum with maxima at 2260 Å., $E^{1\%}_{1\ cm.}$ 254, and at 2860 Å., $E^{1\%}_{1\ cm.}$ 141.

With phosphorus tribromide in pyridine at 0° the acetylene carbinol formed a bromide which retained its acetylene properties; b. p. 53–56° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.5413; d^{25}_{25} 1.076.

Anal. Calcd. for $C_{16}H_{23}Br$: Br, 27.12. Found: Br, 27.0.

The acetylene carbinol also formed a chloride with thionyl chloride in pyridine at 0°. This reaction, however, caused a slight dehydrochlorination since the percentage of chlorine was found to be slightly lower than the theoretical and the product gave, in addition to the 2260 Å band, the 2860 Å. band which is characteristic of the polyvinyl acetylene.

Anal. Calcd. for $C_{16}H_{23}Cl$: Cl, 14.13; active hydrogen (Zer.), 1.0. Found: Cl, 12.64, 12.57; active hydrogen (Zer.), 0.74.

Ozonization of Acetylene Carbinol VII.—About 4.97 g. of acetylene carbinol was ozonized as in the previous cases and the 2,4-dinitrophenylhydrazone precipitated. The precipitate was extracted with sodium bicarbonate and reprecipitated with 20% potassium acid sulfate solution. A yield of about 41% of the crude product calculated as geronic acid was obtained, m. p. 118–123°. This was recrystallized as before, using aqueous acetic acid, aqueous methanol and cyclohexane; m. p. 133–134° (cor.). A mixed m. p. with an authentic derivative of geronic acid showed no depression.

Perhydroacetylenecarbinol.—Acetylene carbinol (10 g.) was hydrogenated in 200 cc. of absolute ethanol in the presence of Raney nickel (0.2 g.) with shaking and under a 15-lb. hydrogen pressure for two days. The product was recovered and found to be still unsaturated, so it was further hydrogenated for several days in alcohol with shaking using platinum oxide (0.12 g.) as catalyst. Finally, the completely saturated carbinol was recovered and fractionated and the fraction (8.5 g.) boiling at 62–66° (10^{-4} mm.) collected and analyzed; $n^{25}D$ 1.4830.

Anal. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.40; active hydrogen (Zer.), 1.0. Found: C, 79.50; H, 13.03; active hydrogen (Zer.), 0.91, 0.81, 0.94.

Oxidation of Perhydroacetylenecarbinol with Aluminum *t*-Butoxide.—A solution of perhydroacetylenecarbinol (0.8 g.) in 25 cc. of anhydrous acetone and 30 cc. pure benzene was heated to 85° then a solution of 2.5 g. of aluminum *t*-butoxide in 25 cc. of benzene was quickly added and the mixture refluxed for eighteen hours. The product was then recovered in the usual manner and distilled under a reduced pressure, b. p. 38–42° (10^{-5} mm.); $n^{25}D$ 1.4848; active hydrogen (Zer.), 0.48; unsaturation, 1.53 ⌐. This product failed to give a solid semicarbazone, phenylsemicarbazone or 2,4-dinitrophenylhydrazone.

Oxidation of Perhydroacetylenecarbinol with Chromic Acid.—About 3 g. of the perhydroacetylenecarbinol was oxidized with chromic acid (1.1 g.) in glacial acetic acid (60 cc.) and 7 cc. of water at 35–40°. The product was recovered and fractionated and the fraction (2.5 g.) boiling at 37–43° (10^{-5} mm.) collected. This had an active hydrogen of 0.21 and an unsaturation of 1.64 ⌐. This product failed to yield a solid semicarbazone, phenylsemicarbazone, or 2,4-dinitrophenylhydrazone. These results seem to indicate that this perhydroacetylenecarbinol is not identical with the perhydrocarbinol obtained from the carbinol VI.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexadien-1,3-yne-5.—Attempts to make this polyvinylacetylene by the direct dehydration of the acetylene carbinol VII using aluminum phosphate at 250–300° or distilling it from small amounts of *p*-toluenesulfonic acid or mixtures of this acid with various anhydrides (acetic, succinic, etc.), or with *p*-toluenesulfonic acid in toluene at 110°, gave very poor yields and much polymerization. Even when the salt-Grignard of the acetylene carbinol was treated with one mole of anhydrous *t*-butyl alcohol and the resulting product distilled under a highly reduced pressure, the yields of the polyvinylacetylene were poor.

Dehydrobromination of the acetylene bromide with quinoline under various conditions failed to remove all of the bromine from the molecule. Even when the acetylene bromide was refluxed with quinoline for long periods of time, the product formed, when fractionated, contained from 6 to 7% bromine. The bromine could easily be removed by refluxing with alcoholic potash, but the product formed had rather low active hydrogen (Zer.).

Dehydrochlorination of the acetylene chloride with alcoholic potash was much more successful. Into 200 cc. of 95% alcohol containing 23 g. of potassium hydroxide under a gentle reflux in an atmosphere of nitrogen was added in the course of fifteen minutes 51.5 g. of acetylene chloride in an equal volume of alcohol. Gentle refluxing was continued for one and one-half hours longer, then about one-third of the alcohol was removed under reduced pressure and the mixture cooled and diluted with two volumes of water. It was then extracted with 3 × 100 cc. of olefin-free petroleum ether and the extract dried and the solvent removed. The residue was distilled under a highly reduced pressure and a product (33 g.) was obtained boiling at 53–56° (10^{-4}–10^{-5} mm.). This was free from chlorine and had an active hydrogen (Zer.) of 0.7 and a hydrogenation number of 4.34 ⌐. Further purification was effected by preparing its silver derivative in alcoholic ammoniacal silver nitrate solution. The silver derivative of the polyvinylacetylene precipitates rapidly while that of the acetylene carbinol comes down very slowly, and this difference in the precipitation rate made the separation of the two possible. The polyvinylacetylene was recovered from its silver derivative by sus-

pending the latter in petroleum ether and either passing through it hydrogen sulfide or adding ammonium thiocyanate. The polyvinylacetylene was recovered and distilled under reduced pressure and the fraction boiling at 55–60° (10^{-4}–10^{-5} mm.) collected and analyzed. It had an ultraviolet absorption spectrum with a maximum at 2860 Å., $E^{1\%}_{1\ cm.}$ 760 and an inflection at 3050 Å., $E^{1\%}_{1\ cm.}$, 404.

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35; active hydrogen (Zer.), 1.0; unsaturation, 5.0 ⊨. Found: C, 88.5; H, 10.1; active hydrogen (Zer.), 0.96; unsaturation, 4.78, 4.95 ⊨.

The polyvinylacetylene is very unstable and darkens on standing, even under nitrogen.

Acknowledgment.—The authors are indebted to Mrs. Alice R. Lowry, Mrs. Silvia P. Solar, Miss Margaret A. Campbell, Miss Zelma Weiss, and Mr. S. M. Nagy for the analyses given in this paper, also to Drs. Henry Rapoport and John N. Ingraham for assistance in some of the early experiments, and to Miss Therese M. Harrington for assisting in the ozonolysis experiments. This article is a part of a research program on the synthesis of vitamins A and D, support of which was derived in part through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Parke, Davis and Company, The Upjohn Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

Summary

1. The application of the Darzens synthesis to β-ionone gives 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylbuten-1-al-4 as the main decarboxylation product.

2. Ozonolysis of the main decarboxylation product and other products derived from it yielded geronic acid, showing the presence of the β-ionone ring and a double bond in conjugation with this ring.

3. 1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexen-1-ol-4, its perhydro derivative and their corresponding ketones have been synthesized from the main decarboxylation product.

4. 1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methyl-4-hydroxyhexen-1-yne-5, its perhydro derivative and 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylhexadien-1,3-yne-5 were also synthesized.

5. The absorption spectra of all the products synthesized were determined and correlated with their structure.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 12, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. V. The Synthesis of [1-(2′,6′,6-Trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5,7-tetraenyl]-10-ethyl Ether[1]

BY NICHOLAS A. MILAS, S. WARREN LEE,[1a] CONRAD SCHUERCH, JR., RICHARD O. EDGERTON,[2] JOHN T. PLATI,[3] FRANK X. GROSSI,[4] ZELMA WEISS[5] AND MARGARET A. CAMPBELL[6]

The synthesis of [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5,7-tetraenyl]-10 ethyl ether[7] or simply homovitamin A ethyl ether (I) and [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5-trien-5-ynyl]-10-ethyl ether or simply 5-dehydrohomovitamin A ethyl ether (II) was undertaken in the early days of our investigation in this field to provide model studies for the corresponding derivatives of the vitamin A itself.

In the first step of this synthesis, 5-ethoxypentanone-2 was prepared from acetoacetic ester by a modification of the procedure of Clarke and Gurin,[8] and was then converted, in liquid ammonia with sodium acetylide or in *t*-butyl alcohol with potassium acetylide, to 3-methyl-6-ethoxyhexa-1-yn-3-ol (III) which was dehydrated over hot aluminum phosphate to 3-methyl-6-ethoxyhexa-3-en-yne-1 (IV).

For the synthesis of 5-dehydrohomovitamin A ethyl ether, the acetylene carbinol (III) and the vinylacetylene (IV) were allowed to react via their Grignard reagents[9] with 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3 methylbuten-1-al-4 (V)[10] to produce, in the first case, the glycol (VI) and, in the second case, the carbinol (VIII). Both of these compounds were successfully dehydrated, with small amounts of *p*-toluenesulfonic acid in toluene, to 5-dehydrohomovitamin A ethyl ether.

The acetylene glycol (VI) had an absorption maximum at 2200–2230 Å. characteristic for a

(1) Since this and other work related to the synthesis of vitamin A was under confidential classification during the War, we wish to point out for purposes of priority the existence of two documents deposited in the Office of the Committee on Medical Research of the O. S. R. D. and describing the synthesis of biologically active vitamin A products using the Darzens aldehyde made from β-ionone as the key intermediate. These documents were dated March 6, 1942.

(1a) Research Associate, 1939–1940. Present address, American Cyanamid Co., Bound Brook, N. J.

(2) Research Associate, 1940–1941. Present address, Eastman Kodak Co., Rochester, N. Y.

(3) Research Associate, 1940–1942. Present address, Hoffman-LaRoche, Nutley, N. J.

(4) Research Assistant, 1942–1945. Present address, Royal Bond, Inc., St. Louis, Mo.

(5) Research Assistant, 1943–1945.

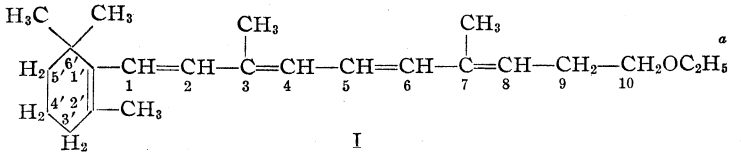
(6) Research Assistant, 1945–1946. Present address, Arthur D. Little, Inc.

(7) Milas, U. S. Patent 2,369,159, Feb. 13, 1945.

(8) Clarke and Gurin, THIS JOURNAL, **57**, 1876 (1935).

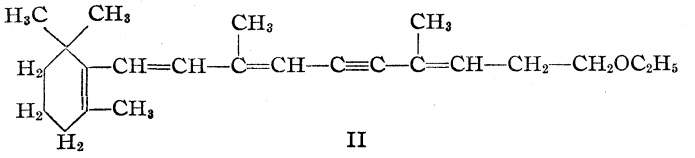
(9) Nesty and Marvel, *ibid.*, **59**, 2662 (1937); Marvel, Mozingo and Kirkpatrick, *ibid.*, **61**, 2003 (1939); Alderson, Ph.D. Thesis, M. I. T., 1939.

(10) Milas, *et al.*, THIS JOURNAL, **70**, 1584 (1948).



I

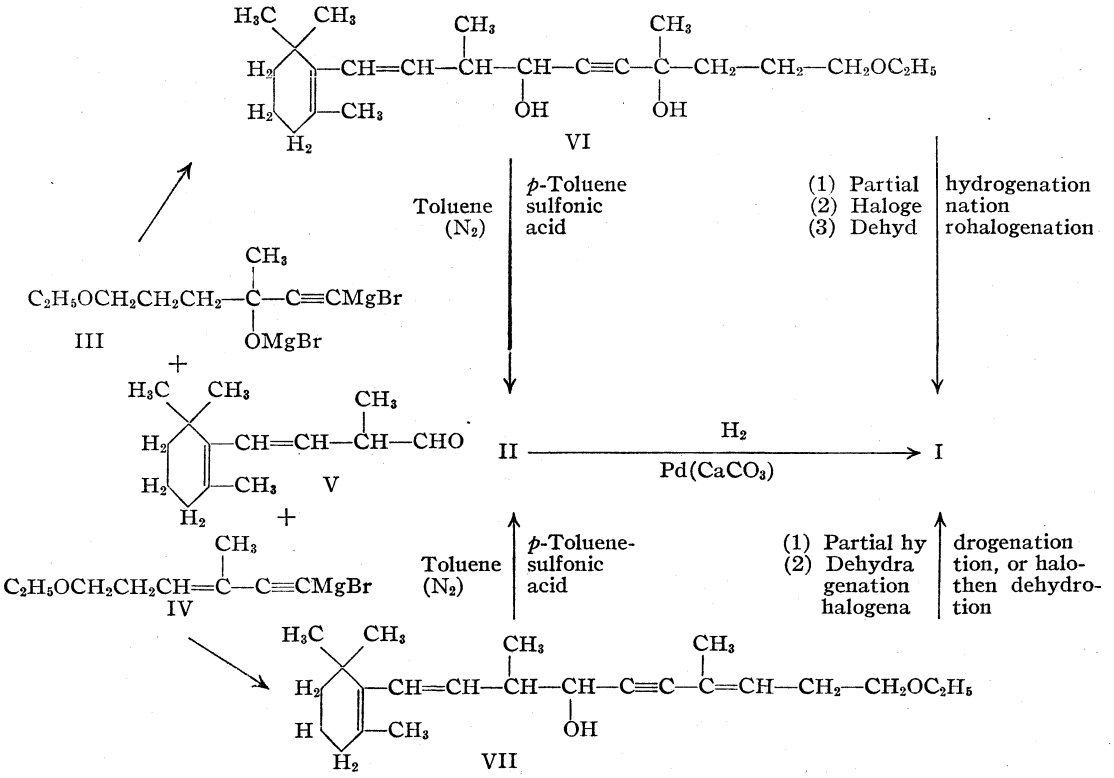
[a] The nomenclature and numbering adopted in this and all subsequent papers of this series is so chosen as to indicate the increase in the carbon side chain and to keep the same numbers present in this chain, irrespective of the increase in the number of carbon atoms, thus facilitating the naming of the intermediate compounds in this field.



II

conjugated system of two double bonds. The existence in the carbinol (VII) of two conjugated systems separated by saturated groups does not seem to have any appreciable effect on the position of the absorption band[11] which appears at 2330 Å.

acid. The crude product obtained from both the glycol VI and carbinol VII, upon a single distillation at pressures $10^{-4}-10^{-5}$ mm., exhibits two bands; one at 3160–3200 Å. and another at 2850–2900 Å. If distillation as a method of purification was repeated several times, the final distillate showed only the 2850–2900 Å. band, and each distillation produced considerable resinification. Other methods were therefore resorted to for the purification of the final products. After a single distillation, the dehydrated product from the carbinol VII was first partitioned between petroleum ether and 90% methanol followed by chromatographic adsorption of the petroleum ether soluble portion on activated alumina. The unadsorbed portion showed a single band at 3210 Å. (Fig. 1, curve A) and gave a blue color with antimony trichloride with absorption maxima at 6220 and 5800 Å. A sample of 5-dehydrohomovitamin



The absorption spectrum of 5-dehydrohomovitamin A ethyl ether (Fig. 1, curves A and C) bears a strong resemblance to that of vitamin A except that it is displaced toward the ultraviolet by about 40 Å., if we take 3250 Å. as the value for the maximum band of natural vitamin A. Both of these substances have been made by dehydration in toluene using catalytic amounts of *p*-toluenesulfonic

(11) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

A ethyl ether obtained by the dehydration of the carbinol VII and distilled once under high vacuum was tested biologically by Professor Robert S. Harris of the Nutritional Laboratories of this Institute. He reported that when fed to vitamin A deficient rats in doses of 98γ per day, it cured xerophthalmia and caused an average weight increase per rat of 32 g. for the 28-day test period.

Similarly, the dehydrated product from the gly-

col VI, after a single distillation, was partitioned and the petroleum ether soluble portion fractionated at low temperatures using absolute methanol as the solvent. The fraction insoluble in methanol below −30° solidified at about −40° but failed to remain solid at higher temperatures. This product exhibited a single band at 3210 Å. (Fig. 1, curve C), while the methanol soluble portion had both the 2850–2900 and the 3160–3200 Å. bands.

When one mole of hydrogen was added to glycol VI in alcohol using 1% palladium hydroxide on calcium carbonate, the ethylenic glycol VIII was produced. This glycol was treated with pyridine hydrobromide in a large excess of pyridine and the product formed dehydrobrominated with alcoholic potash. The final product was partitioned and the petroleum ether portion chromatographed using activated alumina. The unadsorbed portion was distilled once through a molecular still of the falling film type, and the largest fraction showed an absorption maximum at 3280 Å. (Fig. 1, curve B), and a faint inflection at 3670 Å. From the experimental evidence on hand, it is difficult to decide, at present, whether this product is identical in every respect with the homovitamin A ethyl ether produced by other methods used in this investigation.

Early in our work the glycol VIII was treated in pyridine with either thionyl chloride or phosphorus tribromide and the products formed dehydrohalogenated with alcoholic potash, or, as in one case, with sodamide in liquid ammonia. The crude product from one dehydrobromination experiment was found biologically active in doses of about 0.06 mg. per day, but its stability under feeding experiments was low. The products formed by the dehydrohalogenations when further purified by first partitioning, then by low temperature fractionation in methanol, showed a single absorption band between 3210 and 3220 Å. They also gave a deep blue color with antimony trichloride with bands at about 6220 and 5800 Å.

When one mole of hydrogen was added to carbinol VII in the presence of 1% palladium hydroxide on calcium carbonate, the carbinol IX was produced, and was dehydrated in toluene using catalytic amounts of *p*-toluenesulfonic acid. After molecular distillation, followed by low temperature fractionation in methanol, a product was obtained which showed an absorption maximum at 3210 Å. (Fig. 1, curve D).

The addition of one mole of hydrogen in the presence of palladium to 5-dehydrohomovitamin A ethyl ether did not materially change its ultraviolet absorption spectrum except that the extinction coefficient was slightly lowered, but not appreciably enough to indicate a large percentage of 1,4-addition or some other addition which would radically alter the position of the maximum. It may be of interest to note that in all of the above cases, the 5-double bond formed in the final product may be a *cis*-double bond, although in natural carotenoids and vitamin A, according to Zechmeister,[12] this double bond exists only in the *trans*-form.

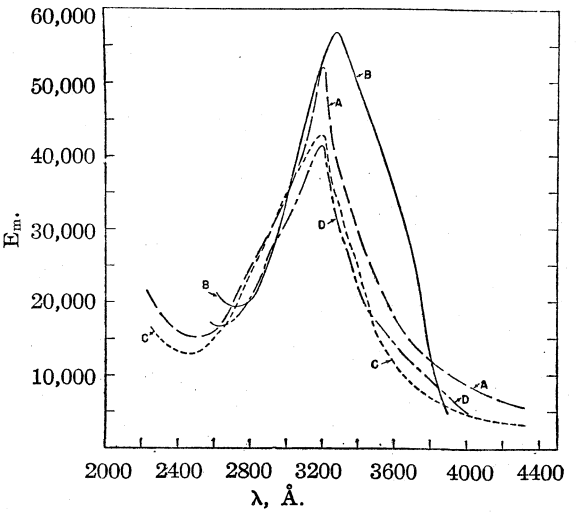


Fig. 1.—Absorption spectra in ethanol of: (A) 5-dehydrohomovitamin A ethyl ether from (VII); (B) homovitamin A ethyl ether via dehydrobromination (pyridine hydrobromide) of partially hydrogenated (VI); (C) 5-dehydrohomovitamin A ethyl ether from (VI); (D) homovitamin A ethyl ether via dehydration of partially hydrogenated (VII).

The ultraviolet absorption spectra of the various compounds reported in this investigation are summarized in Table I.

TABLE I

SUMMARY OF SPECTROSCOPIC DATA

Compound	λmax., Å.	εmol.	log εmol.
Homovitamin A ethyl ether (I) from VIII via dehydrobromination (pyridine hydrobromide). Curve B	3280	56750	4.75
	3670[a]	30000	4.48
Homovitamin A ethyl ether (I) from IX via dehydration. Curve D	3210	41250	4.62
5-Dehydrohomovitamin A ethyl ether (II) from VII via dehydration. Curve A	3210	52000	4.72
5-Dehydrohomovitamin A ethyl ether (II) from VI via dehydration. Curve C	3210	42500	4.63
Compound VI	2200–2230	4470	3.65
Compound VII	2330	21500	4.33

[a] Faint inflection.

Experimental

β-Ethoxyethyl Bromide.—This product was prepared in 59–65% yields, b. p. 125–127°, by a method[13] essentially

(12) Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

(13) Schuerch, B.S. Thesis, M. I. T., 1940.

the same as that published later by Harrison and Diehl[14] except that olefin-free petroleum ether was used as a solvent.

5-Ethoxypentanone-2.—This ketone was obtained in a yield of 26.4% using the procedure described by one of us elsewhere.[7] It had a b. p. of 170.5–171° (763 mm.); $n^{20}D$ 1.4176.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.62; H, 10.77. Found: C, 64.60, 64.50; H, 10.80, 10.80.

Semicarbazone of 5-Ethoxypentanone-2.—This product was recrystallized from ethanol, m. p. 86–87.5°.

Anal. Calcd. for $C_8H_{17}O_2N_3$: N, 22.4. Found: N, 21.7, 22.2.

3-Methyl-6-ethoxyhexa-1-yn-3-ol (Carbinol of III).—This product was also prepared by a procedure described elsewhere[7] and fractionated using a packed column of about 20 theoretical plates; yield, 83%; b. p. 94–95° (15 mm.); $n^{24}D$ 1.4466; $n^{20}D$ 1.4482; MR_D, 44.61; calcd., 44.86; d^{20}_4 0.938.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.24; H, 10.26; unsaturation, 1 ≡; active hydrogen, 2.0; $-OC_2H_5$, 28.8[4] Found: C, 69.23, 69.37; H, 9.77, 9.60; unsaturation, 0.94, 1.06 ≡; active hydrogen (Zer.), 1.9; $-OC_2H_5$, 28.2.

With alcoholic silver nitrate solution the acetylene carbinol forms a white precipitate which explodes on the hot plate.

This acetylene carbinol was also prepared in a somewhat lower yield (30%) by an adaptation of the method of Gould and Thompson.[15] It was identical with that obtained in liquid ammonia with sodium acetylide.

3-Methyl-6-ethoxyhexa-3-en-yne-1 (Vinylacetylene of IV).—Twenty grams of 3-methyl-6-ethoxyhexa-1-yn-3-ol was passed upward under a reduced nitrogen pressure (11 mm.) through a tube containing a mixture of aluminum phosphate and pumice and maintained at temperatures between 270 and 290°. The crude dehydrated mixture was then dried and fractionated under a reduced nitrogen pressure and the fraction boiling at 55–55.5° (12 mm.) collected; yield, 36% per pass; $n^{20}D$ 1.4522; d^{20}_4 0.8538; MR_D, 43.74; calcd., 42.95.

Anal. Calcd. for $C_9H_{14}O$: C, 78.26; H, 10.14; unsaturation, 3 ═; active hydrogen, 1; $-OC_2H_5$, 32.6. Found: C, 77.99, 77.71; H, 10.60, 9.86; unsaturation, 3.07 ═; active hydrogen (Zer.), 0.93, 0.94; $-OC_2H_5$, 30.4, 33.4.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyl-4-hydroxydeca-1,7-dien-5-ynyl]-10-ethyl Ether (VII).—A Grignard reagent was prepared in about 300 cc. of anhydrous ether from 3.9 g. of magnesium and 17.5 g. of ethyl bromide freshly distilled from phosphorus pentoxide. The mixture was then cooled to 0° and added to it dropwise with rapid stirring and in a stream of nitrogen, 22.1 g. of 3-methyl-6-ethoxyhexa-3-en-yne-1 in 25 cc. of anhydrous ether in the course of one-half hour. Stirring was continued at room temperature overnight, then the mixture was cooled to 0° and to it was added dropwise with rapid stirring 30 g. of the aldehyde (V) in an equal volume of anhydrous ether. The mixture was finally stirred overnight in nitrogen at room temperature, then hydrolyzed with an ammonium chloride–ice mixture and the ether layer recovered, dried and the ether removed under reduced pressure. The residue was subjected to a high vacuum, 10^{-4}–10^{-5} mm., at 100° to remove low boiling constituents, leaving a light-yellow, highly viscous liquid. Attempts to crystallize it were unsuccessful. An absorption spectrum of the final product showed a band at 2330 Å.; log $\epsilon_{mol.}$ 4.33.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.54; unsaturation, 5 ═; active hydrogen, 1. Found: C, 80.0, 79.9; H, 10.3, 10.5; unsaturation, 5.68, 5.15 ═ (Pt), 5.28 ═ (Pd); active hydrogen (Zer.) 1.00, 1.23.

(14) Harrison and Diehl, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. XXIII, p. 32.

(15) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935).

Since all of the semimicrohydrogenations were done in aldehyde-free glacial acetic acid, the high values are probably due to a slow hydrogenolysis of the hydroxyl groups.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyl-4,7-dihydroxydeca-1-en-5-ynyl]-10-ethyl Ether (VI).—A Grignard reagent was prepared from 2.1 g. of magnesium and 9.5 g. of ethyl bromide in about 200 cc. of anhydrous ether. The mixture was then cooled to 0° and added to it dropwise with rapid stirring and in a stream of nitrogen, 8 g. of 3-methyl-6-ethoxyhexa-1-yn-3-ol in 40 cc. of dry ether in the course of one-half hour. A thick finely divided semi-solid separated out. The mixture was refluxed gently for about six hours then cooled to 0° and added to it dropwise 8 g. of the aldehyde (V) in 20 cc. of dry ether. To complete the reaction, the mixture was refluxed overnight in an atmosphere of nitrogen, then cooled and hydrolyzed with an ammonium chloride–ice mixture. The ether extract was dried and the ether removed under reduced pressure. To remove the low boiling constituents, the residue was subjected to a high vacuum 10^{-4}–10^{-5} mm. at 100°. A highly viscous amber-colored liquid remained; yield 13 g. (93%). A semimicrohydrogenation (Pt) of this product showed the presence of 5.6 ═. Spectroscopically it had a prominent band at 2230 Å. and indications at 2400–2500, 2700–2800 and 3200–3300 Å., respectively. Further purification of this glycol was effected by partitioning it between equal volumes of petroleum ether and 90% methanol. The glycol went predominantly into the methanol layer from which it was recovered by diluting with water and extracting with petroleum ether. The final product had a single band at 2200–2230 Å.; log $\epsilon_{mol.}$ 3.65. Semimicrohydrogenation, 4.24 ═.

When this glycol was dissolved in dry petroleum ether and the solution allowed to stand at −20° for several weeks, a small amount of white solid separated out. Successive fractionations of the non-crystallizable product from −20 to −78° yielded only a small additional amount of the white solid. After several crystallizations from hot petroleum ether, the white solid had a m. p. of 74.5–75°, a semimicrohydrogenation of 5.53 ═ and a band at about 2200 Å., log $\epsilon_{mol.}$ 3.575. The non-crystallizable highly viscous liquid analyzed as follows:

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 76.19; H, 10.56; unsaturation, 4 ═; active hydrogen, 2. Found: C, 76.5, 76.3; H, 10.8, 10.7; unsaturation, 4.22, 4.46 ═ (Pt); active hydrogen (Zer.), 1.96. Found (crystalline): C, 75.95; H, 10.42.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5-trien-5-ynyl]-10-ethyl Ether (II) via Dehydration of Carbinol (VII).—About 0.3 g. of *p*-toluenesulfonic acid monohydrate was dehydrated in 300 cc. of toluene (thiophene-free) by distilling 75 cc. of the latter. The mixture was then cooled in nitrogen and 10 g. of [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyl-4-hydroxydeca-1,7-dien-5-ynyl]-10-ethyl ether in 200 cc. of toluene was added to it and distillation resumed in a stream of nitrogen until about 200 cc. of toluene was distilled over in the course of twenty minutes. The residual liquid which had turned deeply reddish-brown was cooled to room temperature and shaken in nitrogen with 2 × 50 cc. of 10% sodium hydroxide solution, washed with water, dried and the toluene removed under reduced pressure. The greenish viscous residue (8 g.) was dissolved in absolute methanol and the solution treated with about 1 g. of solid potassium hydroxide which caused the green color to disappear and the solution assumed a yellowish-orange tinge. Enough water was then added to make the methanol 95% and the mixture extracted with two volumes of olefin-free petroleum ether. The solution was washed with water, dried and the solvent removed. The crude light-brown viscous residue was subjected to a vacuum of about 0.01 mm. at 40–50° for about one hour to remove low boiling constituents. This product gave a deep blue color in chloroform with antimony trichloride;

it showed a negligible active hydrogen (Zerewitinoff) and had an unsaturation equivalent to 5.88 double bonds. When 0.0000956 g. was fed to a group of vitamin A deficient rats per day, a weight increase of 32 g. in twenty-eight days resulted, as compared with an increase of 44 g. in a positive control group fed 3 U. S. P. units of Reference Cod Liver Oil per day. All negative controls died.

The crude product was then fractionated once from a specially designed shallow flask sealed on to it a thermometer well and proper receivers to take cuts, and the largest fraction (light orange oil) boiling at 94–106° (10^{-4}–10^{-5} mm.) collected and examined spectroscopically. It showed two bands; one at 2850–2900 Å. and the other at 3160–3200 Å. Repeated fractionations caused considerable decomposition of the chromogen having the 3160–3200 Å. band.

In subsequent preparations, the crude product was fractionated once at 10^{-4}–10^{-5} mm. and the main fraction partitioned between equal volumes of petroleum ether and 90% methanol. Most of the product went into the petroleum ether layer. This fraction was chromatographed in nitrogen through a column 110 cm. long and 10 mm. bore, packed with 40–60-mesh activated alumina, and washed with about 2 liters of petroleum ether. A small yellowish-brown band 2 cm. long developed on the top of the column while the rest of the column was light orange-yellow. The unadsorbed product in petroleum ether was light orange, and when the petroleum ether was removed and the residue fractionated once, the main fraction (light orange oil) boiled at 100–104° (10^{-5} mm.). This had a single band at 3210 Å. and an $\epsilon_{mol.}$ value of 52,000. It also gave a blue color with antimony trichloride.

Anal. Calcd. for $C_{23}H_{34}O$: C, 84.60; H, 10.49; unsaturation, 6 ⌐¬. Found: C, 83.99, 84.06; H, 10.46, 10.25; unsaturation, 5.98 ⌐¬.

The adsorbed material was eluted with absolute alcohol and a small amount of a product recovered in petroleum ether. This was found to have a strong band at 2850–2900 Å. and a weaker one at 3160–3200 Å. All operations in this and subsequent experiments were carried out in a stream of purified nitrogen.

Partial Hydrogenation of Compound VII to Compound IX.—To 16.6 g. of the carbinol VII in 300 cc. of absolute alcohol and an equal weight of 1% palladium hydroxide deposited on calcium carbonate was added the calculated amount of hydrogen to convert the acetylene bond into an olefin bond taking also into consideration the amount of hydrogen necessary to reduce the palladium hydroxide into palladium black. The product was recovered from this solution and used in the dehydration experiment.

Dehydration of Compound IX.—The product from the previous experiment was dehydrated in 300 cc. of toluene containing about 0.4 g. of *p*-toluenesulfonic acid. The dehydrated product was recovered as in the previous case and treated in absolute methanol with solid potassium hydroxide (2 g.); the methanol diluted with water to 95% and extracted with two volumes of petroleum ether, the latter washed with water, dried, and the petroleum ether removed; yield of the crude product, 11 g. The highly viscous reddish-brown residue was dissolved in about 100 cc. absolute methanol and fractionated in nitrogen at successively lower temperatures, using 10° intervals from 0 to −78°. After a number of such fractionations, the entire product was obtained in three fractions: (1) a very small amorphous resinous fraction insoluble in methanol at 0°; (2) a methanol soluble fraction at −40°; (3) a methanol insoluble fraction at −40° or below which exists as a light orange solid below −50°. Fraction (2) was found to have an absorption band with two maxima; one at 2850–2900 Å., $E^{1\%}_{1\ cm.}$ 994, and the other at 3220 Å., $E^{1\%}_{1\ cm.}$ 710. Fraction (3) had only one maximum at 3210 Å., $\epsilon_{mol.}$. 41,250. The last fraction was also analyzed.

Anal. Calcd. for $C_{23}H_{36}O$: C, 84.08; H, 11.05; unsaturation, 5 ⌐¬. Found: C, 83.22; H, 10.78; unsaturation, 4.88 ⌐¬.

Dehydrochlorination of Compound IX.—A small sample of the carbinol IX (1.1 g.) was treated at 0°, in a mixture of 10 cc. petroleum ether, 10 cc. ethyl ether and 0.25 g. anhydrous pyridine, with 0.4 g. of thionyl chloride for fifteen minutes. It was then allowed to warm to room temperature for one-half hour, then heated in nitrogen under reflux for an additional one-half hour. The mixture was then cooled and filtered off the solid pyridine hydrochloride. Finally the solvent was removed under reduced pressure and the residue taken up in 20 cc. hot 95% ethanol containing 1 g. of potassium hydroxide. To complete dehydrochlorination, the mixture was heated in nitrogen for one-half hour at 60–80°, then cooled, diluted with three volumes of water and extracted with petroleum ether. The petroleum ether extract was once partitioned with an equal amount of 95% methanol, washed with water, dried and examined spectroscopically. It showed two bands; one at 2820–2900 Å., $E^{1\%}_{1\ cm.}$ 406, and the other at 3220–3230 Å., $E^{1\%}_{1\ cm.}$ 313.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5-trien-5-ynyl]-10-ethyl Ether via Dehydration of Glycol VI.—About 150 cc. of anhydrous toluene was mixed with 0.03 g. of *p*-toluenesulfonic acid monohydrate, and a little over 50 cc. of toluene was distilled to cause the dehydration of *p*-toluenesulfonic acid. The mixture was then cooled and to it was added about 1 g. of the glycol VI in 25 cc. of toluene. About 50 cc. of toluene was then distilled in nitrogen and the mixture (deep orange) was cooled, the product recovered as in the previous dehydrations and treated with methyl alcoholic potash. It was recovered from this mixture with petroleum ether and distilled (temperature of boiling cyclohexanone) once, using a molecular still of the falling film type. In addition to a small amount of residue, a dark orange-brown viscous liquid (about 0.6 g.) was obtained which had an absorption band at 3200–3210 Å., $E^{1\%}_{1\ cm.}$ 723. This was further purified by fractionation from absolute methanol at temperatures between 0 and −78°. The fraction insoluble in methanol below −40° was recovered and examined spectroscopically. It was found to have a band with a maximum at 3210 Å., $\epsilon_{mol.}$ 42,500. A semimicrohydrogenation showed the presence of 5.93 double bonds.

Partial Hydrogenation of Glycol VI to Glycol VIII.—To 10.8 g. of glycol VI in 200 cc. of absolute alcohol and 11 g. of 1% palladium hydroxide deposited on calcium carbonate was added the calculated amount of hydrogen necessary to convert the acetylene bond into an olefin bond, and the product recovered and used in the dehydrohalogenation experiments.

Dehydrohalogenation of Glycol VIII. (a) Via Phosphorus Tribromide.—A mixture of 6.9 g. of freshly distilled tribromide, 25 cc. of dry benzene and a few drops of pyridine was cooled to −5°. A solution of 4.62 g. of the glycol VIII, 25 cc. of dry benzene and 6.5 g. of pyridine was then added dropwise with shaking in the course of one-half hour. The mixture was then allowed to stand at room temperature in nitrogen for two hours, heated to 70° for twenty minutes, then cooled and poured on cracked ice and immediately extracted with ether. The ether extract was shaken with two 50-cc. portions of cold phosphoric acid, then once with cold water and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed and to the residue was added 80 cc. of hot methyl alcoholic potash containing 10 g. of potassium hydroxide. The mixture was further heated in nitrogen for one-half hour at 70° then cooled, diluted with two volumes of water and extracted with petroleum ether. This crude product was found biologically active in doses of 0.06 mg. per day, but the activity was not maintained until the end of the test, showing considerable instability. This product was further purified by partitioning between equal volumes of petroleum ether and 90% methanol and the product in the petroleum ether layer analyzed spectroscopically. A yield of about 2 g. was obtained at this stage. It showed two maxima in the ultraviolet; one at

2800–2900 Å. and the other at 3210–3230 A. With antimony trichloride in chloroform, it gave two bands; one at 6220 Å. and the other at 5800 Å., the latter being more prominent.

(b) **Via Pyridine Hydrobromide.**—To 30 g. of dry pyridine was added 1.5 g. of dry hydrogen bromide (Dow Chemical Co.) and the mixture cooled to room temperature while nitrogen was allowed to bubble through it. A solution of 2.5 g. of the glycol VIII in 50 cc. of dry benzene was then added to the above mixture and heated on the water-bath in nitrogen for two hours. All of the benzene and most of the pyridine were then removed under reduced pressure, and to the residue, with nitrogen still flowing through the system, was added 100 cc. of hot 95% alcohol containing 10 g. of potassium hydroxide. The mixture was then heated on the water-bath for one-half hour, then cooled, diluted with two volumes of water and extracted with petroleum ether. About 1.8 g. of a yellowish-brown viscous liquid was recovered which, unlike any other crude dehydrohalogenation product, had a single broad absorption band in the ultraviolet between 3200 and 3400 Å. It also gave a deep blue color with antimony trichloride in chloroform. To purify this product further, it was partitioned between equal volumes of petroleum ether and 90% methanol and the petroleum ether portion chromatographed in nitrogen through a column 110 cm. × 1 cm. packed with activated alumina. The column was then washed with 1.5 liters of petroleum ether and the unadsorbed portion (light yellow) was removed from petroleum ether and fractionally purified at 0 to −78° from absolute methanol. A yellow, highly viscous product (*ca.* 1 g.) was finally obtained and to free it completely from methanol, it was dissolved in petroleum ether and the solution extracted with water, dried and examined spectroscopically. It showed an absorption band at 3280 Å., $\epsilon_{mol.}$ 56,750 and a possible inflection at 3670 Å., $\epsilon_{mol.}$ 30,000. Semimicrohydrogenation showed the presence of 4.85 double bonds.

Anal. Calcd. for $C_{23}H_{36}O$: C, 84.08; H, 11.05. Found: C, 82.32; H, 10.90.

This product was highly unstable and easily autoxidizable and in spite of the precautions taken to obtain pure samples for combustions, the carbon analyses were always from 1.5 to 2% low. This difficulty was also encountered in the early stages of the natural vitamin A purifications.

The adsorbed portion was eluted from alumina with absolute alcohol and, after diluting with water, extracted with petroleum ether. It was found to have two bands in the ultraviolet; one at 3440 Å., $E^{1\%}_{1\ cm.}$ 250, the other at 3670 Å., $E^{1\%}_{1\ cm.}$ 188. The amount of this product was too small for further investigation.

Partial Hydrogenation of 5-Dehydrohomovitamin A Ethyl Ether.—A sample of 0.1271 g. of 5-dehydrohomovitamin A ethyl ether having an $E^{1\%}_{1\ cm.}$ (3210 Å.) value of 1250 was placed in a wafer glass capsule sealed flat on one end and, after weighing, drawn into an open capillary on the other end. The sample was placed into a glass key attached to a rod revolving around a ground glass stopper and sealed on to a specially designed vessel of a semimicro-hydrogenation apparatus.[16] The vessel contained an alcoholic suspension of 0.254 g. of 1% palladium hydroxide on calcium carbonate. After the palladium hydroxide was reduced with hydrogen and equilibrium was established in the system, the capsule was crushed and exactly one mole equivalent of hydrogen was allowed to be absorbed. Hydrogenation was discontinued and the hydrogen in the apparatus was quickly replaced with pure nitrogen. The product was then recovered in the usual manner and analyzed spectroscopically. It was found to have an absorption band at 3200–3210 Å., $E^{1\%}_{1\ cm.}$ 1000 with a faint inflection at 2900 Å. (?).

These results seem to indicate that the addition of hydrogen on the en-yne system had taken place mainly on the acetylene bond, since 1,4-addition would have produced an allene which should be optically equivalent to 5.5 double bonds[17] and its absorption maximum should have been in the region of about 3400 Å. However, the possibility of a rearrangement of the allene into an en-yne with one less double bond should not be excluded. Such an en-yne should have a prominent absorption band in the region of 2900 Å. The fact that a faint inflection was found in this region indicates that some of the hydrogen had actually added 1,4 with a subsequent rearrangement of the allene formed.

Acknowledgment.—The authors are indebted to Mrs. Alice R. Lowry, Mrs. Silvia P. Solar, Mrs. C. K. Fitz and Mr. S. M. Nagy for several of the analyses, and to Professor Robert S. Harris for the biological tests. This article is a part of a research program on the synthesis of vitamins A and D, support of which was derived in part through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Parke, Davis and Company, the Upjohn Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

Summary

1. The synthesis of [1-(2′,6′,6′-trimethylcyclohexen - 1′ - yl) - 3,7 - dimethyldeca - 1,3,5,7 - tetraenyl]-10 ethyl ether, or homovitamin A ethyl ether, and [1-(2′,6′,6′-trimethylcyclohexen-1′ - yl) - 3,7 - dimethyldeca - 1,3,5 - trien - 5 - ynyl]-10-ethyl ether, or 5-dehydrohomovitamin A ethyl ether, and that of several new intermediates has been described. Crude preparations of both homovitamin A and 5-dehydrohomovitamin A ethyl ethers have been found to possess antixerophthalmic (vitamin A) activity.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 12, 1947

(16) Rivers, Ph.D. Thesis, M. I. T., Dec., 1941.

(17) Kuhn and Wallfels, *Ber.*, **71B**, 783 (1938); see also Shantz, Cawley and Embree, THIS JOURNAL, **65**, 904 (1943).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. VI. The Synthesis of Biologically Active Vitamin A Ethers[1]

BY NICHOLAS A. MILAS, EMILE SAKAL,[2] JOHN T. PLATI,[3] JOSEPH T. RIVERS,[4] JEAN K. GLADDING,[5] FRANK X. GROSSI,[6] ZELMA WEISS,[7] MARGARET A. CAMPBELL[8] AND HERBERT F. WRIGHT[9]

Following a scheme originally suggested by Milas and McAlevy,[10] Kipping and Wild[11] were the first to claim the synthesis of vitamin A methyl ether. Since no experimental details, analyses or biological results were given, it is difficult to evaluate this synthesis. Soon after the original announcement of the synthesis of various biologically active vitamin A products[12] developed in this Laboratory during the war, Oroshnik,[13] claimed in a note the synthesis of vitamin A methyl ether, but experimental details as well as biological activity of the final product are lacking.

The present paper describes the synthesis of four biologically active vitamin A ethers. Only two, the methyl and the ethyl and their corresponding 5-dehydrovitamin A derivatives were obtained in relatively pure form, while the isopropyl and the *t*-butyl ethers were obtained in much less pure state.

One of the important intermediates in the synthesis of vitamin A ethers is 4-alkoxybutanone-2 (I). Attempts to prepare this alkoxybutanone, in which R represents methyl or ethyl groups, by the direct alkylation of 4-hydroxybutanone-2 with dimethyl or diethyl sulfates were entirely unsuccessful. Rivers[14] prepared 4-ethoxybutanone-2 from β-ethoxypropionyl chloride and cadmium dimethyl[15] but the yields were low and the method could not be adapted easily for the preparation of the various alkyl ethers of 4-hydroxybutanone-2. Killian, Hennion and Nieuwland[16] prepared 4-methoxybutanone-2 from anhydrous methanol and methyl vinyl ketone in the presence of boron trifluoride-etherate. This method was found satisfactory in the preparation of 4-methoxy, 4-ethoxy, 4-isopropoxy and 4-*t*-butoxybutanone-2's. 4-Alkoxybutanone-2 (R = methyl or ethyl) was then condensed in liquid ammonia with lithium acetylide to give 3-methyl-5-alkoxy-pentyn-1-ol-3 (II) which was dehydrated at 250–280° over aluminum phosphate to 3-methyl-5-alkoxy-3-pentenyne-1 (III).

These three intermediates were used in the study of three different routes for the synthesis of vitamin A ethers (see flow sheet). In the first route the aldehyde (IV)[17] was condensed in liquid ammonia with lithium acetylide to give the acetylene carbinol (V) which was then condensed via the Grignard reaction with 4-alkoxybutanone-2 to give the acetylene glycol (VI) in yields of 70–80%. This glycol was also obtained in somewhat higher yields by the condensation of the Grignard of the acetylene (II) with the aldehyde (IV). This glycol has been obtained in two forms; a crystalline and a highly viscous liquid form. Since the double bond between carbon atoms one and two can exist only in the *trans* form,[18] the difference between the crystalline and the liquid glycols may be one of racemic and *meso* forms.[19] The partial hydrogenation of the acetylene glycol (VI) to give the glycol (VII) was found to be selective when 1% palladium deposited on calcium carbonate was used as the catalyst.

Several methods were employed in the conversion of the glycol ether (VII) (R = methyl) into the vitamin A methyl ether (XI). Using phosphorus tribromide in the presence or absence of pyridine, the glycol was converted into the dibromide which was dehydrobrominated with alcoholic potash. The reaction was also studied with phosphorus trichloride, phosphorus triiodide and thionyl chloride. With thionyl chloride partial dehydrochlorination occurred as was indicated by the appearance in the spectrum of the dichloride of a broad band between 3000 and 3300 Å. Of all the halogenating agents, phosphorus tribromide and thionyl chloride gave the best results. In all

(1) (a) First presented in part before the North Jersey Section of the American Chemical Society, April 9, 1945. (b) Since this and other work related to the synthesis of vitamin A was under confidential classification during the War, we wish to point out for purposes of priority the existence of two documents deposited in the Office of the Committee on Medical Research of the O. S. R. D. and describing the synthesis of biologically active vitamin A products using the Darzens aldehyde made from β-ionone as the key intermediate. These documents were dated March 6, 1942.

(2) Research Associate 1941–1943. Present address, Warner Institute for Therapeutic Research, New York, N. Y.

(3) Research Associate 1940–1942. Present address, Hoffman-LaRoche, Nutley, N. J.

(4) Research Assistant, 1941. Present address, du Pont and Company, Buffalo, N. Y.

(5) Research Associate 1941–1943. Present addess, du Pont and Company, Wilmington, Delaware.

(6) Research Assistant 1942–1945. Present address, Royal Bond, Inc., St. Louis, Mo.

(7) Research Assistant 1943–1945.

(8) Research Assistant 1945–1946. Present address, Arthur D. Little, Inc., Cambridge 42, Mass.

(9) Research Associate 1945–1946. Present address, Tufts College, Medford, Massachusetts.

(10) Milas and McAlvy, THIS JOURNAL, **57**, 580 (1935).

(11) Kipping and Wild, *Chemistry and Industry*, 802 (1939).

(12) Milas, U. S. Patents 2,369,157, Feb. 13, 1945; 2,382,086, Aug. 14, 1945; *Science*, **103**, 581 (1945).

(13) Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

(14) Rivers, Ph.D. Thesis, M. I. T., Dec., 1941.

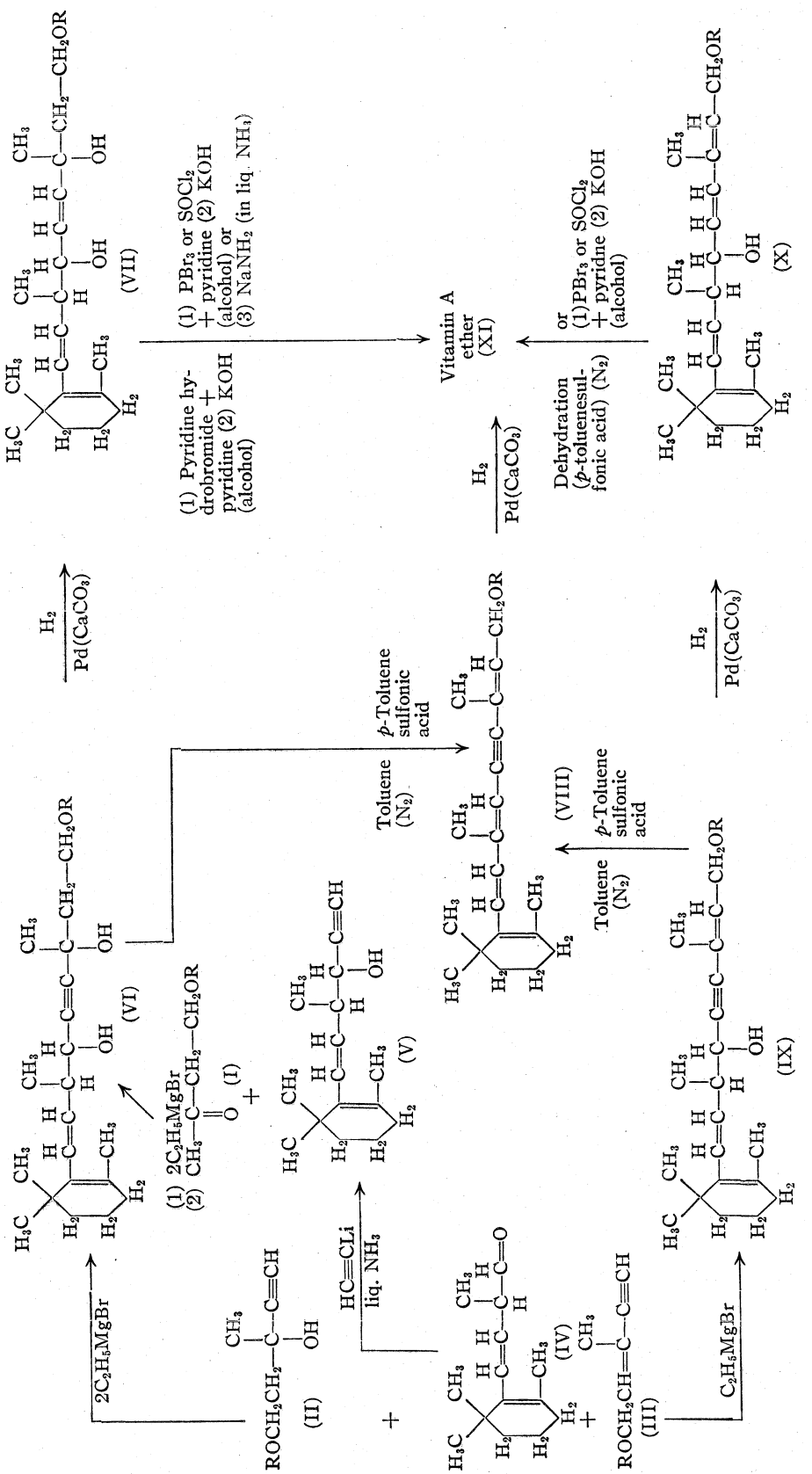
(15) Gilman and Nelson, *Rec. trav. chim.*, **55**, 158 (1936).

(16) Killian, Hennion and Nieuwland, THIS JOURNAL, **58**, 893 (1936).

(17) Milas, *et al.*, *ibid.*, **70**, 1584 (1948).

(18) Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

(19) Dupont, *Compt. rend.*, **149**, 1381 (1909); **150**, 1121 (1910); **158**, 714 (1914); *Ann. chim.*, **30**, 500 (1913); Johnson, "Acetylenic Compounds," Edward Arnold, London, 1946, p. 150.

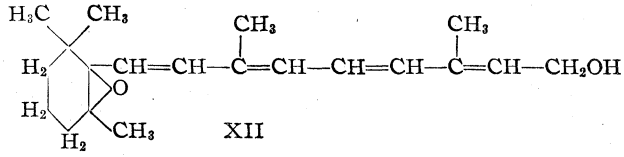


of the cases, however, the product obtained (a pale yellow oil) after a single high vacuum distillation, was found to have two bands in the ultraviolet; one with a maximum at 3250 Å. and the other at 2850–2900 Å. With antimony trichloride in chloroform, it gave a blue color which also showed two bands (Fig. 1, curves with broken lines); one with a maximum at 5800 Å. and another at 6180–6200 Å. Repeated distillation from a shallow vessel at 10^{-5} mm. was detrimental to the chromogen responsible for the absorption band at 3250 Å., which disappeared after five successive distillations.

During the early part of our work we made several preparations through the halogenation of the glycol (VII) (R = methyl, isopropyl, or *t*-butyl) and the dehydrohalogenation of the resulting dihalide. Many of these were assayed biologically on vitamin A deficient rats and a summary of the results is presented in Table I. The glycol (VII) was also tested biologically in order to find out whether the animal organism would cause dehydration, but the results were negative even when very large doses were fed. Preparation (6) was also tested by several other laboratories and all reported appreciable vitamin A activity but not as high as that shown in Table I. Spectroscopically, this sample showed two bands; one at 3250 Å., $E^{1\%}_{1\,cm.}$ 535, the other at 2850 Å., $E^{1\%}_{1\,cm.}$ 655

with feeble indications at 3450 and 3710 Å., respectively. With antimony trichloride in chloroform, it gave a blue color which exhibited two bands at 5800 and 6170 Å., respectively, with the former being the more intense. The product is a light yellow oil boiling at 90–95° (10^{-5} mm.) having negligible active hydrogen (Zer.) and an unsaturation equivalent to 5.08 double bonds. The ultimate analysis, however, gave percentages of carbon varying from 1.5 to 2.0% low. Attempts to purify this product by fractionation at low temperatures were unsuccessful, although the $E^{1\%}_{1\ cm.}$ (3250 Å.) of other samples was raised to 1090 by this method.

The high intensity of the 5800 Å. band (Fig. 1, broken line) suggests the possibility that the vitamin A methyl ether as prepared through the above dehydrohalogenation method is a mixture of the methyl ether and its epoxide. This reasoning finds some support in the recent work of Karrer and Jucker,[20] who found that the chromogen responsible for the 5800 Å. band of the Carr–Price reaction is the epoxide of vitamin A (XII) and not vitamin A, which is responsible only for the 6200 Å. band. From their findings, Karrer and Jucker advanced the hypothesis that in fishliver oils as well as in animal-liver oils, the vitamin A epoxide coexists with vitamin A, and is formed by the auto-oxidation of the latter.[21] The epoxide of vitamin A has also been obtained by treating vitamin A with phthalic acid peracid[22] in a manner similar to that used for the preparation of α- and β-carotene epoxides.[23]



XII

That auto-oxidation of vitamin A is responsible for the 2850–2900 Å. chromogen was shown recently in this Laboratory when an auto-oxidized sample of pure vitamin A was examined spectroscopically. It was found to have a single band at 2850 Å. This is in close agreement with the spectrum of the epoxide of the synthetic methyl ether, the structure of which has not yet been definitely established. Furthermore, both resemble the 5800 Å. chromogen of van Eekelen[24] and the subvitamin A of Embree and Shantz[25] and of Hawkins and Hunter.[26]

Identical results were obtained when the carbinol (X) was treated with phosphorus tribromide and the bromide formed dehydrobrominated with

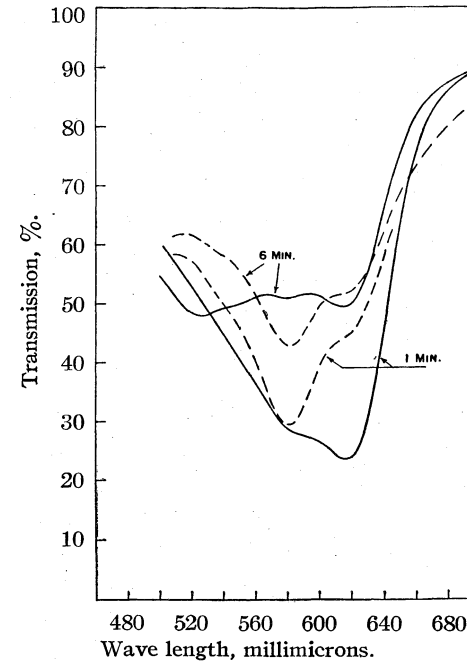


Fig. 1.—Transmission spectra of the antimony trichloride color reaction in chloroform of: (broken line) distilled dehydrobrominated glycol methyl ether (VII), concn., 0.000394%; (solid line) selectively hydrogenated 5-dehydrovitamin A methyl ether (VIII), concn., 0.000192%, taken by the Hardy color analyzer.

alcoholic potash. Since our original publication,[12] Isler, *et al.*,[27] used a similar procedure for the synthesis of vitamin A methyl ether from the carbinol (X) except that the dehydrobromination was carried out with potassium carbonate in acetone. In a more complete publication[28] the same authors used iodine as a catalyst in toluene or ligroin at 95–100° to effect the dehydration of the carbinol (X). The spectroscopic properties of the crude product were similar to those reported by us in the present and earlier publications. The Swiss workers obtained a yellow oil b. p. 90–95° (10^{-5} mm.) having a single band at 3250–3280 Å.; $E^{1\%}_{1\ cm.}$ 1415. When fed to vitamin A deficient rats in doses of 0.8γ and 1.6γ, it was found to be equivalent to 1.1γ and 1.8γ of β-carotene, respectively. Judging from these results, this preparation was not 100% pure vitamin A methyl ether, since the latter has been prepared recently from natural vitamin A by Hanze, *et al.*,[29] who reported a m. p. for this ether of 33–34°, an $E^{1\%}_{1\ cm.}$ (3260 Å.) value of 1660 and a biological potency of about 3,000,000 U.S.P. XXII units per gram.

Sample (10) shown in Table I was prepared by the dehydration in toluene of the methyl ether glycol (VII) using catalytic amounts of *p*-toluene-

(20) Karrer and Jucker, *Helv. Chim. Acta*, **28**, 717 (1945).
(21) Karrer and Jucker, *ibid.*, **28**, 427 (1945).
(22) von Euler, Karrer and Zubris, *ibid.*, **17**, 24 (1934).
(23) (a) Karrer and Rutschmann, *ibid.*, **27**, 1684 (1944); (b) Karrer and Jucker, *ibid.*, **28**, 300, 427, 471 (1945).
(24) van Eekelen, Emmerie, Julius and Wolff, *Nature*, **132**, 171 (1933).
(25) Embree and Shantz, THIS JOURNAL, **65**, 906 (1943).
(26) Hawkins and Hunter, *Biochem. J.*, **38**, 34 (1944).
(27) Isler, Kofler, Huber and Ronco, *Experientia*, **2**, 31 (1946).
(28) Isler, Huber, Ronco and Kofler, Jubilee Volume of Emil C. Barrell, Hoffman–LaRoche and Co., Basle, 1946, p. 31.
(29) Hanze, Conger, Wise and Weisblat, THIS JOURNAL, **68**, 1389 (1946).

TABLE I

SUMMARY OF BIOLOGICAL ASSAYS[a]

MEVA = Methyl ether of vitamin A. iso-PEVA = Isopropyl ether of vitamin A. *t*-BEVA = *t*-butyl ether of vitamin A. DHMEA = 5-Dehydromethyl ether of vitamin A.

	Vitamin preparation	Dose fed per day, γ	Average gain in wt. per rat per 28 days, g.	Remarks[d]
1	MEVA (crude) via dehydrochlorination (PCl_3) of (VII)	331.0[b]	92.0	
2	MEVA (crude) via dehydrobromination (PBr_3) of (VII)	232.0[b]	95.0	
3	Repeat of (2) after standing at 0° in olive oil for one month	531.0[b]	40.0	
4	Repeat of (2), new preparation	176.0[b]	25.0	
5	Repeat of (4), simultaneously	190.0[b]	35.0	
6	Same as (2) distilled three times	3.0[b]	14.0	
7	Repeat of (6) after standing at 0° in olive oil for one month	6.0[b]	−1.5	All rats survived the test
8	Same as (2) distilled four times	3.0[c]	1.6	One out of eight rats died
9	Repeat of (8)	1.5[c]	7.0	Three out of seven rats died on 6th day of test
10	MEVA (distilled) via dehydration of (VII) with *p*-toluenesulfonic acid as catalyst	189.0[b]	45.0	
11	iso-PEVA (distilled) via dehydrobromination (PBr_3)	183.0[b]	57.0	
12	Same as (11) distilled twice	3.0[c]	11.0	One out of six rats died on 10th day of test
13	*t*-BEVA (distilled) via dehydrobromination (PBr_3)	7.4[b]	4.0	Six out of ten rats died during test
14	DHMEA (distilled)	111.0[c]	17.0	
15	Same as (14) distilled twice	6.0[b]	19.0	Only two rats were used for this test

[a] These results were reported to one of us (N. A. M.) during 1941–1942 by Professor Robert S. Harris (M. I. T.). [b] These samples were prepared in olive oil in which the air was replaced by pure nitrogen. To each sample was also added 0.1% of hydroquinone based on the vitamin concentration. [c] These samples were prepared in corn oil in which the air was replaced by pure nitrogen. To each sample was added 0.05% of hydroquinone and 0.05% of lecithin based on the vitamin concentration. [d] All positive control rats were fed 3 U. S. P. units of Reference Cod Liver Oil per day, and showed an average weight increase of 33–44 g. per rat per 28 days. All negative control rats were fed doses of olive or corn oil containing only the antioxidants, and died in the first period of the test.

sulfonic acid. When distilled from a shallow vessel at 10^{-5} mm., the distillate exhibited both the 3250 and the 2850 Å. bands, and gave a blue color with antimony trichloride in chloroform. Hydrogenation showed the presence of 4.98 double bonds and a Zerewitinoff determination showed negligible active hydrogen.

Vitamin A methyl ether was also synthesized by the selective hydrogenation of 5-dehydrovitamin A methyl ether (VIII) which was prepared by the dehydration of the glycol (VI) (R = methyl) using catalytic amounts of *p*-toluenesulfonic acid. The crude 5-dehydrovitamin A methyl ether was purified by partitioning between petroleum ether and 95% methanol followed by low temperature fractionation from methanol and molecular distillation. The ultraviolet absorption of the purest specimen obtained is shown in Fig. 2, curve A. Although the crude product showed two broad bands, one at 3100–3300 Å. and the other at 2800–2900 Å., the purified product showed a single maximum at 3220 Å.; $E^{1\%}_{1\,cm.}$ 1600, and gave the expected unsaturation. Upon ozonization, it yielded geronic acid, indicating the presence of the β-ionone ring in the molecule. When one mole of hydrogen was added to it in the presence of 1% palladium deposited on calcium carbonate, and the product purified by low temperature fractionation from methanol followed by molecular distillation, a specimen [yellow oil, b. p. 90–95° (10^{-4} mm.)] was obtained which had an ultraviolet spectrum [$E^{1\%}_{1\,cm.}$ (3230 Å.), 1560; Fig. 2, curve B] which was very similar to that of the 5-dehydrovitamin A methyl ether. The spectrum of the antimony trichloride color reaction in chloroform is shown in Fig. 1 (solid line curves) taken one minute and six minutes after mixing, respectively. The one-minute curve shows a principal maximum at 6180 Å.; $E^{1\%}_{1\,cm.}$ 3284. Ozonization of this vitamin A methyl ether gave geronic acid, again indicating the presence of the β-ionone ring.

5-Dehydrovitamin A ethyl ether (VIII) (R = ethyl) was also synthesized by the dehydration of either the glycol (VI) or the carbinol (IX) in the presence of *p*-toluenesulfonic acid. The crude product had similar properties to the corresponding 5-dehydrovitamin A methyl ether and was purified by the same procedure. The purest specimen obtained had an ultraviolet absorption spectrum shown in Fig. 2, curve C. Selective hydrogenation did not change appreciably the shape of the band or the position of the maximum.

Since it is well known[18,30] that selective catalytic hydrogenation of an acetylene leads predominantly to a *cis* olefin, and chemical reduction

(30) Campbell and Campbell, *Chem. Rev.*, **31**, 77 (1942).

usually leads to a *trans* olefin, it was thought advisable to study the chemical reduction of 5-dehydrovitamin A ethyl ether and compare the product formed with that obtained from the catalytic hydrogenation. The following chemical methods of selective reduction have been tested with 5-dehydrovitamin A ethyl ether: (1) zinc–copper couple in alcohol[31]; (2) zinc dust in alcoholic potassium hydroxide[32]; (3) zinc and acetic acid in alcohol; (4) "Devarda's" alloy (aluminum–copper–zinc alloy) in aqueous alcoholic potassium hydroxide; (5) Raney alloy in aqueous alcoholic potassium hydroxide; (6) metallic calcium in 90% ethanol; (7) sodium in liquid ammonia.[33] The ultraviolet absorption spectrum and unsaturation were taken before and after each reduction. No reduction was observed, even after prolonged treatment with methods (3) and (6), while method (7) caused complete polymerization of the 5-dehydrovitamin A ethyl ether. Of all the other methods, zinc dust in aqueous alcoholic potassium hydroxide gave the most satisfactory results. A product was obtained by this method which after purification by low temperature fractionation from methanol had an ultraviolet absorption band shown in Fig. 2, curve D. The product also showed an unsaturation of 4.85–5.2 double bonds as compared with the original of 6.0–6.19 double bonds. Although the intensity of the ultraviolet maximum was increased, an increase which might be due to further purification, the position of the maximum was essentially the same (3230 Å.). Moreover, the shape of the absorption curve is somewhat the same as that obtained from the catalytically hydrogenated 5-dehydrovitamin A methyl ether (curve B).

Partially purified specimens of both the methyl and ethyl ethers of vitamin A made by the selective catalytic hydrogenation of the corresponding 5-dehydroethers of vitamin A (VIII) were found biologically active when tested on vitamin A deficient rats. For example, samples with an $E^{1\%}_{1\,cm.}$ (3200–3230 Å.) of about 400 to 500 gave potencies in the neighborhood of 100,000 U.S.P. units per gram. The final purified products have not yet been assayed biologically.

In an attempt to convert the glycol (VII) (R = ethyl) and the carbinol (X) (R = ethyl) into their corresponding bromides with pyridine hydrobromide in excess pyridine followed by treatment with alcoholic potash, we obtained a product (80–90% yield) which showed a broad band in the ultraviolet of very high intensity between 3000 and 3700 Å. and one of low intensity at 2850–2900 Å. and gave a deep blue color with antimony trichloride in chloroform. When partitioned between equal volumes of 83% ethanol and petroleum ether, most of it went into the petroleum ether layer which was chromatographed on activated alumina. The greater part of the product passed through the alumina unadsorbed. This portion was fractionated through a molecular still of the falling film type at 10^{-5} mm. and the largest fraction (80%), a light yellow oil, was analyzed spectroscopically. It was found to have a fine structure of three bands in the ultraviolet (Fig. 3): one at 3300 Å.; $E^{1\%}_{1\,cm.}$ 1690, a second at 3480 Å.; $E^{1\%}_{1\,cm.}$ 1830, and a third at 3670 Å.; $E^{1\%}_{1\,cm.}$ 1520. The shape and position of these bands are identical with similar bands observed recently by Shantz[34] for a hydrocarbon related to vitamin A and containing five double bonds in conjugation. That our substance was not a hydrocarbon was shown by the fact that it still possessed the ethoxyl group. Furthermore, molecular weight determinations and hydrogenation gave values in remarkable agreement with those expected for the vitamin A ethyl ether, although carbon and hydrogen analyses were slightly lower than the theoretical. On standing under nitrogen at 0° for over six months, it partially crystallized into light yellow crystals which melted at about 28–30°. Upon ozonization it yielded geronic acid (as 2,4-dinitrophenylhydrazone) indicating the presence in the molecule of the β-ionone ring. No biological results are as yet available for this substance.

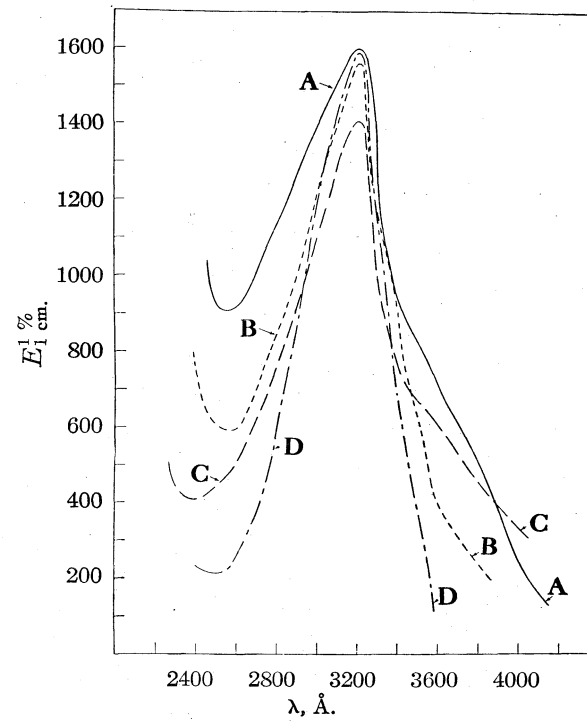


Fig. 2.—Absorption spectra in ethanol of: (A) 5-dehydromethyl ether of vitamin A from (VI); (B) methyl ether of vitamin A via partial hydrogenation of (VIII); (C) 5-dehydrovitamin A ethyl ether via dehydration of either (VI) or (IX); (D) ethyl ether of vitamin A by reduction of (VIII) using zinc dust and alkali.

(31) (a) Straus, *Ann.*, **342**, 190 (1905); (b) Grignard and Teheoufaki, *Compt. rend.*, **188**, 153 (1929); (c) Lebedev, Gulyaeva and Vasil'ev, *J. Gen. Chem.* (U. S. S. R.), **5**, 1421 (1935).

(32) Hurukawa, *J. Electrochem. Assoc. Japan*, **7**, 346 (1939).

(33) Campbell and Edy, THIS JOURNAL, **63**, 216 (1941).

(34) Shantz, *ibid.*, **68**, 2553 (1946).

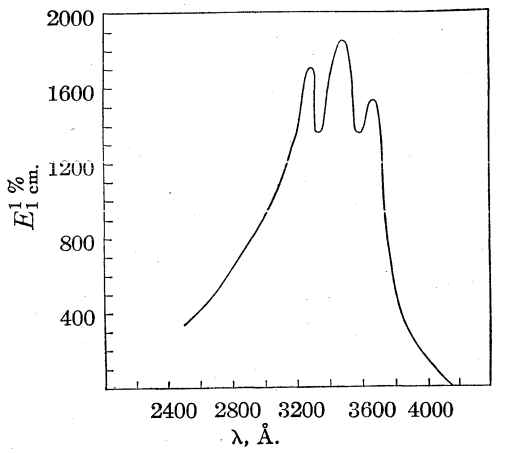


Fig. 3.—Absorption spectrum in ethanol of dehydrobrominated (pyridine hydrobromide) glycol ethyl ether (VII)—"*allo*-vitamin A ethyl ether."

In view of the peculiar nature of its spectrum, one cannot state unequivocally at present that this substance is the normal ethyl ether of vitamin A, in spite of the fact that other evidence seems to point strongly to this conclusion. For this reason, the term "*allo*-vitamin A ethyl ether" is suggested.

A summary of the spectroscopic data of the important compounds discussed in this paper is given in Table II.

TABLE II

SUMMARY OF ULTRAVIOLET ABSORPTION SPECTRA OF ETHERS AND 5-DEHYDROETHERS OF VITAMIN A (IN ALCOHOL)

Vitamin A ether	$\lambda_{max.}$ Å.	$E^{1\%}_{1\,cm.}$	$\epsilon_{mol.}$	log $\epsilon_{mol.}$
DHME (Fig. 2, curve A)[a]	3220	1600	47680	4.68
MEVA (Fig. 2, curve B)[b]	3230	1560	46800	4.67
MEVA[c]	3250	1090	...	..
MEVA[28]	3250–3280	1415	42450	4.63
MEVA (natural)[29]	3260	1660	49800	4.70
DHEE (Fig. 2, curve C)[d]	3220	1410	43992	4.64
EEVA (Fig. 2, curve D)[e]	3230	1590	49926	4.70
EEVA[f]	3250–3270	1500	47100	4.67
EEVA (Fig. 3)[g]	3300	1690	53066	4.70
	3480	1830	57462	4.76
	3670	1520	47728	4.68

[a] 5-Dehydromethyl ether of vitamin A from VI. [b] Methyl ether of vitamin A from VIII. [c] Methyl ether of vitamin A via dehydrobromination of either the dibromide of VII or the bromide of X purified by fractionation at temps. between 0 and −78°. This sample exhibits also the 2850–2900 A. band. [d] 5-Dehydroethyl ether of vitamin A prepared by dehydration of either VI or IX purified via low temperature fractionation and chromatography + molecular distillation. [e] Ethyl ether of vitamin A from VIII via reduction with Zn dust + aqueous alcoholic alkali. [f] Ethyl ether of vitamin A via dehydration of the carbinol X with *p*-toluenesulfonic acid, purified by low temperature fractionation. [g] *allo*-Vitamin A ethyl ether via the dehydrobromination (pyridine hydrobromide) of either VII or X purified by chromatography + molecular distillation.

Experimental

Methyl Vinyl Ketone.—Methyl vinyl ketone was made by the dehydration of β-hydroxyethyl methyl ketone which was prepared by the condensation of acetone with formaldehyde in the presence of small amounts of sodium hydroxide. β-Hydroxyethyl methyl ketone (1150 g.) was best dehydrated by dropping it slowly into hot (160°) *n*-dibutyl phthalate (160 g.) containing 3 g. of iodine and 3 g. of hydroquinone. A yield of 590 g. of crude methyl vinyl ketone was obtained. This was further purified by distilling it from 190 g. of acetic anhydride,[35] followed by fractionation from a six-plate Podbielniak column; b. p. 81°; d^{25}_4 0.842; $n^{22}D$ 1.4095; $n^{15}D$ 1.4120. A yield of 10–15% was obtained based on the formaldehyde used. Pure methyl vinyl ketone is stable for long periods of time over hydroquinone at 0°, but should be freshly distilled as needed.

4-Methoxybutanone-2.—All attempts to make this ketone by the methylation of 4-hydroxybutanone-2 were unsuccessful. It was finally prepared by the method of Killian, Hennion and Nieuwland[16] from methyl vinyl ketone, anhydrous methanol and boron trifluoride-etherate.[36] A yield of 45–51% was obtained based on the amount of methyl vinyl ketone used; b. p. 142–143°; $n^{23}D$ 1.4045. This product had a negligible active hydrogen (Zer.), 0.08.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.8. Found: C, 58.73; H, 9.8.

4-Ethoxybutanone-2.—This ketone was made by two independent methods: (1)[14] From β-ethoxypropionyl chloride [b. p. 43–45° (10 mm.)] and cadmium dimethyl.[15] Best results were obtained when the cadmium dimethyl was prepared from methylmagnesium chloride rather than from the corresponding iodide. A yield of 20% of the ketone was obtained; b. p. 43–45° (16 mm.); 2,4-dinitrophenylhydrazone, m. p. 89–90° (from alcohol).

Anal. Calcd. for $C_{18}H_{16}N_4O_5$: N, 18.95; OC_2H_5, 15.23. Found: N, 19.0, 19.0; OC_2H_5, 15.6.

(2) The second procedure was based on the addition of absolute ethanol to methyl vinyl ketone in the presence of boron trifluoride-etherate. This method was employed several times for the preparation of this ketone, and yields were obtained from 52 to 77%; b. p. 149–150° (764 mm.); 74° (50 mm.); 61–62° (23 mm.).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.32. Found: C, 62.44, 61.98; H, 10.46, 10.28.

4-Isopropoxybutanone-2.—Using the boron trifluoride-etherate method, this ketone was prepared in 33.5% yield; b. p. 72–75° (37 mm.).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.63; H, 10.74. Found: C, 64.63, 64.88; H, 9.90, 10.00; active hydrogen (Zer.), 0.1.

4-*t*-Butoxybutanone-2.—This ketone was prepared by the same method as the previous ketone: b. p. 54–57° (15 mm.); $n^{20}D$ 1.4137.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.7; H, 11.1. Found: C, 66.83, 66.89; H, 12.19, 11.17; active hydrogen (Zer.), 0.14. A semicarbazone was prepared, m. p. 127–129°.

3-Methyl-5-ethoxypentyn-1-ol-3 (II, R = ethyl).—The preparation of this acetylene carbinol from 4-ethoxybutanone-2 and sodium acetylide in liquid ammonia or potassium acetylide in *t*-butyl alcohol resulted in low yields of the desired product and large amounts of resinous produets. However, with lithium acetylide in liquid ammonia, yields of 30–40% of the desired product were obtained in accordance with the following procedure. A liter of liquid ammonia was saturated with dry acetylene and while the latter was passing through the solution, 7.6

(35) White and Howard, *J. Chem. Soc.*, 25 (1943).

(36) Hennion, Hinton and Nieuwland, THIS JOURNAL, **55**, 2858 (1933).

g. of lithium was added with stirring in the course of one hour. Stirring was continued until the solution was decolorized. The mixture was then cooled to −70° and 116 g. of 4-ethoxybutanone-2 was added dropwise in the course of one and one-half hours with acetylene passing through the solution. Stirring was continued for two hours longer, then the ammonia was allowed to evaporate and the residual product acidified with concentrated solution of tartaric acid. Finally, the mixture was extracted several times with ether, the ethereal extracts dried and the ether removed. The crude product was fractionated under reduced pressure and the fraction (46–50 g.) boiling at 67° (7 mm.) collected and analyzed; $n^{25}D$ 1.4370; *MR*, 40.41; calcd. *MR*, 40.32; d^{25}_4 0.922.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.58; H, 9.93; unsaturation, 2.0 ⌐; active hydrogen (Zer.), 2.0. Found: C, 67.59, 67.83; H, 9.44, 9.55; unsaturation, 2.11 ⌐ (Pd); active hydrogen (Zer.), 2.06, 1.95.

Following the same procedure, the corresponding 5-methoxyacetylene carbinol was prepared in 25% yield, b. p. 80–81° (25 mm.).

3-Methyl-5-ethoxy-3-pentenyne-1 (III).—This enyne was prepared by passing upwards through a hot tube (270–280°) charged with a mixture of aluminum phosphate (17 g.) and pumice (37 g.) the acetylene carbinol (II) at the rate of about 0.6 g. per minute and under a nitrogen pressure of 35 mm. A yield of 50% was obtained per pass; b. p. 68–70° (37 mm.); $n^{25}D$ 1.4448; *MR*, 39.4; calcd. 38.33; d^{25}_4 0.839. An absorption spectrum showed a maximum at 2250 Å., log $\epsilon_{mol.}$, 4.095.

Anal. Calcd. for $C_8H_{12}O$: unsaturation, 3.0 ⌐; active hydrogen, 1.0. Found: unsaturation, 3.1 ⌐; active hydrogen (Zer.), 1.01.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-methoxy-1-nonen-yne-5-diol-3,7 (VI, R = methyl).—A Grignard was prepared in 800 cc. of anhydrous ether from 9.8 g. of magnesium and 43.9 g. of freshly distilled ethyl bromide. The mixture was then cooled to 0° in an atmosphere of nitrogen and to it was added, in the course of thirty minutes with rapid stirring, 48.1 g. (active hydrogen, 1.94) of the acetylene carbinol (V) in 50 cc. of anhydrous ether. The mixture was then refluxed gently in nitrogen for five hours, cooled to 0° and to it added, in the course of twenty minutes, 23.3 g. of 4-methoxybutanone-2 in 20 cc. of anhydrous ether. A whitish precipitate separated out immediately. To complete the reaction the mixture was stirred in nitrogen for twenty-four hours, then cooled and hydrolyzed with a mixture of ice (480 g.) and ammonium chloride (48 g.) and the resulting product extracted several times with ether. The combined ether extracts were washed once with 50 cc. of 10% salt solution, dried with anhydrous magnesium sulfate, and the ether removed. The residue was then subjected to a high vacuum (10^{-5} mm.) at 100° for two hours to remove low boiling constituents. A yield of 63.7 g. (88%) of a yellowish highly viscous product was obtained.

Heating the glycol under high vacuum failed to remove entirely the unreacted acetylene carbinol, so further purification was effected by removing the latter as its silver salt. To a solution of 63.7 g. of the crude glycol in 140 cc. of absolute ethanol was added 35.2 g. of silver nitrate in 240 cc. of absolute ethanol and 120 cc. of concentrated ammonia (d = 0.901). The mixture was protected from light and shaken in nitrogen for twenty minutes, then centrifuged to remove the silver salt of the acetylene carbinol. The clear alcoholic layer was then diluted with an equal volume of water and extracted several times with petroleum ether. The combined petroleum ether extracts were washed with water and dried over anhydrous magnesium sulfate. The mixture was then filtered, the petroleum ether removed and the pale yellow residue subjected to a vacuum of 10^{-5} mm. at 50° for one hour. A yield of 49.5 g. of a gummy product was obtained. Attempts to crystallize this glycol were not successful. Analyses are recorded in Table III.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1-nonen-yne-5-diol-3,7 (VI, R = ethyl; left → right).—This glycol ether was prepared in the same manner as the corresponding glycol methyl ether except that the Grignard of the acetylene glycol (V) was added to an ethereal solution of 4-ethoxybutanone-2 instead of the reverse. A yield of 92% of the crude product was obtained. This was purified by removing the unreacted acetylene carbinol as its silver salt and the glycol ether obtained partitioned between equal volumes of 90% methanol and petroleum ether. The glycol ether was recovered from the methanol layer by adding two volumes of 10% salt solution and extracting with petroleum ether. A yield of 85% of the purified product was obtained as a pale yellow gum. An ultraviolet absorption spectrum of this substance showed a principal band with a maximum at 2260 Å.; log $\epsilon_{mol.}$, 4.044. Analytical data are given in Table III.

When this glycol (31 g.) was dissolved in petroleum ether and the solution allowed to stand under nitrogen at −20° for several weeks, a white crystalline product (9.2 g.) separated out, m. p. 41–42°. Further successive coolings of the mother liquor from −20 to −78° failed to produce any more crystalline product. The solid was recrystallized several times from petroleum ether at −10 to −20° until a constant m. p. of 68–69° was obtained. An ultraviolet absorption spectrum of this product showed a band with a maximum at 2260 Å.; log $\epsilon_{mol.}$, 4.12. Analytical data are given in Table III.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1-nonen-yne-5-diol-3,7 (VI, R = ethyl; right → left).—A Grignard was prepared from 19.5 g. of magnesium and 87.5 g. of ethyl bromide. The mixture was cooled to 0° in an atmosphere of nitrogen and to it was added dropwise 57 g. (7.5% excess) of the acetylene carbinol (II, R = ethyl) in the course of one hour. The mixture was then allowed to stir in nitrogen for ten hours, then cooled to 0° and to it was added dropwise 77 g. of the aldehyde (IV) in 100 cc. of ether in the course of one and a half hours. Stirring was continued at room temperature for twenty-four hours, then the mixture was hydrolyzed with a saturated solution of ammonium chloride containing 80 g. of the latter. A yield of 120 g. of the crude glycol was obtained which was purified in the same manner as the glycol prepared from left to right. A yield of 112 g. of the purified product was obtained as a pale yellow gum which had an ultraviolet spectrum with a maximum at 2260 Å.; log $\epsilon_{mol.}$, 3.992. Other analytical data are given in Table III.

When 112 g. of this glycol was dissolved in a liter of petroleum ether and the solution allowed to stand under nitrogen at −20° for several weeks, a white solid (60 g.) separated out which had a m. p. of 41–47°. This was recrystallized several times from petroleum ether at −10 to −20° until a constant m. p. of 67–68° was obtained. An ultraviolet absorption spectrum showed a maximum at 2260 A., log $\epsilon_{mol.}$, 4.018. Other analytical data are given in Table III.

5-Dehydroglycol isopropyl and 5-dehydroglycol *t*-butyl ethers were synthesized in the same manner as the 5-dehydroglycol methyl ether from the Grignard of the acetylene carbinol (V) and 4-isopropoxybutanone-2 and 4-*t*-butoxybutanone-2, respectively. The products were purified only to the stage of removing the volatile constituents by heating at 100° (10^{-4} mm.) for one hour.

The high hydrogenation values shown in Table III are due to partial hydrogenolysis of the hydroxyl groups in the presence of a large excess of catalyst usually required for obtaining quick and accurate estimation of unsaturation with an especially designed semicrohydrogenation apparatus[37] which was thoroughly tested with several known unsaturated compounds.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy 1,7-nonadien-yne-5-ol-3 (IX).—A Grignard was prepared in 300 cc. of anhydrous ether from 1.4 g. of magnesium and 6.0 g. of ethyl bromide. The Grignard was cooled to 0° in nitrogen and to it was added dropwise 6.8 g. of 3-methyl-5-ethoxy-3-pentyne-1 (III). The

(37) Rivers, Ph.D. Thesis, M. I. T., 1941, p. 48.

TABLE III

ANALYTICAL DATA OF 5-DEHYDROGLYCOL ETHERS

5-Dehydroglycol-ethers	Yield, %	M. p., °C.	Analyses C Calcd.	C Found	H Calcd.	H Found	A. H. (Zer.) Calcd.	A. H. (Zer.) Found	H_2 (Pd, Pt) Calcd.	H_2 (Pd, Pt) Found
										4.1 (Pd)
Methyl (1 → r)[a]				75.42		9.97		1.98		5.9 (Pt)
($C_{21}H_{34}O_3$)	74	Gum	75.44	75.09	10.24	10.01	2.0	1.93	4.0	5.4 (Pt)
										4.67(Pd)
Ethyl (1 → r)				75.97		11.01		2.15		4.89(Pd)
($C_{22}H_{36}O_3$)	80–85	Gum	75.81	75.55	10.41	11.17	2.0	2.12	4.0	5.15(Pt)
				75.79		10.79				4.99(Pt)
Ethyl (1 → r)										5.27(Pt)
solid	30–40	68–69	75.81	75.95	10.41	10.42	2.0	2.2	4.0	5.31(Pd)
Ethyl (r → 1)[b]				75.5		10.3		2.06		5.47(Pt)
($C_{22}H_{36}O_3$)	85–88	Gum	75.81	75.2	10.41	10.5	2.0	2.09	4.0	5.16(Pt)
Ethyl (r → 1)				75.6		10.5		1.93		
solid	40–50	67–68	75.81	75.2	10.41	10.6	2.0	2.10	4.0	4.95(Pt)
Isopropyl (1 → r)										
($C_{23}H_{38}O_3$)	54	Gum	...	...	...	...	2.0	1.80	4.0	5.6 (Pt)
t-Butyl (1 → r)				75.1		10.13		1.97		
($C_{24}H_{40}O_3$)	79	Gum	76.55	74.9	10.58	10.02	2.0	1.91	4.0	4.8 (Pt)

[a] (1 → r) indicates the preparation of the glycol by adding the Grignard of the acetylene carbinol (V) to the corresponding 4-alkoxybutanone-2. [b] (r → 1) indicates the preparation of the glycol by adding the Grignard of the acetylene carbinol (II) to aldehyde (IV).

mixture was allowed to stir overnight at room temperature, then cooled to 0° and to it added dropwise in the course of one hour 10.8 g. of the aldehyde (IV) in equal volume of ether and again allowed to stir in nitrogen at room temperature overnight. Finally, the mixture was hydrolyzed with excess cold concentrated ammonium chloride solution and the product recovered and heated for one hour at 100° (10^{-4} mm.) to remove low boiling products; yield, 13.5 g., (75%). This was further purified by distillation in a molecular still of the falling film type and the fraction (almost all of the product) distilling at 156° (0.005 mm.) collected and analyzed; $n^{25}D$ 1.5169. An ultraviolet absorption spectrum showed a maximum at 2320 Å.; log $\epsilon_{mol.}$, 4.315.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36; unsaturation, 5 ⌐¬; active hydrogen (Zer.), 1.0. Found: C, 79.67, 79.80; H, 10.2, 10.16; unsaturation, 5.31 ⌐¬ (Pt), 5.20 (Pd) ⌐¬; active hydrogen, (Zer.), 1.15, 1.1.

Selective Hydrogenation of 5-Glycol Ethers.—Attempts to add two hydrogen atoms to the acetylene bond of the 5-dehydroglycol ethers chemically were not successful. For example, the solid 5-dehydroglycol ethyl ether, m. p. 68–69°, was treated in methanol or in liquid ammonia with sodium or lithium, or with a large excess of calcium in 90% ethanol and in every case the product was recovered unchanged; *e. g.*, melting point, hydrogenation and active hydrogen determinations were identical with the original; even mixed melting point with the original showed no depression. Catalytic hydrogenation in alcohol, however, using 1% palladium deposited on calcium carbonate showed a high degree of selectivity, so that all of our preparations, including that of 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1,7-nonadien-yne-5-ol-3 (IX) were partially hydrogenated by adding one mole equivalent of hydrogen to each. In most of the cases the products recovered were checked by hydrogenation and active hydrogen estimations.

Conversion of the Glycol Ethers (VII) into the Dihalides.—Phosphorus trichloride, tribromide and triiodide were first tried as halogenating agents both in the presence and absence of pyridine. Phosphorus tribromide was found to give the best results. To 100 cc. of dry benzene was added 25 g. of freshly distilled phosphorus tribromide and dry purified nitrogen was allowed to bubble through the solution for five to ten minutes to displace any free hydrogen bromide present. The mixture was then cooled to 0° and, while nitrogen was bubbling through it, 15.3 g. of the glycol (VII, left → right) in 100 cc. of benzene and 22 cc. of dry pyridine was added dropwise in the course of fifteen minutes. The mixture was allowed to stand at 0° for one-half hour, then heated to 60–80° for one hour. The mixture was then cooled, diluted with water and the layers separated. The organic layer was extracted several times with a 5% solution of phosphoric acid, dried and the solvent removed under reduced pressure. The residue was subjected to a high vacuum (10^{-4} mm.) at 50° for one hour; yield of a highly viscous brownish residue, 13 g.

Anal. Calcd. for $C_{21}H_{34}OBr_2$: Br, 34.57. Found: Br, 31.61, 31.60.

The low bromine was due to a partial hydrolysis of the tertiary bromine and to a slight dehydrobromination, since the dibromide showed a small amount of active hydrogen and bands of low intensity at 2850 and 3250 Å.

Dehydrobromination of the Dibromides.—Ordinarily the dehydrobromination was accomplished without isolating the dibromide. Following the above experiment as a typical example, the benzene and other volatile products were removed at the end of the reaction under reduced pressure and to the residue was added 400 cc. of hot 95% alcohol containing 40 g. of potassium hydroxide. Heating was continued in nitrogen at 60–80° under a slightly reduced pressure for one hour, then most of the alcohol was removed and the residue cooled, diluted with six volumes of water and extracted with 4 × 100 cc. of olefin-free petroleum ether. The extract was shaken several times with 5% phosphoric acid solution, then with 10% salt solution, and dried with magnesium sulfate. When the petroleum ether was removed, a yield of 10.9 g. (82%) of the crude product was obtained. This was distilled under a highly reduced pressure and the pale yellow fraction (8 g.) boiling at 90–95° (10^{-4}–10^{-5} mm.) was collected and analyzed. Spectroscopically, this sample had two prominent bands in the ultraviolet, one at 3250 Å.; $E^{1\%}_{1\ cm.}$ 535, the other at 2850 Å.; $E^{1\%}_{1\ cm.}$ 655, and two feeble indications at 3450 and 3710 Å., respectively. With antimony trichloride in chloroform, it gave a deep blue color with maxima at 5800 and at 6180–6200 Å., respectively (Fig. 1, curves with broken lines). Biological results of products prepared by this method are given in Table I, assays 1–9.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.93; H, 10.73; OCH_3, 10.33; unsaturation, 5 ⌐¬; active hydrogen, 0.0. Found: C, 81.88, 82.09; H, 10.95, 11.12; OCH_3, 11.2; unsaturation, 4.96 (Pd), 5.11, 5.17 (Pt) ⌐¬; active hydrogen (Zer.), negligible.

Repeated distillation of a sample having an $E^{1\%}_{1\ cm.}$ (3250 Å.) value of 1000 at 10^{-5} mm. from a shallow vessel caused considerable decomposition of the vitamin ether. In fact, after five consecutive distillations the band at 3250 Å. had vanished completely. Another sample from a single distillation was fractionated in absolute methanol at temperatures between 0 and −78° and the product (pale yellow solid) insoluble below −40° separated and analyzed spectroscopically. It was found to have a prominent band at 3250 Å.; $E^{1\%}_{1\ cm.}$ 1090.

Dehydrochlorination of the Glycol Methyl Ether (VII, left → right) via Thionyl Chloride and Alcoholic Potash.—A solution of 5.96 g. of freshly distilled thionyl chloride in 10 cc. of ether was added dropwise in the course of fifteen minutes to a well-stirred mixture of 8.5 g. of the glycol methyl ether (VII), 3.96 g. of anhydrous pyridine and 20 cc. of ether, maintained at 0° with nitrogen passing through the solution. The mixture was allowed to come to room temperature, then heated on the water-bath to 60–80° for three hours. During this time all the ether had evaporated, and the residue was cooled and extracted with petroleum ether, the latter removed and the residue (7 g.) analyzed. It gave a deep blue color with antimony trichloride in chloroform and a broad band in the ultraviolet between 3000 and 3300 Å. with an $E^{1\%}_{1\ cm.}$ (3250 Å.) value of 350, showing definite spontaneous dehydrochlorination.

To completely dehydrochlorinate the above product, it was mixed with 60 cc. of methanol containing 3 g. of potassium hydroxide and the mixture heated on the water-bath in an atmosphere of nitrogen for two hours, then cooled, diluted with three volumes of water and extracted with petroleum ether, the extract washed with 10% tartaric acid solution and dried over magnesium sulfate. The final product was free from chlorine, and was purified further by fractionation at low temperatures from a 50–50 mixture of absolute methanol and petroleum ether. A small amount of brown solid separated at −70° which had an ultraviolet spectrum in the region of 3100–3300 Å. and gave a deep blue color with antimony trichloride in chloroform, but was discarded because it was found to contain sulfur. The filtrate yielded a product free from sulfur and chlorine and was found to exhibit two maxima in the ultraviolet; one at 2830 Å.; $E^{1\%}_{1\ cm.}$ 650; the other at 3250–3280 Å.; $E^{1\%}_{1\ cm.}$ 502. When fed to vitamin A deficient rats, it was found biologically active in doses of 10 to 28 γ. Other analytical data of this product were no different from those obtained by the dehydrobromination method using phosphorus tribromide. Similar results were obtained by the dehydrochlorination of the glycol ethyl ether (right → left) using thionyl chloride and alcoholic potash.

The dehydrobromination of the glycol isopropyl (VII, R = isopropyl) and the glycol *t*-butyl (VII, R = *t*-butyl) ethers (left → right) was effected in the same manner as that of the corresponding glycol methyl ether using the phosphorus tribromide method. Yields of about 50–60% were obtained. After preliminary purification from methanol at low temperatures, the isopropyl ether was distilled from a shallow vessel and the product, a yellow viscous liquid, boiling at 87–90° (10^{-5} mm.) was collected and tested spectroscopically and biologically. Table I (assays 11 and 12) gives the biological results of this ether. Spectroscopically it exhibited the usual two broad bands; one at 2800–2900 Å. and the other at 3100–3300 Å. The spectrum of the antimony trichloride color also showed two maxima; one at 5800 Å.; $E^{1\%}_{1\ cm.}$ 506, and the other at 6180 Å.; $E^{1\%}_{1\ cm.}$ 367.

The *t*-butyl ether could not be distilled without appreciable decomposition, so it was fractionated at low temperatures from methanol and the fraction which separated out below −30° was tested biologically and spectroscopically. Assay 13 of Table I gives the biological test on rats of this crude sample of vitamin A *t*-butyl ether. Spectroscopically it also gave the two usual broad bands in the ultraviolet. The spectrum of the antimony trichloride color gave the usual two maxima: one at 5800 Å.; $E^{1\%}_{1\ cm.}$ 388 and the other at 6180–6200 Å.; $E^{1\%}_{1\ cm.}$ 200. This work was done during the early part of the war and no further attempt was made to purify these ethers. However, an attempt was made to convert both of these ethers by the method of Rigby[38] into the corresponding palmitic and acetic esters of vitamin A by treating them with palmityl or acetyl chloride in the presence of traces of anhydrous zinc chloride. Partial conversion was actually accomplished, as it was indicated by the saponification number of the esters produced. With acetyl chloride, the acetate produced had a saponification number between 270 and 300, as against the theoretical of 328. In view of the difficulty encountered in the purification of these esters no further work was done along these lines.

Direct Dehydration of Glycol Methyl Ether (VII, left → right).—Preliminary investigation on the direct dehydration of 1,4-glycol model compounds of the type of the glycol (VII) led to the production of dihydrofurans. However, when 5.7 g. of the glycol methyl ether (VII) was dehydrated in toluene (190 cc.) in the presence of 0.3 g. of *p*-toluenesulfonic acid, by distilling in nitrogen 60 cc. of toluene, a product was obtained which behaved like that obtained by the dehydrobromination process. When distilled from a shallow vessel, a yellow oil (2 g.) was obtained boiling at 90–95° (10^{-4}–10^{-5} mm.). It gave a deep blue color with antimony trichloride in chloroform and exhibited the usual dual maxima in the ultraviolet. Upon hydrogenation it absorbed 4.98 moles of hydrogen as against the theoretical of 5 for the methyl ether of vitamin A. A Zerewitinoff determination showed less than 0.1 active hydrogen, indicating the absence of hydroxyl groups. The preliminary assay 10, Table I, shows the biological activity of this product.

Dehydrobromination of Glycol Ethyl Ether (VII, right → left) via Pyridine Hydrobromide and Alcoholic Potash.—To 40 g. of dry pyridine was added 4.5 g. of dry gaseous hydrogen bromide. The partly solid-partly liquid mixture was cooled in nitrogen and to it was added 8.5 g. of solid glycol ethyl ether (VII) in 50 cc. of anhydrous benzene and heated on the water-bath for three hours while nitrogen was slowly bubbling through it. Most of the solvent was then removed under reduced pressure and to the residue was added 100 cc. of 10% hot alcoholic potash, and the mixture again heated on the water-bath for one-half hour. It was then cooled in nitrogen, diluted with three volumes of water and extracted with petroleum ether. The petroleum ether extract was shaken with 5% phosphoric acid solution, then with water and dried over magnesium sulfate. From the final solution was obtained a yellowish-brown viscous liquid (6.5 g.) which gave a deep blue color with antimony trichloride in chloroform, and exhibited two bands in the ultraviolet: one of very high intensity at 3000–3700 Å. and the other of very low intensity at 2850–2900 Å. For further purification, it was partitioned between equal volumes (100 cc.) of 83% ethanol and petroleum ether, the latter was washed with water, dried and passed through a column 4′ × 1″ filled with 40–60 mesh activated alumina (ALORCO). The column was further washed with a total of 1500 cc. of petroleum ether and the latter removed from the washings; a yellow residue (4.5 g.) remained. This was distilled in a molecular still of the falling film type and the largest fraction (3.5 g.), a clear yellow highly viscous liquid, boiling at 95–98° (10^{-4}–10^{-5} mm.) (bath temperature 145–150°), collected and analyzed. This gave a deep blue color with antimony trichloride and a fine structure

(38) Rigby, Ph.D. Thesis, M. I. T., 1930.

in the ultraviolet of three bands (Fig. 3): one at 3300 Å.; $E^{1\%}_{1\ cm.}$ 1690; a second at 3480 Å.; $E^{1\%}_{1\ cm.}$ 1830; and a third at 3670 Å.; $E^{1\%}_{1\ cm.}$ 1520. No distinct bands developed on the alumina, and the product eluted from it with hot ethyl alcohol exhibited the usual two bands in the ultraviolet, but with lower intensity.

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.00; H, 10.89; OC_2H_5, 14.03; unsaturation, 5.0 ═; mol. wt., 314.5. Found: C, 82.78, 83.32; H, 10.50, 10.90; OC_2H_5, 13.26; unsaturation, 4.94, 5.06 ═ (Pt); mol. wt. (in benzene), 313.7, 310.3, 310.2.

After standing at 0° in nitrogen for over six months, it partially crystallized into pale yellow needles which had a m. p. of 28–30°.

The dehydrobromination of the glycol ethyl ether (left → right) by the above method gave similar results, except much lower yields of the desired product. Similarly, the dehydrobromination of the carbinol (X) by the same procedure yielded a product which in its crude form showed two bands in the ultraviolet; one with a low intensity at 2800–2900 Å., and another with a high intensity at 3000–3700 Å.

Dehydration of the Carbinol (X).—To 150 cc. of thiophene-free toluene was added 0.09 g. of *p*-toluenesulfonic acid and 25–30 cc. of toluene distilled to remove traces of water present in the mixture. The toluene solution was then cooled in nitrogen and to it was added 4.5 g. of the carbinol (X) in 60 cc. of toluene. Enough toluene (50–60 cc.) was then distilled in nitrogen until the distillate was completely free from cloudiness. The contents (reddish-brown) of the flask was cooled and treated with 50 cc. of methanol containing 2.5 g. of potassium hydroxide. Enough water was then added to separate the layers, the organic layer removed, washed with water, and dried over magnesium sulfate. When the toluene was completely removed, a reddish-brown viscous liquid (3.8 g.) remained. This gave a blue color with antimony trichloride in chloroform and exhibited two broad bands in the ultraviolet; one at 2800–2900 Å. and the other at 3000–3400 Å., the latter being more intense. To further purify this product, it was partitioned between 100 cc. of petroleum ether and 100 cc. of 90% methanol. Most of the product went into the petroleum ether which was washed with water, dried, and the solvent removed under reduced pressure. The residue was taken up in absolute methanol and fractionated at temperatures between −10 and −78°, the product (a yellow semi-solid) which separated out in various fractions below −40° recovered in methanol and extracted from it with petroleum ether by adding 5% salt solution. From the petroleum ether a product was obtained which gave a deep blue color with antimony trichloride in chloroform and exhibited a single band in the ultraviolet with a well-defined maximum at 3250–3270 Å.; $E^{1\%}_{1\ cm.}$ 1500 and log $\epsilon_{mol.}$ 4.67 (see Table II).

Dehydration of 5-Dehydroglycol Methyl Ether (VI left → right) to 5-Dehydrovitamin A Methyl Ether (VIII).—The 5-dehydroglycol methyl ether (31.5 g.) was dehydrated in toluene (400 cc.) using *p*-toluenesulfonic acid (0.7 g.) in the usual manner. The dehydrated product was first treated with 5% methyl alcoholic potash followed by partitioning between equal volumes of petroleum ether and 90% methanol. The petroleum ether layer was washed with water, dried and the solvent removed; yield, 24 g. This product gave a purplish-blue color with antimony trichloride in chloroform and two broad bands in the ultraviolet: one with a high intensity at 3000–3300 Å., the other with a low intensity at 2800–2900 Å. When distilled under a high vacuum from a shallow vessel, a clear light orange liquid came over at 85–95° (10^{-4}–10^{-5} mm.). This was tested biologically and the results are given in Table I, assay 14. Hydrogenation of this sample showed the presence of 6.35 double bonds and showed negligible active hydrogen (Zer.). Although the hydrogen analysis was close to the theoretical value the carbon was about 2% low. Further purification was effected by alternate distillation and low temperature fractionation from absolute methanol. The results are given in Table IV. The product from the second distillation was again tested biologically (Table I, assay 15).

The final product (see Table IV) was a light orange viscous oil, having the following analytical data:

Anal. Calcd. for $C_{21}H_{31}O$: C, 84.50; H, 10.13; OCH_3, 10.39; unsaturation, 6.0 ═. Found: C, 83.87, 83.60; H, 10.34, 9.92; OCH_3, 11.25; unsaturation, 6.3, 6.08, 6.1 ═ (Pt).

A freshly distilled sample of 5-dehydrovitamin A methyl ether (7.8 g.) with an $E^{1\%}_{1\ cm.}$ (3200 Å.) value of 1000 was selectively hydrogenated in absolute ethanol by adding to it one mole-equivalent of hydrogen in the presence of 1% palladium deposited on calcium carbonate (using one-half the weight of the sample). The crude product was recovered and analyzed spectroscopically. It was found to have a peak at 3220–3230 Å.; $E^{1\%}_{1\ cm.}$ 886. This was further purified by low temperature fractionation from absolute methanol and the fraction insoluble below −30° recovered and distilled under high vacuum. A product (yellow oil) boiling at 90–95° (10^{-4} mm.) was collected and analyzed. It gave a blue color with antimony trichloride in chloroform, the transmission spectrum of which is shown in Fig. 1 (solid line curves). In this case the 6180 Å. maximum is much more intense than that of the 5800 Å. with an $E^{1\%}_{1\ cm.}$ value of 3284. The ultraviolet absorption spectrum showed a single well-defined band with a maximum at 3230 Å.; $E^{1\%}_{1\ cm.}$ 1560 (Fig. 2, curve B). Hydrogenation showed the presence of 5.15 (Pt) double bonds.

TABLE IV

THE EFFECT OF ALTERNATE HIGH VACUUM DISTILLATION AND LOW TEMPERATURE FRACTIONATION ON 5-DEHYDROVITAMIN A METHYL ETHER

No. of distillations (10^{-4}–10^{-5} mm.) and low temp. fractionations	$\lambda_{max.}$, Å	$E^{1\%}_{1\ cm.}$ max.
Second distillation	3180	1300
Third distillation	3180	1200
Fourth distillation	3200	844
First fractionation (methanol) of distilled product (4th time)	3190	1090
Second fractionation	3200	1120
Third fractionation	3200	1140
Distillation of final fractionated sample	3220	1600 (Curve A, Fig. 2)

Ozonization of Vitamin A Methyl Ether (XI).—A sample (1.81 g.) of the vitamin A methyl ether prepared by the foregoing method and kept under nitrogen at −20° for over two years was ozonized by the method of Strain.[39] It yielded about 0.5 g. (26%) of crude sodium bicarbonate soluble geronic acid 2,4-dinitrophenylhydrazone. This was recrystallized several times from aqueous acetic acid and from aqueous methanol; m. p. 133.5–134.5° (cor.). Mixed m. p. with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone showed no depression; 134–134.5° (cor.).

Dehydration of 5-Dehydroglycol Ethyl Ether (VI, left → right).—The 5-dehydroglycol ethyl ether (22 g.) was dehydrated in toluene (550 cc.) in the presence of 0.45 g. of *p*-toluenesulfonic acid using the general procedure adopted in this paper. The crude product was treated with 5% methyl alcoholic potash, then partitioned between equal volumes (200 cc.) of petroleum ether and 90% methanol. The fraction taken by the petroleum ether was recovered (15.5 g.) and fractionated several times in

(39) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

absolute methanol between 0 and −78° and the fractions insoluble below −30° (orange-yellow solid) were combined and distilled from a shallow vessel under a high vacuum. A light orange oil boiling at 95–98° (10^{-4}–10^{-5} mm.) was collected and analyzed. The ultraviolet spectrum showed a single, well-defined band with a maximum at 3210–3220 Å.; $E^{1\%}_{1\,cm.}$ 1400.

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.55; H, 10.33; unsaturation, 6.0 ⌐═; active hydrogen, 0.0. Found: C, 84.58, 85.22; H, 10.90, 11.00; unsaturation, 6.1, 6.2 ⌐═ (Pt), 6.05 ⌐═ (Pd); active hydrogen (Zer.), 0.05 (within experimental error).

Dehydration of 5-Dehydroglycol Ethyl Ether (VI, right → left).—This glycol ethyl ether (20 g.) was dehydrated in the same manner as the previous sample in 500 cc. of toluene and in presence of 0.4 g. of *p*-toluenesulfonic acid. After washing with 5% methyl alcoholic potash and partitioning between petroleum ether and 90% methanol, a product (14 g.) was obtained which had an $E^{1\%}_{1\,cm.}$ (3210 Å.) value of 1320. Further purification was effected by dissolving the product in petroleum ether and passing it with nitrogen through a 4′ × 1″ column packed with 40–60 mesh of activated alumina (ALORCO). The column was then washed with 1.5 liters of petroleum ether and the unadsorbed portion (11–12 g.) was recovered from the petroleum ether and fractionated once at low temperatures from absolute methanol. The fractions insoluble below −30° were collected and distilled under a high vacuum. An orange-yellow oil boiling at 95–100° (10^{-4}–10^{-5} mm.) was collected and analyzed. It had a single, well-defined band with a maximum at 3220 Å.; $E^{1\%}_{1\,cm.}$ 1410 (Fig. 2, curve C). Upon catalytic hydrogenation (Pt) it absorbed 6.1 moles of hydrogen. Molecular weight determinations in benzene by the freezing point method gave the following values: Calcd. for $C_{22}H_{32}O$: 312.5. Found: 310.7, 308.3, 313.

Dehydration of 5-Dehydrocarbinol Ethyl Ether (IX).—About 10 g. of 5-dehydrocarbinol ethyl ether (IX) was dehydrated in 400 cc. of toluene in the presence of 0.2 g. of *p*-toluenesulfonic acid. The resulting mixture was treated with 5% methyl alcoholic potash and the product recovered from it partitioned between petroleum ether and 90% methanol. The fraction (7.5 g.) taken up by the petroleum ether was recovered and fractionated at low temperatures from absolute methanol. The fractions insoluble below −30° were combined and distilled under high vacuum. An orange-yellow oil was obtained boiling at 95–98° (10^{-4}–10^{-5} mm.). This had a single band with a maximum at 3210–3220 Å.; $E^{1\%}_{1\,cm.}$ 1350.

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.55; H, 10.33; unsaturation, 6.0 ⌐═; active hydrogen, 0.0. Found: C, 83.67, 83.38; H, 10.54, 10.31; unsaturation, 6.10, 6.28 ⌐═ (Pt); active hydrogen (Zer.), 0.03 (negligible).

Ozonization of 5-Dehydrovitamin A Ethyl Ether (VIII).—About 1.5 g. of 5-dehydrovitamin A ethyl ether prepared by the dehydration of 5-dehydroglycol ethyl ether (right → left) was ozonized in the usual manner and the 2,4-dinitrophenylhydrazone precipitated. The bicarbonate soluble portion was recrystallized once from aqueous methanol; m. p. 126.5–127.5° (cor.); yield, 0.3 g. (20%). This was again recrystallized from aqueous methanol three times, and a final m. p. of 134–134.5° (cor.) was obtained. Mixed m. p. with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone gave no depression.

Selective Chemical Reduction of 5-Dehydrovitamin A Ethyl Ether.—The selective chemical reduction of the acetylene bond in 5-dehydrovitamin A ethyl ether was studied using the estimation of unsaturation and the extinction coefficient in the ultraviolet as guides in estimating the degree of reduction. No appreciable reduction was observed when zinc dust and acetic acid in ethanol or calcium in 90% ethanol were used as reducing agents. Sodium in liquid ammonia brought about complete destruction of the molecule. Partial reduction was observed with zinc–copper couple in absolute ethanol and with "Devarda's" (Baker) and Raney alloys in 2% of aqueous (1:9) alcoholic potassium hydroxide. The most successful results were obtained with zinc dust in aqueous alcoholic potassium hydroxide. The following is a representative experiment: 5-Dehydrovitamin A ethyl ether (2.03 g.; unsaturation 6.19 ⌐═ (Pt); $E^{1\%}_{1\,cm.}$ 1350) was dissolved in 90 g. of absolute ethanol and to the solution added, with cooling and purified nitrogen slowly bubbling through it, 10 cc. of water, 6 g. of solid potassium hydroxide and 0.6 g. of zinc dust. Nitrogen was allowed to bubble slowly through the mixture for twenty hours, then 20 cc. of water was added and the reaction allowed to proceed five hours longer. Finally, the mixture was diluted with 20 cc. of water and extracted with petroleum ether, the extract washed with water, dried, and the solvent removed under vacuum. The residue (2 g.) was fractionated at low temperatures from 20 cc. of absolute methanol and the fractions (1.5 g., pale yellow solid) separating below −30° combined and analyzed. An ultraviolet absorption spectrum showed a well-defined band with a maximum at 3230 Å.; $E^{1\%}_{1\,cm.}$ 1590 (Fig. 2, curve D). Hydrogenation (Pt) showed the presence of 4.85–5.2 double bonds. The combined filtrates from the above purification exhibited a band at 3220–3230 Å.; $E^{1\%}_{1\,cm.}$ 1215. This experiment was repeated several times, in some cases with a large excess of zinc dust, and the results were identical.

Acknowledgment.—The authors are indebted to Mrs. Alice R. Lowry, Mrs. Silvia P. Solar, and Mr. S. M. Nagy for most of the analyses; to Mrs. Ruth B. Pitt for assistance in some of the tedious purification experiments; to Miss Therese M. Harrington for assistance in the ozonization and other experiments; and to Professor Robert S. Harris for the biological assays. This article is a part of a research program on the synthesis of vitamins A and D, support of which was derived in part through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Parke, Davis and Company, the Upjohn Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

Summary

1. The synthesis of biologically active vitamin A ethers has been achieved via several routes, using 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylbuten-1-al-4 as the key intermediate.

2. Synthetic methyl and ethyl ethers of vitamin A have been obtained in relatively pure form. The isopropyl and *t*-butyl ethers have been obtained in less pure form.

3. Several new intermediates used in the various syntheses are described with complete analytical data for the first time.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 12, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Organic Reactions with Aluminum Chloride. XX. The Action of Aluminum Chloride upon Ethylene Chloride

BY KEIITI SISIDO AND YOSIO YOSIKAWA

In our previous communications[1] in which the Friedel–Crafts reaction of dihalogenoalkanes with benzene were investigated, many anomalies, particularly shifts and splitting off of halogen atoms, were observed. During these researches we were impressed with the need for the fundamental studies of the behavior of these alkylene dichlorides alone in the presence of aluminum chloride, in order to clarify our understanding of the complicated reaction of condensation. The present paper deals with the change of ethylene chloride, one of the simplest homologs of the series, in the absence of an aromatic hydrocarbon, under the ordinary conditions of the Friedel–Crafts reaction.

It was astonishing that, when we treated ethylene chloride with 15% of its weight of aluminum chloride at 80°, a violent reaction ensued and the whole reactant, after only four hours of heating, solidified. In order to study the mechanism of the formation of solid material, it was decided to carry out the experiments under milder conditions. The reaction was now carried out with ethylene chloride and 10% of aluminum chloride at 26 ± 1°, and it was interrupted when the greater part of the dichloride still remained unreacted, so that the distillable intermediate products could be obtained. The reaction was continued for seventy-five minutes and the mass was poured into iced water to decompose aluminum chloride; after recovering the unchanged material, the products were fractionated in the usual way. By this procedure we have isolated the same compounds as the intermediates of a polycondensation product of benzene and ethylene chloride,[2] which we have described in a previous paper,[3] namely, bibenzyl and *m*-bis-(β-phenylethyl)-benzene were identified by analyses and by mixed melting points with authentic specimens. It should be noted that the latter substance was a new compound which we had found just before the War among the intermediates of the above mentioned high molecular material; the constitution was ascertained by the decomposition[3] as well as by the synthesis.[4] The mechanism of the formation of these substances from benzene and ethylene chloride as well as the *meta*-orientation of the reaction were discussed in the previous papers.

The present facts are explained only by the assumption that benzene was formed from ethylene chloride by the action of aluminum chloride; this benzene condenses with the excess of ethylene chloride in the presence of aluminum chloride in the same way as the synthesis of the elastomer by the Friedel–Crafts reaction. During the reaction a considerable amount of hydrogen chloride was liberated, but it was not accompanied by acetylene, ethylene, vinyl chloride or any other unsaturated compound according to qualitative analyses. As these compounds are therefore not regarded as stable intermediates, the route from ethylene chloride to benzene is not certain. It is easy to surmise that an elimination of two moles of hydrogen chloride from ethylene chloride produces a free radical —CH=CH—, three moles of which form a benzene molecule by cyclization. But rigorous proof is lacking.

The formation of benzene from ethylene chloride during the Friedel–Crafts reaction was not observed previously by us, although many investigations were carried out on the condensations of ethylene chloride and aromatic hydrocarbons other than benzene by the action of aluminum chloride. Particularly, we could not find benzene derivatives among the reaction products of ethylene chloride and toluene,[5] ethylbenzene,[6] chlorobenzene,[7] bromobenzene,[8] cymene,[8] biphenyl,[8] naphthalene,[8] phenol,[9] anisole,[9] diphenyl ether,[9] etc., respectively.

Experimental[10]

Ethylene chloride used in this investigation was carefully redistilled and the fraction boiling at 82–83° was submitted to the reaction.

In an ordinary three-necked flask 1190 g. of ethylene chloride was maintained at 25° and 119 g. of newly pulverized anhydrous aluminum chloride was thrown in at once. During the addition, which required one minute, scarcely any elevation of the temperature was remarked. The mixture was stirred for seventy-five minutes at 26 ±

Fraction	Boiling range, °C.	Yield, g.
I	80–140	4.0
II	140–180	3.2
III	180–230	6.7
IV	230–270	3.4
V	270–295	3.0
VI	295–320	4.0
Residue	.....	13.0

(1) Sisido and Nozaki, THIS JOURNAL, **69**, 961 (1947), etc.

(2) Shinkle, U. S. Patent 2,016,026; *C. A.*, **29**, 8175 (1935); etc.; Shinkle, Brooks and Cady, *Ind. Eng. Chem.*, **28**, 275 (1936); Sisido and Katô, *J. Soc. Chem. Ind., Japan*, **43**, 232B (1940); *C. A.*, **35**, 1026 (1941); Klebanskii and Mironenko, *J. Applied Chem., U. S. S. R.*, **14**, 618 (1941).

(3) Sisido and Katô, *J. Soc. Chem. Ind., Japan*, **44**, 25B (1941); *C. A.*, **35**, 4369 (1941).

(4) Sisido, *J. Soc. Chem. Ind., Japan*, **44**, 55B (1941); *C. A.*, **35**, 4370 (1941).

(5) Sisido and Kanari, *J. Soc. Chem. Ind., Japan*, **44**, 170B (1941); Sisido and Siihara, *ibid.*, **45**, 62B (1942).

(6) Sisido and Katô, *ibid.*, **44**, 148B (1941).

(7) Sisido, *ibid.*, **44**, 463B (1941).

(8) Not yet published.

(9) Sisido and Huruya, *J. Soc. Chem. Ind., Japan*, **46**, 674 (1943), (in Japanese).

(10) Microanalyses by Miss Yasuko Meizyô of our Laboratory.

1°, and then was poured into iced water acidified with hydrochloric acid. The organic layer was separated and after drying over calcium chloride the unchanged ethylene chloride, which weighed 755 g., was removed by distillation. The residue was now fractionally distilled under vacuum of 10 mm. and several fractions were obtained.

The fractions I and III crystallized after a day.

The crystals obtained from fraction I were recrystallized three times from alcohol until the melting point was fixed at 51.7–52.0°. This compound was proved to be identical with bibenzyl by a mixed melting point with a known sample.

Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 7.87.

The repeated recrystallizations of the crystals from the fraction III afforded a sample of a melting point of 56.7–57.4°. This agrees in properties with *m*-bis-(β-phenylethyl)-benzene and, when admixed with an authentic specimen, did not depress the melting point, thus proving the identity.

Anal. Calcd. for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.27; H, 7.49.

Summary

By the action of anhydrous aluminum chloride ethylene chloride yields bibenzyl, *m*-bis-(β-phenylethyl)-benzene and finally a polycondensation product.

This phenomenon is explained that at first benzene is formed from ethylene chloride. The resultant benzene then condenses with the excess of ethylene chloride in the sense of the Friedel–Crafts reaction.

KYOTÔ, JAPAN RECEIVED NOVEMBER 23, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Organic Reactions with Aluminum Chloride. XXI. The Cycli-alkylation of Benzene with 1,4-Dibromo-2-butene and the Disproportionation of Hydrogen Atoms

BY KEIITI SISIDO AND HITOSI NOZAKI

The Friedel–Crafts reactions of poly-functional alkylating agents with benzene are often associated with various anomalies, for example, the "cycli-alkylation"[1] and the shift or reduction of halogen atoms.[2] The former reaction may be of unusual interest as a simple method of synthesizing the compounds of polynuclear structures. In continuation of the studies in this field, we have investigated the condensation of 1,4-dibromo-2-butene with benzene.

The dibromobutene dissolved in a large excess of benzene was treated with aluminum chloride at ordinary temperature. Upon fractional distillation of the reaction products, tetralin and 2-phenyl-1,2,3,4-tetrahydronaphthalene were found to have been formed along with a considerable amount of tarry matter. Neither naphthalene nor dihydronaphthalene was produced. Phenyl-substituted butanes which might be expected as a result of the ordinary Friedel–Crafts reaction also failed to be detected.

These observations may indicate that the first stage of the reaction consists in the condensation of one mole of benzene with one mole of the dibromobutene forming 1,4-dihydronaphthalene under the cyclization by the 2-butene residue. As 1,4-dihydronaphthalene rearranges, however, easily into 1,2-dihydro-compound, for example, by the action of sodium ethylate,[3] the hydrogen atoms at the 1,4-position are supposed to be labile. It seemed to us, therefore, necessary to examine the action of aluminum chloride upon 1,4-dihydronaphthalene in order to clarify the mechanism of this condensation.

To a solution of the dihydronaphthalene in benzene was added aluminum chloride and the mixture was allowed to react at ordinary temperature. It was noted that only small quantities of 2-phenyl-1,2,3,4-tetrahydronaphthalene were produced. The main product was found to be a mixture of about equal amounts of naphthalene and tetralin. We have repeated the same experiment introducing hydrogen chloride gas into the reaction mixture and achieved the same result. Treating 1,4-dihydronaphthalene alone with aluminum chloride we obtained also naphthalene and its tetrahydride.

We have also investigated the reaction of aluminum chloride with 1,2-dihydronaphthalene. In addition to considerable amounts of higher-boiling substances there resulted also in this case naphthalene and tetralin in almost equal quantities. Scott and Walker,[4] who studied the nature of the polymerized dihydronaphthalene as a synthetic resin, stated that 1,2-dihydronaphthalene gave, upon treatment with aluminum chloride, a red brittle resin having a molecular weight of 388 as well as a viscous oil, apparently a dihydronaphthalene dimer. We have found that the 1,2-isomer gives more resinous matter than the 1,4-compound.

Among the reaction products of the 1,4-dihydronaphthalene was a higher-boiling fraction, whose elementary analysis indicated the formula $C_{20}H_{20}$, from which, after a week, crystals of composition $C_{20}H_{18}$ separated. As the original fraction upon sulfur-dehydrogenation, gave 2,2′-binaphthyl in a good yield, it is supposed that the fraction consists of a mixture of 1,2,3,4-tetrahydro-2,2′-binaphthyl, $C_{20}H_{18}$, and 1,2,3,4,1′,2′,3′,4′ - (or 1,2,3,4,5′,6′,7′,8′) - octahydro - 2,2′ - bi-

(1) Bruson and Kroeger, THIS JOURNAL, **62**, 36 (1940); see also Price, Chapin, Goldman, Krebs and Shafer, *ibid.*, **63**, 1857 (1941).

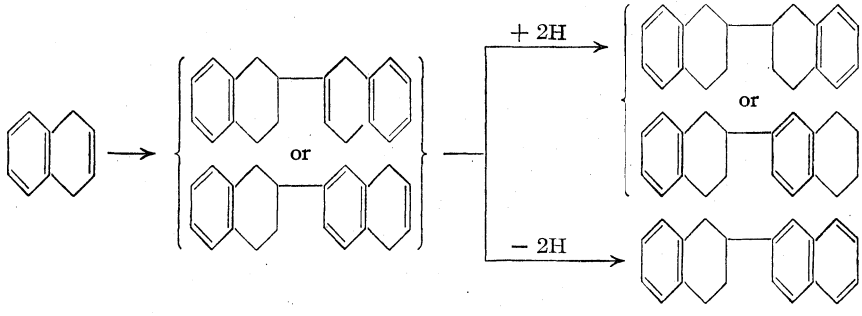
(2) Sisido and Nozaki, *ibid.*, **69**, 961 (1947).

(3) Straus and Lemmel, *Ber.*, **54**, 25 (1921).

(4) Scott and Walker, *Ind. Eng. Chem.*, **32**, 312 (1940).

naphthyl,[5] $C_{20}H_{22}$. This mixture may arise, in our opinion, from the dimer of 1,4-dihydronaphthalene by the disproportionation of hydrogen atoms as shown in the figure. As we could, however, neither isolate the octahydrobinaphthyl nor establish the constitution of the tetrahydro compound, this mechanism has not been proved.

Although we have not characterized the polymers of 1,2-dihydronaphthalene, bisdialin, *i.e.*, tetralino-1,2;2′,1′-(or 1,2;1′,2′)-tetralin of v. Braun and Kirschbaum[5] obtained by the sulfuric acid treatment of this dihydronaphthalene, is to be noticed.



In the Friedel–Crafts reaction of allyl chloride with benzene Nenitzescu and Isacescu[6] obtained 1-phenylpropane as well as 1,2-diphenylpropane and they supposed the formation of 2-chloro-1-phenylpropane as an intermediate. The present condensation of 1,4-dibromo-2-butene with benzene bears a close resemblance to this reaction: in both cases the reduction takes place only at the olefinic double bond and such a reaction product, as, for example, chloroisopropylbenzene or dibromobutylbenzene, respectively, in which only an addition of benzene at the double bond occurred, is not obtained.

As to these facts Nenitzescu and others explained that in the case of the transference of hydrogen by the effect of aluminum chloride the double bond does not act immediately as the acceptor. At first hydrogen chloride adds to the double bond and the chlorine atom is replaced by phenyl radical or by hydrogen atom. This statement holds also for the elucidation of the mechanism of the condensation of 1,4-dibromo-2-butene with benzene. But, since the reaction of dihydronaphthalenes and aluminum chloride consists, at least partly, in the disproportionation of labile hydrogens and since hydrogen chloride plays apparently no role in this case, the possibility that the double bond does act as a hydrogen acceptor, contrary to the opinion of Nenitzescu and others,[6] should be considered.

Experimental[7]

The Friedel–Crafts Reaction of 1,4-Dibromo-2-butene with Benzene.—To a suspension of 12 g. of freshly powdered aluminum chloride in 90 g. of benzene at 24–27° was added with stirring during about four hours a solution of 38 g. of 1,4-dibromo-2-butene prepared from butadiene and bromine, in 50 g. of benzene. The resulting mixture was stirred for an additional three hours at the same temperature. On working up the product in the usual way, there were obtained several fractions:

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I_1	95–115	34	4.3	Colorless oil
II_1	145–175	6	4.9	Yellowish oil
III_1	190–230	6	5.3	Yellow, viscous sirup
IV_1	Residue	..	8.7	Reddish brown resin

Tetralin.—Upon redistillation under ordinary pressure Fraction I_1 came over at 200–210°.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.57; H, 9.50.

This fraction gave no picrate and did not add bromine at −20°; hence, it was concluded that it contained neither naphthalene nor dihydronaphthalene.

When a mixture of 1.3 g. of fraction I_1 and 0.7 g. of sulfur was heated to 200–230° for three and a half hours, there was obtained 0.9 g. of naphthalene, m. p. and mixed m. p. 80°; picrate, m. p. and mixed m. p. 151°.

A solution of 0.4 g. of fraction I_1 in 10 cc. of carbon disulfide was added to 0.8 g. of aluminum chloride and 0.4 g. of phthalic anhydride. The mixture was refluxed for three hours on a water-bath. There resulted 0.5 g. of *o*-(1,2,3,4-tetrahydro-6-naphthoyl)-benzoic acid, m. p. and mixed m. p. 153–155°.[8]

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.03; H, 6.06.

2-Phenyl-1,2,3,4-tetrahydronaphthalene.[9]—Fraction II_1 gave analytical figures which agreed with $C_{16}H_{16}$; d^{20}_4 1.0436.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.58; H, 7.70.

When 1.2 g. of Fraction II_1 was heated to 220° with 0.4 g. of sulfur for four hours and the resulting melt was distilled under reduced pressure, there was obtained 0.7 g. of substance, m. p. 101°. A mixture of this product and 2-phenylnaphthalene of m. p. 101°, prepared from β-naphthylamine according to Hey and Lawton[10] melted without depression.

Anal. Calcd. for $C_{16}H_{12}$: C, 94.08; H, 5.92. Found: C, 93.75; H, 6.05.

In further identification of the dehydrogenation product it was oxidized with chromic anhydride and acetic acid to 2-phenyl-1,4-naphthoquinone,[11] which was obtained as yellow needles, m. p. 109–110°.

Anal. Calcd. for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.84; H, 4.61.

To a boiling mixture of 4.0 g. of fraction II_1, 125 cc. of water and 25 cc. of concentrated sulfuric acid was added under stirring a solution of 12.2 g. of potassium permanganate in 400 cc. of water. After twenty-two hours of stirring the product was extracted with ether. The ethereal solution was washed with dilute sodium hydroxide solution, the aqueous layer separated and acidified with hydrochloric acid. The precipitates were dissolved in ether and this ethereal solution was dried and distilled to

(5) v. Braun and Kirschbaum, *Ber.*, **54**, 597 (1921).

(6) Nenitzescu and Isacescu, *ibid.*, **66**, 1100 (1933). *Cf.* also Nenitzescu, *Z. angew. Chem.*, **52**, 231 (1939).

(7) Microanalyses by Misses Meizyô and Ogawa of our Laboratory.

(8) Underwood and Walsh, THIS JOURNAL, **57**, 940 (1935).

(9) v. Braun and Manz, *Ann.*, **468**, 258 (1926).

(10) Hey and Lawton, *J. Chem. Soc.*, 374 (1940).

(11) Chattaway and Lewis, *ibid.*, **65**, 873 (1894); Zincke and Breuer, *Ann.*, **226**, 23 (1884); Zincke, *ibid.*, **240**, 137 (1887).

remove the solvent. The residue was treated with chloroform. The insoluble portion was separated, sublimed and recrystallized from carbon tetrachloride. There were obtained colorless needles, m. p. 127–129°. A mixture of this product and phthalic anhydride melted at 129–131°. Recrystallizations of the chloroform-soluble portion after removing the solvent gave benzoic acid, m. p. and mixed m. p. 122°.

These results indicated that fraction II_1 was 2-phenyl-1,2,3,4-tetrahydronaphthalene.

Fractions III_1 and IV_1 were not investigated.

The Reaction of 1,4-Dihydronaphthalene with Aluminum Chloride.—1,4-Dihydronaphthalene was prepared by the method of Cook and Hill[12] and purified through its addition product with mercuric acetate.[13]

To 14.2 g. of 1,4-dihydronaphthalene was added at 25° under stirring 1.1 g. of aluminum chloride in small portions. The reaction temperature rose spontaneously to about 90°. After two and a half hours of stirring at 30–40° the mixture was poured onto crushed ice acidified with sulfuric acid. The product was subjected to fractional distillation.

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I_2	202–208	760	4.6	Deposited
II_2	70–110	8	1.0	crystals
III_2	205–220	7	1.1	Yellow
IV_2	300–320	6	0.6	sirup
V_2	Residue	...	...	Black mass

Separation of Naphthalene and Tetralin.—Fractions I_2 and II_2 were combined and the mixture was cooled in ice-salt mixture. The crystals separated were collected. These were found to be naphthalene, m. p. and mixed m. p. 80°; yield 2.0 g.

Anal. Calcd. for $C_{10}H_8$: C, 93.71; H, 6.29. Found: C, 93.97; H, 6.54.

To the mother liquor was added a hot alcoholic solution of picric acid. After removing naphthalene picrate thus separated as yellow needles, m. p. and mixed m. p. 151°, the filtrate was concentrated and dissolved in ether. The ethereal solution was washed with aqueous ammonia and water. When a mixture of this solution, 5 g. of mercuric acetate and 50 cc. of water was stirred for four hours, there could not be obtained the addition product of 1,4-dihydronaphthalene with mercuric acetate. The ethereal layer was separated and washed with water. After removing ether the residue was distilled. At 200–210° tetralin came over, yield 2.1 g.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 91.01; H, 9.48.

A Friedel-Crafts condensation product of this oily substance with phthalic anhydride melted at 156–157°. A mixture of this product with an authentic specimen of *o*-(1,2,3,4-tetrahydro-6-naphthoyl)-benzoic acid melted without depression.

These observations show that Fractions I_2 and II_2 are a mixture of naphthalene and tetralin which does not contain 1,4-dihydronaphthalene.

The Reaction of 1,4-Dihydronaphthalene and Benzene in the Presence of Aluminum Chloride.—To a suspension of 15 g. of aluminum chloride in 100 g. of benzene at 10° was added with stirring during about two and a half hours a solution of 28 g. of 1,4-dihydronaphthalene in 73 g. of benzene. No remarkable rise of temperature was noticed. After an additional thirty minutes the stirring was stopped. The reaction product separated into two layers. The upper layer was decanted, washed and dried. After distilling off of benzene the residue was subjected to fractional distillation.

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I_3	195–217	760	8.0	Deposited
II_3	–145	7	1.1	crystals
III_3	145–170	6	1.6	Colorless oil
IV_3	200–230	6	2.0	Yellow
V_3	Residue	...	0.5	sirup

Hydrolysis of the lower layer of the reaction product gave chiefly tarry matter from which nothing could be identified.

Similar results were obtained when the reaction was carried out in a stream of hydrogen chloride gas.

Naphthalene and Tetralin.—From Fractions I_3 and II_3 were isolated and identified 3.3 g. of naphthalene as well as 3.0 g. of tetralin in the same way as described above.

2-Phenyl-1,2,3,4-tetrahydronaphthalene.—Fraction III_3 gave analytical figures which agreed with $C_{16}H_{16}$.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.71; H, 8.07.

Dehydrogenation of this fraction with sulfur yielded 2-phenylnaphthalene and these observations may indicate that Fraction III_3 is 2-phenyl-1,2,3,4-tetrahydronaphthalene.

The Reaction of 1,2-Dihydronaphthalene with Aluminum Chloride.—1,2-Dihydronaphthalene was prepared by the method of v. Braun and Kirschbaum.[5] The product melted at −8° and proved to be quite free from naphthalene.

To 13.1 g. of 1,2-dihydronaphthalene cooled at −5° was added 1.0 g. of aluminum chloride and the reaction temperature was allowed to rise; after an hour it reached 15° and after additional thirty minutes 30°. When the reaction product was treated as usual, the following fractions were obtained.

Fraction	B. p., °C.	Pressure, mm.	Yield, g.	Appearance
I_4	65–80	7	2.0	Deposited crystals
II_4	200–240	7	1.5	Yellow viscous oil
III_4	Residue	..	*ca.* 6	Yellow resin

Fraction I_4 was separated into 0.5 g. of naphthalene and 0.6 g. of tetralin. Naphthalene was identified by a mixed melting point with a known sample. Tetralin was analyzed.

Anal. Calcd. for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.47; H, 9.32.

When this product was condensed with phthalic anhydride, there was obtained *o*-(1,2,3,4-tetrahydro-6-naphthoyl)-benzoic acid, m. p. and mixed m. p. 153–155°.

The fractions II_4 and III_4 were not investigated.

Hydrogenated Derivatives of Binaphthyl.—Fractions III_2 and IV_2, that is, the fractions boiling about 200° under 6 mm. pressure of the above-mentioned aluminum chloride treatment of 1,4-dihydronaphthalene, were found to consist of the same components. Their analysis gave a figure near $C_{20}H_{20}$.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.79; H, 7.43.

When 1.2 g. of the fraction was heated at 190–240° with 0.6 g. of sulfur for five and one-half hours and the resulting mass was distilled under reduced pressure, there was obtained 1.0 g. of substance, which soon solidified. After triturating with ether to remove a small quantity of oily matter, it was recrystallized from benzene; m. p. 182°. The mixed m. p. with 2,2′-binaphthyl, prepared previously in our Laboratory, showed no depression.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.57; H, 5.98.

The picrate, orange needles, m. p. and mixed m. p. 183–184°.

The fraction became a crystalline mass after about a week of standing, which was freed from oily substance and after five recrystallizations from a mixture of alcohol and benzene gave colorless plates of m. p. 85–88°.

(12) Cook and Hill, THIS JOURNAL, **62**, 1995 (1940).

(13) Sand and Genssler, *Ber.*, **36**, 3705 (1903).

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 93.30; H, 6.91.

From these results we concluded that the fraction consisted perhaps of a mixture of 1,2,3,4,1′,2′,3′,4′- (or 1,2,3,4,5′,6′,7′,8′) - octahydro - 2,2′ - binaphthyl and 1,2,3,4-tetrahydro-2,2′-binaphthyl in nearly equal quantities.

Summary

1. The Friedel–Crafts reaction of 1,4-dibromo-2-butene with benzene yielded tetralin as well as 2-phenyl-1,2,3,4-tetrahydronaphthalene.

2. 1,4-Dihydronaphthalene was found to change into naphthalene and tetralin in the presence of aluminum chloride.

3. An analogous reaction was observed also in the case of 1,2-dihydronaphthalene.

KYÔTO, JAPAN RECEIVED APRIL 29, 1947

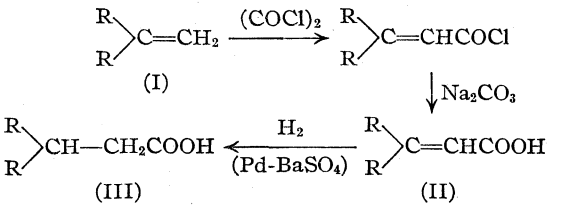
CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE AND THE DEPARTMENT OF ORGANIC CHEMISTRY OF THE HEBREW UNIVERSITY, JERUSALEM]

β,β-Diarylacrylic Acids.[1] I. Synthesis and Properties of Symmetrical and Unsymmetrical β,β-Diarylacrylic Acids.

BY FELIX BERGMANN, MOSHE WEIZMANN, ELCHANAN DIMANT,[1] JOSEF PATAI[1] AND JACOB SZMUSKOWICZ

The reaction of 1,1-diphenylethylene with oxalyl chloride to form β,β-diphenylacrylyl chloride was discovered by Kharasch and co-workers.[2] As part of a program on the investigation of diarylethylenes, we have applied this reaction to a series of symmetrically and unsymmetrically substituted diphenylethylenes (I).

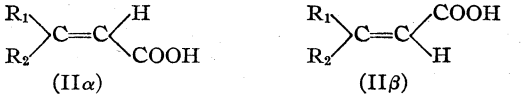
The reaction was found to be a general one; by the use of excess oxalyl chloride (3 to 5 moles) and subsequent hydrolysis of the acid chloride produced, nearly quantitative yields of β,β-diarylacrylic acids (II) were obtained. The application of the reaction to a group of symmetrical and unsymmetrical 1,1-diarylethylenes is summarized in Tables I and II. The corresponding β,β-diarylpropionic acids (III) were easily accessible by catalytic hydrogenation of the acrylic acids (Table III).



The speed of reaction was markedly influenced by the substituents present in the phenyl groups. 1,1-Di-(*p*-anisyl)-ethylene (I,3) reacted completely at room temperature within a half hour, 1,1-diphenylethylene (I,1) had to be refluxed with oxalyl chloride for about two hours, and 1,1-di-(*p*-bromophenyl)-ethylene (I,6) required about eighteen hours for completion of the reaction. The susceptibility of dianisylethylene to substitution by the —COCl group was so great that phosgene in boiling benzene converted it to the dianisylacrylic acid.

The electronic influence of the substituents also influenced the uncatalyzed decarboxylation of the diarylacrylic acids: while the β,β-diphenylacrylic acid (II,1) was stable at 200° and suffered only very slow decarboxylation at 250°, the β,β-di-(*p*-anisyl)-acrylic acid (II,3) was slowly decarboxylated by boiling a solution of it in acetic acid or even by boiling its aqueous suspension. The β-phenyl-β-*p*-anisylacrylic acid was intermediate in stability; carbon dioxide was eliminated from it at about 200°. These results give an explanation of the observation of Bergmann and Bondi[3] that dianisylethylene does not yield a phosphinic acid with phosphorus pentachloride.

When unsymmetrical 1,1-diarylethylenes were refluxed with oxalyl chloride and the mixture hydrolyzed, the two possible isomers (IIα and IIβ) were obtained in most cases.



The use of a large excess of the chloride produced this mixture in good yields, but unavoidable losses during the laborious separation procedures permitted only an approximate estimate of the relative proportion of the two isomers (Table II).

1-Phenyl-1-(*p*-fluorophenyl)-ethylene (I,8) gave rise to a single form of β-phenyl-β-(*p*-fluorophenyl)-acrylic acid (II,8) in nearly quantitative yield; 1-(*p*-tolyl)-1-(*p*-fluorophenyl)-ethylene (I, 11) likewise yielded only one form of the corresponding acid (II,11). On the other hand, the *p*-chloro and *p*-bromo derivatives (II,9 and II,10) were obtained as nearly equimolar, sharply melting mixtures of the two isomers. Resolution of each mixture into the individual isomers showed that the individual melting points lay close to each other and were both higher than that of the mixture.

(1) Part of theses submitted to the Hebrew University, Jerusalem 1947, by Elchanan Dimant and Josef Patai.

(2) Kharasch, Kane and Brown, THIS JOURNAL, **64**, 333 (1942).

(3) E. Bergmann and Bondi, *Ber.*, **63**, 1158 (1930); *ibid.*, **64**, 1455 (1931); *cf.* also Kosolapoff and Huber, THIS JOURNAL, **68**, 2540 (1946).

TABLE I

SYMMETRICAL β,β-DIARYLACRYLIC ACIDS (II) $\begin{matrix}R\\R\end{matrix}\!\!>\!CH{=}CH{-}COOH$

No.	R	Ratio ethylene to oxalyl chloride	Reaction period, hrs.	Yield, %	Melting point, °C.	Recrystallized from	Crystal form	Formula	Composition, % Calcd. C	Calcd. H	Found C	Found H
1	Phenyl[a]	1:5	2	95[b]	167	Acetic acid	.....	.....	..	..	..	...
2	*p*-Tolyl[c]	1:3	5	80	174[d]	Benzene–petr. ether	Flat needles	$C_{17}H_{16}O_2$	81.0	6.35	81.2	6.5
3	*p*-Anisyl[e]	1:3	0.5	75	142	Benzene	Flat prisms	$C_{17}H_{16}O_4$	71.8	5.6	71.9	5.6
4	*p*-Fluorophenyl	1:3	3	70	147	Benzene–petr. ether	Rhombic plates	$C_{15}H_{10}F_2O_2$	69.2	3.8	69.0	4.1
5	*p*-Chlorophenyl	1:5	12	55	175	Benzene–petr. ether	Prismatic rods	$C_{15}H_{10}Cl_2O_2$	61.4	3.4	61.7	3.6
6	*p*-Bromophenyl	1:5	18	35	190–191	Dil. ethanol	Needles	$C_{15}H_{10}Br_2O_2$	47.1	2.6	47.0	2.9
7	α-Naphthyl	1:10	4	75	218	Dil. acetic acid	Plates	$C_{23}H_{16}O_2$	85.2	4.9	85.1	4.7

[a] The anisidide of this acid, prepared from the acid chloride and two equivalents of *p*-anisidine in ether solution, crystallized in white needles, m. p. 163°. *Anal.* Calcd. for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8; N, 4.3. Found: C, 80.1; H, 6.0; N, 4.5. [b] Kharasch (ref. 2) obtained a 50% yield from equimolar proportions of the two reactants. [c] The anisidide, prepared as above, crystallized from methanol in colorless needles, m. p. 153°. *Anal.* Calcd. for $C_{24}H_{23}NO_2$: N, 3.9. Found: N, 4.0. [d] Bergmann, Hoffmann and Meyer, *J. prakt. Chem.*, **135**, 245 (1932), reported a melting point of 168–170°. [e] The melting point of the acid (142°) was almost identical with that of 1,1-di-(*p*-anisyl)-ethylene (141–142°), Linnel and Shaikmahamud, *Quart. J. Pharm. Pharmacol.*, **14**, 64 (1941); *C. A.*, **35**, 6252 (1941). A mixture of the ethylene and the corresponding acid was depressed to 115–120°. Keeping the acid at its melting point converted it to the ethylene.

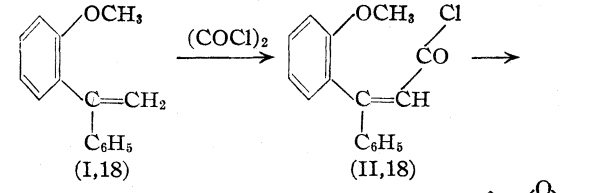
Except for 1-phenyl-1-(*p*-tert-butylphenyl)-ethylene (I,15), the *p*-alkyldiphenylethylenes produced both forms of the acids (II,12; II,13 and II,14). One of the *t*-butyl isomers, m. p. 178°, was isolated in pure form as needles. What may have been the second isomer, recognized by its rod-like crystals, could not be purified satisfactorily because it changed to the first isomer during recrystallization. No decision was made whether the two forms represented dimorphic modifications or whether one of the isomers was unstable.

The β-phenyl-β-(*p*-tolyl)-acrylic acid (II,12) has been described by v. Braun,[4] who prepared it by a Reformatsky reaction and reported the melting point as 140°. This is the melting point which we observed for an equimolar mixture of the two isomers (m. p. 172° and 159°) and constitutes clear evidence that the Reformatsky reaction may yield an isomeric mixture.

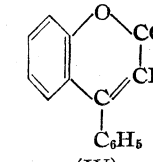
The question of formation of isomeric acids in Reformatsky's reaction cannot yet be answered satisfactorily. In the way the reaction is carried out by Natelson and Gottfried,[5] an ester of substituted β-chloropropionic acid is always the intermediate. An analogous intermediate, *i. e.*, the chloride of a substituted β-chloropropionic acid, could be formed in the oxalyl chloride reaction if addition to the double bond were the primary step. There is, however, another possibility, *viz.*, that the COCl— group directly substitutes hydrogen at the terminal carbon atom of a diarylethylene. The basic assumption for further work on the mechanism of these two reactions must, therefore, be that identical results point to identical reactions mechanisms, whereas a difference in the reaction products would indicate a different course for Kharasch's reaction.

1-Phenyl-1-(*p*-anisyl)-ethylene (I,17) yielded a mixture of isomeric acids which were both obtained in pure form. However, the lower-melting form appeared to be unstable and to pass into the higher-melting acid upon prolonged heating in organic solvents. In general, *para* substituents with a very strong mesomeric effect, such as methoxyl or fluorine, brought about a fast reaction and favored the formation of one isomer over the other.

β-Phenyl-β-(*o*-anisyl)-acrylic acid (II,18) was isolated in small yield; however, if the reaction time was doubled, 4-phenylcoumarin (IV) was produced in about 60% yield. The reaction, in this case, paralleled exactly the observations of Stoermer[6] concerning the dealkylating action of acetyl chloride or phosphorus pentachloride on the acid.



(I,18) (II,18)



(IV)

From the ethylenes containing higher aromatic systems (I,19, I,21 and I,22) approximately equal

(4) v. Braun, Manz and Reinsch, *Ann.*, **468**, 277 (1929).

(5) Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

(6) Stoermer and Friderici, *Ber.*, **41**, 324 (1908); Heilbron, Hill and Walls, *J. Chem. Soc.*, 1701 (1931).

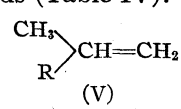
TABLE II

UNSYMMETRICAL β,β-DIARYLACRYLIC ACIDS (II) $\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!CH{=}CH{-}COOH$

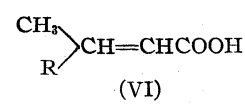
No.	R_1	R_2	Ratio ethylene to oxalyl chloride	Reaction period, hrs.	Method of separation[a]	Yield, %		Melting point, °C.	Mixed m. p. of isomers
8	Phenyl	*p*-Fluorophenyl	1:2	4	C	85		151–152	...
9	Phenyl	*p*-Chlorophenyl[b]	1:3	30	C	Total	90–95		140
						α	40–45	172	
						β	50–55	165–166	
10	Phenyl	*p*-Bromophenyl	1:3	30	C, D	Total	90		147
						α	45	175	
						β	45	169–170	
11	*p*-Tolyl	*p*-Fluorophenyl	1:3	6	C	74		145	...
12	Phenyl	*p*-Tolyl[c]	1:3	20	C	Total	80		140
						α	..	172	
						β	..	159	
13	Phenyl	*p*-Ethylphenyl	1:3	25	D				118
						α	..	173–174	
						β	..	135	
14	Phenyl	*p*-Isopropylphenyl	1:3	20	D	Total	90		123
						α	..	156–157	
						β	..	152	
15	Phenyl	*p*-Butylphenyl	1:3	20	C				...
						α	..	178	
						β	..	(?)	
16	Phenyl	*p*-Cyclohexylphenyl	1:2	10	..	...		190	
17	Phenyl	*p*-Anisyl	1:3	1	A	Total	95		115–120
						α	43	181	
						β	(?)	132–133	
18	Phenyl	*o*-Anisyl	1:3	5[d]	C	...		151[e]	
19	Phenyl	*p*-Xenyl	1:3	45	C	Total	95		...
						α	56	245	
						β	31	194	
20	Phenyl	α-Naphthyl	1:3	8	C	Total	70–75		...
						α	3	222–223[f]	
						β	63	165	
21	Phenyl	β-Naphthyl	1:3	4	B, C	Total	90		...
						α	39	225–226[g]	
						β	33	175	
22	Phenyl	9-Phenanthryl	1:3	20	B	Total	80		200
						α	~20	221–222	
						β	~20	206	

proportions of the isomeric acids were obtained. 1-Phenyl-1-(α-naphthyl)-ethylene (I,20) gave only a very small amount of the high-melting isomer, m. p. 222°. This was in sharp contrast to the result obtained when the acid was made by the Reformatsky reaction, which has been found by various investigators to yield only the high-melting isomer.[7]

The oxalyl chloride reaction was applied to a series of 1-methyl-1-arylethylenes (V) but in no case were two isomeric β-arylcrotonic acids (VI) isolated. Yields were low and the method was inferior to the Reformatsky preparation of these acids (Table IV).



(V)



(VI)

When it was hydrogenated, β-phenyl-β-(*p*-chlorophenyl)-acrylic acid (II,9) absorbed about 150% of the calculated amount of hydrogen and produced a mixture of neutral and acidic products. The neutral substance was identified as 1,1-diphenylethane; the acidic portion yielded about 23% of β,β-diphenylpropionic acid and about 16% of the expected β-phenyl-β-(*p*-chlorophenyl)-propionic acid (III,9).

Similar results were obtained with β,β-di-(*p*-chlorophenyl)-acrylic acid (II,5). In this case

(7) Pirrone, *Chem. Centr.*, **105**, II, 2078 (1934), claims to have evidence for the formation of both isomers of II, 20—although not isolated—in the dehydration of ethyl β-phenyl-β(1-naphthyl)-β-hydroxypropionate. This claim is based on the conversion of the hydroxy ester into a mixture of two indones. However, both of the indones are derived from the same (α-) form of acid II,20. De Fazi, *Gazz. chim. ital.*, **49**, I, 242 (1919); Lipkin and Stewart, THIS JOURNAL, **61**, 3295 (1929).

TABLE II (*Continued*)

Recrystallized from	Crystal form	Formula	Composition, % Calcd. C	Calcd. H	Found C	Found H
Benzene	Polyhedric prisms	$C_{15}H_{11}FO_2$	74.4	4.5	74.6	4.8
Acetic acid	Prismatic plates	$C_{15}H_{11}ClO_2$	69.8	4.3	70.0	4.4
Benzene–petr. ether	Needles				69.6	4.3
Acetic acid	Prisms	$C_{15}H_{11}BrO_2$	59.4	3.6	59.4	3.9
Acetic acid	Rods				59.8	3.6
Benzene–petr. ether	Needles	$C_{16}H_{13}FO_2$	75.0	5.1	74.7	4.9
Benzene–petr. ether	Flat prisms	$C_{16}H_{14}O_2$	80.7	5.9	80.4	6.0
Benzene–petr. ether	Prismatic columns				80.5	6.0
Benzene–petr. ether	Twinned prismatic rods	$C_{17}H_{16}O_2$	80.95	6.35	80.85	6.3
Benzene–petr. ether	Needles				80.8	6.4
Acetic acid	Prismatic plates	$C_{18}H_{18}O_2$	1.2	6.8	81.5	7.1
Dilute acetic acid	Needles				81.6	7.0
Benzene–petr. ether	Prismatic needles	$C_{19}H_{20}O_2$	81.4	7.1	81.3	7.4
Acetic acid	Rods				..	..
Butyl acetate–petr. ether	Clusters of rods	$C_{21}H_{22}O_2$	82.4	7.2	82.2	7.4
Benzene–petr. ether	Pointed prisms	$C_{16}H_{14}O_3$	75.6	5.5	75.7	5.6
Benzene–petr. ether	Needles				..	...
Benzene–petr. ether	Twinned prisms	.....	...	..	..	...
Butyl acetate	Scales	$C_{21}H_{16}O_2$	84.0	5.3	84.3	5.6
Butyl acetate	Prisms	$C_{21}H_{16}O_2$	84.0	5.3	84.1	5.5
Isopropanol	Prismatic rods	$C_{19}H_{14}O_2$	83.2	5.1	83.0	4.8
Dilute ethanol	Needles	$C_{19}H_{14}O_2$	83.2	5.1	83.4	5.3
Butyl acetate	Elongated plates	$C_{19}H_{14}O_2$	83.2	5.1	83.2	5.1
Benzene–petr. ether	Pointed rods	$C_{19}H_{14}O_2$	83.2	5.1	..	...
Xylene	Yellow-brown prisms	$C_{23}H_{16}O_2$	85.2	4.9	85.6	5.1
Xylene	Pale-yellow rods	$C_{23}H_{16}O_2$	85.2	4.9	85.2	5.2

[a] Various methods of separation are described in the Experimental Part. [b] Alexander, Jacoby and Fuson, THIS JOURNAL, 57, 2208 (1935), describe one form of this acid, prepared by Reformatsky's method, with a melting point of 168°. Prof. Fuson kindly compared both isomers with his preparation and found our α-form to be identical with his. [c] Compare ref. 4. [d] After ten hours of reflux a neutral substance was isolated which crystallized from benzene–petroleum ether in prismatic plates, m. p. 104–105°. It was identical with 4-phenylcoumarin. *Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5. Found: C, 80.9; H, 4.4. [e] Stoermer (ref. 5) reported a melting point of 153°. [f] Compare ref. 6. Proof of structure of this isomer was given by Koelsch, *J. Org. Chem.*, 6, 558 (1941), who cyclized it to perinaphthindone. [g] v. Braun (ref. 4) gave the melting point as 217°

the neutral portion was 1,1-di-(*p*-chlorophenyl)-ethane with probably a small amount of diphenylethane. The only acid obtained was β,β-di-(*p*-chlorophenyl)-propionic acid.

These observations indicated that partial decarboxylation occurred, probably under the influence of hydrochloric acid which was formed by catalytic dehalogenation of the aromatic ring. This was surprising since the *p*-chlorophenyl-substituted acids have been found to be stable even under the influence of boiling hydrochloric acid. It is also remarkable that the chlorine atoms in the dichloro acid and in the dichloroethane appeared to be much more stable than the corresponding monochloro derivatives.

Experimental[8]

Synthesis of 1,1-Diarylethylenes (I) and 1-Methyl-1-aryl-methylenes (V).—Most of the ethylenes were prepared as described in earlier papers of this series[9] or else-

(8) All melting points are uncorrected.

(9) Bergmann, Szmuszkowicz and Fawaz, THIS JOURNAL, 69, 1773 (1947); Szmuszkowicz and Bergmann, *ibid.*, 69, 1779 (1947); Bergmann and Szmuszkowicz, *ibid.*, in press.

TABLE III

β,β-DIARYLPROPIONIC ACIDS (III) $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!CHCH_2COOH$

No.	R_1	R_2	Melting point, °C.	Recrystallized from	Crystal form	Formula	Composition, % Calcd. C	Calcd. H	Found C	Found H
1	Phenyl[a]	Phenyl	157	Benzene–petr. ether	Prismatic rods	$C_{15}H_{14}O_2$	..	..	..	...
2	*p*-Tolyl[b]	*p*-Tolyl	188	Alcohol	Prismatic rods	$C_{17}H_{18}O_2$	..	..	..	...
3	*p*-Anisyl[c]	*p*-Anisyl	138–139	Benzene–petr. ether	Needles	$C_{17}H_{18}O_4$	71.3	6.3	71.0	6.5
4	*p*-Fluorophenyl[d]	*p*-Fluorophenyl	108–109	Petroleum ether	Long lancets	$C_{15}H_{12}F_2O_2$	68.7	4.6	68.4	4.6
5	Phenyl	*p*-Fluorophenyl	118	Benzene–petr. ether	Twinned, pointed plates	$C_{15}H_{13}FO_2$	73.8	5.3	74.0	5.4
6	Phenyl	*p*-Chlorophenyl	108	Petroleum ether	Pointed prisms	$C_{15}H_{13}ClO_2$	69.2	5.0	69.4	5.2
7	*p*-Tolyl	*p*-Fluorophenyl	138–139	Petroleum ether	Long rods	$C_{16}H_{15}FO_2$	74.4	5.8	74.7	6.0
8	Phenyl	*p*-Tolyl	144	Acetic acid	Prismatic rods	$C_{16}H_{16}O_2$	80.0	6.7	79.8	6.7
9	Phenyl[e]	*p*-Anisyl	122	Dilute acetic acid	Prismatic rods	$C_{16}H_{16}O_3$	75.0	6.25	74.8	6.3

[a] Ejkman, *Chem. Zentr.*, **79**, II, 1100 (1908); see also Simons and Archer, THIS JOURNAL, **61**, 1521 (1939). [b] This acid was originally reported by Bergmann (Table I, footnote *d*) to melt at 163–164°. Our findings, however, are in agreement with the melting point reported by Cope, THIS JOURNAL, **56**, 721 (1934). [c] Two "isomeric" β,β-di-(*p*-anisyl)-acrylic acids were described by Vyas and Bokil, *Rasayanam*, **1**, 195 (1939); *C. A.*, **34**, 5067 (1940). One of m. p. 141–142°, made by saponification and decarboxylation of the methyl chloride–ethyl sodiomalonate condensation product, was identical with our acid. The other, m. p. 160–161°, was obtained from anisole and acetonedicarboxylic acid. The constitution of the latter acid is now under investigation. [d] Hydrogenated in methanol. [e] Fosse, *Ann. chim.* **13** 105 (1920); Baillon, *ibid.*, **15**, 61 (1921).

TABLE IV

β-ARYLCROTONIC ACIDS (VI) $\begin{matrix} CH_3 \\ R \end{matrix}\!\!>\!C{=}CH{-}COOH$

No.	R	Ratio ethylene to oxalyl chloride	Reaction period, hrs.	Yield, %	Melting point, °C.	Recrystallized from	Crystal form	Formula	Composition, % Calcd. C	Calcd. H	Found C	Found H
1	Phenyl[a]	1:6	..	40	97	.....	.....	.....	..	...	..	...
2	*p*-Xenyl	1:2	4.5	5.5	199	Dilute ethanol	Plates	$C_{16}H_{14}O_2$	80.7	5.9	80.6	5.9
3	α-Naphthyl[b]	1:4	14	..	...	.....	.....	.....	..	...	..	...
4	β-Naphthyl[c]	1:4	13	3.2	172	Butyl acetate	Needles	$C_{14}H_{12}O_2$	79.2	5.7	79.4	5.8
5	9-Phenanthryl	1:4	15	15	214	Butanol	Lancets	$C_{18}H_{14}O_2$	82.4	5.3	82.7	5.5

[a] Kharasch, THIS JOURNAL, **64**, 333 (1942), prepared the acid but did not give experimental details. [b] Because of difficulties encountered in attempts to purify the product, the crude acid was converted to the anilide which crystallized readily from benzene in long needles, m. p. 187°. *Anal.* Calcd. for $C_{20}H_{17}NO$: C, 83.6; H, 5.9; N, 4.9. Found: C, 83.9; H, 6.1; N, 5.2. [c] Banchetti, *Gazz. chim. ital.*, **69**, 398 (1939); *C. A.*, **33**, 8602 (1939), reported a melting point of 170°.

where in the literature. 1,1-Di-(*p*-tolyl)-ethylene (I, 2), which we prepared previously from *p*-methylacetophenone and *p*-tolylmagnesium bromide, was more conveniently synthesized by the method of Bistrzycki[10] in about 60% yield. 1-Phenyl-1-(*p*-cyclohexylphenyl)-ethylene (I,16) and 1-methyl-1-(*p*-xenyl)-ethylene (V,2) are new compounds and were made as follows:

1-Phenyl-1-(*p*-cyclohexylphenyl)-ethylene (I,16): *p*-Cyclohexylbenzophenone[11] (45 g.) in 100 cc. of benzene was added to methylmagnesium iodide (from 38 g. of methyl iodide) in 200 cc. of a 1:1 ether–benzene mixture, and the solution was refluxed for four hours. The crude carbinol was dehydrated by heating to 150–160° for one hour, and the ethylene was purified by distillation, b. p. 181° (0.05 mm.); yield, 100%.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.6; H, 8.4. Found: C, 91.7; H, 8.6.

1-Methyl-1-(*p*-xenyl)-ethylene (V, 2): This ethylene was prepared in an analogous way from 4-acetylbiphenyl and methylmagnesium iodide. The intermediate carbinol was dehydrated at 210–220°. The ethylene crystallized spontaneously and was recrystallized from ethanol. It melted at 108–109°; yield, 60%.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.8; H, 7.2. Found: C, 92.5; H, 7.4.

Synthesis of β,β-Diarylacrylic Acids (II).—As a standard procedure, one mole of ethylene and 3 to 5 moles of oxalyl chloride were refluxed until the evolution of hydrogen chloride ceased. In the case of 1,1-di-(*p*-anisyl)-ethylene (I,3) the reaction was virtually over after one-half hour at room temperature and was completed by refluxing for fifteen minutes.

Excess oxalyl chloride was removed *in vacuo* and the sirupy residue was stirred into an ice-cold sodium carbonate solution. The acid chlorides required from one to two hours for hydrolysis.

The mixture then was boiled with a large amount of water (about one liter per 50 g. of substituted ethylene) to dissolve the sodium salt and to separate it from tars formed as by-products. Charcoal was added and the solution filtered. Part of the sodium salt crystallized from the cooled filtrate; this portion, upon acidification, immediately yielded a pure sample of the desired acid. The remainder of the acid was recovered from the filtrate by acidification and was purified by recrystallization. It was essential in some cases, *e. g.*, with β,β-di-(*p*-anisyl)-acrylic acid (II,3), to avoid high-boiling solvents, because of the possibility of decarboxylation.

The ethylenes containing halogenated phenyl groups

(10) Bistrzycki and Reintke, *Ber.*, **38**, 839 (1905).

(11) Kleene, THIS JOURNAL, **62**, 3523 (1940).

were partially converted into tarry material by the long reflux time necessary to cause them to react. Because of this a lower yield was obtained in these cases.

Details of the conversion of 1,1-diarylethylenes into β,β-diarylacrylic acids are given in Tables I and II.

Reaction of 1,1-Di-(*p*-anisyl)-ethylene and Phosgene.—A slow stream of phosgene was bubbled during ten hours through a boiling solution of 10 g. of 1,1-di-(*p*-anisyl)-ethylene in 50 cc. of benzene. The solvent was distilled *in vacuo* and the residue decomposed with cold sodium carbonate solution. The sodium salt of the acid (II,3) was dissolved by heating and filtered from the insoluble, neutral material. Acidification of the filtrate precipitated 3.5 g. (30%) of β,β-dianisylacrylic acid, m. p. 139–140°.

The dianisylethylene was recovered unchanged when refluxed in a solution of ethyl or amyl chlorocarbonate.

Separation of Isomeric, Unsymmetrical β,β-Diarylacrylic Acids.—Method A—Separation of the acid chlorides: It was found that in the case of β-phenyl-β-(*p*-anisyl)-acrylic acid (II,17), the isomeric acid chlorides differed considerably in their hydrolysis rates. A benzene solution of the mixed chlorides was shaken with water; the solid which separated was the α-isomer, m. p. 181°. After separation of the layers, the benzene solution was shaken with aqueous sodium carbonate. This converted the β-acid chloride into the sodium salt of the β-acid, contaminated with some of the α-acid.

Method B—Separation of the free acids: The mixture of isomers was separated in a few cases by fractional crystallization. This method was especially applicable when the two aryl groups differed appreciably in their molecular weight or in the polar character of the substituent.

Method C—Separation of the sodium salts: In most cases it was observed that on cooling slowly the hot solution of the mixed sodium salts, the salt of the higher-melting acid separated in a fairly pure state. The filtrate upon acidification then gave a mixture enriched in the low-melting isomer, which usually could be separated by fractional crystallization in a Dewar. The separation temperature proved to be critical in some cases. Thus, the α-form of β-phenyl-β-(*p*-chlorophenyl)-acrylic acid (II,9) crystallized in a fairly pure condition at 30–35°. However, at about 15° the β-form also precipitated as its sodium salt. It was important for securing satisfactory separations that very dilute solutions of the sodium salts were used.

Method D—Mechanical separation of the free acids: In some cases Methods A, B and C failed. The mixture of acids was then dissolved in an organic solvent, and the solution was cooled very slowly in a Dewar. The crystals which formed were separated by passing them through a sieve or picking them out with the help of forceps.

Other methods tried, such as chromatographic adsorption on calcium sulfate, fractional acidification or separation of the methyl esters, either were unsuccessful or did not possess any advantage over the four methods outlined.

β-Arylcrotonic Acids (VI).—The reaction of oxalyl chloride with 1-methyl-1-arylethylenes (V) was much more sluggish than with 1,1-diarylethylenes (I), and the products were much more difficult to purify. β-(α-Naphthyl)-crotonic acid (VI,3) was obtained only as an amorphous mass, and was therefore characterized as its anilide. The preparation of five β-arylcrotonic acids is summarized in Table IV.

β,β-Diarylpropionic Acids (III).—The diarylacrylic acids were hydrogenated in ethanol over palladium–barium sulfate at room temperature and normal pressure. Yields were almost quantitative. In a few cases two isomeric acids (IIα and IIβ) were hydrogenated separately in order to prove the existence of geometrical isomerism. When the crude, yellow acrylic acids were used for catalytic reduction, the color faded in the initial phase of the hydrogenation, and the diarylpropionic acids were obtained in an excellent state of purity. Results are given in Table III.

Hydrogenation of β-Phenyl-β-(*p*-chlorophenyl)-acrylic Acid (II,9).—When 4.3 g. of 1-phenyl-1-(*p*-chlorophenyl)-acrylic acid (II,9) was reduced, 50% more hydrogen was absorbed than was calculated for the reduction of the double bond. The reaction mixture smelled strongly of hydrogen chloride and formed a heavy precipitate with silver nitrate. The ethanol was evaporated, the oily residue dissolved in benzene and extracted with warm sodium carbonate solution. The neutral portion was distilled, b. p. 135–140° (0.8 mm.).

Anal. Calcd. for $C_{14}H_{14}$: C, 92.3; H, 7.7. Found: C, 92.1; H, 7.7.

The alkaline extract was boiled with charcoal and filtered. Upon slow cooling a precipitate formed and was filtered; on acidification it yielded 0.7 g. of β-phenyl-β-(*p*-chlorophenyl)-propionic acid (III,6), m. p. 108° (see Table III).

When the sodium carbonate filtrate was acidified, 1 g. of β,β-diphenylpropionic acid precipitated. It crystallized from benzene–petroleum ether in long rods, m. p. 153°; mixed m. p. with authentic sample (m. p. 155°), 154–155°.

Hydrogenation of β,β-Di-(*p*-chlorophenyl)-acrylic Acid (II,5).—The reduction of 6 g. of β,β-di-(*p*-chlorophenyl)-acrylic acid (II,5) was stopped after one molar equivalent of hydrogen had been absorbed. The reaction mixture fumed strongly and was shown to contain hydrogen chloride. It was separated into a neutral and an acidic portion.

The neutral product, after a small forerun at 145° (3 mm.), boiled at 195° (3 mm.). It gave a positive Beilstein test.

Anal. Calcd. for $C_{14}H_{12}Cl_2$: C, 67.0; H, 4.8. Found: C, 66.6; H, 5.0.

The hot sodium carbonate extract was boiled with charcoal, filtered and left overnight. The precipitate was separated and acidified; it proved to be unchanged starting material.

The alkaline filtrate, when acidified, yielded about 1 g. of oily β,β-di-(*p*-chlorophenyl)-propionic acid which solidified when triturated with petroleum ether. It recrystallized from benzene–petroleum ether in flat, rhombic prisms, m. p. 187°. Fuson reported 188–189°.[12]

Anal. Calcd. for $C_{15}H_{12}Cl_2O_2$: C, 61.0; H, 4.1. Found: C, 61.3; H, 4.2.

Summary

The reaction between 1,1-diarylethylenes and oxalyl chloride represents a general method for the preparation of β,β-diarylacrylic acids. The influence of substituents on the speed of the reaction indicates that oxalyl chloride attacks the terminal carbon atom like an electrophilic reagent.

With unsymmetrical 1,1-diarylethylenes a mixture of isomeric β,β-diarylacrylic acids is produced in most cases. Substituents which increase strongly the electron density at the β-carbon atom of the diarylethylenes either yield one isomer only or tend to make the second isomer unstable.

Catalytic hydrogenation of halogenated β,β-diphenylacrylic acids causes partial dehalogenation and decarboxylation.

RECHOVOT, PALESTINE RECEIVED NOVEMBER 3, 1947

(12) Fuson, Kozacik and Eaton, THIS JOURNAL, **55**, 3799 (1933).

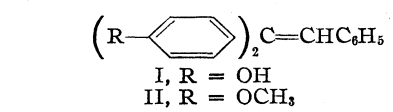
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

β,β-Diarylacrylic Acids. II. A New Synthesis of Triarylethylenes

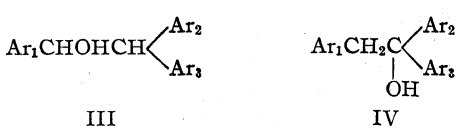
BY FELIX BERGMANN, ELCHANAN DIMANT AND HELENE JAPHE

Triphenylethylene (I) and its derivatives have acquired new interest since the discovery of Robson and Schönberg[1] that the hydrocarbon (I) itself, its dimethoxy derivative (II)[2] and their α-halogen derivatives are endowed with estrogenic activity of prolonged duration. The classical method of synthesis for derivatives of I is the Grignard reaction,[3] in which the carbinols of type III or IV are intermediates. When Ar_2 and Ar_3 represent different aryl groups, two geometrical isomers are possible. However, only very few cases are known where both forms have actually been isolated.[4] There exist also some other, less well known methods of formation of triphenylethylene, *e. g.*, rearrangement of β,β,β-triphenylethylammonium nitrite[5] or condensation of diphenylketene with substituted benzaldehydes[6] in quinoline (with elimination of carbon dioxide).

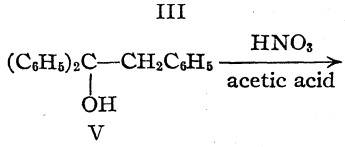
Triphenylethylene itself is unsuitable for direct substitution in a ring, because the common cationoid reagents first attack the central double bond.[7] We observed that 1,1,2-triphenylethanol (V), too, is converted by fuming nitric acid in acetic acid solution into 1,1,2-triphenyl-2-nitroethylene (VI). Apparently dehydration to I precedes nitration at the α-position. When the nitration is carried out without use of a solvent, I and V give a good yield of a tetranitro derivative of the probable structure VII. One nitro group must replace the α-hydrogen, because the α-nitro derivative VI, too, can be converted into the tetranitro compound (VII).



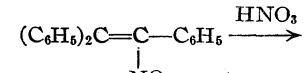
I, R = OH
II, R = OCH_3



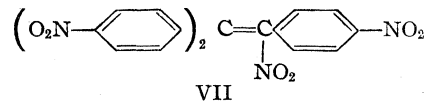
III IV



V



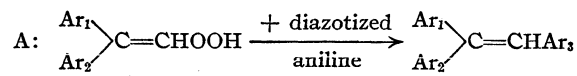
VI



VII

We have been unable to isolate intermediates between the mono- and tetra-nitro derivatives.

A new method of wide applicability was found in the coupling of β,β-diarylacrylic acids VIII with diazotized anilines, in analogy to the Meerwein synthesis of stilbenes from cinnamic acids[8] (scheme A). The data represented in Table I show that meta- and para-substituted anilines give comparable results. The method failed, however, when ortho-substituents were present.



It is noteworthy that under the experimental conditions used, the diarylacrylic acids concerned undergo partial decarboxylation prior to the coupling reaction. Thus, the dianisylacrylic acid (Expt. 2 in Table-I) gave besides the expected 1,1-di-(*p*-anisyl)-2(*p*-nitrophenyl)-ethylene about 50% of dianisylethylene, although we reported previously that the acid loses carbon dioxide in aqueous suspension only upon prolonged boiling.[9]

The Meerwein synthesis of stilbenes yields exclusively the *trans* forms. However, no conclusion about the sterical specificity of the reaction can be drawn from this fact, because only *trans*-cinnamic acids have been used.[10] It was therefore of interest to investigate the coupling of isomeric β,β-diarylacrylic acids (VIII, $Ar_1 \neq Ar_2$). The two forms of β-phenyl-β(*p*-bromophenyl)-acrylic acid (X),[9] upon reaction with diazotized *p*-nitroaniline, yielded the same product (XI). It is evident that in one case isomerization has taken place. In this connection it may be mentioned that α-phenylcinnamic acid, which upon decarboxylation yields *cis*-stilbene,[11] does not undergo a Meerwein coupling, but under the conditions of the experiment yields exclusively *trans*-stilbene.

The most interesting of the new compounds are the nitro derivatives in view of the versatility of the aromatic nitro group, and of the inaccessibility of these derivatives by any other method. It was shown previously,[12] that it is impossible to reduce

(1) Robson, *Proc. Soc. Exptl. Biol. Med.*, **38**, 153 (1938); Robson, Schönberg and Fahim, *Nature*, **142**, 292 (1938).

(2) Schönberg, Robson, Tadros and Fahim, *J. Chem. Soc.*, 1327 (1940).

(3) Hell and Wiegandt, *Ber.*, **37**, 1429 (1904); Ley and Kirchner, *Z. anorg. Chem.*, **173**, 408 (1927); Buisignies, *Compt. rend.*, **151**, 516 (1910); Koelsch, THIS JOURNAL, **54**, 2487 (1932).

(4) F. Bergmann, *ibid.*, **64**, 69 (1942); Koelsch and Prill, *ibid.*, **67**, 1296 (1945).

(5) Hellermann, Cohn and Hoen, *ibid.*, **50**, 1716 (1928); Hellermann and Garner, *ibid.*, **57**, 139 (1935).

(6) Staudinger and Kon, *Ann.*, **384**, 89 (1911).

(7) Shilov, *J. Russ. Phys.-Chem. Soc.*, **62**, 95 (1930); *C. A.*, **24**, 4289 (1930).

(8) Meerwein, Buchner and van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

(9) F. Bergmann and co-workers, THIS JOURNAL, **70**, 1612 (1948).

(10) F. Bergmann and Weinberg, *J. Org. Chem.*, **6**, 134 (1941).

(11) Stoermer and Voht, *Ann.*, **409**, 39 (1915).

(12) F. Bergmann and Schapiro, *J. Org. Chem.*, **12**, 57 (1947).

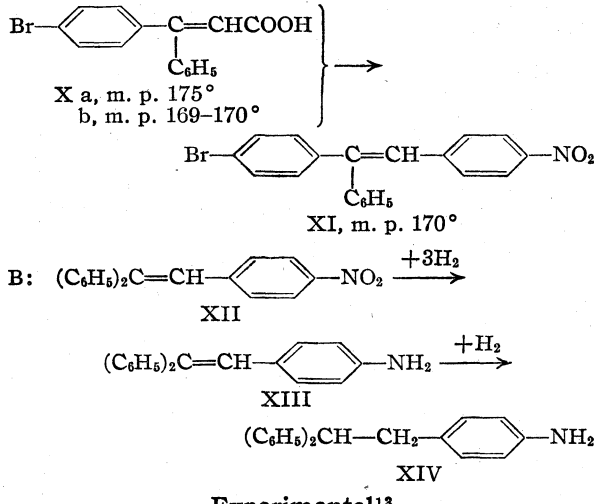
TABLE I

TRIARYLETHYLENES, $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C{=}CHR_3$

R_1	R_2	R_3	B. p. °C.	Mm.	M. p., °C.	Yield, %	Crystal form	Solvent	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
Phenyl[a]		*p*-Nitro	193–194	1.5	148	48	Brown cols.	Butyl acetate	$C_{20}H_{15}O_2N$	79.7	5.0	4.7	79.7	5.3	4.7
p-Anisyl[a]		*p*-Nitro	225–230	1.25	131	28	Prism rods	Benz.–petr. eth.	$C_{22}H_{19}O_4N$	73.1	5.3	3.9	73.3	5.6	3.9
p-Fluorophenyl[a]		*p*-phenyl	200–230	0.25	145	50	Rhombohedr. plates	Benz.–petr. eth.	$C_{20}H_{13}O_2F_2N$	71.2	3.9	4.2	71.3	3.9	4.2
p-Tolyl[b]		*m*-Nitrophenyl	200–220	0.05	102	30[f]	Twinned prisms	*n*-Propanol	$C_{22}H_{19}O_2N$	80.2	5.8	4.3	80.0	6.0	4.2
Phenyl[c]		*p*-Tolyl	140–145	0.05	74	11	Elong. prisms	Ethanol	$C_{21}H_{18}$	93.3	6.7		93.0	7.0	
p-Anisyl[d]		*p*-Tolyl	210–215	1.5	97	Small	Prism rods	Petr. ether	$C_{23}H_{22}O_2$	83.6	6.7		83.8	7.0	
p-Fluoroph.[a]	Phenyl	*p*-Nitrophenyl	210–230	0.15	149.5	35	Coarse prisms	Tol.–petr. ether	$C_{20}H_{14}O_2NF$	75.2	4.4	4.4	75.2	4.6	4.7
p-Bromoph.[e]	Phenyl	*p*-phenyl	240–260	0.8	170	30	Yellow prisms	Toluene	$C_{20}H_{14}O_2NBr$	63.2	3.6		63.1	3.8	

[a] Coupling temp., 25–35°. [b] Coupling temp., 32–45°. [c] Coupling temp., 27–28°. [d] Coupling temp., 27–35°. [e] Coupling temp., 25–50°. [f] Yield calculated on acid consumed. About 50% of the acid was recovered from the alkaline washings by acidification.

catalytically the nitro group of various nitrostilbenes without attack on the double bond. In the nitro-triphenylethylenes, however, the reactivity of the ethylenic bond is lowered so much that the hydrogenation can be interrupted exactly after absorption of three moles of hydrogen to yield about 70% of the unsaturated amine (see scheme B).



Experimental[13]

Meerwein Coupling—General Procedure.—The method used for the coupling reactions may be exemplified for the first case, reaction of diphenylacrylic acid with *p*-nitroaniline. The general results are summarized in Table I.

To a solution of diphenylacrylic acid (9.5 g.) in acetone (200 cc.), cooled to +5°, was added a clear solution of diazotized *p*-nitroaniline (5.8 g.). Solid sodium acetate (11 g.) and a solution of cupric chloride (2 g.) in a little water were added immediately. The temperature was allowed to rise slowly, until at 25° reaction set in. After the strong evolution of gas was over (about fifteen minutes), the mixture was heated to 35° for one hour. Acetone and a small amount of *p*-chloronitrobenzene were removed by steam distillation. The remaining sirup was dissolved in benzene, washed with alkali, dried and distilled *in vacuo*, b. p. 193–194° (1.5 mm.). The yellow-red distillate crystallized upon trituration with ethanol. Recrystallization from butanol or butyl acetate gave brown, polyhedric columns of 1,1-diphenyl-2-(*p*-nitrophenyl)-ethylene (XII), m. p. 148°. The substance is dimorphic and appears sometimes in small yellow prisms of m. p. 158–160°, especially from dilute solutions.

(13) All melting points are uncorrected.

When di-(*p*-anisyl)-acrylic acid was used in the reaction, distillation of the neutral portion gave first a large amount (about 50% of theoretical) of dianisylethylene, b. p. 185–195° (1.2 mm.), followed by the expected coupling product.

In experiment 8, the higher-melting form of β-phenyl-β-(*p*-bromophenyl)-acrylic acid (Xa), m. p. 175°, gave a 30% yield of 1-phenyl-1-(*p*-bromophenyl)-2-(*p*-nitrophenyl)-ethylene (XI), m. p. 170°. The isomeric acid (Xb), m. p. 169–170°, reacted under exactly the same conditions, but only 11% of the expected ethylene was obtained. This compound showed no depression of m. p. with the foregoing reaction product.

Reactions of 1,1-Diphenyl-2-(*p*-nitrophenyl)-ethylene (XII). (a) Bromination.—The ethylene (XII) in chloroform solution showed no visible reaction with bromine at room temperature. Upon heating on a water-bath, strong evolution of hydrogen bromide set in. After five minutes the mixture was cooled and petroleum ether added to precipitate the reaction product. 1,1-Diphenyl-2-(*p*-nitrophenyl)-2-bromoethylene crystallized from butyl acetate in prisms, m. p. 178°.

Anal. Calcd. for $C_{20}H_{14}O_2NBr$: N, 3.7. Found: N, 3.9.

(b) **Catalytic Reduction.**—The ethylene XII (1 g.) was suspended in ethyl acetate (35 cc.) and reduced in the presence of Raney nickel. After absorption of 240 cc. of hydrogen (calcd. for 3 moles, 242 cc.; $T = 239°$; $p = 754$ mm.), the reaction was interrupted. A yellowish oil was isolated, which showed no tendency to crystallize and was therefore acetylated directly. The acetyl derivative of XIII crystallized from butanol in lancets or from toluene–petroleum ether (1:1) in long flat tetragonal prisms, m. p. 169–170°; yield 0.7 g. (70%).

Anal. Calcd. for $C_{22}H_{19}ON$: N, 4.5. Found: N, 4.6.

When the hydrogenation was continued to completion, the speed of the reaction slowed appreciably after the absorption of the first three moles of hydrogen. The oily reduction product (XIV) was transformed again into its acetyl derivative. It crystallized from benzene–petroleum ether in big flat prisms, m. p. 128–129°.

Anal. Calcd. for $C_{22}H_{21}ON$: C, 83.8; H, 6.7; N, 4.4. Found: C, 83.6; H, 6.8; N, 4.7.

Nitration of Triphenylethylene (I) and 1,1,2-Triphenylethanol (V).—(a) In acetic acid: The carbinol V (2 g.) was dissolved in acetic acid (20 cc.) and fuming nitric acid (d. 1.51) (0.55 g., 1.2 equiv.) added dropwise at room temperature. An exothermic reaction took place and the temperature rose to 50°. The mixture was then heated to 65° for twenty minutes and poured onto ice. The granular precipitate was dried and recrystallized from butyl acetate as yellow prisms, m. p. 172° (VI); yield 0.7 g.

Anal. Calcd. for $C_{20}H_{15}O_2N$: C, 79.7; H, 5.0. Found: C, 79.9; H, 5.3.

The same product, but in higher yields, was obtained by the use of 2.2 or 3.2 equivalents of nitric acid. The

product is identical with the substance resulting from nitration of triphenylethylene itself.

(b) Without solvent: The carbinol V (15 g.) was added in small portions to fuming nitric acid (75 cc.) with stirring. A violent reaction took place, which raised the temperature to 70°. The reaction was completed by heating the mixture to 80° for one and one-half hours. Upon standing for several days, the reaction product crystallized out. It was filtered off, washed with nitric acid, then with water and dried; crude yield, 20 g., 83%. The tetranitro derivative (VII?) crystallized from benzene or butyl acetate in yellow prisms, m. p. 205°.

Anal. Calcd. for $C_{20}H_{12}O_8N_4$: C, 55.0; H, 2.8; N, 12.8. Found: C, 55.4; H, 2.6; N, 12.5.

The same product was obtained, but in a less satisfactory form, by nitration of triphenylethylene or α-nitrotriphenylethylene (VI) with fuming nitric acid.

Summary

The coupling of β,β-diarylacrylic acids with diazotized anilines opens a new route to substituted triarylethylenes. Geometrical isomers of the acids yielded identical coupling products.

Under the experimental conditions of this reaction, α-phenylcinnamic acid is decarboxylated to *trans*-stilbene. Decarboxylation is also a side-reaction for β,β-diarylacrylic acids.

1,1-Diphenyl-2-(*p*-nitrophenyl)-ethylene can be reduced catalytically stepwise first to the unsaturated, then to the saturated, amine. Nitration of triphenylethylene, the corresponding carbinol or its α-nitro derivative with fuming nitric acid in the absence of a solvent produces a tetranitro derivative.

RECHOVOT, PALESTINE RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Reactions of Mustard-type Vesicants with α-Amino Acids[1]

BY VINCENT DU VIGNEAUD, CARL M. STEVENS,[2] HAROLD F. MCDUFFIE, JR.,[3] JOHN L. WOOD[4] AND HERBERT MCKENNIS, JR.[5]

Early in World War II it was considered that reactions between mustard gas (H) and certain enzymes possibly played a role in the mechanism of vesication by H-type compounds. As part of a collaborative effort to uncover the mechanism of vesication by chemical warfare agents, reactions between H-type compounds and proteins were studied in a number of laboratories. Prior to our investigations, published work[6] and available unpublished British reports[7] indicated that the properties of several proteins were altered by treatment with mustard gas. To gain insight into the protein-H reactions, this Laboratory and others investigated the preparation and nature of compounds formed by the reaction of H-type vesicants with amino acids. This report covers part of this one aspect of the larger problem.

From the chemical standpoint, studies on mustard gas are complicated by the fact that H contains two reactive halogens. Since it was already known[8] that several compounds of the type $RSCH_2CH_2Cl$ possess vesicant action, we sought to simplify the problem by employing these "one-handed" vesicants in our chemical studies. Although these compounds containing only one β-chloroethyl group are potent vesicants, they are quantitatively much less vesicant than H itself. Qualitatively their physiological action parallels that of H. The "one-handed" agents, therefore, must be capable of entering into the chemical reactions essential to vesication. The fact that the structures and properties of the molecules closely resemble those of H itself makes it highly probable that the mechanism of vesication is essentially the same in each case. These considerations caused us to focus our attention largely on the one-handed vesicants, which for convenience are designated as follows:

$C_6H_5CH_2SCH_2CH_2Cl$	Benzyl-H
$CH_3SCH_2CH_2Cl$	Methyl-H
$CH_3CH_2SCH_2CH_2Cl$	Ethyl-H
$CH_3CH_2CH_2CH_2SCH_2CH_2Cl$	Butyl-H

A survey of the general literature[9] indicated that H-type vesicants reacted readily with sulfhydryl, amino and phenolic hydroxyl groups in alkaline solution. Furthermore, a derivative of an α-amino acid had been reported. It was the product formed by the reaction[10] of H and glycine ethyl ester, having the structure I.[11]

$$S(CH_2CH_2NHCH_2COOC_2H_5)_2 \qquad I$$

In our experiments we studied the reactions of most of the naturally occurring amino acids with vesicants of the type $RSCH_2CH_2Cl$, where R has the structures indicated above.

(1) The work described in this paper was carried out under Contract OEMsr-144 between the Office of Scientific Research and Development and Cornell University Medical College and is described in Progress Reports to the National Defense Research Committee, January, 1942, to October, 1943.

(2) Present address: Department of Chemistry, State College of Washington, Pullman, Wash.

(3) Present address: Bristol Laboratories, Inc., Syracuse, N. Y.

(4) Present address: School of Biological Sciences, The University of Tennessee, Memphis, Tenn.

(5) Present address: Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md.

(6) Berenblum and Wormall, *Biochem. J.*, **33**, 75 (1939).

(7) Berenblum (1940); Pirie (1941); Peters (1941).

(8) See, for instance, Kirner, THIS JOURNAL, **55**, 3501 (1933); Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

(9) See Jackson, *Chem. Rev.*, **15**, 425 (1934).

(10) For recently published observations on this reaction as well as other studies on the reaction of amino acids with H and related compounds, see Boursnell, Francis and Wormall, *Biochem. J.*, **40**, 737 (1946).

(11) Cashmore and McCombie, *J. Chem. Soc.*, 2884 (1923).

TABLE I

N$^{\alpha}$-SUBSTITUTED DERIVATIVES OF AMINO ACIDS WITH MUSTARD-TYPE VESICANTS

Compound	Proc. for prepn.	Solvent for recryst.	Approx. yield, %	M. p., °C.	Molecular formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
N-β-Benzylmercaptoethylglycine[a]	C	Abs. ethanol	40[b]	187–188	$C_{11}H_{15}O_2NS$	58.6	6.71	58.6	6.91
N-β-Benzylmercaptoethyl-DL-alanine[c]	C	Water	50[b]	210–215	$C_{12}H_{17}O_2NS$	60.2	7.16	60.4	7.36
N-β-Benzylmercaptoethyl-DL-valine	B	95% ethanol	40[d]	236–239	$C_{14}H_{21}O_2NS$	62.9	7.91	63.0	7.85
N-β-Benzylmercaptoethyl-L-leucine	A	50% acetic acid	20[d]	229–231	$C_{15}H_{23}O_2NS$	64.0	8.24	64.0	8.13
N-β-Benzylmercaptoethyl-DL-leucine	B	50% ethanol	25[d]	225–228	$C_{15}H_{23}O_2NS$	64.0	8.24	64.1	7.62
N-β-Benzylmercaptoethyl-DL-isoleucine	B	95% ethanol	50[d]	232–233	$C_{15}H_{23}O_2NS$	64.0	8.24	64.0	8.63
N-β-Benzylmercaptoethyl-DL-serine	B	50% ethanol	15[d]	178–184	$C_{12}H_{17}O_3NS$	56.5	6.67	57.0	7.11
N-β-Benzylmercaptoethyl-DL-threonine	B	Water	30[d]	226	$C_{13}H_{19}O_3NS$	N 5.49		N 5.12	
N-β-Benzylmercaptoethyl-DL-phenylalanine	B	Water	40[d]	224–225	$C_{18}H_{21}O_2NS$	68.5	6.71	68.5	6.88
N-β-Benzylmercaptoethyl-DL-methionine	B	Acetic acid	20[d]	209–210	$C_{14}H_{21}O_2NS_2$	56.2	7.07	56.6	7.17
N,N-bis-(β-Benzylmercaptoethyl)-glycine	C	Benzene	4[b]	113–114	$C_{20}H_{25}O_2NS_2$	64.0	6.71	63.9	6.51
N,N-bis-(β-Benzylmercaptoethyl)-L-tryptophan	B	Ethanol–benzene	30[d]	185–188	$C_{29}H_{32}O_2N_2S_2$	69.0	6.39	69.1	6.46
N-β-Butylmercaptoethylglycine	C	Abs. ethanol	10[b]	175–180	$C_8H_{17}O_2NS$	N 7.32		N 7.36	
N-β-Butylmercaptoethyl-DL-leucine	B	50% ethanol	25[d]	260	$C_{12}H_{25}O_2NS$	N 5.66		N 5.59	
N-β-Butylmercaptoethyl-DL-phenylalanine	B	95% ethanol	35[d]	225–226	$C_{15}H_{23}O_2NS$	N 4.98		N 4.79	
N-β-Butylmercaptoethyl-L-tryptophan	B	Ethanol–benzene	5[d]	178–181	$C_{17}H_{23}O_2N_2S$	N 8.77		N 8.60	
N,N-bis-(β-butylmercaptoethyl)-glycine	C	Benzene	5[b]	87–98	$C_{14}H_{29}O_2NS_2$	N 4.55		N 4.40	

[a] The N-acetyl derivative was prepared in 75% yield and recrystallized from dilute alcohol; m. p. 148–149°. *Anal.* Calcd. for $C_{13}H_{17}O_3NS$: C, 58.4; H, 6.41. Found: C, 58.3; H, 6.48. [b] Based on amount of vesicant used. [c] The N-acetyl derivative was prepared in 80% yield and recrystallized from water; m. p. 120–121°. *Anal.* Calcd. for $C_{14}H_{19}O_3NS$: C, 59.8; H, 6.81. Found: C, 60.0; H, 6.43. [d] Based on amount of amino acid used.

A series of crystalline derivatives of the amino acids was obtained, demonstrating reaction of the one-handed vesicants with sulfhydryl, amino, phenolic hydroxyl and imidazolyl groups under the conditions employed. No evidence was found to indicate reaction with alcoholic hydroxyl, guanido or indolyl groupings. The methods of preparation and study of the compounds are presented not only for the intrinsic interest of the compounds themselves, but also for their possible importance in establishing the nature of protein vesicant reactions. In this latter capacity some of the derivatives can be considered as model substances and as reference compounds in cases where it is desirable to isolate the components of hydrolysates from vesicant-treated proteins.

Simple α-Amino Acids.—Other investigators[12] have demonstrated the facile esterification of the free carboxyl group of amino acid derivatives by H-type compounds. In our work we investigated the alkylation of amino groups with particular reference to the actual isolation of derivatives. It appeared likely that the amino groups would be susceptible to mono-, di- or trialkylation by the $RSCH_2CH_2$- radicals. In practice, treatment of the amino acids in alkaline solution did lead to the formation of a mixture of products from which it was possible to isolate crystalline N$^{\alpha}$-alkyl derivatives, N$^{\alpha}$-dialkyl derivatives in some instances, but no N$^{\alpha}$-trialkyl derivatives (quaternary ammonium compounds). After N,N-bis-(β-benzylmercaptoethyl)-glycine was treated with benzyl-H, it was recovered unchanged in 80% of the theoretical yield. This indicates that the formation of a quaternary ammonium compound is probably not a major reaction under the experimental conditions. The alkylation of α-amino groups by H has been discussed in two recent papers[10,12c] covering work done in the war period by other laboratories.

The monosubstituted derivatives of glycine and alanine were readily acetylated in 75–80% yield by treatment in alkaline solution with acetic anhydride. In contrast, the monosubstituted derivatives of valine, leucine and phenylalanine were recovered unchanged in good yield. This difference in behavior held true both for the butyl-H and the benzyl-H series.

The several procedures for preparation of the derivatives are described in the Experimental part and pertinent data are compiled in Table I.

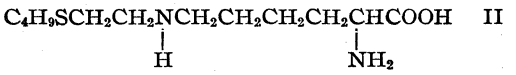
Lysine.—This amino acid was of particular interest since it is known[13] that the ε-amino group is reactive in many proteins. Kurtz[14] showed that treatment of the copper salt of

(12) (a) Bergmann, *et al.*, NRDC Section B4C Reports, April 25, 1942, and August 19, 1942; (b) Bergmann, *et al.*, OSRD Report, May 21, 1943; (c) Moore, Stein and Fruton, *J. Org. Chem.*, **11**, 675 (1946).

(13) Goldschmidt and Kinsky, *Z. physiol. Chem.*, **183**, 244 (1929); Gurin and Clark, *J. Biol. Chem.*, **107**, 395 (1934).

(14) Kurtz, *ibid.*, **140**, 705 (1941).

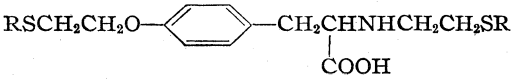
lysine in alkaline solution with benzoyl chloride yielded the N^{ϵ}-benzoyl derivative. The copper salt of lysine was, therefore, treated with butyl-H. A crystalline monosubstituted derivative of lysine was isolated. This is presumably the hydrochloride of structure II.



II

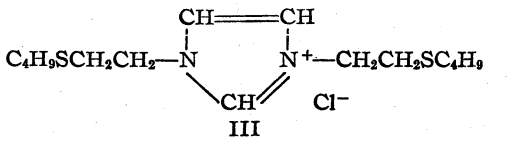
Mercaptoamino Acids.—We were interested particularly in preparing S-substituted vesicant derivatives of mercaptoamino acids because of the possible reactivity of protein sulfhydryl groups with vesicants.[15] The benzyl-H derivatives of the sulfhydryl group of cysteine and homocysteine were obtained in good yield by alkylation with the aid of sodium and liquid ammonia.[16]

Tyrosine.—The phenolic hydroxyl group of tyrosine is stated to be chemically reactive in proteins.[17] The reaction of this group with the vesicants was, therefore, of interest. Treatment of L-tyrosine in strongly alkaline solution with either benzyl-H or butyl-H yielded a mixture of products from which was isolated in each case a disubstituted derivative in 20% yield. The compounds show negative tests for phenolic hydroxyl groups[18] and are, therefore, believed to be O,N-disubstituted derivatives.

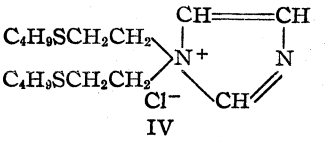


Histidine.—Preliminary studies of the reaction of vesicants with L-histidine and with N^{α}-benzoyl-L-histidine were made using a colorimetric method[19] based on the Pauly diazo reaction.[20] The results indicated a reaction of the vesicant with the imidazole ring. Evidence had been obtained by Moritz and co-workers[21] that the imidazole group of histidine reacted with H, and Ball and co-workers[22] suggested that the effect of H on the oxygen dissociation curve of hemoglobin might be interpreted as indicating a reaction with the imidazole groups of histidine in the intact protein.

We, therefore, studied the reaction of histidine and its derivatives further. Treatment of L-histidine in 0.5 *M* sodium bicarbonate solution with an excess of butyl-H yielded a crystalline substance, the composition of which corresponded to a trialkyl derivative. Treatment of imidazole under similar conditions yielded a disubstituted derivative. By analogy with other alkylation products of imidazole[23] structure III was considered likely for the imidazole derivative, although dialkylation of one N (IV) was not excluded. The

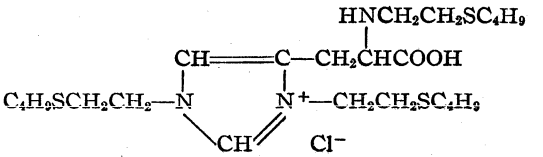


III



IV

structure analogous to structure III, in the case of the histidine derivative, would be structure V.



V

The compound yields no nitrogen in the Van Slyke procedure for the estimation of free amino nitrogen,[24] and is stable to heating under reflux in strong acid.

Using a smaller quantity of butyl-H under slightly different conditions, it was also possible to isolate a monosubstituted derivative of imidazole, and monoalkylation of the imidazole nitrogen alone was also apparently achieved by using N^{α}-benzoylhistidine.

Experimental[25,26]

Derivatives of Simple α-Amino Acids. These derivatives were prepared by one of the following procedures: **A.**—The amino acid (1 mole) was dissolved in 50% ethanol containing 3 moles of sodium carbonate or sodium hydroxide and treated with 2 moles of vesicant. The mixture was stirred for several hours at 30–50°, and then extracted with ether. Neutralization of the aqueous solution with hydrochloric acid precipitated the crude derivative which was recrystallized from the appropriate solvent.

B.—The amino acid was dissolved in slightly more than 3 equivalents of 1 *N* sodium hydroxide in 95% methanol. Two equivalents of vesicant were added and the mixture was allowed to stand for at least twenty-four hours. The solution was then decanted from the precipitated sodium chloride and concentrated *in vacuo*. The residue was dissolved in water. The solution was extracted with ether and then neutralized with hydrochloric acid. The precipitated derivative was collected and recrystallized from the appropriate solvent.

(15) Investigations of vesicant–protein sulfhydryl reactions have been discussed elsewhere: (a) Hellerman, final summarization of NDRC work, Contract OEMsr-94; (b) Banks, Boursnell, Francis, Hopwood and Wormall, *Biochem. J.*, **40**, 745 (1946).

(16) du Vigneaud, Audrieth and Loring, This Journal, **52**, 4500 (1930).

(17) See, for instance, Herriott, *J. Gen. Physiol.*, **19**, 283 (1938); Rutherford, Patterson and Harris, *J. Research Natl. Bur. Standards*, **25**, 451 (1940).

(18) Folin and Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

(19) Macpherson, *Biochem. J.*, **36**, 59 (1942).

(20) Pauly, *Z. physiol. Chem.*, **44**, 159 (1905).

(21) Moritz, Henriques, *et al.*, Progress Report to Division 9, NDRC, August 28, 1942.

(22) Ball, Davis and Ross, Progress Report to Division 9, NDRC, December 19, 1942; Davis and Ross, This Journal, **69**, 1177 (1947).

(23) Pinner and Schwarz, *Ber.*, **35**, 2441 (1902).

(24) Van Slyke, *J. Biol. Chem.*, **12**, 275 (1912).

(25) All melting points were determined on a calibrated hot stage.

(26) The authors are indebted to Dr. Julian R. Rachele and Mr. Roscoe C. Funk, Jr., for the microanalyses.

C.—The amino acid was dissolved in 1 equivalent of 1 *N* sodium hydroxide in 95% methanol and an equal volume of water was added. The vesicant (0.25 equivalent) was added, the mixture was stirred until homogeneous and then was allowed to stand overnight. When glycine was treated under these conditions and the reaction products were isolated by the method described under procedure B, crystalline disubstituted derivatives were obtained. Concentration of the mother liquors to a small volume yielded crystalline monosubstituted derivatives.

The methods of preparation and the properties of the various derivatives are recorded in Table I.

It seems certain that the derivatives prepared from L-tryptophan involve the α-amino group.[27] To check the possibility of a reaction of the indole group with the vesicants, the α-amino group was covered by acetylation. No evidence was found of the reaction of the vesicants with the indole group of N^{α}-acetyl-L-tryptophan.

Derivative of Lysine.—L-Lysine dihydrochloride (2.17 g.) was dissolved in 50 cc. of 2.5% sodium tetraborate. Copper carbonate was added in excess and the solution was heated to boiling and filtered. The solution was brought to *p*H 9.2 with 5 *N* sodium hydroxide and 4 g. of sodium tetraborate was added. Butyl-H (1.7 cc.) was added, and the solution was stirred for twenty-four hours. Then the precipitated copper salt was filtered and washed with water. A suspension of the copper salt (*p*H 9) was treated with hydrogen sulfide and, after removal of copper sulfide, the solution was acidified to litmus with acetic acid. The solvent was removed *in vacuo* leaving a sirup which crystallized on addition of concentrated hydrochloric acid. The material was recrystallized three times from a minimum amount of hot water by addition of ethanol. The yield of this purified product decomposing at 240° was 0.46 g. (15% of the theoretical amount).

Anal. Calcd. for $C_{12}H_{26}O_2SN_2 \cdot HCl$: S, 10.73; Cl, 11.86. Found: S, 10.33; Cl, 11.25.

Derivatives of Cysteine and Homocysteine.—L-Cystine (24 g.) and sodium were added in portions to 400 cc. of liquid ammonia, just enough sodium being added at the end to give a blue color persisting for ten minutes. Then 32.4 cc. of benzyl-H was added dropwise. The liquid ammonia was allowed to evaporate. The solid residue was stirred well with crushed ice until the ice melted. The resulting precipitate was collected. The filtrate was extracted with ether and then neutralized with concentrated hydrochloric acid. A second precipitate resulted. The combined precipitates were recrystallized from hot water. The yield was 25 g. of material melting at 187–189° and having the composition of the expected S-(β-benzylmercapto)-ethylcysteine.

Anal. Calcd. for $C_{12}H_{17}O_2NS_2$: C, 53.1; H, 6.31. Found: C, 53.3; H, 6.21.

The compound was characterized further by conversion to the acetyl derivative which melted at 125° and had the expected neutral equivalent (313).

Under similar conditions, DL-homocystine yielded S-(β-benzylmercapto)-ethylhomocysteine, m. p. 225°.

Anal. Calcd. for $C_{13}H_{19}O_2NS_2$: N, 4.91; S, 22.46. Found: N, 4.60; S, 22.79.

This compound was characterized further by conversion to the acetyl derivative which melted at 70–72°. The neutral equivalent of the acetyl derivative was 324 (calculated, 327).

Derivatives of Tyrosine.—Experiments indicated that the vesicants did not react appreciably with phenolic groups in neutral solution. However, in a strongly alkaline solution it was possible to prepare O,N-disubstituted derivatives of tyrosine. L-Tyrosine (1.81 g.) was shaken for twenty-four hours with 40 cc. of 1 *N* sodium hydroxide, 40 cc. of methanol, and 4.5 cc. of butyl-H. The reaction product was then isolated according to procedure B. An amorphous product weighing 2.4 g. was obtained. On recrystallization from 70% acetic acid, 1.0 g. of a crystalline derivative melting at 208–210° was obtained. The compound gave a negative Millon test, and yielded no color with Folin phenol reagent.[18]

Anal. Calcd. for $C_{21}H_{35}O_3NS_2$: N, 3.39. Found: N, 3.34.

Treatment of L-tyrosine (1.81 g.) with benzyl-H (procedure B) yielded an amorphous product weighing 3.1 g. This product was dissolved in 150 cc. of 50% ethanol containing 3 g. of sodium bicarbonate. The cooled solution deposited 1.0 g. (20%) of the pure O,N-disubstituted derivative. It gave a negative Millon's test and melted at 203–205°. It formed plates on recrystallization from 80% acetic acid.

Anal. Calcd. for $C_{27}H_{31}O_3NS_2$: C, 67.3; H, 6.48. Found: C, 67.6; H, 6.54.

Derivatives of Histidine and Related Compounds. L-**Histidine.**—L-Histidine monohydrochloride monohydrate (10.2 g.) was dissolved in 500 cc. of 0.5 *M* sodium bicarbonate and the solution was stirred vigorously with 36 cc. of butyl-H for twenty-four hours. About 30 cc. of a brown oil separated. This material was extracted three times with 150-cc. portions of ether. The ether-insoluble residue was diluted with 3 volumes of chloroform, and the solution was washed with 10% hydrochloric acid and with water. Evaporation of the chloroform left a sirupy residue which did not crystallize. The sirup was dissolved in chloroform (80 cc.) and stirred for half an hour with Brockmann alumina. The mixture was filtered and the chloroform was removed *in vacuo*. Addition of 10 cc. of acetone to the residue caused slow crystallization.[28] The yield of crystalline material was 0.9–1.4 g. Several recrystallizations from methylene chloride gave a sample melting at 187–188° and having the composition of a trisubstituted histidine derivative.

Anal. Calcd. for $C_{24}H_{46}O_2N_3S_3Cl$: C, 53.4; H, 8.58; N, 7.78; S, 17.80; Cl, 6.56. Found: C, 53.4; H, 7.87; N, 7.65; S, 18.05; Cl, 6.41.

The derivative was recovered quantitatively after being heated in water at 100° for twenty-four hours, and in 75% yield after treatment for twelve hours in refluxing 20% hydrochloric acid.

Imidazole.—Imidazole (0.136 g.) and butyl-H (0.153 g.) were dissolved in 218 cc. of 0.7 *N* potassium hydroxide in 95% methanol. After the solution had been allowed to stand overnight, another 0.153 g. of butyl-H was added, and the resulting mixture was allowed to stand for four hours. The solvents were removed *in vacuo*, 2 cc. of water was added to the residue, and the solution was extracted with 5 cc. of benzene. The benzene layer was evaporated *in vacuo* and 6 cc. of water was added to the residue. A saturated aqueous solution of picrolonic acid was added to the aqueous solution. Seventy-two milligrams of yellow crystalline material melting at 140–155° (dec.) was obtained. The compound, after recrystallization from water, melted at 154–156° (dec.) and had the composition of the picrolonate of a monosubstituted imidazole derivative.

Anal. Calcd. for $C_9H_{16}N_2S \cdot C_{10}H_8O_5N_4$: C, 50.9; H, 5.39. Found: C, 50.0; H, 5.66.

A disubstituted derivative of imidazole was prepared as follows: A solution of imidazole (1.36 g.) in 300 cc. of 0.5 *M* sodium bicarbonate was stirred with 15 cc. of butyl-H for twenty-four hours. The mixture was acidified to congo red with concentrated hydrochloric acid and extracted 3 times with 50-cc. portions of ether. The

(27) In the course of the study of these derivatives, it was observed that the disubstituted derivative of L-tryptophan gives approximately twice the color given by an equimolar amount of L-tryptophan when treated with the Folin phenol reagent.[18] Further study showed that all of the N^{α}-disubstituted vesicant derivatives of the amino acids gave a blue color with the reagent.

(28) If the material did not crystallize at this point, it was washed with ether, dissolved in 30 cc. of methylene chloride and washed with water. Evaporation of the solvent left a sirup which crystallized on addition of acetone.

aqueous solution was then extracted 3 times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate. The chloroform solution upon evaporation gave a light yellow oil which crystallized upon addition of ether. The yield was 0.23 g., and additional material was obtained by further chloroform extractions. For analysis the crude product was crystallized from a mixture of benzene and acetone. After the product had been dried at 3 mm. over potassium hydroxide for twenty minutes, it had the approximate composition of a monohydrate, m. p. 50–52°.

Anal. Calcd. for $C_{15}H_{29}N_2S_2Cl \cdot H_2O$: C, 50.8; H, 8.80. Found: C, 51.4; H, 8.62.

On long drying *in vacuo* at 40°, the above material lost 93% of the calculated weight for 1 molecule of water of hydration. It then melted at 56–57°.

Anal. Calcd. for $C_{15}H_{29}N_2S_2Cl$: C, 53.5; H, 8.67; N, 8.31; S, 19.03; Cl, 10.52. Found: C, 53.1; H, 8.79; N, 8.00; S, 19.50; Cl, 10.14.

N^{α}-Benzoyl-L-histidine.—Three grams of N^{α}-benzoyl-L-histidine[29] was dissolved in 25 cc. of water by addition of 1 *N* sodium hydroxide with stirring. Then 1.5 cc. of butyl-H was added, and the mixture was stirred for five hours. The *p*H was maintained at 8–9 by gradual addition of 1 *N* sodium hydroxide. Methanol (10 cc.) was also added portionwise to increase the solubility of the vesicant. The reaction mixture was evaporated to about one-half volume *in vacuo* and then extracted with ether. The aqueous layer was acidified to *p*H 4 with 11 cc. of 1 *N* hydrochloric acid. The oil which separated was removed. The aqueous solution was acidified with 1 cc. of 1 *N* hydrochloric acid and extracted with chloroform. Evaporation of the chloroform left an oil which was crystallized from ethanol by addition of ether. Recrystallization of the compound from water yielded 200 mg. of rosettes, m. p. 188–190°.

Anal. Calcd. for $C_{19}H_{25}O_3N_3S$: S, 8.54. Found: S, 8.37.

Summary

1. A series of N-substituted derivatives of the simple α-amino acids with benzyl-H (benzyl β-chloroethyl sulfide) and butyl-H (butyl β-chloroethyl sulfide) has been prepared by treatment of the various amino acids in alkaline solution with the corresponding vesicant. The following derivatives have been prepared: N-monosubstituted benzyl-H derivatives of glycine, DL-alanine, DL-valine, L-leucine, DL-leucine, DL-isoleucine, DL-threonine, DL-phenylalanine and DL-methionine; N^{α}-monosubstituted butyl-H derivatives of glycine, DL-leucine, DL-phenylalanine and L-tryptophan; N^{α}-disubstituted benzyl-H derivatives of glycine and L-tryptophan; N^{α}-disubstituted butyl-H derivative of glycine.

2. Treatment of the copper salt of L-lysine in alkaline solution with butyl-H yielded a crystalline monosubstituted derivative. By analogy with benzoylation data this compound is believed to be the N^{ϵ}-substituted derivative.

3. S-Substituted derivatives of L-cysteine and DL-homocysteine with benzyl-H have been prepared by reaction of the vesicant with the corresponding sodium mercaptides in liquid ammonia solution.

4. O,N-Disubstituted derivatives of L-tyrosine with benzyl-H and butyl-H have been prepared.

5. A trisubstituted butyl-H derivative of L-histidine was obtained by treatment of the amino acid in alkaline solution with the vesicant. Under similar conditions imidazole yielded mono- and disubstituted derivatives, and N^{α}-benzoyl-L-histidine yielded a monosubstituted derivative.

6. The data provide a further and direct demonstration that the following groups in amino acids are capable of reacting with H-type vesicants: α-amino group, ϵ-amino group, imidazolyl group, sulfhydryl group and phenolic hydroxyl group.

NEW YORK, N. Y. RECEIVED NOVEMBER 13, 1947

(29) Gerngross, *Z. physiol. Chem.*, **108**, 50 (1919).

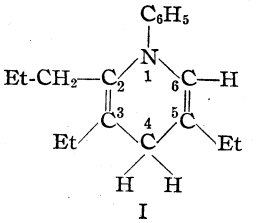
[CONTRIBUTION FROM THE RESEARCH DIVISION OF THE B. F. GOODRICH COMPANY]

N-Phenyl-3,5-diethyl-2-propyl-1,4-dihydropyridine

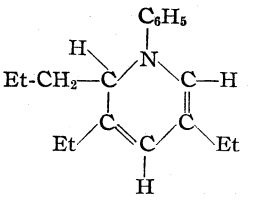
BY DAVID CRAIG, LAURA SCHAEFGEN AND WILLARD P. TYLER

During a study of the reaction of butyraldehyde with aniline in the presence of acetic acid, it has been found possible to isolate a weak base having the formula $C_{18}H_{25}N$. The present paper deals with the structure of this base.

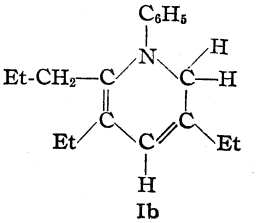
The empirical formula and the method of synthesis suggest dihydropyridine structures I, Ia, or Ib or the open chain anil structure II. The pyrolysis of the compound in the presence of cobaltous chloride forms aniline and 1,3,5-triethylbenzene. The formation of triethylbenzene, $C_{12}H_{18}$, supports these formulations since the linking together of three butyraldehyde residues is thereby indicated. Hydrogenation, depending on conditions, yields di, tetra and decahydro derivatives, in accord with the N-phenyldihydropyridine formulas, but thus far has given no evidence of the



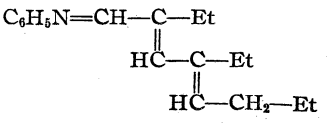
I



Ia

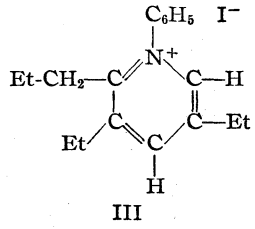


Ib



II

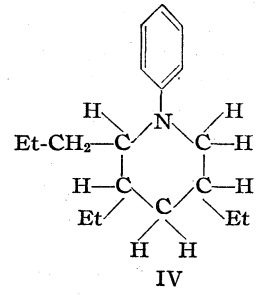
formation of hexahydro or dodecahydro derivatives required of formula II. Dehydrogenation of the new compound occurs upon contact with reduced platinum oxide in acetic acid solution. The product is the corresponding acetate of III. Oxidation with iodine or sulfur in acidic media, containing appropriate anions, produces quaternary salts, *e.g.*, the iodide III. This type of oxidation would be expected of structures I, Ia, or Ib, but would not be expected of the anil II. The anil in such media would be expected to yield hydrolysis products, *i.e.*, aniline and an unsaturated aldehyde. Neither these nor their oxidation products have been observed in the reaction mixtures. Thus oxidation as well as hydrogenation of the new compound supports a dihydropyridine structure and eliminates from consideration an open chain anil structure such as II.



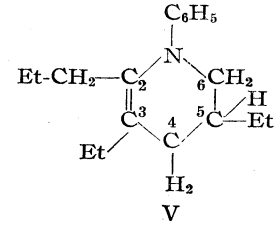
III

Karrer[1] has studied the formation and behavior of N-phenyl-1,2-dihydropyridine, a compound closely related to the $C_{18}H_{25}N$ base. His assignment of structure was based in part on the prompt reaction of his compound with maleic anhydride[2] although a well characterized reaction product was not reported. In contrast, the reaction of one molecule of the $C_{18}H_{25}N$ base with one of maleic anhydride is comparatively sluggish and a well characterized adduct[3] may be isolated. The N-phenyl-1,2-dihydropyridine also reacted rapidly and irreversibly with hydrochloric acid to form unidentified products. Again in contrast, the $C_{18}H_{25}N$ base reacts immediately only as a weak organic base. However, on long contact with hydrochloric acid it dissolves and then irreversibly undergoes disproportionation. The products are the quaternary chloride corresponding to III and the dihydro derivative obtained by hydrogenation. The N-phenyl-1,2-dihydropyridine is unstable in the atmosphere whereas the $C_{18}H_{25}N$ base has been kept for ten years or more substantially unchanged. The $C_{18}H_{25}N$ base is yellow. Karrer reported and we have confirmed that the 1,2-dihydropyridine is colorless. Neither of these dihydropyridines is fluorescent. The differences and similarities in their behavior constitute the chemical basis for the assignment of the 1,4-dihydro structure I to the $C_{18}H_{25}N$ base.

Knowledge of the structure of the $C_{18}H_{25}N$ base facilitates the identification of some of its derivatives. Thus the decahydro derivative is N-cyclohexyl-3,5-diethyl-2-propylpiperidine and the tetrahydro derivative is the corresponding N-phenylpiperidine IV. The dihydro derivative has been assigned structure V on the basis, (a) that it reacts as a vinylamine toward hydrochloric acid, and (b) that there would be less hindrance to the addition of hydrogen to the Δ^5 double bond than to the Δ^2 bond of compound I.



IV



V

The study of the ultraviolet absorption spectra of compound I and its derivatives supports the assigned structures. Figure 1 shows that the spectrum for compound I is very different from that of N-phenyl-1,2-dihydropyridine but very similar to that of the methyl derivative prepared by the reaction of methylmagnesium iodide with the pyridinium salt III. Compound I and the methyl derivative are therefore considered to be 1,4-dihydropyridines, the methyl group in the latter compound being in the 6 or 4-position.

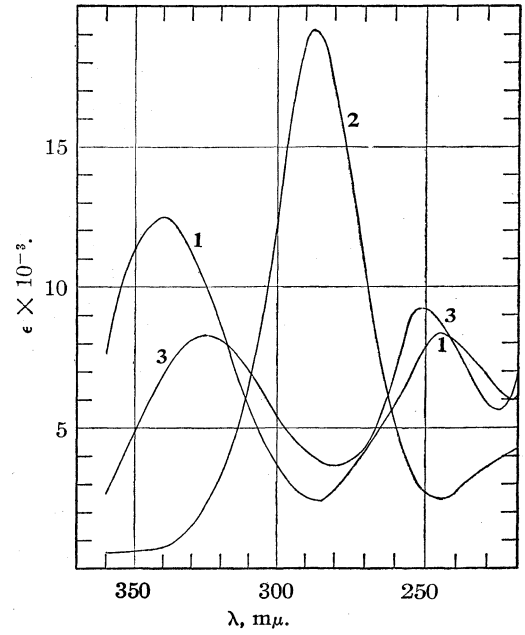


Fig. 1.—Spectra of I (1), N-phenyl-1,2-dihydropyridine (2), and the methyl derivative of I (3).

Figure 2 compares the spectrum of the pyridinium ion of III with the spectra of 3,5-diethyl-2-propylpyridinium ion and N-phenylpyridinium ion. They resemble each other closely. Evidently the tetracovalent nitrogen atom effectively insulates the conjugation of the benzene ring from

(1) Karrer, *Helv. Chim. Acta*, **20**, 72 (1937).

(2) Mumm and Diederichsen, *Ann.*, **538**, 198 (1939), reported that 1,2-dihydro-1,2,6-trimethyl-4-phenyl-3,5-dicarbethoxypyridine reacted with maleic anhydride to form a 1:1 adduct and that the corresponding 1,4-dihydro isomer did not react.

(3) The structure of this adduct is the subject of a second paper.

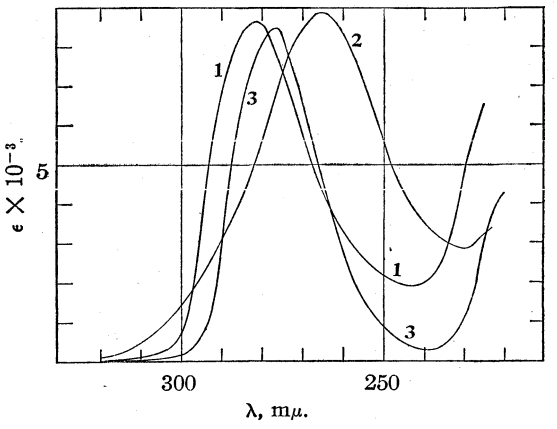


Fig. 2.—Spectrum of the cation of III, obtained by subtraction of the absorption of KI from that of III, (1); spectrum of N-phenylpyridinium chloride (2); spectrum of 3,5-diethyl-2-propylpyridinium ion (3) in 1.2 *N* HCl in 90% methanol.

that of the pyridine ring. The maxima for the trialkyl pyridinium salts appear at longer wave lengths because of the usual bathochromic effects of the alkyl groups on the pyridine nucleus.

Figure 3 presents the spectrum of N-phenyl-3,5-diethyl-2-propylpiperidine IV along with that of N-phenylpiperidine and di-*n*-butylaniline. It is of interest to note the similarities and differences among these spectra. The piperidines are, in one sense, dialkylanilines and would be expected to possess a well-defined fundamental band such as the long wave length band of di-*n*-butylaniline. Extension of the discussion of Remington[4] on steric effects caused by hindrance to ease of formation of a planar configuration can explain the somewhat distorted shape of the fundamental band in the piperidines. This follows as a result of the tendency of the piperidine ring to be puckered. Further comparison shows the similarity between the spectra of N-phenylpiperidine and of IV which supports the structure assigned to the latter compound as a result of the method used for its preparation.

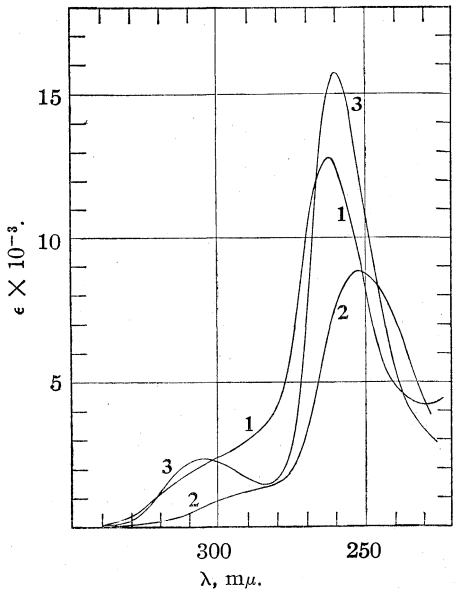


Fig. 3.—Spectra of IV (1), N-phenylpiperidine (2), and di-*n*-butylaniline (3).

The absorption spectrum of the tetrahydropyridine V is entirely different from that of the corresponding piperidine IV. The greater intensity and longer wave lengths at which the absorption of V occurs indicates that the double bond must be conjugated with the nitrogen atom.[5] The spectrum observed for V in conjunction with the hydrogenation of the $C_{18}H_{25}N$ base to form V is evidence against structures Ia and Ib for the dihydropyridine since by 3,6- or 2,5-addition such structures would be expected to lead to Δ^4- and Δ^3-tetrahydropyridines.

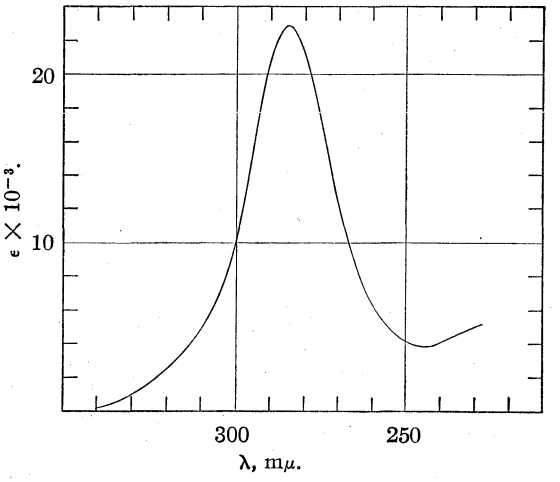
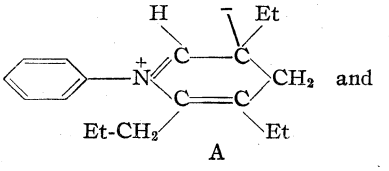
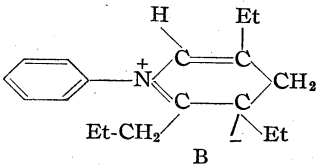


Fig. 4.—Spectrum of V.

Attachment of two vinyl groups to the nitrogen atom as in structure I makes it possible to write, among others, the nearly equivalent resonance forms, A and B, for the first excited state. This



A



B

leads to considerable stabilization of the first excited electronic level by resonance, and hence, absorption at a longer wave length than would be

(4) Remington, THIS JOURNAL, **67**, 1838 (1945).

(5) Bowden, Brauda, Jones and Weedon, *J. Chem. Soc.*, 45 (1946).

true for structures Ia and Ib for which the forms contributing to the first excited state would have quite different energies. Thus, the 1,4-dihydropyridine reported here has its first maximum at 340 mμ whereas N-phenyl-1,2-dihydropyridine has a maximum at 286 mμ.

Experimental Part

Absorption Spectra.—The spectra were measured in methanol solution except where specified otherwise using a Beckman quartz spectrophotometer, Model DU.

N-Phenyl-3,5-diethyl-2-propyl-1,4-dihydropyridine, Compound I.—One mole (93 g.) of aniline was added dropwise to a mixture of four moles (288 g.) of butyraldehyde containing 8.7 g. of acetic acid and 6 moles (108 g.) of water during thirty minutes. During this period the mixture was stirred and cooled to about 10° with ice water. The mixture was then heated to reflux and maintained at reflux for five hours. The final liquid temperature was 98°. After removal of the water layer, containing most of the acetic acid, butyraldehyde and 2-ethylhexenal were removed by steam distillation during four hours. The remaining oil was dried at reduced pressure. It was a fluid, light brown oil with a characteristic odor and a refractive index of $1.575^{20}D$. The product was distilled to supply a 55% yield of light yellow oil which came over at about 125° at 0.5 mm. pressure. The refractive index of this oil was $1.5725^{20}D$. By redistillation the refractive index was raised to 1.5740. This product was nearly odorless.

Anal. Calcd. for $C_{18}H_{25}N$: C, 84.64; H, 9.87; N, 5.49; mol. wt., 255. Found: C, 84.56; H, 10.26; N, 5.29; mol. wt. in freezing benzene, 241, 242.

Pyrolysis of Compound I.—A mixture of 150 g. of I and 2 g. of anhydrous cobaltous chloride was placed in a 500-ml. distilling flask equipped with a stirrer. The mixture was heated rapidly with stirring to about 275° when decomposition set in. The temperature was raised to 310° during twenty minutes. The distillate amounted to 115 g. and the residue to 35 g. The distillate was extracted with a mixture of 80 ml. of concd. hydrochloric acid and 160 ml. of water. The oil layer was separated, washed with water, dried over potassium carbonate, and distilled. A yield of 15 g. (16%) of colorless oil was obtained which distilled at 210–212°.

Anal. Calcd. for $C_{12}H_{18}$: C, 88.83; H, 11.17. Found: C, 88.99; H, 11.05.

The hydrocarbon was identified by the preparation of the trinitro derivative by the method of Gattermann, *et al.*[6] This derivative melted at 111° alone or when mixed with an authentic specimen of 1,3,5-triethyl-2,4,6-trinitrobenzene.

The acid layer was made basic with strong caustic. The oil which precipitated was dried and distilled. In this way, 14 g. (25%) of aniline and an unidentified oil which distilled at 184–186° at 17 mm. was secured. The aniline was identified by the preparation of the acetyl derivative. The oil analyzed approximately for $C_{18}H_{25}N$. After heating with $CoCl_2$ at 300° it was recovered unchanged.

N-Phenyl-3,5-diethyl-2-propyl-1,4,5,6-tetrahydropyridine.—This compound was formed by shaking 25.5 g. of compound I with 10 g. of Raney nickel and 25 ml. of alcohol under 3 atmospheres of hydrogen for three hours. The pressure drop then corresponded to 1.05 moles of hydrogen per mole of I. The product, isolated in 92% yield, distilled at 115 to 120° at 0.2 mm. and had a refractive index of $1.5518^{20}D$. It required five minutes of shaking for complete solution in six volumes of 6 *N* hydrochloric acid.

Anal. Calcd. for $C_{18}H_{27}N$: C, 83.98; H, 10.58; N, 5.44. Found: C, 83.87, 83.73; H, 10.87, 10.93; N, 5.41, 5.47.

(6) Gattermann, *et al.*, *Ber.*, **32**, 1124 (1899).

N-Phenyl-3,5-diethyl-2-propylpiperidine.—Hydrogenation of compound I over Raney nickel between 30 and 100° and from 3 to 100 atmospheres produced this derivative quite smoothly although the product contained small quantities of the dihydro base and probably the decahydro derivative as well. In a typical run 13.3 g. of I dissolved in 50 ml. of alcohol was shaken with 12 g. of Raney nickel in a copper lined autoclave for ten hours at 70 atmospheres pressure of hydrogen and 50°. The product was distilled at 0.2 mm. Fraction A distilled at 112–115° and Fraction B at 115–120°. These fractions were almost colorless. The combined yield was 93%. The refractive indices $n^{20}D$ of the fractions were 1.5290 and 1.5350, respectively.

Anal. Calcd. for $C_{18}H_{29}N$: C, 83.33; H, 11.27; N, 5.40. Found for A: C, 83.30, 83.40; H, 11.40, 11.32; N, 5.34, 5.40. Found for B: C, 83.46, 83.40; H, 11.24, 11.31; N, 5.42, 5.36.

Although these fractions thus appeared to be analytically pure, their ultraviolet absorption spectra disclosed the presence of the above tetrahydropyridine. It may therefore be inferred that small amounts of some hydrogen rich compound such as the decahydro derivative were present. Extraction with dilute hydrochloric acid removed most of these impurities. The compound thus purified had one absorption maximum (Fig. 3). It had a refractive index of $1.5320^{20}D$.

N-Cyclohexyl-3,5-diethyl-2-propylpiperidine.—This compound was secured by heating 64.5 g. of compound I and 10 g. of Raney nickel at 150° for twenty hours under about 100 atmospheres of hydrogen. The main product, which was isolated in 45% yield, distilled at 103–110° at 0.1 mm. and had a refractive index of $1.4868^{20}D$. Its ultraviolet absorption spectrum had one low peak at 263 mμ probably due to the presence of a trace of the incompletely reduced phenyl derivative. The compound was colorless.

Anal. Calcd. for $C_{18}H_{35}N$: C, 81.42; H, 13.31; N, 5.28. Found: C, 81.37, 81.48; H, 13.15, 13.24; N, 5.29, 5.35.

N-Phenyl-3,5-diethyl-2-propyl-pyridinium Iodide, III.—A turbid mixture containing 2.55 g. (0.01 mole) of compound I, 50 ml. of alcohol, 10 ml. of acetic acid, and 10 ml. of 25% potassium iodide was titrated rapidly with 1 *N* potassium iodate. Only a small amount of the iodate was required to produce a clear solution. An iodine color was apparent when 17.2 ml. had been added. This color deepened during a period of ten minutes and required 0.1 ml. of 0.1 *N* thiosulfate solution to reduce it to the color of the iodine end-point. The sample thus is equivalent to 17.1 ml. of the *N* iodate solution which is 85.5% of the amount (20.0 ml.) required for the reaction

$$C_{18}H_{25}N + I_2 \longrightarrow C_{18}H_{24}NI + HI$$

The conditions of titration were investigated in a preliminary way. The reaction is favored by an excess of iodide ion and can be conducted with alcoholic iodine solution instead of iodate solution. Acetic acid is a satisfactory acid and may be used in considerable excess while hydrochloric acid has a strongly inhibitory action. The solutions from four such titrations were evaporated at reduced pressure until all of the alcohol and most of the acetic acid were removed. Excess 48% sodium hydroxide then was added. This precipitated an oil which crystallized on standing overnight. The crystals were dissolved in a little butanol and the solution filtered. The filtrate after being diluted with one liter of cold ether yielded 12.5 g. of brown solid, m. p. 90–95°. This solid was dissolved again in butanol and precipitated with ether to provide a crop of light brown crystals, m. p. 105–106°. The yield of these amounted to 11.5 g. or 75% of the theoretical amount. Solution in dry alcohol and fractional precipitation with ether gave bright yellow plates, m. p. 107–108°.

Anal. Calcd. for $C_{18}H_{24}NI$: C, 56.66; H, 6.35; N, 3.67; I, 33.33. Found: C, 56.76, 56.71; H, 6.37, 6.38; N, 3.79, 3.73; I, 33.34, 33.26.

The iodide can be produced in good yield by the action of sulfur on compound I in acetic acid solution followed by the addition of sodium or potassium iodide and working up the mixture as described above.

The iodide is very soluble in water, alcohols, ketones, esters and acetic acid. It is insoluble in hydrocarbons such as benzene and hexane. Three liquid phase systems are formed with benzene and water and a solid addition compound is produced with carbon tetrachloride which is sometimes useful in recovering the salt from aqueous solutions.

The iodine content is quantitatively precipitated with aqueous 0.1 *N* silver nitrate. The iodide does not react at moderate temperature with maleic anhydride or with hydrogen over Raney nickel. With sulfur no reaction occurs unless a sulfur "acceptor" is present. Suitable "acceptors" are unsaturated compounds such as styrene or rubber. Reaction also occurs readily with sulfur in the presence of alkali.

N-Phenyl-3,5-diethyl-6 or 4-methyl-2-propyl-1,4-dihydropyridine.—One reaction indicating the quaternary nature of the iodide III is the Freund reaction with excess methylmagnesium iodide in ether solution. The product of this reaction, which was obtained in 82% yield, had a refractive index of $1.5510^{20}D$ and distilled at 105–106° at 0.2 mm. The ultraviolet absorption spectrum of this compound, given in Fig. 1, is similar to that of compound I. The methyl group must be attached to either the 6 or the 4-position of the dihydropyridine ring.

Anal. Calcd. for $C_{19}H_{27}N$: C, 84.69; H, 10.10; N, 5.20. Found: C, 84.44, 84.39; H, 9.83, 9.89; N, 5.54, 5.48.

The reaction of compound I (0.1 mole) with sulfur (0.1 atom) during twenty-four hours on the steam-bath formed hydrogen sulfide and a semicrystalline black mass. Extraction with benzene yielded about 1 g. of nearly colorless crystals which melted at 156–157° after solution in a mixture of acetone and alcohol followed by precipitation with ether.

Anal. Calcd. for $C_{18}H_{25}NSO_4$: C, 61.50; H, 7.18; N, 3.99. Found: C, 61.43, 61.51; H, 7.17, 7.26; N, 4.14, 4.07.

This compound was identified as the acid sulfate corresponding to the quaternary iodide III described above from which it also was prepared by addition of sulfuric acid and distilling off hydroiodic acid at reduced pressure. The product so produced melted at 156–157° alone or when mixed with the analyzed sample. This compound was also secured by shaking I in acetic acid solution with reduced platinum oxide and adding sulfuric acid to the mixture when the evolution of hydrogen had ceased. Most of the acetic acid was evaporated at reduced pressure and the last traces removed by addition of sodium carbonate. The acid sulfate was extracted with warm acetone and precipitated by the addition of ether.

The benzene filtrate from the acid sulfate was evaporated and the resulting solid crystallized twice from alcohol. The yield amounted to 8 g. of bright yellow crystals melting at 127°. The melted product resolidified and then melted again at 132°.

Anal. Calcd. for $C_{18}H_{23}NS$: C, 75.74; H, 8.13; N, 4.91; S, 11.22. Found: C, 75.29, 75.24; H, 8.14, 8.05; N, 5.12, 5.07; S, 11.53, 11.60.

The structure of this compound is believed to be N-phenyl-3,5-diethyl-2-propyl-6-thiopyridone formed by the oxidation of a pseudo form of the pyridinium hydrosulfide.

The Reaction of I with Hydrochloric Acid.—The rate of reaction depends primarily on the concentration of the acid and on the temperature. In the cold and with dilute acid the rate is very slow. A mixture of 12.5 g. of I and 10 g. of 36.5% hydrochloric acid was shaken for twenty minutes at 20°. Gradually solution occurred as might be expected of a vinylamine. The oil precipitated by the addition of caustic to this solution was I. A similar mixture of acid and I was refluxed at 116° for two hours. The product was water soluble. It was neutralized with 6 g. of sodium carbonate. Then 100 ml. of hexane was added and the mixture shaken with small portions of water until free of water soluble substances. The hexane layer was dried over potassium carbonate and distilled. After the hexane 2.5 g. of light yellow oil distilled at 120–125° at 0.7 mm. It had a refractive index, $n^{20}D$ of 1.5523.

Anal. Calcd. for $C_{18}H_{27}N$: C, 83.98; H, 10.58; N, 5.44. Found: C, 83.82, 83.60; H, 10.55, 10.53; N, 5.43, 5.47.

The analysis and refractive index are in agreement with the supposition that this product is identical with the N-phenyl - 3,5 - diethyl - 2 - propyl - 1,4,5,6 - tetrahydropyridine secured by the hydrogenation of compound I. The substantial identity of the two $C_{18}H_{27}N$ samples finally was established by their ultraviolet absorption spectra. The water layer on evaporation at reduced pressure in the presence of 2.5 g. of potassium iodide yielded a mixture of salts which was extracted with butanol. On addition of ether to the butanol extract there was obtained a crop of yellow crystals which after solution and precipitation melted at 105–107° alone or when mixed with N-phenyl-3,5-diethyl-2-propylpyridinium iodide. The yield was 4.5 g.

Reaction with Maleic Anhydride.—A mixture of 5.1 g. of compound I and 1.8 g. of maleic anhydride was stirred with a thermometer. The immediate formation of a red colored product occurred, usually followed by a temperature rise from 30 to 50° during about twenty minutes. In case the temperature did not rise spontaneously the mixture was heated to about 50°. Reaction then became rapid and it was necessary to cool the mixture in order to keep the temperature from rising above about 60°. During about ten minutes longer a solid began to separate and it soon became impossible to stir the mixture. The temperature was allowed to fall and the mixture was allowed to stand overnight. It melted at 112 to 115°. The product was powdered and extracted with 50 ml. of hexane. The residue melted at 115–117° and weighed 4.7 g. This weight represents a yield of 78%. The melting point was raised to 119–120° by recrystallizing from acetone or alcohol and the product was then colorless.

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.64, 74.70; H, 7.71, 7.74; N, 4.02, 4.00.

Occasionally while working up the reaction products of maleic anhydride with impure samples, a second compound was isolated. This was a white solid melting with decomposition at 153° when recrystallized from alcohol.

Anal. Calcd. for $C_{22}H_{29}NO_4$: C, 71.12; H, 7.87; N, 3.77. Found: C, 71.05, 71.01; H, 8.06, 8.00; N, 3.79, 3.38.

This compound, which is the hydrate of the adduct, melts with almost quantitative loss of water to form the original adduct.

Acknowledgment.—The reaction of aldehydes with amines has been examined by many workers in this Laboratory, including Dr. A. W. Sloan. Their results constituted the basis on which the work reported here was initiated. Particular acknowledgment is due Drs. W. L. Semon and H. L. Trumbull for their interest and suggestions.

Summary

1. A main product of the condensation of excess butyraldehyde with aniline in the presence of weak acids has been found to be N-phenyl-3,5-diethyl-2-propyl-1,4-dihydropyridine.

2. The reactions of the dihydropyridine which were investigated include pyrolysis, hydrogenation, dehydrogenation, oxidation, reaction with sulfur, vinylamine type behavior toward acids,

and reaction with maleic anhydride. These reactions led to the isolation of some nine new compounds.

3. Vinylamine behavior may be recognized as an important property of some of the new compounds, especially in connection with their ultraviolet absorption spectra.

AKRON, OHIO RECEIVED OCTOBER 10, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO[1]]

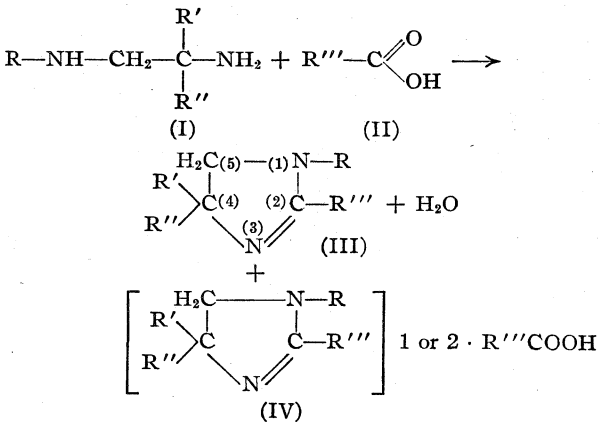
The Synthesis of Imidazolines from 1,2-Diamines and Carboxylic Acids

BY J. L. RIEBSOMER

Chitwood and Reid[2] prepared a series of 2-alkyl-2-imidazolines by distilling or heating the appropriate diacylethylenediamine with sodium, magnesium, zinc, magnesium oxide or sodium hydroxide. Thus 2-methyl-2-imidazoline was produced in 68% yield when diacetylethylenediamine was heated at 270° with magnesium. The yields were less satisfactory with the other inorganic reagents. When ethylenediamine and acetic acid were heated 2-methyl-2-imidazoline was produced in 19% yield and when monoacetylethylenediamine hydrochloride was heated with sodium hydroxide a 26% yield of the imidazoline formed. Hofmann[3] prepared the same imidazoline upon distillation of a sodium acetate and ethylenediamine hydrochloride mixture.

Hill and Aspinall[4] prepared a series of 2-alkyl and 2-aryl substituted imidazolines by heating monoacylethylenediamines.

The technique employed for the preparation of the imidazolines reported here was to add benzene to a mixture of the 1,2-diamine and carboxylic acid and to distil the benzene through a four-foot packed column. As the benzene distilled, water formed from the reaction was carried out as an azeotropic mixture. The column was equipped with a suitable head so that the benzene returned and the water was separated. It might have been anticipated that the imidazoline would be the only product formed by this process. In nearly all instances studied, however, a higher boiling substance was produced along with the imidazoline. Indeed in some instances the higher boiling product was formed almost exclusively. The course of most of these reactions may be formulated as

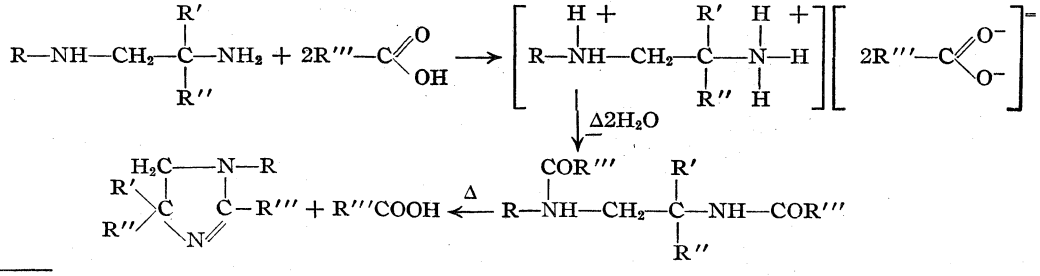


(I) (II) (III) (IV)

R′ and R″′ were H, alkyl, or aryl. R′ and R″ were H or alkyl. The most complete study was made in the case in which R was isopropyl and R′ and R″ were methyl. In this instance R″ was H, alkyl groups from CH_3 to $C_{17}H_{35}$ or aryl.

A few exceptions to the general reaction were noted. When 2,3-dimethyl-2,3-butanediamine reacted with acetic acid none of the expected compounds (III) or (IV) were isolated but a low yield of the diacetate was found. Likewise 1,2-butanediamine and acetic acid reacted to form the diacetyl derivative of the amine along with the imidazoline.

A possible mechanism to account for the formation of the imidazolines by this method may be represented as follows:



The evidence for the existence of the compounds of type (III) seems to be entirely satisfactory. The analyses, neutral equivalents and mode of synthesis all point to the same conclusion.

(1) Most of this work was completed while the author was at DePauw University, Greencastle, Indiana.

(2) Chitwood and Reid, THIS JOURNAL, **57**, 2424 (1935).

(3) Hofmann, *Ber.*, **21**, 2332 (1888).

(4) Hill and Aspinall, THIS JOURNAL, **61**, 822 (1939).

The non-committal formulation of compounds of type (IV) suggests doubt as to their structures. While most of these compounds gave analyses corresponding to one mole of the imidazoline attached to two moles of the acid, there were a few examples studied in which the molar ratio was one of the imidazoline to one of the acid. These exceptions were found mainly in those instances in which R was aryl. It is also of interest to note that the ratio of (IV) to (III) tended to increase as the chain length of R''' increased.

The examination of the nature of compounds of type (IV) was carried out mainly with the products formed from N-(2-aminoisobutyl)-isopropylamine and acetic and stearic acids. When acetic acid was used in this reaction a 26% yield of 2,4,4-trimethyl-1-isopropyl-2-imidazoline and a 32.7% yield of the complex corresponding to (IV) were obtained. The complex in this instance contained two moles of the acid.

This complex was a colorless, viscous oil when freshly distilled. Upon prolonged standing it turned yellow. It was readily soluble in water and insoluble in ether or petroleum ether suggesting salt-like properties. The fact that it distilled at 124–125° at 16 mm. is not characteristic of salts but does not preclude this possibility. It reacted either with strong acids or strong bases with the evolution of considerable heat, which suggested that it was made up of both acidic and basic constituents not firmly combined chemically. Its neutral equivalent was 258 (using 0.1 normal alkali and phenolphthalein). The end-point was not sharp but this figure indicated the acidic constituent to be of greater influence than the basic constituent.

When this complex was treated with cold aqueous sodium hydroxide solution 2,4,4-trimethyl-1-isopropyl-2-imidazoline was formed in good yield. When this imidazoline was mixed with two molar equivalents of acetic acid the complex was formed in high yield. And finally when one mole of N-(2-aminoisobutyl)-isopropylamine reacted with three moles of acetic acid, the complex was produced in 89% yield while no imidazoline was isolated.

The Raman spectrum for 2,4,4-trimethyl-1-isopropyl-2-imidazoline showed lines which would be expected from —C=N— linkage. When a similar experiment was attempted with the corresponding complex a continuous spectrum was obtained from which no definite conclusions could be drawn.[5]

What has been said for the complex produced from acetic acid and N-(2-aminoisobutyl)-isopropylamine can for the most part be repeated for the analogous product formed from the same diamine and stearic acid. In this instance the complex was formed nearly quantitatively and none of the corresponding imidazoline was isolated.

No evidence has been found to establish unequivocally the structure of compounds of type (IV). One might assume simple salt formation with the acid involving the acceptance of a proton by one or both nitrogen atoms. But this assumption of salt formation is open to the objection that imidazolines always form mono-hydrogen halide salts and they titrate potentiometrically as mono-acid bases. This latter observation makes it clear that one of the nitrogen atoms must be very weakly basic. It would be rather unexpected to find this weakly basic nitrogen capable of accepting a proton from acetic or stearic acid and not capable of doing so from hydrochloric acid. It would, therefore, be reasonable to suggest that most of the compounds of type (IV) may be molecular complexes made up of one mole of the acid and one mole of the salt—the latter being formed by the reaction of one mole of acid with one mole of the imidazoline.

(5) The author is indebted to Dr. M. J. Murray for the Raman spectra studies.

Experimental

The experimental procedure for the preparation of all these compounds was substantially the same. One molar equivalent of the diamine and one molar equivalent of the carboxylic acid were mixed with a little benzene and heated from 140 to 220°. The benzene–water mixture was distilled through a 4′ × $^5/_8$″ helix-packed column which was equipped with a decanter still-head filled with benzene, and arranged to drain off the water layer and to return the benzene to the column. Heating was continued until one molar equivalent of water was removed. In some instances one molar equivalent of the diamine and three of the acid were heated until two molar equivalents of water had been removed. The latter procedure generally gave high yields of compounds of type (IV) and none of (III).

After the reaction was complete the product was usually distilled. In some instances the product was a solid and was crystallized from a suitable solvent.

Two specific examples will suffice to illustrate the preparation of most of the compounds.

Preparation of 2,4,4-Trimethyl-1-isopropyl-2-imidazoline and its Molecular Complex.—A mixture of 130.1 g. (1 mole) of N-(2-aminoisobutyl)-isopropylamine and 60 g. (1 mole) of acetic acid was heated at 190–200° for three hours. During this period 21.5 g. of water was removed. The product was distilled and three main fractions were taken. The first came over at 60–63° (38 mm.), and was shown by its refractive index, density and neutral equivalent to be unreacted N-(2-aminoisobutyl)-isopropylamine, 57.4 g., 44% recovery. The second, which boiled at 94–96° (38 mm.), was the imidazoline, 41 g., 26.6% yield. The third fraction, with b. p. 124–125° (16 mm.), was the complex, 29.9 g., 32.7% yield.

In another experiment, 65 g. (0.5 mole) of N-(2-aminoisobutyl)-isopropylamine and 90 g. (1.5 moles) of acetic acid were mixed and heated to 180–220° for three hours until 18 g. (1 mole) of water was removed. The product, which distilled at 128–130° (19 mm.), was the complex; yield, 89%.

Anal. Calcd. for the complex $C_{13}H_{26}N_2O_4$: N, 10.20. Found: N, 9.89.

No imidazoline (VII) was isolated from the product.

TABLE A

2-SUBSTITUTED-4,4-DIMETHYL-1-ISOPROPYL-2-IMIDAZOLINES

2-Substituent R=	Yield, %	B. p. °C.	Mm.	d^{20}_{20}	$n^{20}D$	Formula	Analyses, % Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N	Neut. equiv. Found	Neut. equiv. Calcd.
H	13.3	81–82	19	0.8738	1.4525	$C_8H_{16}N_2$	68.13	11.33	19.61	68.52	11.52	19.99	139.6	140.1
CH_3	23.0	72–75	15	.875	1.454	$C_9H_{18}N_2$			18.2			18.1	152	154
C_2H_5	12.9	92	22	.8713	1.4550	$C_{10}H_{20}N_2$	71.62	11.68	16.68	71.37	11.92	16.64	166.3	168.1
C_3H_7	19.0	97–100	20	.8626	1.4549	$C_{11}H_{22}N_2$	71.34	12.04	15.22	72.45	12.11	15.36	179.5	182.1
C_3H_7 (iso)	10.0	88	20	.8522	1.4498	$C_{11}H_{22}N_2$	72.54	11.94	15.11	72.45	12.11	51.36	182.1	182.1
C_4H_9	18.2	112–115	18	.8753	1.4592	$C_{12}H_{24}N_2$	71.43	12.01	14.14	73.41	12.43	14.22	197.5	196.2
C_5H_{11}	15.4	125–128	18			$C_{13}H_{26}N_2$			13.14			13.32	212.9	210.2
$C_{11}H_{23}$[a]		160–162	8			$C_{19}H_{38}N_2$	76.98	12.97	9.34	77.47	13.22	9.51	295.1	294.1
$C_{13}H_{27}$[a]		219–222	18			$C_{21}H_{42}N_2$	77.64	12.98	8.51	78.15	13.13	8.69	327.0	322.2
$C_{15}H_{31}$[a]		183–185	3		1.4691	$C_{23}H_{46}N_2$	78.07	13.26	7.73	78.78	13.25	7.99	361.6	350.3
$C_{17}H_{35}$[a]						$C_{25}H_{50}N_2$	78.97	13.21	7.07	79.33	13.35	7.39	403.7	378.2
Phenyl[a]		163–166	28		1.5210	$C_{14}H_{20}N_2$	77.59	9.50	13.10	77.74	9.33	12.96	215.4	216.1

[a] Obtained by treating the corresponding molecular complexes (IV) with alkali.

TABLE B

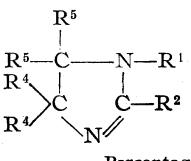
MOLECULAR COMPLEXES OF TYPE (IV) FROM 2-SUBSTITUTED-4,4-DIMETHYL-1-ISOPROPYL-2-IMIDAZOLINES[e]

2-Substituent R=	Yield, %	B. p., °C.	d^{20}_{20}	$n^{20}D$	Formula	Analyses, % Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N	Neut.[b] equiv.
H[a]		150–151 (28)			$C_{10}H_{18}N_2O_4$			12.20			12.06	
CH_3	32.7	124–125 (16)	1.026	1.4609	$C_{13}H_{26}N_2O_4$	57.27	9.24	10.04	56.91	9.55	10.20	258[b]
C_2H_5[c]	56.6	129–130 (20)	1.0012	1.4610	$C_{16}H_{32}N_2O_4$	60.17	9.88	8.56	60.73	10.14	8.86	290[b]
C_3H_7[c]	51.8	106–109 (2)	0.9759	1.4600	$C_{19}H_{38}N_2O_4$	63.04	10.67	7.74	63.65	10.68	7.81	356[b]
i-C_3H_7[c]	56.5	128–132 (20)	0.9744	1.4588	$C_{19}H_{38}N_2O_4$	61.94	10.77	7.47	63.65	10.68	7.81	
C_4H_9[c]	64.9	150 (22)	0.9525	1.4607	$C_{22}H_{44}N_2O_4$	65.51	11.18	6.79	65.94	11.10	6.97	
C_5H_{11}[c]	65.2	157–160 (20)		1.4619	$C_{25}H_{50}N_2O_4$	67.91	11.48	6.42	67.81	11.39	6.33	
$C_{11}H_{23}$[c]	87.8	160–162 (1)			$C_{43}H_{86}N_2O_4$	74.33	12.58	4.69	74.27	12.62	4.03	
$C_{13}H_{27}$[c]	92.5	206–209 (6)			$C_{49}H_{98}N_2O_4$	76.16	12.81	3.64	75.51	12.68	3.59	
$C_{15}H_{31}$[c]	Almost	M. p. 43–43.5			$C_{55}H_{110}N_2O_4$	76.30	12.65	3.33	76.48	12.85	3.24	
$C_{17}H_{35}$[c]	quant.	M. p. 54–55			$C_{61}H_{122}N_2O_4$	77.25	13.02	2.82	77.27	13.00	2.96	
Phenyl[d]	73				$C_{26}H_{32}N_2O_4$			6.27			6.15	

[a] Obtained by treating the imidazoline with formic acid. [b] Using phenolphthalein and 0.1 *N* alkali. [c] Reagents mole to mole ratio. [d] One mole of amine allowed to react with 3 moles of the acid. [e] When these complexes were treated with alkali they were converted to the corresponding imidazolines, which had the same properties as when produced directly from the reactions.

TABLE C

SUBSTITUTED IMIDAZOLINES

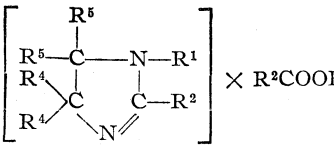


Amine used	R^1	R^2	R^4	R^5	Formula	B. p. °C.	Mm.	Percentage composition C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	Neut. equiv. Calcd.	Neut. equiv. Found
A^1-aniline[g,f]	C_6H_5	CH_3	CH_3	H	$C_{12}H_{16}N_2$[g,o]	144–152	28	76.55	76.22	8.61	8.76	14.88	14.86	...	...
A^1-aniline[a]	C_6H_5	$C_{17}H_{35}$	CH_3	H	$C_{28}H_{48}N_2$[k]	39–40[b]		81.47	81.47	11.73	11.78	6.79	6.77	412.4	412.2
A^1-*m*-toluidine[a,l]	C_7H_7	CH_3	CH_3	H	$C_{13}H_{18}N_2$	155–158	20	77.15	76.16	8.97	9.15	13.85	14.29	202.1	195.5
A^1-*n*-butylamine[a,m]	C_4H_9	CH_3	CH_3	H	$C_{10}H_{20}N_2$[h]	105–108	26	71.34	70.89	11.98	12.35	16.65	16.77	168.2	160.7
A^1-*n*-butylamine[a]	C_4H_9	$C_{17}H_{35}$	CH_3	H	$C_{26}H_{52}N_2$[k]	223–226	3	...	...	...	...	7.13	7.05	392.4	392.2
A^1-*s*-butylamine[a]	C_4H_9	CH_3	CH_3	H	$C_{10}H_{20}N_2$[o,k]	100–102	30	71.34	71.03	11.98	12.50	16.65	17.04	168.2	168.1
A^1-*s*-butylamine[a]	C_4H_9	$C_{17}H_{35}$	CH_3	H	$C_{26}H_{52}N_2$[k]	200–221	3	...	...	...	...	7.13	7.03	...	...
A^2-A^3[c]	C_6H_{13}	CH_3	CH_3[d]	H	$C_{13}H_{26}N_2$[i,o,k]	131–132	35	74.21	73.74	12.47	12.48	13.32	13.42	210.2	208.4
A^2-A^3[c]	C_6H_{13}	$C_{17}H_{35}$	CH_3[d]	H	$C_{29}H_{58}N_2$[j,k]	233–235	3	...	...	...	...	6.44	6.46	434.5	432.5
A^4-2,3-diaminobutane[e]	H	C_6H_{11}	CH_3	CH_3	$C_{12}H_{24}N_2$[k]	143	23	73.39	53.28	12.33	12.21	14.27	14.09	...	...
1,2-Butanediamine[n]	H	CH_3	C_2H_5[p]	H	$C_6H_{12}N_2$	116–118	24	64.23	64.11	10.79	10.88	24.97	23.86	112.3	112.3

[a] A^1 = N-(2-aminoisobutyl)—. [b] Melting point. [c] A^2 = N-(2-amino-2-methylbutyl); A^3 = -1,3-dimethylbutylamine. [d] One R^4 = ethyl. [e] A^4 = 2,3-dimethyl. [f] Yield, 87. [g] d^{20}_{20} 1.0143; $n^{20}D$ 1.5527. [h] d^{20}_{20} 0.8678; $n^{20}D$ 1.4550. [i] d^{20}_{20} 0.8694; $n^{20}D$ 1.4568. [j] d^{20}_{20} 0.8573; $n^{20}D$ 1.4635. [k] Prepared by treatment of molecular complex of type (IV) with alkali. [l] Yield, 76. [m] Yield, 15. [n] Yield, 20. [o] Molar ratio of acid to amine allowed to react was 3 to 1. In other instances equimolecular quantities were used. [p] This compound may be 4- or 5-ethyl.

TABLE D

MOLECULAR COMPLEXES OF IMIDAZOLINES AND ORGANIC ACIDS



Amine used	Yield, %	R1	R2	R4	R5	Formula	B. p. °C.	B. p. Mm.	Percentage composition C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
A1-aniline[a]	94	C_6H_5	$C_{17}H_{35}$	CH_3	H	$C_{46}H_{84}N_2O_2$[b]	40–43[c]		79.23	79.56	12.15	11.99	4.02	4.63
A1-*m*-toluidine[a]	76	C_7H_7	$C_{17}H_{35}$	CH_3	H	$C_{47}H_{86}N_2O_2$[b]	53–55[c]		79.36	78.07	12.20	12.26	3.94	3.50
A1-butylamine[a]	28	C_4H_9	CH_3	CH_3	H	$C_{14}H_{28}N_2O_4$[d]	112	2	58.29	59.51	9.80	10.25	9.72	10.32
A1-butylamine[a]	87	C_4H_9	$C_{17}H_{35}$	CH_3	H	$C_{44}H_{88}N_2O_2$[b]	220–222	2	...	...	...	...	4.13	4.20
A1-*s*-butylamine[a]	73	C_4H_9	CH_3	CH_3	H	$C_{14}H_{28}N_2O_4$[d]	134–136	26	58.29	58.05	9.83	9.86	9.72	10.02
A1-*s*-butylamine[a]	84	C_4H_9	$C_{17}H_{35}$	CH_3	H	$C_{62}H_{124}O_4$[d]	213–216	2	77.42	77.14	12.79	13.14	2.91	2.87
A1-A2[a,e]	80	C_6H_{13}	CH_3	CH_3	H	$C_{17}H_{34}N_2O_4$[d]	139–140	26	...	...	...	...	8.48	8.48
A2[f]	..	C_6H_{13}	$C_{17}H_{35}$	CH_3[g]	H	$C_{47}H_{94}N_2O_2$[b]	219–221	2	78.45	78.47	13.18	13.21	3.89	3.94
A4[h]	67	H	C_5H_{11}	CH_3	CH_3	$C_{24}H_{48}N_2O_4$[d]	168–169	2	67.23	67.95	11.24	11.29	8.97	8.51

[a] A1 = N-(2-aminoisobutyl)—. [b] X = 1. [c] Melting point. [d] X = 2. [e] A2 = -1,3-dimethylbutylamine. [f] N-(2-amino-2-methylbutyl)-1,3-dimethylbutylamine. [g] One R^4 is ethyl. [h] 2,3-Dimethyl-2,3-diaminobutane.

Conversion of the Complex to 2,4,4-Trimethyl-1-isopropyl-2-imidazoline.—To 40 g. of the complex was added 70 ml. of 10% aqueous sodium hydroxide. The alkaline solution was extracted with ether, and the ether solution dried over solid potassium hydroxide. The ether was removed and distillation gave a 15 g. fraction, b. p., 78–80° (15 mm.). There was almost no forerun or residue; yield, 72%.

Anal. Calcd. for the imidazoline, $C_9H_{18}N_2$: N, 18.17; neut. equiv., 154.1. Found: N, 18.10; neut. equiv., 159.2.

Conversion of 2,4,4-Trimethyl-1-isopropyl-2-imidazoline to the Complex.—To 3.08 g. (0.02 mole) of the imidazoline was added 2.4 g. (0.04 mole) of acetic acid. The mixture evolved heat. Upon distillation, the entire product boiled at 122–124° (15 mm.), 4.5 g., 90% yield.

Anal. Calcd. for the complex, $C_{13}H_{26}N_2O_4$: N, 10.20. Found: N, 10.11.

Preparation of 4,4-Dimethyl-1-isopropyl-2-heptadecyl-2-imidazoline Molecular Complex with Stearic Acid.—A mixture of 32.5 g. (0.25 mole) of N-(2-aminoisobutyl)-isopropylamine and 71.1 g. (0.25 mole) of stearic acid was heated to 190–200° for three hours. During the heating process 4.5 g. (0.25 mole) of water was removed. The product was transferred to a distillation flask and 13.3 g. of the original diamine (41%) was recovered. A white, solid, undistilled residue remained. After three crystallizations from acetone, it melted at 54–55°; yield of the complex, 95%.

Conversion of the Stearic Acid Complex to 4,4-Dimethyl-1-isopropyl-2-heptadecyl-2-imidazoline.—To 30 g. of the complex was added 150 ml. of 10% potassium hydroxide and the mixture was extracted with ether. The ether solution was dried over solid potassium hydroxide and the ether removed *in vacuo*. The residue was distilled and a fraction boiled at 204–206° (3 mm.); yield of the imidazoline, 8.3 g. The residue remaining from the ether extraction was acidified with hydrochloric acid. A white solid formed which on the basis of its neut. equiv., its melting point (and mixed melting point) was identified as stearic acid.

Conversion of 4,4-Dimethyl-1-isopropyl-2-heptadecyl-2-imidazoline to the Stearic Acid Complex.—A mixture of 1.135 g. (0.003 mole) of the imidazoline and 1.706 g. (0.006 mole) of stearic acid was warmed over steam just long enough to melt the stearic acid. The product melted at 54–55° after recrystallization from acetone. A mixed m. p. with the complex prepared above (m. p. 54–55°) showed no depression.

Similar experiments to those described above were attempted with N-(2-aminoisobutyl)-aniline and benzoic acid, with N-(2-aminoisobutyl)-isopropylamine and trichloroacetic acid and with N-(2-aminoisobutyl)-isopropylamine and *o*-chlorobenzoic acid, but the expected products did not result from any of these examples.

When 2,3-dimethyl-2,3-butanediamine was allowed to react under the usual conditions with acetic acid, none of the expected imidazoline was isolated but only a 10% yield of the diacetate, m. p. 156–157°.

Anal. Calcd. for 2,3-dimethyl-2,3-butanediamine diacetate, $C_{10}H_{24}N_2O_4$: C, 50.84; H, 10.24; N, 11.96. Found: C, 50.84; H, 10.14; N, 11.98.

A 15% yield of diacetyl-1,2-butanediamine, m. p. 150–151°, was obtained from the reaction of 1,2-butanediamine and acetic acid, in addition to a low yield of the expected imidazoline.

Anal. Calcd. for diacetyl-1,2-butanediamine, $C_8H_{16}N_2O_2$: C, 55.79; H, 9.95; N, 16.26. Found: C, 55.88; H, 9.50; N, 16.26.

Acknowledgment.—The author wishes to express his gratitude to Commercial Solvents Corporation for generous support of this project. Thanks are especially due to Dr. P. F. Tryon of that organization who did considerable preliminary work on this problem.

Summary

1. A series of imidazolines has been prepared by heating 1,2-diamines and organic acids under conditions to remove water during the process.

2. Most of these imidazolines react with the acids from which they are formed to produce molecular complexes involving one or two moles of the acid and one mole of the imidazoline.

3. These complexes can be converted to the imidazolines readily by treatment with dilute alkali.

4. When one amino group of the diamine is secondary, the yields are better than when both amino groups are primary.

5. As the molecular weight of the acids becomes larger the yields of the complexes increase and the yields of the imidazolines decrease.

ALBUQUERQUE, NEW MEXICO

RECEIVED DECEMBER 24, 1947

[DEPARTMENT OF BIOCHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO]

The Decomposition of 2,5-Dinitrobenzoic Acid by Alkali

BY WILSON D. LANGLEY

In attempts to explain the color given by 2,5-dinitrobenzoic acid in alkaline solution the effect of alkali alone upon the dinitro acid was studied.

Pure 2,5-dinitrobenzoic acid (m. p. 177–178°) in sodium bicarbonate solution is yellow and may be boiled with but slight intensification of color. In strong alkali (0.4 *N* sodium hydroxide), however, even at room temperature, intensification of color to deep red occurs over several weeks. The deep color develops quickly when the solution is heated. After one hour of heating, followed by acidification with hydrochloric acid, 2-hydroxy-5-nitrobenzoic acid, 5-hydroxy-2-nitrobenzoic acid and a non-crystalline brown acid were isolated. Nitrous acid and ammonia also were present in small amounts. Neither unchanged 2,5-dinitrobenzoic acid nor 2,5-dihydroxybenzoic (gentisic) acid could be detected. That the colored acid was probably a mixture of azo and hydrazo compounds was indicated by the composition of the material, and by its close similarity to colored substances which were subsequently prepared by reduction of 2,5-dinitrobenzoic acid with glucose in sodium carbonate solution (not reported herein). At this alkalinity 2,5-dinitrobenzoic acid is not decomposed, and under the conditions used, aromatic nitro compounds in general give rise to azo dyes.

After heating 2-hydroxy-5-nitrobenzoic acid in 0.4 *N* sodium hydroxide for one hour, the unchanged acid was recovered in 60% yield, and no other product could be isolated. No deep color was formed. With similar heating in alkali, 5-hydroxy-2-nitrobenzoic acid was recovered unchanged in 50% yield, a very small amount of unidentifiable red material being formed. Tests with ferric chloride gave no blue color with these alkaline solutions, from which it is concluded that gentisic acid was not present. It is evident from these findings that the hydrolysis of 2,5-dinitrobenzoic acid by strong alkali leads to the ready replacement of either, but not of both, atoms of nitrogen from the dinitrobenzoate.

Experimental

Isolation of the Acids.—For a typical hydrolytic decomposition, 2.0 g. of 2,5-dinitrobenzoic acid was suspended in 50 ml. of water, and 0.8 g. of sodium bicarbonate was added. When the evolution of carbon dioxide had ceased, an equal volume of 0.8 *N* sodium hydroxide was added. This solution was refluxed for one hour, during which time it became deep red. It was cooled, was acidified to congo red with 10% hydrochloric acid and was chilled, whereupon 0.63 g. of brown material separated. The filtrate upon being evaporated to 50 ml. and filtered yielded 0.025 g. more of the brown product.

The 50 ml. was evaporated nearly to dryness, and sodium chloride and a small amount of 2-hydroxy-5-nitrobenzoic acid were filtered off. Addition of ethanol to the filtrate aided in removing more sodium chloride. The sirupy concentrate was extracted repeatedly with about 50 ml. of boiling toluene, the water remaining being distilled off with toluene vapor. Upon cooling the toluene, crystals separated and were filtered off; by several repetitions of the process with the toluene filtrate a total of 0.35 g. of crystalline material was obtained. A negligible amount of dark colored oil insoluble in the toluene but readily soluble in butanol remained, together with a small amount of ammonium chloride. After recrystallization of the product from toluene (0.3 g. dissolved in 90 ml. of boiling toluene, from which 0.235 g. was recovered), it melted at 165–166°, which is the melting point of 5-hydroxy-2-nitrobenzoic acid. Equiv. wt. found, 92.7, 91.5; calculated for hydroxynitrobenzoic acid, 91.5. The *p*-nitrobenzyl ester was prepared and after recrystallization from ethanol melted at 200–202°. The corresponding ester prepared from 2-hydroxy-5-nitrobenzoic acid which was purchased, melted at 115°.

The 0.65 g. of brown precipitate obtained above was extracted three times with about 50-ml. portions of boiling toluene, from which, after cooling, separated 0.22 g. of crystalline material, m. p. 224–225°. Mixed with 2-hydroxy-5-nitrobenzoic acid, the melting point was unchanged. The residue insoluble in toluene was then extracted with boiling water, and was filtered. The slightly soluble brown material separated as an oil, and the filtrate, after chilling, yielded 0.15 g. more of 2-hydroxy-5-nitrobenzoic acid. This process of fractionation was repeated several times when separation of the products seemed to be complete. The air dried brown solid decomposed gradually from about 250 to 300°. It repeatedly came out of 20% ethanol or from dilute 1,4-dioxane as an oil. It was readily soluble in hot butyl or in benzyl alcohol, from which it was precipitated as brown powder by careful addition of toluene. This powder was soluble in sodium bicarbonate with evolution of carbon dioxide. Since it did not give intensification of color upon being heated in 0.4 *N* sodium hydroxide, unchanged 2,5-dinitrobenzoic acid was not present. Attempts were made to obtain crystalline esters, the amide, and copper, barium, and calcium salts, but oils were always obtained. Combustion of the brown acid showed that it contained 47.4% carbon and 2.8% hydrogen. Nitrogen values by the Elek and Sobotka modifications of the Kjeldahl process[1] indicated the substance to be a mixture, as did titration values attempted with the deeply colored solutions, but the analyses established that two atoms of nitrogen per carboxyl group were present. The data, together with the physical properties, suggested strongly that the colored material was a mixture of azo and hydrazo compounds. Extraction with ether removed enough of an oil component so that the residue could be crystallized from hot 50% ethanol. In polarized light three different crystal forms were detected. After filtering off the first crop of obviously impure crystals, a second homogeneous crop melted sharply at 262°, but the crystals were too small for indices of refraction to be determined.

Subsequent experimental work involved the synthesis of 2-nitroso-5-nitrobenzoic acid, and of 2-nitro-5-nitrosobenzoic acid. Both nitroso acids failed to react with the 2,5-aminonitrobenzoic acids even in the presence of rather vigorous dehydrating agents. Therefore synthesis of the desired azo compounds having known structures for comparison with the above colored acid is still to be accomplished.

For the synthesis of 2-nitroso-5-nitrobenzoic acid, 2-amino-5-nitrobenzoic acid was prepared through the following series of reactions described by Hewitt and Mitchell,[2]

(1) Elek and Sobotka, THIS JOURNAL, **48**, 501 (1926).

(2) Hewitt and Mitchell, *J. Chem. Soc.*, **91**, pt. 2, 1258 (1907).

and by Green and Day[3]: 2-acetamido-5-nitrotoluene → 2-acetamido-5-nitrobenzoic acid → 2-amino-5-nitrobenzoic acid.

The 2-amino-5-nitrobenzoic acid was then oxidized with Caro's acid as follows:

2-Nitroso-5-nitrobenzoic Acid.—A solution containing 2.5 ml. of water and 10 ml. of sulfuric acid (sp. gr. 1.85) was cooled to 5°. To it was added 4.1 g. of 2-amino-5-nitrobenzoic acid, the mass being broken up with a glass rod. Then 10 ml. more of cold sulfuric acid was poured in, followed by 25 g. of powdered ammonium persulfate. When a uniform paste was obtained, 20 ml. of ice water was added, whereupon the aminonitrobenzoic acid dissolved. The solution was warmed to 40°, and was held at that temperature. A brown precipitate separated after thirty minutes. After one and one-half hours another 10 g. of ammonium persulfate was added, the solution now being allowed to come to room temperature and to stand overnight. Then 50 g. of cracked ice was added and after fifteen minutes the cold solution was filtered with gentle suction through hardened filter paper. The brown product was washed with ice water and, after being dried in warm air, weighed 3.61 g. No more product could be obtained by further diluting and chilling the filtrate. The unpurified acid was cream colored and melted with decomposition at 202°. For recrystalllization 1 g. was dissolved in 20 ml. of 50% ethanol and was chilled, 0.40 g. being recovered.

Anal. Equiv. wt., 0.2770 g. subs. neutd. 14.73 ml. of 0.0957 *N* sodium hydroxide to phenolphthalein endpoint. Calcd. for $C_7H_4O_5N_2$: equiv. wt., 196. Found: equiv. wt. 196.6.

2-Nitro-5-nitrosobenzoic Acid.—For the synthesis of this acid a series of reactions corresponding to that given above was carried out: 3-aminotoluene → 3-acetamidotoluene → 3-acetamido-6-nitrotoluene → 3-acetamido-6-nitrobenzoic acid → 3-amino-6-nitrobenzoic acid. The 3-amino-6-nitrobenzoic acid was oxidized as has been described under 2-nitroso-5-nitrobenzoic acid. The sulfate was less soluble than that of 2-amino-5-nitrobenzoic acid, and was oxidized in more dilute solution. The crude, light brown product was recrystallized from dilute ethanol as follows: 1 g. was dissolved in 5 ml. of hot 95% ethanol and 12 ml. of hot water was added. After rapid filtration and cooling of the filtrate, 0.88 g. of 2-nitro-5-nitrosobenzoic acid, m. p. 270–270.5°, was filtered off.

Anal. Equiv. wt., 0.1270 g. subs. neutd. 6.11 ml. of 0.1058 *N* NaOH; 0.1737 g. subs. neutd. 8.42 ml. of 0.1058 *N* NaOH. Calcd. for $C_7H_4O_5N_2$: equiv. wt., 196. Found: equiv. wt., 196.6, 194.9.

Evaporation of the filtrates from the recrystallization yielded about 50 mg. of the nitrosonitro acid, and further evaporation to about 25 ml. yielded a light colored oil, which soon crystallized and proved to be 2,5-dinitrobenzoic acid.

(3) Green and Day, THIS JOURNAL, **64**, 1167 (1942).

Summary

By alkaline hydrolysis of 2,5-dinitrobenzoic acid either nitro group may be replaced by hydroxyl, giving rise to 2-hydroxy-5-nitrobenzoic acid, and to 5-hydroxy-2-nitrobenzoic acid. Gentisic acid seemed not to be formed. A brown oil also was isolated. This was a mixture probably of azo and hydrazo compounds, which were not identified.

Synthesis of 2-nitroso-5-nitrobenzoic acid and of 2-nitro-5-nitrosobenzoic acid showed these substances to be practically colorless and unlike the colored product formed by the action of alkali upon 2,5-dinitrobenzoic acid. Both nitroso acids were non-reactive toward the 2,5-aminonitrobenzoic acids.

BUFFALO 3, NEW YORK RECEIVED SEPTEMBER 23, 1947

[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

Ultrasonic Investigation of Molecular Properties of Liquids. II.[1] The Alcohols[1a]

BY ALFRED WEISSLER

Although several investigators[2,3,4,5] have measured the velocity of sound in a variety of liquids, the application of their data to chemical problems has been relatively neglected.[6] Inasmuch as a sound wave is a mechanical impulse transmitted from molecule to molecule, one expects the properties of the molecule to affect the rate of transmission of this impulse.

The use of ultrasonic frequencies permits the apparatus to be of conveniently small size, yet still avoid earlier errors due to wall effect. At one kilocycle the wave length in many liquids is about one meter, while at one megacycle (the frequency employed in this investigation) the wave length is about one millimeter.

For the present work, thirty liquid alcohols were selected as a suitable group of compounds in which correlations could be made between sound velocity and chemical structure. Specifically, sound velocity is of interest in connection with molecular weight, molecular volume, adiabatic compressibility, and the ratio of specific heats.

Experimental

Each alcohol (of the highest purity commercially available from such sources as Eastman Kodak Co., Connecticut Hard Rubber Company, and Carbide and Carbon Chemicals Corporation) was fractionally distilled through a 40-cm. Widmer column shortly before using; the higher boiling compounds were fractionated at a reduced pressure of about 1 mm. A middle fraction of narrow boiling range was selected in each case.

Sound velocity measurements were made by means of

(1) Part I, Weissler, Fitzgerald, and Resnick, *J. Appl. Phys.*, **18**, 434 (1947).

(1a) The opinions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the navy service at large.

(2) Willard, *J. Acoust. Soc. Am.*, **19**, 235 (1947).

(3) Pellam and Galt, *J. Chem. Phys.*, **14**, 608 (1946).

(4) Parthasarathy, *Proc. Ind. Acad. Sci. (A)*, **3**, 285, 482, 519 (1936); **4**, 59, 213 (1936).

(5) Bergmann, "Der Ultraschall," 3rd ed., Edwards Brothers, Ann Arbor, Mich., 1944, p. 174.

(6) See, however, (a) Freyer, Hubbard and Andrews, THIS JOURNAL, **51**, 759 (1929); (b) Kincaid and Eyring, *J. Chem. Phys.*, **6**, 620 (1938); Kittel, *J. Chem. Phys.*, **14**, 614 (1946).

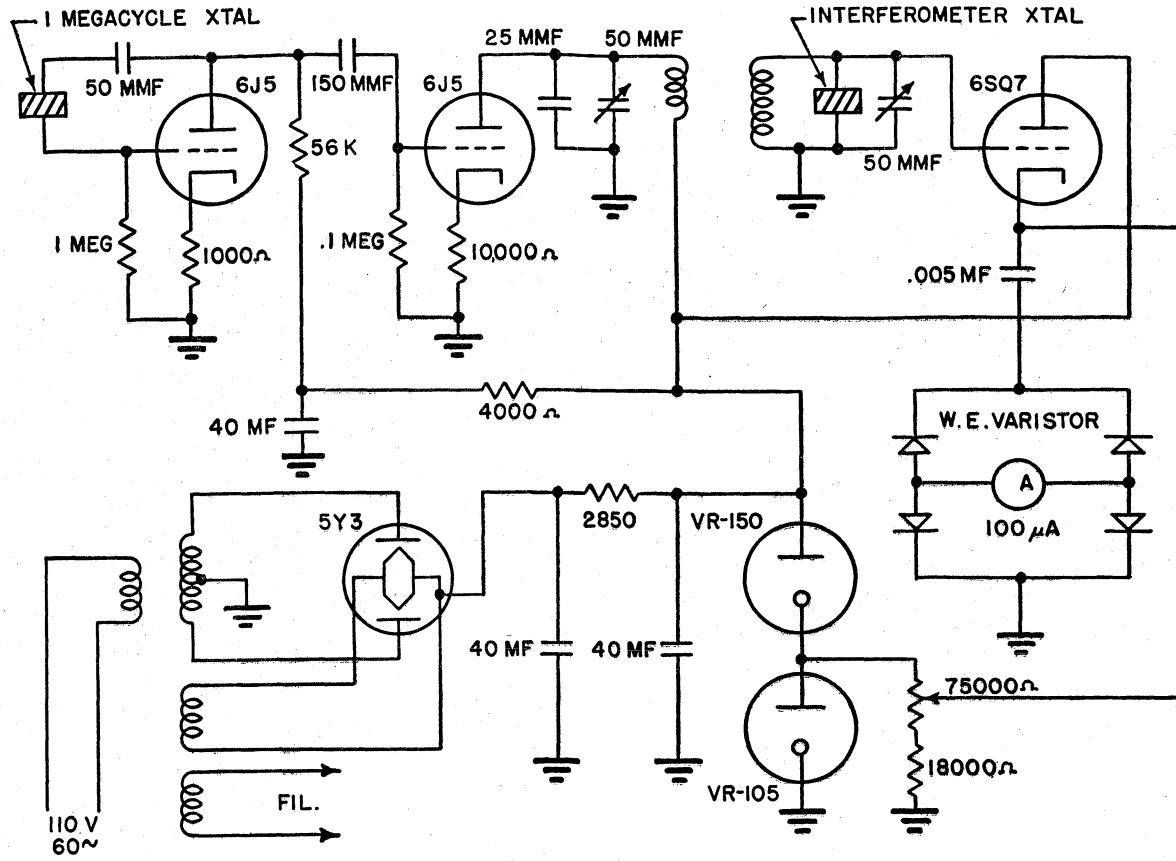


Fig. 1.—Circuit design for interferometer for one megacycle.

an ultrasonic interferometer of conventional type.[6a,7,8] As may be seen in Fig. 1, the circuit includes a power supply, crystal-controlled vacuum-tube oscillator of one megacycle frequency, r. f. amplifier, and microammeter for measuring the current through the interferometer crystal. This latter crystal is the quartz piezoelectric transducer which changes the oscillations from electrical to mechanical.

Figure 2 is a sectional view of the brass interferometer cell, diameter 7 cm. and height 11 cm., immersed in a temperature controlled (±0.05°) oil-bath. The cell contains the liquid to be measured, a sensitive thermometer, a manual stirrer for eliminating temperature gradients, the quartz crystal source of ultrasound, and a movable reflecting plate of nickel-plated brass. As the reflector is moved vertically through the liquid by the micrometer head, cyclical variations in the ultrasonic standing wave pattern recur at distances of integral half-wave lengths: depending on its distance from the source, the reflector will sometimes be at a node of the transmitted wave, sometimes at an anti-node. This causes corresponding cycles in the current through the interferometer crystal, which are observed on a suitable microammeter. The micrometer-head travel required for an interval of two current maxima, then, is equal to the wave length; and the velocity of sound is of course the product of this wave length and the frequency. In practice, one uses an interval of twenty maxima, which makes possible a precision of a few hundredths of one per cent.

Although the instrument described requires about 350 ml. of liquid for a measurement, a new three-megacycle interferometer now in use at this Laboratory requires only 15 ml. of sample.

(7) Pierce, *Proc. Am. Acad.*, **60**, 269 (1925).

(8) Klein and Hershberger, *Phys. Rev.*, **37**, 760 (1931).

Results and Discussion

The velocity of sound at 30° in each of these thirty alcohols is listed in Table I, together with the density and refractive index. It is apparent that sound velocity increases (but not linearly) with molecular weight in this series,[9] and that it decreases as the molecule becomes more highly branched. A saturated or unsaturated ring, however, causes a considerable increase in velocity.

Also shown in this table are the molar refraction and molar sound velocity of each alcohol. As expected, the observed refractions agree well with those calculated by summing Denbigh's bond refractions,[10] particularly in the absence of extensive branching. The deviation exceeds 1% only in the case of furfuryl alcohol; such anomalous behavior has previously been reported for the furans.[11]

(9) Rao, *J. Chem. Phys.*, **9**, 682 (1941), reveals greater irregularities in other series.

(10) Denbigh, *Trans. Faraday Soc.*, **36**, 936 (1940).

(11) Fajans in "Physical Methods of Organic Chemistry," A. Weissberger, ed., Interscience Publishers, New York, N. Y., 1945, p. 677.

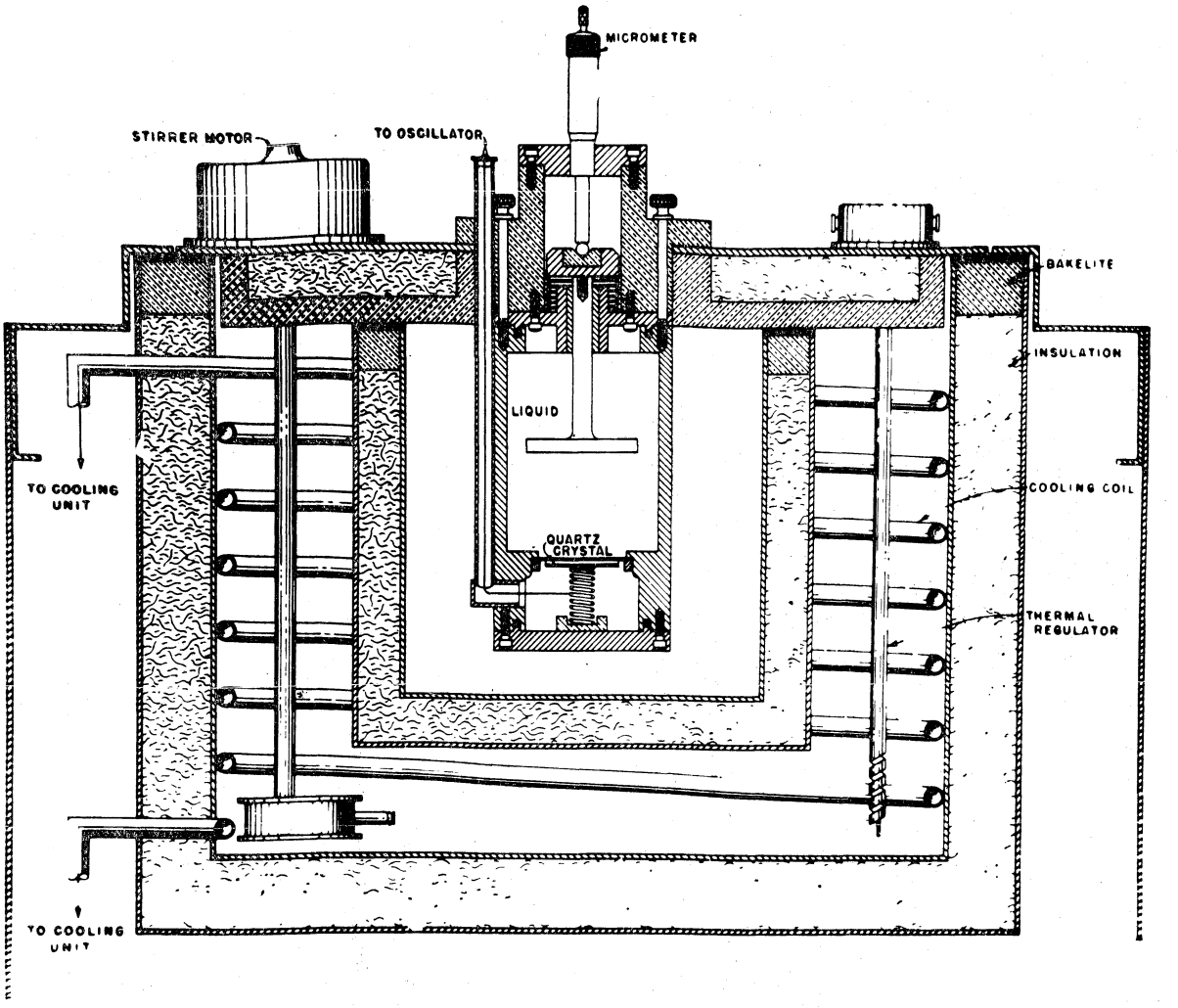


Fig. 2.—Ultrasonic interferometer immersed in thermoregulated oil-bath.

Molar Sound Velocity.—M. R. Rao has proposed[9] the following empirical constant involving sound velocity

$$R = v^{1/3}M/d \qquad (1)$$

where M is the molecular weight, v the sound velocity, d the density, and R may be called the molar sound velocity. For each pure liquid (except a few such as water) R is invariant with respect to temperature. Further, like the other forms of molar volume it is an additive and constitutive property, and is therefore quite analogous to molar refraction except that a theoretical explanation for its constancy has not yet been adduced. An empirical function (the cubic root of sound velocity) which decreases slightly with increasing temperature is used here as a means of correcting the molar volume for thermal expansion. It should be pointed out that R is relatively insensitive to the intermolecular forces which determine the compressibility, since it is inversely proportional to the sixth root of the compressibility.

The observed molar sound velocities computed from equation (1) are compared in Table I with the values calculated by summing Lagemann's bond increments[12] for R. The average deviation is seen to be about 2%, but it is notable that nearly all the errors are in the same direction. This, together with the greater precision of the present measurements, suggests the desirability of a revision of the increment values. For example, changing the R increment for $-CH_2-$ from 195 to 190 would reduce the average deviation to a few tenths of a per cent.

A comparison between the velocity of light (*i. e.*, refractive index) and the velocity of sound is illuminating. Both yield information on the size, shape, and functionality of molecules: the velocity of sound is determined by the distance and elastic forces between them, while the velocity of light depends on their electrical and magnetic characteristics. Both properties can be readily

(12) Lagemann and Dunbar, *J. Phys. Chem.*, **49**, 428 (1945).

TABLE I

SOME PROPERTIES OF ALCOHOLS AT 30°

Alcohol	Sound velocity, meters per second	Density $^{30}_4$	n_D	Molar sound velocity Obs.	Molar sound velocity Calcd.	Molar sound velocity Deviation, %	Molar refraction Obs.	Molar refraction Calcd.	Molar refraction Deviation, %
Methyl	1088.9	0.7816	1.3258	421.7	419.1	+0.63	8.27	8.31	−0.48
Ethyl	1127.4	.7809	1.3578	614.0	613.8	+0.04	12.95	12.94	+ .08
n-Propyl	1193.2	.7966	1.3821	800.2	808.4	−1.02	17.56	17.57	− .06
n-Butyl	1225.3	.8018	1.3956	989.2	1003.0	−1.38	22.19	22.20	− .05
n-Amyl	1254.8	.8089	1.4075	1175.4	1197.7	−1.86	26.85	26.83	+ .07
n-Hexyl	1288.6	.8124	1.4150	1368.6	1392.3	−1.70	31.49	31.46	+ .10
n-Octyl	1331.9	.8182	1.4260	1751.0	1781.6	−1.72	40.78	40.72	+ .15
n-Decyl	1363.8	.8233	1.4340	2131.8	2170.9	−1.80	50.06	49.98	+ .16
n-Dodecyl	1388.0	.8269	1.4400	2513.6	2560.2	−1.82	59.39	59.24	+ .25
Isopropyl	1125.2	.7779	1.3732	803.5	808.4	−0.60	17.61	17.57	+ .23
Isobutyl	1176.5	.7950	1.3921	984.3	1003.0	−1.87	22.21	22.20	+ .05
s-Butyl	1196.8	.7983	1.3932	985.8	1003.0	−1.72	22.17	22.20	− .14
t-Butyl	1101.6	.7756	1.3825	987.0	1003.0	−1.60	22.27	22.20	+ .32
Isoamyl	1220.4	.8028	1.4038	1173.3	1197.7	−2.03	26.84	26.83	+ .04
t-Amyl	1180.4	.8029	1.4001	1160.2	1197.7	−3.13	26.62	26.83	− .78
2-Methylbutyl	1225.3	.8061	1.4055	1170.1	1197.7	−2.31	26.83	26.83	.00
Pentanol-3	1223.7	.8099	1.4058	1164.1	1197.7	−2.81	26.72	26.83	− .41
2-Ethylbutyl	1277.0	.8227	1.4174	1347.3	1392.3	−3.23	31.26	31.46	− .64
4-Methylpentanol-2	1201.3	.8003	1.4087	1357.0	1392.3	−2.54	31.54	31.46	+ .25
Heptanol-2	1266.8	.8098	1.4172	1552.5	1587.0	−2.17	36.10	36.09	+ .03
2,4-Dimethylpentanol-3	1241.1	.8192	1.4189	1524.5	1587.0	−3.94	35.81	36.09	− .78
5-Ethylnonanol-2	1326.5	.8267	1.4362	2290.3	2365.6	−3.19	54.52	54.61	− .16
Benzyl	1508.2	1.0375	1.5363	1195.2	1199.6	−0.37	32.51	32.55	− .12
β-Phenylethyl	1512.6	1.0122	1.5283	1385.3	1394.3	−0.64	37.18	37.18	.00
γ-Phenylpropyl	1523.3	0.9938	1.5231	1576.7	1588.9	−0.77	41.87	41.81	+ .14
Cyclohexanol	1448.3	0.9411	1.4629	1204.1	1206.2	−0.18	29.31	29.33	− .07
Furfuryl	1433.6	1.1238	1.4801	984.3	945.0	+4.16	24.80	25.53	−2.86
Tetrahydrofurfuryl	1467.8	1.0455	1.4490	1110.2	1076.3	+3.15	26.20	26.47	−1.02
Allyl	1215.5	0.8432	1.4090	735.1	742.7	−1.03	17.03	17.10	−0.41
Ethylene glycol	1643.5	1.1068	1.4290	661.8	652.0	+1.50	14.49	14.49	0.00

measured in liquids with an accuracy of five significant figures. In sharp contrast to optical dispersion, sound velocity in liquids does not vary appreciably with frequency, but its relative change with temperature is five to ten times greater than that of refractive index. After thermal equilibrium is established, interferometric determination of the sound velocity requires less than five minutes, but the relatively large sample needed is a disadvantage. For ordinary liquids, the range of sound velocity encountered is 0.8 to 2.0 × 10^5 cm./sec., compared to the refractive index range of 1.3 to 1.8.

Determination of Molecular Weight.—Within a homologous series of liquids, linear relationships exist[12] between any two of several molar constants such as molar sound velocity, molar refraction, parachor and molar viscosity.[13] An example of such a relation is the one involving refraction and sound velocity

$$R = AN + B \qquad (2)$$

where A and B are, respectively, the slope and intercept. Upon substitution of the definitions of R and N, this yields an expression for the molecular weight

$$M = \frac{Bd}{v^{1/3} - A\left(\frac{n^2 - 1}{n^2 + 2}\right)} \qquad (3)$$

in terms of the two "series" constants A and B and the observed sound velocity, density and refractive index. One expects the slope A to be nearly the same for all homologous series, because the difference between successive members is always $-CH_2-$.

In Figure 3 the above-mentioned linearity is verified for the normal primary alcohols up to dodecyl, the highest member which is liquid at room temperature. The slope A of this line is 40.92, and the vertical intercept B is 82.50. Even the branched compounds lie very nearly on the same line,[14] while for the ω-phenylalkanols the slope

(13) Souders, THIS JOURNAL, 60, 154 (1938).

(14) Dr. Richard K. Cook of the National Bureau of Standards has pointed out that such a result is not surprising, inasmuch as both variables plotted include the factor M, which changes much more rapidly than v, n or d. For a more sensitive test of the linearity, he suggests rearranging equation (3) to

$$\frac{A}{v^{1/3}}\left(\frac{n^2 - 1}{n^2 + 2}\right) + \frac{Bd}{Mv^{1/3}} = 1$$

the graph of which shows appreciable deviations from a straight line.

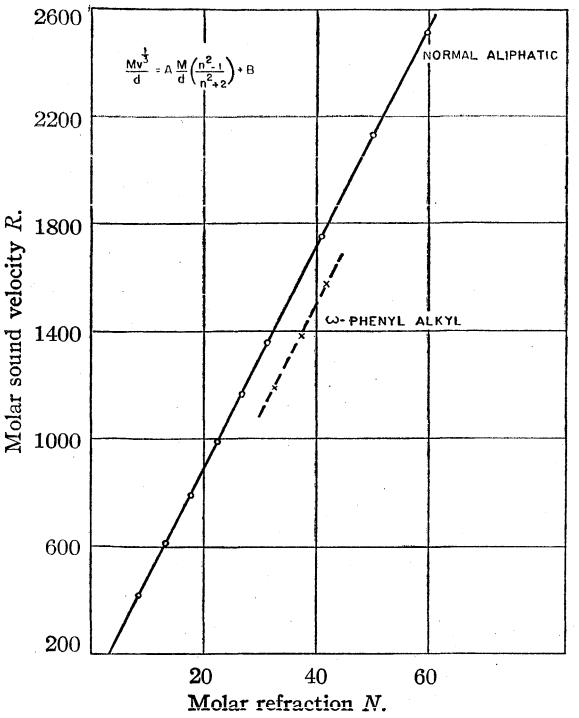


Fig. 3.—Linear relation between molar refraction and molar sound velocity, for primary alcohols.

is exactly the same but the intercept is −136.0.

Using the above values for A and B, the molecular weights of the aliphatic alcohols were computed from equation (3). It is evident from Table II that the average error is only 2% for the primary normal members, but is considerably greater where extensive branching occurs. For the three phenylalkanols, taking B as −136, the average error is only 0.3%.

From one point of view, this method may be considered as a determination of molecular weight through linear interpolation or extrapolation, by means of a suitable combination of physical properties.[15] (The molecular weight is not in general a linear or necessarily even a single-valued function of a single physical property.) Volatility or solubility of the liquid is not required, in contrast with other methods.

Because of the association of alcohols, one might suppose that the molecular weights found should be appreciably higher than the theoretical. However, the constants A and B automatically include any correction of this nature which might be involved.

Estimation of van der Waals b.—Sound velocities in liquids have been used by Schaafs[16] to estimate the size of molecules, through the value of b in the van der Waals equation of state. According to kinetic theory, this quantity represents four times the actual volume of the molecules in one mole of a fluid in thermal motion.

Solving the van der Waals equation for the pressure, and substituting M/d for V, gives

$$P = \frac{RT}{M/d - b} - \frac{d^2 a}{M^2} \qquad (4)$$

If one differentiates this with respect to density, remembers that the square of sound velocity is equal to the derivative of pressure with respect to density, and accepts certain approximations made by Schaafs, the result is:

$$b = \frac{M}{d} - \frac{RT}{v^2 d}\left[(1 + Mv^2/3RT)^{1/2} - 1\right] \qquad (5)$$

This method for obtaining b is much easier than the customary evaluation from the critical data; nevertheless, it is sometimes considered unreliable and caution is required in its use. First, the concept of b is not defined with high precision[17]; it is not constant over a range of temperatures and pressures, and different methods for measuring it give divergent results. Thus, the values obtained from equation (5) and listed in Table III show only fair agreement with such

TABLE II

DETERMINATION OF MOLECULAR WEIGHT BY THE SOUND VELOCITY METHOD

$$M = \frac{82.50d}{v^{1/2} - 40.92\left(\frac{n^2 - 1}{n^2 + 2}\right)}$$

Alcohol	Molecular weight Theoretical	Found	Error, %
Methyl	32.04	31.67	− 1.15
Ethyl	46.07	45.15	− 2.00
n-Propyl	60.09	60.74	+ 1.08
n-Butyl	74.12	75.34	+ 1.64
n-Amyl	88.15	94.92	+ 7.68
n-Hexyl	102.17	105.54	+ 3.30
n-Octyl	130.22	130.31	+ 0.07
n-Decyl	158.28	156.86	− 0.90
n-Dodecyl	186.33	184.38	− 1.05
Isopropyl	60.09	59.75	− 0.6
Isobutyl	74.12	80.87	+ 9.1
s-Butyl	74.12	77.75	+ 4.7
t-Butyl	74.12	80.58	+ 8.7
Isoamyl	88.15	96.83	+ 9.8
t-Amyl	88.15	102.54	+16.3
2-Methylbutyl	88.15	100.61	+14.1
Pentanol-3	88.15	102.96	+16.8
2-Ethylbutyl	102.17	123.41	+20.8
4-Methylpentanol-2	102.17	126.98	+24.3
Heptanol-2	116.20	127.25	+ 9.5
2,4-Dimethylpentanol-3	116.20	156.45	+34.6
5-Ethylnonanol-2	172.30	235.98	+37.0
Benzyl[a]	108.13	108.80	+ 0.62
β-Phenylethyl[a]	122.16	122.16	0.00
γ-Phenylpropyl[a]	136.19	135.70	− 0.36

[a] For these compounds, the value of B in equation (3) is −136.0.

(15) It has recently been shown by E. L. Warrick, THIS JOURNAL, 68, 2455 (1946), that molecular weight within a polymer-homologous series can be determined from the refractive index alone, without using an additional property such as sound velocity.

(16) Schaafs, *Z. Physik*, 114, 110, 251 (1939); 115, 69 (1940).

(17) Slater, "Introduction to Chemical Physics," McGraw-Hill, New York, N. Y., 1939, pp. 186, 408.

other values as one-third of the critical volume, or four times the molar refraction (Table I). Second, certain assumptions were employed in the derivation of equation (5), for example that the van der Waals equation of state is applicable to liquids, and that the partial derivative of b with respect to density is equal to $2M/3d^2$.

TABLE III

ADDITIONAL PROPERTIES OF ALCOHOLS AT 30°

Alcohol	van der Waals b, ml. per mole	Adiabatic compressibility, 10^{-12} sq. cm. dyne^{-1} Present work	Other investigators	Ratio of specific heats
Methyl	37.0[a]	107.90	108.6,[b] 107.75,[c] 108.2[d]	1.198
Ethyl	54.0[a]	100.75	100.5,[b] 100.86,[c] 99.7[d]	1.188
n-Propyl	69.9[a]	88.17	89.4[b]	1.180
n-Butyl	86.2	83.07	84.4[b]	1.178
n-Amyl	102.2	78.52		
n-Hexyl	118.6	74.13		
n-Octyl	151.1	68.89		
n-Decyl	183.5	65.30		
n-Dodecyl	215.9	62.77		
Isopropyl	71.3	101.54	100.6[b]	1.178
Isobutyl	86.8	90.88	91.2[b]	1.166
s-Butyl	86.5	87.46		
t-Butyl	88.6	106.25		
Isoamyl	102.9	83.63	84.9[b]	1.157
t-Amyl	102.7	89.38		
2-Methylbutyl	102.5	82.62		
Pentanol-3	102.0	82.45		
2-Ethylbutyl	117.0	74.54		
4-Methyl-pentanol-2	120.0	86.58		
Heptanol-2	135.6	76.95		
2,4-Dimethyl-pentanol-3	133.9	79.25		
5-Ethyl-nonanol-2	199.1	68.75		
Benzyl	99.1	42.37		
β-Phenylethyl	115.1	43.18		
γ-Phenyl-propyl	131.0	43.36		
Cyclohexanol	100.9	50.66	50.3[e]	
Furfuryl	82.6	43.30		
Tetrahydro-furfuryl	92.7	44.39		
Allyl	61.8	80.27	80.8[b]	1.192
Ethylene glycol	52.9	33.45	34.0[b]	1.130

[a] Values of $b = V_c/3$ for these alcohols are 39.3, 55.7, and 73.4, respectively (I. C. T.). [b] Shiba, *Sci. Pap. Inst. Phys. Chem. Research (Tokyo)*, **16**, 205 (1931). [c] Tyrer, *J. Chem. Soc.*, **105**, 2534 (1914). [d] Fryer, Hubbard and Andrews, THIS JOURNAL, **51**, 759 (1929). [e] Bhagavantam and Rao, *Proc. Ind. Acad. Sci.*, **9A**, 312 (1939).

The additivity of b is demonstrated for the primary normal alcohols in Fig. 4. The values for branched isomers show small changes, but ring compounds of comparable molecular weight exhibit a considerable decrease. Inasmuch as the sound velocity term in equation (5) represents a relatively small correction to the molar volume term, the linearity in Fig. 4 correlates with the familiar additive character of the molar volume.

Determination of Adiabatic Compressibility.— From acoustic theory, the velocity of sound in a medium is

$$v = (1/K_{ad}d)^{1/2} \qquad (6)$$

where K_{ad} is the adiabatic compressibility. The pressure changes which occur during the propagation of a sound wave are so rapid as to prevent heat flow to and from the surroundings.

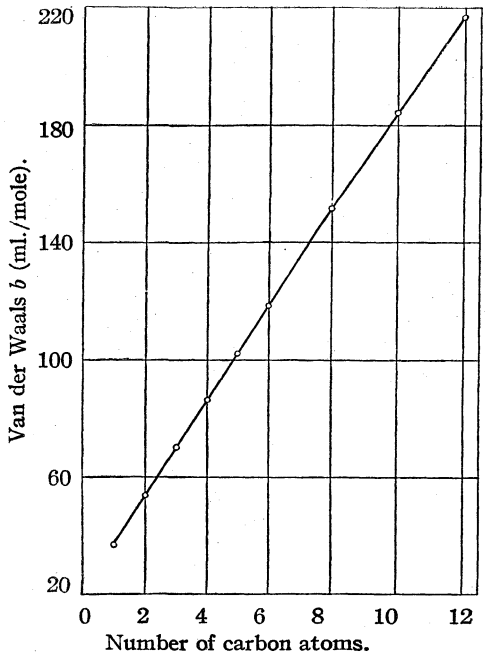


Fig. 4.—Additivity of van der Waals b, for primary normal alcohols.

Table III lists the adiabatic compressibilities of the alcohols, calculated from sound velocity and density as indicated in equation (6). The results agree well with those obtained (mainly from mechanical piezometers) by other investigators. It is apparent that K_{ad} decreases with molecular weight, increases with branching, and is small for ring compounds. The plot of K_{ad} against number of carbon atoms on log–log paper (Fig. 5) reveals more quantitative relations. From the slopes of these lines, adiabatic compressibility is found to be approximately a function of the inverse fourth root of the number of carbons in the molecule, for primary normal alcohols. For iso alcohols, it depends on the inverse 2.6th root; and for tertiary, on the inverse 1.3rd root. The reciprocals of these exponents are in the ratio 3:2:1

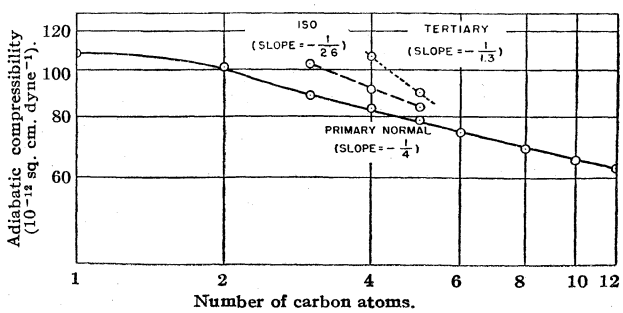


Fig. 5.—Adiabatic compressibility of aliphatic alcohols.

for the cases of no branching, single branching and double branching, respectively, but the precise significance of this result is not apparent.

The compressibility of the methanol molecule estimated from bond force-constants is about 1/1000 as large as the observed compressibility. This indicates that it is the space between the molecules which is compressed, rather than the molecules themselves.

The adiabatic compressibility is of interest in thermodynamics. For example, the ratio of isothermal to adiabatic compressibilities is equal to the ratio of specific heats

$$K_{is}/K_{ad} = c_p/c_v = \gamma \qquad (7)$$

The isothermal compressibility can be obtained either from static measurements or from

$$K_{is} = K_{ad} + T\alpha^2/c_p d \qquad (8)$$

where T is the absolute temperature, α the coefficient of thermal expansion, and c_p the heat capacity at constant pressure.

Sufficient data are available[18] in several cases for calculating[19] the ratio of specific heats from equations (7) and (8). The results in Table III show that γ decreases slightly as the complexity of the molecule increases, as expected because of the larger number of degrees of freedom.

Acknowledgments.—The author is indebted to Dr. G. R. Ringo for many stimulating discussions, to Dr. H. W. Carhart for samples of several of the alcohols, and to The Quaker Oats Company for samples of furfuryl and tetrahydrofurfuryl alcohols.

Summary

The velocity of sound at 30° has been measured in thirty liquid alcohols, using a one-megacycle ultrasonic interferometer. Densities and refractive indices at 30° are also reported.

To illustrate the applicability of sound velocities in chemical studies, these data have been used to calculate molecular weight, van der Waals b, adiabatic compressibility, and the ratio of specific heats. The compressibility has been correlated semi-quantitatively with molecular structure.

The analogy between molar sound velocity and molar refraction has been discussed.

RECEIVED AUGUST 25, 1947

(18) Shiba, *Sci. Pap. Inst. Phys. Chem. Research (Tokyo)*, **16**, 205 (1931).

(19) It is necessary to avoid using the large body of isothermal compressibility data which has been determined for high pressures, because the excess pressure attained in the ultrasonic interferometer is only a very small fraction of an atmosphere.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Accuracy of Estimation of Hydrogen Peroxide by Potassium Permanganate Titration

BY CHARLES E. HUCKABA[1a] AND FREDERICK G. KEYES[1b]

Introduction

The usual method for analyzing aqueous solutions of hydrogen peroxide is by titration in acid solution with a standard solution of potassium permanganate. However the complete reliability of this method for very accurate determinations has been questioned, because of some doubt as to the optimum conditions for carrying out the titration.

A search of the literature revealed varying recommendations as to the proper sulfuric acid concentration, and some uncertainty as to the rate of addition of the permanganate to the peroxide solution. For example, if the rate of addition is too great, some manganese dioxide may be formed due to a local depletion of acid in the solution and bring about catalytic decomposition of a portion of the peroxide.

There are three possible methods for carrying out the determinations of hydrogen peroxide: titration, colorimetry and decomposition. Titration methods using the following reagents have been described in the literature[2]: potassium permanganate, ceric sulfate, potassium iodide–sodium thiosulfate, sodium arsenite and titanium trichloride. However in each case there has been observed either disagreement regarding the best procedure for performing the titration, or uncertainty as to the reliability of the method. The colorimetric method is applicable only for detecting a few parts per million of peroxide.

The method based on the decomposition of the peroxide with a suitable catalyst followed by measuring the amount of oxygen evolved would appear in principle to combine simplicity and reliability. The reaction occurs as follows

$$2H_2O_2 \xrightarrow{\text{catalyst}} 2H_2O + O_2$$

There are no known side reactions to introduce error as is present in some of the titration procedures.

(1) (a) Results recorded in this article are from a thesis submitted as partial fulfillment of the requirements for the degree of Master of Science in Chemical Engineering at the Massachusetts Institute of Technology; (b) Department of Chemistry, Massachusetts Institute of Technology.

(2) J. S. Reichert, S. A. McNeight and H. W. Rudel, *Ind. Eng. Chem., Anal. Ed.*, **11**, 194 (1939). This paper surveys the titration procedures for peroxide to date.

The inconvenience of the decomposition method in practice would bar it from general use. However there seems to be no doubt that it is an "absolute" method of analysis. Therefore it was concluded that considering the existing confusion concerning other methods, the decomposition procedure was the only completely reliable method with which the titration methods could be compared.

The objective of this investigation involves then the constructing of a suitable apparatus for carrying out the absolute or gasometric analysis by decomposition as a basis for the comparison with the convenient permanganate titration procedure. No record of such a comparison has been found in the literature. The necessity for such a comparison is apparent.

The Gasometric Method

An apparatus was assembled as shown in the drawing for carrying out the analysis by decomposition. It consisted chiefly of a reaction vessel of two sections connected by a ground glass joint, a moisture trap, a Töpler pump, a volumometer, a manometer, a thermometer and a McLeod pressure gage.

The mercury levels in the Töpler pump and the volumometer were controlled by applying either pressure or vacuum to the steel mercury containers. Very accurate control of mercury introduction was attained through the use of steel needle valves. For the volumometer extremely fine adjustment of the mercury levels was afforded by a small piston-type injector.

Small monel metal bellows were placed between the steel tubing from the mercury containers and the glass of both the Töpler pump and the volumometer to absorb any shocks that might occur.

A mixture of Dry Ice and methyl alcohol (t = 78.5°) was used as the refrigerant around the moisture trap, and proved to be adequate. The thermometer was strapped to the outside of the volumometer with asbestos tape. Vacuum for the system was furnished by a mercury diffusion pump capable of producing a high vacuum.

The volumometer was calibrated by weighing the amount of mercury needed to fill the space between the three pointers and the top. The following results were obtained:

Top of volumometer to	Volume, cc.	Precision
Top pointer	34.038	1:3000
Middle pointer	100.341	1:2500
Bottom pointer	202.041	1:3500

The following procedure was used in making a run with the decomposition apparatus:

The manometer, volumometer and Töpler pump were evacuated and closed off from the remainder of the system. The mercury level in the volumometer was adjusted to a point just below the delivery tube from the Töpler pump to seal the manometer off from the volumometer. An 8-10 cc. sample

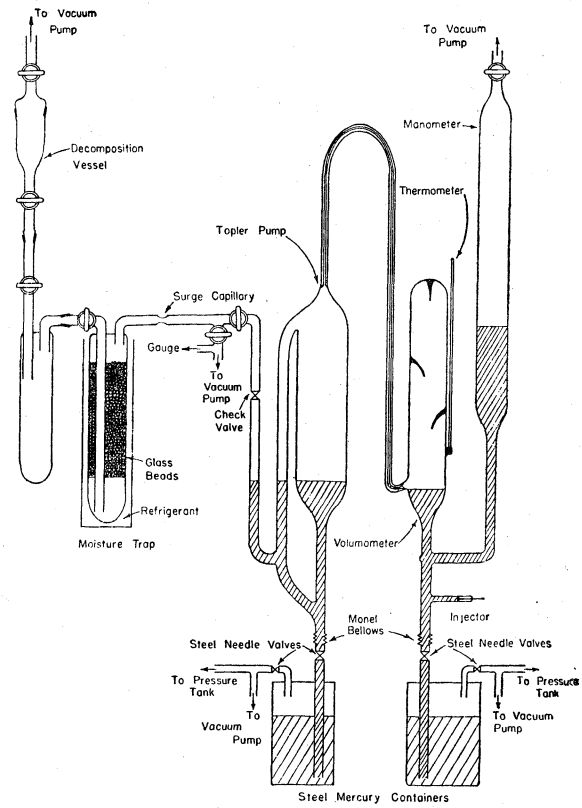


Fig. 1.—Decomposition apparatus.

of 2 to 3% hydrogen peroxide was weighed out in the top part of the reaction vessel, which had previously been cleaned with hot fuming sulfuric acid to prevent premature decomposition of the peroxide. After this part of the reaction vessel had been attached, the remainder of the apparatus was evacuated. With the reaction vessel closed off from the rest of the system, the peroxide was transferred to the cooled (−78°) lower part of the vessel. This was followed by two portions of distilled water of approximately 10 cc. each to rinse all of the peroxide into the lower vessel. Next a great excess of liquid catalyst was introduced in the same manner exercising great precaution not to let air leak into the bottom vessel. The dissolved air in the rinse water and liquid catalyst was removed by applying a vacuum in the top part of the reaction vessel prior to admission of the liquid.

As the peroxide thawed, the decomposition started and it was allowed to go to completion. Tests made by adding huge excesses of several catalysts to the residues proved that the reaction was in truth complete.

The evolved oxygen was transferred to the volumometer by means of the Töpler pump. About eight passes with the Töpler pump which has a volume of about 600 cc. was sufficient to complete the transfer. Completeness of transfer was evidenced by a pressure reading of about 10^{-4} mm. of

mercury in the pump, and by the fact that no appreciable amount of gas was transferred by the last pass with the pump.

The mercury level in the volumometer was adjusted until it was only a few millimeters below the bottom pointer. The temperature of the gas was then allowed to reach equilibrium with that of the surroundings, as evidenced by constancy of the mercury level in the manometer. The mercury level in the volumometer was finally adjusted by means of the injector until it just made contact with the bottom pointer. The mirror nature of the mercury surface made adjustment to a fine point very accurate (±0.001 mm.).

The difference in mercury levels in the volumometer and manometer were read with a Geneva cathetometer. The cathetometer, of special construction, consists of two telescopes which are mounted on a vertical invar metal bar and each telescope eyepiece is equipped with a micrometer cross-hair arrangement which allows the mercury levels to be read to 0.002 mm. The brass scale used with this cathetometer was calibrated by the Bureau of Standards and found to be accurate to about three parts in 100,000.

The space above the mercury in the manometer was evacuated, and therefore the difference in mercury levels corrected for capillarity was the absolute pressure of the gas in the volumometer. The temperature was read from the thermometer attached to the volumometer.

The gas in the volumometer was the oxygen produced from the decomposed peroxide plus the dissolved air in the sample of peroxide.

It was first attempted to remove this dissolved air by alternate freezing, and pumping away the air. However, it was discovered that the peroxide decomposed during the thawing operation.

Since the removal of air from the peroxide was impractical, it was decided to apply a correction for the dissolved air. To determine the value of the correction, several blank runs were made using a sample of water which had been stored under similar conditions to the peroxide. It was assumed that the amount of air dissolved in 3% hydrogen peroxide is the same as that in water.

The procedure used in the blank runs was exactly the same as that employed in the runs with peroxide. The average value obtained was 0.022 cc.[3] of air at standard temperature and pressure per gram of water at 25°. The value given is somewhat higher than will be found in the literature and this is due to the fact that the number corresponds to a measurement made using the exact procedure where two quantities of pumped rinse water were used. This value was used to correct the observed volumes of gas evolved from the decomposition.

Calculation of the weight of oxygen was carried out by using a simplified approximation of the Beattie–Bridgeman equation of state for oxygen as follows[4]

$$v = (2.5644T/P) + B_0$$

$$B_0 = \left(1.445 - \frac{1447}{2.5644T} - \frac{1.5 \times 10^6}{T^3}\right)$$

where

v is the specific volume of oxygen in cc. per gram,
P = pressure in normal atmospheres
T = 273.16 + t (°C.)

The total volume of oxygen was divided by the specific volume to obtain the weight of oxygen, from which the percentage by weight of hydrogen peroxide in the original solution was calculated.

The Titration with Potassium Permanganate

A survey of the literature was conducted to obtain the available information pertaining to all phases of the titration of hydrogen peroxide with permanganate. General agreement was found concerning procedures for the preparation and storage of the permanganate solution. The following procedure was actually used.

Permanganate of potassium of high purity was dissolved in hot distilled water which had been boiled for about fifteen minutes and the solution allowed to stand in a stoppered bottle for a week. The precipitated manganese dioxide was removed by filtering the solution through the sintered glass plate of a funnel. The solution was then stored in a pyrex bottle which had been covered with a coat of black paint. The bottle was fitted with a siphon having a stopcock in the line for convenient withdrawal of the solution. During withdrawal of the solution air entered the bottle through a fiber glass filter to remove air-borne dust.

If proper care is taken in its preparation and storage, a solution of potassium permanganate is quite stable. The results of several studies reported by Bruhns,[5] Halverson and Bergeim,[6] Kato[7] and others substantiated this fact, and show that no great deterioration occurs in as much as one to three years. However for very accurate work the solution should be standardized about once a month. The solution prepared for this investigation dropped in concentration about one part in a thousand in approximately six weeks.

The standardization of the permanganate solution can be carried out by using sodium oxalate, arsenious acid, iron, potassium dichromate and other primary standards. Of these, sodium oxalate is probably the most convenient and thus the most widely used. The confusion concerning the best procedure for carrying out the standardization with sodium oxalate was cleared up by the work of Fowler and Bright[8] at the National Bureau

(3) The reproducibility of the blank measurements was such that the maximum error in the corrected volume of oxygen was not greater than a part in 4000.

(4) J. A. Beattie and O. C. Bridgeman, *Proc. Am. Acad. Arts Sci.*, **63**, 229 (1928).

(5) G. Bruhns, *Chem. Ztg.*, **47**, 613 (1923).

(6) J. O. Halverson and O. Bergeim, *Ind. Eng. Chem.*, **10**, 119 (1918).

(7) T. Kato, *J. Chem. Soc. Japan*, **48**, 17 (1927).

(8) R. M. Fowler and H. A. Bright, *J. Research Natl. Bur. Standards*, **15**, 493 (1935).

of Standards. Their investigation showed that McBride's procedure[9] gave results that are about 0.4% too high compared with the results obtained by using arsenious acid, pure iron, and potassium dichromate. Fowler and Bright worked out a procedure that gave results within 0.03%, or within the experimental error of the results obtained by the other methods. The recommended method using sodium oxalate was used in this investigation.

The oxalate used had a purity of about 99.98%. A precision of approximately one part in 3500 was realized in the standardization. The titer of the permanganate was 0.4899% by weight corresponding to a normality of about 0.16.

As stated above, considerable disagreement is expressed in the literature regarding the optimum conditions for carrying out the titration of an aqueous solution of hydrogen peroxide with potassium permanganate. The situation was also confused by the fact that in most cases no reasons for the given procedure were stated.

The various recommendations for the weight ratio of sulfuric acid to hydrogen peroxide ranged from 50/1 to 300/1. No specific recommendations were given as to the correct rate of addition of the permanganate to the peroxide solution. Kolthoff and Stenger[10] state that the results are influenced by this rate of addition, and while the error is almost negligible at slow rates, it is more serious at fast rates. L. J. Heidt[11] also reports the influence of rate of addition on the results.

The following procedure for the titration was used in this investigation: A 10-g. sample of 2–3% peroxide was weighed out in a glass-stoppered flask,[12] and rinsed with approximately 50 cc. of distilled water into a beaker containing 150 cc. of distilled water and 7 cc. of 95% sulfuric acid. The distilled water (conductivity water) had been boiled for fifteen minutes to destroy any organic matter, and then cooled to room temperature before use. The rate of addition of the permanganate solution was approximately 35–40 cc. per minute. The titration was carried out at room temperature and with moderate stirring.

The weight ratio of acid to peroxide in this procedure was about 65/1, which corresponds closely to that recommended in Scott's "Standard Methods of Analysis."[13] However the procedure described, while corresponding in some respects to that given by Scott and others, was used as a point of departure with the thought of introducing alterations as shown by experience to be necessary under comparison with the absolute method by oxygen measurement.

As an aid in achieving accuracy, a weight buret (capacity 500 cc.) instead of the usual volumetric type was used in both the standardization of the permanganate and in the titrations. The permanganate was standardized in terms of per cent. by weight of permanganate in the solution instead of normality. By touching the tip of the buret to the stirring rod, the end-point can be determined within about a third of a drop or about 0.017 g. If it is desired to obtain the end point closer than one-third of a drop, a correction for the amount of permanganate needed to color the solution can be estimated by determining what fraction of a drop of permanganate added to a volume of water equal to that of the solution produces a coloration of equal intensity to that at the end point of the titration. Approximately 100 cc. of 0.4899 weight per cent. permanganate were required in the procedure outlined.

The permanganate titration cannot be used if any organic matter is present in the peroxide solution. Some commercial peroxide contains small amounts of organic compounds added as stabilizers against decomposition. In this case the ceric sulfate titration has been recommended by various authors[2,14,15] since ceric sulfate will not react with organic matter.

Experimental Results

Using the procedures outlined above, runs were made to compare the permanganate titration with the gasometric method for analyzing hydrogen peroxide solutions. Seven runs were made using osmic acid as the decomposition catalyst, and three were made using lead oxide as the catalyst. Since varying amounts of two different catalysts left the same results unaltered, it was concluded that the catalyst is effective in causing complete decomposition into oxygen and water. The osmic oxide was used in basic solution and the lead oxide in a water suspension.

Table I shows the results of the runs made. The values reported for the gasometric method represent only one trial because the time required for carrying out the procedure was about five hours, and approximately four hours were required to prepare the apparatus for another run as the trap system had to be pumped free of moisture after each run. After this time had elapsed, the peroxide would have changed in concentration sufficiently (about one part in 500) to have made the data therefrom unreliable for comparison with the previous run. The values reported for the titration represent the average of three titrations, with the greatest deviation from the average about one part in 3000 to 4000.

(9) R. S. McBride, THIS JOURNAL, **34**, 393 (1912).

(10) I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1942, p. 175.

(11) Personal communication.

(12) The inside of glass ware can be made anti-catalytic by treating with hot fuming sulfuric acid. If this procedure fails, the surface of the glass probably has catalytic dust particles fused into its surface. We have preferred to construct glass ware from tubing scrupulously cleaned with fuming sulfuric acid, rinsed with the purest distilled water and using air in the glass blowing filtered through fresh medical cotton.

(13) W. W. Scott, "Standard Methods of Chemical Analysis," 5th ed., D. Van Nostrand Co., New York, N. Y., 1939, p. 2181.

(14) N. H. Furman and J. H. Wallace, THIS JOURNAL, **51**, 1449 (1929).

(15) H. H. Willard and P. Young, *ibid.*, **55**, 3260 (1933).

TABLE I

Run no.[a]	Wt. % H_2O_2 by absolute method	Wt. % H_2O_2 by titration	Average	Deviation from average
1	2.3105	2.3032	2.3069	1:625
2	1.9628	1.9638	1.9633	1:4000
3	1.9196	1.9262	1.9228	1:625
4	1.9066	1.9091	1.9079	1:1450
5	1.8378	1.8380	1.8379	1:18,000
6	1.7652	1.8035	1.7844	1:95
7	2.8004	2.7992	2.7998	1:4700
8	2.8002	2.8029	2.8015	1:2200
9	2.8068	2.8076	2.8072	1:7000
10	2.8095	2.8102	2.8099	1:8000

[a] Osmic acid was used as the catalyst in runs 1–7; lead oxide was used as the catalyst in runs 8–10.

The results show a favorable comparison of the permanganate titration with the gasometric method. The average deviation from the average of the two methods is about one part in 5000. It is to be noted that the runs using the osmic acid catalyst and those using the lead oxide catalyst in varying amounts led to the same result. Therefore it is assumed the catalyst ran the reaction to completion.

Run 6 in which there was a part in 95 deviation from the average cannot be explained except by some undetected error in carrying out the procedure.

While it was not the purpose of this investigation to determine the effect of varying all conditions under which the titration may be performed, a few variations were made. The results of these tests indicate that variation in the titration procedure, as outlined above, had little effect on the results. Thus, doubling the acid concentration produced a difference of about one part in 10,000 which is within the experimental error. Tests made at rates of addition of 10 cc. per minute and at 50 cc. per minute differed by about the same amount, which may be taken to indicate that some flexibility can be tolerated in the titration procedure.

Conclusions

The experimental results show that, even where accurate results are required, the permanganate titration, using the procedure given above, can be used for determining the concentration of aqueous solutions of hydrogen peroxide. The procedure can be modified somewhat as indicated and still give sufficiently accurate results, but just how far modifications can be carried without causing decreased accuracy remains to be determined.

In applying the proposed procedure to more concentrated solutions, it is suggested that a sample containing an equivalent amount of hydrogen peroxide to that contained in 10 g. of 3% solution be used. For instance in analyzing a solution near 90%, 0.33 g. of the solution would contain approximately 0.3 g. of hydrogen peroxide, which in turn is approximately the amount contained in 10 g. of 3% solution. If the size of the sample is varied from that stated, precaution should be exercised that the weight ratio of sulfuric acid to hydrogen peroxide is at least 60–70 to 1. There is no reason to believe that higher ratios are harmful, but they are unnecessary. With lower ratios the chance of manganese dioxide formation increases, and for that reason should be avoided.

The rate of addition of the permanganate should be about 35–40 cc. per minute or slower. Excessively fast rates of addition increase the probability of the formation of manganese dioxide, which as previously stated is highly catalytic toward the decomposition of hydrogen peroxide. The titration should of course be carried out at room temperature, since higher temperatures cause loss by vaporization of the peroxide.

The results also indirectly substantiate the procedure recommended by Fowler and Bright[8] for standardization of potassium permanganate solutions. If the standardization procedure had given erroneous results, the good agreement of the titration values with those of the gasometric method would not have been possible.

The authors express their acknowledgment to the Naval Bureau of Ordnance for the support and release of this work.

Summary

An apparatus and procedure has been described for carrying out the "gasometric" method by decomposition for determining the concentration of aqueous solutions of hydrogen peroxide. The results obtained by this method were compared with those obtained by titration with potassium permanganate. On the basis of the good agreement between the two methods, a procedure for performing the titration was recommended. Also, the method recommended by Fowler and Bright[6] for the standardization of the potassium permanganate solution against sodium oxalate has been substantiated.

CAMBRIDGE 39, MASSACHUSETTS

RECEIVED AUGUST 7, 1947

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, A DIVISION OF THE SOCONY-VACUUM OIL CO., INC., RESEARCH AND DEVELOPMENT LABORATORIES]

Metalation Studies in the Thiophene Series. II. Transmetalation of the Alkylthiophenes

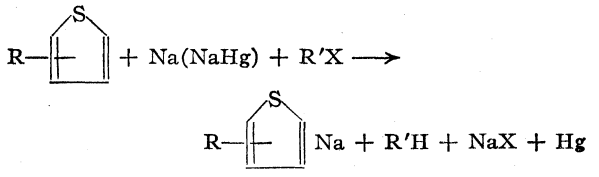
BY JOHN W. SCHICK AND HOWARD D. HARTOUGH

The authors previously reported the metalation of the thiophene and 2-halothiophenes to yield 2-thienylsodium and 5-halo-2-thienylsodium. Subsequent carbonation and acidulation yielded the 2-thiophenecarboxylic acid and 5-halo-2-thiophenecarboxylic acids,[1] respectively.

An extension of these studies to the alkylthiophenes, namely, 2-methyl-, 3-methyl-, 2-*t*-butyl-, 2-*t*-amyl-, 2-(1,1,3,3-tetramethylbutyl)- and 2-(1-phenylethyl)thiophene, has produced a convenient method for preparing alkyl-substituted 2-thiophenecarboxylic acids.

5-Methyl-2-thiophenecarboxylic acid was prepared in low yield by Gilman and Breuer[2] from 2-methylthiophene, dibenzylmercury and sodium. Hartough and Conley[3] have prepared the substituted acids by the sodium hypochlorite oxidation of the acetylalkylthiophenes.

It was found that the alkylthiophenes do not metalate directly with sodium. Metalation, however, was accomplished via the transmetalation reaction by interaction of an alkylthiophene, metallic sodium, and an alkyl or aryl halide in a neutral solvent.



Substitution of a 70–90% sodium amalgam for metallic sodium gave increased yields in some cases.

Table I records the substituted alkyl-2-thiophenecarboxylic acids that were prepared by the described general procedure.

Experimental

General Procedure.—A cold mixture of 16 g. (0.25 mole) of ethyl chloride, in 200 ml. of anhydrous ether, was cooled dropwise over a one hour period to a stirred, externally cooled mixture of 12 g. (0.5 gram atom) of freshly prepared sodium sand, 49 g. (0.5 mole) of 2-methylthiophene and 100 ml. of anhydrous ether. The reaction was carried out under nitrogen. After the addition of the ethyl chloride was completed, the reaction mixture was stirred for an additional two hours at room temperature. Carbonation of the organo-metallic compound was accomplished with pieces of Dry Ice. The temperature was kept below 30° with ice. Two hundred milliliters of distilled water was added cautiously to destroy the small amount of unreacted sodium. The aqueous layer was separated and acidified with 70 ml. of hydrochloric acid. The crystalline product was filtered and recrystallized.

Bromobenzene and *n*-butyl bromide were also substituted for ethyl chloride with good results.

TABLE I

ALKYL-2-THIOPHENECARBOXYLIC ACIDS FROM THE CORRESPONDING ALKYLTHIOPHENES

Alkyl-2-thiophenecarboxylic acid	Yield, %	Recrystallized from	Melting point, °C.	Neutral equivalent Calcd.	Obs.
5-Methyl-	70	Water	138–138.5[a]	142	143
4-Methyl-[c]	42	Water	119–121[b]	142	141.6
5-*t*-Butyl-	85	Water	124–125	184	186
5-*t*-Amyl-	46	Pet. ether	86.5–87.5	198	198
5-(1,1,3,3-Tetramethylbutyl)-	66	Pet. ether	122–123	240	241
5-(1-Phenylethyl)-	60	Water	99.5–101.5	232	235

[a] Ref. 3, m. p. 137–138°. [b] Ref. 3, m. p. 120–121°. [c] 3-Methylthiophene metalated exclusively in the 5-position. No trace of the normal substitution product, 3-methyl-2-thiophenecarboxylic acid, could be detected.

Acknowledgment.—The authors wish to express their appreciation to Dr. D. E. Badertscher for his advice and interest and to Mrs. Josephine Sindoni Piel who carried out some of the experiments.

Summary

The alkylthiophenes, namely, 2-methyl-, 3-methyl-, 2-*t*-butyl-, 2-*t*-amyl-, 2-(1,1,3,3-tetramethylbutyl)-, and 2-(1-phenylethyl)-thiophene were metalated with metallic sodium or sodium amalgam to yield the corresponding 2-thiophenecarboxylic acid upon carbonation and acidulation.

PAULSBORO, NEW JERSEY RECEIVED JULY 14, 1947

(1) Schick and Hartough, THIS JOURNAL, **70**, 286 (1948).
(2) Gilman and Breuer, *ibid.*, **56**, 1123 (1934).
(3) Hartough and Conley, *ibid.*, **69**, 3096 (1947).

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, (A DIVISION OF SOCONY-VACUUM OIL COMPANY, INC.), RESEARCH AND DEVELOPMENT DEPARTMENT]

Metalation Studies in the Thiophene Series. III. Condensation of Thienyl- and Substituted Thienyl-sodium Compounds with Ethylene Oxide

BY JOHN W. SCHICK AND HOWARD D. HARTOUGH

The preparation of the carboxylic acids of thiophene,[1] halothiophenes[1] and the alkylthiophenes[2] has been previously described. Although organometallic compounds are reported to react similarly to Grignard reagents, the only literature references that can be found deal with their reactions with carbon dioxide and formaldehyde or its polymers. Amylsodium, phenylsodium and benzylsodium have been condensed only with trioxymethylene[3] to yield hexyl alcohol (28%), benzyl alcohol (17%) and phenylethyl alcohol (17%), respectively.

The study of the reaction of ethylene oxide with thienyl-, halothienyl- and alkylthienylsodium compounds was undertaken in order to obtain the corresponding ethanols and vinyl compounds. Previously, the simple alcohols such as 2-thienylcarbinol[4] and 2-(2-thienyl)-ethanol[5] were prepared from 2-thienylmagnesium bromide or iodide and monomeric formaldehyde and ethylene oxide, respectively.

2-Thienylsodium and substituted 2-thienylsodiums, namely, 4-methyl-, 5-methyl-, 5-*t*-butyl- and 5-chlorothienylsodium, were condensed with ethylene oxide to yield the corresponding thienylethanols. Dehydration of the thienylethanols by conventional means yielded vinyl and substituted vinyl-thiophenes which may be useful in the plastics and rubber industries. Table I records several vinylthiophenes thus obtained with their observed properties. The vinylthiophenes polymerized at room temperature, and more rapidly at elevated temperatures in the presence of a catalyst, benzoyl peroxide, to yield very pale yellow to orange colored, clear polymers.

Experimental

2-(2-Thienyl)-ethanol.—A mixture of 118 g. (1.0 mole) of 2-chlorothiophene in 500 ml. of benzene was added to a freshly prepared sodium amalgam sand[1] containing 50 g. (2.17 gram atoms) of sodium and 20 g. (0.10 gram atom) of mercury and the reaction mixture was stirred and refluxed for three hours in a nitrogen atmosphere. The mixture was cooled to 0–10° in an ice-bath and 44 g. (1.0 mole) of ethylene oxide in 100 ml. of benzene was added over a twenty-minute period. The temperature rose rapidly to about 50° and then slowly fell. The ice-bath was removed and the stirring was continued until the temperature dropped to 25°. A solution containing 125 ml. of concentrated hydrochloric acid in 325 ml. of distilled water was cautiously added with stirring and the whole solution was filtered to remove salt and sludge. The benzene layer was separated, dried over anhydrous sodium sulfate and the benzene removed by distillation. The residue was distilled under reduced pressure. Sixty grams (47%) of 2-(2-thienyl)-ethanol, a white oily fluid having the odor of roses, was obtained; b. p. 99–100° (7 mm.); $n^{20}D$ 1.5478.

The phenylurethan was recrystallized from petroleum ether, m. p. 52–53°.

Anal. Calcd. for $C_{13}H_{13}O_2NS$: S, 12.96; N, 5.67. Found: S, 12.95; N, 5.79.

2-(5-Chloro-2-thienyl)-ethanol.—One mole (118 g.) of 2-chlorothiophene was converted to the corresponding 5-chloro-2-thienylsodium by a method described earlier.[1] To the ice-cooled reaction mixture was added 66 g. (1.5 moles) of ethylene oxide in 200 ml. of ether over a period of one hour. The mixture was then stirred at room temperature for thirty minutes and then warmed to reflux for two hours. Unreacted sodium was decomposed with 150 ml. of alcohol and a solution of 170 ml. of concd. hydrochloric acid in 500 ml. of water added cautiously over a period of thirty minutes. The resultant emulsion was broken with sodium chloride. The ether layer was separated, dried and the ether distilled. Thirty-five grams (22%) of 2-(5-chloro-2-thienyl)-ethanol, a white, oily fluid having the odor of roses was obtained; b. p. 98.5–100° (1–2 mm.); $n^{20}D$ 1.5576. The phenylurethan derivative was recrystallized from petroleum ether, m. p. 57–58°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.81.

2-(4-Methyl-2-thienyl)-ethanol.—A cold mixture of 64 g. (1.0 mole) of ethyl chloride in 300 ml. of diethyl ether was added dropwise over one hour (in a nitrogen atmosphere) to a stirred mixture of sodium amalgam sand containing 46 g. (2.0 gram atoms) of sodium and 12 g. (0.06 gram atom) of mercury and 147 g. (1.5 mole) of 3-methylthiophene in 200 ml. of diethyl ether which was cooled to 0–5°. After the addition was completed, the ice-bath was removed and the temperature kept below the reflux temperature of ether for one hour, after which it was warmed to the reflux temperature for fifteen minutes. The reaction was cooled below 10° and a cold solution of 44 g. (1.0 mole) of ethylene oxide in 100 ml. of ether was added with stirring over a period of one hour. The temperature was permitted to rise to room temperature. The reaction mixture was worked up as described in the preparation of 2-(5-chloro-2-thienyl)-ethanol. Seventy-one grams (51%) of 2-(4-methyl-2-thienyl)-ethanol was obtained; b. p. 87–89° (2 mm.); $n^{20}D$ 1.5397. The phenylurethan derivative was recrystallized from petroleum ether, m. p. 68–69°.

TABLE I

VINYLTHIOPHENES

	B. p., °C.	Mm. Hg pressure	$n^{20}D$	Yield, %	Formula	Sulfur, % Calcd.	Sulfur, % Found
2-Vinylthiophene	65.5–66.5	48	1.5720	80	C_6H_6S	29.1	28.9
4-Methyl-2-vinylthiophene	86.5–87.5	45	1.5590[a]	95	C_7H_8S	25.8	25.7
5-*t*-Butyl-2-vinylthiophene	104–105	24	1.5357	94	$C_{10}H_{14}S$	19.3	19.9

[a] Refractive index at 25°.

(1) Schick and Hartough, THIS JOURNAL, **70**, 286 (1948).
(2) Schick and Hartough, *ibid.*, **70**, 1645 (1948).
(3) Morton and Fallwell, *ibid.*, **60**, 1429 (1938).
(4) Steinkopf, *Ann.*, **540**, 23 (1939).
(5) Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942).

Anal. Calcd. for $C_{14}H_{15}O_2NS$: S, 12.26; N, 5.35. Found: S, 12.15; N, 5.43.

2-(5-*t*-Butyl-2-thienyl)-ethanol.—To two moles of sodium amalgam sand was added 32 g. (0.5 mole) of ethyl chloride and 70 g. (0.5 mole) of 2-*t*-butylthiophene in 200 ml. of ether in a similar manner to that described directly above. After cooling below 10°, 22 g. (0.5 mole) of ethylene oxide in 100 ml. of ether was added during a one-hour period. The temperature rose rapidly but was controlled at about 30° by means of an ice-bath. After this addition the mixture was stirred for ninety minutes at ambient temperatures and then treated as described in the preparation of 2-(5-chloro-2-thienyl)-ethanol. Sixty-three grams (68%) of 2-(5-*t*-butyl-2-thienyl)-ethanol, a white, viscous fluid, was obtained; b. p. 115–116° at 3 mm.; $n^{20}D$ 1.5198. The phenylurethan derivative was recrystallized from petroleum ether, m. p. 73–74°.

Anal. Calcd. for $C_{17}H_{21}O_2NS$: S, 10.56; N, 4.62. Found: S, 10.71; N, 4.71.

General Procedure for Preparing the Vinylthiophenes.—The thienylethanol was dehydrated to the corresponding vinylthiophene by heating the ethanol with a large excess (1:4) of molten potassium hydroxide at a reduced pressure (45–50 mm.). The vinylthiophene distilled along with water and the distillate was extracted with ether. After drying the ether solution with anhydrous sodium sulfate, the ether was removed on a steam-bath and the residue was distilled under reduced pressure.

The 2-(5-chloro-2-thienyl)-ethanol did not dehydrate well by this method and the low yield of a vinyl compound did not contain the theoretical amount of chlorine.

Acknowledgment.—The authors wish to thank Dr. D. E. Badertscher for his advice and interest, and Mrs. Josephine Sindoni Piel, who carried out some of the experiments.

Summary

2-(2-Thienyl)-, 2-(5-*t*-butyl-2-thienyl)-, 2-(4-methyl-2-thienyl)- and 2-(5-chloro-2-thienyl)-ethanol have been prepared from the corresponding thienylsodium compound and ethylene oxide in yields of 47, 68, 51 and 22%, respectively.

Dehydration of several of the thienylethanols, namely, 2-(2-thienyl)-, 2-(4-methyl-2-thienyl)- and 2-(5-*t*-butyl-2-thienyl)-ethanol with molten potassium hydroxide at reduced pressure yielded the corresponding vinylthiophenes in yields of 80, 95 and 94%.

PAULSBORO, NEW JERSEY RECEIVED JULY 14, 1947

[CONTRIBUTION FROM THE FINE CHEMICALS DIVISION, NOPCO CHEMICAL CO.]

Acylation of Benzene Compounds with Iodine as a Catalyst

BY SAUL CHODROFF AND HOWARD C. KLEIN

Iodine has been used successfully as a catalyst in acylations of furan and thiophene.[1] It was of interest to extend this reaction to benzenoid compounds. Acylations were successful with the more active members of the benzene series, such as anisole[2] and acetanilide, whereas the alkylated benzenes, toluene and cumene, failed to react. As previously noted,[1] the aroyl halides gave higher yields than aliphatic anhydrides. Dibasic aliphatic anhydrides, such as succinic anhydride, failed to react with anisole. As might be expected from the reduced aromaticity of the benzenoid compounds compared to furan and thiophene, the reactions were not exothermic, required longer periods of time and higher temperatures, and generally required higher catalyst concentrations for optimum yields, the range of $2\text{–}7 \times 10^{-2}$ mole of iodine per mole of reactant being quite effective.

The influence of catalyst concentration on yield in the reaction between naphthalene and benzoyl chloride was marked; the yield of ketone rose from 15 to 52% as the molar ratio of iodine to reactants was increased from 2.1×10^{-2} to 7.6×10^{-2}. The reaction favors the formation of the α-isomer predominantly, for, the ratio of the α to β isomers in the mixture of the crude benzoylnaphthalenes was 95 to 5, as determined by the precipitation of the picrate of the β isomer from a benzene solution,[3] after standing for two weeks at 5°.

Acknowledgment.—The authors are grateful to Dr. Roland Kapp of this Laboratory for encouragement and interest in the promotion of this work.

Experimental

***p*-Acetylanisole.**—Two hundred and fourteen grams (2.0 moles) of anisole and 102 g. (1.0 mole) of acetic anhydride were refluxed for two hours in the presence of 2 g. of iodine. After cooling, the dark brown solution was taken up in 300 ml. of ethylene dichloride and washed successively with dilute potassium carbonate, sodium bisulfite, and water. Drying over sodium sulfate, removal of the solvent, and distillation of the residue gave 98.6 g. (66%) of *p*-acetylanisole, b. p. 120–125° (5 mm.), as a colorless oil. Crystallization from aqueous methanol yielded crystals, m. p. 38°. The product formed a semicarbazone, m. p. 198–198.5°.[4]

***p*-Benzoylanisole.**—To a mixture of 37.8 g. (0.35 mole) of anisole and 22.4 g. (0.18 mole) of benzoyl chloride, was added 1 g. of iodine. The solution was refluxed gently for eight hours, until the evolution of hydrogen chloride had subsided. After cooling, the solution was diluted with 100 ml. of benzene, washed with potassium carbonate, sodium bisulfite, and water. The dried solvent was removed on the steam-bath and the residue distilled, yielding 33.8 g. (88.6%) of *p*-benzoylanisole, b. p. 175–179° (1 mm.), as a yellow liquid which solidified,

(1) Hartough and Kosak, THIS JOURNAL, **68**, 2639 (1946).

(2) NOTE ADDED IN PROOF.—After this manuscript had been submitted, Kosak and Hartough, *ibid.*, **69**, 3144 (1947), reported the acetylation of ansole in 45% yield, using phosphoric acid as a catalyst. They also indicated that iodine and other acid catalysts may be employed in this reaction without reporting the yield.

(3) Rousset, *Bull. soc. chim. France*, [3] **15**, 71 (1896).

(4) Wahl and Silberzweig, *Bull. soc. chim.*, [4] **11**, 69 (1912), list m. p. of 197°.

m. p. 53–55°. Crystallization from 90% methanol raised the m. p. to 61–62.5°. A 2,4-dinitrophenylhydrazone was obtained, m. p. 180°.[5]

p-**Acetylaniline.**—Fifty-four grams (0.4 mole) of acetanilide and 50 ml. of acetic anhydride were refluxed with 4 g. of iodine, distilling the acetic acid formed through a 38-cm. Vigreux column. In fifteen minutes, 30 ml. of distillate was collected, b. p. 110–120°. An additional 25 ml. of acetic anhydride was added to the reaction mixture and 25 ml. of distillate collected, the final vapor temperature rising to 132°. The reaction mass was poured into 250 ml. of water, the oil extracted twice with 75-ml. portions of ethylene dichloride and the excess iodine washed out with bisulfite. Removal of the solvent left a tarry residue which was hydrolyzed by refluxing for one hour with 50 ml. of concentrated hydrochloric acid. After being made strongly alkaline, the unreacted aniline was steam distilled and the residual black tar extracted twice with 75-ml. portions of ethylene dichloride, washed until neutral and dried over sodium sulfate. The solvent was removed and the residue distilled, yielding 10.5 g. (19.4%) of a golden yellow oil, b. p. 165–168° (6 mm.), which solidified, m. p. 67–68°. Crystallization from hot water gave white crystalline *p*-acetylaniline, m. p. 105–106°; acetyl derivative, m. p. 165–166°.[6]

Refluxing the reactants for two hours without removal of the acetic acid formed reduced the yield of *p*-acetylaniline to 7%.

α-**Phenyl Naphthyl Ketone.**—Twenty-five and six-tenths g. (0.2 mole) of naphthalene was refluxed gently with 28 g. (0.2 mole) of benzoyl chloride in the presence of 4 g. of iodine. A vigorous evolution of hydrogen chloride began immediately and ceased within two hours. The reaction mass was taken up in 150 ml. of ethylene dichloride, washed with dilute sodium hydroxide and bisulfite and the solvent and unreacted naphthalene removed by steam distillation. The black, tarry mass was extracted with benzene, washed with water and dried over sodium sulfate. The solvent was removed and the residue distilled, yielding 23.9 g. (51.7%) of a golden yellow, viscous liquid, b. p. 165–169° (1 mm.) which slowly solidified, m. p. 73–74°. The product was crystallized from ethanol, m. p. 74–75°, and gave an oxime, m. p. 161°.[7] One gram of the crude ketone dissolved in 20 ml. of benzene containing 1 g. of picric acid deposited, after fourteen days at 5°, 100 mg. of the picrate of the *β*-isomer, m. p. 112–113°, equivalent to 5% of *β*-benzoylnaphthalene.[3]

Summary

Acylations have been carried out successfully on the more active members of the benzene series, using iodine as a catalyst.

(5) Ferrante and Bloom, *Am. J. Pharm.*, **105**, 383 (1933), report m. p. of 180°.

(6) Kunckell, *Ber.*, **33**, 2641 (1900), report m. p. of 166–167°.

(7) Betti and Poccianti, *Gazz. chim. ital.*, **45**, I, 374 (1915), list m. p. of 161°.

HARRISON, NEW JERSEY RECEIVED DECEMBER 20, 1947

[CONTRIBUTION FROM THE UNIVERSITY OF CHICAGO TOXICITY LABORATORY]

The Volatility and Vapor Pressure of Ten Substituted 2-Chloroethylamines[1]

BY C. ERNST REDEMANN,[2] SAUL W. CHAIKIN AND RALPH B. FEARING[3]

In a study of the toxicity and vesicancy of the so-called nitrogen mustards it soon became apparent that neither the necessary volatility nor vapor pressure data for assessing these agents were available. The first member of this group of 2-chloroethylamines to be prepared, and its potent vesicant action described, was tris-(2-chloroethyl)-amine.[4] However, no vapor pressure data were given nor were any subsequently reported. It was, therefore, necessary to measure the volatility before any quantitative evaluation of these compounds could be made. In the course of this study the volatility and vapor pressure were determined for ten substituted 2-chloroethylamines at temperatures between 0 and 60°. Their numerical values are reported here.

The method employed for measuring the volatility and the equations by which the vapor pressure was calculated from the volatility have been described in two earlier reports.[5] The equations derived for these compounds should not be used at temperatures much outside the specified range without recognizing that the values so computed may have errors considerably larger than the probable error over the 0 to 60° interval.

Experimental

The details of the measurements and the apparatus have been given in earlier reports.[5]

All the compounds employed in this study were prepared in laboratories other than that of the authors. The source of each compound is given in Table I. All but one of the 2-chloroethylamines were received as the hydrochlorides, well crystallized compounds of definite, reproducible melting point, which could be readily purified by crystallization from suitable solvents. These hydrochlorides were usually received in an analytically pure form and were stored in a cool, dry place until they were used. Each hydrochloride was converted into the free base by treatment with a cold 50% aqueous solution of potassium hydroxide. Where practical the base was separated from the aqueous solution without use of any solvent; when the amine phase would not separate cleanly from the aqueous phase the former was diluted with ethyl ether before separation. The amines were dried over anhydrous potassium carbonate before distillation. The dry amine was distilled under reduced pressure, the pressure being so chosen that the amine boiled below 100° in all but two cases (see Table I). For eight of the ten amines the boiling point was constant; for *t*-butyl-bis-(2-chloroethyl)-amine a one degree boiling range was tolerated, and for 4-(2-chloroethyl)-morpholine the sample submitted was too small to purify before use and was therefore run as received.

Since these amines slowly give self-condensation products, especially when not completely dry, they were placed in the vaporizer immediately after distillation and

(1) This work was carried out under contract with the National Defense Research Committee of the Office of Scientific Research and Development.

(2) Present address: 770 S. Arroyo Parkway, Pasadena 2, Calif.

(3) Present address: 622 N. East Ave., Oak Park, Ill.

(4) Ward, THIS JOURNAL, **57**, 914 (1935).

(5) (a) Bent and Francel, *ibid.*, **70**, 634 (1948); (b) Redemann, Chaikin and Fearing, *ibid.*, **70**, 631 (1948).

TABLE I

CONSTANTS OF THE SAMPLES OF THE TEN 2-CHLOROETHYLAMINES USED AND PRECISION OF DATA

Amine	Boiling point °C.	Mm.	Refractive index, n_D	Density G./cc.	°C.	Constants A	A'	B	Percentage deviation from smoothed curve of points calcd. from least sq. equation Maximum	Mean	L_{ev}, Cal./mole
$R—N(C_2H_4Cl)_2$											
Ethyl[a]	85.5	12	1.4653[d]	1.0861	23	9.01892	12.45482	2868.9	1.71	0.97	13,100
n-Propyl[a]	96	10		1.05929	23.3	9.01884	12.47955	2966.7	1.76	.56	13,600
n-Butyl[a]	106.3	9		1.0365	25	9.28361	12.78578	3169.8	2.7	.57	14,500
Isobutyl[a]	79	2		1.0328	20	9.42242	12.92461	3152.5	0.22	.17	14,400
s-Butyl[a]	100	7.5		1.0455	25	9.16684	12.66901	3109.5	.42	.16	14,200
t-Butyl[a]	71–72	2		1.0484	22	9.13430	12.63649	3050.9	.26	.11	14,000
Cyclohexyl[a]	103[c]	1	1.4944[d]	1.0964	21	8.60897	12.16478	3258.8	.49	.28	15,000
2-Chloroethyl[a]	94	1	1.4925[e]	1.2093	25	9.41621	12.92221	3393.4	.54	.31	15,500
4-(2-Chloroethyl) morpholine[b]				1.1062	22	8.91971	12.29993	2808.7	1.59	1.48	12,900
bis-(2-Chloropropyl) methylamine[a]	56	2	1.458[f]	1.0381	21.5	8.99698	12.46728	2850.4	2.70	1.74	13,000

[a] Prepared in the laboratory of Dr. G. H. Coleman. [b] Supplied by Dr. M. S. Kharasch. Quantity too small for further purification. Fifteen per cent. had to be evaporated before a constant volatility was reached. [c] Melting point, −3°. [d] 25°. [e] 25.2°. [f] 21°.

were run as promptly as feasible. When there was evidence of self-condensation having occurred during a determination, as shown by the separation of a solid quaternary ammonium salt (see Discussion), the vaporizer unit was cleaned and filled with freshly distilled amine before continuing the measurements.

Dry nitrogen was used as the entrainment gas to avoid possible oxidation of the compounds. The values for the boiling point, refractive index and density of the samples of the compounds studied are given in Table I.

Discussion

This series of compounds presented certain difficulties which were not encountered in our previous studies.[5b,6] The chlorine atom in the β-position to the amino group, while not highly reactive, still shows sufficient activity to react slowly at room temperature with the amino group in an adjacent molecule. Since the amines studied in this series are all tertiary amines, reaction with the β-halogen of an adjacent molecule leads to the production of a quaternary ammonium compound. In these cases the quaternary ammonium chlorides are very sparingly soluble and were observed to crystallize from the reaction mixture. The insolubility of the salts was helpful for two reasons, first, it served as an index of the amount of polymerization which had taken place and, second, the solubility proved to be so low that it did not alter the vapor pressure measurably, as shown by the fact that volatilities measured for samples free from polymer agreed within experimental error with volatilities measured upon samples with some crystalline polymer. Nevertheless, a vigorous effort was made to make measurements only upon samples free from any solid polymer.

It was also observed that much longer time of contact was necessary in order to produce equilibrium between the liquid and its vapor with this group of compounds than was found for any other group of compounds studied. Consequently, for most of these runs the rate of flow of the nitrogen through the saturator was reduced 50 to 75% over the values used for other compounds of similar boiling point.

In Table I are recorded, in addition to the previously mentioned properties, the three constants A, A', and B for the equations

$$\log p = A - B/T \quad (1)$$

$$\log WT = A' - B/T \quad (2)$$

computed by the method of least squares from the experimental points and also the percentage deviation from the smoothed curve of the points calculated from the least squares equation. The constants apply when the pressure, p, is expressed in millimeters of mercury, the temperature, T, is the centigrade temperature plus 273.2 and the volatility, W, is expressed in milligrams of agent per liter of air (or nitrogen). An average value for the molar heat of evaporation, L_{ev}, in calories per mole over the temperature range 0 to 60° is also given for each compound. These values were calculated from equation (1).

The mean percentage deviation of the *experimental* points from the smoothed curve is under 2% for all compounds except cyclohexyl-*bis*-(2-chloroethyl)-amine which has a mean deviation of 5.4%. This arises from the very small volatility of this compound, since the amine collected for weighing was only about 5 mg. at the lowest temperature.

Acknowledgment.—Thanks are due to Miss Dora Benedict for her helpful work in making some of these measurements.

(6) Redemann, Chaikin, Fearing and Benedict, THIS JOURNAL, 70, 637 (1948).

Summary

1. The volatility of ten substituted 2-chloroethylamines has been measured between 0 and 60° by an air saturation method.

2. From the measured volatilities vapor pressures have been calculated. Logarithmic equations have been developed for both the vapor pressure and the volatility as a function of the temperature.

3. The mean molar latent heat of evaporation over the temperature range 0 to 60° has been computed from the vapor pressure equation for each compound.

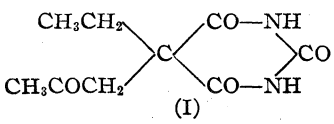
CHICAGO 37, ILLINOIS RECEIVED DECEMBER 5, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

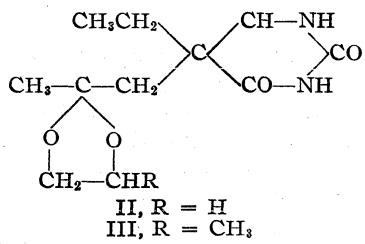
Cyclic Acetals Related to Ethylacetonylbarbituric Acid

BY CHARLES D. HURD AND MARGARET L. MCAULEY

This investigation deals with the synthesis and reactions of certain new derivatives of ethylacetonylbarbituric acid (I). This acid was synthesized from sodium ethylbarbiturate and chloroacetone, instead of the previously used[1] bromoacetone. To use chloroacetone, it was found that sodium iodide was an effective catalyst.[2] Yields of 75% of I were obtained with this catalyst as contrasted with 10–32% yields without it. Butylacetonylbarbituric acid was similarly prepared and with the same high yield. In view of this, it is of interest to note that no significant reaction product could be obtained when solutions of sodium ethylbarbiturate, 2-chloromethyl-2-methyldioxolane (made from chloroacetone and ethylene glycol), and sodium iodide were mixed and treated similarly. Ethyl *sodio*-butylmalonate also failed to give a reaction product with 2-chloromethyl-2-methyldioxolane at refluxing temperature in alcohol solution.



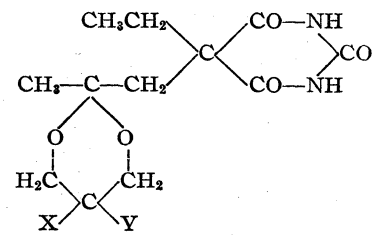
(I)



II, R = H
III, R = CH_3

Dioxolanes of the structure II or III were synthesized by reaction of ethylacetonylbarbituric acid with ethylene glycol or propylene glycol in the presence of *p*-toluenesulfonic acid. The water formed in the reaction was removed as formed by slowly distilling benzene or toluene from the reaction mixture. The compounds formed were high melting, crystalline solids.

1,3-Dioxanes represented by formula IV, V were synthesized similarly from I by reaction with trimethylene glycol or tris-(hydroxymethyl)-nitromethane. These compounds all melt above 200°. Conditions were not found for satisfactory interaction of (I) and 2-nitro-2-methyl-1,3-propanediol.



IV (X = Y = H)
V (X = NO_2, Y = CH_2OH)
VI (X = NH_2, Y = CH_2OH)
VII (X = NHAc, Y = CH_2OH)

The nitro group in 5-ethyl-5-(1-methyl-4-nitro-4 - hydroxymethyl - 2,6 - dioxacyclohexyl)-methylbarbituric acid (V) was readily reduced at 100° to an amino group under a hydrogen pressure of 1600 lb./sq. in., using Raney nickel catalyst The amine (VI) is moderately soluble in water. In accordance with its dipolar ion character, it is insoluble in non-polar solvents. Conditions were not found for the acetylation of this amine by acetic anhydride, but acetylation to VII was achieved readily by the use of ketene.

We are indebted to Edgar B. Carter, Lucy Johnson and G. M. Everett of Abbott Laboratories for pharmacological tests made on the above compounds. These compounds were tested: II, III, IV, butylacetonylbarbituric acid (VIII), and acetonylbarbituric acid (IX). The compounds were non-toxic toward mice by intravenous injection in doses of 50 to 200 mg./kg., but such doses produced no hypnotic effect. To test anticonvulsant activity, mice were given 400 mg./kg. orally and after various periods of time were tested with 100 mg./kg. of metrazol with results shown in Table I.

It is seen that all except IX show some anticonvulsant action. Compound III was tested further with oral doses of 500 mg./kg. After periods of 10, 30, 60, 120 minutes, 100 mg./kg. of metrazol was given. All mice showed jerks and approximately half showed convulsions after all

(1) (a) Kirsanov and Ivashchenko, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1576 (1938); (b) Dox and Houston, THIS JOURNAL, **46**, 252 (1924).

(2) Hurd and Perletz, *ibid.*, **68**, 38 (1946).

TABLE I

ANTICONVULSANT ACTIVITY

Conv. = convulsions. Conv. F = convulsions with some fatalities

Compound	15 min.	30 min.	60 min.
II	Conv. F	Jerks, conv.	Jerks
III	Conv.	Jerks	Jerks, conv.
IV	Conv. F	Jerks	Jerks
VIII	Conv.	Jerks	Jerks, conv.
IX	Conv. F	Jerks, conv. F	Jerks, conv. F

time intervals. The protection against the minimum convulsant dose (75 mg./kg. of metrazol) was also unsatisfactory. All test animals had jerks and three out of six had convulsions.

Experimental

Ethylacetonylbarbituric Acid.—For this synthesis, ethylbarbituric acid of m. p. 193–194° was prepared in accordance with the method of Fischer and Dilthey[3] except for the modification of not separating the sodium ethylbarbiturate. Instead, water was added to dissolve it, then the free acid was precipitated by adding concentrated hydrochloric acid and chilling. The yield was 83%, in contrast to the reported yield of 45%.

A solution of 72.2 g. of ethylbarbituric acid, 40 ml. of alcohol and 900 ml. of 0.5 *N* sodium hydroxide was adjusted to neutrality to litmus. It was stirred vigorously while a mixture of 91 ml. of chloroacetone, 10 g. of sodium iodide and 300 ml. of alcohol was added rapidly. After a half hour of refluxing, the solvents were removed at 40 mm. pressure, thereby causing separation of a solid which was collected, washed with a little water, and dried; yield, 81.6 g., or 74.6%. The m. p. was 237–238°, agreeing with 238–239° listed in the literature.[1]

When 2.5 g. of sodium iodide was used instead of 10 g. the yield was about the same, but when longer or shorter reaction times were taken, the yield dropped. The yield was about 50% with either ten minutes or one hour of refluxing, and the yield dropped to 39% with two hours of refluxing.

If no sodium iodide was present, the yield changed progressively from 10 to 32% with a refluxing change from thirty minutes to two hours. The yield was no better using the method of Dox and Houston.[1b]

Butylacetonylbarbituric Acid.—Substitution of butylbarbituric acid for ethylbarbituric acid in the above preferred procedure (use of sodium iodide and thirty minutes of refluxing) gave rise to a 75% yield of butylacetonylbarbituric acid. Kirsanov and Ivashchenko[1] used bromoacetone (no sodium iodide) and reported yields of 50–70%.

Ethyl Acetonylmalonate.—This compound has been made previously from bromoacetone.[4] The present synthesis uses chloroacetone.

To a suspension of 15 g. of finely divided sodium in 500 ml. of dry ether was added 33 ml. of absolute alcohol. After twelve hours, when hydrogen was no longer evolved, 99 ml. of ethyl malonate was added, followed by slow addition of a solution of 52 ml. of chloroacetone in 90 ml. of dry ether. Three hours later the mixture was filtered and the filtrate distilled, thereby recovering 59 g. of ethyl malonate and obtaining 32.5 g. of ethyl acetonylmalonate, b. p. 110–111° (2 to 4 mm.). This is a 61% yield, based on unrecovered malonic ester.

Black tarry materials resulted from the interaction of ethyl acetonylmalonate with ethyl iodide in the presence either of anhydrous potassium carbonate, or dimethylaniline, or sodium ethoxide solutions at refluxing temperatures. About half of the ethyl acetonylmalonate was recovered. Likewise, no ethyl butylacetonylmalonate was obtained starting with ethyl butylmalonate, chloroacetone, and refluxing sodium ethoxide solution.

Reaction of Ethylacetonylbarbituric Acid (I) with Glycols.—This general procedure was followed. Five to fifteen grams of (I) was taken for each run. For each mole of (I) there was added 1.3 moles of the glycol and 0.1 g. of *p*-toluenesulfonic acid. Then 120–250 ml. of benzene or toluene was added. The apparatus was set for distillation with an automatic separator for the hydrocarbon and water in the distillate, the hydrocarbon layer being continuously returned to the flask. Reaction proceeded for about fifty hours. The products were then separated and purified by crystallization. Usually a little of the (I) was recovered. Yields were in the range of 61–69%, based on unrecovered (I). 2-Nitro-2-methyl-1,3-propanediol was the only glycol tested which failed to react, and 83% of I was recovered.

5-Ethyl-5-(1-methyl-2,5-dioxacyclopentyl)-methylbarbituric acid (II), 5-ethyl-5-(1,3-dimethyl-2,5-dioxacyclopentyl)-methylbarbituric acid (III), and 5-ethyl-5-(1-methyl-2,6-dioxacyclohexyl)-methylbarbituric acid (IV) were made, respectively, using ethylene glycol, propylene glycol, and trimethylene glycol. These compounds were purified by crystallization from benzene, then from water. Analytical data and properties are listed in Table II. Analyses were by the micro Dumas method, by T. S. Ma.

TABLE II

Compound	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
II	216–217	$C_{11}H_{16}N_2O_5$	10.94	10.37
III	202–204	$C_{12}H_{18}N_2O_5$	10.37	10.27
IV	264–265	$C_{12}H_{18}N_2O_5$	10.37	10.24
V	239–240, dec.	$C_{13}H_{19}N_3O_8$	12.17	12.23
VI	236–237, dec.	$C_{13}H_{21}N_3O_6$	13.33	12.78
VII	231–232, dec.	$C_{15}H_{23}N_3O_7$	11.80	11.25

That compounds II and I form a eutectic, m. p. 191–192°, may be demonstrated simply by crystallization of a mixture of equal amounts of the pure ingredients from water.

Tris-(hydroxymethyl)-nitromethane was the glycol used in the synthesis of 5-ethyl-5-(1-methyl-4-nitro-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric acid (V). The crude reaction product was washed thoroughly with water and then crystallized from water. A mixture of I (m. p. 237–238°) and V melts at 213–216°. Since I melts without decomposition whereas V blackens and evolves gas on fusion, it is easy to distinguish one from the other in spite of the close melting points. The solubility in water is another difference, since 0.2 g. of I or V require 5.5 and 14.6 cc., respectively, of boiling water for solution.

5-Ethyl-5-(1-methyl-4-amino-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric Acid (VI), by Reduction of V.—Two catalytic reductions of V (3.5, 6.4 g.) in purified dioxane (20 ml.) at 1600 lb./sq. in. of hydrogen pressure with Raney nickel catalyst (0.2, 1.0 g.) at 100–125° gave rise to 55–58% of amine (VI). Thirty minutes was required for the calculated drop in pressure. The product was crystallized from dioxane or from equal parts of dioxane and ethyl acetate. To dissolve 0.2 g. of VI in boiling water, 14.6 ml. is required, thus showing the same solubility as V.

Reaction with Ketene.—A stream of ketene was bubbled at the rate of 0.47 mole per hour for five minutes into a warm solution of 1.4 g. of VI in 100 ml. of water. On cooling, 0.64 g. of 5-ethyl-5-(1-methyl-4-acetamido-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric acid (VII) separated. From the filtrate, 0.56 g. of VI was recovered. The amide was crystallized from water. This material depressed the m. p. of I and VI. It dissolved readily in dilute sodium hydroxide. Hydrolysis by boiling dilute hydrochloric acid (ten minutes) gives rise to I, m. p. and mixed m. p. 239–240°.

(3) Fischer and Dilthey, *Ann.*, **355**, 334 (1908).

(4) Gault and Salomon, *Compt. rend.*, **174**, 754 (1922); *Ann. chim.*, **2**, 133 (1924).

No evidence for the acetylation of VI was obtainable, using acetic anhydride in pyridine or in glacial acetic acid. Also V was unacetylated by treatment with acetic anhydride and sodium acetate at 100°.

Summary

Ethylacetonylbarbituric acid may be made in good yields from sodium ethylbarbiturate and chloroacetone in the presence of a little sodium iodide. Several cyclic acetals were prepared by reaction of ethylacetonylbarbituric acid with glycols, including a nitro glycol. The nitro acetal was hydrogenated to an amino acetal, and the latter was acetylated with ketene to an acetamido acetal. Pharmacological toxicity data and anticonvulsant tests are included.

EVANSTON, ILLINOIS RECEIVED DECEMBER 8, 1947

NOTES

Amide Vinylogs

BY ROBERT H. BAKER AND ARTHUR H. SCHLESINGER[1]

In a survey of the behavior of ethoxymethylenediketones and esters as alkylating agents toward amines, amides, the Grignard reagent and in Friedel–Crafts and other type reactions some new compounds have been encountered and are described below.[2]

Ethoxymethyleneacetoacetic ester reacts readily with aminoacetic ester and with progressive difficulty with *p*-aminobenzoic ester and urethan to produce open chain amide vinylogs which are cleaved by hydrogen (PtO_2, 2 atm., 25°) as are derivatives of typical amines.[3] Thiourea reacts to form the mercaptopyrimidine similar to the cyclization product of the urea derivatives.[3]

Experimental[4]

Ethyl α-(N-Carbethoxyaminomethylene)-acetoacetate.—Equimolar quantities of ethyl ethoxymethyleneacetoacetate and ethyl carbamate were heated at 143–165° for 1.7 hours and then cooled at 0° for three hours to induce crystallization. Three crystallizations from cyclohexane, employing activated alumina as decolorizing agent, produced yellow needles, m. p. 40.5–41.0°; 13% yield.

Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.3; H, 6.55; N, 6.11. Found: C, 52.4; H, 6.90; N, 6.10.

Ethyl α-(*p*-Carbethoxyanilinomethylene)-acetoacetate.—This was produced similar to the above from ethyl *p*-aminobenzoate at 110–135° for one hour. It was decolorized in hot ethanol solution by alumina. Five crystallizations from ethanol, then from cyclohexane and finally ethanol gave colorless crystals, m. p. 105°, 70% yield.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 63.0; H, 6.26; N, 4.60. Found: C, 63.2; H, 6.50; N, 4.50.

Ethyl α-(N-Carbethoxymethylaminomethylene)-acetoacetate.—Slow addition of freshly distilled glycine ethyl ester to an equivalent of the ethoxymethylene compound at 0° produced a vigorous reaction, and the contents of the reaction flask were solid within thirty minutes. Two crystallizations from 70% ethanol gave matted colorless needles, m. p. 71.0–71.5°; 66% yield.

Anal. Calcd. for $C_{11}H_{17}NO_5$: C, 54.4; H, 7.00; N, 5.76. Found: C, 55.2; H, 7.15; N, 5.58.

Ethyl 2-Mercapto-4-methylpyrimidine-5-carboxylate.—Thiourea and an equivalent of the ester vinylog were heated at 150° for thirty minutes. The mixture frothed vigorously and a hard, red solid was obtained which was purified by digestion on the steam-bath with ethanol. The liquors upon chilling gave a red powder which was treated three more times in a similar manner. The red product, 52% yield, failed to melt but sintered at 160° and decomposed. Sublimation *in vacuo* failed to improve its appearance. It is soluble in 10% sodium hydroxide solution and decolorizes iodine.

Anal. Calcd. for $C_8H_{10}N_2O_2S$: N, 14.10. Found: N, 13.94.

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED SEPTEMBER 12, 1947

(1) Allied Chemical and Dye Corporation Fellow, 1946–1947.

(2) Except toward amines the results were largely of a negative nature and cannot be published here, *cf.* A. H. S., Ph.D. Thesis, 1947.

(3) Baker and Schlesinger, THIS JOURNAL, 68, 2009 (1946).

(4) Microanalyses by Patricia Craig and Nelda Mold.

Some Quaternary Ammonium Salts of Substituted Thiazoles

BY CARL T. BAHNER, DONALD PICKENS[1] AND DOROTHY BETTIS BALES[2]

The biological results obtained by Shear and associates[3] at the National Cancer Institute using quaternary salts derived from pyridine and its homologs and benzologs have led us to prepare similar quaternary salts containing the thiazole ring. Particular interest attaches to this series in view of the fact that thiamin chloride is a quaternary salt containing this ring. The substituted thiazoles which we have used are 4-methyl-2-β-hydroxyethylthiazole, 2,4-dimethylthiazole, 2-ethyl-4-methylthiazole, 4-methylthiazole, benzothiazole, and 2-methylbenzothiazole. These have been caused to react with phenacyl and substituted phenacyl bromides and with phenylethyl and cyclohexylethyl halides. Most of these bases reacted with the phenacyl bromides readily upon

(1) Present address: Department of Chemistry, University of Tennessee, Knoxville, Tennessee.

(2) Present address: Jefferson City High School, Jefferson City, Tennessee.

(3) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.; Hartwell and Kornberg, THIS JOURNAL, 68, 1131 (1946).

TABLE I

Salt from benzothiazole and	Empirical formula	M. p.,[a] °C.	Yield, %	Ionic halogen, % Calcd.	Found
β-Cyclohexylethyl bromide	$C_{15}H_{20}NSBr$	181	40	26.80	26.75
p-Iodophenacyl bromide	$C_{15}H_{11}NSOBrI$	249–254 dec.	60	17.34	17.26
Phenacyl bromide	$C_{15}H_{12}NSOBr$	244 dec.	65	23.93	24.07[b]
Phenacyl bromide oxime[c]	$C_{15}H_{13}N_2SOBr$	197	30		
β-Phenylethyl iodide	$C_{15}H_{14}NSI$	176	45	34.56	34.39
p-Phenylphenacyl bromide	$C_{21}H_{16}NSOBr$	248	50	19.49	19.57
2,4-Dimethylthiazole and					
β-Cyclohexylethyl bromide	$C_{13}H_{22}NSBr$	193	35	26.25	26.09
p-Iodophenacyl bromide	$C_{13}H_{13}NSOBrI$	227 dec.	55	18.25	18.25
Phenacyl bromide	$C_{13}H_{14}NSOBr$	235[d]	60	25.60	25.57
β-Phenylethyl iodide	$C_{13}H_{18}NSI$	233	45	36.70	36.66
2-Ethyl-4-methylthiazole and					
p-Bromophenacyl bromide oxime	$C_{14}H_{16}N_2SOBr_2$	215–222 dec.	50	19.02	18.80
p-Iodophenacyl bromide oxime	$C_{14}H_{16}N_2SOBrI$	206–212 dec.	50	17.11	16.98
p-Methylphenacyl bromide	$C_{15}H_{18}NSOBr$	142	45	23.49	23.20
m-Nitrophenacyl bromide	$C_{14}H_{15}N_2SO_3Br$	200–215 dec.	70	21.53	21.31
2-Methylbenzothiazole and					
β-Phenylethyl iodide	$C_{16}H_{16}NSI$	195	60	33.29	33.24
4-Methyl-5-β-hydroxyethylthiazole and					
p-Iodophenacyl bromide	$C_{14}H_{15}NSO_2BrI$	242 dec.	45	17.07	17.18
Phenacyl bromide	$C_{14}H_{16}NSO_2Br$	172–173	55	23.35	23.34
β-Phenylethyl iodide	$C_{14}H_{18}NSOI$	160	30	33.83	33.73
4-Methylthiazole and					
β-Cyclohexylethyl bromide	$C_{12}H_{20}NSBr$	155	70	27.54	27.48
p-Iodophenacyl bromide	$C_{12}H_{11}NSOBrI$	228–235 dec.	70	18.85	18.85
p-Iodophenacyl bromide oxime	$C_{12}H_{12}N_2SOBrI$	202 dec.	40	18.20	18.20
m-Nitrophenacyl bromide	$C_{12}H_{11}N_2SO_3Br$	231–232 dec.	60	23.29	23.25
Phenacyl bromide	$C_{12}H_{12}NSOBr$	211	90	26.80	26.75

[a] Melting points below 200° are corrected. Others are uncorrected. [b] Also analyzed for C and H by Dr. Carl Tiedcke. Calcd.: C, 53.89; H, 3.59. Found: C, 53.78; H, 3.72. [c] Made by treating phenacylbenzothiazolium bromide with hydroxylamine hydrochloride, a method which gave a very small yield, and also in better yield by mixing benzothiazole with phenacyl bromide oxime prepared by the method given by Korten and Seboll for obtaining the *syn*-form; *Ber.*, **34**, 1907 (1901). On account of difficulty in carrying out a Volhard analysis on this particular compound a Kjeldahl nitrogen analysis was made by Marvel Fielden. Calcd.: N, 8.02. Found: N, 7.91. [d] A melting point of 216° was reported for this compound, crystallized from a different solvent by Kondo and Nagasawa, *J. Pharm. Soc. Japan*, **57**, Abstracts, 308–310 (1937).

heating to 100° for about five minutes, using a small amount of chloroform or ethanol as solvent in those cases where the starting materials alone did not form a homogeneous liquid at 100°, but the benzothiazole and 4-methyl-2-β-hydroxyethylthiazole reacted somewhat more slowly. The phenylethyl and cyclohexylethyl halides were much less reactive and were usually heated with the base three or four days at 100° in a sealed tube. Some substituted benzothiazoles, such as 2-chlorobenzothiazole, 2-methylmercaptobenzothiazole, and 2-phenylbenzothiazole gave little or no crystalline quaternary salt on heating with phenacyl bromide.

The quaternary salts obtained were purified by recrystallization from ethanol and the ionic halogen content determined by Volhard analysis. (Hartwell and Kornberg[4] had found that some compounds which gave satisfactory combustion analyses held the halogen in non-ionic form and appeared not to be the expected quaternary salts.)

(4) Hartwell and Kornberg, THIS JOURNAL, **68**, 868 (1946).

Samples of the salts listed in Table I have been submitted to the National Cancer Institute for testing. Results of the screening tests will be taken into account in planning further syntheses in this series.

Intermediates.—Phenacyl bromide, *p*-bromophenacyl bromide, *p*-phenylphenacyl bromide, β-cyclohexylethyl bromide, benzothiazole, 2-methylmercaptobenzothiazole, 2-phenylbenzothiazole, 2-chlorobenzothiazole, and 2-methylbenzothiazole were purchased from Eastman Kodak Company and phenylethyl iodide from Edcan Laboratories. The 4-methyl-2-β-hydroxyethylthiazole was furnished by Merck and Company. The other halides used were prepared in the usual way by halogenation of the corresponding methylaryl ketones or by the Friedel–Crafts reaction of bromoacetyl bromide with the proper substituted aromatic hydrocarbon. The other substituted thiazoles were made by the method of Schwarz.[5]

(5) W. E. Bachmann, "Organic Syntheses," Vol. XXV, John Wiley and Sons, New York, N. Y., 1945, p. 35.

Acknowledgment.—The authors are pleased to acknowledge their indebtedness to Dr. M. J. Shear, Dr. Jonathan L. Hartwell, and Dr. Albert J. Dalton for valuable suggestions and encouragement, to Merck and Company for the supply of 4-methyl-2-hydroxyethylthiazole, and to the National Cancer Institute for a grant-in-aid in support of this work.

CONTRIBUTIOM FROM THE
DEPARTMENT OF CHEMISTRY OF
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN. RECEIVED DECEMBER 3, 1947

Density Data for Two Methylchlorosilanes

BY E. W. BALIS, W. F. GILLIAM, E. M. HADSELL, H. A. LIEBHAFSKY AND E. H. WINSLOW

Density data for dimethyldichlorosilane (DDS) and for methyltrichlorosilane (MTS), which were used several years ago to lay the foundation for a successful routine method to aid in controlling chlorosilane distillation, are given below. There appear to be no comparable earlier published data.

Pure Compounds.—As a by-product of painstaking distillation work done in 1943, the details of which are to be published later, the following densities (g./ml. at 25°) were obtained on chlorosilanes among the purest ever prepared here: for DDS, 1.0663; for MTS, 1.2691. The corresponding weight percentages of chlorine by hydrolysis were: DDS, 54.93 *vs.* 54.95 (theor.); MTS, 71.19 *vs.* 71.17 (theor.), the deviations from the theoretical being comparable with the possible uncertainty in the atomic weight of silicon.[1]

Temperature Coefficients.—For the interval 25–30°, dilatometric measurements on the best materials available from the pilot plant in 1944[2] yielded the following values for the change in density with temperature (g./ml./°C.): DDS, 0.00145; MTS, 0.00173. These precise results are in good agreement with older data (0.0015 and 0.0018, respectively) obtained on a Westphal balance.

The 50-ml. dilatometer was designed and manipulated to give a precision better than 0.005% in a density determination. Special techniques were required to mitigate the difficulty of handling the methylchlorosilanes, and the dilatometer itself did not change weight by more than a few tenths milligram—if at all—during the measurements.

Volume Additivity.—In order to establish whether any volume change on mixing DDS and MTS is negligible for purposes of routine control, the routine density-balance (to be described elsewhere) was used on DDS[2] and MTS[2], and on six solutions carefully prepared by weight therefrom. The measured densities are given in Table I alongside densities calculated for the solutions on the assumption of volume additivity.

TABLE I

VOLUME ADDITIVITY OF DDS AND MTS AT 27°

Weight fraction DDS	Measured densities, g./ml.	Calculated densities, g./ml.
MTS	1.2593	....
DDS	1.0618	....
0.81450	1.0939	1.0936
.66014	1.1217	1.1216
.42930	1.1665	1.1662
.42930	1.1659	1.1662
.29397	1.1940	1.1940
.14036	1.2275	1.2273

The measured densities tend to exceed those calculated by an amount comparable with the experimental error; consequently, volume additivity could permissibly be assumed in the control work. The data in Table I indicate that this pair of methylchlorosilanes belongs among those for which volume additivity comes closest to being realized, which suggests that a thorough investigation of these and other chlorosilanes along lines laid down by Young[3] would be welcome.

(1) Baxter, Guichard and Whytlaw-Gray, THIS JOURNAL, **69**, 731 (1947). The chlorine titrations were not of atomic weight precision. Correction of the final average chlorine contents for all conceivable sources of error would lower the percentages by 0.02; taking 28.10 as the atomic weight of silicon would produce the same change in the theoretical values. The density data have been corrected for all conceivable sources of error.

(2) The methylchlorosilanes used in the work on temperature coefficients and volume additivity were sufficiently pure for these purposes as the following data show. DDS, density at 25°, 1.065 g./ml.; wt. % Cl by hydrolysis, 54.72, 54.64. MTS, density at 25°, 1.263 g./ml.; wt. % Cl by hydrolysis, 70.64, 70.69.

(3) Young, "Distillation Principles and Processes," Macmillan and Co., Limited, London, England, 1922, pp. 31 *et seq.*

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, NEW YORK RECEIVED DECEMBER 17, 1947

p-Bromobenzyl Bromide in the Identification of Some Aromatic Carboxylic Acids

BY B. A. FIEKERS AND E. M. DI GERONIMO

As part of a study of suitable derivatives for the identification of organic acids, *p*-bromobenzyl esters of benzoic acid, some of its derivatives and similar acids have been prepared and characterized in this Laboratory. The general preparation of these esters is given by the equation.

$$p\text{-BrC}_6\text{H}_4\text{CH}_2\text{Br} + \text{NaOCOR} \longrightarrow \text{NaBr} + p\text{-BrC}_6\text{H}_4\text{CH}_2\text{OCOR}$$

Experimental

***p*-Bromobenzyl Bromide.**—This was prepared from *p*-bromotoluene by bromination of the side-chain, using ultraviolet light, quartzware and heat.[1] The solid product was purified by recrystallization from alcohol until a constant melting point (61.5°) was obtained.

Preparation of the Esters.—The sodium salt of the acid was formed by dissolving a slight excess of the acid in 5 ml. of 0.5 *M* sodium carbonate solution. The mixture was refluxed on a steam-bath and water was added sparingly, when necessary, until solution was complete. 1.25 g.

(1) Weizmann and Patai, THIS JOURNAL, **68**, 150 (1946).

(0.005 mole) of *p*-bromobenzyl bromede and 10 ml. of 95% ethyl alcohol were then added and the mixture was refluxed. The refluxing was continued for an hour after the solution had again cleared. When necessary, more alcohol was added in order to bring the reagent into solution. The solution was then cooled rapidly in a stream of cold water and finally in an ice mixture. The esters were filtered and recrystallized from alcohol until constant melting points were obtained. Departures from this general procedure are noted in Table I. All given temperatures are uncorrected.

Analysis.—The Parr bomb was used in conjunction with the Volhard titration method.

TABLE I

p-BROMOBENZYL ESTERS OF SOME AROMATIC CARBOXYLIC ACIDS

Acid	Obs., m. p., °C. Acid	Ester	Halogen, % Calcd. Ester	Found Ester
Benzoic	122	45	27.47	27.54
o-Hydroxybenzoic	159	71	26.04	26.20
m-Hydroxybenzoic	201	97[a]	26.04	26.10
p-Hydroxybenzoic	213	146	26.04	26.04
o-Nitrobenzoic	147	69	23.79	23.87
m-Nitrobenzoic	141	114	23.79	23.90
p-Nitrobenzoic	242	121	23.79	23.93
Cinnamic	133	79[b,d]	25.21	25.29
o-Nitrocinnamic	240	98[c,d]	22.08	22.19
p-Nitrocinnamic	286	136[d]	22.08	22.24
o-Toluic	104	46	26.25	26.33
m-Toluic	109	Oil		
p-Toluic	179	72[e]	26.25	26.29
o-Chlorobenzoic	142	57	35.47	35.59
Anisic	184	95	24.89	25.01

[a] Crystallized with partial evaporation. [b] 5 ml. excess of water required to dissolve the salt. [c] Potassium salt of the acid was prepared from potassium carbonate. [d] Acetone replaced alcohol as solvent for this reaction. [e] Slightly more than 5 ml. excess of water required to dissolve the salt.

Acknowledgment.—The authors are pleased to acknowledge an experimental survey of this problem done by J. Benotti under the direction of T. L. Kelly.

DEPARTMENT OF CHEMISTRY
COLLEGE OF THE HOLY CROSS
WORCESTER 3, MASS. RECEIVED DECEMBER 19, 1947

cis and *trans* Forms of β-(*p*-Chlorophenyl)-cinnamic Acid

BY REYNOLD C. FUSON AND HAROLD L. JACKSON

In view of results communicated to us privately by Dr. F. Bergmann,[1] we have modified the procedure of Alexander, Jacoby and Fuson[2] for the preparation of β-(*p*-chlorophenyl)-cinnamic acid by the Reformatsky method and have been able to isolate the acid in *cis* and *trans* modifications.

In the revised procedure 5 g. of crude ethyl β-phenyl-β-(*p*-chlorophenyl)-β-hydroxypropionate, made by the method of Alexander, Jacoby and Fuson,[2] was heated under reflux for two hours with 50 ml. of glacial acetic acid and 25 ml. of acetic anhydride. The acetic acid and acetic anhydride were removed by distillation at the aspirator. The residue was distilled under 1–2 mm. pressure, and the product that distilled between 65 and 69° was collected.

This distillate was treated with 10 g. of sodium hydroxide dissolved in 20 ml. of water and 10 ml. of ethanol. The alkaline hydrolysis mixture was heated under reflux for twenty hours. When the cooled solution was poured into 100 ml. of cold water, a white crystalline solid precipitated. The mixture was made acid with dilute hydrochloric acid. The product melted over a range of 140 to 157°; yield, 3.4 g. Fractional crystallization of this product from dilute ethanol yielded two isomers; one melted at 164.8–165.7° and the other at 173.0–173.8°. Mixed melting point determinations with samples, kindly supplied by Dr. Bergmann, showed these acids to be identical with his low-melting and high melting compounds.

Infrared absorption spectra[3] indicated that the two forms were *cis* and *trans* isomers. The presumption that the low-melting isomer was the *cis* modification was supported by the observation that it was more soluble in diethyl ether than the high-melting isomer.

From these results it appears that the compound described by Alexander, Jacoby and Fuson[2] and melting at 168° must have been an impure sample of the *trans* acid, the contaminant being presumably the *cis* isomer.

(1) See Bergmann, THIS JOURNAL, **70**, 1612 (1948).
(2) Alexander, Jacoby and Fuson, *ibid.*, **57**, 2208 (1935).
(3) Infrared absorption spectra were determined by Mrs. J. L. Johnson.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS RECEIVED FEBRUARY 16, 1948

2-Benzofuryllithium and 3-Benzofuryllithium

BY HENRY GILMAN AND DONALD S. MELSTROM

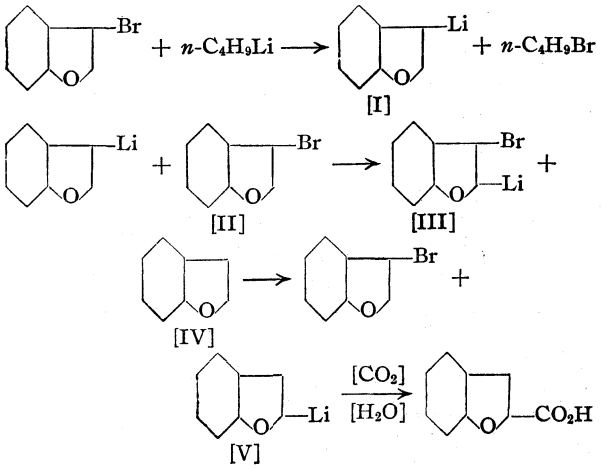
2-Bromobenzofuran does not react with magnesium, under conventional conditions, to give a Grignard reagent.[1] However, Reichstein and Baud[2] showed that the activated magnesium–copper alloy[3] react with 3-bromobenzofuran to give, subsequent to carbonation, about 1% of 3-benzofurancarboxylic acid in addition to 28% of *o*-hydroxyphenylacetylene.

By means of the recently developed halogen–metal interconversion reaction, we have shown that 2-bromobenzofuran reacts with *n*-butyllithium to give, on carbonation, a 62% yield of pure 2-benzofurancarboxylic acid.

The yield of 3-benzofurancarboxylic acid, from 3-bromobenzofuran and *n*-butyllithium, was 12%. However, this reaction was particularly interesting because of the formation of appreciable quantities of the isomeric 2-benzofurancarboxylic acid. It is probable that the 2-acid was formed from the 3-bromo compound in essential accordance with

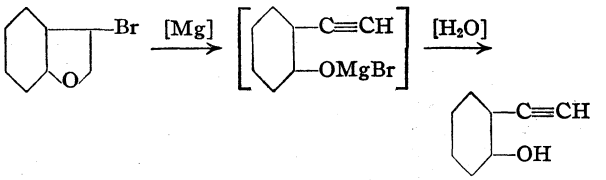
(1) E. W. Smith, unpublished studies.
(2) Reichstein and Baud, *Helv. Chim. Acta*, **20**, 892 (1937).
(3) Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

the following transformations. That is, the initially formed 3-benzofuryllithium [I] metalated [II] in the highly reactive *ortho*- or 2-position to give 3-bromo-2-benzofuryllithium [III] which then metalated the unsubstituted benzofuran [IV] in the expected 2-position to give 2-benzofuryllithium [V]. Another possible explanation in-



volves intramolecular metalation, or essentially rearrangement of the 3-lithium compound to the 2-lithium compound. A related transformation occurs when 3-bromodibenzofuran is treated with *n*-butyllithium and the acids obtained were 3-dibenzofurancarboxylic acid and 4-dibenzofurancarboxylic acid.[4] It is highly probable that a related so-called rearrangement will be observed with other systems in which there is available a hydrogen which is quite sensitive to metalation.[5]

From a room temperature reaction between 3-bromobenzofuran and three equivalents of *n*-butyllithium we obtained a 67% yield of *o*-hydroxyphenylacetylene. It has been suggested[2] that this compound, isolated from the reaction between magnesium and 3-bromobenzofuran, owes its formation to an intramolecular cleavage. In



support of this postulate is the difficulty of forming Grignard reagents from β-halogen ethers like β-bromoethyl phenyl ether (which gives phenol and ethylene),[6a] and 2-bromomethyltetrahydrofuran (which gives γ-vinylpropyl alcohol).[6b]

(4) Gilman, Willis and Swislowsky, THIS JOURNAL, **61**, 1371 (1939).

(5) A case in point is the simple monocyclic furan type. The phenyl alkyl ethers may not show the reaction under usual conditions because the metalation proceeds generally with more difficulty than the halogen-metal interconversion reaction. See, Gilman, Moore and Baine, *ibid.*, **63**, 2479 (1941), for some factors influencing the rates of these reactions.

(6) (a) Grignard, *Compt. rend.*, **138**, 1048 (1904); (b) Robinson and Smith, *J. Chem. Soc.*, 195 (1936).

However, substituents may have a marked effect because 2,4,5-triphenyl-3-furyllithium is formed in yields of at least 66% from 2,4,5-triphenyl-3-bromofuran and *n*-butyllithium[7]; and 3-furylsodium and -potassium are formed by the direct action of 3-iodofuran with sodium–potassium alloy.[8] Also, there is a possibility that the cleavage reaction is not confined to β-halogen ethers because the reaction mixture of 2-bromobenzofuran and *n*-butyllithium appeared to contain some of the *o*-hydroxyphenylacetylene as evidenced by the unusually characteristic odor of this compound.

Experimental

2-Bromobenzofuran and *n*-Butyllithium.—First, the 2-bromobenzofuran was prepared from benzofuran dibromide[9] in accordance with the following directions of E. W. Smith.[1] One-tenth mole of crude, dry benzofuran dibromide was distilled at atmospheric pressure. A vigorous evolution of hydrogen bromide occurred, and the oily fraction distilling at 200–235° was collected. This distillate was dissolved in ether, and then washed successively with water, 10% sodium carbonate solution, and again with water. After drying over sodium sulfate, the ether was removed and the 2-bromobenzofuran was obtained (55% yield) by fractional distillation.

Then, a solution of 2 g. (0.01 mole) of 2-bromobenzofuran in a few cc. of ether was added all at once to a solution of 0.014 mole of *n*-butyllithium in 50 cc. of ether, cooled to −70° in a Dry Ice–acetone bath. The reaction mixture was stirred for two minutes and then carbonated. The yield of crude 2-benzofurancarboxylic acid, melting at 187–189°, was 1.4 g. (86%). Crystallization from dilute ethanol yielded 1.04 g. (62%) of pure acid melting at 192.5–193°. The compound was identified by a mixed m. p. determination with an authentic specimen.[9] In experiments carried out at room temperature, the yield of crude 2-benzofurancarboxylic acid after a reaction period of twenty minutes was 62%, and after forty minutes the yield was 28%. The aqueous filtrates from the acid had the characteristic odor of *o*-hydroxyphenylacetylene, indicating that some cleavage of the benzofuran ring had taken place.

3-Bromobenzofuran and *n*-Butyllithium.—The 3-bromobenzofuran was prepared by the following sequence of reactions: coumarin dibromide → 2-benzofurancarboxylic acid → benzofuran[2] → benzofuran dibromide → 3-bromobenzofuran.[1,2,10] The compound, which melted at 35.5–36° after crystallization from petroleum ether (b. p. 28–38°) at −20°, appeared to be unstable and discolored on standing.

A solution of 2 g. (0.01 mole) of 3-bromobenzofuran in a few cc. of ether was added quickly to a solution of 0.014 mole of *n*-butyllithium in 50 cc. of ether at −70°. The reaction was then stirred for two minutes, and after carbonation there was obtained 0.23 g. (14%) of acid melting at 154–159°. Crystallization from a mixture of benzene and petroleum ether (b. p. 60–68°) gave 0.19 g. (12%) of acid melting at 160–161°, with no change in melting point subsequent to another crystallization from dilute ethanol. The reported melting point is 162° (cor.).[11] A mixed melting point with the 2-isomer showed a depression.

Anal. Calcd. for $C_9H_6O_3$: neut. equiv., 162. Found: neut. equiv., 164 and 161.

Then a series of experiments was carried out varying the time of the reaction and the temperature, and in each case

(7) Gilman and Melstrom, THIS JOURNAL, **68**, 103 (1946).

(8) Gilman and Wright, *ibid.*, **55**, 2893 (1933).

(9) Fittig and Ebert, *Ann.*, **216**, 162 (1883).

(10) Stoermer and Kahlert, *Ber.*, **35**, 1636 (1902).

(11) Titoff, Müller and Reichstein, *Helv. Chim. Acta*, **20**, 883 (1937).

the only acid isolated was 2-benzofurancarboxylic acid in the following crude yields: 13, 10, 23.5, 13 and 16%. From an experiment carried out in petroleum ether (b. p. 28–38°) with 3 g. (0.025 mole) of 3-bromobenzofuran and a slight excess of *n*-butyllithium, there was obtained, after carbonation and hydrolysis, 0.15 g. of crude *o*-hydroxyphenylacetylene and a trace of unidentified acid melting at 127–129° (possibly *o*-hydroxyphenylpropiolic acid).

o-Hydroxyphenylacetylene from 3-Bromobenzofuran.—A solution of 10 g. (0.051 mole) of 3-bromobenzofuran in 30 cc. of ether was added during five minutes to a solution of 0.154 mole of *n*-butyllithium in 220 cc. of ether at room temperature. The solution was stirred for one hour and then hydrolyzed by pouring on iced dilute hydrochloric acid. The yield of *o*-hydroxyphenylacetylene, distilling at 95–98° under 10 mm., was 4 g. (67%). A part of the phenol was converted to the *p*-nitrobenzoate by treatment with *p*-nitrobenzoyl chloride in pyridine. The melting point was 108–109°, and the reported melting point is 107–108° (cor.).[2]

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED JULY 18, 1947

Syntheses in the Pyrazene Series: The Preparation and Properties of Pyrazine Sulfonic Acid

BY EUGENE HORT AND PAUL E. SPOERRI

Although recent electron diffraction studies have shown that benzene and pyrazine have very similar structures,[1] direct substitution with the usual electrophilic reagents, which proceeds so well with benzene operates only with great difficulty or not at all with pyrazine. This deactivation seems to be due to the electron-withdrawing inductive and resonance effects of the nitrogen atoms.[2] Even under such severe conditions as those used in the cleavage of lumazine,[3] *i. e.*, treatment with 100% sulfuric acid at 240°, sulfonation has not been observed. In fact, no direct sulfonation of the pyrazine nucleus has ever been reported. It seemed, therefore, of interest to attempt the synthesis of pyrazine sulfonic acid by means of indirect methods.

Methods based on the oxidation of pyrazine thiol were considered impractical because of the susceptibility of pyrazine to strong oxidizing agents. The reaction of chloropyrazine with sodium sulfite solutions was therefore investigated. Since chloropyrazine had previously been found to possess a chlorine atom intermediate in activity between an alkyl and aryl halide,[4] this method was adopted for the preparation.

Chloropyrazine was obtained by the following sequence of operations. Lumazine prepared according to Cain, Mallette and Taylor,[5] was cleaved to 2-hydroxy-3-pyrazinoic acid and then to hydroxypyrazine according to Weijlard, Tishler and Erickson.[3] Chloropyrazine was then prepared by the method of Erickson and Spoerri[4] with the notable exception that phosphorus oxychloride (in a ratio of five moles to one of hydroxypyrazine) was used as sole chlorinating agent.[6]

Experimental[7]

Chloropyrazine was heated in a sealed tube for twelve hours at 150° with a solution of sodium sulfite. The resulting solution was evaporated and the product crystallized from alcohol as bundles of white needles. Analysis after drying at room temperature *in vacuo* showed that the product was sodium pyrazine sulfonate monohydrate. It was extremely soluble in water, slightly soluble in alcohol, insoluble in ether and petroleum ether, and melted at 295°. Neither silver nitrtae nor barium chloride precipitated an insoluble salt.

The free pyrazine sulfonic acid was prepared by treatment of the sodium salt suspended in dry ether with dry hydrogen chloride gas followed by filtration and evaporation of the ether. It was found to be extremely hygroscopic and unsuitable for an analysis even after extensive drying at 50° *in vacuo*. Its aqueous solution gave a strong acid reaction with hydrion paper.

Three grams (0.026 mole) of 2-chloropyrazine, 4.0 g. (0.032 mole) of anhydrous sodium sulfite, and 25 ml. of water were sealed in a Carius tube and thoroughly mixed. The 2-chloropyrazine remained as a separate layer and some of the sodium sulfite remained undissolved. After keeping the tube at 150° for twelve hours and then allowing to cool, it was opened and the homogeneous yellow solution was evaporated to dryness *in vacuo*. The yellow solid residue was extracted with three 50-ml. portions of boiling 95% ethanol. On cooling the solution, masses of white needle clusters separated and were filtered. The filtrate was evaporated to dryness and extracted with two 8-ml. portions of boiling 95% ethanol. The combined extracts were allowed to stand (crystallization is slow), filtered, and the crystals added to the previously obtained portion; yield, 0.75 g. (15%) of colorless needles, m. p. 295°.

The analytical sample was recrystallized twice from 95% ethanol and dried at room temperature for sixty hours *in vacuo* over phosphorus pentoxide. *Anal.* Calcd. for $(C_4H_3N_2)SO_3Na\cdot H_2O$: C, 24.00; H, 2.52; S, 16.02; Na, 11.49. Found: C, 24.08; H, 2.79; S, 16.02; Na, 11.50.

(1) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., Schomaker and Pauling, THIS JOURNAL, **61**, 1776 (1939).

(2) Krems and Spoerri, *Chem. Rev.*, **40**, 328 (1947).

(3) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

(4) Erickson and Spoerri, *ibid.*, **68**, 401 (1946).

(5) Cain, Mallette and Taylor, *ibid.*, **68**, 1996 (1946).

(6) Suggested in a personal communication from B. Klein of G. D. Research Inst., Inc.

(7) Microanalyses performed by Dr. Otto Schwarzkopf, 62-12 79th Street, Elmhurst, Long Island, New York.

CHEMISTRY DEPARTMENT
BROOKLYN POLYTECHNIC INSTITUTE
BROOKLYN 2, NEW YORK RECEIVED DECEMBER 11, 1947

3,4,5-Triiodobenzoyl Chloride as a Reagent for Alcohols

BY DAVID C. O'DONNELL, JOHN K. KELLEY, JR.,[1] ROBERT F. O'MALLEY[1] AND ROY H. UPHAM[1]

The use of 3,4,5-triiodobenzoyl chloride for the identification of cellosolves and carbitols has been reported previously.[2] Since the compound is relatively stable to water, it was applied to the monohydric alcohols. The alcohols were used as obtained from the manufacturer without further purification. The acid chloride of the 3,4,5-triiodobenzoic acid was prepared by the method of Klemme and Hunter.[3]

(1) Taken from theses submitted in partial fulfilment for the M.S. degree.

(2) O'Donnell and Carey, THIS JOURNAL, **68**, 1865 (1946).

(3) Klemme and Hunter, *J. Org. Chem.*, **5**, 508–511 (1940).

TABLE I

ESTERS OF 3,4,5-TRIIODOBENZOIC ACID

Alcohol used	M. p., °C.	Yield, %	Formula	Iodine, % Calcd.	Found
Methyl	168.2–168.8[a]	36	$C_8H_5O_2I_3$	74.11	73.50
Ethyl	160.8–161.6	59	$C_9H_7O_2I_3$	72.12	72.40
n-Propyl	124.8–125.2[a]	63	$C_{10}H_9O_2I_3$	70.26	70.17
Isopropyl	133.7–134.2[a]	59	$C_{10}H_9O_2I_3$	70.26	70.71
n-Butyl	103.0–103.7	42	$C_{11}H_{11}O_2I_3$	68.48	68.84
Isobutyl	107.6–108.1	56	$C_{11}H_{11}O_2I_3$	68.48	69.05
s-Butyl	95.4–95.8	37	$C_{11}H_{11}O_2I_3$	68.48	68.18
n-Amyl	88.0–88.6	50	$C_{12}H_{13}O_2I_3$	66.80	66.73
Isoamyl	72.3–72.9	14	$C_{12}H_{13}O_2I_3$	66.80	65.93
2-Methyl-1-butanol	63.0–63.4	36	$C_{12}H_{13}O_2I_3$	66.80	67.11
2-Pentanol	72.6–73.4[a]	23	$C_{12}H_{13}O_2I_3$	66.80	67.11
3-Pentanol	74.4–75.6	27	$C_{12}H_{13}O_2I_3$	66.80	67.22
n-Hexyl	98.6–99.0	61	$C_{13}H_{15}O_2I_3$	65.21	65.42
2-Hexanol	99.1–99.9[b]	50	$C_{13}H_{15}O_2I_3$	65.21	65.21
n-Heptyl	58.5–58.9	30	$C_{14}H_{17}O_2I_3$	63.67	64.28
2-Heptanol	55.0–55.6[b]	23	$C_{14}H_{17}O_2I_3$	63.67	63.19
n-Octyl	71.2–71.8	51	$C_{15}H_{19}O_2I_3$	62.20	61.60
n-Nonyl	71.5–72.3	37	$C_{16}H_{21}O_2I_3$	60.81	61.11
n-Decyl	72.5–73.2[b]	50	$C_{17}H_{23}O_2I_3$	60.83	60.69
n-Dodecyl	76.9–77.3[b]	49	$C_{19}H_{27}O_2I_3$	56.99	57.07
Myristyl	80.2–81.2[a,b]	71	$C_{21}H_{31}O_2I_3$	54.69	54.58
Cetyl	79.9–80.8[a,b]	67	$C_{23}H_{35}O_2I_3$	52.57	52.58
Octadecyl	84.5–85.5[a,b]	74	$C_{25}H_{39}O_2I_3$	51.29	51.30
Cyclohexanol	151.1–151.9[a]	36	$C_{13}H_{13}O_2I_3$	65.42	65.29
Allyl	126.0–126.5[b]	58	$C_{10}H_7O_2I_3$	70.53	70.75
Benzyl	128.0–128.6[b]	44	$C_{14}H_9O_2I_3$	64.54	64.46
β-Phenylethyl	117.2–117.8	68	$C_{15}H_{11}O_2I_3$	63.05	63.36
γ-Phenyl-*n*-propyl	78.0–78.8[c]	52	$C_{16}H_{13}O_2I_3$	61.59	62.26

[a] Ethyl alcohol as solvent. [b] Granules. [c] Plates.

Experimental

To 1 g. of the acid chloride in a 10-cm. test-tube was added 0.5 cc. of the liquid alcohol or 0.5 g. of the solid alcohol and the mixture gently heated over a micro burner until the evolution of hydrogen chloride ceased. This usually required about ten minutes. The molten mass was then poured into 20 cc. of an ice and water mixture. Most of the esters solidified instantly. Those that came down as oils usually changed to solids in a few minutes, but in a few instances it was necessary to wash the oil with a 20% solution of alcohol to obtain a solid. One recrystallization will usually give a pure compound, but the results in Table I are from compounds which were recrystallized twice, with the exception of the ethyl and the 3-pentanol esters which were recrystallized three times. Either methyl or 95% ethyl alcohol can be used as a recrystallizing solvent. Methyl alcohol was used for the compounds in the table unless otherwise indicated. They crystallized in needles, unless otherwise noted. The isoamyl ester when crystallized from 95% ethyl alcohol sometimes came down as needles with the melting point shown and sometimes as plates with a melting point of 40.4–40.8°. The plates after melting, solidification and remelting had a melting point of 72.3–72.9°. When recrystallized from methyl alcohol, it always had the melting point of 72.3–72.9°. The melting points were all taken by Anschütz thermometers, which were checked against a thermometer with a Bureau of Standards certificate.

CHEMISTRY LABORATORY
BOSTON COLLEGE
CHESTNUT HILL 67, MASS.

RECEIVED DECEMBER 19, 1947

The Potassium Permanganate Test for Detection of Unsaturation[1]

BY V. N. IPATIEFF, W. W. THOMPSON[2] AND HERMAN PINES

Many books suggest for the detection of unsaturation (particularly in compounds insoluble in water) a procedure comprising treatment of an acetone solution of the compound dropwise with a 2% potassium permanganate solution, until the purple color of the permanganate persists.

It was found that such procedure gave a negative test for unsaturation with several olefinic compounds. The results with the various hydrocarbons tested were not consistent. For example, β-pinene showed a negative test for unsaturation, while α-pinene showed a positive test. It was found, however, that when the olefins showing a positive test were redistilled, the unsaturation test for olefins was negative. These results indicate that the olefins on standing might have undergone some changes, which caused the discoloration of the permanganate solution.

Absolute or 96% ethanol is a more suitable solvent for the unsaturation test; in the presence of olefins the color of the permanganate solution is

(1) This work was made possible in part through the financial support of Universal Oil Products Company.

(2) American Chemical Society Predoctoral Fellow (1947–1948).

discolored instantaneously. When a mixture of ethanol and acetone is used as a solvent, the rate of discoloration of the permanganate solution increases with the increase of alcohol concentration. Ethanol *per se* in the absence of olefins does not discolor the permanganate solution even after five minutes of standing. Methanol and 2-propanol act in a similar fashion as ethanol.

It was found that the addition of only a small amount of water to acetone increases the rate of discoloration when tested for unsaturation. A 5% solution of water in acetone seems to be a suitable solvent for the unsaturation test.

The procedure used for testing the various compounds was essentially as follows: One drop of a 2% aqueous solution of potassium permanganate was added to 0.1 cc. (0.1 g. if solid) of the compound dissolved in 2 cc. of the investigated solvent. Test was indicated as positive (+) when the color of the potassium permanganate changed within five seconds after the addition of the permanganate. If the potassium permanganate color persisted for longer than five minutes, the test was reported to be negative (−). The length of time required to discolorize the permanganate is expressed in seconds.

The tables summarize the results obtained.

TABLE I

COMPARISON OF ETHANOL WITH ACETONE IN PERMANGANATE TEST FOR UNSATURATION

Compounds tested	Solvents: Ethanol	Solvents: Acetone
Amylenes	+	15 sec. (−)[a]
Octene	+	−
Butadiene	+	45 sec.
Cyclohexene	+	−
α-Pinene	+	−
3-Methylcyclohexene	+	−
1,1,3-Trimethyl-x-cyclohexene	+	30 sec. (−)[a]
β-Pinene	+	−
Dihydrolimonene	+	−
Limonene	+	−
Terpineol	+	180 sec.
Allyl alcohol	+	20 sec.
Cholesterol	−	−
Ergosterol	20	−
Mesityl oxide	+	+
Isophorone	+	20 sec.
Acetylacetone	20	240 sec.
Crotonic acid	+	10 sec.
Crotonaldehyde	+	+
Cholesteryl acetate	−	−
Dihydropyran	+	30 sec.

[a] Test after redistillation of the hydrocarbons.

TABLE II

EFFECT OF MIXTURES OF ETHANOL/ACETONE ON RATE OF PERMANGANATE TEST OF OLEFINS

Alcohol concentration, vol. % / Compounds tested	100	80	60	40	20	0
	Time in seconds for color change					
Limonene	0	5	15	30	60	>300
Cyclohexene	0	5	15	40	120	>300
Methylcyclohexene	0	10	30	90	240	>300

THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY
DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS

RECEIVED JULY 24, 1947

Hydrolytic Titrations of Lead with Potassium Cyanide

BY LOUIS MEITES

In the course of a study of hydrolytic titrations of various divalent cations with potassium cyanide, it was found that the atypical behavior of plumbous ion was of particular interest. It is well known that most such titrations are characterized by a continuous rise in *p*H on addition of cyanide, with sharp increases at points corresponding to quantitative formation of insoluble compounds, such as $M(CN)_2$, or complex ions, such as $M(CN)_4^=$.

Titration of an aqueous solution of lead nitrate, however, gives, after an ill-defined end-point at about 1.5 mole of cyanide per mole of lead, a sharp downward break in *p*H at a mole ratio of about 1.8. This break is of the order of 0.25 *p*H unit, and it is followed by a steady rise in *p*H as the titration is continued, with no clear indication of any further end-point to a mole ratio of at least eight.

In 50% ethanol a pronounced end-point (taken as the point of maximum slope) is observed at a mole ratio of 1.002 ± 0.004, and it is followed by, first, a downward break similar to that found in aqueous medium, and then, at a mole ratio of 1.50 ± 0.01, a second sharp end-point.

The insoluble products of the reactions in 50% ethanol were isolated by titrating 500-ml. portions of an 0.05 *M* solution of lead nitrate with standard potassium cyanide until the previously determined *p*H values at the respective end-points, as measured with a Beckman glass electrode *p*H meter, had been exactly reached. The products were filtered off, washed with 50% ethanol and ether, and air-dried. They were analyzed by decomposition in platinum over a very low flame, followed by ignition at a dull red heat, and both gave light yellow plumbous oxide apparently uncontaminated by any trace of a red higher oxide. The compound formed at the first end-point evolved much nitrogen dioxide during its decomposition. Found: PbO, 78.1, 78.2; calculated for Pb(OH)(NO_3), 77.99%. The other compound gave off only a faint odor of cyanogen. Found: PbO, 87.4, 87.3; calculated for $Pb(OH)(CN)\cdot Pb(CN)_2$, 87.62%. This substance has not previously been described in the literature.

The reactions taking place during this titration may, therefore, be represented by the equations

$$Pb^{++} + CN^- + H_2O + NO_3^- \longrightarrow Pb(OH)(NO_3) + HCN \quad (1)$$

and

$$2Pb(OH)(NO_3) + 2CN^- + HCN \longrightarrow Pb(OH)(CN)\cdot Pb(CN)_2 + H_2O + 2NO_3^- \quad (2)$$

The sudden decrease in *p*H between the two end-points is accounted for by the assumption that the concentration of cyanide ion must reach a certain value before reaction (2) is initiated, but that, once started, it progresses to a point at which most of the free cyanide ion has been removed.

The products formed during the titration in aqueous medium were prepared by adding known volumes of standard potassium cyanide to known volumes of standard lead nitrate solution, filtering, and air-drying. They were analyzed as described above. Addition of 1.50 mole of cyanide per mole of lead gave another new compound. Found: PbO, 81.8, 81.8; calculated for $Pb_2(OH)(NO_3)(CN)_2$, 81.85%. This compound evolved nitrogen dioxide during its decomposition. The substance formed at a mole ratio of 2.00 (*i.e.*, after the downward break) was again the hydroxytricyanide described above.

Consequently, the stoichiometry of the reactions in aqueous medium is described by the equations

$$2Pb^{++} + NO_3^- + H_2O + 3CN^- \longrightarrow Pb_2(OH)(NO_3)(CN)_2 + HCN \quad (3)$$

and

$$Pb_2(OH)(NO_3)(CN)_2 + CN^- \longrightarrow Pb(OH)(CN)\cdot Pb(CN)_2 + NO_3^- \quad (4)$$

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, NEW JERSEY RECEIVED NOVEMBER 29, 1947

The Structure of Uranium Hydride

BY LINUS PAULING AND FRED J. EWING

R. E. Rundle[1] has recently reported the results of an X-ray investigation of uranium hydride, UH_3. He found that there are eight molecules of this substance in the unit cube, with $a_0 = 6.631$ Å., and that the uranium atoms have the β-tungsten arrangement, with two UI at 000 and 1/2 1/2 1/2 and six UII at 1/2 1/4 0, etc. He suggested that each uranium I atom is surrounded by twelve hydrogen atoms, on the lines connecting the UI atom with the twelve surrounding UII atoms, and that there are half-bonds between hydrogen and each of the two uranium atoms ligated to it.

In this note we point out that consideration of the interatomic distances supports this proposal, and, moreover, leads to the conclusion that uranium hydride contains a new form of uranium, with small valence, similar to the low-valent forms of chromium and manganese previously reported.[2]

A hydrogen atom in a metallic hydride may be at the center of a tetrahedron of metal atoms, or of an octahedron of metal atoms.[3] In zirconium hydride, ZrH, for example, the zirconium atoms are in a cubic closest packed arrangement, and it seems likely from consideration of the interatomic distances that the hydrogen atoms occupy tetrahedral positions, corresponding to the sphalerite structure. The single-bond radius of hydrogen is then calculated from the zirconium–hydrogen distance 2.06 Å., with use of the zirconium single-bond radius 1.454 Å. and the correction 0.36 Å. for bond-number 1/4, to be 0.25 Å. In palladium hydride, PdH_x, the tetrahedral positions are too small for hydrogen atoms, which instead occupy octahedral positions; the palladium-hydrogen distance 2.03 Å., with palladium single-bond radius 1.28 Å. and correction 0.47 Å. for bond-number 1/6, then leads to 0.28 Å. for the hydrogen radius. This radius lies between 0.25 and 0.32 Å in most metallic hydrides, in good agreement with the range of values for non-metallic hydrides, 0.28 to 0.32 Å.[4]

In uranium hydride the U–H distance of 1.85 Å. (assuming the hydrogen to be midway between UI and UII) is approximately equal to that predicted, namely, the single-bond radius of uranium, 1.42, plus the radius of hydrogen, 0.27, plus the correction for bond number 1/2, 0.18, a total of 1.87 Å. There is no satisfactory position in the uranium hydride structure for hydrogen with coordination number larger than two. In UH_3 each UI atom forms twelve bonds with bond number 1/2 with the surrounding hydrogen atoms, corresponding to a valence of six for uranium I. Each UII forms four such bonds with four surrounding hydrogen atoms, and also forms two bonds with adjacent UII atoms, at 3.316 Å., the calculated bond-number for these bonds being 0.16. This leads for uranium II to the value 2.3 for the valence. No form of uranium metal or intermetallic compound of uranium has been reported so far in which uranium has this low valence, but a low-valent form of chromium and one of manganese have already been reported, so that a similar form for uranium is not entirely unexpected.

It is interesting to point out that the Brillouin-zone treatment of the β-tungsten structure provides some basis of understanding of the stability of this structure for both β-tungsten and uranium hydride. The first expected Brillouin zones correspond to the strong reflections {210} and {211}, which lead to about 16 electrons per unit cube. There then occurs another Brillouin polyhedron, bounded by the strong reflections {222}, {320}, and {400}. (A fourth strongly reflecting form, {321}, does not further truncate this polyhedron.) The content of this polyhedron is 53.5 electrons

(1) R. E. Rundle, THIS JOURNAL, **69**, 1719 (1947).
(2) L. Pauling, *ibid.*, **69**, 542 (1947).
(3) G. Hägg, *Z. physik. Chem.*, **B11**, 433 (1930); **B12**, 33 (1931). Hägg's assignment of the hydrogen atoms to these positions was based on the assumption that the effective radius of hydrogen in metallic hydrides is about the same as in non-metallic hydride molecules.
(4) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1940, p. 168.

per unit cube. The brittleness of uranium hydride suggests that it has a filled-Brillouin-polyhedron structure. The number of electrons per unit calculated from the formula and the assumed valences 6 for UI, 2.3 for UII, and 1 for H is 49.8, which is slightly less than the theoretical value. It is possible that UII actually has valence 3 (like the low-valent form of its congener chromium), each atom forming four half-bonds with hydrogen and two (somewhat strained) half-bonds with its two UII neighbors; this valence would then lead to 54 valence electrons in the unit cube, in excellent agreement with the theoretical value.

The possibility that somewhat different effective radii, corresponding to difference in hybridization of the orbitals, should be used for metals in forming bonds with hydrogen than with other metal atoms may be mentioned. It has been pointed out before[5] that the very strong metal–metal bonds in gallium, β-tungsten, and α-uranium, for which bond numbers of about 1.3 are calculated from the metallic radii, may really be single bonds, the effective radii being a few hundredths of an ångström less than usual for these bonds and greater for the other bonds. Thus in ZrH each of the twelve bonds formed by a zirconium atom with its zirconium ligands is calculated with the usual radius 1.454 Å. to have bond number 0.17, which leads to the low valence 3.04 for zirconium. In order for the valence 4 of zirconium to be effective, the single-bond radius of the metal in its Zr–Zr bonds would have to be taken as 1.50 Å. Similarly the single-bond radius of palladium effective in the Pd–Pd bonds in PdH is required to be 1.33 Å. instead of 1.278 Å. to conform with the valence 5.78. An increase in effective single-bond radius of UII for the U–U bonds in UH_3 and a decrease for the H–UII bonds would permit UII to be exercising the valence 3, found for its congener chromium in the A3 modification of this element.

The electron number per unit cube in β-tungsten itself is 48 (for valence 6) or 46.24 (for valence 5.78, as assumed in Ref. 2), corresponding to a metallic structure with partial filling of a Brillouin zone.

(5) L. Pauling, "The Nature of the Bonds in Metals and Intermetallic Compounds," paper presented before Section 1, 11th International Congress of Pure and Applied Chemistry, London, July 1947.

CONTRIBUTION NO. 1159 FROM THE
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA RECEIVED NOVEMBER 18, 1947

Nitrogen-substituted Chloroalkylamines[1]

BY RICHARD F. PHILLIPS, CLIFFORD H. SHUNK AND KARL FOLKERS

Two nitrogen-substituted β,β′-dichlorodiethylamines were prepared by a procedure in which the Mannich reaction[2] is an essential step.

4-(β,β′-Dichlorodiethylamino)-2-butanone Perchlorate.—To 10 g. of β,β′-dichlorodiethylamine hydrochloride[3] dissolved in 40 ml. of absolute ethanol, 15 ml. of acetone and 3 g. of paraformaldehyde were added. After heating at reflux for ten minutes, an additional gram of paraformaldehyde was added; heating was continued for fifteen minutes. Evaporation at 40° under reduced pressure left an oil, which did not crystallize. The oil was dissolved in 75 ml. of water. After filtering, 10 g. of 70% perchloric acid was added to the filtrate. On cooling, 12.0 g. of crystalline material was deposited, m. p. 112–115°. On recrystallization from water, the melting point reached a constant value of 115–116°. A sample was dried at room temperature in a vacuum desiccator.

Anal. Calcd. for $C_8H_{16}O_5NCl_3$: C, 30.74; H, 5.16; N, 4.48; Cl, 34.03. Found: C, 31.19; H, 5.65; N, 5.00; Cl, 32.89 (Parr bomb).

Apparently some perchloric acid was lost by dissociation on crystallization from water.

4-(β,β-Dichlorodiethylamino)-2-butanone Hydrobromide.—To a suspension of 10 g. of the perchlorate in 50 ml. of water, a solution of 5 g. of sodium hydroxide in 10 ml. of water was added while cooling in ice. The colorless oil which separated was extracted with ether. The ether extract was dried over potassium carbonate, filtered, cooled in ice–salt mixture and saturated with dry hydrogen bromide. An oil was precipitated which crystallized on treatment with a small amount of acetone; wt. 9.2 g., m. p. 90–100°. Recrystallization of the salt from acetone raised the melting point to 108–111°; further recrystallization from absolute ethanol gave a constant melting point of 112–113°. The analytical sample was dried at room temperature in a vacuum desiccator.

Anal. Calcd. for $C_8H_{15}ONCl_2 \cdot HBr \cdot 0.5H_2O$: C, 31.80; H, 5.67; N, 4.64; Br^-, 26.45. Found: C, 31.65; H, 5.38; N, 4.75; Br^-, 26.52 (Volhard titration).

4-(β,β′-Dihydroxydiethylamino)-2-butanone Hydrochloride.—Ten grams of diethanolamine was converted to the hydrochloride by treatment with 9 ml. of concentrated hydrochloric acid. Water was removed by evaporation under reduced pressure. The residue was treated with absolute ethanol and evaporated again. After this treatment had been repeated once more, the residual viscous oil was dissolved in a mixture of 40 ml. of absolute ethanol and 16 ml. of acetone. Five grams of paraformaldehyde was added. After heating at reflux for twelve hours, evaporation of the clear solution at 60° under reduced pressure gave a viscous oil which crystallized from ethanol–acetone. The crystalline product was deliquescent. After storage in a vacuum desiccator it weighed 15 g. and melted at 75–80° in a sealed capillary tube. Two further recrystallizations of this product raised the melting point to a constant value of 83–85°. The substance appears to be unstable on heating. At 57° *in vacuo*, a sample lost 15% of its original weight in three hours.

Anal. Calcd. for $C_8H_{17}O_3N \cdot HCl$: Cl^-, 16.75. Found: Cl^-, 16.42 (Volhard titration, sample dried at room temperature in a vacuum desiccator).

4-(β,β′-Dihydroxydiethylamino)-2-butanol.—A solution of 10 g. of 4-(β,β′-dihydroxydiethylamino)-2-butanone hydrochloride in 125 ml. of methanol was shaken with 0.4 g. of platinum oxide catalyst and hydrogen at a pressure of 30–45 lb. per sq. in. The theoretical amount of hydrogen was absorbed within six hours. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 30 ml. of water. An excess of concentrated potassium hydroxide solution was added while cooling the flask in

(1) This paper is based in part on work done for the Office of Scientific Research and Development under Contract OEMsr-1124 with Merck & Co., Inc.

(2) "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, Chapter 10, p. 303.

(3) Mann, *J. Chem. Soc.*, 464 (1934); Ward, THIS JOURNAL, **57**, 915 (1935).

ice. Saturation of the alkaline solution with potassium carbonate precipitated an oil. The mixture was extracted with chloroform. The chloroform extracts were dried over potassium carbonate and evaporated under reduced pressure. The residue on distillation gave 7.1 g. of material, b. p. 132–154°(0.23 mm.).

2,2′-Dichloro-N-(3-chlorobutyl)-diethylamine Hydrochloride and Picrate.—A solution of 3.5 g. of 4-(β,β′-dihydroxydiethylamino)-2-butanol in 5 ml. of chloroform was saturated with hydrogen chloride. After removal of the chloroform and the excess hydrogen chloride under reduced pressure, 5 ml. of benzene and 5.6 ml. of thionyl chloride were added. The mixture was heated at 55° until hydrogen chloride ceased to be evolved (about thirty minutes). The chloroform and excess thionyl chloride were removed under reduced pressure. Ten milliliters of absolute ethanol was added and removed under reduced pressure. The residual dark oil was cooled, seeded with crystalline material (obtained first through the picrate), and placed in a vacuum desiccator over sodium hydroxide at 0.5 mm. After a short time, the oil changed to a crystalline mass which was dissolved in acetone–ether and allowed to crystallize, wt. 3.7 g., m. p. 106–107°. On recrystallization from acetone–ether, the melting point reached a constant value of 106–108°.

Anal. Calcd. for $C_8H_{16}NCl_3 \cdot HCl$: C, 35.71; H, 6.37. Found: C, 36.05; H, 6.06.

The picrate was obtained from the oily hydrochloride as follows: One gram of the oil was dissolved in 10 ml. of 95% ethanol and added to 25 ml. of ethanol containing 0.85 g. of picric acid. The addition of water precipitated an oil. The solvent was decanted, and the oil crystallized after standing for a few days in an open flask. The crystals were washed with cold ethanol, m. p. 93–95°. On recrystallization from ethanol, the compound had a constant melting point at 95.5–96.5°.

Anal. Calcd. for $C_{14}H_{19}O_7N_4Cl_3$: C, 36.42; H, 4.15; N, 12.13. Found: C, 36.71; H, 4.24; N, 11.90.

The hydrochloride was obtained in crystalline form from the picrate as follows: One-half gram of the picrate was suspended in 25 ml. of cold water. A layer of ether and 5 ml. of 2.5 *N* sodium hydroxide were added. The mixture was shaken and filtered to remove sparingly soluble sodium picrate. The ether layer was separated and dried over Drierite. Dry hydrogen chloride was passed into the solution. A colorless oil was precipitated. The ether was decanted, and the oil became crystalline after standing in a vacuum desiccator over sodium hydroxide. The material was recrystallized from acetone–ether, m. p. 105–107°.

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, N. J.

RECEIVED DECEMBER 2, 1947

The Reaction of Ketene with 2-Nitro-4-chlorophenylsulfenyl Chloride and Other Organic Halogen Compounds

BY ARTHUR ROE AND J. W. MCGEEHEE

It is known that aryl sulfenyl chlorides will add to olefins forming aryl β-chloroethyl sulfides.[1-3] Aliphatic sulfenyl chlorides likewise add to olefins.[4] Ketene contains an olefinic linkage, and we have found that 2-nitro-4-chlorophenylsulfenyl chloride will react with ketene to form 2-nitro-4-chlorophenylmercaptoacetyl chloride in good yield. This acid chloride was not isolated as such but converted to 2-nitro-4-chlorophenylmercaptoacetic acid, which had previously been prepared by Pollack, Riesz and Kahane[5] by the reaction of sodium chloroacetate with the sodium salt of 2-nitro-4-chlorophenylmercaptan. The new synthesis here reported seems to offer an easy approach to the mercaptoacetic acids.

The ready reaction of ketene with 2-nitro-4-chlorophenylsulfenyl chloride made it advisable to see if ketene would also react with arylsulfinyl and arylsulfonyl chlorides. The results were negative; ketene did not react with benzenesulfinyl chloride or with benzenesulfonyl chloride (no solvent used).

In view of Staudinger's report[6] of a reaction between diphenylketene and acid chlorides, we attempted to bring about a reaction between ketene and certain acid chlorides (propionyl, *n*-butyryl, *i*-valeryl and benzoyl) at temperatures ranging from −70 to 100°, both without catalyst and in the presence of a variety of catalysts (aluminum chloride, stannic chloride and sulfuric acid); the only reaction observed was polymerization of the ketene. This work was done before the publication of the article by Blomquist, Holley and Sweeting[7] describing the reaction of ketene with various compounds containing active halogens.

Experimental

2-Nitro-4-chlorophenylmercaptoacetic Acid.—2-Nitro-4-chlorophenylsulfenyl chloride was prepared by the chlorination of bis-(2-nitro-4-chlorophenyl) disulfide.[3] Ketene from a lamp delivering about 0.5 mole of ketene per hour was bubbled through a solution of 30 g. (0.13 mole) of 2-nitro-4-chlorophenylsulfenyl chloride in 100 ml. of dry chloroform; the solution was cooled in an ice-bath. The reaction was stopped after an hour and the chloroform solution carefully poured on 250 ml. of ice in a beaker. When the ice had melted the beaker was warmed to evaporate the chloroform; a bright yellow precipitate formed as the evaporation proceeded. The crude acid was dissolved in dilute sodium carbonate solution, filtered, and precipitated by the addition of dilute sulfuric acid; recrystallization from ethanol produced 21 g. (61%) of long yellow needles of 2-nitro-4-chlorophenylmercaptoacetic acid, m. p. 209–210° (in agreement with the literature value[5]). Conversion of the acid to 2-nitro-4-chlorophenylsulfonylacetic acid (m. p. 157–158°), 3-hydroxy-6-chloro-1,4-benzothiazine (m. p. 204–205°), and 5,5′-dichloro-7,7′-dinitrothioindigo was carried out as described by Pollack[5]; the melting points obtained are in agreement with those he reported.

(1) Lecher and Stöcklin, *Ber.*, **58**, 414 (1925).

(2) Kharasch, Wehrmeister and Tigerman, THIS JOURNAL, **69**, 1612 (1947).

(3) Turner and Connor, *ibid.*, **69**, 1009 (1947).

(4) Fuson, Price and co-workers, *J. Org. Chem.*, **11**, 469, 475 (1946).

(5) Pollack, Riesz and Kahane, *Monatsh.*, **49**, 213 (1928).

(6) Staudinger, Göhring and Schöller, *Ber.*, **47**, 40 (1914).

(7) Blomquist, Holley and Sweeting, THIS JOURNAL, **69**, 2336 (1947).

UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C.

RECEIVED NOVEMBER 22, 1947

Hydroxymethyl Derivatives of Phenols

BY I. W. RUDERMAN

A number of phenol alcohols, some of which are not described in the literature, were recently prepared for the purpose of extending a study[1] of the

(1) I. W. Ruderman, *Ind. Eng. Chem., Anal. Ed.*, **18**, 753 (1946).

TABLE I

DERIVATIVES OF α^1,α^3-XYLENEDIOL

Substituents	Formula	% Yield, crude	M. p.,[b] °C.	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
5-Ethyl-4-hydroxy-[c]	$C_{10}H_{14}O_2$	82.4	92.0–92.5	65.92	65.68	7.74	7.69
4-Hydroxy-5-isopropyl-[c]	$C_{11}H_{16}O_2$	89.6	89.6–90.0	67.32	67.36	8.22	8.33
5-*s*-Butyl-4-hydroxy-[d]	$C_{12}H_{18}O_2$	82.3	79.0–79.3	68.54	68.60	8.63	8.90
5-*s*-Butyl-2-hydroxy-[e]	$C_{12}H_{18}O_2$	95.4	75.4–76.3	68.54	68.39	8.63	8.93

[a] Microanalyses were carried out by Miss L. E. May. [b] Melting points are corrected. [c] Recrystallized once from benzene and once from 1,2-dichloroethane. [d] Recrystallized once from carbon tetrachloride and once from benzene. [e] Reacted for forty-eight hours; recrystallized once from benzene.

quantitative bromination of phenols and phenol alcohols. It is the aim of this note to describe the preparation of these new compounds, and to comment briefly on the reaction employed.

Hydroxymethyl derivatives of phenols are most conveniently prepared by the reaction due to Lederer[2] and Manasse,[3] according to which the phenol is treated with formaldehyde in the presence of an alkaline catalyst, at room or elevated temperature depending upon the strength of the catalyst. Since the reaction may proceed beyond the desired hydroxymethyl stage to produce condensed products such as dihydroxydiphenylmethanes[4,5,6] and higher polymers, it is not uncommon in preparing a derivative to obtain a crystalline dimer or an oil which cannot be crystallized. The present work indicates that the experimental conditions are more critical than one might infer from the literature, so that the reaction should be carried out under carefully controlled, and hence reproducible, conditions if undesirable condensation is to be avoided. In this way, a procedure which is satisfactory for one phenol may often be successfully applied to a large number of other phenols. Moreover, should analysis indicate that a large yield of dimer has been obtained, the conditions can be accurately modified (the temperature, reaction time or catalyst concentration decreased; the mole ratio of formaldehyde to phenol increased) so that the desired hydroxymethyl derivative is obtained. It has also been found that when an oil is obtained upon acidification of the alkaline solution, it is far better to proceed to crystallize the oil *in situ* by intense refrigeration than to extract the oil with ether and to attempt to crystallize the ether extract. The procedure described below has given good results not only for the new compounds reported, but for other phenol alcohols.

Experimental

General Procedure.—One-quarter of a mole of the phenol was dissolved in 100 g. (0.25 mole) of a 10% aqueous sodium hydroxide solution, and the solution was cooled to 25–30°. Forty-four and six-tenths grams (0.55 mole) of 37% formaldehyde was added, and the reaction mixture in a stoppered flask was placed in a constant temperature bath at 27° for twenty-four hours. When the solution was acidified with 5 *M* acetic acid, an oil separated out. Upon refrigeration of the mixture (oil plus watery layer) in a Dewar flask containing a freezing mixture of solid carbon dioxide and trichloroethylene, the oil crystallized. The solid mass was filtered off and dried *in vacuo*.

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK 27, NEW YORK

RECEIVED DECEMBER 10, 1947

(2) L. Lederer, *J. prakt. Chem.*, **50**, 223 (1894); U. S. Patent 563,975 (1896).

(3) O. Manasse, *Ber.*, **27**, 2409 (1894); U. S. Patent 526,786 (1894); *ibid.*, **35**, 3844 (1902).

(4) K. Auwers, *ibid.*, **40**, 2524 (1907).

(5) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932).

(6) A. Zinke, F. Hanus and E. Ziegler, *J. prakt. Chem.*, **152**, 126 (1939).

On the Distribution of Water in Cellulose and Other Materials*

BY ROBERT SIMHA AND JOHN W. ROWEN

The distribution of water molecules in cellulose and similar textile materials is of theoretical and industrial importance. However, the mechanism of their interaction is not completely understood. It is a well known fact that the water content of these systems increases in a characteristic way dependent upon the vapor pressure, as shown for the case of cellulose in Fig. 1. This familiar sigmoid curve is characteristic of a large variety of systems: *e. g.*, protein-water,[1] titanium dioxide–water[2] and sulfuric acid–water.[3] These systems differ in structure and chemical properties and it would therefore be surprising if the same mechanism of sorption were operating in each. The question then arises, does the distribution of water in cellulose lead to a system more akin to a solution or is it indeed a system more nearly like the one involved in the adsorption of water by titanium dioxide?

One might speculate that in the limit of low vapor pressure the combination of the polymer with water is more nearly an adsorption phenomenon. Actually the shape of the pertinent curves and the amounts involved correspond to what has been observed in adsorption. In the opposite limit of high vapor pressure the process might be more appropriately considered as a "solution" phenomenon.

* This material formed part of a paper presented at the 113th meeting of the American Chemical Society, held at Chicago, Illinois April, 1948.

(1) H. B. Bull, THIS JOURNAL, **66**, 1499 (1944).

(2) G. E. Boyd and H. K. Livingston, *ibid.*, **64**, 2383 (1942).

(3) E. I. Valko, "Cellulose and Cellulose Derivatives," edited by E. Ott, Interscience Publishers Inc., New York, N. Y., 1943.

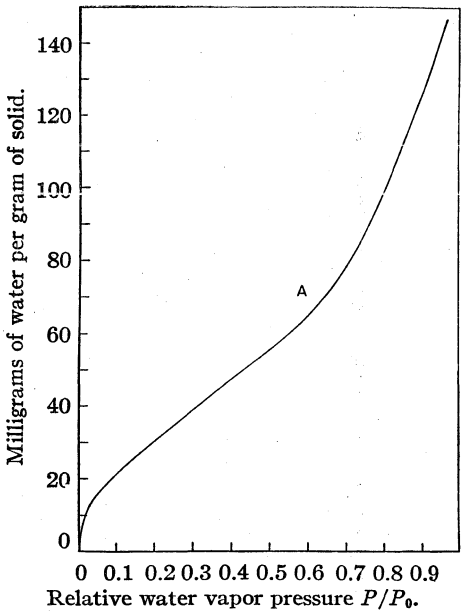


Fig. 1.—Sorption of water vapor by cellulose at 25°.

Such a concept has been advanced[4] in order to account for the upward curvature at higher pressures (beyond A in Fig. 1).

There is no complete theory at present of the mixing of a partially crystalline polymer such as cellulose with a liquid. Nevertheless it appears of interest to apply current statistical treatments[5,6,7] of polymer–liquid mixtures to the cellulose–water and similar systems. The results of such an analysis may then be compared with the results obtained from the application of modern adsorption theory[8] to the same system. In this note such a comparison is made based on experimental data obtained in this laboratory.[9]

Using the notation of references (5) and (6), we may write

$$\ln a_1 \doteq \ln (P/P_0) = \ln v_1 + v_2 + \mu(v_2)^2 \qquad (1)$$

where a_1 is the activity, P/P_0 the relative pressure, v_1 the volume fraction of water and v_2 the volume fraction of polymer. A term of the order of the reciprocal of the chain length has been omitted in (1). μ is the well-known semi-empirical interaction parameter appearing in these theories.

The relationship resulting from the Brunauer–Emmett–Teller treatment is

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m C} + \frac{C - 1}{V_m C}\frac{P}{P_0} \qquad (2)$$

where V is the volume of water adsorbed, V_m is the fixed volume of water adsorbed when a unimolecular layer completely covers the surface, and C is a constant which is related to the energy of binding between the gas molecules in the first layer and the absorbent. According to this theory, a plot of $P/V(P_0 - P)$ against P/P_0 should be a straight line with $1/V_m C$ as the intercept and $C - 1/V_m C$ as its slope.

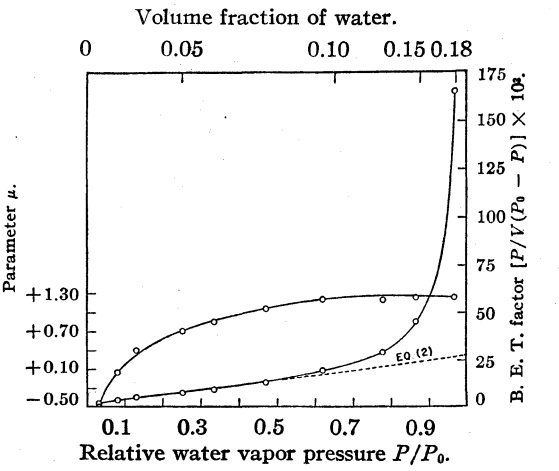


Fig. 2.—Application of equations (1) and (2) to the cellulose–water system. Dotted line indicates plot of equation (2).

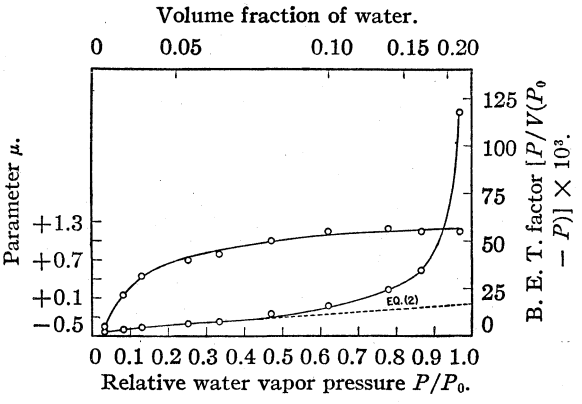


Fig. 3.—Application of equations (1) and (2) to the silk–water system. Dotted line indicates plot of equation (2).

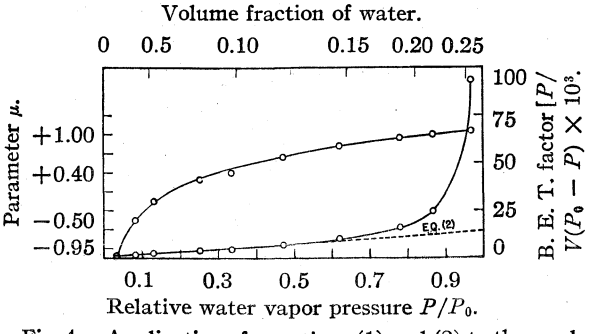


Fig. 4.—Application of equations (1) and (2) to the wool–water system. Dotted line indicates plot of equation (2).

(4) P. H. Hermans, "Monographs on the Progress of Research in Holland, Contribution to the Physics of Cellulose Fibers," Appendix I by J. J. Hermans, Elsevier Publishing Co., Inc., Amsterdam, Brussels, 1946.

(5) P. J. Flory, *J. Chem. Phys.*, **10**, 51 (1942).

(6) M. L. Huggins, *Ann. N. Y. Acad. Sci.*, **43**, 1 (1942).

(7) E. A. Guggenheim, *Proc. Roy. Soc.* (*London*) **183A**, 213 (1944).

(8) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(9) J. W. Rowen and R. L. Blaine, *Ind. Eng. Chem.*, **39** (1947).

The data[9] obtained on cellulose, silk and wool–water systems are plotted for comparison in Figs. 2, 3 and 4, according to equation (1) and equation (2), respectively. It is noted that for $P/P_0 < 0.5$, the data follow the straight line relationship called for by equation (2). Thereafter a more rapid increase is observed. The agreement over such a wide range is remarkable although unexpected on the basis of the assumptions underlying the derivation of equation (2). On the other hand it will be seen that the parameter μ starts out with a negative value, increases slowly and then assumes a fairly constant positive value of about 1.0–1.25 for $P/P_0 > 0.6$. In terms of the volume fraction v_1 of water the total range of measurements corresponds to $0.01 < v_1 < 0.26$. In the region of $0.10 < v_1 < 0.26$, equation (1) is obeyed by cellulose and silk. In wool μ varies approximately from 0.93 to 1.05 over the range $0.18 < v_1 < 0.26$. The various energy and entropy contributions to the quantity μ are different at high and low polymer concentrations.[10] These changes can lead to a variation of the "constant" μ. For rubber–benzene mixtures, the only system so far studied over the whole concentration range,[11,12] no significant change of μ was observed. In any case the deviations from equation (1) obtained by us over a relatively narrow range of volume fractions are too large to be caused by the above-mentioned effect. The limiting values obtainable from these data are $\mu = 1.25$, 1.15, and 1.05 for cellulose, silk and wool, respectively. If the polymer is regarded effectively as a network, allowance must be made for the free energy change accompanying elastic distortion during sorption. The model of a Hookean isotropic medium, subject to a deformation dependent on the concentration, leads merely to a slight reduction in the μ-values reported. These are larger than those usually found by means of solution or swelling measurements for other polymers.[13,14] Also, an examination of the temperature coefficients of μ leads to negative values of the heat term and reduced entropies which indicate that mixing is not a random process. In view of the nature of the systems considered here this is not surprising.

These results provide some support for the concept mentioned earlier. They suggest that the combination of water with these textile materials in the limit of low vapor pressures can be described in terms of adsorption theory. However, as one approaches the limit of high vapor pressures the system can be analyzed in terms of a theory of polymer–liquid mixtures. In the intermediate region between the two extremes a gradual transition occurs. It will be of interest to study the effect of variation in the nature of the liquid upon the properties of these systems.

(10) P. J. Flory, *J. Chem. Phys.*, **13**, 453 (1945).

(11) G. Gee and L. R. G. Treloar, *Trans. Faraday Soc.*, **38**, 147 (1942).

(12) G. Gee and W. J. C. Orr, *ibid.*, **42**, 507 (1946).

(13) M. L. Huggins, *Ann. N. Y. Acad. Sci.*, **44**, 431 (1943).

(14) R. F. Boyer and R. S. Spencer, *J. Polymer Sci.*, **2**, 157 (1947).

NATIONAL BUREAU OF STANDARDS
WASHINGTON, D. C. RECEIVED NOVEMBER 28, 1947

p-Aminosalicylic Acid (4-Amino-2-hydroxybenzoic Acid)

BY JOHN T. SHEEHAN

When *m*-aminophenol and ammonium carbonate react under pressure an acid is obtained which melts at 148°.[1] In the original publication no identification is made beyond that of *m*-aminophenolcarboxylic acid. To determine whether the acid formed is *p*-aminosalicylic acid (4-amino-2-hydroxybenzoic acid) which is of current interest in the chemotherapy of tuberculosis,[2,3] the preparation was repeated in this Laboratory.

It was found that the acid could be isolated directly from the reaction mixture rather than as the hydrochloride as originally described. It could also be precipitated as the barium salt, from which the acid can be readily obtained in purer form. The identity of the acid was established as *p*-aminosalicylic acid by converting it through the diazonium salt into 4-chlorosalicylic acid and comparing this with a sample of the same compound prepared by reacting 2,4-dichlorobenzoic acid with barium hydroxide. Finally a comparison of antibacterial activity[4] disclosed no difference between the acid prepared by the present method and another sample of *p*-aminosalicylic acid.[5]

Experimental

p-Aminosalicylic Acid.—A mixture of 150 g. (1.37 moles) of *m*-aminophenol, 600 g. of ammonium carbonate (6.25 moles) and 750 ml. of water was heated in a rocker-type autoclave at 110° for twelve hours. The mixture was filtered and the filtrate concentrated *in vacuo* to a volume of 450 ml. The solution was then acidified to *p*H 5 and extracted with three 250-ml. portions of ether, from which 75 g. of *m*-aminophenol was recovered. The aqueous solution from the extraction was adjusted to *p*H 2–3 and the *p*-aminosalicylic acid filtered off and washed with water. The product weighed 47 g. and was crystallized from warm alcohol. Alternatively, it can be purified through the barium salt. A 22% yield of product melting at 146–147°[6] was obtained. *Anal.* Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.57; N, 9.15. Found: C, 55.03; H, 4.91; N, 9.13.

4-Chlorosalicylic Acid.—Fifteen and three-tenths grams (0.1 mole) of the above acid were diazotized and con-

(1) German Patent 50,835; *Friedlander*, **2**, 139 (1887–90).

(2) Lehman, *Lancet*, **250**, 15 (1946).

(3) Youmans, *Quart. Bull. Northwestern Univ. Med. School*, **20**, 420 (1946); *C. A.*, **41**, 1011 (1947).

(4) The chemotherapeutic investigation was made under the direction of Dr. G. W. Rake in the Division of Microbiology of this Institute.

(5) Supplied by Calco Chemical Division, American Cyanamid Co., Bound Brook, New Jersey.

(6) The reported melting point of *p*-aminosalicylic acid is 220° (dec.); Seidel, *Ber.*, **34**, 4351 (1901); Seidel and Bittner, *Monatsh.*, **23**, 415 (1902). Since the acid was prepared by reducing *p*-nitrosalicylic acid with tin and hydrochloric acid it seems likely that the melting point of the hydrochloride, which we found decomposes about this temperature, is recorded despite the fact that the empirical formula and analyses given are for the free acid.

verted to the chloride.[7] Nine grams of 4-chlorosalicylic acid was obtained, m. p. 211° after crystallization from water. No depression in m. p. was observed when this product was mixed with the substance prepared below. *Anal.* Calcd. for $C_7H_5O_3Cl$: C, 48.71; H, 2.92; Cl, 20.54. Found: C, 48.52; H, 3.04; Cl, 20.69.

A mixture of 6 g. of 2,4-dichlorobenzoic acid, 20 g. of barium hydroxide hydrate, 60 ml. of water and 0.5 g. of copper-bronze was heated in a sealed tube for six hours at 160–170°. The product was filtered and then suspended in water and decomposed with hydrochloric acid. Crystallized from hot water, the chlorosalicylic acid, 2.9 g, melted at 211–212°. 4-Chlorosalicyclic acid is reported to melt at 211°; 2-chloro-4-hydroxybenzoic acid at 159°.[8]

(7) The procedure described in "Org. Syn.," Coll. Vol. I, p. 163, 1st ed., was followed except that threefold volumes of acid were employed to facilitate the reaction of the insoluble acid hydrochloride and its insoluble diazonium salt. In addition, chlorobenzene was added during the decomposition of the diazonium salt, to extract the product as formed.

(8) Hodgson and Jenkinson, *J. Chem. Soc.*, 1740 (1927).

DIVISION OF MEDICINAL CHEMISTRY
THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
NEW BRUNSWICK, N. J. RECEIVED FEBRUARY 16, 1948

The Preparation of Phthalaldehyde

BY S. WAWZONEK AND R. E. KARLL[1]

Varying yields have been reported for the preparation of phthalaldehyde from *o*-xylene.[2] It has been found that, by using all-glass apparatus and the procedure described below, *o*-xylene and *o*-methylbenzyl bromide can be brominated in 64% yield to $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene. Under similar conditions *o*-methylbenzyl chloride gives the same yield of a mixture of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene and $\alpha,\alpha,\alpha',\alpha'$-chlorotribromo-*o*-xylene. *o*-Methylbenzyl chloride is the most suitable starting material since the best commercially available *o*-xylene is only 90% pure while *o*-methylbenzyl bromide is a powerful lachrymator.

The tetrahalo-*o*-xylenes can be hydrolyzed to phthalaldehyde of melting point 55.5° in a 90% yield by the method of Thiele.[2a] The only modification made in this procedure was to saturate the aqueous solution of the aldehyde with sodium chloride instead of sodium sulfate.

Experimental[3]

$\alpha,\alpha,\alpha',\alpha'$-Tetrahalo-*o*-xylene.—*o*-Methylbenzyl chloride[4] was brominated according to the directions given in "Organic Syntheses"[5] with the following modifications. All-glass equipment was used together with a Trubore glass stirrer. From 132.6 g. of *o*-methylbenzyl chloride, 245 g. of product was obtained by taking up the reaction mixture in hot chloroform (300 ml.) and cooling; m. p., 106°. Repeated recrystallizations from ethanol gave a white crystalline compound melting at 110–111°. A mixture with tetrabromo-*o*-xylene (m. p., 115.5°) melted at 112°.

Anal. Calcd. for $C_8H_6ClBr_3$: Br, 63.6. Calcd. for $C_8H_6Br_4$: Br, 78.20. Found: Br, 72.89, 72.97.

(1) Abstracted from a thesis by R. E. Karll presented to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the M.S. degree, June, 1947.

(2) (a) Thiele and Gunther, *Ann.*, **347**, 106 (1906); Thiele and Weitz, *ibid.*, **377**, 8 (1910); (b) Sandstrom and Lillevik, *Ind. Eng. Chem., Anal. Ed.*, **13**, 781 (1941); (c) Fieser and Pechet, THIS JOURNAL, **68**, 2577 (1946).

(3) Melting points are corrected.

(4) Smith and Spillane, THIS JOURNAL, **62**, 2640 (1940).

(5) "Organic Syntheses," Vol. **20**, John Wiley and Sons, Inc., New York, N. Y., p. 92.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA RECEIVED NOVEMBER 13, 1947

Ethyl Acetamidoacetoacetate

BY RICHARD H. WILEY AND OLIN H. BORUM

The reduction of oximinoacetoacetic ester over palladium catalyst in acetic anhydride gives a product, m. p. 46–47.5°, which has been characterized as acetamidoacetoacetic ester, $CH_3CONHCH(COCH_3)CO_2C_2H_5$. The only known previous reference[1] to this compound describes a less convenient method of preparation and reports a melting point of 141°.

Experimental

Ethyl Oximinoacetoacetate.—This compound was prepared by the method of Adkins and Reeve.[2]

Ethyl Acetamidoacetoacetate.—Thirty-two grams of ethyl oximinoacetoacetate and 6.9 g. of palladium catalyst[3] were shaken in 50 ml. of acetic anhydride at room temperature under 30 lb. hydrogen pressure for ten hours. After separating from the catalyst and removing the excess acetic anhydride, 35 g. of acetamidoacetoacetic ester b. p. 128–140° (3–4 mm.) was obtained. Refractionation gave 25.7 g. b. p. 125–132° (3–4 mm.) which solidified on standing, m. p. 46–47.5°.

Anal. Calcd. for $C_8H_{13}O_4N$: C, 51.33; H, 7.0; N, 7.48. Found: C, 51.13; H, 7.0; N, 7.50.

This solid gave qualitative tests for carbonyl with 2,4-dinitrophenylhydrazine reagent and for enol with alcoholic ferric chloride. Reaction with phenylhydrazine in ether, according to the procedure of Michael[4] for the preparation of the phenylhydrazone of acetoacetic ester, gave a yellow precipitate of the phenylhydrazone, m. p. 131.5–132.5°.

Anal. Calcd. for $C_{14}H_{19}O_3N_3$: C, 60.63; H, 6.9; N. 15.15. Found: C, 60.43; H, 6.96; N, 15.10.

(1) Cerchez and Colesiu, *Compt. rend.*, **194**, 1954 (1932).

(2) Adkins and Reeve, THIS JOURNAL, **60**, 1328 (1938).

(3) R. Mozingo, *et al.*, *ibid.*, **67**, 2093 (1945). Washed free of chloride.

(4) A. Michael, *Am. Chem. J.*, **14**, 519 (1892).

VENABLE CHEMICAL LABORATORY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NORTH CAROLINA RECEIVED JANUARY 8, 1948

The Decomposition of *o*-Methoxybenzene Diazonium Chloride

BY H. E. WOODWARD AND A. A. EBERT, JR.

M. L. Crossley and others[1] have reported that the decomposition of *o*-methoxybenzene diazonium chloride can be assumed to consist of two de-

(1) THIS JOURNAL, **69**, 1160 (1947).

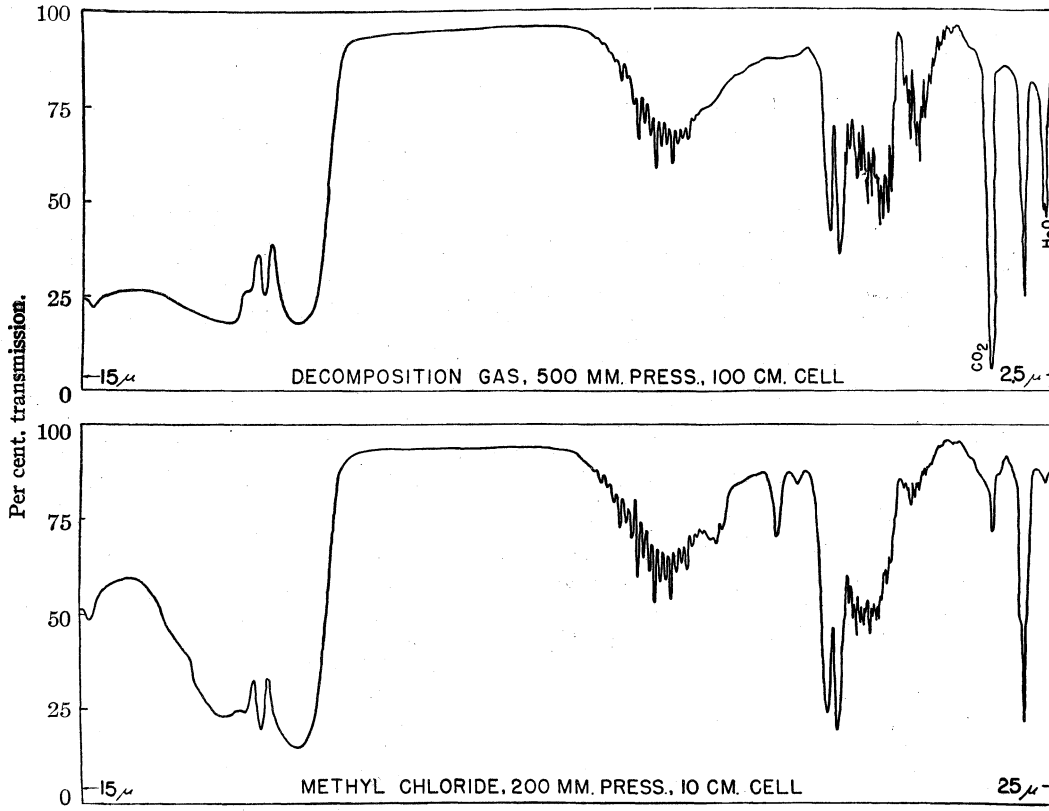


Fig. 1.—Comparison of spectra of methyl chloride and gas sample obtained from decomposition of *o*-methoxybenzene diazonium chloride.

composition reactions occurring simultaneously, one a slow single-step reaction to give guaiacol, and the other a pair of consecutive reactions to give catechol. They regretted that they did not find methyl chloride or methyl alcohol to substantiate their hypothesis.

We have obtained some evidence that their hypothesis is correct by infrared spectral analysis of the evolved nitrogen in the following manner: A solution of the diazonium salt was prepared from *o*-anisidine with 2.5 equivalents of hydrochloric acid and 1 equivalent of sodium nitrite. This solution was heated for about six hours at 90–95° and the evolved gas was passed through Drierite and soda-lime (to remove carbon dioxide used in sweeping air out of the apparatus) and collected over mercury. The gas was transferred to an infrared absorption cell which had an optical path length of one meter. With the gas at a pressure of 500 mm. the spectrum was recorded between 2.5 and 15 microns. The characteristic absorption spectrum of methyl chloride clearly was evident as shown in Fig. 1. A quantitative determination showed that the mole fraction of methyl chloride was 0.026. No other products were detected.

E. I. DU PONT DE NEMOURS & CO.
ORGANIC CHEMICALS DEPARTMENT
JACKSON LABORATORY
DEEPWATER, NEW JERSEY RECEIVED OCTOBER 14, 1947

2-Substituted-thiazolidine-4-carboxylic Acids

BY HAROLD SOLOWAY,[1] FRANK KIPNIS, JOHN ORNFELT AND PAUL E. SPOERRI

Schubert[2] has reported on the interaction of a number of aldehydes with cysteine to produce substituted thiazolidine carboxylic acids. Other workers[3] have extended the reaction and Ratner and Clarke[4] found that the mechanism consisted in hemimercaptal formation, followed by dehydration and cyclization.

Recently, with the discovery that penicillin contained a thiazolidine moiety within the molecule, interest was revived in this class of heterocyclics, and further syntheses have been announced.[5]

The present work reports on the interaction of a representative group of aldehydes with cysteine to produce thirteen new 2-substituted-thiazolidine-4-carboxylic acids. The new compounds form

(1) Abstracted from a thesis by Harold Soloway submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(2) Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

(3) Génévois and Cayrol, *Bull. soc. chim.*, [5] **6**, 1223 (1939); Woodward and Schroeder, THIS JOURNAL, **59**, 1690 (1937); Micheel and Emde, *Ber.*, **72**, 1728 (1939).

(4) Ratner and Clarke, THIS JOURNAL, **59**, 200 (1937).

(5) British Patent 584,918 (1947); Neher, Wettstein and Miescher, *Helv. Chim. Acta*, **29**, 1815 (1946); Brack, *ibid.*, **30**, 1 (1947).

TABLE I

2-SUBSTITUTED-THIAZOLIDINE-4-CARBOXYLIC ACIDS

R	M. p. °C.[a]	Yield, %	Formula	Analyses,[b] % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1′-Ethylpentyl	163–164	97	$C_{11}H_{21}NO_2S$	57.10	9.15		56.71	8.72	
2′-Thienyl	145–146	94	$C_8H_9NO_2S_2$	44.63	4.21		44.25	4.17	
Methylene-3′,4′-dioxyphenyl	167–168 dec.	99	$C_{11}H_{11}NO_4S$	52.16	4.38		52.60	4.40	
Benzyl	165–166 dec.	90	$C_{11}H_{13}NO_2S$	59.17	5.87		58.97	5.98	
4′-Methoxyphenyl	156–158 dec.	95	$C_{11}H_{13}NO_3S$	55.21	5.48		54.74	5.67	
2′-Phenylethyl	159–160 dec.	94	$C_{12}H_{15}NO_2S$	60.73	6.37		61.06	6.27	
4′-Hydroxy-3′-methoxyphenyl	164–166 dec.	95	$C_{11}H_{13}NO_4S$			5.49			5.53
4′-Hydroxyphenyl	167–169 dec.	93	$C_{10}H_{11}NO_3S$			6.22			6.54
2′-Hydroxyphenyl	164–166	99	$C_{10}H_{11}NO_3S$			6.22			6.04
1′-Ethylpropyl	173–175	43	$C_9H_{17}NO_2S$			6.89			6.70
3′,4′-Diethoxyphenyl	149–151 dec.	96	$C_{14}H_{19}NO_4S$			4.71			4.65
n-Hexyl	150–152	99	$C_{10}H_{19}NO_2S$			6.45			6.28
i-Propyl	180–182	41	$C_7H_{13}NO_2S$			7.99			7.70

[a] Melting points were taken on a Fisher–Johns apparatus. [b] Carbon and hydrogen analyses by Oakwold Laboratories, Alexandria, Va.; nitrogen analyses by H. Soloway.

colorless crystals which melt, in most cases, with decomposition, have solubility properties reminiscent of α-amino acids, and show a tendency to revert to the original components on solution in polar solvents.

Experimental

The method of Schubert[2] was used in all cases, and the results obtained are listed in Table I.

2-(2′-Thienyl)-thiazolidine-4-carboxylic acid.—L(+)-Cysteine hydrochloride[6] (5 g., 0.028 mole) and 3 g. (0.035 mole) of potassium acetate were dissolved in 43 ml. of distilled water. To this solution was added 3.56 g. (0.0318 mole) of freshly distilled thiophene-2-aldehyde in 45 ml. of 95% ethanol. On shaking vigorously, precipitation occurred. After refrigeration overnight, the crystalline product was separated by filtration, washed with 20 ml. of cold ethanol, and recrystallized from the same solvent, giving a 94% yield of product melting at 145–146°.

(6) Purchased from General Biochemicals, Inc., Chagrin Falls, Ohio.

RESEARCH LABORATORIES
AMERICAN HOME FOODS, INC.
MORRIS PLAINS, N. J.
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, NEW YORK

RECEIVED NOVEMBER 21, 1947

NEW COMPOUNDS

6-β-Hydroxyethoxy-4-(3′-diethylaminomethyl-4′-hydroxyanilino)-quinoline

2-Diethylaminomethyl-4-aminophenol dihydrochloride[1] (13.3 g.) and 6-β-hydroxyethoxy-4-chloroquinoline[2] (11.2 g.) were refluxed in isopropyl alcohol (550 cc.) for twenty-four hours. The dihydrochloride of 6-β-hydroxyethoxy-4-(3′-diethylaminomethyl-4′-hydroxyanilino)-quinoline precipitated and was filtered from the hot reaction mixture. Suspending the precipitate in fresh, hot isopropyl alcohol, then filtering, gave 20 g. of dihydrochloride. This material (20 g.) was dissolved in water (150 cc.), ether (200 cc.) was added, and the mixture was made alkaline with potassium carbonate with shaking. The free base was filtered off, triturated in a mortar with water, and crystallized from acetone (16 volumes). When dried to a melting point of 144–145° the compound contained one-half mole of water; yield, 40%. The substance was a tan powder, soluble in acetone, slightly soluble in benzene or chloroform, and very slightly soluble in ether.

Anal. Calcd. for $C_{22}H_{27}O_3N_3 \cdot 0.5H_2O$: C, 67.67; H, 7.23; N, 10.74; H_2O, 2.31. Found: C, 67.41; H, 7.25; N, 10.87; H_2O, 2.33.

(1) Kindly presented by Parke, Davis and Company.

(2) Ramsey and Gretcher, THIS JOURNAL, 69, 1659 (1947).

DEPARTMENT OF RESEARCH IN PURE CHEMISTRY
MELLON INSTITUTE
PITTSBURGH 13, PENNSYLVANIA
VIRGINIA G. RAMSEY

RECEIVED SEPTEMBER 26, 1947

Substituted Amides of *p*-Cyclohexylbenzoic Acid

A number of substituted amides of *p*-cyclohexylbenzoic acid were prepared by a reaction of the acid chloride with the corresponding amine in benzene solution. The standard method described by Shriner and Fuson[1] was employed. However, as the amounts of amine employed in each instance was double to triple the molar quantity specified

TABLE I

SUBSTITUTED AMIDES OF *p*-CYCLOHEXYLBENZOIC ACID

N-*p*-cyclohexylbenzoyl	M. p., °C.	Solvent	Yield, %	Empirical formula	N Analyses, % Found	N Analyses, % Calcd.
Aniline	198–198.5	*b*, *c*, *d*	39	$C_{19}H_{21}NO$	5.08	5.01
p-Toluidine	205.0	*b*	52	$C_{20}H_{23}NO$	4.59	4.78
m-Toluidine	149.5–150.0	*d*	23	$C_{20}H_{23}NO$	4.55	4.78
o-Toluidine	153.0	*a*	67	$C_{20}H_{23}NO$	4.86	4.78
p-Bromoaniline	250.5	*a*, *b*	46	$C_{19}H_{20}NOBr$	3.76	3.91
m-Bromoaniline	164.0	*b*	39	$C_{19}H_{20}NOBr$	3.83	3.91
o-Bromoaniline	106.0–106.2	*b*	50	$C_{19}H_{20}NOBr$	3.78	3.91
3-Bromo-4-aminotoluene	123.5–124.0	*a*	80	$C_{20}H_{22}NOBr$	3.67	3.76
5-Bromo-2-aminotoluene	223.5	*b*, *c*	60	$C_{20}H_{22}NOBr$	3.63	3.76
3-Nitro-4-aminotoluene	134.0	*c*	86	$C_{20}H_{22}N_2O_3$	7.75	8.28

[a] Ethyl acetate. [b] Benzene. [c] 1,4-Dioxane. [d] Ethyl alcohol. [e] *n*-Propyl alcohol.

(1) Ralph L. Shriner and Reynold C. Fuson, "The Systematic Identification of Organic Compounds," 2nd Ed., John Wiley & Sons, Inc., New York, N. Y., 1940, pp. 132–133.

by these authors, it was found desirable to wash the benzene solution of the crude amide with several times the amount of 5% hydrochloric acid called for by them.

The crude amides were dissolved in hot ethyl or *n*-propyl alcohol, diluted in several instances with water. The solutions were filtered hot after the addition of activated carbon together with kieselguhr, and the filtrates chilled to obtain the recrystallized products. A substantial quantity of a second crop of satisfactory purity was obtained by concentration of the mother liquors from the recrystallization of the derivatives of *p*-bromoaniline and 3-bromo-4-aminotoluene. The melting points reported are the best values obtained after recrystallization from a variety of solvents.

The derivatives and their properties are listed in Table I. All melting points are corrected.

DE PAUL UNIVERSITY
CHICAGO, ILLINOIS
MALCOLM F. DULL[2]
WILLIAM J. BYER[3]

RECEIVED DECEMBER 8, 1947

(2) Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa.

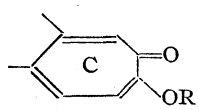
(3) Present address: 1537 Juneway Terrace, Chicago 26, Ill.

COMMUNICATIONS TO THE EDITOR

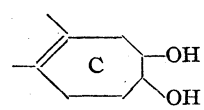
THE STRUCTURE OF RING C OF COLCHICINE[1]

Sir:

It has been suggested,[2] without experimental support, that ring C of colchicine is seven-membered (I, R = CH_3). We have obtained evidence which favors the Dewar and definitely excludes the Windaus[3] formulation.



I

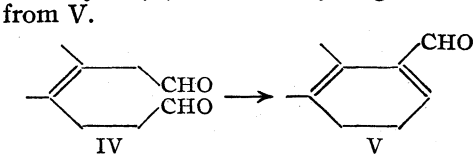


II

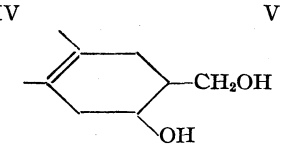
Colchiceine (I, R = H) (m. p. 175.5–176°; calcd. for $C_{21}H_{23}O_6N$: C, 65.45; H, 5.97; N, 3.66. Found: C, 65.65; H, 6.06; N, 3.45; benzoate, m. p. 207–209°, calcd. for $C_{28}H_{27}O_7N$: C, 68.70; H, 5.90; N, 2.86. Found: C, 68.87; H, 5.90; N, 2.78), prepared from purified colchicine,[4] was reduced with Raney nickel in methanol at room temperature and atmospheric pressure for one day, taking up three moles of hydrogen. The product was first crystallized from methanol, yielding about 26% of crude hexahydrocolchiceine[5] (II), m. p. 195.5–197°. Repeated crystallization from methanol–ether afforded the pure compound, m. p. 205.5–206° (calcd. for $C_{21}H_{29}O_6N$: C, 64.39; H, 7.47; N, 3.58. Found: C, 63.68; H, 7.39; N, 3.65; diacetate, m. p. 167°; calcd. for $C_{25}H_{33}O_8N$: C, 63.14; H, 6.99; N, 2.95. Found: C, 63.01; H, 6.83; N, 3.37).

Hexahydrocolchiceine was oxidized with periodic acid in 50% aqueous methanol at *p*H 4. At a lower *p*H side reactions appeared to take place. In a typical experiment hexahydrocolchiceine, m. p. 201–202°, $[\alpha]^{21.5}D$ −205 ± 1° (*c* = 1.544, methanol), $[\alpha]^{19}D$ −162 ± 1° (*c* = 1.436, 50% aqueous methanol) gave an uptake of 0.86 mole periodate after ten minutes, 0.92 mole after ninety minutes, unchanged after eighteen hours. At the end of the reaction, the rotation of the reaction mixture (50% aqueous methanol) had fallen to $[\alpha]^{19}D$ −109 ± 1° (*c* = 1.401). These results indicate the presence of one 1,2-glycol group in hexahydrocolchiceine.

A chloroform extract of the reaction mixture yielded a yellow mobile sirup (III), strong Schiff and Tollens reactions, and reduced Fehling solution. On standing, it slowly lost its aldehydic properties. Efforts to obtain a semicarbazone or dimedone derivative have been unsuccessful, but an alcoholic solution of III with 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid gave amorphous mono-2,4-dinitrophenylhydrazone, m. p. 103–107° (dec.) (after chromatography on alumina) (calcd. for $C_{27}H_{29}O_8N_5$: C, 58.77; H, 5.30; N, 12.7. Found: C, 59.65; H, 5.39; N, 12.84). The oxidation of II presumably gives the dialdehyde (IV) which cyclises spontaneously to the monoaldehyde (V), or the dehydrogenation product from V.



IV V



VI

On the Windaus structure, hexahydrocolchiceine would be a 1,3-glycol (VI) and no oxidation should occur with periodate; the above results are in agreement with (I).

Work is continuing on this and other reduction products of colchicine and its derivatives.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK
H. R. V. ARNSTEIN
D. S. TARBELL
H. T. HUANG
G. P. SCOTT

RECEIVED MARCH 25, 1948

(1) Aided by a grant from the National Institute of Health.

(2) Dewar, *Nature*, **155**, 141 (1945).

(3) Windaus, *Ann.*, **439**, 59 (1924).

(4) Ashley and Harris, *J. Chem. Soc.*, 677 (1944).

(5) Bursian, *Ber.*, **71**, 245 (1938).

RECOIL-ACTIVATED AND THERMAL EXCHANGE REACTIONS BETWEEN SULFUR-35 AND CARBON DISULFIDE

Sir:

Two interesting exchange reactions have been observed in research on the preparation of S^{35}-tagged CS_2 (CSS*). Each reaction presents an interesting chemical phenomenon, namely, the exchange of a free sulfur atom or ion with one bound in the CS_2 molecule, and each is applicable to the preparation of CSS*. Such *atomic* exchange reactions, involving energetic covalent bonds, have been found in the past to be much slower.

The activation energy in the first of these reactions is supplied by the specific nuclear process which results in formation of S^{35}. Two experiments have been performed to date, each utilizing the n,p reaction on Cl^{35} to make the 87-day S^{35}. In the first experiment, a solution of CS_2 in CCl_4 (10 volume per cent. CS_2) was placed in the stray neutron field near the Massachusetts Institute of Technology cyclotron for one month. The total S^{35} activity and that present as CS_2 were assayed by Carius analysis. For the CS_2 analysis, exhaustive extraction with Na_2CO_3 solution was followed by distillation of the mixture to remove the other S^{35}-containing compounds ($CSCl_2$ etc. No effort was made to separate CCl_4 and CS_2). About 50% of the S^{35} formed in compounds not volatile below room temperature was present as CSS*. In the second experiment, a solution of one gram of C_2Cl_6 in 1 ml. of CS_2 was sealed in a quartz vial for a thirty-day bombardment in the Oak Ridge pile, and assayed as described above, except that upon receipt, the sample was kept frozen until aliquoted for total S^{35} analysis to avoid loss of the more volatile compounds (of $BaCS_3$). In this case, 12% was recovered as CSS*. The lower value in the second experiment may be attributed (a) to the precaution taken to recover volatile compounds, and (b) to the greater variety and number of radiation-induced side reactions possible in the higher neutron flux of the pile. The specific activity of S^{35} as CSS* in the Oak Ridge sample attained a value of greater than one millicurie per gram.

The second reaction, now being studied, is the exchange of sulfide ion in aqueous solution with CS_2 as a separate phase. The reaction proceeds through sulfide exchange with thiocarbonate ion ($CS_3^=$), and like the electron transfer reactions of thallium[1] and iron[2] recently reported appears to be catalyzed by precipitation (of $BaCS_3$). On the other hand, when the $CS_3^=$ is decomposed with acid and the resulting CS_2 extracted with CCl_4 and analyzed, this exchange shows a half-time of about forty minutes (sulfide concentration about 0.5 M, thiocarbonate about 0.15 M, pH 9.5, 30°). Investigation of the kinetics of this reaction continues.

(1) R. J. Prestwood and A. C. Wahl, THIS JOURNAL, **70**, 880 (1948).

(2) L. Van Alten and C. N. Rice, *ibid.*, **70**, 883 (1948).

This work has been supported in part by the Office of Naval Research. We wish to express our thanks to the crew of the M.I.T. cyclotron and to the American Viscose Corporation for supplying the radioactive sulfur.

DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS. RAYMOND R. EDWARDS

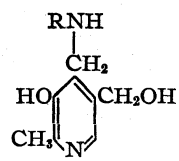
BIOPHYSICAL LABORATORY
HARVARD MEDICAL SCHOOL FRANCES B. NESBETT
BOSTON 15, MASS. A. K. SOLOMON

RECEIVED APRIL 1, 1948

PYRIDOXYLAMINES

Sir:

Pyridoxal has been reductively coupled with certain amines, including several pressor amines, to give compounds of structure I. For example,



I

β-phenylethylamine, tyramine, tryptamine, isobutylamine, histamine (amines derived from naturally occurring amino acids), as well as benzylamine reacted with pyridoxal to give yellow Schiff bases, which were hydrogenated over a platinum catalyst to give pyridoxyl-β-phenylethylamine dihydrochloride, II (m. p. 227–228°, dec.), pyridoxyltyramine dihydrochloride, III (m. p. 238–239°, dec.), pyridoxyltryptamine hydrochloride, IV (m. p. 222–223°, dec.), pyridoxylisobutylamine hydrochloride, V (m. p. 204–205°, dec.), pyridoxylhistamine dihydrochloride, VI (m. p. 236–237°, dec.), and pyridoxylbenzylamine dihydrochloride, VII (m. p. 220–221°, dec.). These new compounds as well as the intermediary Schiff bases were also analytically characterized.

These pyridoxylamines, which are derivatives of both pyridoxine and the pressor amines, are being studied for vitamin B_6 activity and for pressor activity.

The tests of these compounds for vitamin B_6 activity in deficient rats were made by Dr. Gladys Emerson and Miss Elizabeth Wurtz of the Merck Institute for Therapeutic Research, who have found that compounds II, III, IV and VII show activities which range between 50 and 100% of the activity of a molar equivalent of pyridoxine. Such high biological activity for these new compounds is in contrast to the low activity which has been found for previous structural modifications of the vitamin B_6 group.[1]

(1) Unna, *Proc. Soc. Exptl. Biol. Med.*, **43**, 122 (1940); Harris and Wilson, THIS JOURNAL, **63**, 2526 (1941); Harris, *ibid.*, **63**, 3363 (1941).

Extensions of these chemical and biological studies will be detailed later.

DOROTHEA HEYL
EILEEN LUZ
STANTON A. HARRIS
KARL FOLKERS
RESEARCH LABORATORY
MERCK AND CO., INC.
RAHWAY, N. J.

RECEIVED MARCH 20, 1948

EVIDENCE FOR THE INVOLVEMENT OF GLUTATHIONE IN THE MECHANISM OF PENICILLIN ACTION

Sir:

Several authors have suggested the involvement of —SH groups in the antibacterial action of penicillin (see review[1]). The similarity in the molecular structure of glutathione and of penicillin[2,3] suggests the possible involvement of glutathione in the antibiotic action of penicillin. The following experiments (supported partly by the Cutter Laboratories, Berkeley, California) bear on this question.

When standard penicillin assay plates are flooded with a 1% solution of 2,6-dichlorophenolindophenol in a saturated aqueous solution of sodium bicarbonate the inhibition zones promptly stain intensely blue, and are sharply delineated from the faintly bluish uninhibited background by a narrow colorless rim that locates the ring of enhanced growth that circumscribes each zone. Similar patterns obtain on plates pretreated for five minutes with acetone, which blocks —SH groups from cysteine but not those from glutathione.[4] However, if —SH groups of glutathione are blocked by flooding the plates for ten minutes with a 10% solution of formaldehyde in saturated sodium bicarbonate the 2,6-dichlorophenolindophenol is no longer reduced to the colorless form in the ring of enhanced growth, which now stains deep blue.

The reducing activity in the regions of enhanced growth may be strikingly revealed also by flooding plates with a 0.5% aqueous solution of 2,3,5-triphenyltetrazolium chloride, whereupon these regions become intensely red, while the zones of inhibition remain uncolored. Pretreatment of the plates with 10% formaldehyde blocks this reaction. When such plates are subsequently flooded with the tetrazolium reagent, the red color fails to develop, except at the extreme outer margin of the ring of enhanced growth where it is very faint.

Such simple experiments do not themselves afford unequivocal proof of the participation of glutathione in the mechanism of penicillin action. However, it is generally assumed that —SH groups are involved. Our results indicate that some of these —SH groups are less reactive than those of cysteine, and in view of the work on the role of glutamine revealed by Gale and Taylor[5,6,7] it seems reasonable to deduce the involvement of glutathione.

(1) R. Pratt and J. Dufrenoy, *Bact. Rev.*, **12**, 79 (1948).
(2) E. Fischer, *Science*, **106**, 146 (1947).
(3) R. Pratt and J. Dufrenoy, *J. Bact.*, in press (1948).
(4) L. Genevois and P. Cayrol, *Enzymol.*, **6**, 352 (1939).
(5) E. F. Gale and E. S. Taylor, *Nature*, **158**, 676 (1946).
(6) E. F. Gale and E. S. Taylor, *J. Gen. Microbiol.*, **1**, 314 (1947).
(7) E. F. Gale, *Nature*, **160**, 407 (1947).

UNIVERSITY OF CALIFORNIA
COLLEGE OF PHARMACY
THE MEDICAL CENTER
SAN FRANCISCO 22, CALIF.
ROBERTSON PRATT
JEAN DUFRENOY

RECEIVED FEBRUARY 12, 1948

IMPROVED ION EXCHANGE METHOD FOR SEPARATING RARE EARTHS IN MACRO QUANTITIES[1]

Sir:

Previous communications from this laboratory[2] described ion exchange methods by which rare earths were separated from one another in kilogram quantities. The process consisted essentially of absorbing the mixed rare earths on the top of long columns of commercial IR-100 Amberlite resin, in the acid cycle, and then eluting by means of citric acid solutions whose *p*H had been adjusted to the required value by the addition of ammonium hydroxide. While these processes represented an enormous saving, in man-hours required per gram of pure rare earth produced, over the old processes of fractional crystallization, etc., they were not ideal in the sense that when a mixture of rare earths was present, shapes of the elutions bands were such that there was a slight trailing of the preceding rare earth across the main band of the following one. This cut down the amount of pure rare earth obtained from any one pass of the column and frequently resulted in the necessity of recycling considerable quantities of the material.

Considerable work has been done in this Laboratory concerning the nature of the separation process. Good spectroscopic evidence has been obtained that at least four complexes of the rare earths with citrate solution exist and that each of these in turn becomes important as the *p*H range and citric acid concentrations are changed. Recently, it has been found that separation of the rare earths in large amounts can be markedly increased by eluting with a 0.1% citric acid solution in the *p*H range between 5.0 and 5.5. Under these conditions both the front and rear edges of the elution band (amount of rare earth eluted per liter plotted against liters of the eluant passed through the column) are steep and the tops of the eluting bands are flat. Furthermore, the bands separate from each other until the front edge of the one rare earth band is riding on the rear edge of the preceding band. Increasing the length of the column beyond the limit necessary to do this does not separate the bands any further, so there is good evidence that the one rare earth is replacing the

(1) This document is based in part on work performed under Contract No. W-7405 eng-82 for the Atomic Energy Project.
(2) Spedding, *et al.*, THIS JOURNAL, **69**, 2777, 2786, 2812 (1947).

other rare earth on the column as the material is eluted. It was also noted that in the cases tested the *p*H of the solution which comes from the column varies with the rare earth being eluted and differs by about 0.05 of a *p*H unit for adjacent rare earths. With binary mixtures of 50–50% neodymium–praseodymium and neodymium–samarium, it has been found possible to recover from 60 to 90% of each of the rare earths in such purity that the other rare earths could not be detected spectrophotometrically in these fractions.

Work is being continued and the details of this process will be presented in a paper soon to be submitted for publication.

CONTRIBUTION NO. 29
FROM THE INSTITUTE FOR ATOMIC RESEARCH AND THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE
AMES, IOWA

F. H. SPEDDING
E. I. FULMER
BUELL AYERS
T. A. BUTLER
JACK POWELL
A. D. TEVEBAUGH
ROBERT THOMPSON

RECEIVED FEBRUARY 9, 1948

LEAF XANTHOPHYLLS

Sir:

Recently, a violaxanthin-like xanthophyll called xanthophyll-epoxide has been reported as a new leaf pigment.[1] However, earlier observations indicate that this leaf xanthophyll is spectroscopically identical with violaxanthin, obtained originally from pansies (*Viola*).[2] Moreover, leaf violaxanthin and pansy violaxanthin are chromatographically identical in Tswett columns of magnesia or of sugar.[3]

Karrer and co-workers also claim that, in spite of other similarities, violaxanthin and leaf violaxanthin (their xanthophyll-epoxide) yield different pigments when treated with acids[1]

violaxanthin ⟶ auroxanthin
xanthophyll-epoxide ⟶ flavoxanthin.

By contrast, I have found violaxanthin from the two sources to react with acids in the following way

pansy violaxanthin ⟶ flavoxanthins ⟶ auroxanthin
leaf violaxantin ⟶ flavoxanthins ⟶ auroxanthin

Obviously, pansy violaxanthin and leaf violaxanthin are identical with respect to their reaction with acids. This xanthophyll, whether obtained from pansies or from leaves, should, therefore, be called violaxanthin, not xanthophyll-epoxide.

In spite of Karrer's assertions to the contrary,[1] numerous experiments confirm the complexity of the leaf pigment mixture. The leaves of some fifty plants, ranging from ferns to angiosperms, have yielded the following pigments: chlorophylls a and b (with traces of chlorophylls a′ and b′), neoxanthin, zeaxanthin, violaxanthin, lutein, cryptoxanthin-like pigments and β-carotene ± α-carotene. In leaves of eleven species of cycads representing six genera, taraxanthin, identical with taraxanthin from dandelions, accompanies the pigments just enumerated. In most of these plants, lutein is the principal xanthophyll, violaxanthin is slightly less abundant, neoxanthin occurs in small amounts, and zeaxanthin and the cryptoxanthin-like pigments are present in very small proportions. Traces of flavoxanthins are sometimes found in the leaf extracts.

When the pigments of fresh leaves are extracted with methanol or acetone, transferred to petroleum ether, adsorbed in columns of powdered sugar, and washed with petroleum ether containing 0.5% propanol, the following sequence of adsorbed pigments is obtained: neoxanthin, violaxanthin, (flavoxanthins), chlorophyll b, (taraxanthin), lutein plus zeaxanthin[4] plus chlorophyll b′, chlorophyll a, chlorophyll a′, crytpoxanthin-like pigments and the non-adsorbed carotenes.

1,2-Dichloroethane, formerly employed for the resolution of leaf xanthophylls by adsorption,[5] decomposes easily, especially in the presence of moisture, yielding hydrochloric acid. Unless special precautions are observed, the action of this acid on the leaf xanthophylls dissolved in dichloroethane may decrease the amount of violaxanthin and increase the amounts of flavoxanthins and isolutein.[5]

All these facts confirm the identity of violaxanthin from leaves and from pansies. They indicate that flavoxanthins can be converted into auroxanthin. They illustrate the complexity and the lability of the leaf xanthophylls. They point to precautions to be observed in the handling of leaf xanthophylls, and they illustrate problems in nomenclature arising from the use of different names for a single substance.

(1) Karrer, Krause-Voith and Steinlin, *Helv. Chim. Acta*, **31**, 113 (1948).

(2) Kuhn, Winterstein and Lederer, *Z. physiol. Chem.*, **197**, 141 (1931).

(3) Strain, Manning and Hardin, *Biol. Bull.*, **86**, 169 (1944).

(4) Strain, THIS JOURNAL, **70**, 588 (1948).

(5) Strain, "Leaf Xanthophylls," Carnegie Inst. Wash., Publ. 490, Washington 1938.

CARNEGIE INSTITUTION OF WASHINGTON
DIVISION OF PLANT BIOLOGY
STANFORD, CALIFORNIA
HAROLD H. STRAIN

RECEIVED MARCH 29, 1948

A SYNTHESIS OF STREPTIDINE

Sir:

There has been reported[1] the synthesis of hexaacetylstreptamine from D-glucosamine by a method which establishes its configuration, and that of streptidine, as all-*trans*. We wish to record herein the conversion of hexaacetylstreptamine to streptidine sulfate monohydrate, thus completing the synthesis of the latter from D-glucosamine. Hexaacetylstreptamine was saponified with aqueous sodium hydroxide under reflux and the product was crystallized as the sulfate. The

(1) M. L. Wolfrom and S. M. Olin, Abstracts of Papers, 113th Meeting, Am. Chem. Soc., Chicago, Illinois, April 19–23, p. 5Q (1948).

resultant streptamine sulfate[2-4] was characterized by its X-ray powder diffraction diagram, which was identical with that of an authentic specimen obtained from streptomycin. Streptamine sulfate was treated with the stoichiometric amount of barium hydroxide and the resultant aqueous solution of the free base was heated at 70–80° for forty-eight hours with an equivalent amount (added in portions) of S-methylthiopseudourea sulfate.[5] A crystalline reaction product was obtained which, when triturated with dilute ammonium hydroxide, yielded streptidine sulfate monohydrate,[2,3,6,7] identified by its X-ray powder diffraction diagram,[8] nitrogen analysis (calcd., 22.2%; found, 22.1) and octaacetyl derivative[7] (m. p. 259–261°, unchanged on admixture with an authentic specimen prepared from streptomycin).

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY M. L. WOLFROM
COLUMBUS, OHIO W. J. POLGLASE[9]

RECEIVED MARCH 19, 1948

(2) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell, W. A. Strong, J. T. Alberi, Q. R. Bartz, S. B. Binkley, H. M. Crooks, Jr., I. R. Hooper and M. C. Rebstock, *Science*, **103**, 53 (1946).

(3) J. Fried, G. A. Boyack and O. Wintersteiner, *J. Biol. Chem.*, **162**, 391 (1946).

(4) R. L. Peck, C. E. Hoffhine, Jr., Elizabeth W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

(5) B. Rathke, *Ber.*, **14**, 1774 (1881); R. Phillips and H. T. Clarke, THIS JOURNAL, **45**, 1755 (1923).

(6) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, *Science*, **102**, 506 (1945).

(7) R. L. Peck, R. P. Graber, A. Walti, Elizabeth W. Peel, C. E. Hoffhine, Jr., and K. Folkers, THIS JOURNAL, **68**, 29 (1946).

(8) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, *ibid.*, **69**, 1052 (1947).

(9) Bristol Laboratories Research Fellow of The Ohio State University Research Foundation (Project 224).

NEW BOOKS

Quantitative Organische Mikroanalyse. Fifth Austrian Edition. By F. PREGL and H. ROTH. Springer-Verlag, Vienna, 1947. 317 pp. 80 Figs. 16 × 23.5 cm. Price $7.40 (Swiss Francs 32.--).

F. Pregl's "Die quantitative organische Mikroanalyse" has had three original editions (1st, 1916, 2nd, 1922, and 3rd, 1929). Since Pregl's death on Dec. 13, 1930, two revisions by H. Roth have appeared: the first in 1935 and the second, or present fifth edition, in 1947.

Since neither the fourth nor the present fifth edition have been previously discussed in THIS JOURNAL, it was thought expedient to not only examine these two revisions but also compare them with the third and last original Pregl edition. This is being done in the table given herewith.

TABLE I

Chapters	Number of pages 3rd edition	4th edition	5th edition
Balances	14	16	14
Methods of elementary analysis	175	164	175
Carbon and hydrogen	69	66	59
Oxygen	...	...	11
Nitrogen (Dumas)	30	20	20
Nitrogen (Kjeldahl)	11	8	7
Halogen	21	28	25
Sulfur	15	12	19
Miscellaneous	28	26	28
Methods of structure analysis	29	86	78
Molecular weight determinations	15	24	16
Determ. of physical constants	2	25	20
Total	256	328	317

As can be seen from the table, the two revisions differ from the last and original Pregl edition chiefly by an enlargement in the structure analytical section. Thus, in this field, there have been added the well-known iodometric determination of O-, S- and N-alkyls by F. Vieboeck and C. Brecher and three methods by R. Kuhn and co-workers, such as a gasometric determination of active hydrogen, an oxidation procedure (acetic acid) and a method of ozonolysis (acetone). In the field of elementary analysis the additions involve iodometric methods for the determination of oxygen (J. Unterzaucher) and of sulfur (W. Zimmermann), a hydrogenation method for nitrogen (A. Lacourt) and an alkalimetric determination for chlorine and bromine (M. K. Zacherl).

The fifth edition differs from the fourth by the iodometric methods for the determination of oxygen (1940) and sulfur (1943) and the determination of nitrogen by hydrogenation (1940) cited above. On the other hand, the chapter on molecular weight determinations has been weakened by the omission of any and all ebullioscopic methods. The literature references are incomplete and none goes beyond 1943. There is no author index, nor does the book contain any log or nitrogen reduction tables. Use of ordinary balances in quantitative organic microanalysis is not mentioned.

In view of the foregoing, which at the same time might also be regarded as an indication of the progress of organic microchemistry in Central Europe for the last twelve years, the present edition appears to be rather a "Second Printing" of the fourth edition, or first revision. The bypassing of Pregl's original and still active laboratory at the University of Graz, Austria, his successor and original co-workers as co-authors appears inexcusable and is most unfortunate.

JOSEPH B. NIEDERL

Violin Varnish. A Plausible Re-creation of the Varnish Used by the Italian Violin Makers between the Years 1550 and 1750, A. D. By JOSEPH MICHELMAN. Published by Joseph Michelman, 5050 Oberlin Boulevard, Cincinnati, Ohio, 1946. 185 pp. 14 × 21 cm. Price, $3.75.

The question of the varnishes used by the great Italian violin makers of the mid-sixteenth to the mid-eighteenth centuries has always provoked great curiosity and specula-

tion. Violin makers and scientists still disagree about the actual contribution of varnish to the tonal qualities of the violin, but most consider that it is an important one. Unfortunately, the varnish formulas used by the master violin makers were shop secrets and little opportunity has been found to analyze, even on a micro scale, the varnish on the very few instruments that have come down to us. In this brief volume the author, who apparently is well versed in modern varnish technology, has attempted to reconstruct the work-shop receipts of the famous violin artisans from a study of the materials then available, and to analyze the properties of the finishes produced thereby.

After carefully surveying the existing literature on violin varnish, the author discusses the materials used in its manufacture by the master Italian violin makers, which included Venetian turpentine (oleoresin from the European larch), potash, alum, copperas, linseed oil, alcohol, and red dye obtained from the madder root and the different mordant salts used to fix it. Next follow several chapters describing in detail numerous experiments with these materials to establish the old formulas, without the aid of modern laboratory devices, and possible receipts that the violin makers might have used. In these experiments small batches, comprising often only a few grams or cubic centimeters of the principal ingredients, were employed. One wonders whether proper conditions for varnish making can be established on such a small scale. Many of the experiments involve the preparation of metal rosinates which, combined with linseed oil, the author believes were used for under-coats or sub-varnishes. Combinations of aluminum and iron rosinates made from potassium rosinate could have been used to produce the brown undertone so frequently seen. The color of top varnishes could have been obtained by combining various natural dyes with metal rosinates and linseed oil; among them the extract from madder root or modern alizarin gives best results. The author then lists a series of simple formulas for violin varnishes for the use of the amateur, followed by a discussion of materials and methods which the modern varnish technologist might employ.

The collector of old violins and the modern amateur violin maker will find this volume of much interests The subject matter is well organized and the book i. attractively printed.

RUTHERFORD J. GETTENS

BOOKS RECEIVED

February 10, 1948–March 10, 1948

TURNER ALFREY, JR. "Mechanical Behavior of High Polymers." Vol. VI. Interscience Publishers, Inc., 215 Fourth Ave., New York 3, New York, 1948. 581 pp. $9.50.

D. J. BELL. "Introduction to Carbohydrate Biochemistry". Second Edition 1948; published 1940, reprinted 1943. Clifton House, Publishers, Euston Road, London, N.W.1, England. 107 pp. 6s.

WILLIAM MANSFIELD CLARK. "Topics in Physical Chemistry". The Williams and Wilkins Company, Baltimore 2, Maryland, 1948. 738 pp. $10.00.

ROBERT B. DEAN. "Modern Colloids. An Introduction to the Physical Chemistry of Large Molecules and Small Particles." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1948. 303 pp. $3.75.

C. C. FURNAS. "Research In Industry. Its Organization and Management." D. Van Nostrand Company, Inc., 250 Fourth Ave., New York, N. Y., 1948. 574 pp. $6.50.

A. G. GAYDON. "Dissociation Energies and Spectra of Diatomic Molecules." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1947. 239 pp. $5.00.

W. K. RIEBEN. "Über die Kaliumbestimmung in Biologischer Substanz." Benno Schwabe and Co., Verlag, Basel, Switzerland. Imported by Grune and Stratton, Inc., Medical Publishers, New York City, 1947. 73 pp. $9.00 (paper); $12.00 (bound).

FOSTER DEE SNELL and CORNELIA T. SNELL. "Colorimetric Methods of Analysis." D. Van Nostrand Company, Inc., 250 Fourth Ave., New York, N. Y., 1948. 239 pp. $4.50.

A. SZENT-GYÖRGYI. "Nature of Life. A Study of Muscle." Academic Press, Inc., 125 E. 23rd St., New York 10, N. Y., copyright 1948. 91 pp. $3.00.

WILLIAM MAYO VENABLE. "The Interpretation of Spectra." Reinhold Publishing Corporation, 330 West 42nd St., New York 18, N. Y., 1948. 200 pp. $6.00.

R. TECWYN WILLIAMS. "Detoxication Mechanisms." John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1947. 288 pp. $5.50.

ALFRED VON ZEERLEDER. "Technologie der Leichtmetalle." Rascher, Verlag, Zürich, Switzerland, 1947. 364 pp.

"Abridged Scientific Publications from the Kodak Research Laboratories." Vol. XXVIII. Eastman Kodak Company, Publishers, Rochester, New York. 280 pp.

"Lignin. Chemistry and Utilization." Bulletin No. 19, January, 1948. (Report of Conference at New Haven, Connecticut, September, 1947.) Northeastern Wood Utilization Council, P. O. Box 1577, New Haven 6, Conn. 135 pp. $2.00.

"Newer Methods of Preparative Organic Chemistry." First American Edition. Translated and revised from the German. Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y. 657 pp. $8.50.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 70 MAY 27, 1948 NUMBER 5

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

A Quantitative Study of Reversible Boundary Spreading in the Electrophoresis of Proteins[1]

BY ROBERT A. ALBERTY

Introduction

The usual criterion for the electrophoretic homogeneity of a protein is that it migrates as a single boundary in an electric field in buffers of various hydrogen ion concentrations and ionic strengths. However, this alone is not sufficient evidence that all the protein molecules have the same electrophoretic mobility, and further evidence regarding the electrophoretic homogeneity may be obtained by studying the rate with which the protein gradient spreads in the electrical field. If the molecules in a protein "family" vary with respect to electrophoretic mobility because of differences in net charge or size or shape, the protein gradient will spread faster in the electrical field than expected for diffusion alone but will become sharper upon reversal of the field.[2] While in the case of a heterogeneous protein spreading is observed at both boundaries in the U-tube, in the case of spreading caused by conductivity[3] or pH[4] gradients in the moving protein gradient, spreading at one boundary is accompanied by sharpening at the other. Spreading and sharpening caused by these superimposed gradients may be minimized by performing the electrophoresis experiment at the average isoelectric point of the protein.[5] Convection caused by the temperature gradient set up in the electrophoresis cell by electrical heating or caused by electroosmosis along the cell wall may also spread the protein boundary. Such convection effects would not be reversed by reversing the electric field because they are a result of turbulence, and so it is possible to test electrophoresis experiments for their presence.

Reversible electrophoresis spreading has been cited as evidence for the electrophoretic heterogeneity of *Helix pomatia* and *Helix nemoralis* hemocyanins,[6,7] ovomucoid,[5] alfalfa mosaic virus,[8] horse pseudoglobulin GI,[9,10] pectin[11] and bovine γ_1- and γ_2-globulins.[12]

Two quantitative methods for representing boundary spreading have been proposed,[6,13] but neither of these has been used to calculate the actual distribution in mobility among the protein molecules. The purpose of this paper is to present a quantitative method for the determination of the mobility distribution in certain cases.

Theory

If the electrophoresis of a heterogeneous protein with a mobility distribution $g(u)$ is carried out under conditions such that no convection is caused by temperature gradients or electroosmosis in the electrophoresis cell and there are no conductivity or pH gradients through the boundary between protein solution and buffer, the refractive index gradient, $\partial n/\partial x$, as a function of height in the electrophoresis cell, x, at time t_D after the formation of the boundary and time t_E after application of the electric field, is given by equation

(1) Presented before the Division of Physical and Inorganic Chemistry, Atlantic City, April 18, 1947.

(2) Tiselius, *Nova Acta Reg. Soc. Scient. Upsala*, (IV) **7**, No. 4 (1930).

(3) Longsworth and MacInnes, THIS JOURNAL, **62**, 705 (1940).

(4) Longsworth, *J. Phys. Coll. Chem.*, **51**, 171 (1947).

(5) Longsworth, Cannan and MacInnes, THIS JOURNAL, **62**, 2580 (1940).

(6) Tiselius and Horsfall, *Ark. Kem. Min. Geol.*, **13A**, No. 18 (1939).

(7) Horsfall, *Ann. N. Y. Acad. Sci.*, **39**, 203 (1939).

(8) Lauffer and Ross, THIS JOURNAL, **62**, 3296 (1940).

(9) Sharp, Cooper and Neurath, *J. Biol. Chem.*, **142**, 203 (1942).

(10) Sharp, Hebb, Taylor and Beard, *ibid.*, **142**, 217 (1942).

(11) Speiser, Copley and Nutting, *J. Phys. Coll. Chem.*, **51**, 117 (1947).

(12) Hess and Deutsch, THIS JOURNAL, **70**, 84 (1948).

(13) Sharp, Taylor, Beard and Beard, *J. Biol. Chem.*, **142**, 193 (1942).

(1).[14] D is the diffusion constant which is assumed to be the same for all the protein molecules, u is electrophoretic mobility, E is the electric field strength, and $(n_1 - n_2)$ is the difference in refractive index of the protein solution and buffer. The boundary will spread faster than expected for diffusion alone because of the difference in rates of migration of the protein ions.

$$\frac{\partial n}{\partial x} = \frac{(n_1 - n_2)}{2\sqrt{\pi D t_D}} \int_{-\infty}^{+\infty} g(u) e^{\frac{-(x - uEt_E)^2}{4Dt_D}} du \quad (1)$$

If diffusion is negligible during the electrophoresis experiment, Sharp, *et al.*,[10] point out that equation (1) assumes a simple form, and a heterogeneity constant, H, may be defined by

$$H = \Delta\sigma / \Delta t E \quad (2)$$

where $\Delta\sigma/\Delta t$ is the time rate of change of the standard deviation, σ, of the refractive index gradient. For this case, H characterizes the mobility heterogeneity of the protein and the mobility distribution may be determined directly from the gradient curves.

If diffusion is not negligible during the electrophoresis experiment, it is theoretically possible to obtain the mobility distribution $g(u)$ from the experimental refractive index gradient curves by using equation (1), but this is not a practical method for studying the distribution in mobilities because of the difficulties in computation. However, a suitable function for $g(u)$ with parameters to be evaluated from the experimental curves may be introduced in equation (1). In the case of a protein at its "average" isoelectric point so that the most frequent molecule has a mobility of zero, it is convenient to try a Gaussian distribution function with h, the heterogeneity constant, the parameter to be evaluated.

$$g(u) = \frac{1}{h\sqrt{2\pi}} e^{-u^2/2h^2} \quad (3)$$

h has the dimensions of mobility and is the standard deviation for the mobility distribution which has been normalized to unity. Substituting this form of $g(u)$ in (1) and integrating, we obtain the equation giving the refractive index gradient as a function of height in the cell for such a protein during electrophoresis.

$$\frac{\partial n}{\partial x} = \frac{(n_1 - n_2)}{\sqrt{2\pi}\sqrt{E^2h^2t_E^2 + 2Dt_D}} e^{-x^2/2(E^2h^2t_E^2 + 2Dt_D)} \quad (4)$$

This equation shows that if there is a Gaussian distribution of mobilities, the electrophoresis gradient curves should be Gaussian, as is closely realized for the systems studied.

The heterogeneity constant, h, may be evaluated by noting that the standard deviation, σ, of the experimental curve should be

$$\sigma = \sqrt{E^2h^2t_E^2 + 2Dt_E + 2D\Delta t} \quad (5)$$

if the electrophoresis is started after the boundary has been diffusing Δt seconds. $2D\Delta t$ is the square of the standard deviation of the gradient curve at the moment the electric field was applied, σ_0^2. Rearranging

$$D^* = \frac{\sigma^2 - \sigma^2}{2t_E} = D + \frac{E^2h^2}{2} t_E \quad (6)$$

D^* is the "apparent diffusion constant" calculated from the experimental gradient curves during the electrophoresis.[15] According to this equation, the apparent diffusion constant should plot as a straight line against time of electrophoresis and extrapolate back to the normal diffusion constant at zero time. If the protein is heterogeneous and has a Gaussian distribution of mobilities, the straight line will have a slope $E^2h^2/2$ from which the heterogeneity constant h may be calculated. Since the heterogeneity constant is the standard deviation for the mobility distribution, the actual mobility distribution curves may be constructed using a table of values for the Gaussian probability function.

Equation (5) for the standard deviation of the electrophoresis curves in terms of the heterogeneity constant h may be used to show the relationship between the heterogeneity constant, H, introduced by Sharp, Taylor, Beard and Beard[13] and h. For the case in which electrophoresis and diffusion start simultaneously

$$H = \frac{\sigma}{tE} = \sqrt{\left(\frac{2D}{E^2}\right)\frac{1}{t} + h^2} \quad (7)$$

This shows that if diffusion is negligible, $H = h$. If diffusion is not negligible, H will decrease with time approaching h asymptotically.

As a check on irreversible spreading during electrophoresis, the direction of the electric field may be reversed for an equal period of time. The manner in which the apparent diffusion constant varies with time during the reversal period may be shown by using equation (5). If t_E is the total time the current has been flowing in both direc-

(14) This equation has been but slightly modified from that given by Sharp, Hebb, Taylor and Beard.[10] The times in the equation have been given subscripts to indicate whether they are the time of diffusion or electrophoresis so that the more general case in which these are not equal may be treated. Sharp, *et al.*, prefer to use a modified diffusion constant D_1 which may not be the same as D since they state variations in mobility of individual particles with time may affect the rate of diffusion under the influence of an electric field. If, however, as assumed by Tiselius (ref. 2, p. 26) diffusion is simply superimposed on the electrophoretic migration, it should not be necessary to distinguish between two diffusion constants provided convection can be eliminated, and no distinction is made in this paper.

(15) The apparent diffusion constant may be calculated from the gradient curves by any of the standard methods which will all give the same result provided the refractive index gradient is Gaussian in form. In this paper the apparent diffusion constants have been calculated from enlarged tracings of the photographs by using the half width x, of the gradient curves at the inflection point $\frac{Y}{\sqrt{e}}$, or from the area, A, and maximum height, Y,

$$D_\sigma^* = \frac{x^2 - x_0^2}{2t_E G^2} \qquad D_A^* = \frac{\left(\frac{A}{Y}\right)^2 - \left(\frac{A}{Y}\right)_0^2}{4\pi t_E G^2}$$

If x, A and Y are measured in centimeters on a tracing of the photograph, G is the number of cm. on the tracing paper corresponding to one cm. in the electrophoresis cell.

tion, and t_1 is the time after which the current was reversed, for $t_E > t_1$

$$D^* = D + \frac{E^2h^2}{2}\frac{(2t_1 - t_E)^2}{t_E} \qquad (8)$$

Thus the apparent diffusion constant decreases with time and becomes equal to the diffusion constant at $t_E = 2t_1$. The slope of the D^* *vs.* t_E plot immediately after reversing the current ($t_E = t_1$) is $-\frac{3}{2}E^2h^2$, and when $t_E = 2t_1$ the slope is zero showing that an error of a few minutes in the time of reversing the current will generally not cause D^* to differ significantly from D.

More general distribution functions with as many constants as justified by the precision of the experimental data may be used in place of the error function.[16] In cases in which the gradient curves are symmmetrical but not Gaussian, the sum of two or more Gaussian distribution functions may be used to represent the mobility distribution $g(u)$. Such a distribution function may be integrated conveniently when substituted in equation (1), and the parameters may be evaluated from the successive moments of a single gradient curve by the same method used in determining the diffusion constants and relative amounts of two or more independently diffusing molecules in a polydisperse system.[17]

Experimental

The optical system used in this work was the cylindrical lens schlieren optical system with a schlieren lens on each side of the thermostat arranged so that light from the horizontal slit passed through the cell in a parallel beam.[18] A diagonal slit (0.50 mm. wide) was used in the optical system, and the photographs were taken on Eastman Kodak Co. CTC plates and enlarged and traced. The gradient curves were obtained by averaging the ordinates of the two edges of the band of light and constructing the corresponding mean curve. It was found that the diffusion constants determined by this method did not vary with the exposure time as did those determined by the diagonal knife edge method.

It was found that when diffusion boundaries were formed in the standard Tiselius electrophoresis cell by the usual method and compensated into the optical system at the rate of 2–3 cm. per hour using a mechanically driven syringe, thirty to ninety minutes had to be added to the diffusion times in order to obtain a constant diffusion constant for short time diffusions (less than ten hours).[19] The quality of the initial boundary is very important in an electrophoresis spreading experiment since it must be carried out in a short period compared to the usual 3–4 day diffusion experiment. As shown by equation (6), the apparent diffusion constant may be calculated even when the initial gradient is diffuse, provided it is Gaussian, by using the method of differences, and this is satisfactory if the electrophoresis spreading is large. However, in the case of a homogeneous protein the spreading of the gradient during the experiment is not large and D^* calculated by the method of differences is subject to rather large experimental errors. In order to avoid the correction for the width of the initial boundary, the sharpening technique of Kahn and Polson[20] may be applied. In forming these so-called "sharpened" boundaries for some of the electrophoresis spreading experiments, a capillary was lowered into the protein boundary after it had been compensated into the cell, which was set up with both sides open to the atmosphere, and the diffuse portion of the boundary was drawn off by suction at a rate of about 0.4 cc. per minute. The sharpening of the boundary was followed with the schlieren optical system, and when the boundary became no sharper, the suction was practically stopped while the capillary was carefully withdrawn, and this time was taken as the starting time for the diffusion. Figure 1 shows the results of a short diffusion of crystallized bovine albumin[23] using a sharpened boundary. The zero time correction was negligible after one hour, and the agreement between the diffusion constants calculated by two methods indicates the precision obtained with the schlieren optical system. The average diffusion constant, 3.1×10^{-7} cm.^{2} sec.$^{-1}$ at 1.5°, is in agreement with earlier values.[21]

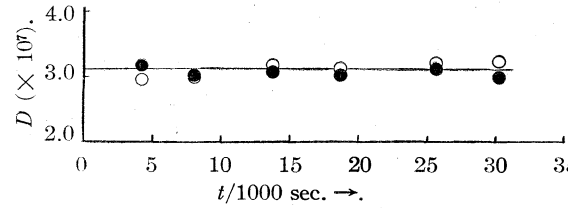


Fig. 1.—Diffusion constant for crystallized bovine albumin, $\Gamma/2 = 0.1$, pH 4.6, 0.6% protein, at 1.5°. ●, calculated from the half width at the inflection point; O, calculated from the height and area.

The disadvantage of applying the sharpening technique in electrophoresis spreading experiments is the difficulty of sharpening both boundaries simultaneously. When only one of the boundaries is sharpened and conclusions are drawn from its behavior alone, sharpening or broadening of the peak caused by the field and pH gradients may go undetected, and an erroneous conslusion as to the homogeneity of the protein may be drawn.

More than the usual care to avoid thermal convection must be taken in electrophoresis spreading experiments. In electrophoresis load tests with alternating current Tiselius[22] found that power dissipations of 0.5 to 1 watt/cc. could be used in flattened electrophoresis cells near the temperature of maximum density of water. Loads of about 0.15 watt/cc. are used routinely in this Laboratory with the standard 11-cc. cells, but for spreading experiments the loads were kept below 0.015 watt/cc. It has been found that loads which do not cause convection in short experiments (two hours) may cause convection in prolonged spreading experiments as the density gradient becomes progressively less.

In order to reduce the difference in buffer salt concentration in the protein solution and equilibrium buffer caused by the Donnan effect and to reduce optical errors inherent in measuring high refractive index gradients, protein concentrations of 0.5 to 0.8% were used in all experiments. The electrophoresis samples were dialyzed two days in the cold before electrophoresis. The conductivity of the equilibrium buffer measured at the temperature of the thermostat (1°) was used in calculating the potential gradient, and the pH of the buffers was measured at 25° using a glass electrode.

(16) For examples of such functions see Rinde, "The Distribution of the Sizes of Particles in Gold Sols," Inaugural Dissertation, Upsala, 1928; Lansing and Kraemer, THIS JOURNAL, **57**, 1369 (1935); Jullander, *Ark. Kem. Min. Geol.*, **21A**, No. 8, 14 (1945).

(17) Neurath, *Chem. Rev.*, **30**, 357 (1942).

(18) Svensson, *Kolloid Z.*, **87**, 181 (1939); **90**, 141 (1940).

(19) This is similar to the observation by Longsworth that diffusion boundaries compensated into the electrophoresis cell are imperfect, THIS JOURNAL, **69**, 2510 (1947).

(20) Kahn and Polson, *J. Phys. Coll. Chem.*, **51**, 816 (1947).

(21) Cohn, Hughes and Weare, THIS JOURNAL, **69**, 1753 (1947); Stern, Singer and Davis, *J. Biol. Chem.*, **167**, 321 (1947).

(22) Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

Results

Bovine Albumin.—The isoelectric point of crystallized bovine albumin was found to be *p*H 4.6 at 0.10 ionic strength in acetate buffers. A number of spreading experiments carried out at this *p*H showed that although there was partial resolution of about 5% of another protein constituent, the same rate of boundary spreading was observed in both limbs of the U-tube. The additional protein component would not appear to be α- or β-globulin.[23] In these experiments the boundaries were compensated into the electrophoresis cell at a rate of about 1 cm. per hour, and after they had diffused until the maximum gradient was recorded by the optical system, a photograph was taken to determine σ_0 and the electric field applied. In the experiment shown in Fig. 2 one boundary was sharpened and the electric field applied immediately. The vertical arrows indicate the reversal time and the end of the experiment. The fact that the apparent diffusion constant at the end of the experiment is in agreement with the diffusion constant obtained from free diffusion (3.1×10^{-7} cm.^{2} sec.$^{-1}$, Fig. 1) is evidence that thermal and electroosmotic effects of the current did not disturb the boundaries appreciably. This is in agreement with the observation of Longsworth[24] that the correct diffusion constant for a raffinose boundary in 0.1 *N* lithium chloride was obtained in an electric field provided the power dissipation was not too great and is contrary to the conclusion of Janssen[25] that boundaries of non-electrolytes spread more rapidly in an electric field than expected from diffusion alone. A small amount of reversible spreading is evident in the case of bovine albumin, and although this amount of electrical spreading is not much greater than the experimental error, the electrical heterogeneity of bovine serum albumin at its isoelectric point has been confirmed by spreading experiments at 0.01 ionic strength where higher field strengths may be used.[26]

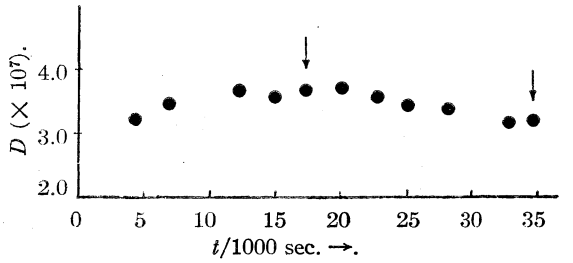


Fig. 2.—Electrophoretic spreading experiment with crystallized bovine albumin at $\Gamma/2 = 0.10$, *p*H 4.61 at 1.59 volts/cm. and 0.0135 watt/cc. using a sharpened boundary. The apparent diffusion constants were calculated by the inflection point method.

Human γ_2-Globulin.—Human γ_2-globulin[27] was studied by electrophoresis spreading experiments at several ionic strengths. The sample of protein used contained less than 2% of γ_1- and β-globulins and albumin as judged by electrophoresis at *p*H 8.6, $\Gamma/2 = 0.10$. Some of the refractive index gradient curves obtained during the electrophoresis of human γ_2-globulin at its average isoelectric point at 0.10 ionic strength are given in Fig. 3. The experimental refractive index gradient curves in solid lines are plotted with their bisecting ordinates located at the time at which the photograph was taken. The superimposed dashed curves give the patterns which would have been obtained if the spreading had been caused by diffusion alone (calculated using $D_0^0 = 2.0 \times 10^{-7}$). Note that after the direction of the electric field was reversed at 300 minutes, the experimental gradient curves became sharper and that after the electric field had been applied for equal times in the two directions, the experimental gradient was just that expected from diffusion alone. Figure 4 shows a comparison of a refractive index gradient curve obtained in the electrophoresis of human γ_2-globulin with the Gaussian probability curve in normal coördinates.[28] This gradient is nearly enough Gaussian

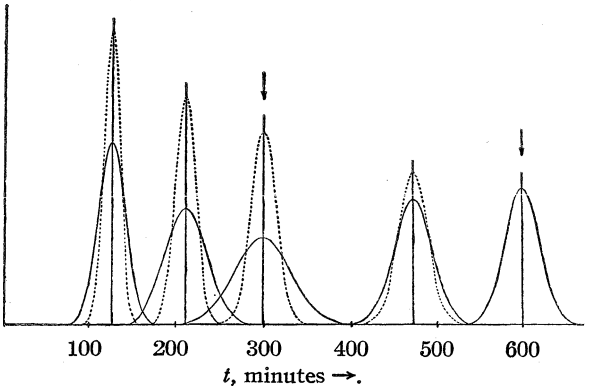


Fig. 3.—Refractive index gradient curves (solid lines) from the electrophoresis of human γ_2-globulin at $\Gamma/2 = 0.1$, *p*H 7.27, at 1.70 volts/cm. and 0.0131 watt/cc. using a sharpened boundary. The superimposed dashed curves give the patterns which would have been obtained if the spreading had been caused by diffusion alone. The field was reversed after 300 minutes.

(23) The crystallized bovine albumin was from Lot 46 prepared by Armour Laboratories, Chicago, Illinois. Electrophoresis experiments in *p*H 8.6, 0.1 ionic strength diethyl barbiturate buffer indicate no appreciable content of globulin impurities, while immunological tests carried out as described by Cohn, Hughes and Weare, THIS JOURNAL, **69**, 1755 (1947), indicate that less than 0.01% α-globulin is present. Thus the immunological tests would indicate that any impurity could not be the same protein as that which constitutes most of the alpha globulin component of plasma. They do not eliminate the possibility that another protein component similar to albumin in its antigenic behavior may be present. Private communication from Dr. J. B. Lesh.

(24) Longsworth, THIS JOURNAL, **69**, 1288 (1947).

(25) Janssen, *Rec. trav. chim.*, **65**, 564 (1946).

(26) Alberty, Anderson and Williams, Colloid Symposium, Stanford University, June, 1947, *J. Phys. Coll. Chem.* **52**, 217 (1948).

(27) Deutsch, Alberty and Gosting, *J. Biol. Chem.*, **165**, 21 (1946).

(28) Lamm, *Nova Acta Reg. Soc. Scient. Upsala*, (IV), **10**, No. 6 (1937).

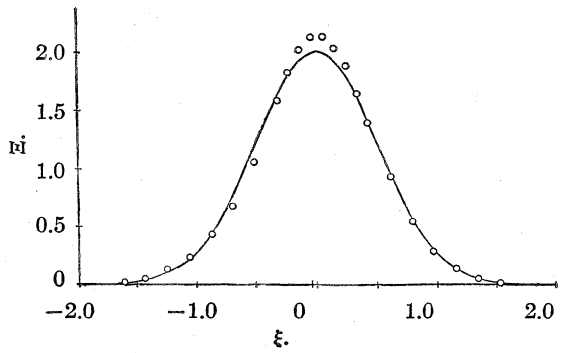


Fig. 4.—Comparison of the third experimental refractive index gradient curve given in Fig. 3 (circles) with the Gaussian probability function (solid curve) in normal coördinates.

that the mobility distribution may be represented by the error function. Figure 5, which shows the variation in apparent diffusion constant during the sharpened electrophoresis experiments represented in Fig. 3, indicates that D^* plots as a straight line *vs.* t_E during the period before the current was reversed as predicted by equation (6) for a Gaussian distribution of mobilities. The apparent diffusion constants calculated by the height and area method were somewhat higher than those calculated by the inflection point method in the case of the gradients spread both by diffusion and electrical heterogeneity, as would be expected because of the deviation of the gradients from perfect Gaussian form (Fig. 4). Since the apparent diffusion constant calculated from the half width at the inflection point is less affected by the resolution of small amounts of γ_1- and β-globulin from the main peak, the heterogeneity constant was calculated from the slope of the straight line through these points. The initial straight line extrapolates back to the diffusion constant for γ_2-globulin at zero time, and the heterogeneity constant, h, calculated from the slope is 0.52×10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$. When the direction of the current was reversed for an equal period of time, the correct diffusion constant was obtained, and this indicates that irreversible spreading caused by thermal convection and electroosmosis were negligible in this experiment. The values expected for the apparent diffusion constant during the reversal period were calculated using equation (8) and $h = 0.52 \times 10^{-5}$. The calculated values are represented by the solid curve in Fig. 5, and the agreement with the experimental points is further evidence that the electrical heterogeneity of human γ_2-globulin may be represented by a Gaussian mobility distribution.

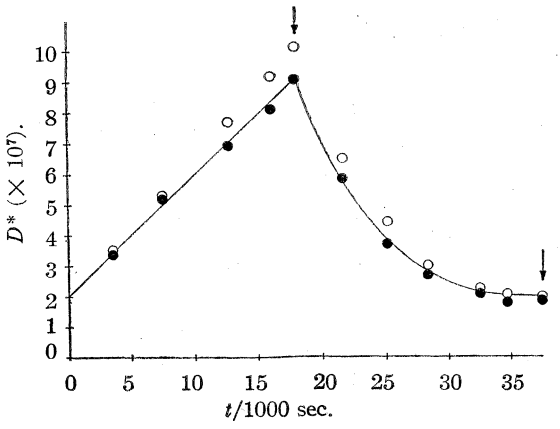


Fig. 5.—Plot of apparent diffusion constant *vs.* time of electrophoresis for the electrophoresis experiment with human γ_2-globulin given in Fig. 3: ●, calculated from half width at inflection point; ○, calculated from height and area.

The heterogeneity constant, H, of Sharp, *et al.*,[13] calculated from the data of this experiment using equation (2) has been plotted against time in Fig. 6. As expected H drifts downward because diffusion is not negligible, and H approaches the value of the heterogeneity constant, h, calculated from Fig. 5, asymptotically. In Fig. 6 the solid curve through the experimental points has been calculated from equation (7) using $h = 0.52 \times 10^{-5}$, $D = 2.0 \times 10^{-7}$, and adequately represents the experimental points.

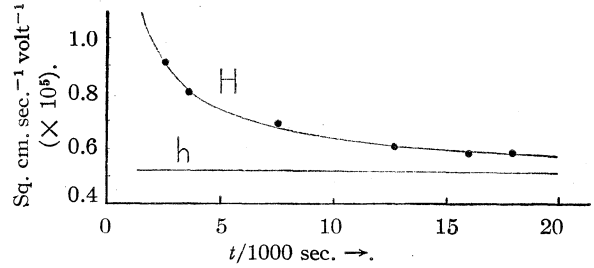


Fig. 6.—Plot of H *vs.* time of electrophoresis for human γ_2-globulin during the initial period of the experiment given in Fig. 3.

In order to study the variation of h for human γ_2-globulin with ionic strength, electrophoresis spreading experiments were also performed at 0.15 and 0.010 ionic strengths close to the isoelectric points under these conditions. The data on these experiments are given in Table I, and the

TABLE I

ELECTROPHORESIS SPREADING EXPERIMENTS WITH HUMAN γ_2-GLOBULIN

Γ/2	pH	Buffer[a]	Heating watt/cc.	E volt/cm.	h[b]
0.010	8.12	0.01 *N* NaV	0.0145	6.27	0.88×10^{-5}
					$.98 \times 10^{-5}$
.10	7.27	.04 *N* NaCac	.0131	1.70	$.52 \times 10^{-5}$
		.06 *N* NaCl			
.15	6.70	.02 *N* NaCac	.0155	1.40	$.40 \times 10^{-5}$
		.13 *N* NaCl			$.38 \times 10^{-5}$
.16	8.01	.01 *N* NaV	.0140	1.67	$.40 \times 10^{-5}$
		.05 *M* $CaCl_2$			$.43 \times 10^{-5}$

[a] V = diethyl barbiturate, Cac = cacodylate. [b] The heterogeneity constant (in cm.^{2} sec.$^{-1}$ volt^{-1}) obtained on the ascending side is placed below that obtained on the descending side.

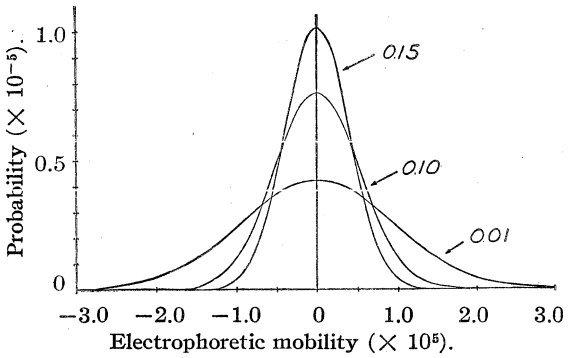


Fig. 7.—Mobility distributions for human γ_2-globulin at several ionic strengths.

mobility distributions are plotted in Fig. 7. The agreement between the heterogeneity constants obtained on the ascending and descending sides is evidence that electrical sharpening and spreading effects are of negligible importance. However, it should be pointed out that agreement between the heterogeneity constants determined from ascending and descending boundaries is not sufficient evidence that sharpening and spreading caused by conductivity and *p*H gradients is negligible in the case of a heterogeneous protein at a *p*H away from the isoelectric point. For example, in the case of human γ_2-globulin at *p*H 8.6, $\Gamma/2 = 0.10$, veronal buffer, the ascending peak has very nearly the same shape as the descending peak,[29] in spite of the tendency to sharpen on the ascending side because of the conductivity effect. This is probably not a result of the *p*H effect or a reversal of the conductivity effect because $(1/u)(du/dp\mathrm{H})$ and u are quite small.[4] The ascending boundary is more diffuse than expected from a superposition of the conductivity effect and diffusion in this case probably because the protein boundary velocity is greater on the ascending side, and this causes the actual separation of two molecules of different mobility in the heterogeneous protein to be greater on the ascending side after a given time than on the descending. Consequently too great a value for the heterogeneity constant would be obtained from both boundaries. In the experiments described here, the mobilities of the center of the boundaries were very low (less than 0.3×10^{-5} cm.^{2} sec.$^{-1}$ volt^{-1} uncorrected for electrode volume changes), and the difference in mobility on the ascending and descending sides was no larger than the usual experimental error.

Discussion

Variation of Heterogeneity with Ionic Strength.—The variation in mobility heterogeneity with ionic strength is a combination of a number of factors. In the case of human γ_2-globulin some euglobulin is not soluble at the average isoelectric point at 0.01 ionic strength so that the protein studied at this ionic strength is not identical with that studied at 0.10 and 0.15 ionic strength. The valence of a protein molecule a given number of *p*H units away from the isoelectric point generally decreases with decreasing ionic strength.[30] However, in spite of this decrease in valence, the electrophoretic mobility a given number of *p*H units from the isoelectric point generally increases with decreasing ionic strength[31] because of the decrease in the screening effect of the ionic atmosphere[32] and the modification of the viscous flow of solvent past the moving particle.[33] Assuming to a first approximation that the γ_2-globulin molecule may be represented by a sphere of 55 Å. radius (calculated from $D_0^0 = 2.0 \times 10^{-7}$), the effect of ionic strength on mobility may be estimated from electrophoretic theory.[31,33,34] The mobility resulting from a given net charge should be proportional to $\phi(\kappa a)/(1 + \kappa a)$ where κ is the reciprocal of the "thickness" of the ion atmosphere, a is the radius of the protein molecule, and $\phi(\kappa a)$ is Henry's function. Assuming that the net charge distribution in γ_2-globulin at the isoelectric point is independent of ionic strength, the standard deviation of the mobility heterogeneity should be proportional to $\phi(\kappa a)/(1 + \kappa a)$. Since the values of this function at 0.01, 0.10, and 0.15 ionic strengths at 0° are 0.379, 0.178, and 0.153, the heterogeneity constants expected at 0.01, 0.10, and 0.15 ionic strength are 1.11×10^{-5}, (0.52×10^{-5} assumed) and 0.45×10^{-5}. Although this is not an exact calculation it is seen that the direction and magnitude of the variation in h observed experimentally (Table I) is in agreement with that expected from electrophoretic theory.

Northrop[35] and Rothen[36] have concluded that the reversible electrophoresis spreading shown by crystalline diphtheria antitoxin of constant solubility can not be attributed to a heterogeneous preparation but is connected with electroösmosis because the spreading was diminished by the addition of calcium chloride to their buffer to a concentration of 0.05 *M*. In order to test for this possibility with human γ_2-globulin, a similar experiment was performed. It was not found possible to prepare the 0.067 *M*, *p*H 7.2, veronal buffer mentioned by Rothen because of the insolubility of the diethylbarbituric acid at this *p*H and 1°, and so the experiment was performed by using the 0.01 ionic strength veronal buffer indicated in Table I. Some of the buffer used for the spreading experiment at 0.01 ionic strength was made 0.05 *M* in calcium chloride by the addition of solid calcium chloride. Although a smaller potential gra-

(29) Cohn, Oncley, Strong, Hughes and Armstrong, *J. Clin. Invest.*, **23**, 417 (1944), Fig. 2.

(30) Cannan, Kibrick and Palmer, *Ann. N. Y. Acad. Sci.*, **41**, 247 (1941); Cannan, Palmer and Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).

(31) Tiselius and Svensson, *Trans. Faraday Soc.*, **36**, 16 (1940).

(32) Debye and Hückel, *Physik Z.*, **24**, 305 (1923).

(33) Henry, *Proc. Roy. Soc.* (*London*), **A133**, 106 (1931).

(34) Longsworth, *Ann. N. Y. Acad. Sci.*, **41**, 267 (1941).

(35) Northrop, *J. Gen. Physiol.*, **25**, 465 (1942).

(36) Rothen, *ibid.*, **25**, 487 (1942).

dient had to be used in the case of the buffer containing calcium chloride, reversible spreading was observed, and the slope of the graph of D^* *vs.* time of electrophoresis yielded a heterogeneity constant of 0.42×10^{-5} (average of two limbs). Although this value for the heterogeneity constant is smaller than that obtained in the 0.01 ionic strength buffer ($h = 0.93 \times 10^{-5}$) before the addition of calcium chloride, it is about what should be expected at the higher ionic strength of the calcium chloride buffer ($\Gamma/2 = 0.16$) for reasons outlined in the preceding paragraph. The heterogeneity constant obtained with the calcium chloride buffer is in good agreement with that obtained at 0.15 ionic strength (0.02 *N* NaCac, 0.13 *N* NaCl) and does not indicate that the reversible spreading of human γ_2-globulin is caused by electroosmosis.

Sensitivity.—Spreading experiments at lower ionic strengths are a more sensitive test of electrophoretic homogeneity because higher electric field strengths may be employed without causing thermal convection and the standard deviation of the mobility distribution of a heterogeneous protein is greater at lower ionic strengths as illustrated in Fig. 7. As electrophoresis spreading experiments are carried out at present, the smallest heterogeneity constant which may be determined is limited by the conductivity of the buffer and the sensitivity of the schlieren optical system. Assuming an increase of 1×10^{-7} in the apparent diffusion constant during five hours electrophoresis is the minimum increase which may be measured and 0.015 watt/cc. is the maximum permissible heat dissipation in an electrophoresis cell of 0.77 cm.^{2} cross section, the smallest heterogeneity constant which could be determined in a buffer of 50×10^{-4} ohm^{-1} cm.$^{-1}$ conductivity at 0° is 0.2×10^{-5} while in a buffer of 1×10^{-4} ohm^{-1} cm.$^{-1}$ conductivity, 0.03×10^{-5} would be detected.

Interpretation.—Several of the possible interpretations of the reversible electrophoresis spreading of γ_2-globulin may be eliminated. Since this protein is apparently homogeneous with respect to sedimentation and diffusion, the variation in mobility cannot be attributed to a difference in the frictional coefficients of the molecules. Also the spreading cannot be attributed to the existence of different charged forms of identical protein molecules which are in equilibrium in a solution of given *p*H and ionic strength because any individual molecule in the system is constantly giving up and taking on protons, so that the time average of its net charge, considered over an appreciable time interval in which many proton exchanges take place, is identical with the mean net charge of all the molecules in the system.[37] Therefore, on the basis of electrophoresis spreading experiments it may be concluded that human γ_2-globulin consists of a mixture of molecules differing with respect to their average net charge.

The actual variation in net charge among the molecules in human γ_2-globulin as indicated by reversible electrophoresis spreading is not large. Calculation of the proportionality constant between valence of the protein ion and electrophoretic mobility by the method of Abramson, Moyer and Gorin[38] at 0.10 ionic strength (assuming a cylindrical molecule with an axial ratio of 7 and a molecular weight of 160,000) indicates that a molecule with a mobility equal to the standard deviation of the mobility distribution (0.52×10^{-5}cm.^{2} sec.$^{-1}$ volt^{-1}) has a net charge of approximately 3 electrons. This variation in net charge among the molecules would indicate a small variation in their contents of the ionizable amino acids, a variation in arrangement resulting in different end groups or perhaps only a variation in steric effects of groups neighboring ionizable amino acids residues which affects the dissociation constants. Human γ_2-globulin prepared from plasma pools contains antibodies to many different antigens,[39] and therefore according to present theories of antibody structure the molecules have a variety of different configurations. It might be expected therefore, that the molecules would not be identical with respect to net charge at a given *p*H and ionic strength even if they were identical with respect to amino acid composition.

Acknowledgments.—The author wishes to express his appreciation to Dr. J. W. Williams for his interest and helpful suggestions. He is also indebted to Dr. J. O. Hirschfelder for helpful suggestions, to Mr. E. A. Anderson for assistance in the laboratory, and to Dr. G. Kegeles for his review of the manuscript. Financial support which was received from the National Institute of Health is gratefully acknowledged.

Summary

1. A method for the determination of the electrophoretic mobility distribution in a heterogeneous protein having a Gaussian distribution of mobilities has been developed for the case in which diffusion during the electrophoresis experiment is not negligible. In this case the apparent diffusion constant is a linear function of time of electrophoresis and the heterogeneity constant, *h*, which is the standard deviation of the mobility distribution, may be calculated from the slope.

2. It has been shown that electrophoresis spreading experiments may be carried out under conditions such that spreading caused by the conductivity and *p*H effects, thermal convection, and electroösmosis are negligible.

3. Crystallized bovine serum albumin has been found to show a small amount of reversible spreading at its isoelectric point at 0.10 ionic

(37) Cohn and Edsall, "Proteins, Amino Acids, and Peptides as Ions and Dipolar Ions," Reinhold Publishing Corp., New York, N. Y., 1943, *cf.* p. 468.

(38) Abramson, Moyer and Gorin, "The Electrophoresis of Proteins," Reinhold Publishing Corp., New York, N. Y., 1942.

(39) Enders, *J. Clin. Invest.*, **23**, 510 (1944); Deutsch, Alberty, Gosting and Williams, *J. Immun.*, **56**, 183 (1947).

strength. Human γ_2-globulin shows a large amount of reversible spreading and the standard deviation for the mobility distribution has been found to vary with ionic strength in the direction expected from electrolytic solution theory.

MADISON, WISCONSIN RECEIVED AUGUST 12, 1947

[CONTRIBUTION FROM ALLERGEN RESEARCH DIVISION, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

Photochemistry of Tryptophan, *p*-Dimethylaminobenzaldehyde and Reaction Products in Sulfuric Acid Solution[1]

BY JOSEPH R. SPIES AND DORRIS C. CHAMBERS

During a previously reported study[2] of the color-forming reactions between tryptophan, *p*-dimethylaminobenzaldehyde (DAB) and sodium nitrite in sulfuric acid solution, it became necessary to study the effects of light on the reactants and reactions involved. This paper describes a method for studying the effects of illumination (the term "illumination" refers to exposure to light by a procedure described below), the effect of light on the stability of tryptophan, the effects of light on reactions I and II,[3] and a photochemical "after effect" produced by illumination of DAB in acid solution. The reactions were carried out in 19 *N* sulfuric acid because this concentration was found suitable for the determination of tryptophan in proteins by a procedure to be described in later papers.

Photochemical development of color from the colorless condensation product of tryptophan and DAB was first reported by Boyd[4] who attributed this effect to the ultraviolet rays of sunlight.[5]

The effect of illumination on the stability of tryptophan in 19 *N* acid at 25° is shown in Table I. Light accelerates the decomposition of tryptophan as losses of 3, 11 and 34% occurred on illumination for one-half, one and three hours, respectively, compared with a loss of only 8% on standing in the dark for forty-eight hours.

The effects of illumination during reaction I under conditions such that reactions I and II were proceeding simultaneously are shown in Table II. Illumination for the first ten seconds of reaction I caused no increase in pre-nitrite color[6] nor any loss of tryptophan. But illumination for thirty seconds caused an increase in pre-nitrite color and destruction of 6% of the tryptophan. The pre-nitrite color increased with time of illumination until after 180 minutes it amounted to 76% of the total. The loss of tryptophan, caused by illumination, increased to 25% of the total during the first five minutes of reaction I and then remained constant. Reaction I is 87% completed in five minutes (Table VI).[2] Therefore the destructive effects of illumination occur chiefly during the condensation of tryptophan and DAB.

TABLE I

EFFECT OF LIGHT ON THE STABILITY OF FREE TRYPTOPHAN IN 19 *N* SULFURIC ACID AT 25°[a]

Time illuminated or dark, hours	Loss of tryptophan, % Illuminated	Loss of tryptophan, % Dark[b]
0	0	..
0.1	0	0
.25	0	..
.50	3	0
1	11	0
2	..	0
3	34	..
4	..	3
24	..	6
48	..	8

[a] Procedure: nine ml. of 21.4 *N* acid at 25° was placed in tube A, Fig. 2, and 100 γ of tryptophan in 1.0 ml. of water was added. The solution was mixed and tube A was placed at once in holder B through which water at 25 ± 0.1° was circulating. Illumination was started twenty seconds after adding the tryptophan to the acid solution. After the desired interval of illumination the solution was poured onto 30 mg. of DAB in a 25-ml. glass-stoppered Erlenmeyer flask. Tryptophan was then determined by procedure C, Paper I.[2] [b] Results taken from Table VII, Paper I[2].

Rate of reaction II caused photochemically is rapid at first and then becomes quite slow as 70, 88 and 93% of the color was developed by five, twenty, and 120 minutes illumination, respectively.[7] After five minutes of illumination only 94% of the potentially available color could be obtained by subsequent oxidation with sodium nitrite. This destructive effect, however, was not progres-

(1) Paper II in a series entitled, "Chemical Determination of Tryptophan." Presented at the 111th meeting of the American Chemical Society held at Atlantic City, New Jersey, April, 1947. Not subject to copyright.

(2) Spies and Chambers, *Anal. Chem.*, **20**, 30 (1948).

(3) The condensation of tryptophan and DAB to form the leuco base is called reaction I and the oxidative development of the blue color, either photochemically or with sodium nitrite, is designated reaction II.

(4) Boyd, *Biochem. J.*, **23**, 78 (1929).

(5) Ruemele, *Z. Untersuch. Lebensm.*, **79**, 453 (1940), observed that light effected the formaldehyde–tryptophan colorimetric reaction but no detailed study was made.

(6) The term pre-nitrite color will refer to that color which develops in a test solution either spontaneously or as a result of exposure to light. The term post-nitrite color refers to that color which develops in a test solution after addition of sodium nitrite.

(7) Procedure: To 1.607 mg. of tryptophan and 482 mg. of DAB in a glass-stoppered Erlenmeyer flask was added 160.7 ml. of 19 *N* acid. The solution was kept in the dark at 25° for twenty-two hours. After illumination of 10 ml. aliquots of this solution pre-nitrite transmittancies were read and expressed as per cent. of the maximum color obtainable under ideal conditions of the test (procedure E, Paper I[2]).

TABLE II

EFFECT OF ILLUMINATION ON REACTION I[a]

Time illuminated	% Total color formed[b] Pre-nitrite	Post-nitrite	Loss
0	13	100	0
1 sec.	15	100	0
10 sec.	13	100	0
30 sec.	19	94	6
1 min.	29	89	11
5 min.	65	75	25
15 min.	68	72	28
30 min.	70	72	28
1 hr.	72	75	25
3 hr.	76	76	24

[a] Procedure: Eight ml. of 23.8 *N* acid and 1.0 ml. of 2 *N* acid containing 30 mg. of DAB were mixed and cooled to 25°. To this solution was added 100 γ of tryptophan in 1.0 ml. of water. Immediately after mixing, the solution was placed in tube A, Fig. 2, which was then placed in B, Fig. 2, through which water at 25 ± 0.1° was circulating. Illumination was started twenty seconds after adding the tryptophan. After the desired interval of illumination the solution was poured into a 25-ml. glass-stoppered Erlenmeyer flask which was stored in the dark at 25° for twenty to twenty-four hours. Pre-nitrite transmittancies were then read. Color was then developed by adding 0.1 ml. of 0.04% sodium nitrite solution. Post-nitrite transmittancies were read after the solutions had stood for thirty minutes in the dark. [b] Transmittancies were converted to weight of tryptophan then expressed as the per cent. of the maximum color obtainable with an equal quantity of tryptophan under ideal conditions of the test.[2]

sive because whether the illumination was for five or 120 minutes the same amount of color could subsequently be obtained with sodium nitrite.

Illumination of test solutions, in which the color had already been fully developed with sodium nitrite, for ninety minutes caused no loss in color intensity thus showing the stability of the blue colored substance to light.

The color formed photochemically has an absorption curve similar to that formed by sodium nitrite as shown in Fig. 1. The wave length of maximum density was 590 to 600 mu in both curves B and G and a characteristic absorption peak occurred at 425 mu.

Illumination of DAB in 21.4 *N* acid before the addition of tryptophan to the test solution produced considerable pre-nitrite color as "after effect."[8] The effect of time of illumination on the intensity of the pre-nitrite and post-nitrite colors is shown in Table III. The pre-nitrite colors of all non-illuminated control solutions of DAB represented from 2.5 to 4.5% of the total color. But when DAB was illuminated for five seconds, one, five, fifteen and sixty minutes, prior to addition of the tryptophan, the pre-nitrite color represented 5.1, 20, 45, 55 and 58% of the total color, respectively. Losses of tryptophan from 1.5 to 5.4%

(8) The photochemical "after effect" is discussed in some detail by Kistiakowsky, "Photochemical Processes," The Chemical Catalog Co., Inc., New York, N. Y., 1928, and Dhar, "The Chemical Action of Light," Blackie and Son, Limited, London and Glasgow, 1931. In general, this term refers to those photochemical reactions which occur after cessation of illumination.

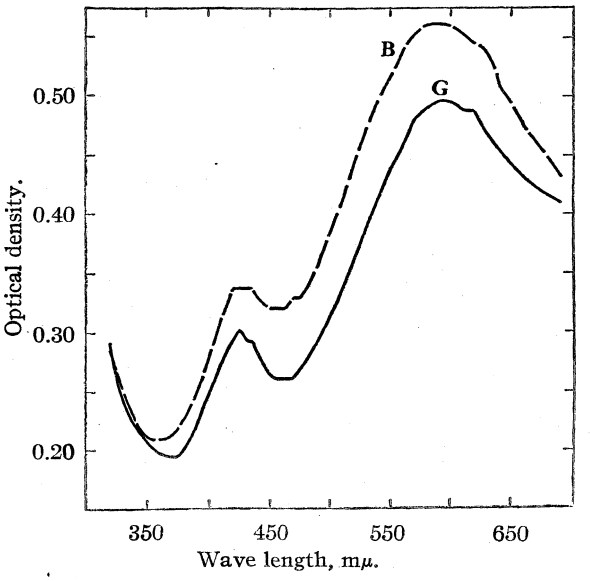


Fig. 1.—Absorption curves of tryptophan-DAB color developed with sodium nitrite (Curve B, taken from Fig. 1, Paper I) and light (Curve G, illuminated for 20 minutes). 100 γ of tryptophan was used for each test. Transmittancies were determined with a Beckman spectrophotometer with 10-mm. cuvettes.

TABLE III

EFFECT OF TIME OF ILLUMINATION ON THE PHOTOCHEMICAL AFTER EFFECT OF DAB IN 21.4 *N* ACID AT 25°[a]

Time illuminated	% Total color formed[b] Pre-nitrite Illuminated	Pre-nitrite Control	Post-nitrite Illuminated	Post-nitrite Control	Loss by illuminated
5 sec.	5.1	4.5	98.5	100	1.5
1 min.	20	3.2	96.8	100	3.2
5 min.	45	3.2	96.4	100	3.6
15 min.	55	2.5	94.6	100	5.4
60 min.	58	3.2	94.6	100	5.4

[a] Procedure for all tests was standardized so that the only variable was the interval of illumination. For each illumination test a control test was run in the same way except that the test was kept in the dark for a period of time equal to the illumination interval of the corresponding test. Following is an example of the test illuminated for five minutes and the control. Thirty mg. of DAB, in Tube A, was dissolved in 9.0 ml. of 21.4 *N* acid, and Tube A was placed in B through which water at 25 ± 0.1° was circulating. Two minutes after adding the acid the tube was illuminated for five minutes. Tube A was left in B for one minute after stopping the illumination and then 100 γ of tryptophan in 1.0 ml. of water was added to the test. The solution was mixed and poured into a 25-ml. glass-stoppered Erlenmeyer flask. The solution was cooled in the water-bath at 25° for two minutes and then placed in a dark chamber at 25° for four hours. Pre-nitrite transmittancy was then read using a control containing 30 mg. of DAB in 10 ml. of 19 *N* acid. To the solution was added 0.1 ml. of 0.04% sodium nitrite. Post-nitrite transmittancy was read after the test had stood thirty minutes in the dark. The control test was similar except that the solution was allowed to stand in Tube A in B in the dark for eight minutes before adding the tryptophan solution. [b] Transmittancy readings were converted to micrograms of tryptophan and then expressed as the per cent. of the maximum color obtainable with an equal quantity of tryptophan under ideal conditions of the test.[2]

resulted from using illuminated DAB solutions. These losses are attributed to the oxidative action of illuminated DAB on tryptophan before completion of reaction I a time when tryptophan is very sensitive to oxidative destruction as previously shown.

The rate of pre-nitrite development of color which resulted when tryptophan was added to previously illuminated solutions of DAB in 21.4 *N* acid is shown in Table IV. The pre-nitrite color of control tests ranged from 2.4 to 13% in four to seventy-one hours while the pre-nitrite color in tests in which DAB had been illuminated increased from 19% in fifteen minutes to a maximum of 71% in forty-seven hours. Eight to 10% of the tryptophan originally present was destroyed by the illuminated DAB solutions.

TABLE IV

RATE OF COLOR DEVELOPMENT RESULTING FROM PHOTOCHEMICAL AFTER EFFECT CAUSED BY ILLUMINATION OF DAB IN 21.4 *N* ACID AT 25°[a]

Time after addition of tryptophan to reading of pre-nitrite transmittancy, hours	% Total color formed[b] Pre-nitrite Illuminated	Pre-nitrite Control	Post-nitrite Illuminated	Post-nitrite Control	Loss by illumination, %
0.25	18				
1	34				
2	44				
4	55	2.4			
24	71	6.6	92	100	8
47	71	11			
71	69	13	86	96	10

[a] Procedure for all tests was standardized so that the only variable was the interval between addition of the tryptophan to the illuminated solution of DAB and reading the pre-nitrite transmittancy. For illumination experiments in which the time was four, twenty-four, forty-seven and seventy-one hours control tests were run in the same way except that illumination of DAB was omitted. Following is an example of the twenty-four-hour test: 30 mg. of DAB was placed in Tube A, Fig. 2, and dissolved in 9.0 ml. of 21.4 *N* acid. Tube A was then placed in B at 25° for two minutes. The solution was then illuminated for fifteen minutes and after standing one minute more 100 γ of tryptophan in 1.0 ml. of water was added. The solution was mixed and poured into a 25-ml. glass-stoppered Erlenmeyer flask which was then cooled in the water-bath at 25° for two minutes. The flask was placed in a dark chamber at 25° for twenty-four hours. Pre-nitrite transmittancy was then read. A blank solution containing 10 ml. of 19 *N* acid was used for all tests. To the solution was then added 0.1 ml. of 0.04% sodium nitrite solution and after standing in the dark for thirty minutes post-nitrite transmittancy was determined. [b] Transmittancy readings were converted to micrograms of tryptophan and then expressed as the per cent. of the maximum color obtainable with an equal quantity of tryptophan under ideal conditions of the test.[2]

In another series of experiments it was shown that pre-nitrite color of the same intensity was obtained whether the tryptophan was added five seconds or twenty hours after stopping the illumination of DAB. Therefore, once a solution of DAB has been exposed to light it appears to retain its oxidative capacity indefinitely.

Discussion

The mechanism of the photochemical development of color from the tryptophan–DAB condensation product probably involves oxidation by dissolved oxygen through the medium of DAB in the role of oxygen acceptor. The primary process is probably the formation of the peracid of DAB which then oxidizes the tryptophan–DAB complex to form the blue-colored compound. Cole[9] noted that color slowly developed without addition of an oxidizing agent when an acid solution of benzaldehyde and tryptophan stood a few days. Cole did not mention the possible effect of light in this reaction but believed that oxidation resulted from benzoyl peroxide formed by atmospheric oxygen. Bäckström,[10] who studied the photochemical oxidation of benzaldehyde and heptanal, postulated a chain mechanism for the photochemical formation of the peracids because the quantum yield was very large. According to Bäckström the quantum yield of benzoic acid was nearly constant in the region of 2536 to 3660 Å. Boyd[4] believed the photochemical effect observed by him was caused by ultraviolet light. The present experiments indicate that photochemical oxidation is caused by visible light, because most of the ultraviolet light would have been absorbed by the double thickness of Pyrex glass in the illumination apparatus shown in Fig. 2. Furthermore, when a test solution in a quartz flask was exposed to the radiations of a mercury vapor ultraviolet light, with visible light filter, no marked photochemical development of color occurred. It is recognized, however, that the destructive effects of illumination may have been caused by low-intensity ultraviolet light which may pass through Pyrex glass and water.

Whether DAB was illuminated fifteen or sixty minutes, the photochemical after effect, in four hours, produced pre-nitrite color equivalent to 55 to 58% of the total potentially available color. This proportion of the color was probably not determined by the availability of dissolved oxygen because in a test in which oxygen was bubbled into the solution during the fifteen minute illumination period the same amount of pre-nitrite color developed as when illumination was conducted in a closed tube. These results suggested the possibility that the after effect might be caused by a trace of contaminant in the DAB which was the limiting factor in determination of the magnitude of the after effect. To test this hypothesis, tests containing 10, 30, 60 and 100 mg. of DAB per test were illuminated fifteen minutes each and the after effect produced in twenty-four hours was determined. Pre-nitrite colors representing 58, 72, 72 and 72% of the total, respectively, were obtained. If the after effect were dependent on a contaminant in the DAB the proportion of pre-ni-

(9) Cole, *J. Physiol.*, **30**, 311 (1903–1904).

(10) Bäckström's work has been discussed in detail by Kistiakowsky and Dhar, ref. 8.

trite color should have increased in proportion to the quantity of DAB used per test. This did not occur. Therefore it was concluded that the after effect was caused by DAB and not by a contaminant.

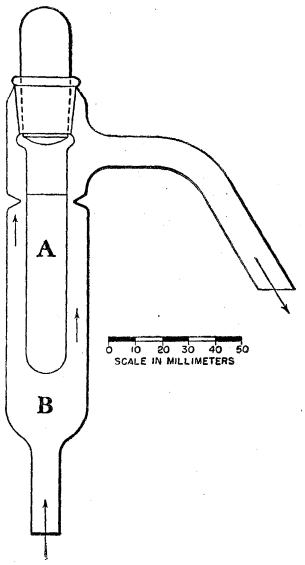
Illumination during the first five minutes of reaction I caused a loss of 25% of the tryptophan, but illumination of free tryptophan for thirty minutes and illumination of the final condensation product of tryptophan and DAB for 120 minutes caused only 3 and 6% losses, respectively. These observations indicate that an intermediate compound in the condensation of tryptophan and DAB is more susceptible to destruction by light than is either free tryptophan or the condensation product. The importance of protecting test solutions in analytical procedures from light particularly during the first five minutes of reaction I is therefore obvious. It is also important to protect acid solutions of DAB from light because loss of as much as 10% of the tryptophan may result from using illuminated DAB solutions.

Experimental

General procedure, apparatus and materials used in this study have been described in detail in a previous paper.[2] Transmittancies were determined with a Coleman spectrophotometer, Model 11, excepting the curves in Fig. 1 which were obtained with a Beckman quartz spectrophotometer. New procedures or variations from procedures previously described[2] are given in footnotes in the tables.

Reagent grade sulfuric acid was distilled using all glass joints. The first 8% of the distillate was discarded and a fraction representing about 85% boiling at 327 to 332° (uncor.) was collected in a receiver closed with a calcium chloride tube. This acid was used to prepare the sulfuric acid solutions used for experiments described in Tables III and IV as well as for some of the other tests.

Light Source and Illumination Procedure.—The light source was a 115-volt, No. 2 Photoflood, Mazda lamp made by General Electric Co. Lamps were mounted in a nine-inch aluminum coated reflector. The procedure for illumination was standardized as follows. The solution to be illuminated was placed in Tube A, Fig. 2. Tube A was placed in the glass holder B through which water at 25 + 0.1° was circulated at a rate of 5 liters per minute. Under these conditions the rise in temperature of the solution in Tube A was no more than 0.1 to 0.2° regardless of the length of time of illumination. The solution was illuminated with the outer tip of the light bulb 9 inches from the center of B so that the rays of light fell perpendicularly on the side of Tube A. The intensity of Photoflood lamps gradually declines with use. To minimize this effect fresh lights were used for short periods and used bulbs for longer periods of illumination.



Water at 25 ± 0.1°.

Fig. 2.—Illumination apparatus.

Summary

The photochemistry of tryptophan, *p*-dimethylaminobenzaldehyde and their reaction products in sulfuric acid has been studied. Evidence indicates that an intermediate compound formed in the condensation of tryptophan and *p*-dimethylaminobenzaldehyde is more susceptible to destruction by light than is either free tryptophan or the final condensation product. The photochemical development of color is caused by a visible portion of the spectrum and not by ultraviolet light. Previously illuminated acid solutions of *p*-dimethylaminobenzaldehyde cause the development of color and also some destruction of tryptophan as after effect when tryptophan is subsequently added to such solutions. Probable mechanism of the photochemical reactions is discussed.

WASHINGTON 25, D. C. RECEIVED JULY 26, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

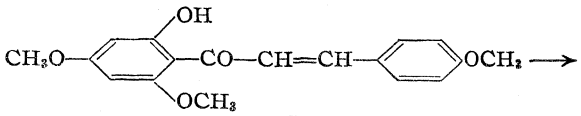
Flavonones and Related Compounds. V. The Oxidation of 2'-Hydroxychalcones with Alkaline Hydrogen Peroxide

BY T. A. GEISSMAN AND DAVID K. FUKUSHIMA

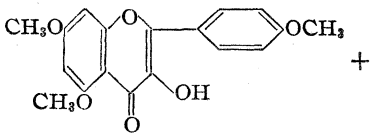
The oxidation by means of alkaline hydrogen peroxide of 2'-hydroxychalcones (and the corresponding flavanones) to 3-hydroxyflavones was first described by Algar and Flynn[1] and Oyamada,[2] and later studied in more detail by Murakami and Irie[3] and by Reichel and Steudel.[4] The results of these studies led to the conclusion[1,4] that the reaction was a general one, and could be applied to 2'-hydroxychalcones having methoxyl groups in a variety of positions in the two aromatic nuclei.

This method was chosen for the preparation of a sample of kampferol (3,4',5,7-tetrahydroxyflavone) which was required for comparison with some of this material isolated from carnation flower petals in the course of studies on the inheritance of color variation in this species.[5,6]

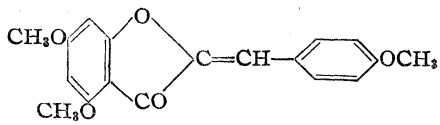
The oxidation of 2'-hydroxy-4',6',4-trimethoxychalcone (I) with alkaline hydrogen peroxide did yield a small amount of the desired flavonol (II), but the predominant product of the reaction was 4',4,6-trimethoxybenzalcoumaranone (III)



I



II



III

The formation of benzalcoumaranones in this reaction has not been encountered in previous studies,[1-4,7] and it is significant to note that in none of the earlier work were chalcones used which were derivatives of 2,4,6-trihydroxyacetophenone. Oxidation to the flavonol has been the only course observed when the chalcone is the benzal, anisal, veratral or piperonal derivative of 2-hydroxy-, 2-hydroxy-4-methoxy-, 2-hydroxy-3,4-dimethoxy-, or 2-hydroxy-3,4,5-trimethoxyacetophenone.[7]

It appeared likely that the presence of the 6'-methoxy group in I was responsible for the unexpected course of its reaction with alkaline hydrogen peroxide. Further studies showed that 2'-hydroxy-4',6'-dimethoxychalcone (IV), 2'-hydroxy-4',6',3,4-tetramethoxychalcone (V), and 2'-hydroxy-6'-methoxy-3,4-methylenedioxychalcone (VI) yielded the corresponding benzalcoumaranones, a trace of the flavonol (quercetin-3',4',5,7-tetramethyl ether) accompanying the benzalcoumaranone in the case of V only.

These new observations afford a further insight into the course of this reaction, substantiating in part certain of the conclusions of some of the earlier investigators and invalidating others. Oyamada[2] assumed that the reaction proceeded through the flavanone in each case, but the ease with which flavanones are opened in alkali to the salts of the corresponding 2'-hydroxychalcones renders this interpretation difficult to test,[4] and it is probable that the chalcone (as the salt) is the reactive species whether the chalcone or the flavanone is used as the starting material. Algar and Flynn concluded that an ethylene peroxide or a glycol was the intermediate since an oxido intermediate would be expected to lead to a flavone or a benzalcoumaranone.[1] It is apparent that this reasoning is somewhat contradictory, since an oxide and a glycol are at equivalent oxidation levels and at a different level from an ethylene peroxide. Murakami and Irie[3] attempted to show that the first step in the reaction is the formation of the oxido compound but were unable to prepare the latter from 2'-hydroxychalcone. They did succeed in showing that under mild conditions of treatment with alkaline hydrogen peroxide, 3-hydroxyflavanone was formed, and Reichel and Steudel[4] demonstrated that this compound is readily oxidized in alkaline solution to flavonol.

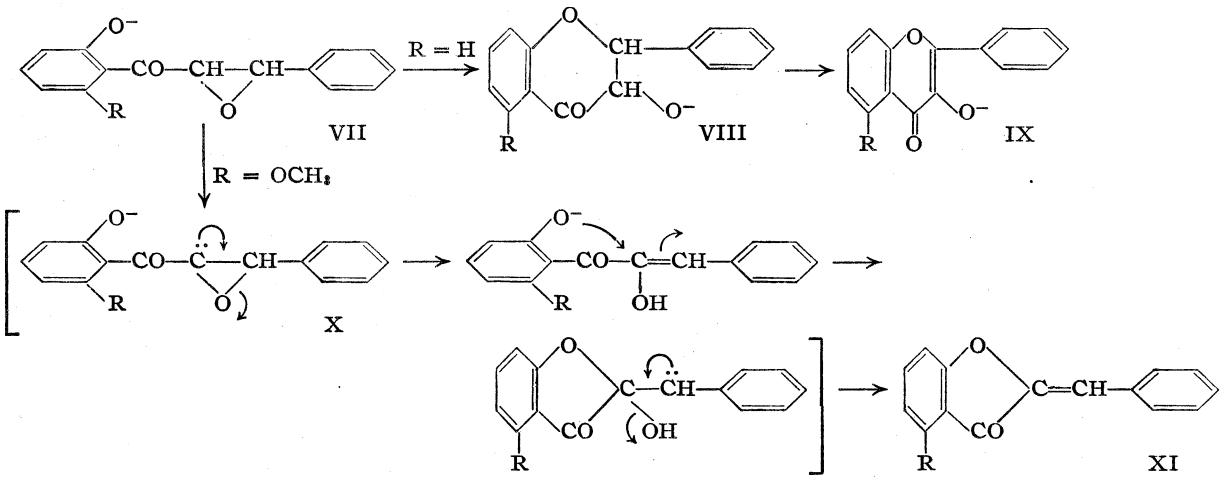
In the course of the present work numerous attempts were made to prepare the oxides of 2'-hydroxy-, 2'-acetoxy- and 2'-benzoyloxychalcone, but these attempts were unsuccessful. In the case of the acyl derivatives the extraordinarily facile removal of the acyl groups was the first reaction that occurred even under mildly alkaline conditions. Baker and Robinson[8] have also attempted without success to prepare 2'-hydroxychalcone oxide.

Reichel and Steudel[4] have offered an electronic interpretation of the reaction, using 2'-hydroxychalcone as the example, in which the successive steps were considered to be the addition of the hydroperoxide ion to the chalcone (ion), the rearrangement of the addition product to yield the

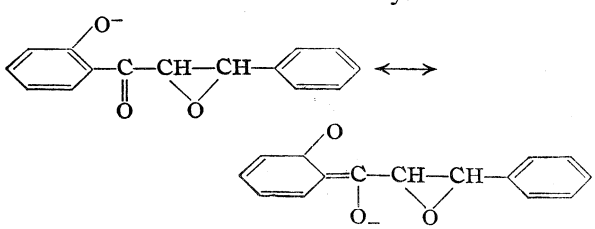
(1) Algar and Flynn, *Proc. Roy. Irish Acad.*, **B42**, 1 (1934).
(2) Oyamada, *Bull. Chem. Soc. Japan*, **10**, 182 (1934).
(3) Murakami and Irie, *Proc. Imp. Acad. Tokyo*, **11**, 229 (1935).
(4) Reichel and Steudel, *Ann.*, **553**, 83 (194).
(5) Mehlquist and Geissman, *Ann. Missouri Bot. Gardens*, **36**, 39 (1947).
(6) Geissman and Mehlquist, *Genetics*, **32**, 410 (1947).
(7) Bargellini and Oliverio, *Ber.*, **75B**, 2083 (1942).
(8) Baker and Robinson, *J. Chem. Soc.*, 1798 (1932).

glycol (*o*-hydroxyphenyl-α,β-dihydroxyphenethyl ketone) and the displacement of the β-hydroxy group by the attack of the 2′-, anionic, oxygen atom to close the ring to 3-hydroxyflavanone.

A simpler and more satisfactory picture of the course of the reaction, and one which includes a consideration of the new observations described here, is that the first intermediate is indeed the oxide (VII). This reacts further to yield the flavanone (VIII) probably by a direct nucleophilic attack by the anionic oxygen atom upon the β-carbon atom, followed by oxidation to the flavonol (IX). When a substituent is present in the 6′-position of the chalcone, this course is not (exclusively) followed. It is probable that when R is a group which can offer substantial inhibition to the resonance in the system involving the anionic oxygen atom and the ortho carbonyl group, the result is an increase in the effective acidity of the α-hydrogen atom. Attack of a base upon this hydrogen atom gives rise to X, in which the oxide ring is opened by the attack of the electron pair on the adjacent (α-) carbon atom, leading through the changes formulated below to the benzalcoumaranone (XI)



This mechanism does not exclude the possibility that a mixture of the two possible products will be formed, since it does not suggest, and there is no reason to expect, that when R = OCH_3, the course VII → VIII → IX is excluded. The effect of the 6′-substituent is seen to be one of favoring the course leading to the benzalcoumaranone, since when resonance in VII of the system



is possible the series VII → X → XI would be less likely.

An alternative explanation for the effect of a 6′-substituent in directing ring closure to the benzalcoumaranone is that a direct steric effect favors the formation of a 5-membered rather than a 6-membered ring. Arnold and Rondestvedt[9] have shown that a 6-membered ring offers more steric hindrance to the position ortho to its point of juncture with another ring than does a 5-membered ring. In the present case, the more favorable bond angles in XI would allow less hindrance between R and the carbonyl group peri to it than in the case of IX, and might offer a plausible reason for a faster reaction in the ring closure to the benzalcoumaranone.

Results obtained in related studies indicate, however, that this explanation is not an adequate one. There appears to be a close analogy between the alkaline hydrogen peroxide oxidation of 2′-hydroxychalcones and the ring closure of 2′-hydroxy-α,β-dibromodihydrochalcones with alkali.[10-12] In the latter reaction, too, the number and position of the alkoxyl groups in the two aromatic rings influences the course of the reaction and determines whether a flavone or a benzalcoumaranone is formed. When the original chalcone is derived from 2,4,6-trihydroxyacetophenone, benzalcoumaranone formation is favored; but it is important to note that in this reaction the direction of ring closure is influenced also by the nature of the substituents in the benzal ring, and to some degree by the conditions of the reaction. Consequently, it appears that here simple steric effects are not the most important directing influences. It is with these observations in mind that the suggestion is made that benzalcoumaranone and flavonol formation are the result of two different kinds of attack upon a common intermediate, and that the course of the reaction is determined pri-

(9) Arnold and Rondestvedt, THIS JOURNAL, **68**, 2176 (1946).

(10) Kostanecki, *et al.*, *Ber.*, **31**, 696, 705, 1758, 2951 (1898); **32**, 315, 318, 1030, 2260 (1899).

(11) Warriar, Khanolkar, Hutchins and Wheeler, *Current Sci.*, **5**, 475 (1937); Nadkarni, Warriar and Wheeler, *J. Chem. Soc.*, 1798 (1937); Hutchins and Wheeler, *ibid.*, 91 (1939).

(12) Auwers and Anschütz, *Ber.*, **54**, 1543 (1931).

marily by the effects of substituents upon the reactivity of the α- and β-carbon atoms in the chalcone derivative.

Experimental[13]

Oxidation of 2'-Hydroxy-4',6',4-trimethoxychalcone.—To an ice-cold solution of 2.06 g. of 2'-hydroxy-4',6',4-trimethoxychalcone in a mixture of 14 ml. of 16% aqueous sodium hydroxide and 40 ml. of methanol was added 5.3 ml. of 15% hydrogen peroxide (analyzed before use). The mixture was kept at 5° overnight and the yellow solid which separated was collected, washed with methanol (A, see below) and recrystallized from acetone. The pure product formed canary yellow needles, m. p. 166.5–167.5°. It gave a deep crimson color with concentrated sulfuric acid, and no color with ferric chloride nor with magnesium–hydrochloric acid in alcoholic solution.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 69.23; H, 5.12; OCH_3, 29.81. Found: C, 68.99; H, 5.11; OCH_3, 29.42.

The compound showed no depression of melting point when mixed with a sample of 4',4,6-trimethoxybenzalcoumaranone prepared by treatment of 2-hydroxy-4,6-dimethoxyphenyl-α,β-dibromo-β-anisylethyl ketone with alcoholic alkali.

From the methanol washings (A) of the crude benzalcoumaranone was obtained 0.29 of crude, crystalline material which upon repeated recrystallization from methanol yielded 0.05 g. of 5,7,4'-trimethoxyflavonol, m. p. 150–153° (reported,[14] 150–151°). This compound gave in concentrated sulfuric acid a yellow solution with a green fluorescence, and a pink solution when treated with magnesium and concentrated hydrochloric acid in alcoholic solution. Demethylation with hydriodic acid and acetylation of the product yielded kampferol tetraacetate,[14] m. p. 182–184°.

Oxidation of 2'-Hydroxy-4',6',3,4-tetramethoxychalcone.—To a cold solution of 0.70 g. of 2'-hydroxy-4',6',-3,4-tetramethoxychalcone in a mixture of 30 ml. of methanol and 6 ml. of 16% aqueous sodium hydroxide was added 3 ml. of 15% hydrogen peroxide. The yellow solid which separated upon standing overnight at 5° was collected. The crude material melted at about 165° and recrystallization effected only a partial purification. After a short treatment with sodium acetate–acetic anhydride, followed by decomposition of the excess acetic anhydride with ice water and recrystallization of the product from dilute alcohol, afforded tiny, canary-yellow needles of the benzalcoumaranone, m. p. 173–174°, reported[15] 175°). The compound gave the characteristic deep crimson-magenta color in concentrated sulfuric acid.

The alkaline filtrate was diluted with water, acidified and extracted with ether. After washing the ether solution with sodium bicarbonate solution the solvent was removed, yielding 0.12 g. of a crude solid. Crystallization from alcohol yielded 0.07 g. of 5,7,3',4'-tetramethoxyflavonol, m. p. 193–194° (reported,[16] 197–198°). Its alcoholic solution gave a bluish-red coloration with magnesium and hydrochloric acid and a brownish-green color with ferric chloride.

Oxidation of 2'-Hydroxy-4',6'-dimethoxychalcone.—A cold solution of 0.48 g. of 2'-hydroxy-4',6'-dimethoxychalcone, 20 ml. of methanol, 5 ml. of 16% aqueous sodium hydroxide and 2.5 ml. of 15% hydrogen peroxide was kept at 5° overnight. The yellow precipitate weighed 0.30 g., and after recrystallization from alcohol melted at 152–153°. The melting point of 2-benzal-4,6-dimethoxycoumaranone-3 has been reported as 150–151°.[17] With concentrated sulfuric acid the compound gave a deep yellow-orange color.

From the alkaline filtrate was isolated only a small amount of 2-hydroxy-4,6-dimethoxybenzoic acid (neut. equiv. calcd., 198.1; neut. equiv. found, 197.4).

Oxidation of 2'-Hydroxychalcone. Method of Oyamada.—The oxidation of 1.0 g. of 2'-hydroxychalcone was carried out as described by Oyamada.[2] The yield of flavonol was 0.57 g.

Method of Murakami and Irie.—Two grams of 2'-hydroxychalcone, oxidized according to the procedure of Murakami and Irie,[3] yielded 1.0 g. of 3-hydroxyflavanone along with a small amount of flavonol. The flavanone melted at 177–180° (reported,[3] 174–177°).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04. Found: C, 74.53; H, 5.03.

Oxidation of 2'-Hydroxy-4'-methoxychalcone.—To a cold suspension of 1.0 g. of 2'-hydroxy-4'-methoxychalcone in 7 ml. of 15% aqueous sodium hydroxide was added 3 ml. of 13% hydrogen peroxide. After standing at 5° overnight, the mixture was filtered, yielding 0.84 g. of the sodium salt of 7-methoxyflavonol. The flavonol was obtained by treatment of the sodium salt with acid; it melted at 174.5–175.5° after recrystallization from alcohol. Kostanecki and Stoppani reported a m. p. of 180° for this compound.[18] It gave a yellow, blue-green fluorescing solution in concentrated sulfuric acid and an olive-green color with ferric chloride.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.39; H, 4.50. Found: C, 71.60; H, 4.47.

It formed a colorless **acetate**, m. p. 176–177°.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.51. Found: C, 69.25; H, 4.53.

2'-Hydroxy-6'-methoxy-3,4-methylenedioxychalcone

Two grams of 2-hydroxy-6-methoxyacetophenone was moistened with 2 ml. of methanol, and 5 ml. of 60% aqueous potassium hydroxide was added. To the pasty, greenish solid resulting was added 2.0 g. of piperonal, and the mixture shaken vigorously. The mixture grew warm, a deep red-brown color developed and a thick, oily phase separated. After fifteen minutes, during which time the mixture was shaken frequently, enough methanol was added to produce a clear solution (*ca.* 5 ml.) and the solution was poured into iced, dilute hydrochloric acid. The red-orange gum which separated crystallized when ether was added. After recrystallization from chloroform–petroleum ether the product (3.4 g.) formed brilliant orange needles, m. p. 137–138°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.43; H, 4.70. Found: C, 68.49; H, 5.15.

Oxidation of 2'-Hydroxy-6'-methoxy-3,4-methylenedioxychalcone: 4-Methoxy-3',4'-methylenedioxybenzalcoumaranone.—To a suspension of 1.0 g. of the chalcone in 5 ml. of methanol was added 5 ml. of 20% aqueous sodium hydroxide, followed by 2.0 ml. of 30% hydrogen peroxide. The mixture was shaken; after about fifteen seconds it grew warm and suddenly set almost to a paste with the appearance of a yellow solid. After standing for an hour at 0° the semi-solid mixture was stirred with water and ether, and filtered. The solid weighed 0.50 g. It was not a salt; it gave a brilliant magenta color with concentrated sulfuric acid and no color with magnesium–alcoholic hydrochloric acid. It was soluble in pyridine, chloroform and hot, glacial acetic acid, and crystallized from the latter solvent as small, bright yellow needles, m. p. 222–223.5°, resolidifying upon cooling.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.89; H, 4.09. Found: C, 68.79; H, 4.48.

The alkaline filtrate contained no material having the properties of a flavonol.

Summary

1. The oxidation of 2'-hydroxychalcones with alkaline hydrogen peroxide yields flavonols when the chalcones are unsubstituted in the 6'-position.

(13) Melting points are uncorrected.

(14) Kostanecki, Trampe and Tambor, *Ber.*, **37**, 2096 (1904).

(15) Perkin, *J. Chem. Soc.*, 951 (1920).

(16) Kostanecki, Lampe and Tambor, *Ber.*, **37**, 1404 (1904).

(17) Feuerstein and Kostanecki, *ibid.*, **31**, 1758 (1898).

(18) Kostanecki and Stopanni, *ibid.*, **37**, 1184 (1904).

When a methoxyl group is present in the 6′-position the predominant product is a benzalcoumaranone.

2. A mechanism is suggested to account for these results, and an analogy is drawn between this reaction and the ring closure of 2′-hydroxychalcone dibromides with alkali.

LOS ANGELES, CALIFORNIA RECEIVED JULY 28, 1947

[CONTRIBUTION NO. 233 FROM CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

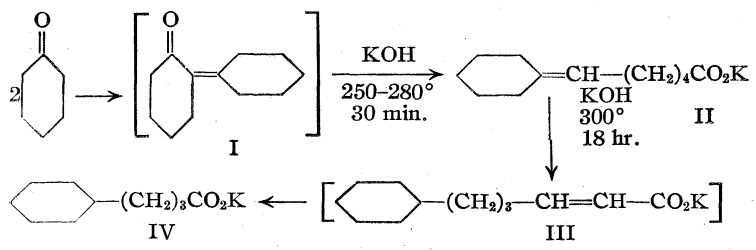
The Action of Alkali on Cyclohexanones

BY THEODORE L. CAIRNS, ROBERT M. JOYCE AND RICHARD S. SCHREIBER

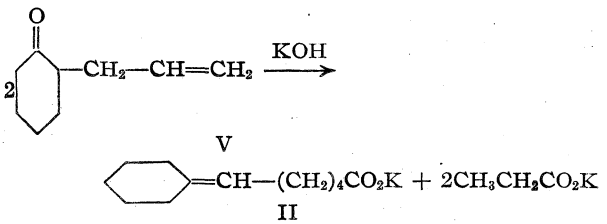
The cleavage of certain ketones by alkali with the formation of acids is well known for aromatic,[1] aralkyl,[2] and activated ketones such as β-keto acids. Relatively little work has been done with simple aliphatic ketones. This paper reports the results of an investigation of the nature of the products formed when cyclohexanone and one of its 2-substituted derivatives are treated with molten alkali. Other workers have shown that acids of unknown structure along with large amounts of neutral condensation products resulted when cyclohexanone was heated with potassium hydroxide at 180–190° for twenty-four hours.[3]

Three distinct types of reactions between cyclohexanone and potassium hydroxide have now been found, depending on the temperature used. The results can best be explained on the basis of the series of changes involving (1) formation of cyclohexylidenecyclohexanone (I), (2) cleavage of the ketone ring to a cyclohexylidenecaproic acid (II) and (3) migration of the double bond and degradation of the intermediate α,β-unsaturated acid to cyclohexanebutyric acid (IV). These transformations are shown in the accompanying equations and are discussed below.

At temperatures up to 220° the addition of cyclohexanone to molten potassium hydroxide resulted in the formation of a white crystalline solid which yielded only neutral products when treated with water. In the temperature range 250–280° a similar white precipitate formed momentarily but was very rapidly converted by an exothermic reaction to a yellow oil (II). When cooled, this yellow oil solidified and, after solution in water and acidification, a 12-carbon unsaturated acid was obtained. The position of the double bond in the acid from II was not established but no doubt exists concerning the carbon skeleton since this product yielded cyclohexanecaproic acid when hydrogenated. Prolonged treatment of II with molten alkali resulted eventually in a *saturated* 10-carbon acid identified as cyclohexanebutyric acid (IV). This transformation may involve the migration of the double bond of II into the α,β-position (III) followed by a retrograde aldol reaction to give cyclohexanebutyraldehyde which in turn would be converted by the alkali to IV. Support for the mechanism as pictured above is found in the fact that cyclohexylidenecyclohexanone yielded II when heated with molten potassium hydroxide.



In the case of 2-allylcyclohexanone (V) an unusual cleavage took place with the formation of the potassium salts of propionic acid and the acid II, derived from cyclohexanone, in accordance with the equation



The fact that propionic acid, and not acrylic acid, was isolated indicates that this change may involve the migration of the double bond in the allyl side chain into conjugation with the carbonyl group and hydrolytic removal of this residue with the formation first of propionaldehyde and then of propionic acid.

Experimental[4]

Action of Potassium Hydroxide on Cyclohexanone (280°—thirty minutes).—Two hundred twenty-five (225) grams of solid potassium hydroxide was fused in a heavy-walled glass tube in an atmosphere of nitrogen. To this was added, with vigorous agitation, 43.6 g. of cyclohexanone over a period of thirty minutes while the temperature was maintained between 260 and 280°. The mixture was cooled and dissolved in water to form a clear solution with

(1) Bachmann, THIS JOURNAL, **57**, 737 (1935).
(2) Lock and Bock, *Ber.*, **70B**, 916 (1937).
(3) Wallach and Behnke, *Ann.*, **369**, 99 (1909).

(4) We are indebted to Dr. J. W. Stillman of these laboratories, under whose supervision the microanalyses reported here were carried out.

no evidence of any alkali-insoluble material. After acidification with concentrated hydrochloric acid and cooling, the solution was extracted with two portions of diethyl ether. The ether extract was then dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation. The resulting residue, on distillation, yielded 14.7 g. of an acid (corresponding to II) boiling at 145–153° (2–3 mm.), $n^{20}D$ 1.4385.

Anal. Calcd. for $C_{12}H_{20}O_2$: neut. equiv., 196. Found: neut. equiv., 205.3.

This acid was found to be soluble in aqueous sodium bicarbonate, giving a solution which reduced potassium permanganate. It rapidly absorbed bromine with the evolution of hydrogen bromide and the formation of an oily derivative.

The ethyl ester prepared from this unsaturated 12-carbon acid had the properties: b. p. 131° (5 mm.); $n^{25}D$ 1.4642; d^{25}_4 0.9365.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.96; H, 10.78; sap. equiv., 224.3; M_R, 65.87 (from atomic refractivity constants given in Lange, "Handbook of Chemistry," 3rd Edition, 1939, p. 855). Found: C, 75.22, 75.59; H, 10.52, 10.97; sap. equiv., 223.9; M_R, 66.12 (R. Lorentz and H. Lorenz formula).

Hydrogenation of the acid in the presence of Raney nickel catalyst at 125° and 120 atm. hydrogen pressure for three hours yielded cyclohexanecaproic acid, from which was obtained a solid *p*-bromophenacyl ester identical with the *p*-bromophenacyl ester of an authentic sample of cyclohexanecaproic acid.[5]

Action of Potassium Hydroxide on Cyclohexanone (300°—eighteen hours).—A stainless steel bomb was charged with 125 g. of cyclohexanone and 250 g. of potassium hydroxide, the air was flushed out with nitrogen, and the mixture heated with agitation at 300° for eighteen hours. At the end of this time, the mixture was cooled and the grayish solid which separated was removed and discarded. The remaining oily product was extracted with water and the aqueous extract acidified with hydrochloric acid to yield an oily, water-insoluble acid. This acid on distillation gave a fraction amounting to 25 g. boiling at 160–180° (10 mm.). Redistillation of this product yielded cyclohexanebutyric acid boiling at 136–139° (4 mm.), m. p. 26.5–28.5°.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65; neut. equiv., 170.2. Found: C, 70.52; H, 10.34; neut. equiv., 178.5.

The *p*-bromophenacyl ester of this acid was found to melt at 76–77° and showed no depression in melting point when mixed with a sample of the *p*-bromophenacyl ester of an authentic sample of cyclohexanebutyric acid.

2-Allylcyclohexanone.—This was prepared by the method of Cornubert[6] using allyl chloride instead of allyl iodide, b. p. 80–87° (13–15 mm.), $n^{25}D$ 1.4662 to 1.4669.[6,7]

Action of Potassium Hydroxide on 2-Allylcyclohexanone.—In an atmosphere of nitrogen 20 g. of 2-allylcyclohexanone was added with stirring to 75 g. of potassium hydroxide at 240–250°. After twenty minutes the mixture was cooled, and the upper layer of yellowish solid was separated mechanically from the lower layer of potassium hydroxide and dissolved in water. Neutral products were removed from the aqueous layer by extraction with ether, and the aqueous layer was then acidified with the formation of a yellow oil. After separation and drying of the oil, it yielded, upon distillation, two fractions, the first (2 g.), boiling at 33–34° (5 mm.), and the second (4 g.) boiling at 157–170° (5 mm.).

The first fraction was demonstrated to be propionic acid: neut. equiv. Calcd. for $C_3H_6O_2$: 74.1. Found: 75.5, 75.6.

The *p*-bromophenacyl ester, m. p. 57.5–59°, showed no depression in melting point when mixed with the ester of an authentic specimen of propionic acid. The *p*-bromophenacyl ester of acrylic acid melted at 67.5–68° and mixtures of this ester with that of the ester in question melted at 53.5–56.5°.

The second, high-boiling fraction was shown to yield cyclohexanecaproic acid when hydrogenated.

Summary

1. Treatment of cyclohexanone with molten potassium hydroxide at 250–280° yields a 12-carbon unsaturated acid, and at 300° cyclohexanebutyric acid.

2. 2-Allylcyclohexanone is converted by molten potassium hydroxide at 250° to the same 12-carbon unsaturated acid; the allyl side chain appears as propionic acid.

(5) Supplied through the courtesy of the Dow Chemical Company. See also Hiers and Adams, THIS JOURNAL, **48**, 2385 (1926).

(6) Cornubert and Maurel, *Bull. soc. chim.*, **49**, 1498 (1931).

(7) Cope, Hoyle and Heyl, THIS JOURNAL, **63**, 1843 (1941).

WILMINGTON, DELAWARE RECEIVED DECEMBER 19, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

p-Toluenesulfonates of 20-Hydroxypregnanes

BY LEWIS HASTINGS SARETT

The conversion of pregnane-3(α),20-diol 3-acetate 20-tosylate to Δ^{17}-pregnene-3(α)-ol by treatment with pyridine has been described.[1] The present work reports some additional applications of this useful procedure for the preparation of substituted ethylenes from secondary alcohols.[2]

Pregnane-3(α),12(α),20-triol 3,12-diacetate[3] (I), was prepared by catalytic reduction of pregnane-3(α),12(α)-diol-20-one diacetate.[4] With *p*-toluenesulfonyl chloride I yielded a diacetate tosylate, which on refluxing with collidine gave a crystalline mixture of Δ^{17}- and Δ^{20}-pregnene-3(α),12(α)-diol diacetate (IIa and IIb). From the mixture obtained by hydroxylation of II, a readily crystalline 3(α),12(α),17,20-tetrol (III) could be separated. Periodate cleavage then yielded *etio*-cholane-3(α),12(α)-diol-17-one, isolated as the diacetate (IV).[5] Oxidation of the amorphous glycol mixture which remained gave some *etio*-desoxycholic acid (V).

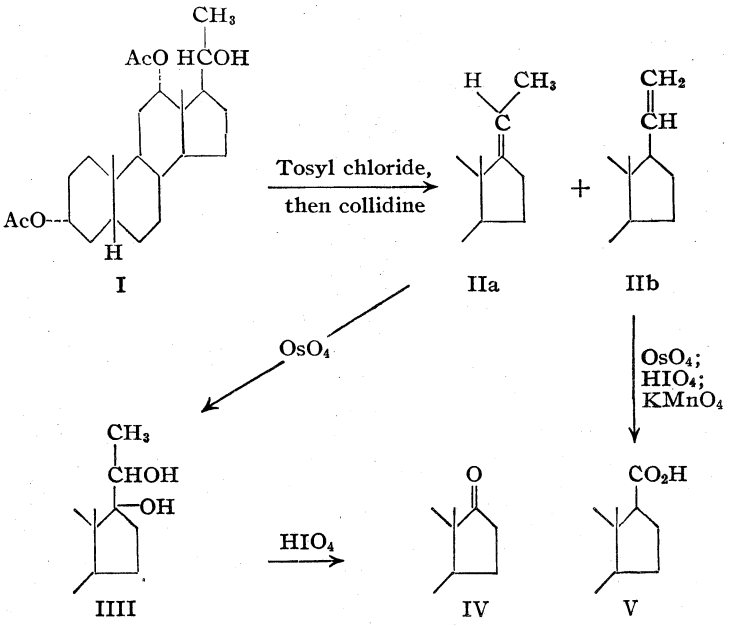
(1) Hirschmann, *J. Biol. Chem.*, **140**, 797 (1941).

(2) See, for example, *inter alia*, Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912); Barnett and Reichstein, *Helv. Chim. Acta*, **21**, 426 (1938; v. Euw and Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(3) The configuration of the C-12 hydroxyl group in desoxycholic acid is taken as α, in accordance with the proofs of Gallagher and Long, *J. Biol. Chem.*, **162**, 495 (1946), and of Sorkin and Reichstein, *Helv. Chim. Acta*, **29**, 1218 (1946).

(4) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

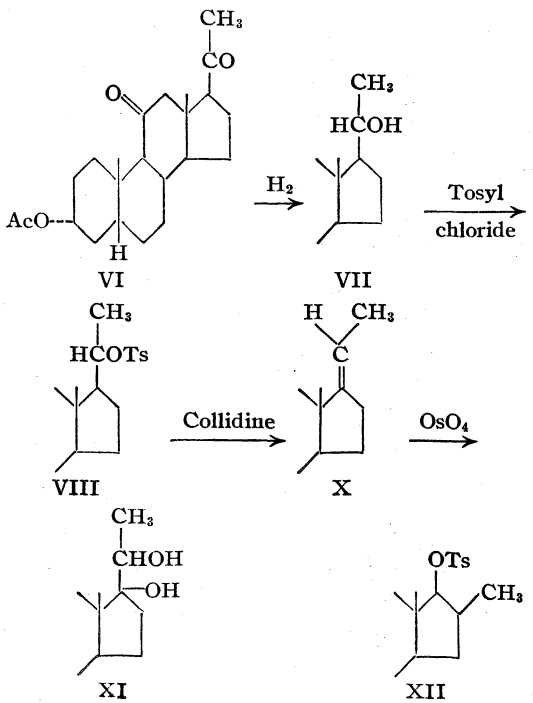
(5) We are indebted to Dr. L. F. Fieser of Harvard University for an authentic sample of this compound for comparison.



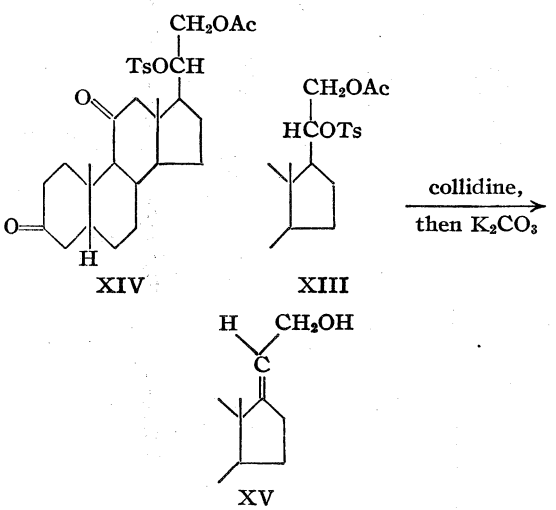
A more thorough investigation of the 11-keto series was facilitated by the ready crystallizability of the intermediates; in addition the reactions appeared to proceed more smoothly. The reduction of pregnane-3(α)-ol-11,20-dione acetate (VI) afforded one of the possible pregnane-3(α),20-diol-11-one 3-acetate epimers (VII) in an 85% yield. The other was present only to the extent of a few per cent. With *p*-toluenesulfonyl chloride VII gave the acetate tosylate VIII, which occurred in several crystalline modifications.

After treatment of the tosylate with collidine, a crystalline mixture of the Δ^{17} and Δ^{20} derivatives was obtained in which the Δ^{17} isomer (or isomers) preponderated. Ozonolysis of this mixture of acetates gave *etio*-cholane-3(α)-ol-11,17-dione acetate together with some 3(α)-acetoxy-11-keto-*etio*-cholanic acid. A pure Δ^{17}-pregnene-3(α)-ol-11-one (X) could be isolated by saponification of the mixture of acetates and repeated recrystallization of the product. Hydroxylation of X gave a triolone (XI), which with chromic acid was oxidized to *etio*-cholane-3,11,17-trione.

An additional product of the reaction of pregnane-3(α),20-diol-11-one 3-acetate 20-tosylate (VIII) with collidine was an isomeric acetate tosylate. Reductive hydrolysis of this material with sodium amalgam gave a ketodihydroxy derivative isomeric with pregnanediolones. Evidently a fundamental rearrangement occurred, probably to a D-homo derivative such as XII.



The applicability of the tosylate-collidine method for introducing the 17,20 double bond was tested also in the 21-acetoxy series. Partial acetylation of pregnane-20(β),21-diol-3,11-dione[6] and the epimeric glycol[6] gave the respective 21-monoacetates from which the corresponding acetate tosylates (XIII and XIV) were prepared. Only one of these mixed esters—that derived from the arbitrarily designated 20(β) series—reacted readily with collidine at the boiling point. It gave a non-crystalline acetate which was very easily hydrolyzed to a derivative of the empirical formula $C_{21}H_{30}O_3$; m. p. 128°; $[\alpha]^{25}D$ +63°. This substance upon hydroxylation with osmium tetroxide, followed by acetylation of the resulting triol, gave the same pregnane-17(α),20,21-triol-3,11-dione diacetate previously obtained by hydroxylation of a Δ^{17}-pregnene-21-ol-3,11-dione.



(6) Sarett, THIS JOURNAL, 68, 2478 (1946).

This latter compound melted erratically at about 150° and had $[\alpha]_D$ +56° but was not obtained analytically pure. Both the 128° and the 150° pregnenes gave amorphous acetates. An attempt to repeat the preparation of the higher melting pregnene gave only the lower melting product. Although, unfortunately, none of the former has been available for direct comparison, the data suggest that the two Δ^{17}-pregnene-21-ol-3,11-dione compounds are merely crystal modifications.

Experimental[7]

Δ^{17}- and Δ^{20}-Pregnene-3(α),12(α)-diol Diacetate (IIa and IIb).—A solution of 1.02 g. of pregnane-3(α),12(α)-diol-20-one diacetate in 50 cc. of acetic acid was shaken with 0.5 g. of platinum oxide under hydrogen until the theoretical quantity of hydrogen was taken up. The solution was then filtered, concentrated *in vacuo* and dissolved in ether. The ethereal solution was washed with aqueous carbonate, then with water, and concentrated to dryness. A sample of the crude pregnane-3(α),12(α),20-triol 3,12-diacetate was chromatographed but could not be obtained crystalline. The diacetate (1.02 g.) was then dissolved in 2 cc. of pyridine and treated with 850 mg. of *p*-toluenesulfonyl chloride. After standing at room temperature for sixteen hours, the solution was diluted with water and extracted with ether. The ethereal solution was washed with aqueous carbonate, dilute hydrochloric acid and with water and concentrated to dryness. The amorphous diacetate tosylate weighed 1.262 g. It was next refluxed with 20 cc. of collidine for twenty-five minutes, the solution cooled, diluted with ether, washed with dilute sulfuric acid and with water. The ethereal solution was concentrated to dryness and the residue was crystallized twice from methanol. The product (580 mg.) consisted of a mixture of Δ^{17}- and Δ^{20}-pregnene-3(α),12(α)-diol diacetate, m. p. 155–159°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.74; H, 9.78.

Hydroxylation of Δ^{17}- and Δ^{20}-Pregnene-3(α),12(α)-diol Diacetate.—A solution of 560 mg. of pregnene mixture (m. p. 155–159°) in 10 cc. of absolute ether was treated with 500 mg. of osmium tetroxide and 350 mg. of dry pyridine. After ten minutes the ether was removed *in vacuo*, the residue dissolved in 30 cc. of alcohol and the solution treated with 1.0 g. of sodium sulfite dissolved in 20 cc. of water. The mixture was refluxed for three hours and then filtered. To the filtrate was added 10 cc. of 1 *N* aqueous potassium hydroxide and the whole refluxed an additional half hour. The alcohol was removed *in vacuo* and the residual suspension extracted with chloroform. Concentration of the washed chloroform solution, followed by crystallization of the residue from acetone gave 80 mg. of a crude pregnane-3(α),12(α),17,20-tetrol (III), m. p. 253–259°. This material was not purified further but was suspended in 5 cc. of methanol to which was added 1.11 cc. of water containing 55 mg. of periodic acid. The suspension was swirled from time to time and after forty-five minutes the tetrol had dissolved. The solution was permitted to stand for an additional half hour and then concentrated to a small volume *in vacuo*. The aqueous suspension was extracted with ethyl acetate. Concentration of the ethyl acetate to a small volume gave a crystalline precipitate consisting of starting material. This was removed and the material in the mother liquors (67 mg.) heated in the steam-bath with a small volume of pyridine and acetic anhydride for thirty minutes. The acetylation mixture was then diluted with water and worked up in the usual manner. Crystallization of the product from ether–petroleum ether gave 45 mg. of *etio*-cholane-3(α),12(α)-diol-17-one diacetate, m. p. and mixed m. p. 157–158°.

(7) All rotations were taken in acetone; c~1.0. All melting points are corrected.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.78. Found: C, 70.76; H, 8.89.

The mother liquors of the tetrol III were concentrated to dryness *in vacuo* and weighed 320 mg. They were similarly oxidized with periodic acid and then acetylated with pyridine–acetic anhydride as before. The crude diacetoxy-*etio*-cholanic aldehyde was then dissolved in 7 cc. of acetone and treated with 2.5 cc. of 5% aqueous potassium permanganate. After standing at room temperature for forty-five minutes, the mixture was concentrated to a small volume in a stream of air at 15°, then acidified with dilute sulfurous acid and extracted with ether. The ethereal solution was extracted with 1 *N* aqueous potassium hydroxide solution and the latter was then heated on the steam-bath for one hour. The alkaline solution was cooled, acidified with dilute hydrochloric acid and the precipitate washed and dried. Crystallization of the amorphous powder (60 mg.) from acetone gave 46 mg. of *etio*-desoxycholic acid, m. p. and mixed melting point, 290–294°.

Pregnane-3(α),20-diol-11-one 3-Acetate (VII).—A solution of 6.15 g. of pregnane-3(α)-ol-11,20-dione acetate in 125 cc. of acetic acid was shaken under hydrogen with 1.0 g. of platinum oxide. After six hours the theoretical amount of hydrogen had been taken up and the reaction had stopped. The solution was filtered and a large volume of water was added to the filtrate. The crystalline precipitate was washed with water and dried. It weighed 6.10 g. and melted at 182–199°. After recrystallization from benzene–petroleum ether and from dilute acetone, the product melted at 205–206°: $[\alpha]^{25}_D$ +66°; yield, 83%.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.65. Found: C, 73.07; H, 9.98.

A sample of the combined mother liquors of the monoacetate was heated with pyridine–acetic anhydride and then chromatographed over alumina. The crystalline fractions melting above 200° were combined and after several recrystallizations from alcohol and from ether pure pregnane-3(α),20(*epi*)-diol-11-one diacetate, m. p. 234–235°, was obtained. The yield was 1.5% based on the 20-ketone (VI).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.95; H, 9.24.

Pregnane-3(α),20-diol-11-one Diacetate.—A sample of pregnane-3(α),20-diol-11-one 3-acetate (m. p. 205–206°) was heated with acetic anhydride-pyridine on the steam-bath for fifteen minutes. The addition of water gave the crystalline diacetate, m. p. 160.5–161.0°; $[\alpha]^{25}_D$ +81°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.88; H, 9.18.

Pregnane-3(α),20-diol-one-11.—A sample of pregnane-3(α),20-diol-11-one 3-acetate (m. p. 205–206°) was refluxed for fifteen minutes with 1 *N* methanolic potassium hydroxide. The crystalline diol was precipitated with water and recrystallized from acetone. It melted at 236–238°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.47; H, 10.20.

Pregnane-3(α),20(*epi*)-diol-11-one.—A sample of pregnane-3(α),20(*epi*)-diol-11-one diacetate (m. p. 234–235°) was saponified similarly. The diol melted at 219°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.29; H, 10.29.

Pregnane-3(α),20-diol-11-one 3-Acetate 20-Tosylate (VIII).—To a solution of 4.75 g. of pregnane-3(α),20-diol-11-one 3-acetate in 9 cc. of pyridine was added 4.0 g. of recrystallized *p*-toluenesulfonyl chloride. The solution was permitted to stand at room temperature overnight and was then treated with sufficient water to destroy the excess acid chloride. After further dilution with water, extraction with chloroform, and successive washings with dilute hydrochloric acid, dilute sodium carbonate and water, the solution was concentrated to

dryness *in vacuo*. Crystallization from ether–petroleum ether gave 6.80 g. of solvated product, melting at 100°, resolidifying and melting again at 141–143°. Recrystallization from dilute methanol gave a non-solvated product, m. p. 144–145°; $[\alpha]^{25}D$ +57.5°.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 67.89; H 7.97. Found: C, 67.92; H, 7.86.

After standing at room temperature for a month, the sample melted at 173°. In subsequent preparations only this higher melting form was obtained.

Δ^{17}-Pregnene-3(α)-ol-11-one (X).—A solution of 6.50 g. of pregnane-3(α),20-diol-11-one 3-acetate 20-tosylate in 50 cc. of redistilled collidine was refluxed for twenty-five minutes. The solution was cooled, diluted with petroleum ether, washed with dilute hydrochloric acid and with water and concentrated to a small volume. Crystals (200 mg.) of the isomeric acetate tosylate XII (?) separated and were filtered and set aside. The mother liquors were concentrated to dryness and the residue crystallized from methanol at 0°. The crude pregnenes weighed 3.61 g. and melted at 60–82°. The mixture was refluxed for thirty minutes with 30 cc. of 1.1 *N* methanolic potassium hydroxide, then diluted with water and permitted to crystallize. After a number of recrystallizations from methanol 1.4 g. of pure Δ^{17}-pregnene-3(α)-ol-11-one was obtained. It melted at 191–192° and had $[\alpha]^{25}D$ +55°. Refluxing the tosylate with 2 *N* methanolic potassium hydroxide gave smaller yields of this unsaturated compound.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.68; H, 10.12. Found: C, 79.57; H, 10.10.

A sample was converted to the acetate (IX) with pyridine–acetic anhydride. After recrystallization from methanol it melted at 125°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.07; H, 9.56. Found: C, 77.03; H, 9.54.

Isomeric Tosylate (XII) (?).—The 200 mg. of crystals which separated from the collidine reaction product described above was recrystallized from methanol and melted at 197–200°, $[\alpha]^{25}D$ +46.5°. It was almost entirely stable to further treatment with collidine.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 68.81; H, 8.24. Found: C, 68.70; H, 8.36.

Isomeric Diol from XII (?).—A suspension of 300 mg. of the tosylate XII (?) m. p. 197–200°, in 12 cc. of methanol and 3 cc. of water was stirred with 25 g. of 4% sodium amalgam overnight. The suspension was decanted from mercury and filtered. Recrystallization from a large volume of methanol gave a product which melted at 294–297°, and was isomeric with pregnanediolone.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.70; H, 10.25.

Similar reduction of a sample of VIII (m. p. 173°) gave pregnane-3(α),20-diol-11-one, m. p. and mixed m. p. 236–238°.

Diacetate of Isomeric Diol.—A sample of isomeric diol (m. p. 294–297°) was heated with pyridine–acetic anhydride on the steam-bath for one hour. The addition of water gave crystals, m. p. 183°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.99; H, 9.02.

Ozonolysis of Crude Δ^{17}-Pregnene-3(α)-ol-11-one Acetate (IX).—Twenty-five grams of crude pregnene-17-ol-3(α)-one-11 acetate (an amorphous product direct from the detosylation with collidine was used) was ozonized and the product treated according to a previously described procedure.[8] A total of 8.43 g. of acidic material was obtained which was saponified and gave upon crystallization from ethyl acetate 2.13 g. of 3(α)-hydroxy-11-keto-*etio*-cholanic acid, m. p. and mixed m. p. 296–298°. The neutral fraction (16.5 g.) gave 10.2 g. of ketones from which 7.2 g. of pure *etio*-cholanol-3(α)-11,17-dione was obtained.

Pregnane-3(α),17,20-triol-11-one (XI).—A sample (100 mg.) of Δ^{17}-pregnene-3(α)-ol-11-one (X) in 20 cc. of absolute ether was treated with 100 mg. of osmium tetroxide and two drops of pyridine. After one hour the mixture was concentrated to dryness *in vacuo*, dissolved in 5 cc. of alcohol and treated with a solution of 300 mg. of sodium sulfite in 5 cc. of water. The mixture was refluxed for two hours, filtered, concentrated to a small volume, diluted with water and extracted with chloroform. The chloroform extract was concentrated to dryness and the residue crystallized from ether. The triol melted at 189–191°. A second crystalline form, m. p. 210–212°, was obtained by crystallization from benzene. The compound showed a strong tendency to separate as a gel from non-polar solvents and could not be obtained free of solvents. Prolonged heating appeared merely to lead to decomposition.

The diacetate was prepared with pyridine–acetic anhydride in the usual manner. It melted at 227–228°, $[\alpha]^{25}D$ +24°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.82. Found: C, 69.06; H, 8.65.

***etio*-Cholane-3,11,17-trione from XI.**—A solution of 450 mg. of pregnane-3(α),17,20-triol-11-one (XI) (purified through the diacetate) in 5.5 cc. of 90% acetic acid was treated with 10 cc. of 90% acetic acid containing 500 mg. of chromic acid. After fifty minutes at room temperature, the solution was diluted with water and extracted twice with chloroform. The washed chloroform solution was concentrated to dryness and the residue was chromatographed over 10 g. of acid washed alumina. The fractions from 9:1 ether–chloroform to 1:9 ether–chloroform contained the *etio*-cholanetrione, m. p. and mixed m. p. 134–135°. Subsequent fractions gave a product, m. p. 177–182°, the amount of which was too small to permit complete purification.

Pregnane-20(α),21-diol-3,11-dione 21-Acetate 20-Tosylate (XIV).—To a solution of 378 mg. of pregnane-20(α),21-diol-3,11-dione (m. p. 182–183°) in 1.05 cc. of absolute dioxane was added 576 mg. of a dioxane solution containing 161 mg. of acetic anhydride and 138 mg. of pyridine. After standing at room temperature for sixty hours, the solution was evaporated *in vacuo* and the residue chromatographed. Ether–chloroform mixtures eluted crystals of 21-monoacetate which after several recrystallizations from ether melted at 166–170° and weighed 97 mg. A total of 186 mg. of this partially purified monoacetate was treated with 125 mg. of tosyl chloride in 0.2 cc. of pyridine. After standing at room temperature overnight, the solution was diluted with water and taken up in ether. The washed ethereal solution was concentrated to dryness. The amorphous tosylate (254 mg.) was sparingly soluble in dry ether.

Pregnane-20(β),21-diol-3,11-dione 21-Acetate 20-Tosylate (XIII).—A sample (362 mg.) of pregnanediol-20(α),21-dione-3,11 (m. p. 168°) was similarly converted to the monoacetate. The crude product was chromatographed and gave 227 mg. of crude monoacetate together with some diacetate and starting material. The amorphous monoacetate with tosyl chloride gave 212 mg. of tosylate, m. p. 176–180°. After two recrystallizations from acetone a sample melted at 193–194°.

Anal. Calcd. for $C_{30}H_{40}O_7S$: C, 66.15; H, 7.40. Found: C, 66.26; H, 7.23.

A sample (250 mg.) of the 20(α)-tosylate (XIV) was refluxed for twenty-five minutes with collidine. Only 20% of the theoretical amount of collidine *p*-toluenesulfonate was formed. Chromatography of the product gave a small amount of oily reaction product, the remainder consisting of starting material or a rearrangement product thereof. Saponification of the detosylated material gave a non-crystalline product.

Δ^{17}-Pregnene-21-ol-3,11-dione (XV).—A solution of 166 mg. of crystalline 20(β)-tosylate (XIII) in 4 cc. of collidine was refluxed for twenty-five minutes. The solution was cooled and diluted with petroleum ether; 86 mg. (82%) of collidine *p*-toluenesulfonate separated. The solution was then diluted with ether, washed with dilute hydrochloric acid and concentrated to dryness,

The residue (130 mg.) was chromatographed over 3.5 g. of alumina. The eluates obtained with 10-cc. portions of 3:7, 2:8 and 1:9 petroleum ether–ether, with 10 cc. of ether and with 10 cc. of 9:1 ether–chloroform were combined and gave 69 mg. of amorphous Δ^{17}-pregnene-21-ol-3,11-dione acetate. This was dissolved in 3.5 cc. of methanol and treated with a solution of 2 cc. of water containing 60 mg. of potassium carbonate and 60 mg. of potassium bicarbonate. After two hours at room temperature, the solution was acidified with 2 drops of acetic acid and concentrated to a small volume *in vacuo*. The oily precipitate was dissolved in chloroform, washed and the solution concentrated to dryness. The residue (54 mg.) was chromatographed over 2 g. of alumina. The fraction eluted with 1:1 ether–chloroform and mixtures with an increasing proportion of chloroform could be crystallized from a small volume of ether. The combined crystals weighed 30 mg. and melted at 127.5–128°. Recrystallization from ether raised the melting point to 128–128.5°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.63; H, 9.38.

A 5-mg. sample was permitted to stand at room temperature with acetic anhydride–pyridine for two hours. The product was an oil, from which the original alcohol could be obtained by saponification.

Δ^{17}-Pregnene-21-ol-3,11-dione from Δ^{17}-Pregnene-3(α),21-diol-11-one 21-Hemisuccinate.—A sample of 159 mg. of the 21-hemisuccinate of Δ^{17}-pregnene-3(α),21-diol-11-one was oxidized and then saponified as previously described[8]. Crystallization of the product gave 70 mg. of Δ^{17}-pregnene-21-ol-3,11-dione, m. p. 128°. It did not depress the melting point of XV.

Pregnene-17(α),20,21-triol-3,11-dione Diacetate from XV.—A sample (82 mg.) of Δ^{17}-pregnene-21-ol-3,11-dione, (XV), m. p. 128°, was treated with osmium tetroxide, hydrolyzed and acetylated as previously described.[8] The crystalline diacetate weighed 72 mg., melted at 212–213°, and had $[\alpha]^{25}D$ +95°. A mixed melting point with the original sample showed no depression.

Acknowledgment.—For valuable suggestions concerning this work the author is indebted to Dr. K. Folkers and Dr. R. T. Major of these laboratories, and to Dr. E. S. Wallis of Princeton University. For the microanalyses reported herein acknowledgment is made to Messrs. R. Boos, W. H. Humphrey, E. Thornton, J. McGregor and R. Funk.

Summary

The application of the *p*-toluenesulfonate-tertiary amine reaction to certain 20-hydroxypregnenes is described. In the case of pregnane-20(β),21-diol-3,11-dione 21-acetate 20-tosylate, Δ^{17}-pregnene-21-ol-3,11-dione was obtained.

(8) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

RAHWAY, N. J. RECEIVED DECEMBER 5, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of 2-Alkylbutadienes[1]

BY C. S. MARVEL, R. L. MYERS[2] AND J. H. SAUNDERS[3]

The observation[4] that emulsion copolymers of isoprene with styrene contain more diene units joined in the 1,4-manner than do the corresponding butadiene–styrene copolymers suggested the importance of investigating other 2-alkylbutadienes. The literature on the synthesis of this class of dienes is very limited. 2-Ethyl-1,3-butadiene has been reported as a product of dehydrohalogenation of 3-methyl-3,4-dibromopentane,[5] but no evidence of structure was presented. 2-Isopropyl-1,3-butadiene has been prepared by von Braun and Keller[6] by the Hofmann degradation of 2-isopropyl-1,4-diaminobutane. While this method gave a well-characterized product, the starting materials needed for the synthesis are not readily available. This communication describes the synthesis of 2-isopropyl-1,3-butadiene[7] by various routes, one of which appears to be a good general method for making 2-alkylbutadienes.

2-Isopropylbutadiene was first obtained by dehydration of 2-isopropyl-1,4-butanediol through acetylation and pyrolysis. The diol was synthesized by the method of Adkins and Wojcik.[8] The final yield of diene based on diethyl isopropylidenesuccinate was about 4%. An attempt to find an improved preparation of diethyl isopropylsuccinate through the addition of isopropyl-metal halides to diethyl maleate or fumarate did give the ester in 30% yields but the over-all reaction was still not a satisfactory one for preparative work.

A second series of reactions was then investigated. The starting material was isovaleraldehyde (I). It was converted either to isopropylacrolein (III) or to 2-isopropyl-3-hydroxypropionaldehyde (II) and then by the Grignard reaction and subsequent dehydration to the desired diene. Different sequences of reactions were tried and these are indicated in the chart.

The final choice of steps is that indicated by the heavy arrows. The Mannich intermediate[9] (VI) was not isolated but was converted directly to isopropylacrolein (VII). The unsaturated carbinol

(1) The work described in this manuscript was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Present address: General Electric Company, Schenectady, New York.

(3) Present address: Monsanto Chemical Company, Anniston, Alabama.

(4) I. M. Kolthoff, T. S. Lee and Mary Anne Mairs, *J. Polymer Sci.*, **2**, 220 (1947).

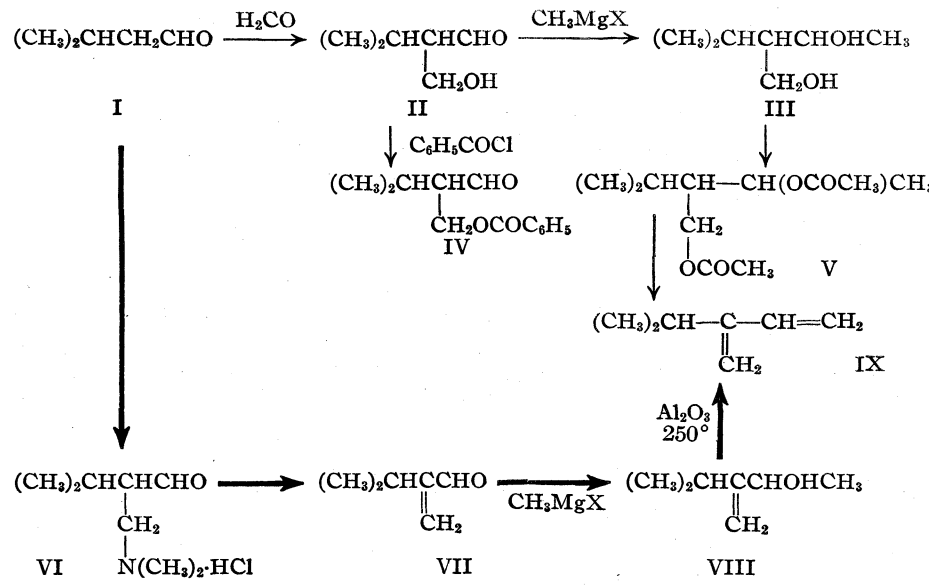
(5) Pariselle and Simon, *Compt. rend.*, **173**, 86 (1921).

(6) von Braun and Keller, *Ber.*, **64**, 2617 (1931).

(7) The desirability of synthesizing this diene was first brought to our attention by Drs. W. E. Messer and V. C. Neklutin of the United States Rubber Company.

(8) Adkins and Wojcik, THIS JOURNAL, **55**, 4939 (1933); **56**, 2424 (1934).

(9) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).



(VIII) was also dehydrated by converting to the acetate and pyrolyzing this ester. This method may be useful in large scale work to effect dehydration. The over-all yield of diene from isovaleraldehyde is about 11%. The reactions are relatively simple to carry out in the laboratory on a fairly large scale.

By use of the preferred scheme outlined above *n*-butyraldehyde was converted to 2-ethylbutadiene and *n*-heptaldehyde was converted to 2-*n*-amylbutadiene.

Experimental

Diethyl Isopropylidenesuccinate.—Diethyl isopropylidenesuccinate was prepared according to the procedure of Adkins and Wojcik[8] with slight modifications. Sodium ethoxide was prepared in ether suspension by the method of Brühl[10] and used without isolation. The reaction was run for four hours at 0° after the addition of the acetone and diethyl succinate mixture to the sodium ethoxide suspension. The reaction mixture was then permitted to warm to room temperature and stand for sixteen hours prior to hydrolysis. Longer reaction times did not increase the yield. From 136 g. (2.0 moles) of sodium ethoxide in 1500 ml. of ether, 217.5 g. (1.25 moles) of diethyl succinate, and 116 g. (2.0 moles) of acetone there was obtained 120 g. (45%) of diethyl isopropylidenesuccinate, b. p. 91–96° (1 mm.), $n^{20}D$ 1.4521. When 2.0 moles of sodium ethoxide, 1.5 moles of ester, and 2.4 moles of acetone were used the yield was 53%. Other variations in the concentrations of reactants did not increase the yield.

The product was redistilled through a 12-in., helix-packed column to obtain pure diethyl isopropylidenesuccinate which boiled at 100–102° (2 mm.), $n^{20}D$ 1.4550, d^{20}_4 1.0304.

Adkins and Wojcik[8] reported the b. p. 115–122° (7 mm.).

Diethyl Isopropylsuccinate by Reduction of Diethyl Isopropylidenesuccinate.—A total of 815 g. (3.81 moles) of diethyl isopropylidenesuccinate was reduced over Raney nickel in a high pressure bomb without solvent. With an initial pressure of 1700 p. s. i. at 25° only one-third of the theoretical amount of hydrogen was taken up. The pressure was raised to 2150 p. s. i., the temperature to 100°, and the reduction was completed. The nickel was removed by filtration and the diethyl isopropylsuccinate was reduced to the glycol without purification.

Diethyl Isopropylsuccinate from Diethyl Fumarate and Isopropylmagnesium Bromide.—In a 1-liter, three-necked, round-bottomed flask equipped with a reflux condenser and a dropping funnel with calcium chloride tubes, and a Hershberg stirrer were placed 50 g. (0.3 mole) of diethyl fumarate and 250 ml. of dry ether. A Grignard reagent prepared in the usual manner from 7.07 g. (0.3 mole) of magnesium, 35.8 g. (0.3 mole) of isopropyl bromide and 300 ml. of ether was added dropwise to the reaction flask with vigorous stirring. The reaction mixture was stirred for an additional fifteen minutes after all of the Grignard reagent had been added.

The reaction mixture was worked up in the usual manner and the residual oil was distilled through a 12-in., helix-packed column. The yield of diethyl isopropylsuccinate was 18.8 g. (29.8%), b. p. 65° (0.5 mm.) or 82° (1 mm.), $n^{20}D$ 1.4261. A sample which was redistilled for analysis boiled at 123–125° (20 mm.), $n^{20}D$ 1.4284, d^{20}_4 0.9925.

Anal.[11] Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.82; H, 9.10.

Adkins and Wojcik[8] who prepared this compound by the reduction of diethyl isopropylidenesuccinate reported the b. p. 110–112° (8 mm.). Neklutin[12] who prepared this compound in a manner similar to that of Adkins and Wojcik,[8] reported b. p. 71–78° (0.8 mm.), $n^{29}D$ 1.4288.

The use of 50% mole excess of diethyl fumarate did not increase the yield. When diethyl maleate was substituted for diethyl fumarate, the results were essentially the same (30.2% yield).

Five grams of diethyl isopropylsuccinate was hydrolyzed by refluxing for six hours with 40 ml. of 25% sodium hydroxide solution. The solution was cooled, extracted with ether and acidified. The white solid thus obtained was recrystallized from acetone and water, m. p. 115.5–116.5°. Roser[13] reported a melting point of 114° for *dl*-isopropylsuccinic acid. Henry and Paget[14] reported a melting point of 117° for this compound.

Diethyl Isopropylsuccinate from Diethyl Maleate and Isopropyl-cadmium Halide.—A Grignard reagent was prepared in the usual way, using 28.6 g. (1.18 moles) of magnesium, 143 g. (1.16 moles) of isopropyl bromide,

(10) Brühl, *Ber.*, **35**, 3510 (1902); **37**, 2066 (1904).

(11) We are indebted to Mr. H. S. Clark, Illinois State Geological Survey, for all microanalyses reported in this communication.

(12) Neklutin, private communication.

(13) Roser, *Ann.*, **220**, 271 (1883).

(14) Henry and Paget, *J. Chem. Soc.*, 70 (1928).

and 1000 ml. of dry ether in a 3-liter, three-necked, round-bottomed flask. The reaction mixture was stirred for fifteen minutes after the addition of the halide had been completed, and then was cooled to 0° by means of an ice–salt bath and was maintained at that temperature. During one and one-quarter hours 212 g. (1.16 moles) of anhydrous cadmium chloride was added in small portions to the reaction flask. The suspension was stirred for three-quarters of an hour and a solution of 200 g. (1.16 moles) of diethyl maleate in 500 ml. of ether was added dropwise to the reaction mixture during a period of three and one-half hours. During the addition of the ester the reaction mixture became very gummy and hard to stir. A less vigorous glass stirring shaft was substituted for the Hershberg stirrer and the reaction was continued. Stirring at 0° was continued for five hours.

The reaction mixture was worked up in the usual way and the residual oil was distilled through a 6-in., helix-packed column. The recovery of diethyl maleate was 69.5 g. (34.8%). The yield of diethyl isopropylsuccinate was 48 g. (29.3%), b. p. 118–126° (20 mm.), $n^{20}D$ 1.4311.

A similar experiment which involved longer reaction times between the isopropyl bromide and magnesium and between the isopropylmagnesium bromide and cadmium chloride did not give an increased yield.

2-Isopropyl-1,4-butanediol.—The diethyl isopropylsuccinate obtained from the reduction of the diethyl isopropylidenesuccinate was reduced over copper chromite at 260°, with an initial pressure of 6000 p. s. i.[8] Only about two-thirds of the theoretical amount of hydrogen was taken up.

The reduction mixture was filtered through a fluted filter paper to remove most of the catalyst, and the filtrate was distilled through a 12-in., helix-packed column. The recovery of diethyl isopropylsuccinate was 76.5 g. (9.4%). The yield of 2-isopropyl-1,4-butanediol was 72.5 g. (15.8%), b. p. 145–146° (18 mm.), $n^{20}D$ 1.4535, d^{20}_4 0.9672.

Adkins and Wojcik reported b. p. 119–122° (3 mm.), $n^{25}D$ 1.4535.

Diacetate of 2-Isopropyl-1,4-butanediol.—In a 200-ml., round-bottomed flask were placed 22 g. (0.167 mole) of 2-isopropyl-1,4-butanediol, 75 g. (0.73 mole) of acetic anhydride, and 1 g. of pyridine. The flask and its contents were set aside for three days. At the end of that time the acetic acid was removed by distillation through a 12-in., helix-packed column at atmospheric pressure, and the acetic anhydride was distilled at 100 mm. The residue was carefully fractionated. The yield of diacetate was 28.7 g. (80%), b. p. 105° (3 mm.), $n^{20}D$ 1.4346. A sample was redistilled for analysis, b. p. 96° (1.5 mm.), $n^{20}D$ 1.4349, d^{20}_4 1.0055.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.32; H, 9.19.

2-Isopropyl-1,3-butadiene.—A 20-mm. Pyrex tube was packed for a distance of 12 in. with glass beads and heated in a furnace to 575 ± 10°. Twenty-eight grams (0.13 mole) of the diacetate of 2-isopropyl-1,4-butanediol was dropped through the hot tube at a rate of one drop every second. The pyrolysate was dissolved in 25 ml. of ether and washed twice with 50 ml. of water. The washings were combined and extracted with two 20-ml. portions of ether. All three ether solutions were combined and dried over 1 g. of anhydrous magnesium sulfate. The drying agent was removed and the ether solution was fractionated through a 4-in., helix-packed column. The fraction boiling at 82–84° was collected, $n^{20}D$ 1.4280. Since this fraction contained a trace of acetic acid it was dried over 0.25 g. of anhydrous potassium carbonate. The yield of 2-isopropylbutadiene thus obtained was 4 g. (32%), $n^{20}D$ 1.4339. von Braun and Keller[6] reported b. p. 86–87°, $n^{23}D$ 1.4321, $d^{24.5}_4$ 0.7276.

Maleic Anhydride Adduct of 2-Isopropylbutadiene.—In a 2-oz., screw-cap bottle were placed 5 ml. of dry benzene, 1 ml. (0.73 g., 0.0076 mole) of 2-isopropylbutadiene and 0.49 g. (0.005 mole) of maleic anhydride. The bottle was capped and rotated in a water-bath at 50° for twenty-two hours. The adduct was precipitated from the benzene solution by the addition of 5 ml. of low petroleum ether. After recrystallization from benzene and low petroleum ether the adduct melted at 86–86.5°.

The various maleic anhydride adducts obtained from 2-isopropylbutadiene produced by the different methods described in this paper had the same melting points, and mixed melting points showed no depression. A sample of this adduct was submitted for analysis.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.21; H, 7.21.

α-Isopropylacrolein by the Mannich Method.—In a 5-liter, three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a thermometer were placed 975 g. (12.0 moles) of dimethylamine hydrochloride, 900 g. (12 moles) of a 40% solution of formalin, and 860 g. (10 moles) of isovaleraldehyde. The flask was heated by an oil-bath maintained electrically at 70° and stirred for twenty-four hours. The flask was then fitted for steam distillation, and the contents steam-distilled until organic material no longer separated from the distillate. The water layer was removed, and the organic material was dried over anhydrous magnesium sulfate. Distillation through an 18-in., electrically heated, helix-packed column yielded 113.5 g. of recovered isovaleraldehyde (13.1%), b. p. 92–95°, an intermediate fraction, 117 g., b. p. 95–105°, $n^{20}D$ 1.4115–1.4170, and 453 g. of α-isopropylacrolein, b. p. 105–108°, $n^{20}D$ 1.4223, d^{20}_4 0.8389, a yield of 52.6% (based on unrecovered isovaleraldehyde). Because of the unstable nature of the compound a good analysis was difficult to obtain, but a sample which was freshly distilled gave fair results.

Anal. Calcd. for $C_6H_{10}O$: C, 73.43; H, 10.27; *MR*, 29.79. Found: C, 72.92; H, 10.15; *MR*, 29.74.

A 2,4-dinitrophenylhydrazone, prepared according to a standard procedure,[15] melted at 164.5–165°.

Anal. Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07. Found: C, 51.92; H, 5.10.

2-Isopropyl-3-hydroxypropionaldehyde.—In a 5-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, a dropping funnel, and condenser were placed 430 g. (5 moles) of isovaleraldehyde, 1200 g. (16 moles) of a 40% solution of formalin, and 1000 ml. of ethyl ether. Stirring was begun, and 1 liter of a 10% solution of potassium carbonate was added dropwise. After the addition of the alkali (four hours) stirring was continued an additional twenty-hours at room temperature. The organic layer was then separated and the aqueous layer was extracted three times with 300-ml. portions of ethyl ether. The extracts were combined with the original organic layer and the solution dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration and flash distillation of the ether, the residual liquid was distilled through a 6-in., helix-packed column. There was obtained 215 g. of unreacted isovaleraldehyde, and 150 g. (52%) of 2-isopropyl-3-hydroxypropionaldehyde, b. p. 83.5° (9.5 mm.), $n^{20}D$ 1.4603, d^{20}_4 1.0517. A sample of the material was redistilled for analysis.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.42; *MR*, 30.45. Found: C, 61.48; H, 10.60; *MR*, 30.05.

An attempt to prepare a 2,4-dinitrophenylhydrazone[15] resulted in yellow plates, m. p. 123–126°, which on recrystallization from ethanol turned red and melted at 158–159°. This melting point is almost that of the derivative for α-isopropylacrolein and a mixture of this product with that known derivative melted at 161–164°. The lack of depression indicated that the present compound had dehydrated on recrystallization.

Benzoate of 2-Isopropyl-3-hydroxypropionaldehyde.—In a 3-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, a dropping funnel and reflux condenser were placed 214 g. (1.85 moles) of 2-isopropyl-

(15) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., J. Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

3-hydroxypropionaldehyde and 584 g. (4 moles) of benzoyl chloride. The flask was cooled by means of an ice-bath. To the stirred and cooled mixture was added 1000 ml. of a 10% solution of sodium hydroxide at a rate such that the temperature of the reaction did not exceed 35°. Following the addition of the alkali, stirring was continued for one-half hour. The semi-solid reaction mixture was dissolved in 600 ml. of benzene, and the solution was washed with 10% sodium carbonate solution until the washings were alkaline. The benzene was removed, and the residue was distilled through a 6-in., helix-packed column. The yield of the benzoate was 55 g. (13.5%), b. p. 103° (0.3 mm.), $n^{20}D$ 1.4820. A 2,4-dinitrophenylhydrazone of the material was prepared,[15] m. p. 130.5°.

Anal. Calcd. for $C_{19}H_{20}O_6N_4$: C, 56.99; H, 5.03. Found: C, 56.87; H, 5.06.

α-Isopropylacrolein by Pyrolysis of the Benzoate.—Fifty-five grams (0.25 mole) of the benzoate of 2-isopropyl-3-hydroxypropionaldehyde was passed dropwise through a 19-mm. outside diameter Pyrex tube packed for a distance of 12 in. with 4-mm. glass beads and heated to 575° by means of a combustion furnace. Distillation of the pyrolysate yielded 12 g. (50%) of α-isopropylacrolein, b. p. 108.5°, $n^{20}D$ 1.4223.

α-Isopropylacrolein by Dehydration of the Aldol.—After several preliminary attempts resulted in only polymeric material, a solution of 29 g. (0.25 mole) of 2-isopropyl-3-hydroxypropionaldehyde in 40 ml. of benzene was refluxed with 1.0 g. of iodine. Distillation of the material yielded 4.5 g. of α-isopropylacrolein, b. p. 108.5°, $n^{20}D$ 1.4230 (18%). Attempts to dehydrate the aldol by passing over activated alumina at 350° in a Pyrex tube, and by dropping on fused potassium acid sulfate at 225° produced only polymeric material.

2-Isopropyl-3-hydroxy-1-butene.—In a 5-liter, three-necked, round-bottomed flask fitted with a dropping funnel, a reflux condenser (both connected to calcium chloride drying towers) and a mechanical stirrer were placed 116.5 g. (4.84 moles) of magnesium turnings and 500 ml. of dry ether. A solution of 675 g. (4.84 moles) of methyl iodide in 1200 ml. of absolute ether was added with stirring as rapidly as control of the reaction would permit. After formation of the Grignard complex, a solution of 379 g. (3.87 moles) of α-isopropylacrolein in 1000 ml. of dry ether was added dropwise. After completion of the reaction the mixture was poured onto about 3 kg. of crushed ice. The complex was decomposed with dilute hydrochloric acid, and the ether layer was separated. The aqueous layer was extracted three times with 300-ml. portions of ethyl ether and combined with the original ether layer. After drying the ether solution over anhydrous magnesium sulfate, the drying agent was removed, and the ether was removed by distillation through a 6-in., helix-packed column. Distillation of the residual material through an 18-in., helix-packed column yielded 330.9 g. (75%) of 2-isopropyl-3-hydroxy-1-butene, b. p. 84° (75 mm.), $n^{20}D$ 1.4361, d^{20}_4 0.8473.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36; *MR*, 35.59. Found: C, 73.60; H, 12.27; *MR*, 34.82.

2-Isopropyl-1,3-butadiene by the Alumina Dehydration of 2-Isopropyl-3-hydroxy-1-butene.—One hundred grams of 2-isopropyl-3-hydroxy-1-butene was passed dropwise through an 18-mm. outside diameter Pyrex tube packed for a distance of 18 in. with 6–8 mesh activated alumina and heated to 250° by means of an electrically heated jacket. The pyrolysate was collected in a 500-ml. suction flask cooled in a Dry Ice–ethanol bath. The product was dried and distilled to yield 25.8 g. (30.4%) of 2-isopropyl-1,3-butadiene, b. p. 85–86°, $n^{20}D$ 1.4340, d^{23}_4 0.723. von Braun and Keller[6] reported b. p. 86–87°, $n^{23}D$ 1.4321, $d^{24.5}_4$ 0.7276. A higher-boiling fraction was also obtained, b. p. 75° (90 mm.), $n^{20}D$ 1.4130. This material is presumably 3,4-dimethylpentanone-2, b. p. 136–138°, which van Romburgh[16] reported b. p. 135–136°, d^{20}_4 0.815.

(16) van Romburgh, *Rec. trav. chim.*, **5**, 228 (1886).

An analogous rearrangement was observed with the corresponding ethyl derivative reported later.

2-Isopropyl-3-acetoxy-1-butene.—In a 125-ml. Erlenmeyer flask was placed a mixture of 28.8 g. (0.25 mole) of 2-isopropyl-3-hydroxy-1-butene, 36 g. (0.35 mole) of acetic anhydride and a few drops of pyridine. The mixture was allowed to stand overnight, washed with three 25-ml. portions of distilled water and distilled through a 6-in., helix-packed column to yield 31.1 g. (0.196 mole) of 2-isopropyl-3-acetoxy-1-butene, b. p. 89° (66 mm.), $n^{20}D$ 1.4256, d^{20}_4 0.8857, a yield of 79%. A sample of this material was redistilled for analysis.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32; *MR*, 44.96. Found: C, 69.09; H, 10.31; *MR*, 45.20.

2-Isopropyl-1,3-butadiene from the Pyrolysis of 2-Isopropyl-3-acetoxy-1-butene.—Pyrolysis of 82.7 g. (0.53 mole) of 2-isopropyl-3-acetoxy-1-butene was accomplished by passing the material dropwise through a 19-mm. Pyrex tube packed for a distance of 12 in. with 4-mm. glass beads and heated to 500° by means of a combustion furnace. Distillation of the washed and dried pyrolysate yielded 11.7 g. (23%) of 2-isopropyl-1,3-butadiene, b. p. 85–87°, $n^{20}D$ 1.4345.

2-Isopropyl-1,3-butanediol.—By the usual Grignard procedure, a solution of methylmagnesium iodide was prepared from 59 g. (0.42 mole) of methyl iodide, 10.0 g. (0.42 atom) of magnesium turnings and 200 ml. of anhydrous ethyl ether. To this solution was added 24 g. (0.21 mole) of 2-isopropyl-3-hydroxypropionaldehyde in 200 ml. of dry ethyl ether. The reaction was fairly violent, presumably because of the consumption of one-half of the Grignard reagent by the hydroxyl group. The complex was decomposed by pouring over ice and acidifying with dilute hydrochloric acid. After extraction of the aqueous layer with three 75-ml. portions of ethyl ether the combined ether extracts were dried over anhydrous magnesium sulfate, the ether was removed and the residue distilled through a 12-in., helix-packed column. There was obtained 20.0 g. (0.151 mole) of 2-isopropyl-1,3-butanediol, b. p. 106° (4 mm.), $n^{20}D$ 1.4528, a yield of 72%. A sample of the diol was redistilled for analysis.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.34; H, 12.37.

2-Isopropyl-1,3-diacetoxybutane.—A mixture of 20.0 g. (0.15 mole) of 2-isopropyl-1,3-butanediol, 45 g. (0.45 mole) of acetic anhydride, and a few drops of pyridine was placed in a 125-ml. Erlenmeyer flask and allowed to stand overnight. The resulting solution was washed with three 10-ml. portions of distilled water, separated and the organic solution was distilled through a 6-in., helix-packed column. There was obtained 25.0 g. (0.116 mole) of 2-isopropyl-1,3-diacetoxybutane, b. p. 127° (24 mm.), $n^{20}D$ 1.4330, d^{20}_4 1.0026, a yield of 77%. A sample of the material was redistilled for analysis.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32; *MR*, 56.51. Found: C, 61.21; H, 9.24; *MR*, 56.06.

Pyrolysis of this material in a manner described above for the 2-isopropyl-3-acetoxy-1-butene yielded only 0.5 g. (4.5%) of 2-isopropyl-1,3-butadiene in addition to some higher boiling materials that were not characterized.

α-Ethylacrolein.—In a 5-liter, three-necked, round-bottomed flask fitted with an efficient stirrer, a reflux condenser, and a thermometer were placed 405 g. (5.0 moles) of dimethylamine hydrochloride, 324 g. (4.5 moles) of *n*-butyraldehyde, and 375 g. (5 moles) of 40% formalin. The flask and its contents were heated to 60°, maintained by an electrically heated oil-bath, and stirred for six hours. The condenser was arranged for distillation and the mixture was subjected to steam distillation until organic material no longer separated in the distillate. The organic layer was separated, dried and distilled through an 18-in., helix-packed column. Distillation yielded 280 g. of α-ethylacrolein, b. p. 91–92°, $n^{20}D$ 1.4205, a yield of 73.5%. α-Ethylacrolein has been previously

prepared by Sommelet[17] who heated over oxalic acid the 1,3-diethyl ether of 2-ethylglycerol. It has also been prepared by passing 2-ethylallyl alcohol over zinc oxide at 350°, but again no physical constants were given.[18] A semicarbazone of the material was prepared, m. p. 185.5–186°. Sommelet reported[17] 192.5°. A 2,4-dinitrophenylhydrazone was prepared according to the method of Shriner and Fuson,[15] m. p. 166.5–167°.

Anal. Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58. Found: C, 50.06; H, 4.41.

2-Ethyl-3-hydroxy-1-butene.—In a 5-liter, round-bottomed, three-necked flask fitted with a dropping funnel, a reflux condenser (protected from the atmosphere by calcium chloride towers) and a mechanical stirrer, was placed 1000 ml. of a 4 molar solution of methylmagnesium bromide in ether (Arapahoe Chemicals Company). To this was added with stirring a solution of 280 g. (3.3 moles) of α-ethylacrolein in 1500 ml. of absolute ether. An ice collar around the top of the flask permitted relatively rapid addition of the ether solution. The reaction was stirred an additional hour and then poured onto crushed ice. The Grignard complex was decomposed by adding dilute hydrochloric acid until complete solution had been effected. The ether layer was separated and the aqueous layer extracted with two 300-ml. portions of ether. The ether extracts were combined with the original organic layer and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the ether was removed through a 6-in., helix-packed column and the residual liquid distilled through an 18-in., helix-packed, electrically heated column equipped with a total reflux partial take-off head. A total of 282 g. of 2-ethyl-3-hydroxy-1-butene was collected, b. p. 83° (100 mm.), $n^{20}D$ 1.4350, d^{20}_4 0.8491, a yield of 85.5%.

Anal. Calcd. for $C_6H_{12}O$: C, 71.92; H, 12.08; *MR*, 30.97. Found: C, 72.04; H, 11.99; *MR*, 30.77.

2-Ethyl-1,3-butadiene.—Dehydration of 2-ethyl-3-hydroxy-1-butene was accomplished by passing 50.0 g. (0.5 mole) dropwise through a 19-mm. outside diameter Pyrex tube packed for a distance of 18 in. with crystalline potassium acid sulfate and heated to 190–200° by means of an electrically heated jacket. The pyrolysate was collected in a 500-ml. filter flask immersed in a Dry Ice–methanol bath. The product was washed with water, and dried over anhydrous magnesium sulfate and distilled. Distillation yielded 17.5 g. of 2-ethyl-1,3-butadiene, b. p. 72–74°, $n^{20}D$ 1.4488, d^{20}_4 0.7173, a yield of 42.8%.

Anal. Calcd. for C_6H_{10}: C, 87.73; H, 12.27. Found: C, 87.87; H, 12.27.

There was also obtained an 8.0 g. sample of material which did not have the physical constants of the original carbinol. A sample of this material, b. p. 60° (95 mm.), $n^{20}D$ 1.4012, d^{20}_4 0.8130, was redistilled for analysis.

Anal. Calcd. for $C_6H_{12}O$: C, 71.92; H, 12.08. Found: C, 71.36; H, 11.77.

This material discharged bromine in carbon tetrachloride but with much evolution of hydrogen bromide. It reduced potassium permanganate and reacted with the 2,4-dinitrophenylhydrazine reagent. This indicated that it was not the original 2-ethyl-3-hydroxy-1-butene. A 2,4-dinitrophenylhydrazone derivative prepared according to the directions of Shriner and Fuson[15] had a constant melting point of 70–71° after three recrystallizations from 95% ethanol. This corresponds to the 71.2° reported by Drake and Veitch[19] for the derivative of methyl *s*-butyl ketone. A comparison of the physical properties of the unknown with those of this ketone further confirms their identity.

	Unknown	Methyl *s*-butyl ketone
B. p.	60° (95 mm.)	117° (760 mm.)
$n^{20}D$	1.4012	$n^{18}D$ 1.4002
d^{20}_4	0.8130	0.815

α-*n*-Amylacrolein.—In a 5-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser were placed 800 g. (9.9 moles) of dimethylamine hydrochloride, 740 g. (9.9 moles) of 40% formalin, and 855 g. (7.5 moles) of *n*-heptaldehyde. The flask and its contents were heated to 70° and maintained at that temperature by means of an electrically heated oil-bath. Stirring was continued for eighteen hours. The flask was then equipped for steam distillation and the contents were steam-distilled until organic material no longer separated from the distillate. The organic material was separated from the water layer and distilled through an 18-in., helix-packed, electrically heated column. There was obtained 650.5 g. of α-*n*-amylacrolein, b. p. 72° (30 mm.), $n^{20}D$ 1.4373, a yield of 69%. A sample of the material was redistilled for analysis.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.15; H, 10.90.

A 2,4-dinitrophenylhydrazone prepared according to the directions of Shriner and Fuson[15] had a constant melting point of 134–134.5° after three recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{14}H_{20}O_4N_4$: C, 54.89; H, 5.92. Found: C, 55.20; H, 6.43.

2-*n*-Amyl-3-hydroxy-1-butene.—In a 3-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel both fitted with calcium chloride towers to exclude moisture, was placed 53 g. (2.2 atoms) of magnesium turnings, and 300 ml. of dry ether. To this was added with stirring a solution of 312 g. (2.2 moles) of methyl iodide in 750 ml. of dry ether. An ice collar around the top of the flask permitted very rapid addition of the methyl iodide solution. The mixture was permitted to stir an additional half-hour after the methyl iodide had been added. To this was then added a solution of 252.4 g. (2.0 moles) of α-*n*-amylacrolein in 700 ml. of dry ether. The mixture was allowed to stir an additional half-hour and was then poured onto about 2 kg. of crushed ice. The complex was decomposed with dilute hydrochloric acid, the ether layer separated, and the aqueous layer extracted three times with 300-ml. portions of ether. The ether extracts were combined with the original ether layer and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the ether was removed by distillation through a 12-in., helix-packed column and the residual liquid distilled through an 18-in., helix-packed, electrically heated column. A total of 203.0 g. (71.5%) of 2-*n*-amyl-3-hydroxy-1-butene was collected, b. p. 68° (3 mm.), $n^{20}D$ 1.4448. A sample of the material was redistilled for analysis.

Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 76.14; H, 12.25.

2-*n*-Amyl-1,3-butadiene.—Dehydration of 536.6 g. (3.78 moles) of 2-*n*-amyl-3-hydroxy-1-butene was accomplished by passing the material dropwise over activated alumina in a 19-mm. outside diameter Pyrex tube packed for a distance of 18 in. and heated to 240–250° by means of an electrically heated jacket. The dehydration products were collected in a 500-ml. suction flask cooled in a Dry Ice–methanol-bath. The water layer was separated and the organic material distilled through an 18-in., helix packed column. There was obtained 103 g. (22%) of 2-*n*-amyl-1,3-butadiene, b. p. 148–149°, $n^{20}D$ 1.4510, d^{20}_4 0.7578.

Anal. Calcd. for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 86.94; H, 13.04.

A higher-boiling fraction was obtained which was believed to be 3-methyloctanone-2, by analogy to the reaction that produced methyl *s*-butyl ketone from 2-ethyl-3-hydroxy-1-butene. This compound has been prepared by Powell, Murray and Baldwin[20] who reported b. p. 64–65° (18 mm.), $n^{27}D$ 1.424, d^{27}_4 0.832. The frac-

(17) Sommelet, *Ann. chim.*, [8] **9**, 562 (1906).

(18) French Patent 777,032, July 16, 1934, *Chem. Zentr.*, **106**, II, 757 (1935).

(19) Drake and Veitch, THIS JOURNAL, **57**, 2623 (1935).

(20) Powell, Murray and Baldwin, *ibid.*, **55**, 1153 (1933).

tion obtained in this work had the constants, b. p. 109° (65 mm.), $n^{20}D$ 1.4269. A 2,4-dinitrophenylhydrazone was prepared which had a constant melting point of 111–112° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{15}H_{22}O_4N_4$: C, 55.88; H, 6.88. Found: C, 55.80; H, 6.90.

Summary

2-Ethyl-, 2-isopropyl- and 2-*n*-amyl-1,3-butadiene have been prepared by a general procedure which can presumably be applied to other 2-alkylbutadienes.

Experiments covering alternate routes to various of the intermediates and final products have been recorded.

URBANA, ILLINOIS RECEIVED NOVEMBER 13, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Synthesis of Unsaturated Fatty Acids[1]

BY KAMALLUDIN AHMAD AND F. M. STRONG

Despite the large number of unsaturated fatty acids which occur in the most diverse types of living organisms and their great technical and biological importance, only a very few have been synthesized to date by methods which could be expected to lead to pure products of unequivocal structure.[2] Recent improvements in methods for selectively hydrogenating acetylenes to olefins[3,4,5] and the ease of building up relatively long aliphatic chains by condensing alkyl halides with acetylene or alkyl acetylenes[6] suggested the possibility of obtaining unsaturated fatty acids from acetylenic alkyl halides *via* the nitrile or Grignard reagent:

$$R{-}C{\equiv}C{-}(CH_2)_nX \longrightarrow R{-}C{\equiv}C(CH_2)_n{-}COOH \longrightarrow R{-}CH{=}CH{-}(CH_2)_n{-}COOH$$

It was expected that acetylenic halides of the required type would be formed by reaction of alkyl acetylenes with, for example, bromo- or iodochlorides since acetylene itself readily yields analogous products.[7]

$$RC{\equiv}CH + I(CH_2)_n{-}Cl \xrightarrow{NaNH_2} RC{\equiv}C{-}(CH_2)_nCl$$

The feasibility of this method of synthesis has been tested by the preparation of 6-hendecenoic acid from 1-hexyne and 1-chloro-4-iodobutane according to the scheme

$$CH_3(CH_2)_3{-}C{\equiv}CH + I(CH_2)_4Cl \xrightarrow{NaNH_2} CH_3(CH_2)_3C{\equiv}C{-}(CH_2)_4Cl \xrightarrow[NaOH]{NaCN} CH_3(CH_2)_3C{\equiv}C{-}(CH_2)_4COOH \xrightarrow[Ni]{(H)} CH_3(CH_2)_3CH{=}CH(CH_2)_4COOH$$

The desired product was obtained with no particular difficulty, and the olefinic bond was found by oxidative degradation to be present in the expected position.

Experimental

1-Chloro-4-iodobutane.—Sodium iodide was refluxed in acetone solution with a three-molar proportion of 1,4-dichlorobutane[8] until less than 3% of the iodine remained in the inorganic form (five to six hours). Fractional distillation gave a 71% yield (based on the sodium iodide) of 1-chloro-4-iodobutane, b. p. 93–94.5° (17 mm.), of 94% purity.

Anal. Calcd. for C_4H_8ClI: I, 58.1. Found: I, 54.4.

Since the impurity was most probably unreacted dichlorobutane, the product was used without further purification.

1-Chloro-5-decyne.—A three-liter, three-neck round-bottom flask was fitted with a stirrer, dropping funnel, gas inlet tube, and block tin condenser cooled with a chloroform–Dry Ice mixture. Fifteen-hundred ml. of liquid ammonia was placed in the flask, the stirrer was started, and 0.3 g. of ferric nitrate and 1 g. of sodium were added. Dry air was bubbled through the solution for a few minutes until the blue color was discharged, after which an additional amount of 14.6 g. (0.68 g. atom, total) of sodium was added slowly in small portions. After the reaction had been in progress for thirty minutes, 1 g. of sodium peroxide was added. After two and one-half hours the mixture assumed a dull gray color, and the conversion of the sodium to sodamide was judged to be complete.[9]

An amount of 41 g. (0.50 mole) of 1-hexyne[10] was then introduced dropwise with stirring over a period of two hours, and after an additional interval of three hours, 117 g. (0.54 mole) of 1-chloro-4-iodobutane was added during four hours. Stirring was continued four hours longer, and the mixture was then allowed to stand at room temperature until the ammonia had evaporated. About 150 ml. of water was cautiously added, the mixture filtered, and the organic layer collected in ether. The ether solution was washed free from inorganic halides with water, and fractionally distilled. The main fraction, 45.4 g. (53%), b. p. 143–145° (51 mm.), contained 2.5% of iodine. Redistillation gave 31 g. of iodine-free product, b. p. 110–112° (15 mm.); $n^{25}D$ 1.4592, d^{25}_4 0.9238, *MR* (calcd.) 51.4, *MR* (found) 51.1. The yield of pure product thus amounted to 36%.

Anal. Calcd. for $C_{10}H_{17}Cl$: Cl, 20.53. Found: Cl, 19.6, 20.6.

6-Hendecynoic Acid.—To a solution of 16 g. (0.33 mole) of sodium cyanide in 25 ml. of water were added 115 ml. of 95% ethanol and 25.7 g. (0.15 mole) of 1-chloro-5-decyne. The mixture was refluxed until the bulk of the chloride had been converted to the inorganic

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station.

(2) K. S. Markley, "Fatty Acids," Interscience Publishers, Inc., New York, N. Y., 1947, p. 554.

(3) Campbell and Eby, THIS JOURNAL, **63**, 2683 (1941).

(4) Thompson and Shaw, *ibid.*, **64**, 363 (1942).

(5) H. Adkins, private communication.

(6) Vaughn, Hennion, Vogt and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

(7) Henne and Greenlee, THIS JOURNAL, **67**, 484 (1945).

(8) E. I. du Pont de Nemours and Company, Electrochemical Division, generously donated this material.

(9) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(10) Farachan Laboratories, Cleveland, Ohio.

form (fifteen hours), after which 20 g. of sodium hydroxide was added and the refluxing continued overnight. Most of the alcohol was then distilled off, water added, and the alkaline solution extracted with ether. Acidification of the aqueous solution caused the separation of an oily liquid which was collected in ether, and fractionated to give 19 g. of material b. p. 126–150° (0.5 mm.). Since the neutral equivalent was high, the entire fraction was again dissolved in aqueous alkali and extracted with ether to remove neutral impurities. Isolation of the acid fraction as before, followed by distillation gave 10.4 g. (38%), b. p. 124–125° (0.17 mm.); $n^{25}D$ 1.4566, d^{25}_4 0.9537, *MR* (calcd.) 52.5, *MR* (found) 52.1.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96; neutral equivalent, 182.3. Found: C, 72.1; H, 9.98; neutral equivalent, 181.5, 182.0.

Quantitative microhydrogenation showed an uptake of 1.98 moles of hydrogen per mole of compound. Calculated, 2.00 moles. The *p*-phenyl phenacyl ester was prepared according to the directions given by Price and Griffith,[11] and after recrystallization from 65% ethanol melted at 58°.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.49. Found: C, 79.78; H, 7.00.

Hendecanoic Acid.—An amount of 0.9774 g. of the above 6-hendecynoic acid was dissolved in 15 ml. of alcohol, and shaken at room temperature in an atmosphere of hydrogen with 59.8 mg. of platinum oxide catalyst. Absorption of the theoretical amount of hydrogen was complete in fifteen minutes. The catalyst and solvent were removed, and the product crystallized from a small volume of acetone. Colorless crystals, m. p. 28°, were obtained. The m. p. of hendecanoic acid has been reported to be 28.8–29.2°.[12]

Anal. Calcd. for $C_{11}H_{22}O_2$: neutral equivalent, 186.3. Found: neutral equivalent, 186.2, 186.0.

A small sample was converted to the *p*-phenyl phenacyl ester, which was recrystallized from 65% alcohol, and melted at 79.5°. The literature value is 79.5–80°.[11]

6-Hendecenoic Acid.—An alcoholic solution of 4.8 g. of 6-hendecynoic acid was shaken under approximately 3 atmospheres pressure of hydrogen in the presence of Raney W6 nickel catalyst.[13] One molar equivalent of hydrogen was absorbed in a few minutes, and the reduction was then immediately stopped. After removing the catalyst and solvent the product was distilled, and yielded 3.00 g. (62%) of a colorless liquid, b. p. 130–134° (0.15 mm.); $n^{25}D$ 1.4492, d^{25}_4 0.9208, *MR* (calcd.) 54.1, *MR* (found) 53.7.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.68; H, 10.91; neutral equivalent, 184.3. Found: C, 71.3; H, 10.69; neutral equivalent, 185.0.

Quantitative microhydrogenation resulted in the absorption of 0.97 mole of hydrogen per mole of the compound; calculated, 1.00 mole.

The *p*-phenyl phenacyl ester was prepared in the usual way and melted at 41°.

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 8.04. Found: C, 79.2; H, 8.10.

Oxidative Degradation of 6-Hendecenoic Acid.—One gram of 6-hendecenoic acid was oxidized with dilute alkaline permanganate by the procedure of Lapworth and Mottram.[14] Since the expected dihydroxy acid did not precipitate on acidification of the reaction mixture, the acidic solution was thoroughly extracted with ether. Removal of the ether followed by extraction of the residue with petroleum ether and drying gave 0.31 g. of the crude dihydroxy acid, which was not further purified.

The acidic aqueous solution and petroleum ether washings were combined, evaporated to dryness under reduced pressure, and the residue taken up in absolute alcohol. The solution was neutralized with sodium hydroxide, and the acid present converted to the *p*-phenyl phenacyl ester in the usual way. The recrystallized product melted at 146°. The *bis*-*p*-phenyl phenacyl ester of adipic acid is reported to melt at 148°.[15] A mixed melting point with an authentic specimen showed no depression.

The crude dihydroxy acid (0.31 g.) was dissolved in 5 ml. of anhydrous acetic acid and treated with 0.45 g. of lead tetraacetate. After shaking for twenty minutes at room temperature and five minutes at 45°, the mixture was cooled, diluted with 5 ml. of water, and 0.3 g. of hydroxylamine hydrochloride, 0.3 g. of sodium acetate, and 3–4 drops of methanol were added. The crystals which separated on standing overnight at 7° were filtered, washed with cold, dilute sodium hydroxide solution, then with water and dried. The product melted at 51°. *n*-Valeraldehyde oxime melts at 52°.[16] A mixed melting point with an authentic specimen showed no depression.

Discussion

Suitable selection of the intermediate halides should permit extension of the present synthesis to a wide variety of saturated, olefinic and acetylenic straight and branched chain acids, while reaction of the intermediate acetylenes with aldehydes, ketones or acid halides should result in hydroxy or keto derivatives. A series of straight chain, mono-unsaturated acids is being prepared in this Laboratory.

No effort was made to isolate the two geometrical isomers of 6-hendecenic acid. However, the present synthesis should offer opportunities for obtaining such isomers, since the partial hydrogenation of the acetylenic bond can be stereochemically controlled.[17]

Summary

A convenient and practical synthesis of mono-unsaturated fatty acids has been suggested. Alkyl acetylenes react with iodochlorides to form acetylenic chlorides which in turn, *via* the nitrile or Grignard reaction and subsequent selective hydrogenation of the triple bond, are converted to the mono-unsaturated fatty acids. The method promises to be of general utility for synthesizing a variety of fatty acids and related long chain aliphatic substances.

MADISON, WISCONSIN RECEIVED NOVEMBER 17, 1947

(11) Price and Griffith, THIS JOURNAL, **62**, 2884 (1940).

(12) Kulka and Sandin, *ibid.*, **59**, 1347 (1937).

(13) Adkins and Billica, *ibid.*, **70**, 695 (1948).

(14) Lapworth and Mottram, *J. Chem. Soc.*, **127**, 1628 (1925).

(15) Drake and Sweeney, THIS JOURNAL, **54**, 2060 (1932).

(16) Huntress and Mulliken, "Identification of Pure Organic Compounds, Order 1," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 51.

(17) Campbell and Eby, THIS JOURNAL, **63**, 216 (1941).

[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT, OREGON STATE COLLEGE]

Quinazolines. V. The Synthesis of 2-(and 3)-*o*-Aminobenzyl-4-quinazolones[1]

BY A. TOMISEK AND BERT E. CHRISTENSEN

During an investigation of the acid hydrolysis of 3-(4′-quinazolyl)-4-quinazolone it became necessary to synthesize both the 2- and 3-*o*-aminobenzylquinazolones.

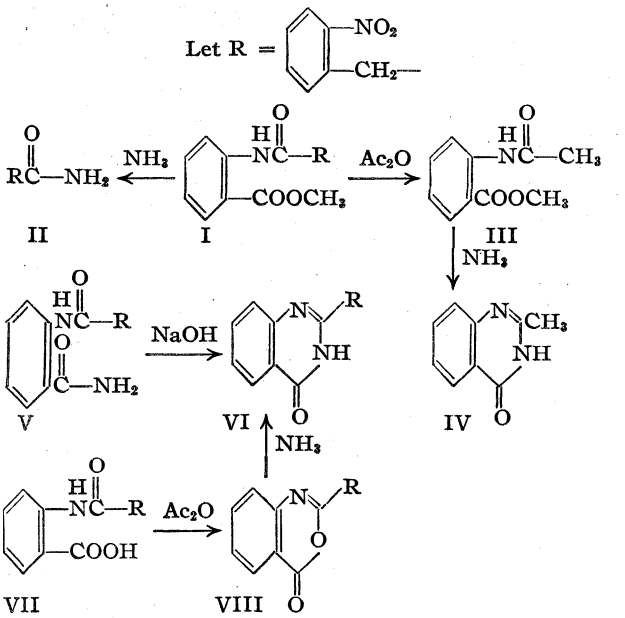
Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was prepared as a possible intermediate for the synthesis of the 2-(*o*-aminobenzyl)-4-quinazolone. Weddige,[2] Zacharias,[3] and Thieme[4] had successfully cyclized similar compounds (I) (R = methyl) using ammonia. However, Thieme[4] had reported amide ammonolysis as a side reaction. In this instance (R = nitrobenzyl) (I) the ammonolysis product (*o*-nitrophenylacetamide) (II) was obtained in good yield with no trace of the quinazolone.

Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was then refluxed with acetic anhydride in an attempt to prepare the anthranil. The un-isolated product of this reaction was in turn converted to the quinazolone by the use of concentrated ammonia. However, 2-methyl-4-quinazolone (IV) was obtained instead of the desired product, which indicated that transacylation to the methyl acetylanthranilate (III) had preceded the cyclization. Since both mono and diacetyl methyl anthranilate instead of acetanthranil are obtained by the action of acetic anhydride on methyl anthranilate,[5] the course of the above reaction was probably *via* methyl acetylanthranilate (III) and acetylanthranilamide.

The synthesis of the 2-(*o*-nitrobenzyl)-4-quinazolone (VI) was finally accomplished by two methods. N-(*o*-Nitrophenylacetyl)-anthranilamide (V) was prepared by the condensation of anthranilamide with *o*-nitrophenylacetyl chloride and then converted to 2-(*o*-nitrobenzyl)-4-quinazolone (VI) by aqueous base.

N-(*o*-Nitrophenylacetyl)-anthranilic acid (VII) was readily dehydrated to 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII), which in turn was also converted to the desired quinazolone in good yield. This last reaction probably proceeds *via* the anthranilamide (V) since this intermediate has been isolated in certain analogous cases.[6]

The synthesis of 3-(*o*-nitrobenzyl)-4-quinazolone was based upon the work of Bogert and Geiger,[7] in which it was shown that the N-alkylation of sodium 4-quinazolonate could be carried out with benzyl chloride. The extent of O-alkylation involved in the benzylation has been determined, but the precaution was taken to destroy by acid hydrolysis any O-ether which may have formed.



Experimental[8]

Methyl N-(*o*-Nitrophenylacetyl)-anthranilate (I).—A benzene solution of O-nitrophenylacetyl chloride, prepared with thionyl chloride from 5 g. of the acid,[9] was added to a dry benzene solution containing 4 ml. of methyl anthranilate. To this mixture was added gradually with stirring 40 ml. of 25% potassium hydroxide.

After washing the *warm* benzene solution with acid and then removing the solvent, the residue was dissolved in hot acetone, decolorized with charcoal, cooled and crystallized. The yield was 6.0 g. (69%), m. p. 131–133°. Recrystallization from alcohol or acetone gave white crystals, m. p. 133.5–134°.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.1; H, 4.49; N, 8.92. Found: C, 61.3; H, 4.64; N, 8.92.

Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was heated in a bomb with absolute alcoholic ammonia for eight hours at 180°. A good yield of *o*-nitrophenylacetamide (II) was obtained in place of a cyclized product.

One gram of methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was refluxed for fifteen hours in 4 ml. of acetic anhydride. The reaction mixture was added cautiously to an excess of hot 14% ammonia, containing a few drops of 10% potassium hydroxide. The mixture was heated on the steam-bath for one hour, and then refluxed with an excess of potassium hydroxide to destroy the acetamide. The cooled, filtered solution was brought to neutrality with hydrochloric acid. After standing two days, 0.14 g. of crude 2-methyl-4-quinazolone (IV) crystallized. This material was recrystallized from alcohol and identified by a mixed melting point test.

(1) Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 120, School of Science.

(2) Weddige, *J. prakt. Chem.*, [2] **36**, 145 (1887).

(3) Zacharias, *ibid.*, [2] **43**, 441 (1891).

(4) Thieme, *ibid.*, [2] **43**, 473 (1891).

(5) Private communication.

(6) Bogert, Amend and Chambers, THIS JOURNAL, **32**, 1297 (1910).

(7) Bogert and Geiger, *ibid.*, **34**, 527 (1912).

(8) All melting points are corrected.

(9) Mayer and Balle, *Ann.*, **403**, 188 (1914).

N-(*o*-Nitrophenylacetyl)-anthranilamide (V).—A dioxane solution of *o*-nitrophenylacetyl chloride prepared from 5 g. of the acid was added to 50 ml. of a dioxane solution, containing 7.6 g. of anthranilamide.[10]

After several hours the precipitate was removed, triturated with water, refiltered and thoroughly dried. Additional product was obtained by concentrating the dioxane solution. The combined fractions were decolorized and recrystallized from hot pyridine–benzene solution, yield, 6.06 g. (73%), m. p. 167–170°. Recrystallization from pyridine–benzene and pyridine–water gave product with m. p. 172–173°.

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.2; H, 4.38; N, 14.04. Found: C, 59.9; H, 4.64; N, 14.24.

2-(*o*-Nitrobenzyl-4-quinazolone (VI) from Nitrophenylacetylanthranilamide.—A mixture consisting of 3.46 g. of N-(*o*-nitrophenylacetyl)-anthranilamide (V), 12 ml. of pyridine, 12 ml. of water and 1 ml. of 10% sodium hydroxide after standing for one day at room temperature was made more basic by the addition of 75 ml. of 10% sodium hydroxide. The solution was then filtered and the crude product isolated by neutralizing the filtrate. The precipitate was extracted with boiling glacial acetic acid from which it crystallized on cooling; yield 2.85 g. (88%) of 2-(*o*-nitrobenzyl)-4-quinazolone, (VI). The product recrystallized from glacial acetic acid and pyridine–water for analytical purposes was white granular crystals, m. p. (dec.) 254.5°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.15; H, 3.73; N, 14.76.

N-(*o*-Nitrophenylacetyl)-anthranilic Acid (VII).—A dioxane solution of *o*-nitrophenylacetyl chloride prepared from 5 g. of the acid was mixed with 50 ml. of dioxane solution containing 20 g. of anthranilic acid. After several hours the crude N-(*o*-nitrophenylacetyl)-anthranilic acid (VII) was removed by filtration, triturated with water and then recrystallized from glacial acetic acid. A second fraction was obtained by dissolving the residue left after evaporation of the mother liquor in dilute sodium hydroxide and then reprecipitating the product with hydrochloric acid, recrystallizing it from glacial acetic acid and dioxane–water. The yield was 82% (4.9 and 1.9 g.). This combined yield, recrystallized again, melted with slow evolution of gas, m. p. 224–225°.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.03; N, 9.33. Found: C, 60.1; H, 4.02; N, 9.03.

2-(*o*-Nitrobenzyl-4-keto-3,1,4-benzoxazine (VIII).—Five grams of N-(*o*-nitrophenylacetyl)-anthranilic acid (VII) was refluxed for thirty minutes in 20 ml. of pure acetic anhydride. Four and four-tenths grams of 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII) crystallized from the cooled and seeded solution, m. p. 162–164°. This product when recrystallized from pyridine–water, alcohol, then pyridine–alcohol gave white plates, m. p. 165–166°.

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.8; H, 3.57; N, 9.92. Found: C, 63.6; H, 3.85; N, 10.10.

2-(*o*-Nitrobenzyl-4-quinazolone (VI) from Nitrobenzylbenzoxazone.—A suspension of 5 g. of 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII) in 25 ml. of 50% pyridine was saturated with ammonia and allowed to stand with occasional stirring for six hours. One milliliter of 10% sodium hydroxide was then added and the mixture was set aside for an additional twenty-four hours. Isolation procedure was the same as for the synthesis from the anthranilamide; yield 3.6 g. (72%).

2-(*o*-Aminobenzyl)-4-quinazolone.—To a suspension of 5 g. of 2-(*o*-nitrobenzyl)-4-quinazolone in 300 ml. of dilute sodium hydroxide was added a solution containing 33 g. (10% excess) of hydrated ferrous sulfate in 100 ml. of water. The reaction mixture was maintained at 80° for seven hours. The ferrous–ferric hydroxides were separated by centrifuging and washed repeatedly with dilute sodium hydroxide until the wash liquors gave no further precipitate upon neutralization. Combined precipitates obtained by the neutralization of the washings and the mother liquor were decolorized with charcoal and recrystallized from pyridine–water. The yield of 2-(*o*-aminobenzyl)-4-quinazolone was 3.68 g. (80%). It was recrystallized for analysis from dioxane and dioxane–water; the white, voluminous powder melted (decomposition) over a wide range, starting at about 250°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.21; N, 16.72. Found: C, 71.4; H, 5.32; N, 16.58.

2-(*o*-Acetaminobenzyl)-4-quinazolone.—The corresponding amino compound (1.0 g.) was acylated in the usual manner. The product was recrystallized from pyridine–water, and acetic acid–water, to yield white needles of m. p. 258°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: N, 14.33; Found: N, 14.52.

3-(*o*-Nitrobenzyl)-4-quinazolone.—To an aqueous solution containing ten grams of *o*-nitrobenzyl chloride, prepared according to the directions of Haeussermann and Beck[11] was added 13 g. of 4-hydroxyquinazolone and 5.9 g. of 85% potassium hydroxide pellets and 200 ml. of alcohol.

After refluxing for six hours the alcoholic solvent was removed and replaced with a mixture of dilute hydrochloric acid and benzene. This mixture was refluxed for fifteen minutes to hydrolyze any benzyl quinazolyl ether. The benzene layer was then separated and thoroughly extracted with 3 *N* hydrochloric acid. The combined fractions were treated with an excess of sodium hydroxide and the crude product (3 g.) separated by filtration. After decolorizing with charcoal the product was recrystallized from benzene, pyridine–water and acetic acid–water to yield a pure white product m. p. 169–170°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.1; H, 3.94; N, 14.94. Found: C, 64.3; H, 4.12; N, 14.96.

3-(*o*-Aminobenzyl)-4-quinazolone.—A uniform suspension of 2.83 g. of 3-(*o*-nitrobenzyl)-4-quinazolone and 7.27 g. of stannous chloride dihydrate in 30 ml. of glacial acetic acid was prepared. The mixture was saturated with dry hydrogen chloride and allowed to stand for ten hours. The gummy precipitate which formed was dispersed by two or three minutes of gentle heating and the mixture was then poured into water. The aqueous suspension was made strongly basic with sodium hydroxide and filtered. The precipitate was extracted with boiling pyridine, and water was added to complete a crystallization from pyridine–water. The 1.62 g. (64%) of crude, white plates were decolorized with charcoal and recrystallized from alcohol, dioxane–water and pyridine, m. p. 178°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.21; N, 16.72. Found: C, 71.5; H, 5.39; N, 16.69.

Summary

2-(*o*-Nitrobenzyl)-4-quinazolone was prepared by (1) the cyclization of N-(*o*-nitrophenylacetyl)-anthranilamide and (2) by ammonolysis of 2-(*o*-nitrobenzyl-4-keto-3,1,4-benzoxazine.

3-(*o*-Nitrobenzyl)-4-quinazolone was prepared by the reaction of *o*-nitrobenzyl chloride and sodium 4-quinazolonate.

CORVALLIS, OREGON RECEIVED DECEMBER 6, 1947

(10) Kolbe, *J. prakt. Chem.*, [2] **30**, 475 (1884); Erdmann, *Ber.*, **32**, 2164 (1899).

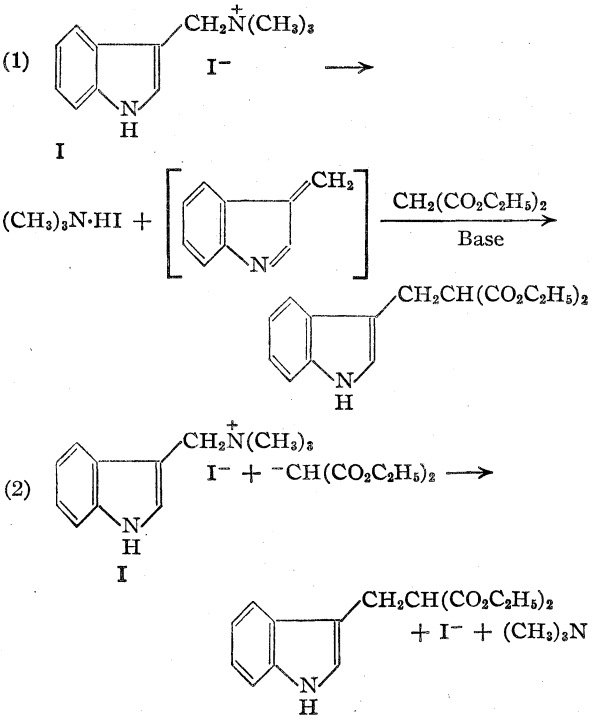
(11) Haeussermann and Beck, *Ber.*, **25**, 2445 (1892).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Alkylation with the Methiodide of 1-Methyl-3-dimethylaminomethylindole (1-Methylgramine)[1]

BY H. R. SNYDER AND ERNEST L. ELIEL

Alkylations with gramine[1,2] and its quaternary salts[3] proceed with such ease as to suggest that the mechanisms of the reactions differ from those of alkylations with simple amines and quaternary salts containing a radical of the benzyl type. Two possible mechanisms for reactions with gramine methiodide are shown in equations 1 and 2. The first, consisting in the elimination of trimethylamine hydriodide and a Michael-type addition, is patterned after that suggested by Mannich[4] for alkylations with salts from ketonic Mannich bases.



In the second mechanism it is assumed that the trimethylamine molecule is displaced from the quaternary ammonium ion by the anion of the substance being alkylated. Mechanisms similar to 1 and 2 can be written for reactions of the tertiary amine, gramine.

A consideration of the two mechanisms suggested that reactions of 1-methylgramine (III) and its quaternary salt (IV) be examined. This paper reports the preparation of these two substances and the reaction of the quaternary salt (IV) with aqueous sodium cyanide.

Application of the Mannich reaction to 1-methylindole[5] (II) gave the methylgramine (III) in about 80% yield. The methiodide (IV), obtained in nearly quantitative yield from the base and methyl iodide in ethanol, reacted readily with aqueous sodium cyanide. The expected 1-methylindoleacetonitrile (V) was obtained in about 50% yield, along with a much smaller amount of a more volatile isomer. The structure of this isomeric product is under investigation.

In the proof of the structure of the nitrile (V) the acid (VI) was prepared by hydrolysis. The product obtained melted slightly lower than that described in the literature,[6,7] and its picrate melted about twelve degrees lower than that previously reported.[6] However, reduction of the nitrile with sodium and ethanol gave 1-methyltryptamine (VIII), several derivatives of which had melting points identical with previously reported values. Also, 1,3-dimethylindole (VII) was produced in small quantity in the sodium–alcohol reduction,[8] and it proved to be identical with an authentic specimen made from skatyl sodium and methyl iodide. Decarboxylation of the acid produced the same 1,3-dimethylindole. The various samples of the dimethylindole were compared as pic-

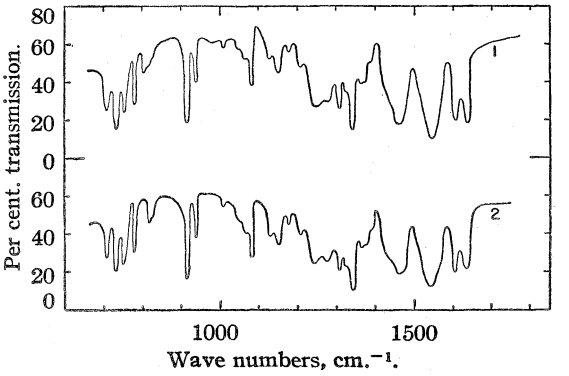


Fig. 1.—1, Infrared absorption spectrum of picrate of 1,3-dimethylindole from skatole. 2, Infrared absorption spectrum of picrate of 1,3-dimethylindole from 1-methylgramine (decarboxylation of 1-methylindole-3-acetic acid).

(1) This is the seventh of a series of papers on quaternary ammonium salts; for the preceding paper, see Snyder and Katz, THIS JOURNAL, **69**, 3140 (1947).

(2) Lyttle and Weisblat, *ibid.*, **69**, 2118 (1947).

(3) Snyder, Smith and Stewart, *ibid.*, **66**, 200 (1944); Snyder and Smith, *ibid.*, **66**, 350 (1944); Albertson and Tullar, *ibid.*, **67**, 502 (1945).

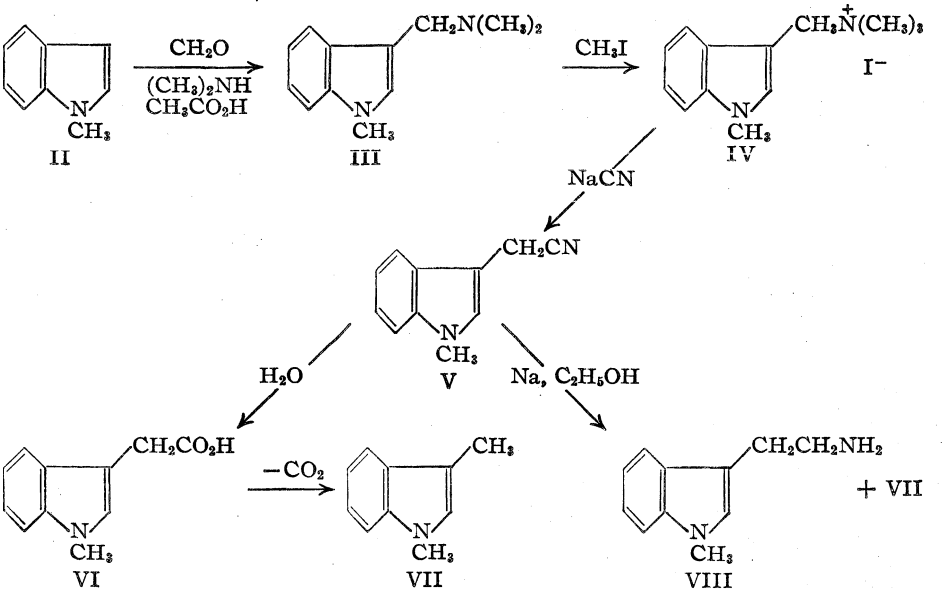
(4) Mannich, Koch and Barkousky, *Ber.*, **70**, 355 (1937).

(5) This synthesis is believed to be the first application of the Mannich reaction to an N-alkylindole. Bauer and Andersag [U. S. Pat. 2,222,344 (*C. A.*, **35**, 1807 (1941))] mention a somewhat similar reaction of N-methylindole with formaldehyde and an alkali cyanide to yield the β-acetonitrile, but no example is given.

(6) Piccini, *Atti acad. Lincei*, [5] **8**, I, 315 (1899).

(7) King and L'Ecuyer, *J. Chem. Soc.*, 1901 (1934).

(8) Majuna and Hoshino [*Ber.*, **58**, 2045 (1925)] observed the formation of skatole in a similar reduction of β-indoleacetonitrile.



rates by the aid of melting points, mixed melting points, and infrared absorption analyses[9] (see the figure). These observations prove that the methylindoleacetic acid obtained by hydrolysis of the nitrile had the structure VI.

The formation of the nitrile (V) from IV and sodium cyanide in water solution shows that the salt (IV), like gramine methiodide (I), is more reactive than simple quaternary salts containing benzyl groups. For example, benzylphenyldimethylammonium chloride is not cleaved by aqueous sodium cyanide.[3] It is probable that alkylations with gramine methiodide and the methylgramine methiodide proceed by the same mechanism, and that reactions of gramine methiodide do not proceed through a process of the Michael type (equation 1). The study of this problem is being continued.

Experimental[10,11]

1-Methylindole (II), prepared from N-methylphenylhydrazine and pyruvic acid by the method of Fischer and Hess[12] boiled at 134–135° (31 mm.) and had n^{20}D 1.6062. Material prepared by the methylation of the sodium derivative of indole with methyl iodide[13] was unsatisfactory owing to contamination by –N–H compounds, the presence of which was revealed by infrared absorption analysis.

1-Methyl-3-dimethylaminomethylindole (III).—A mixture of 36 ml. of 25% aqueous dimethylamine and 40 ml. of glacial acetic acid was cooled in an ice-bath; when the temperature had fallen to 5°, 15 ml. of 40% aqueous formaldehyde was added. The resulting mixture was cooled to 5° and added in one lot to 23.7 g. of N-methylindole. The reaction mixture was shaken gently until it became homogeneous; during the shaking the temperature rose to about 50°. The mixture then was allowed to stand at room temperature for twenty-four hours. The reaction mixture was poured into a solution of 40 g. of sodium hydroxide in 400 ml. of water, and the oil which separated was collected by extraction with one 300-ml. portion and one 200-ml. portion of ether. The ether extracts were washed exhaustively with 1 *N* hydrochloric acid (until the extracts no longer became turbid when made alkaline), about 500 ml. of the acid being required. The combined acid extract was made alkaline by the addition of an excess of 10% sodium hydroxide solution. The liberated base was collected by extraction with two 200-ml. portions of ether. The ether extract was washed, dried, and concentrated, and the residue distilled *in vacuo*. The main fraction, collected at 94–97° (0.2 mm.), weighed 26.3–26.9 g. (77.5–79.3% yield). The analytical sample was redistilled; b. p. 94–96° (0.2 mm.); n^{20}D 1.5743.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.52; H, 8.57. Found: C, 76.64; H, 8.62.

The **picrate** crystallized from alcohol as yellow prisms melting at 145–146°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.81; H, 4.59. Found: C, 52.05; H, 4.55.

1-Methyl-3-dimethylaminomethylindole Methiodide (IV).—To a solution of 8.5 g. of the base (III) in 40 ml. of absolute ethanol was added in one portion 7.8 g. of methyl iodide. An exothermic reaction occurred, so the mixture was cooled to prevent the loss of methyl iodide. The mixture was allowed to stand for one hour at room temperature, during which period most of the product crystallized. Crystallization was completed by cooling, and the solid was collected and washed twice with absolute ethanol and thrice with anhydrous ether. After drying under nitrogen the salt weighed 14.3–14.6 g. (96–98%); the instantaneous decomposition point, determined on a Maquenne block, was 193°. The analytical sample, recrystallized three times from absolute ethanol, decomposed at 195°.

Anal. Calcd. for $C_{13}H_{19}N_2I$: C, 47.28; H, 5.84; N, 8.43. Found: C, 47.37; H, 5.84; N, 8.51.

1-Methylindole-3-acetonitrile (V).—To a solution of 10 g. of sodium cyanide in 100 ml. of water was added 16.5 g. of the crude methiodide (IV) and the mixture was boiled under reflux for two and one-fourth hours, during which period an oil separated from the aqueous solution and a solid appeared in the condenser. The oil and solid were collected from the cooled mixture by extraction with two 50-ml. portions of ether. The ether solution was washed three times with water, dried over sodium sulfate, filtered, and concentrated; the residue was distilled *in*

(9) The authors are indebted to Mrs. Agatha Roberts Johnson for the absorption studies.

(10) All melting points are corrected.

(11) Microanalyses by Miss Theta Spoor and Miss Betty A. Snyder.

(12) Fischer and Hess, *Ber.*, **17**, 561 (1884).

(13) Weissgerber, *ibid.*, **43**, 3522 (1910).

vacuo. A small fraction (*ca.* 0.6 g.), which solidified in the receiver, was collected at 96–122° (0.15 mm.); it melted at 70–71° after three recrystallizations from petroleum ether (b. p. 30–60°). The main fraction, b. p. 123–131° (0.15 mm.), weighed 5.2–5.4 g. (60–64%); it solidified after standing in the ice-box and melted at 58–59° after an extraction with petroleum ether followed by two recrystallizations from a mixture of ether and petroleum ether (b. p. 30–60°).

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92. Found: (higher-melting product) C, 77.54; H, 6.16; (lower-melting product) C, 77.89; H, 5.95.

1-Methylindole-3-acetic Acid (VI).—A mixture of 2 g. of the lower-melting nitrile (V) with a solution of 5 g. of potassium hydroxide, 5 ml. of water, and 20 ml. of 95% ethanol was refluxed for seventeen hours. The solution was diluted with 50 ml. of water and distilled to remove most of the alcohol. The resulting clear solution was extracted three times with ether, heated with Norit, and filtered. The filtrate was very cautiously acidified with 3 *N* hydrochloric acid, and the first (dark-colored) solid which separated was removed by filtration. The acid (VI) was precipitated by acidification of the filtrate to congo red paper. It was collected on a filter, washed with ice-water, and dried in a vacuum desiccator. The material so obtained was a nearly white solid melting at 127–128.5°; wt. 2 g. (90%). Recrystallization from benzene improved the color but had no effect on the melting point; recrystallization from water and high-vacuum sublimation likewise had no effect on the melting point.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86; N, 7.40. Found: C, 70.03; H, 5.99; N, 7.41.

The **picrate** crystallized from benzene as red needles melting at 160.5–161.5°.

Anal. Calcd. for $C_{17}H_{14}N_4O_9$: C, 48.81; H, 3.37. Found: C, 48.91; H, 3.49.

1,3-Dimethylindole: From VI.—In the lower bulb of a two-bulb microdistillation apparatus 0.55 g. of the acid (VI) was heated at 200° until gas evolution ceased. The resulting brown oil was distilled into the upper bulb at 20 mm., with the bath temperature at 140–170°. The light-colored distillate ($n^{20}D$ 1.5920) was converted to the picrate which, after two recrystallizations from absolute ethanol, melted at 142.5–143.5° (lit., 143–144°).

From Skatole.—A modification of the method of Weissgerber[13] was employed. The product was fractionated at atmospheric pressure and the portion boiling at 220–240° was redistilled over sodium. The distillate from this treatment was fractionated *in vacuo* and the fraction boiling at 122–127° (20 mm.) was collected; $n^{20}D$ 1.5901. Infrared absorption analysis of this material showed the presence of appreciable amounts of —NH— compounds. The **picrate** obtained from this fraction melted at 141–142° after five recrystallizations from absolute ethanol, and the melting point was not changed by admixture of the picrate described in the previous paragraph.

1-Methyltryptamine (VIII).—To a hot solution of 3.4 g. of the nitrile (V) in 60 ml. of absolute ethanol was added, over a period of ten minutes, 4 g. of finely cut sodium. The mixture was refluxed until all the metal had dissolved; it was then diluted with 60 ml. of water and concentrated *in vacuo* to remove most of the alcohol. The residual solution was diluted with 40 ml. of water and extracted with two 100-ml. portions of ether. The base (*ca.* 2.4 g.) was recovered from the ether solution by extraction with 2 *N* hydrochloric acid (*ca.* 75 ml.), neutralization of the acid with an excess of aqueous sodium hydroxide, extraction of the alkaline solution with ether, drying of the ether solution, removal of the solvent, and distillation of the residue. It was obtained as a nearly colorless oil boiling at 108–110° at about 0.1 mm. The picrate melted at 178–179° (lit.[14] 180–181°), the hydrochloride at 199–201° (lit.[15] 198°), and the phthalimide at 176.5–177° (lit.[15] 177.5°).

The ether extract of the reaction mixture, after the extraction with 2 *N* hydrochloric acid described above, was concentrated. The resulting oil, wt. about 1.2 g., was distilled from a modified test-tube at about 0.1 mm. Two fractions, approximately equal in weight, were obtained, one boiling at a bath temperature of 90–100° and the other at 140–170°. The first fraction was identified as 1,3-dimethylindole by conversion to the picrate, m. p. 142–143°; the melting point of this picrate was not depressed by admixture with either of the samples described above, and its infrared absorption curve was identical with that shown in the figure. The higher-boiling fraction crystallized when seeded and was identified as 1-methylindole-3-acetonitrile by mixed melting point.

Summary

1-Methylindole reacts with formaldehyde and dimethylamine in the presence of acetic acid to give 1-methyl-3-dimethylaminomethylindole in good yield. The methiodide of this base reacts readily with aqueous sodium cyanide to give 1-methylindole-3-acetonitrile, along with a small amount of an isomeric substance. The structure of 1-methylindole-3-acetonitrile is proved by hydrolysis to 1-methylindole-3-acetic acid and by reduction to 1-methyltryptamine and 1,3-dimethylindole. The methiodide of 1-methyl-3-dimethylaminomethylindole and the methiodide of gramine (3-dimethylaminomethylindole) are more reactive as alkylating agents than simple quaternary ammonium salts containing benzyl groups.

URBANA, ILLINOIS RECEIVED NOVEMBER 29, 1947

(14) Spaeth and Lederer, *Ber.*, **63**, 2106 (1930).

(15) Manske, *Can. J. Research*, **5**, 597 (1931).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Preparation of Substituted Tricyclohexylgermanes

BY O. H. JOHNSON AND W. H. NEBERGALL

Generally the use of an excess of Grignard reagent on germanium tetrachloride yields tetrasubstituted germanium compounds. Bauer and Burschkies,[1] using the conventional Grignard reaction, found that the action of an excess of cyclohexylmagnesium bromide on germanium tetrachloride resulted solely in bromotricyclohexylgermane, apparently according to the reaction

$$3C_6H_{11}MgBr + GeCl_4 \longrightarrow (C_6H_{11})_3GeBr + MgBr_2 + 2MgCl_2$$

The results reported by Bauer and Burschkies led us to determine whether other groups could be substituted for bromine in the tricyclohexylgermanium compound. Accordingly we have prepared a number of new compounds by means of the reaction of bromotricyclohexylgermane with various Grignard reagents and with sodium metal.

Bromotricyclohexylgermane was prepared from cyclohexyl bromide and germanium tetrachloride[2] by the method of Bauer and Burschkies. The substituent groups for the bromine atom in the bromotricyclohexylgermane were introduced by forming Grignard reagents in the usual manner with the appropriate alkyl or aryl halide and adding the bromotricyclohexylgermane in dry benzene

$$RMgBr + (C_6H_{11})_3GeBr \longrightarrow (C_6H_{11})_3GeR + MgBr_2$$

The reaction between bromotricyclohexylgermane and methyl-, ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl-, and benzylmagnesium bromides proceeded smoothly. It was found that the isopropyl, the phenyl and the cyclohexylmagnesium bromides did not react under the conditions that gave good yields of the *n*-alkyl and benzyl compounds. Failure to introduce the isopropyl, phenyl and cyclohexyl groups may be due to possible steric effects.

Formation of hexacyclohexyldigermane by the Wurtz synthesis using sodium metal and bromotricyclohexylgermane was successful.

Experimental

Substituted Germanes.—Grignard reagent was prepared by treating 0.264 mole of alkyl bromide with 0.270 mole of magnesium in 200 ml. of absolute ether. To this mixture was added 0.032 mole of bromotricyclohexylgermane dissolved in 100 ml. of dry benzene. The ether was removed by distillation and the reaction mixture refluxed on the steam-bath for three hours. The excess Grignard was destroyed by dilute acetic acid. The aqueous and the organic layers were separated and the aqueous layer extracted twice with 50 ml. of benzene. The benzene solution was dried over anhydrous calcium chloride and the benzene removed by distillation, leaving an oily liquid. This residual oily liquid was dissolved in boiling absolute ethanol and upon cooling the substituted tricyclohexylgermane precipitated as fine white crystals. The product was purified by recrystallizing four times from absolute ethanol.

Substituted Digermane.—An excess of sodium was added to a solution of 5.5 g. of bromotricyclohexylgermane in 75 ml. of dry toluene and refluxed for two hours. The hot mixture was filtered, allowed to cool and about one-half of the toluene removed by air evaporation by an electric fan. The cooling and the evaporation of the solvent were accompanied by the precipitation of white crystals. These crystals were filtered off, washed with dry toluene, and dried in a pistol for two hours using toluene for a refluxing agent. The analysis indicated that it was hexacyclohexyldigermane, m. p., d. *ca.* 316°; yield, 85%.

Anal. Calcd.: C, 67.31; H, 10.33; Ge, 22.54. Found: C, 67.15; H, 10.59; Ge, 22.49.

Comments on Analytical Procedure.—The standard microcombustion method for determining carbon and hydrogen gave consistently low values for carbon. The cause of these low results is believed to be the formation of germanium carbides which resisted oxidation. To minimize this factor the procedure was modified[3] by increasing the volume of oxygen to 150 ml. for a period of thirty minutes followed by a current of air for another thirty minutes, the heating being continued for twenty minutes after the oxygen was discontinued. The platinum boat was placed as close to the furnace as possible to limit the area to be heated.

Germanium was determined as the dioxide by an adaptation of the method of Bauer and Burschkies.[1] A sample of 0.05 to 0.07 g. weight was heated in a platinum crucible over a steam bath for an hour with a mixture of three parts fuming nitric acid and one part concentrated sulfuric acid. The crucible and mixture were then heated on an electric hot-plate until a brown color appeared. More fuming nitric acid was added from time to time and the process repeated several times until a white residue remained upon evaporation. The residue was ignited and weighed as germanium dioxide.

Results.—Table I gives the results of the analyses and the melting points of the compounds prepared.

TABLE I

SUBSTITUENT TRICYCLOHEXYLGERMANES

Substituent	M. p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Germanium, % Calcd.	Germanium, % Found
CH_3	48.0–48.5	65	67.71	67.25	10.72	11.00	21.55	21.59
C_2H_5	38.5–39.0	56	68.41	68.46	10.91	11.31	20.68	20.58
n-C_3H_7	124–125	70	69.08	69.10	11.04	11.55	19.88	19.77
n-C_4H_9	152.5–153.5	61	69.68	69.16	11.17	11.60	19.15	19.20
n-C_5H_{11}	78–79	71	70.25	69.27	11.27	11.27	18.47	18.52
$C_6H_5CH_2$	54–54.5	69	72.66	72.03	9.76	10.26	17.57	17.52

(1) Bauer and Burschkies, *Ber.*, **65B**, 956 (1932).

(2) Obtained from Research Department, Eagle-Picher Co., Joplin, Mo.

(3) As suggested by R. W. Amidon who made the analyses for carbon and hydrogen.

Solubility.—The compounds prepared were found to be insoluble in water, slightly soluble in acetone and cold ethanol and soluble in ether, benzene, toluene, chloroform, petroleum ether and hot ethanol.

Summary

1. Seven new compounds of germanium, methyl-, ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl- and benzyltricyclohexylgermane, and hexacyclohexyldigermane have been prepared and some properties described.

2. Possible steric effects were encountered in attempts to introduce the isopropyl, the phenyl and the cyclohexyl group as the fourth group into tricyclohexylgermane.

3. Hexacyclohexyldigermane was prepared from bromotricyclohexylgermane by the Wurtz synthesis.

MINNEAPOLIS, MINN. RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY OF BROWN UNIVERSITY]

Properties of Electrolytic Solutions. XXXII. Conductance of Some Long Chain Salts in Ethylene Chloride and Nitrobenzene at 25°[1]

BY HAROLD E. WEAVER[2] AND CHARLES A. KRAUS

I. Introduction

Conductance measurements with aqueous solutions[3] of salts containing hydrocarbon chains of progressively increasing length indicate that the characteristic effect—ascribed to micelle formation—first becomes noticeable with the *n*-nonyl group. In order to determine whether similar effects occur in solutions of such electrolytes in non-aqueous solvents, measurements were carried out with several salts in ethylene chloride and nitrobenzene. At the time that this investigation was initiated, no data were available on the conductance of long chain salts in solvents other than water; in the meantime, however, results of measurements by several investigators have appeared.[4]

The following salts have been studied: octadecyltrimethylammonium and octadecyltributylammonium nitrates in ethylene chloride and dioctadecyldimethylammonium, octadecyltributylammonium and octadecylpyridonium nitrates in nitrobenzene. The octadecyl salts are well adapted to the purpose of the present investigation since octadecyl alcohol of high purity is readily available and the quaternary salts are readily crystallized from a variety of solvents.

II. Experimental

Apparatus and Procedure.—These have been fully described in earlier papers of this series. Bright platinum electrodes were used.

Materials.—Ethylene chloride was purified according to the method described by Mead.[5] The specific conductance was always less than 5×10^{-11}, making solvent corrections unnecessary.

Nitrobenzene was purified as described by Witschonke.[6] The specific conductance of the material was less than 5×10^{-10} so that corrections were unnecessary.

n-Octadecyl alcohol served as the starting material in the preparation of the salts used in this investigation. One recrystallization of the alcohol from nitromethane gave a product which melted at 57.5–58.5°.

n-Octadecyl iodide was obtained by heating the alcohol with iodine and red phosphorus in a sealed tube at 180° for one hour according to the method of Levene, West and van der Scheer.[7] The resulting mixture was extracted with hexane, in which the iodide is very soluble; the excess phosphorus was separated by filtration. The *n*-octadecyl iodide was recrystallized from hexane by slow cooling to 0° in a refrigerator; m. p., 34–35°.

n-Octadecyltri-*n*-butylammonium iodide was prepared by heating *n*-octadecyl iodide with tri-*n*-butylamine (10% excess) in a stoppered flask at 60° for from four to six days. The salt was recrystallized from hexane containing a trace of alcohol; m. p., 97–98°.

n-Octadecyltrimethylammonium iodide was prepared by heating *n*-octadecyl iodide with trimethylamine (20% excess) in a water–alcohol solution in a sealed tube at 60° for from a week to ten days. The salt was recrystallized from hexane containing 3–5% of alcohol; m. p., 234.5–236°.

n-Octadecylpyridonium iodide was prepared by heating *n*-octadecyl iodide with excess pyridine for from twelve to eighteen hours at 60° in a stoppered flask. The excess pyridine was evaporated and the salt was recrystallized from hexane containing a trace of alcohol; m. p., 101.5–103°.

Di-*n*-octadecyldimethylammonium iodide was prepared by Dr. E. C. Evers by heating *n*-octadecyl iodide with excess dimethylamine in water–alcohol solution. The product was recrystallized from hexane containing a trace of alcohol; m. p., 154°.

The corresponding nitrates were obtained from the iodides by metathesis with silver nitrate in an alcohol–water mixture containing 75% alcohol. As a rule, several hours of digestion at 60° were required to coagulate the colloidal silver iodide. Care was exercised to avoid peptization of the coagulated silver iodide on filtration. The solutions were evaporated to dryness and the salts redissolved and crystallized from suitable solvents.

Di-*n*-octadecyldimethylammonium nitrate is very soluble in pure hexane but crystallizes on cooling to Dry Ice temperatures; m. p., 79–81°.

(1) This paper is based on a portion of a thesis presented by Harold E. Weaver in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, May, 1940.

(2) University Fellow at Brown University, 1938–1939; Metcalf Fellow, Brown University, 1939–1940.

(3) E. L. McBain, Dye and Johnson, THIS JOURNAL, **61**, 3210 (1939).

(4) Ward, *J. Chem. Soc.*, I, 522 (1939); *Proc. Roy. Soc. (London)*, **176A**, 512 (1940); Ralston and Hoerr, THIS JOURNAL, **68**, 2460 (1946); Thompson and Kraus, *ibid.*, **69**, 1016 (1947).

(5) Mead, Fuoss and Kraus, *Trans. Faraday Soc.*, **32**, 594 (1936).

(6) Witschonke and Kraus, THIS JOURNAL, **69**, 2472 (1947).

(7) Levene, West and van der Scheer, *J. Biol. Chem.*, **20**, 525 (1915).

The other nitrates were recrystallized from hexane containing alcohol in amounts varying from a trace for the *n*-octadecylpyridonium and *n*-octadecyltri-*n*-butylammonium salts to two or three per cent. for *n*-octadecyltrimethylammonium nitrate. The solutions were cooled to 0° in a refrigerator. The melting points were: *n*-octadecyltrimethylammonium nitrate—softens at 170°—melts to a clear liquid at 190°; *n*-octadecyltri-*n*-butylammonium nitrate, 90–91°; *n*-octadecylpyridonium nitrate, 71–73°.

It may be noted that accurate observation of the melting point of long chain salts is often difficult because of gradual changes in the crystalline structure. In addition, pronounced shrinkage occurs between 90 and 100° and in some cases this extends as far as the actual melting point.

III. Results

Values of the equivalent conductance, Λ, and the concentration, *C*, in moles per liter of solution, are presented in Tables I and II. In Table I are given the results in ethylene chloride solution; the densities of the solutions have been taken as that of the pure solvent, 1.2455.[8] In Table II are given the results for nitrobenzene solutions; the densities of the solutions have been taken as 1.1986,[9] the value for pure nitrobenzene. All measurements were at 25 ± 0.01°. Although two series of measurements were made with each salt, with one exception, results from only one of these are reported here; the additional determinations, however, are shown on the plots.

TABLE I

CONDUCTANCE OF LONG CHAIN SALTS IN ETHYLENE CHLORIDE

n-Octadecyltri-*n*-butylammonium nitrate		*n*-Octadecyltrimethylammonium nitrate	
$C \times 10^5$	Λ	$C \times 10^5$	Λ
118.8	20.31	65.73	10.68
35.86	28.86	34.06	13.90
7.989	41.26	11.79	20.93
3.365	47.55	4.559	29.24
2.098	50.19	3.594	31.52
0.7825	54.38	2.050	37.34
0.5478	55.39	1.467	60.68

TABLE II

CONDUCTANCE OF LONG CHAIN SALTS IN NITROBENZENE

n-Octadecyltri-*n*-butylammonium nitrate		Di-*n*-octadecyldimethylammonium nitrate		*n*-Octadecylpyridonium nitrate	
$C \times 10^5$	Λ	$C \times 10^5$	Λ	$C \times 10^5$	Λ
116.7	28.10	107.8	26.78	156.4	27.78
29.93	29.74	32.56	28.50	61.28	29.63
8.761	30.53	12.40	29.40	23.61	30.82
5.366	30.73	82.13	27.31	10.47	31.57
3.196	30.87	27.84	28.72		
1.976	31.04	12.13	29.42		

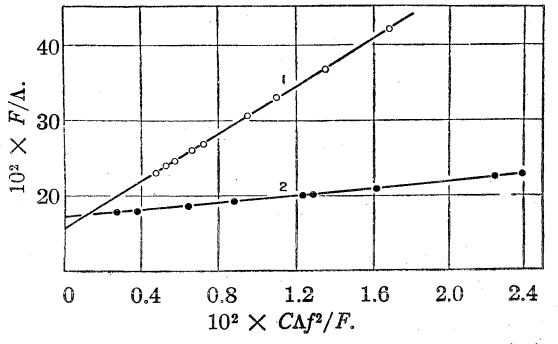


Fig. 1.—Fuoss plots for long chain salts in ethylene chloride: 1, *n*-octadecyltrimethylammonium nitrate; 2, *n*-octadecyltri-*n*-butylammonium nitrate.

(8) Walden and Busch, *Z. physik. Chem.*, **140A**, 89 (1929).

IV. Discussion

1. Ethylene Chloride.—The conductance data for ethylene chloride solutions have been analyzed by the method of Fuoss. The results are shown graphically in Fig. 1; values of Λ_0 and *K* for each salt are presented in Table III. Solutions of long chain salts begin to show deviations from the theoretical at concentrations of approximately 1.5×10^{-4} *N*.

TABLE III

CONSTANTS OF SOME LONG CHAIN ELECTROLYTES IN ETHYLENE CHLORIDE

Salt	Λ_0	Λ_0^+	$K \times 10^4$
$(n\text{-}C_{18}H_{37})(CH_3)_3NNO_3$	63.7	23.6	0.157
$(n\text{-}C_{18}H_{37})(n\text{-}C_4H_9)_3NNO_3$	58.2	18.1	1.27

The cation conductances shown in Table IV have been obtained using Tucker's value of 40.1 for the limiting conductance of the nitrate ion.[10]

Since the plots of F/Λ against $C\Lambda f^2/F$ are straight lines in the concentration range investigated, it appears that, at these concentrations, the behavior of solutions of long chain salts is normal. There is no evidence of micelle formation at concentrations up to several thousandths normal.

The interrelation between ion conductances and chain length remains qualitative until additional data are available. It may be pointed out here that the conductance of the octadecyltrimethylammonium ion with 21 carbon atoms is slightly higher than that of the tetra-*n*-amylammonium ion[10] with 20 carbon atoms.

The dissociation constants of the long chain salts exhibit no exceptional properties. When only one long hydrocarbon group is present in the

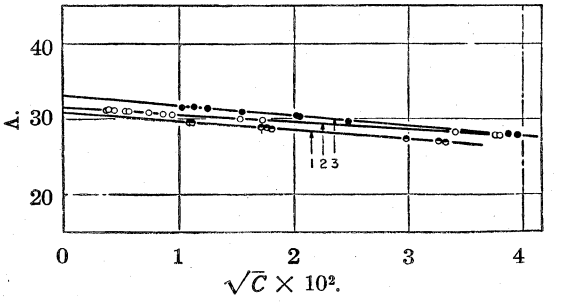


Fig. 2.—Square root plots for long chain salts in nitrobenzene: 1, *n*-octadecyltrimethylammonium nitrate; 2, *n*-octadecyltri-*n*-butylammonium nitrate; 3, *n*-octadecylpyridonium nitrate.

(9) Walden and Birr, *ibid.*, **163A**, 281 (1932).

(10) Tucker and Kraus, THIS JOURNAL, **69**, 457 (1947).

cation, the value of the dissociation constant is approximately that which might have been expected for an ion-pair in which the distance of closest approach is determined by the field around the three smaller alkyl groups.

2. Nitrobenzene.—In Table IV are given the limiting conductances of three quaternary ammonium nitrates containing long hydrocarbon chains in the cation. The cation conductances are given in column 3 and have been calculated on the assumption that the nitrate ion has a conductance of 22.6.[6]

TABLE IV

LIMITING CONDUCTANCES OF ELECTROLYTES IN NITROBENZENE

Salt	Λ_0	Λ_0^+
$(n\text{-}C_{18}H_{37})_2(CH_3)_2NNO_3$	30.7	8.1
$(n\text{-}C_{18}H_{37})(n\text{-}C_4H_9)_3NNO_3$	31.5	8.9
$(n\text{-}C_{18}H_{37})(C_5H_5N)NO_3$	32.9	10.3

The above Λ_0 values for the three salts have been obtained by extrapolation of the plots shown in Fig. 2, in which values of Λ_0 are plotted against values of $C^{1/2}$. These plots are linear over a considerable range of concentrations although the slopes of the lines are somewhat greater than the theoretical; this is doubtless due to ion-pair formation. Ion conductances decrease with increasing number of carbon atoms in the cation but rather less than one might otherwise expect.

V. Summary

1. The conductance of octadecyltrimethylammonium and octadecyltributylammonium nitrates in ethylene chloride and of octadecyltributylammonium, dioctadecyldimethylammonium and octadecylpyridonium nitrates in nitrobenzene have been measured.

2. These long chains salts are normal electrolytes over the concentration range studied in both ethylene chloride and nitrobenzene.

3. Limiting conductances and dissociation constants have been evaluated in ethylene chloride and limiting conductances in nitrobenzene.

4. Ion conductances have been evaluated in both solvents.

PROVIDENCE, R. I. RECEIVED DECEMBER 16, 1947

[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY OF BROWN UNIVERSITY]

Properties of Electrolytic Solutions. XXXIII. The Conductance of Some Salts in Acetone at 25°[1]

BY MYRON B. REYNOLDS[2] AND CHARLES A. KRAUS

I. Introduction

Acetone is a solvent that differs markedly in type from those previously investigated in this Laboratory; it has a dielectric constant of 20.5 and is a fair solvent for a number of uni-univalent inorganic salts. Solutions in this solvent have been investigated earlier by several different investigators[3] but with the exception of Lannung, who was chiefly concerned with solubilities, their results are uncertain because of the high conductance of the solvent which introduced large and often uncertain corrections with solutions of low concentration. In this connection, it may be pointed out that, since the only laws that are known to apply to electrolytic solutions are of limiting type, it is of particular importance that experimental errors be kept at a minimum at low concentrations. *If a solvent cannot be adequately purified, there is little point in carrying out conductance measurements.*

In the present investigation, the solvent has been purified to a point where correction for solvent conductance was negligible. The electrolytes investigated were, for the most part, salts of the tetrabutylammonium ion with various negative ions. The picrates of lithium, sodium and potassium were measured as were also potassium iodide and thiocyanate. It may be noted that numerous salts which have been measured by earlier investigators were found to be too difficultly soluble in the pure solvent to permit of ready measurement.[3b]

Owing to uncertainties in the value of the physical constants of acetone, these (dielectric constant, viscosity and density) were redetermined.

The results of conductance measurements have been treated by the method of Fuoss[4] and values of the limiting conductance, Λ_0, and the dissociation constant, K, have been derived. Ion conductances have been evaluated according to the method of Fowler.[5]

II. Experimental

Apparatus.—Conductance measurements were carried out as described in earlier papers of this series, using a Jones type a. c. bridge and Erlenmeyer conductance cells with bright platinum electrodes. All measurements were carried out at 25 ± 0.01°.

The dielectric constant of acetone was measured at 25°,

(1) This paper comprises a portion of a thesis presented by Myron B. Reynolds in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, June, 1947.

(2) Anthony Fellow at Brown University, 1946–1947; present address: Research Laboratory, General Electric Company, Schenectady, N. Y.

(3) (a) Walden, Ulich and Busch, *Z. physik. Chem.*, **123**, 429 (1926); (b) Lannung, *ibid.*, **161A**, 255 (1932); (c) Hughes and Hartley, *Phil. Mag.*, **15**, 610 (1933); and others.

(4) FUOSS, THIS JOURNAL, **57**, 488 (1935).

(5) Fowler and Kraus, *ibid.*, **62**, 2237 (1940).

using a parallel substitution type a. c. bridge[6] and a cell especially designed to minimize lead errors. Solvent conductance was also measured with this bridge.

Solvent viscosity was measured at 25°, using a modified Ostwald viscometer calibrated against water and benzene. Solvent density was determined by means of an Ostwald–Sprengel pycnometer.

Materials.—Commercial acetone[7] was dried by agitation over calcium chloride and then distilled twice from activated alumina pellets.[8]

In each distillation, the middle fraction only was saved and the final distillation was preceded by a few hours of refluxing. The conductance of acetone prepared in this way was in the range of 1 to 2 × 10^{-9} reciprocal ohm centimeters; corrections for solvent conductance were thus negligible.

Tetra-*n*-butylammonium triphenylborofluoride was prepared by Dr. G. L. Brown, of this Laboratory, and purified by successive recrystallizations from ether–ethanol mixtures. It was dried at room temperature *in vacuo;* m. p. 165–166°.

Tetra-*n*-butylammonium picrate from laboratory stock was recrystallized from ethanol, and dried *in vacuo* at slightly elevated temperature; m. p. 89°.

Tetra-*n*-butylammonium iodide from laboratory stock was purified by recrystallization from nitromethane and dried *in vacuo* at room temperature; m. p. 146°.

Tetra-*n*-butylammonium bromide was prepared by treating *n*-butyl bromide with tri-*n*-butylamine in ethanol solution at about 70°. The crude salt was recrystallized several times from ethyl acetate and twice from benzene–petroleum ether mixtures; a portion was recrystallized from an ether–ethyl acetate mixture. Both samples were dried to constant weight *in vacuo* at 50 to 60°; m. p. 118°.

Tetra-*n*-butylammonium nitrate was prepared by Dr. H. L. Pickering, of this Laboratory, purified by recrystallizations from benzene, and dried *in vacuo* at room temperature; m. p. 149°.

Tetra-*n*-butylammonium perchlorate was prepared in this Laboratory by Dr. L. E. Strong. Further purification was effected by recrystallization from ether–acetone mixtures, followed by drying *in vacuo* at room temperature; m. p. 213°.

Tetraethylammonium picrate, furnished by Dr. C. J. Carignan, of this Laboratory, was recrystallized from ethanol and dried to constant weight *in vacuo* at 65–80°.

Tetramethylammonium triphenylborofluoride from laboratory stock was recrystallized from acetone and from acetone–ethanol mixtures and dried *in vacuo* at room temperature; m. p. 186°.

Tetramethylammonium fluoride was prepared in this Laboratory by Dr. C. J. Carignan. The salt was purified by precipitation from ethanol solution by addition of ethyl acetate and also by recrystallization from ethanol–acetone mixtures. Samples were dried to constant weight at 50° *in vacuo;* m. p. 268–269°, with decomposition.

Lithium picrate, prepared in this Laboratory, by Dr. C. J. Carignan, was purified both by recrystallizations from ethanol–nitromethane mixtures and from acetone–nitromethane mixtures. The salt was dried *in vacuo* at 80°.

Sodium picrate was prepared by neutralizing an ethanol solution of picric acid with aqueous sodium hydroxide solution. The resulting salt was recrystallized several times from ethanol–water mixtures and dried to constant weight *in vacuo* at 70–80°.

Pure samples of potassium picrate were available from laboratory stock and were dried to constant weight *in vacuo* at 65°.

Reagent grade potassium iodide was recrystallized from water and also from water–ethanol mixtures. The recrystallized samples were dried *in vacuo* at 70°.

Reagent grade potassium thiocyanate was further purified by recrystallization from water and from acetone–water mixtures, and dried *in vacuo* at 50°.

(6) L. E. Strong, Thesis, Brown University, 1940.

(7) The acetone was kindly donated by the Tennessee Eastman Corporation.

(8) Harshaw AL-4 "Catalyst Pellets."

III. Results

Physical Constants.—The dielectric constant of acetone was determined with thirteen different

TABLE I

CONDUCTANCES OF VARIOUS SALTS IN ACETONE AT 25°

Tetra-*n*-butylammonium triphenylborofluoride		Tetra-*n*-butylammonium picrate	
$C \times 10^4$	Λ	$C \times 10^4$	Λ
0.4517	130.0	0.4237	147.9
0.8237	128.5	0.9049	146.0
1.584	126.0	1.717	143.3
3.213	122.4	3.588	139.2
7.003	116.8	7.129	133.7
15.47	109.1	17.02	124.4
Tetra-*n*-butylammonium perchlorate		**Tetra-*n*-butylammonium nitrate**	
0.3115	178.4	0.4074	181.6
0.7118	176.2	0.8190	178.8
1.479	172.5	1.291	176.2
3.142	167.3	2.879	169.6
6.860	159.3	8.414	155.4
20.16	144.0	25.27	134.3
Tetra-*n*-butylammonium bromide		**Tetra-*n*-butylammonium iodide**	
0.3287	177.8	0.3086	175.4
0.6875	174.8	0.4963	174.1
1.523	169.1	1.019	171.2
3.504	159.7	2.674	164.5
9.188	143.6	9.215	149.1
21.48	125.1	25.98	131.1
Tetraethylammonium picrate		**Tetramethylammonium triphenylborofluoride**	
0.4129	171.9	0.4044	160.2
0.7731	170.1	0.8572	157.6
1.535	167.2	1.606	154.2
3.188	162.8	3.371	148.6
7.044	156.0	7.145	140.3
19.19	144.7	18.30	126.3
Tetramethylammonium fluoride		**Lithium picrate**	
0.3422	172.2	0.3453	150.2
0.6672	166.1	0.7875	144.0
1.385	155.5	1.397	137.5
2.880	140.0	3.003	125.2
6.492	118.4	6.398	109.3
		20.92	79.79
Sodium picrate		**Potassium picrate**	
0.5370	154.0	0.2834	161.7
1.073	148.2	0.7824	157.6
2.348	138.0	1.981	150.9
4.878	124.9	3.183	145.9
10.57	107.9	9.448	129.7
21.99	90.35	23.14	111.8
Potassium iodide		**Potassium thiocyanate**	
0.4962	186.8	0.2722	196.8
1.086	183.6	0.8890	191.5
3.142	175.8	2.748	181.3
6.124	168.4	7.564	165.5
13.11	156.7	18.45	146.3
24.41	145.4		

samples the specific conductance of which varied between 0.51 and 1.7 × 10^{-9}. The average value found for the dielectric constant was 20.47, with a mean deviation of 0.05 and a maximum deviation of 0.2.

The viscosity was determined with sixteen different samples of acetone of which only two had a specific conductance above 2 × 10^{-9}; thirteen of these samples were identical with those used in the dielectric constant measurements. The average value of the viscosity in poise was found to be 3.040 × 10^{-3} with a mean deviation of 0.008 × 10^{-3}.

The density of acetone was determined to be 0.7845. All the above values were at 25°.

Conductances.—Equivalent conductances, Λ, and concentrations, C, expressed in moles of salt per liter of solution, are given in Table I. Two or more series of measurements were carried out with salt samples resulting from successive recrystallizations and the salts were assumed to be pure when conductances for successive recrystallizations for a given salt agreed within the limit of experimental error, 0.1%.

IV. Discussion

The data of Table I were analyzed by the method of Fuoss by plotting values of F/Λ against values of $c\Lambda f^2/F$. The plots are shown in Figs. 1, 2 and 3, on which appear values for two series of measurements for each salt. Inspection of the plots will show that Λ_0 may be determined with considerable precision, particularly in the case of the stronger salts. All plots are linear within the limit of experimental error up to about 7 × $10^{-4}N$.[8a] The slopes of the plots serve in the evaluation of the dissociation constant, K, of the ion pairs; the curves are the steeper, the lower the constant. Values of Λ_0 and K as determined

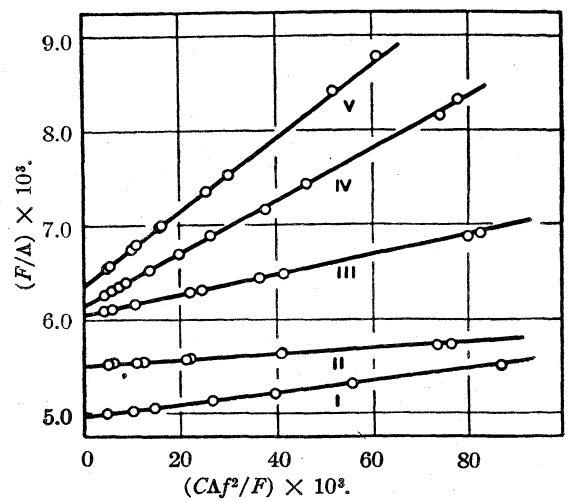


Fig. 1.—Fuoss plots for salts in acetone: I, KCNS; II, n-Bu_4NClO_4; III, KPi; IV, NaPi; V, LiPi.

(8a) The critical concentration for acetone is 2.8 × 10^{-3} [Fuoss, THIS JOURNAL, **57**, 2604 (1935)].

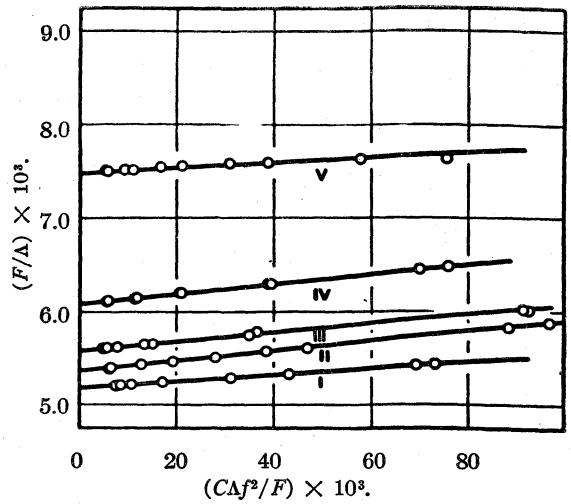


Fig. 2.—Fuoss plots for salts in acetone: I, KI; II, n-Bu_4NNO_3; III, n-Bu_4NI; IV, Me_4NFBPh_3; V, n-Bu_4NFBPh_3.

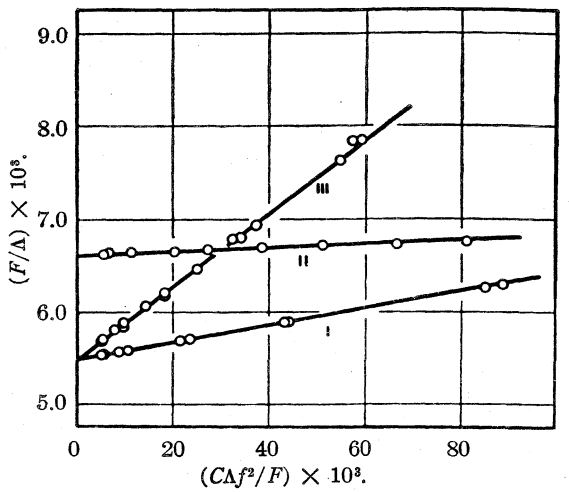


Fig. 3.—Fuoss plots for salts in acetone: I, n-Bu_4NBr; II, n-Bu_4NPi; III, Me_4NF.

by means of the plots are given in columns 2 and 3 of Table II.

TABLE II

CONSTANTS OF VARIOUS SALTS IN ACETONE AT 25°

Salt	Λ_0	$K \times 10^3$	Λ_0^+	Λ_0^-
$(n\text{-}C_4H_9)_4NFB(C_6H_5)_3$	134.2	19.7	67.1	67.1
$(n\text{-}C_4H_9)_4NPi$	152.4	22.3	..	85.3
$(n\text{-}C_4H_9)_4NClO_4$	182.4	9.58	..	115.3
$(n\text{-}C_4H_9)_4NNO_3$	187.2	5.46	..	120.1
$(n\text{-}C_4H_9)_4NBr$	183.0	3.29	..	115.9
$(n\text{-}C_4H_9)_4NI$	179.4	6.48	..	112.3
$(C_2H_5)_4NPi$	176.5	17.5	91.2	...
$(CH_3)_4NFB(C_6H_5)_3$	165.1	6.93	98.0	...
$(CH_3)_4NF$	183	0.77	..	85
LiPi	158.1	1.03	72.8	...
NaPi	163.7	1.35	78.4	...
KPi	165.9	3.43	80.6	...
KI	192.8	8.02	80.5	...
KCNS	201.6	3.83	..	121.0

Ion Conductances.—Ion conductances have been evaluated by the method of Fowler according to which the two ions of tetrabutylammonium triphenylborofluoride are assumed to have the same conductance. The value so found for the tetrabutylammonium ion is 67.1 and the ion conductances recorded in columns 4 and 5 of Table II are based on this value.

The conductance of negative ions is markedly higher than that of comparable positive ions. Thus the conductance of the perchlorate ion is 115.3 while that of the tetramethylammonium ion is only 98.0. The conductance of the alkali metal ions decreases markedly with decreasing atomic weight, the change from sodium to lithium being particularly marked. Considering the tetraethylammonium ion with nine atoms other than hydrogen and a conductance of 91.2, the low conductance of the lithium ion (72.8) indicates a high degree of interaction with the solvent dipoles. There may be actual solvation of the lithium ion, but we have no satisfactory means of distinguishing between solvation and simple interaction of the charge on the ion with the dipoles of the solvent molecules. The low conductance of the tetramethylammonium ion in comparison with that of the perchlorate ion cannot well be ascribed to solvation in the strict sense of the term.

The high conductance of the thiocyanate ion, as also that of the nitrate ion, is worthy of note. The bromide ion has a slightly higher conductance than the iodide ion, but the fluoride ion has a very low conductance. But, even here, we find the conductance of an exceptionally small negative ion markedly greater than that of the ion of the much larger potassium atom, 85 as against 80.6.

There is only one case among the salts in the table where ion conductances as derived from different pairs of ions may be compared. The conductance of the potassium ion as derived from its picrate is 80.6 while that derived from the iodide is 80.5. The difference lies within the limit of experimental error.

There is only scanty material in the literature that can be employed for purposes of comparison. Seemingly, the most reliable conductance measurements with solutions of salts in acetone are due to Ross Kane but, unfortunately, the details of his measurements are unavailable, and only rounded ion conductances at 25° have been reported.[9]

In the case of several salts (KI and Et_4NPi), our conductance values are in good agreement with those of Ross Kane. In other instances, the difference usually lies between 0.5 and 1.0%. If Ross Kane's limiting conductance values were obtained by extrapolation of the usual square root plot, discrepancies might well be accounted for by extrapolation errors.

Dissociation Constants.—In accord with the dielectric constant of acetone (D 20.47), solutions of salts in this solvent are fairly highly ionized, but all show marked ion pair association so that the evaluation of Λ_0 by extrapolation of the Λ–$\sqrt{C}$ plot is not permissible.

Since the energy necessary to separate a pair of ions is a function of the distance between centers of charge in the ion pairs, it follows that salts having large ions have relatively large dissociation constants while salts with small ions will have small constants. Since large ions have lower conductances than small ions, we should expect that salts having ions of lower conductance would have larger dissociation constants.

However, such a simple relation does not hold, chiefly, because of certain specific factors:

1. The effective size of an ion may be due either to a large structure, as in the case of the tetrabutylammonium ion, or, on the other hand, it may be the result of interaction of a small ion with the molecules (dipoles) of the solvent. In the latter case, the solvent molecules may, in some instances, be definitely attached to the ion; in others, the structure may be a very loose one; and, in still others, both types of interaction may be involved. The smallest ions, lithium and fluoride, have very low conductances but yield relatively small dissociation constants. Evidently, solvent molecules, which may be attached to the free ions, are largely lost in the ion pairs. The nitrate ion has a much higher conductance than the bromide ion, yet its tetrabutylammonium salt is much stronger than the corresponding bromide.

2. Steric effects have a marked influence on the dissociation constant. Thus, potassium iodide is much stronger than potassium picrate, yet the constant of tetrabutylammonium picrate is three times that of the iodide. Then again, the constant for tetrabutylammonium picrate is but little greater than that of the corresponding tetraethylammonium salt. This indicates that the picrate ion penetrates into the shell of butyl groups about the nitrogen atom to a depth that approximates the dimensions of the tetraethylammonium group.

As was shown in an earlier paper of this series,[10] a quantity "a," which may be interpreted as an approximation to the distance between charges in the ion pairs, may be computed from the dissociation constant. For the salts whose constants are given in Table II, the value of "a" varies from 2.42 Å. for tetramethylammonium fluoride to 9.48 Å. for tetrabutylammonium picrate. That interaction with solvent molecules is a factor in determining ion-pair dimensions in acetone, even in the case of lithium picrate, is shown clearly by the results with the same salt in nitrobenzene (D 34.5).[11] The "a" distance for this salt in the two solvents is, respectively, 2.55 and 0.62 Å. The dissociation constant of 1.03×10^{-3} for lithium picrate in acetone of dielectric constant 20.5 as against one of 6×10^{-8} in a solvent of dielectric

(9) Murray-Rust, Gatty, MacFarlane and Hartley, *Ann. Reports. Chem. Soc.*, **27**, 351 (1930).

(10) Fuoss and Kraus, THIS JOURNAL, **55**, 1019 (1933).

(11) Witschonke and Kraus, *ibid.*, **69**, 2472 (1947).

constant 34.5 can only be due to interaction between the ions (in the ion pairs) with the acetone molecules, on the one hand, and lack of such interaction with nitrobenzene molecules, on the other. A comparison of sodium and potassium picrates in acetone and nitrobenzene shows that these salts behave in a manner similar to that of lithium picrate. The Walden conductance viscosity product for the sodium and potassium ions in acetone is 0.238 and 0.242, respectively, while in nitrobenzene[11] it is 0.295 and 0.322. Thus, the free ions in this solvent are of very nearly the same size. The corresponding K values $\times 10^4$ are, respectively, 13.5 and 34.3 in acetone and 0.28 and 6.86 in nitrobenzene. The effective size of these ions in the ion pairs is much smaller in nitrobenzene than in acetone and is progressively more so as the (lattice) ion is smaller.

V. Summary

A simplified procedure for the purification of acetone has been developed, making use of activated alumina pellets.

The density, viscosity and dielectric constant of purified acetone at 25° have been determined.

Conductance data have been obtained for fourteen different salts in acetone solution at 25°.

Limiting conductances and dissociation constants have been calculated for these salts, using the extrapolation method of Fuoss.

Limiting ion conductances have been computed by the method of Fowler.

Anion conductances have been found to be, in general, greater than corresponding cation conductances, suggesting specific solvent interaction with cations.

The conductance of the fluoride ion has been found to be markedly lower than that of the other halide ions and abnormally low for an anion.

PROVIDENCE, R. I. RECEIVED JANUARY 14, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND THE DEPARTMENT OF AGRICULTURAL BACTERIOLOGY UNIVERSITY OF WISCONSIN]

The Effect of Various Gases on Nitrogen Fixation by *Azotobacter*[1]

BY DOROTHY M. MOLNAR, R. H. BURRIS AND P. W. WILSON

Molecular hydrogen was demonstrated by Wilson and his associates[2,3,4] to inhibit nitrogen fixation, specifically and competitively, in both free-living *Azotobacter* and the symbiotic system of red clover plus *Rhizobium*. It has been suggested[5] that the inhibition might be primarily a physical effect dependent on the relative adsorption of the two gases on the surface of the nitrogen-fixing enzyme. The observation that the enzyme-substrate dissociation constants of hydrogen and nitrogen in *Azotobacter* have essentially the same ratio as their van der Waals constants offers some support for this view.[6] Although this may be only fortuitous, an examination of the effect of gases with different physical properties, appears to be desirable.

Experimental

Methods.—Cultures of *Azotobacter vinelandii* were maintained by daily transfer to 50 ml. of Burk's medium[3] in 500-ml. Erlenmeyer "shake" flasks. Weekly tests for purity were made by microscopic examination (Gram stain) and by inoculation of beef extract–peptone broth.[5] For the microrespirometer studies, ten drops of a culture (seventeen to nineteen hours) was diluted with 40 ml. of sterile Burk's medium, and 2 ml. transferred to the respiration flask. The conventional techniques for supplying different gas mixtures in respiratory experiments were followed.[7] Manometer readings were taken at half-hour intervals over a period of five hours, at 30°. The gas mixtures were: p_{N_2}, 0.2 atm.; p_{O_2}, 0.2 atm.; helium, argon, neon, hydrogen, ethane, or nitrous oxide, 0.6 atm. At a partial pressure of nitrogen of 0.2 atm. the rate of fixation is about 95% of maximum (in the absence of a competitive inhibitor, such as H_2), and small variations in the pressure (± 0.02 atm.) cause little change. The partial pressure of oxygen likewise is near optimum; to insure that is was kept reasonably constant, the oxygen used in respiration was replaced periodically. The mixtures were made from ordinary cylinder gases (about 98–99% pure) with the exception of the nitrous oxide, which was the grade used for anaesthesia. Errors arising from variation in the composition were reduced by preparing separate mixtures for the replicate experiments.

In a few trials, the conclusions from the microrespiration data were checked by estimating the initial and final total nitrogen in representative flasks by a modification of the micromethod of Johnson.[8] One macro experiment was made: Ten ml. of an eighteen-hour culture was diluted with 300 ml. of sterile Burk's medium, and 25-ml. aliquots were pipetted into sterile 250 ml. Erlenmeyer flasks. Each flask contained a tube of potash to absorb respiratory carbon dioxide and was made gas-tight with a rubber stopper fitted with an inlet tube. After the desired gas mixture was supplied through the inlet tube, the flasks were incubated in a conventional shaking apparatus at 30° for fifteen hours, then total nitrogen determined on aliquots by the micromethod.

Results and Discussion

The van der Waals constant a for the gases tested varied from 0.00007 (helium) to 0.01074

(1) Supported in part by grants from the Rockefeller Foundation and from the Research Committee of the Graduate School from funds provided by the Wisconsin Alumni Research Foundation.

(2) Wilson, "The Biochemistry of Symbiotic Nitrogen Fixation," University of Wisconsin Press, Madison, Wisconsin, 1940.

(3) Wyss and Wilson, *Proc. Natl. Acad. Sci.* (*U. S.*), **27**, 162 (1941).

(4) Wyss, Lind, Wilson and Wilson, *Biochem. J.*, **35**, 845 (1941).

(5) Burk and Burris, *Ann. Rev. Biochem.*, **10**, 587 (1941).

(6) Wilson and Burris, *Bact. Rev.*, **11**, 41 (1947).

(7) Umbreit, Burris and Stauffer, "Manometric Techniques and Related Methods for the Study of Tissue Metabolism," Burgess Publishing Co., Minneapolis, Minn., 1945.

(8) Johnson, *J. Biol. Chem.*, **137**, 575 (1941).

(ethane); a wide range in physical properties such as solubility, adsorption on solids, boiling point, are known to be associated with this variation. If the physiological response of *Azotobacter* to hydrogen is to be ascribed to the physical characteristics of the gases in the mixture supplied as expressed in the van der Waals forces, one should expect some correlation of nitrogen fixation with the value of a of the diluent gas. The data in Tables I, II and III and in Fig. 1 demonstrate that there is no such correlation.

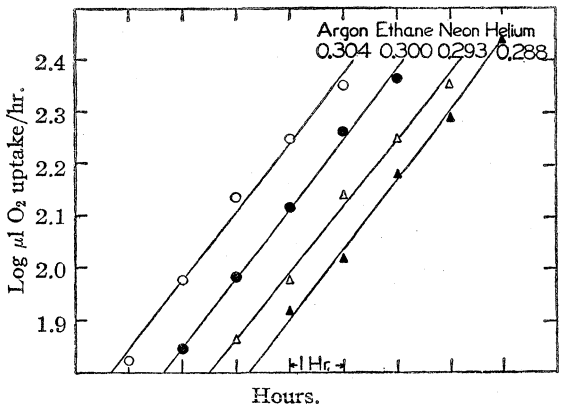


Fig. 1.—Effect of different gases on nitrogen fixation by *Azotobacter vinelandii*. Points are the means of duplicates for ethane, of triplicates for the others. Each division of the abscissa in Figs. 1 and 2 is one hour.

Table I summarizes results from two representative experiments. The initial and final rates of respiration are included to illustrate the effect of the gas tested on final total nitrogen as measured by rate of respiration. But, as has been emphasized in the previous papers,[3,4] a more suitable criterion of the effect is given by the first order velocity constant of growth, k. The values of k were estimated from the slopes of the lines obtained when the rate of respiration was plotted as a function of time. The standard deviation of k, S_k, was calculated by the usual statistical procedure; it measures the departure of the points from a straight line and is in effect an estimate of the precision of the data. The slope of each line, and hence k, was calculated by the method of least squares. The variation in the k values of the replicate samples measures the reproducibility of the results. Considering these variations, together with the observed values of S_k, it is concluded that for single determinations differences of 10–20% are necessary for significance, but if 2–3 replicates are combined, differences of 5–10% are probably significant. The precision obtained when replicate samples are combined is illustrated graphically by the lines in Fig. 1.

Table II summarizes the results of all the microrespiration experiments. For convenience, the van der Waals constant, a, is included, together with the boiling point of the gases, a physical property known to be correlated with a. In each experiment a helium control was included since it has been previously demonstrated that this gas does not affect fixation; this point was checked occasionally by including an air control. It is evident from the table that the physiological function of nitrogen fixation in *Azotobacter* shows no such response to changes in the van der Waals forces of the diluent gas as does a typical physical quantity (b. p.). Explanation of inhibition of nitrogen fixation in *Azotobacter* by a hypothesis based on purely physical competition between hydrogen and nitrogen, therefore, appears unlikely. The

TABLE I

EFFECT OF VARIOUS GASES ON NITROGEN FIXATION BY *Azotobacter* (MICRORESPIRATION DATA)

Gas[a]	Rate of respiration[b] Initial	Final	k[c]	S_k
		Experiment I		
Nitrous oxide	78	117	0.108	0.006
	74	136	.163	.004
	67	139	.196	.010
	80	140	.145	.004
Helium	82	245	.271	.015
	90	255	.262	.007
	83	263	.283	.012
Ethane	81	226	.246	.019
	85	260	.269	.023
	77	265	.301	.021
Air	90	258	.267	.011
	103	288	.267	.018
		Experiment II		
Helium	91	310	0.285	0.015
	86	318	.306	.008
	90	286	.274	.004
Ethane	79	270	.292	.003
	80	286	.308	.019
Neon	75	289	.311	.019
	80	269	.285	.015
	77	256	.271	.013
Argon	72	283	.306	.016
	73	275	.306	.019
	67	306	.301	.023

[a] Atmosphere: 20% N_2, 20% O_2, 60% indicated gas. [b] Microliters O_2/hr./flask, at 30°. [c] First order velocity constant of fixation; S_k, its standard deviation, measures closeness of fit of points to line.

TABLE II

SUMMARY OF THE MICRORESPIRATION EXPERIMENTS

Gas	van der Waals $a \times 10^5$	B. p., °C.	Expts.	Inhibition of N fixation[a]
Ethane	1074	88.3	3	−6.4 ± 4.5
Nitrous oxide	754	89.5	10	45.0 ± 3.9
Nitrogen	277	195.8	..	.....
Argon	268	185.7	3	−1.6 ± 3.1
Neon	42	245.9	3	1.8 ± 4.0
Hydrogen	49	252.8	5	35.2 ± 7.3
Helium	7	268.9	..	.....

[a] Based on helium control: negative results indicate stimulation.

physiological explanation,[9] based on enzyme mechanisms, thus receives indirect support.

An important by-product of these experiments was the demonstration that nitrous oxide is a specific inhibitor of nitrogen fixation by *Azotobacter vinelandii*. Because of the possible implication of this discovery for the mechanism of fixation, ten separate experiments were made to establish this finding. Inhibition was obtained in every trial, ranging from 21 to 63% with an average of 45 ± 3.9%. Confirmation of the data from the microrespiration experiments by determining the actual quantities of nitrogen fixed is furnished by the results given in Table III.

TABLE III

EFFECT OF VARIOUS GASES ON NITROGEN FIXATION BY *Azotobacter* (TOTAL NITROGEN DATA)

Experiment[a]	Diluent gas	Time, hr.	Final total N γ/ml.
III	He		28.88
(8.75)	N_2O	7	17.50
	H_2		20.38
IV	He		23.38
(8.33)	N_2O	7	15.69
	H_2		15.00
V	He	7	19.60
(5.60)	N_2O		10.00
VI	He	15	48.5
(5.20)			46.0
	A		42.6
			50.6
	N_2O		17.4
			15.4
			23.4
			14.8

[a] Figures in parentheses in this column represent initial nitrogen content in γ/ml. Experiment VI is a macro experiment; the others are samples taken from microrespiration experiments.

That the inhibition by nitrous oxide is specific for nitrogen fixation as distinguished from assimilation of combined nitrogen is shown by the results in Table IV and in Fig. 2. Assimilation of ammonium apparently is slightly stimulated by nitrous oxide in the atmosphere, but as this effect is not consistently obtained in all trials, its establishment would require much more additional evidence.

Previously, only hydrogen and carbon monoxide were known to influence the fixation reaction *specifically* in *Azotobacter*. Not only does the finding that nitrous oxide is likewise a specific inhibitor provide a new tool for investigation but it may also possess special significance for the mechanism. In a recent review Wilson and Burris[6] suggested that a possible intermediate in the fixation reaction might be a compound that is formally analogous to hyponitrous acid though not necessarily identical with it. The fact that nitrous oxide, the anhydride of hyponitrous acid, is not utilized by

(9) Lee and Wilson, *J. Biol. Chem.*, **151**, 377 (1943).

TABLE IV

COMPARISON OF EFFECT OF NITROUS OXIDE ON ASSIMILATION OF FREE AND COMBINED NITROGEN BY *Azotobacter* (MICRORESPIRATION DATA)

Expt.	Source of N	Gas added (0.6 atm.)[a] He	H_2	N_2O
VII	N_2	0.361	0.124	0.150
		.361	.143	.116
	NH_4^+	.319	.299	.325
		.323	.304	.323
VIII	N_2	.278	.194	.138
		.320	.199	.140
	NH_4^+	.327	.300	.375
		.317	.340	.394
IX	N_2	.290	.228	.182
		.297	.221	.143
	NH_4^+	.306	.350	.320
		.306	.331	.320

[a] Data are *k* values calculated from lines.

Azotobacter but does interfere with the assimilation of molecular nitrogen could be interpreted as supporting evidence for this view. Final decision as to its significance must await a more detailed study, particularly whether the inhibition is competitive or non-competitive.

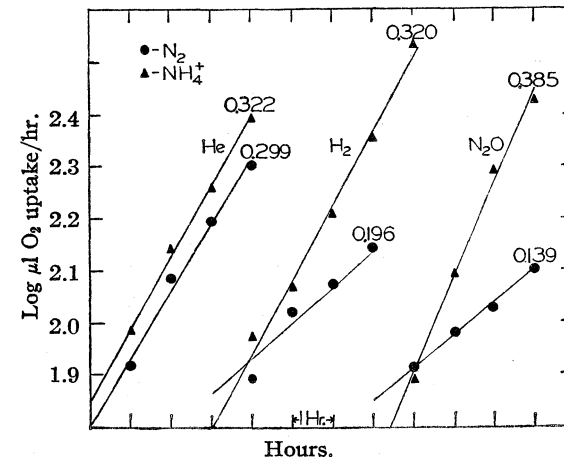


Fig. 2.—Specific inhibition of nitrogen fixation by *Azotobacter vinelandii*. Each point is the mean of duplicates.

Summary

The hypothesis that the inhibition by molecular hydrogen of nitrogen fixation in *Azotobacter* is explicable on the basis of the physical properties of the two gases was tested by comparing the effects of helium, argon, neon, hydrogen, nitrous oxide and ethane on the fixation reaction. The microrespiration technique was used for most of the experiments, but the results were verified by total nitrogen determinations.

The van der Waals constant, *a*, of the gases tested ranged from 0.00007 to 0.01074. Although the physical properties of the gases are correlated with the van der Waals forces, no such correlation

appeared in their effect on the physiological function of nitrogen fixation in *Azotobacter*. It is concluded, therefore, that an explanation based on the relative physical properties of hydrogen and nitrogen is unlikely.

Nitrous oxide was found to be a specific inhibitor for nitrogen fixation by *Azotobacter*. Its inhibition may have important implications for the mechanism of the reaction.

MADISON 6, WISCONSIN RECEIVED DECEMBER 9, 1947

[CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA]

Kinetics of the Reactions between Iodine and Certain Substituted Phenols

BY CHOH HAO LI

In previous studies[1] it was shown that the reaction of tyrosine with iodine follows a bimolecular rate law and that the most reactive iodinating agent is hypoiodous acid. It was also demonstrated[2] that the formation of diiodotyrosine is catalyzed by phosphate and other basic ions. The present investigation extends such studies with other para substituted phenols.

Reactions were carried out at 25° in acetate buffers of *p*H 5.23 and 5.65 containing different iodide ion concentrations. *p*-Chlorophenol and *p*-hydroxyphenylethylamine (tyramine), C. P. crystalline preparations, were employed without further purification; glycyl-tyrosine was kindly supplied by Dr. J. S. Fruton and the late Dr. Max Bergmann. The reaction rates were followed in the manner previously[1] described. The rate law was found to be identical with that for the formation of diiodotyrosine and may be expressed by the equation

$$-\mathrm{d(Phenol)}/\mathrm{d}t = k_2(\mathrm{phenol})(\mathrm{I_3^-}) \qquad (1)$$

where k_2 is the specific rate constant for the reaction Phenol + $2I_2 \rightarrow$ diiodophenol + $2H^+$ + $2I^-$

Table I summarizes the specific rate constants for the formation of diiodophenols[3]; the values for the reaction between iodine and tyrosine were estimated from previous studies.[1] The concentrations are in moles per liter, and time in minutes. It may be noted that the product of $k_2(I^-)^2$ in each buffer appears to be rather constant at the range of iodide concentration studied. In concentrations of iodide beyond the range studied, $k_2(I^-)^2$ was not found to be constant.

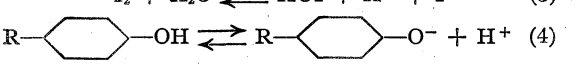
In the study of diiodotyrosine formation,[1] it was found that the reaction involves four paths: namely, iodine and phenol, iodine and phenolate, hypoiodous acid and phenol, and hypoiodous acid and phenolate. It was further noted that the most reactive pair is hypoiodous acid and phenolate, whereas the reaction between iodine and phenol is the least reactive. For first approximations, the reaction between iodine and phenol may be represented by equation (1a).

$$-\mathrm{d(phenol)}/\mathrm{d}t = k'(\mathrm{phenol})(\mathrm{HOI}) + k''(\mathrm{phenolate})(\mathrm{HOI}) \qquad (1a)$$

From the equilibria

$$I^-_3 \rightleftharpoons I_2 + I^- \qquad (2)$$

$$I_2 + H_2O \rightleftharpoons HOI + H^+ + I^- \qquad (3)$$



(4)

TABLE I

SPECIFIC REACTION RATE, k_2, OF IODINATING *p*-CHLOROPHENOL, GLYCYLTYROSINE, TYRAMINE AND TYROSINE[a] IN ACETATE BUFFERS OF *p*H 5.23 AND *p*H 5.65 CONTAINING DIFFERENT IODIDE CONCENTRATION AT 25°

k_2 in gram moles per liter per minute

(I^-) $m \times 10^2$	*p*-Chlorophenol		Tyramine		Glycyl-tyrosine		Tyrosine	
	*p*H 5.23	*p*H 5.65	*p*H 5.23	*p*H 5.65	*p*H 5.23	*p*H 5.65	*p*H 5.23	*p*H 5.65
3.34	0.135(0.128)[b]	0.40(0.34)	0.70(0.72)	2.03(2.29)	0.91(0.94)	3.15(3.21)	0.52(0.53)	1.82(1.94)
4.08	.081(.085)	.26(.26)	.45(.45)	1.63(1.49)	.63(.63)	2.16(2.14)	.38(.36)	1.20(1.30)
4.84	.060(.061)	.18(.18)	.35(.38)	1.09(1.07)	.45(.49)	1.55(1.55)	.28(.26)	0.90(0.93)
6.34	.033(.035)	.11(.11)	.20(.22)	0.63(0.62)			.16(.15)	0.53(0.54)

[a] Reaction rates for tyrosine are from a previous paper (see ref. 1). [b] The figures in parentheses are computed values from Equations 7, 8, 9 and 10.

Equation (1a) becomes

$$-\frac{\mathrm{d(phenol)}}{\mathrm{d}t} = \frac{K_2}{(I^-)^2(H^+)}\left[k'K_3 + \frac{k''K_3K_4}{(H^+)}\right](\mathrm{phenol})(\mathrm{I_3^-}) \qquad (5)$$

where K_2, K_3 and K_4 are the equilibrium constants of equations 2, 3, and 4, respectively. Thus, by comparing the equations (1) and (5), the observed specific rate constant, k_2, is a function of iodide and

(1) Li, THIS JOURNAL, **64**, 1147 (1942).

(2) Li, *ibid.*, **66**, 228 (1944).

(3) The preparation of N-glycyl-3,5-diiodotyrosine has been reported by Abderhalden and Guggenheim [*Ber.*, **41**, 1241 (1908)]. Diiodotyramine has also been prepared by Abderhalden and his coworkers [*Arch. ges. Physiol.*, **195**, 167 (1922)]. As far as we are aware there is no report concerning the preparation of *p*-chloro-3,5-diiodophenol. In the present experiments we have observed that *p*-chloro-3,5-diiodophenol is very insoluble in acetate buffers and it is gradually crystallized out in fine needles as the reaction proceeds. The colorless crystals have a melting point at 108.5°. *Anal.* Calcd. for $HOC_6H_2I_2Cl$: I, 66.74. Found: I, 66.82.

hydrogen ion concentration as shown by the expression

$$k_2 = \frac{K_2}{(I^-)^2(H^+)}\left[k'K_3 + \frac{k''K_3K_4}{(H^+)}\right] \quad (6)$$

It is obvious from equation (6) that when the hydrogen-ion concentration is maintained unchanged, the product of $k_2(I^-)^2$ becomes a constant. Since the equilibrium constants[4] of equations (2) and (3) and the dissociation constants of *p*-chlorophenol,[5] tyramine,[6] glycyltyrosine[7] and tyrosine[8] are known, the specific rate constants k' and k'' can be computed from the data in Table I. The results are summarized in Table II. Therefore, in a solution of known hydrogen-ion and iodide-ion concentrations, the observed specific rates for iodinating *p*-chlorophenol, tyrosine, tyramine and glycyltyrosine may be computed from the equations

TABLE II

THE COMPUTED VALUES OF k' AND k'' FOR *p*-CHLOROPHENOL, TYRAMINE, TYROSINE AND GLYCYLTYROSINE IN ACETATE BUFFER AT 25°

Phenols	Dissociation constant K (10^{11})	$k' \times (10^{-6})$	$k'' \times (10^{-10})$
p-Chlorophenol	66.0 (5)[a]	1.7	0.2
Tyrosine	8.5 (8)	8.1	1.1
Glycyltyrosine	4.0 (7)	12.0	40.0
Tyramine	1.26 (6)	10.0	58.0

[a] Numbers in parentheses refer to the reference in the text.

p-Chlorophenol:

$$k_2 = \frac{1}{(I^-)^2(H^+)}\left[7.2 \times 10^{-10} + \frac{5.5 \times 10^{-16}}{(H^+)}\right] \quad (7)$$

Tyrosine:

$$k_2 = \frac{1}{(I^-)^2(H^+)}\left[3.4 \times 10^{-9} + \frac{4.0 \times 10^{-16}}{(H^+)}\right] \quad (8)$$

Tyramine:

$$k_2 = \frac{1}{(I^-)^2(H^+)}\left[4.2 \times 10^{-9} + \frac{3.06 \times 10^{-15}}{(H^+)}\right] \quad (9)$$

Glycyltyrosine:

$$k_2 = \frac{1}{(I^-)^2(H^+)}\left[5.0 \times 10^{-9} + \frac{6.7 \times 10^{-15}}{(H^+)}\right] \quad (10)$$

The computed specific rates are listed in Table I; it may be noted that the agreements between the calculated and observed values are satisfactory.

From Table II, it is evident that, in each phenol studied, the value of k' is always much smaller than that of k''. This indicates that the phenolate ion is far more reactive than the undissociated phenol. It is also clear that the smaller is the dissociation constant of a phenol, the faster is the reaction rate. For instance, the dissociation constant of *p*-chlorophenol is fifty times higher than that of tyramine and yet the latter reacts with hypoiodous acid much faster than *p*-chlorophenol.

It is of interest to note that the specific rate for glycyltyrosine is greater than the value for tyrosine. It appears to indicate that the presence of a peptide linkage enhances the rate of iodination. This inference may also be arrived at by an experiment using carbobenzoxyglutamyltyrosine. In acetate buffer of *p*H 5.65 containing an iodide concentration of 3.34×10^{-2} *m* at 25°, the biomolecular specific rate, k_2, of iodinating carbobenzoxyglutamyltyrosine was found to be 4.24 gram-mols per liter per minute which is more than twice the specific rate for tyrosine. Whether the conclusion can be generalized for other peptides requires further investigation.

The absence of the carboxyl group in tyrosine causes an increase in iodination rate. Thus, k'' for tyramine is about 50 times larger than that for tyrosine. On the other hand, a replacement of $-CH_2CH_2NH_2$ group in tyramine by —Cl radical greatly diminishes the specific rates of iodination. No satisfactory explanation can be offered at present to correlate the structure of substituents on the iodination rate of phenols.

Summary

The rate of the reactions between iodine and *p*-chlorophenol, tyramine and glycyltyrosine have been determined at 25° in acetate buffers. In the range of iodide concentrations studied, the rate can be represented by: rate = k' (phenol)(HOI) + k'' (phenolate)(HOI). The specific rate of the reaction between phenolate and hypoiodous acid decreases in the order: tyramine > glycyltyrosine > tyrosine > *p*-chlorophenol.

BERKELEY, CALIFORNIA RECEIVED MAY 29, 1947

(4) (a) Bray and MacKay, THIS JOURNAL, **32**, 914 (1910); (b) Bray, *ibid.*, **32**, 932 (1910).

(5) Murray and Gordon, *ibid.*, **57**, 110 (1935).

(6) Ogston, *J. Chem. Soc.*, 1713 (1936).

(7) Greenstein, *J. Biol. Chem.*, **95**, 485 (1932).

(8) Hitchcock, *J. Gen. Physiol.*, **6**, 747 (1925).

[CONTRIBUTION OF THE CHEMICAL LABORATORIES OF THE BATTELLE MEMORIAL INSTITUTE AND THE OHIO STATE UNIVERSITY]

Preparation and Structure of the Carbides of Uranium[1]

BY LAWRENCE M. LITZ,[2] A. B. GARRETT AND FRANK C. CROXTON

This paper presents data on the preparation and crystal structure of the carbides of uranium, namely, UC and UC_2. On hydrolysis, the dicarbide, UC_2, is reported to yield a mixture of gaseous, liquid, and solid hydrocarbons, a fair percentage being in the high molecular weight range.[3] This unusual fact led to a program on the investigation of the hydrolysis of heavy metal carbides, of which work this research is a part.

Preparation.—In preparing uranium carbide, previous investigators had treated U_3O_8, the "green" oxide of uranium, with graphite in an electric arc furnace. The product obtained by this method was a crystalline carbide of questionable composition containing varying amounts of impurities. In 1896, Henri Moissan,[3] who first prepared this substance, assigned it the formula U_2C_3. Later, uranium carbide was prepared by others by this method, and they assigned the formula UC_2 to the resulting compound.[4]

Because it was desirable that the carbide to be used for the hydrolysis reactions should be of high purity and definite composition, other methods of preparation were investigated. The finely divided carbide needed for the studies is pyrophoric; hence a method of preparing it in the hydrolysis apparatus was devised. The reaction between uranium metal and methane was investigated as a probable method of making the carbide with the required properties. It is known that some metals react with hydrocarbons, such as methane, below the thermal decomposition temperature of the hydrocarbons, according to the equation

$$xM + yCH_4 = M_xC_y + 2yH_2$$

It was found that finely divided uranium metal would undergo such a reaction at temperatures as low as 625°. The product of this reaction was not the dicarbide, UC_2, as had been expected, but rather a monocarbide, UC, which had not been reported previously in the literature. It has been learned since that the monocarbide, UC, was prepared and studied earlier on the Manhattan Project.[5]

The identity of the monocarbide was determined from the following experimental facts: (1) The pressure change on reaction indicated that only one mole of methane reacted per mole of uranium. (2) A molecular weight of 250 was calculated from the weight of carbide produced per unit weight of uranium metal. (3) Chemical analysis indicated the absence of free carbon and confirmed the formula UC. (4) X-Ray diffraction studies showed that, to the limit of detection, metallic uranium and free graphite were absent. (5) A single phase having a face-centered cubic structure was indicated for the monocarbide; the dicarbide, UC_2, is tetragonal.

The apparatus in which the reaction between methane and uranium metal was carried out is illustrated in Fig. 1. It is designed so that the hydrolysis studies may also be carried out following the preparation of the carbide. The basic parts are the "Vycor" furnace tube, surrounded by an electrical resistance furnace; vacuum pumps capable of evacuating the system to a pressure of 10^{-5} mm. of mercury; a McLeod gage and mercury manometers for pressure measurement; a Toepler pump which is used to transfer gases from one part of the system to another; reservoirs for purified hydrogen and methane; and, a constant-volume buret. Advantage is taken of the ease of formation and decomposition of uranium hydride, as determined by F. H. Driggs,[6] to convert the uranium metal into a very finely divided form. A weighed quantity of metal is placed in a platinum boat in the furnace tube and the system is evacuated. Hydrogen is then admitted and allowed to react with the metal at 225°, where the equilibrium pressure of the hydride is about 3 mm. When all of the metal has been converted to hydride, the temperature is raised to 450°, where the equilibrium pressure is greater than 700 mm., and the hydride is caused to decompose by keeping the pressure in the system below this value. This cycle is repeated three times, after which the hydrogen is pumped off, the temperature increased to the desired reaction temperature, and a measured quantity of methane is added. The reaction is allowed to proceed until equilibrium is reached, after which the gaseous products are withdrawn for analysis and a second charge of methane is added. This process is continued until no further reaction is observed. When a fixed quantity of methane is added each time, the resulting equilibrium pressure of methane and hydrogen, at a fixed temperature, is dependent on the substances present in the solid phase. Thus, the equilibrium pressure over a mixture of uranium and uranium monocarbide is higher than that over a mixture of uranium monocarbide and uranium dicarbide. By plotting the equilibrium pressure against the per cent. of carbon in the solid phase, as determined by the amount of methane which has reacted, vertical breaks in the curve will be obtained

(1) (a) Presented before the Inorganic and Physical Chemistry Division of the American Chemical Society at the Chicago meeting, 1946; (b) this material is to be included as part of the thesis to be presented by Lawrence M. Litz to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the Ph.D. degree.

(2) Battelle Memorial Institute Fellow, 1945–1947. Present address: Barrett Division, Allied Chemical & Dye Corp., Philadelphia, Pa.

(3) H. Moissan, *Ann. chim. phys.*, [7] **9**, 302 (1896).

(4) P. Lebeau, *Compt. rend.*, **152**, 955 (1911); O. Ruff, *Z. anorg. Chem.*, **72**, 65 (1911).

(5) Pending publication of the Manhattan District's work in this field, the following statement is made at the suggestion of Dr. F. H. Spedding, Project Director of the Atomic Research Institute, Ames, Iowa: "The monocarbide, UC, was discovered on the Manhattan Project at the Iowa State College at Ames in 1942 through X-ray diffraction. The lattice and structure were determined by R. Rundle, and the chemical identity was established by V. H. Carter and A. D. Tevebaugh. The U-C phase diagram was carefully studied in the UC range by Carter, A. H. Daane, Rundle, and A. I. Snow. These studies will be published when released." This information was, however, unknown to the present authors until after the completion of the studies reported in this paper.

(6) U. S. Patent 1,816,830 (1929).

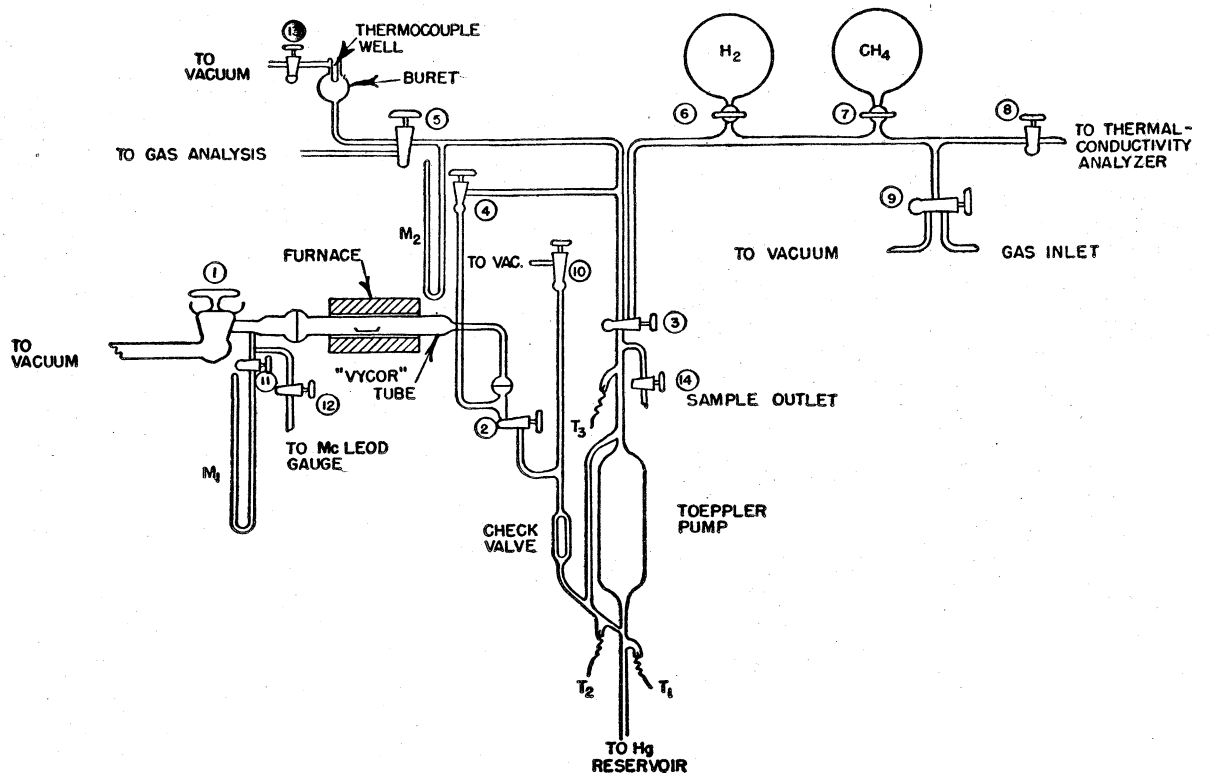


Fig. 1.—Vacuum apparatus for the investigation of the uranium metal–methane reaction.

which will indicate phase changes. In the case of uranium, no lower carbides than the monocarbide were observed, and the rate of reaction between the methane and the monocarbide at temperatures up to 900° was too slow to allow investigation of higher carbide phases.

Other methods of preparing both these carbides were investigated. The following equations indicate the reactions which were successfully used

(1)	$U + C = UC$	(2100°)
(2)	$U + 2C = UC_2$	(2400°)
(3)	$U_3O_8 + 11C = 3UC + 8CO$	(1800°)
(4)	$U_3O_8 + 14C = 3UC_2 + 8CO$	(2400°)

By treating uranium metal with graphite at 2100°, well-defined metallic crystals of the monocarbide were produced. By increasing the reaction temperature to approximately 2400°, the dicarbide was obtained. The preparation of the monocarbide by reaction of the U_3O_8 with graphite is accomplished easily by heating a powdered mixture of the two, of stoichiometric proportions, as indicated by equation (3), to 1800°, a sintered, coke-like mass being produced by this means. Higher temperatures are again required to prepare pure UC_2, for if the mixture, made up according to the indicated equation, is heated to temperatures below 2400°, the proportion of UC_2 in the product decreases as lower temperatures are used. At 2400°, the dicarbide is formed as large crystalline masses by this latter process. Both the monocarbide and the dicarbide form crystals which are hard and brittle and metallic in appearance. In neither case were these large enough for single crystal X-ray studies.

Because the preparation of the dicarbide, UC_2, made necessary the use of very high temperatures, the furnace assembly (Fig. 2) was employed. H is a 30-turn, water-cooled, copper induction coil which was activated by a 60KVA Ajax high-frequency converter. The graphite crucible A was heated inductively and it, in turn, heated the graphite crucible B, which carried the reactants, by radiation. Temperatures were measured through the hole in the lid by means of a Leeds and Northrup optical pyrometer. Heat loss was prevented by the lampblack insulation J, and excessive burning at the top was inhibited by the sillimanite cover D. Because of the arrangement at the top of the crucible A, influx of air into the reacting system was at a minimum, and there was no noticeable oxidation of the crucibles B and C, or of the product.

X-Ray Measurements.—The X-ray diffraction patterns were recorded both photographically and by a motor-driven spectrometer synchronized with a Brown recording potentiometer. The crystal lattice constants were determined with a Debye–Scherrer cylindrical camera of 37.8-mm. radius using Cu-Kα radiation. A suspension of the fine powder in Canada balsam was painted on a hair which was then mounted on the geometric axis of the camera in a fixture which rotated it during the exposure. Quantitative intensity measurements were made on an X-ray spectrometer using a Geiger tube as the detector. This can be connected either to a standard scaling circuit or to an integrating circuit connected to the potentiometer.

For accurate work, the motor drive and potentiometer were cut out of the system and the quantity of radiation per unit-time interval was counted at manually set positions of the detector. To obtain the intensity, the number of counts was plotted as a function of angle and the area under the curve determined, the intensity being proportional to the area. To insure total reflection of the incident beam, the sample employed was made of a thick block of the finely ground carbide, sieved to pass 325-mesh screen. Considerable difficulty was encountered with these compacts because of what appeared to be orientation of the particles. In the case of the monocarbide, this was evidenced by a very large increase in intensity of the (200) line relative to the (111) line, the former being approximately twice as strong as the latter in the most extreme case encountered. As is seen in Table I, the calculated values are in the reverse order. By suspending the sample in paraffin wax or by using a carbide

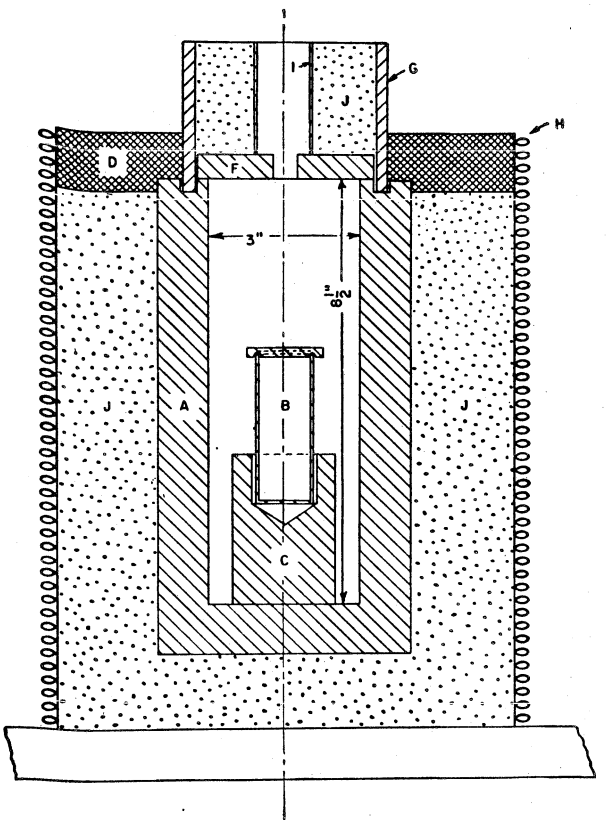


Fig. 2.—High-temperature induction furnace for preparation of uranium carbides.

TABLE I

COMPARISON OF OBSERVED SPACINGS AND INTENSITIES WITH CALCULATED VALUES FOR TWO POSSIBLE URANIUM MONOCARBIDE STRUCTURES

Spacings calculated using $a_0 = 4.955$ Å. Intensities calculated relative to the (111) line for the sodium chloride and zinc blende types of structures. Observed intensities obtained spectrometrically and photographically. Visual estimates of line intensities on photographic film: VS = very strong, S = strong, MS = moderately strong, M = medium, W = weak, and VW = very weak.

hkl	*d*, calcd.	*d*, obsd.	*I*/*I* (111) calcd. NaCl	*I*/*I* (111) calcd. ZnS	*I* estd. photog.	*I*/*I* (111) obsd. spect.
111	2.861	2.868	1.000	1.000	VS	1.00
200	2.477	2.477	0.600	0.470	S	0.62
220	1.752	1.752	.430	.394	MS	.44
311	1.494	1.496	.444	.435	S	.44
222	1.430	1.433	.148	.118	W	.16
400	1.239	1.240	.058	.054	VW	.05
331	1.137	1.138	.175	.169	M	.19
420	1.108	1.110	.179	.150	M+	.19
422	1.011	1.012	.157	.144	M	——
333	0.954	0.954	.048	.046	M	——
511	.954		.143	.140		
440	.876	.877	.100	.092	W	——
531	.838	.837	.409	.402	S	——
600	.826	.826	.061	.049	MS	——
442	.826		.245	.196		
620	.783	.783	.485	.444	S	——

of very small crystal size, as is prepared by reaction of very finely divided uranium metal with methane, this effect may be eliminated.

Because of the arrangement of the X-ray tube in the spectrometer, only those lines obtained by diffraction through a Bragg angle less than 45° can be measured. Therefore, for those lines appearing in the back-reflection direction, only estimated intensity values, obtained from the Debye–Scherrer films, could be determined. Also, in the case of the dicarbide, many of the lines were too close together for adequate resolution, and only four of the relatively important lines were measured and these are listed in Table II. Relative intensities were determined in all cases.

TABLE II

COMPARISON OF OBSERVED SPACINGS AND INTENSITIES WITH CALCULATED VALUES FOR TWO POSSIBLE URANIUM DICARBIDE STRUCTURES

Calculated spacings for $a_0 = 3.54$ Å., $c_0 = 5.99$ Å. Intensities calculated relative to the (101) line for the calcium carbide structure with $z = 3/8$, and for the elongated calcium fluoride type of structure. Observed intensities obtained spectrometrically and photographically. Visual estimates of line intensities on photographic film: VS = very strong, S = strong, M = medium, W = weak, VW = very weak, VVW = very, very weak.

hkl	*d*, calcd.	*d*, obsd.	*I*/*I* (101) calcd. CaC_2	*I*/*I* (101) calcd. CaF_2 elong.	*I* estd. photog.	*I*/*I* (112) × 0.31 obsd. spect.
101	3.046	3.040	1.000	1.000	VS	——
002	2.981	2.982	0.262	0.199	M	——
110	2.503	2.496	.397	.262	S	0.40
112	1.920	1.919	.310	.310	S	.31
200	1.770	1.771	.140	.123	M	.17
103	1.737	1.739	.254	.203	S	.24
211	1.531	1.527	.268	.258	S	——
202	1.523		.147	.113		
004	1.496	1.497	.029	.033	VW	——
114	1.284	1.285	.072	.063	W	——
220	1.251	1.253	.039	.034	VW	——
213	1.240	1.241	.137	.113	M	——
301	1.158	1.156	.050	.049	W	——
222	1.154		.055	.044		
204	1.142	1.145	.046	.053	W	——
105	1.133	1.134	.057	.045	W	——
310	1.119	1.118	.053	.035	W	——
312	1.048	1.047	.088	.087	M	——
303	1.015	1.016	.047	.037	VW	——
006	0.997	1.001	.011	.008	VVW	——
321	.969	0.969	.085	.082	M	——
224	.960	.960	.040	.047	VW	——
215	.955	.956	.100	.082	M	——
116	.926	.928	.046	.046	W	——
314	.896	.896	.081	.071	W	——
400	.885	.881	.030	.026	M	——
323	.881		.116	.093		
206	.869	.871	.054	.042	W	——
411	.850	.849	.107	.103	M	——
402	.849		.059	.047		
305	.840	.841	.068	.055	M	——
330	.834	.832	.039	.026	M	——
107	.831		.061	.059		
332	.804	.803	.082	.082	W	——
420	.792	.791	.106	.106	M	——
413	.788	.788	.246	.196	S	——

Crystal Structure of Uranium Monocarbide.—The diffraction pattern obtained by the Debye–Scherrer method indicated that uranium monocarbide is face-centered cubic with $a_0 = 4.955$ Å. The observed spacings and intensities are given in Table I. In deciding on the positions of the carbon atoms, one is faced with two possibilities. If the carbon atoms occupy the octahedral interstices in the lattice formed by the uranium atoms, the sodium chloride structure is obtained, as in Fig. 3a; whereas, if the alternate tetrahedral holes are

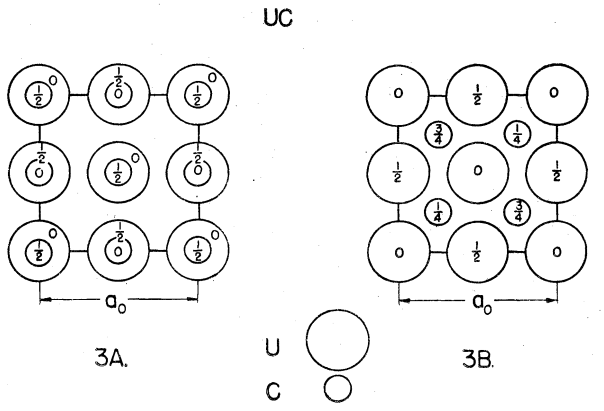


Fig. 3.—A, Sodium chloride structure; B, zinc sulfide structure.

filled, the zinc blende structure, Fig. 3b, is obtained. The space groups and the equivalent points for the two structures are

Sodium chloride structure $O_h^5 - Fm3m$
(0,0,0; 0,1/2,1/2; 1/2,0,1/2; 1/2,1/2,0) +
U 4(*a*) 0,0,0
C 4(*b*) 1/2,1/2,1/2

Zinc blende structure $T_d^2 - F\bar{4}3m$
(0,0,0; 0,1/2,1/2; 1/2,0,1/2; 1/2,1/2,0) +
U 4(*a*) 0,0,0
C 4(*c*) 1/4,1/4,1/4

The calculated values of Table I are the intensities relative to the (111) line for each of the structures. The relation

$$I \propto pF^2 \frac{1 + \cos^2 2\theta}{\sin^2 \theta \cos \theta}$$

was used to obtain the calculated intensities. p is a multiplicity factor, F, the crystal structure factor, and the trigonometric function of the Bragg angle, θ, contains the Lorentz and polarization factor and a geometric factor entering because of the experimental method. The intensity of the diffracted radiation from both the thin sample on the hair and the thick block of powdered material is given by this formula. Because the necessary data were not available, the structure factor was not corrected for temperature effect. Only the constant of proportionality is different for the two methods, and this is not of interest in the calculation of relative intensities. All of the required quantities were obtained from the "Internationale Tabellen."[7]

By comparing the measured intensities, as obtained on the X-ray spectrometer, with those calculated for the two possible structures, it was found that satisfactory agreement is obtained with the sodium chloride structure. The relative magnitude of the first two lines is particularly significant. The Debye–Scherrer films also support the sodium chloride structure in that it is observed that the (420) line is of slightly greater intensity than the (331) line. The calculations indicate the reverse to be true for the zinc blende structure. The proximity of these two lines on the photographic film permits rather accurate estimates of their relative intensity—a fact suggested to the authors by R. Rundle, who determined the structure of this compound for the Manhattan District project.

Crystal Structure of Uranium Dicarbide.—The dicarbide is reported in the literature to have a tetragonal structure with $c/a = 1.7$ for the body-centered tetragonal cell,[8] in agreement with the observations of the authors. However, the lattice constants are not given and in order to obtain them it was necessary to index the lines. This was accomplished with the aid of a Davey chart for body-centered tetragonal lattices. The values obtained were $a_0 = 3.54$ Å., $c_0 = 5.99$ Å. The observed spacings and those calculated from these values of the lattice constants are given in Table II. It has been noticed that when the dicarbide contains some monocarbide, as the result of incomplete conversion, a noticeable decrease in the lattice spacing occurs, particularly in the direction of a_0.

The problem of determining the positions of the carbon atoms in uranium dicarbide is somewhat more complicated than in the monocarbide. The

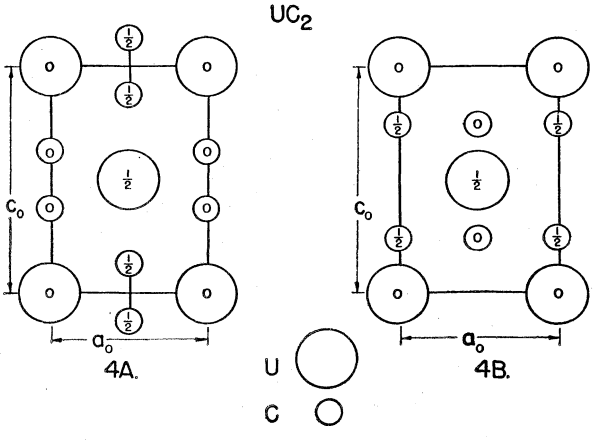


Fig. 4.—A, Calcium carbide structure; B, elongated fluorite structure.

(7) "Internationale Tabellen zur Bestimmung von Kristallstrukturen," 2 Band, 1935.

(8) *Strukturber.*, **2**, 276 (1928–1932); G. Hagg, *Z. physik. Chem.*, **B 12**, 42 (1931).

two structures which might be obtained by adding another carbon atom to the structures considered for the monocarbide are indicated in Fig. 4. By placing two carbon atoms in each of the octahedral interstices in the uranium lattice in a manner so that the carbon–carbon axis are parallel to one edge of the unit cell, one obtains the calcium carbide structure indicated in Fig. 4a. This was the structure assigned to uranium dicarbide by Hagg, presumably because the axial ratio is the same as that of calcium carbide. In the other structure, derived from the zinc blende structure, each carbon atom is at the center of a deformed tetrahedron, as in Fig. 4b. This is similar to the fluorite structure with tetragonal deformation. The space groups and equivalent points for these two structures are given below

Calcium carbide structure
D_{4h}^{17} (0,0,0; $\frac{1}{2},\frac{1}{2},\frac{1}{2}$) +
U 2(*a*) 0,0,0
C 4(*e*) 0,0,*z*; 0,0$\bar{z}$

Elongated fluorite structure
D_{4h}^{17} (0,0,0; $\frac{1}{2},\frac{1}{2},\frac{1}{2}$) +
U 2(*a*) 0,0,0
C 4(*d*) $\frac{1}{2}$,0,$\frac{1}{4}$; 0,$\frac{1}{2}$,$\frac{1}{4}$

Intensity calculations made for several values of the carbon-to-carbon distance of the two adjacent carbon atoms in the calcium carbide structure showed variations too small in magnitude to aid in deciding the correct distance. The values in the fifth column of Table II are for $z = 3/8$, which corresponds to a carbon-to-carbon distance of 1.50 Å., slightly less than the single bond distance.

The observed intensities are seen to be in best agreement with the calcium carbide structure. Points of significance are the relative intensities of the (110) and (112) lines and the (204) and (105) lines, where the calculated intensity gradient is in the opposite sense for the two structures. In both cases, the observed values are in the direction predicted by the calcium carbide structure. Because of the low resolving power of the spectrometer, adjacent lines overlap in several instances and, for this reason, only the (110), (112), (200), and (103) lines were measured spectrometrically. The general trend of values obtained from the spectrometer is in agreement with the estimated order of intensities obtained from the photographic method.

Discussion.—Before the completion of the experimental work on the determination of the positions of the carbon atoms, the problem had been approached using the concept of atomic radii. Calculations applying this method had indicated that the structures arrived at later experimentally were the less likely. In the case of both the monocarbide and the dicarbide, the uranium radii required to provide atom-to-atom contact in Structures 3A and 4A were decidedly greater than those existing in the metal and, since the radii of a metal usually decrease on compound formation, these structures had appeared unlikely. With the zinc blende and elongated fluorite structures, Figs. 3B and 4B, the required uranium radii agreed very well with metallic radii for uranium. The evidence obtained from the X-ray diffraction studies appears rather strong in the other direction, and it would seem that these materials represent an anomaly in the theory of atomic radii. The pronounced orientation effect observed with the monocarbide also supports the conclusion that its structure is that of sodium chloride, as the strengthening of the (200) line indicates cleavage along the cube faces. Since cleavage usually occurs along planes of highest density of atoms, and this is the (100) plane in the sodium chloride and the (111) plane in the zincblende structure, the former is preferred.

Information gathered in the study of the hydrolysis of these carbides may help to clarify this apparent anomaly.

Summary

Uranium dicarbide, UC_2, and the previously unreported monocarbide, UC, have been prepared by several methods. The crystal lattice constants have been determined for the two structures, and X-ray diffraction evidence is presented which indicates that the monocarbide has the sodium chloride type of structure, and the dicarbide has the calcium carbide type of structure.

The lattice constants observed are: UC, a_0 = 4.995 Å.; UC_2, a_0 = 3.54 Å.; c_0 = 5.99 Å.

COLUMBUS, OHIO RECEIVED JUNE 23, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANITOBA]

Liquid and Vapor Curves in the System Ethyl Alcohol–Benzene–Carbon Tetrachloride at Constant Pressure

BY A. N. CAMPBELL AND W. J. DULMAGE

While the constituent binary systems of the system alcohol–benzene–carbon tetrachloride have been investigated repeatedly, only an imperfect study of the ternary system exists. This is that of Schreinemakers,[1] who determined by a dynamic method the boiling temperatures under different pressures of ternary mixtures of these substances. From the pressure–temperature curves thus obtained, he deduced the pressure–concentration relations and, more important to the present work, the temperature–concentration relations. The latter data when plotted on a plane triangle give the projection of the boiling point surface for different constant pressures, and this diagram, given by Schreinemakers, is similar to Fig. 3 of this paper. Despite the rather crude method used by Schreinemakers, his results are in qualitative, and rough quantitative, agreement with ours.[2]

Although Schreinemakers' treatment of the vapor pressure relations is adequate, liquid–vapor composition data are necessarily lacking, since his experimental method was incapable of giving such information. Hence, the vapor surface corresponding to Schreinemakers' liquid surface was unknown. It was the aim of the present study to complete Schreinemakers' work, by an investigation of the liquid–vapor equilibria under isobaric conditions. The pressure chosen was that of the standard atmosphere (760.0 mm. at 0°) and the boiling points of all mixtures were determined, although, for reasons detailed later, we claim no greater absolute accuracy than $\pm 0.05°$ for the temperature measurements.

For the sake of completeness, the binary systems were also investigated, although two of these systems, *viz.*, alcohol–benzene and alcohol–carbon tetrachloride, have been investigated previously in an exhaustive manner: as is well known, these systems show azeotropic minima on their boiling point curves. Considerable doubt has existed hitherto regarding the system benzene–carbon tetrachloride. Because of the closeness of the boiling points of the constituents and the close similarity in composition between liquid and equilibrium vapor, and other criteria, it has been suggested that this system may exhibit an azeotropic mixture of minimum boiling point very close to the carbon tetrachloride end of the curve. Indeed, Young[3] states that "it is certain that benzene and carbon tetrachloride form such a mixture" (of minimum boiling point); and again (ref. 3, p. 92.) "these two liquids can form such a mixture, though the difference between the maximum pressure and the vapor pressure of carbon tetrachloride is probably too small to be determined by direct experiment." Hildebrand,[4] however, states, without authority, that carbon tetrachloride does not form a minimum boiling point mixture with benzene. Lecat,[5] whose work is considered definitive up to the year of its publication, leaves the question open. We show in this paper that, despite an apparent minimum of about 0.05°, which the inaccuracy of our temperature measurements deprives of significance, the vapor phase is never richer in benzene than the liquid phase, over a range from 1 to 99% benzene; that is, there is no reversal of composition, as there would be in passing through an azeotropic point.

Experimental

The apparatus used for the establishment of equilibrium was that of Scatchard.[6] The advantages of Scatchard's equilibrium still are that traditional difficulties such as superheating of liquid, reflux condensation and entrainment of vapor, and lack of equilibrium are eliminated by the use of a Cottrell-type pump, a double boiler, and a hold up trap. This still simplifies the removal of liquid and condensed vapor samples from the inner boiler and the condensate trap, respectively. The barostat, shown in Fig. 1, was modelled on that of Matthews and Faville,[7] but modified by the introduction of two controlled stages, as shown in Fig. 1. In the first stage, which was controlled simply by an ordinary magnetic relay, the pressure was kept by the pump at about 20 mm. above that in the second stage, which was controlled by the device of Leroy,[8] using an electronic relay which operated when the circuit broke. The mercury column in stage 2 was thermostatically controlled and of such a length as to correspond to 760.0 mm. of mercury at 0°. The final adjustment was made by boiling pure water in Scatchard's apparatus under barostatic control, and altering the pressure in stage 2 by small additions and removals of mercury until the water boiled at 100.00°.

To obviate the possibility of a flutter in the mercury surface we introduced the second slow leak L_1, the effective orifice of which was such as to give approximate balance between the two leaks, L_1 and L_2. Under these conditions no tremor of the mercury could be detected in the field of vision of a telescope and the boiling point of pure benzene remained absolutely constant as measured by a Beckmann thermometer.

Temperature Measurement.—As we possessed neither a multiple junction thermocouple nor a resistance thermometer, we were obliged to measure temperature with a

(1) F. A. H. Schreinemakers, *Z. physik. Chem.*, **47**, 445 (1903); **48**, 257 (1904).

(2) *Cf.* Table 7 of Schreinemakers' paper,[1] **48**, 275, where the data are given (in weight per cent.) for plotting the isotherms at p = 760 mm.

(3) Young, "Distillation Principles and Processes," 1st ed., MacMillan and Co., London, 1922, p. 47.

(4) Hildebrand, "Solubility," 2nd ed., Reinhold Publishing Corporation, New York, N. Y., 1936, p. 129.

(5) "La Tension de Vapeur des Mélanges de Liquides: l'Azeotropisme," Lamertin, Brussels, 1918.

(6) G. Scatchard, C. L. Raymond and H. H. Gilman, THIS JOURNAL, **60**, 1275 (1938).

(7) J. H. Matthews and K. E. Faville, *J. Phys. Chem.*, **22**, 3 (1918).

(8) D. J. Leroy, *Ind. Eng. Chem.*, **17**, 652 (1945).

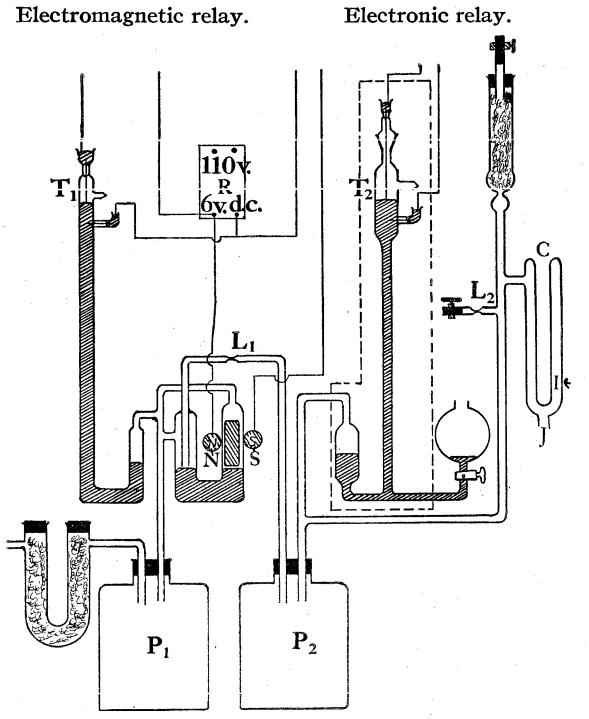


Fig. 1.—Barostat apparatus: T_1, T_2, mercury and tungsten contacts; P_1, P_2, carboys acting as buffers; NS, electromagnet; L_1, leak from crude to sensitive barostat; L_2, leak to atmosphere; I, condenser of Scatchard apparatus.

mercury-in-glass thermometer, graduated to 0.1° Such is the uncertainty of the exposed stem correction, that we do not feel justified in claiming a higher absolute accuracy than ±0.05°, although the agreement between consecutive determinations on the same day is no doubt better than this. About two hours of boiling were allowed for the attainment of equilibrium in each determination. After the reading of temperature, samples were removed from "liquid" and "vapor" chambers for analysis. There is a small, and probably inevitable, error introduced when using Scatchard's apparatus at pressures above that of the laboratory. Since sampling must be done immediately boiling is discontinued, on opening the apparatus there is a tendency for boiling to recommence when the pressure falls. This may produce a small amount of distillation, and the resulting disturbance of equilibrium can be detected.

Method of Analysis.—The method of analysis, which is very accurate, has been described elsewhere.[9] The method consists in the determination of refractive indices and densities, and yields an analytical accuracy of 0.3% of the total of each component, using pure materials. Our liquid and vapor curves are therefore correct to this limit. In the binary systems, density determinations only were made, and here the accuracy is still higher. Unfortunately, the flatness of the boiling point curves and the uncertainty of our temperature measurements renders a precise comparison of our data with existing data impossible, but there is no doubt the agreement is very good for the two well established systems, alcohol–benzene and alcohol–carbon tetrachloride.

Purity of Materials.—All materials were purified by the methods used by Campbell and Miller[9] when they calibrated the analytical curves.

(9) A. N. Campbell and S. I. Miller, *Can. J. Research*, **B25**, 228–242 (1947).

Distillation Curves.—After determining the liquid–vapor relations in the ternary system (Fig. 3) and knowing the boiling temperature of each point plotted, it is an easy matter to draw a diagram descriptive, in a qualitative manner, of the course of distillation, that is, the direction in which the residue will change its composition with rising temperature. This has been done in Fig. 4. A few rough experiments were carried out to confirm this. Certain typical mixtures were submitted to distillation through a fractionating column, and successive distillates, and occasionally the residue, analyzed. Barostatic control was not imposed and the results therefore correspond to an average laboratory pressure of 740 mm.

Results

The results for the equilibrium concentrations of liquid and vapor are expressed numerically in Table I and graphically in Figs. 2 and 3, where concentrations are expressed in mole per cent.: the figures for the well-known binary systems:

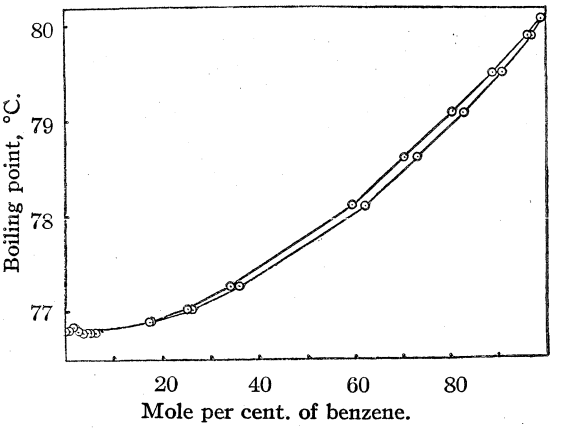


Fig. 2.—Boiling point–composition diagram for the system benzene–carbon tetrachloride.

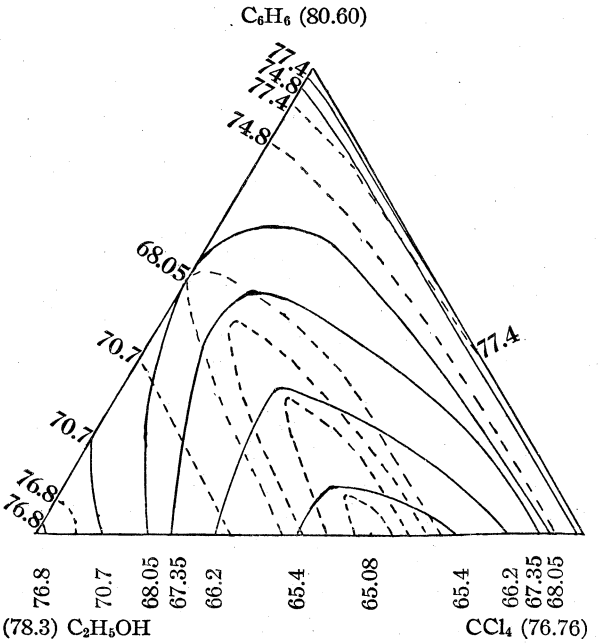


Fig. 3.—Liquid and vapor isothermals in the ternary system (concentrations in mole per cent.).

benzene–alcohol and carbon tetrachloride–alcohol are not given. In the ternary figure (Fig. 3) the full curves represent liquid solutions and the dotted curves equilibrium mixtures of vapor; the pairs are identified by the temperatures which are given at the end of each curve. To avoid confusion, no tie-lines have been drawn, but these can be put in by the reader from the data of Table I.

TABLE I

LIQUID AND VAPOR COMPOSITIONS SYSTEM CARBON TETRACHLORIDE–BENZENE

B. p., °C.	Liquid compn. Mole % C_6H_6	Vapor compn. Mole % C_6H_6
80.12	100.00	100.00
80.05	99.28	99.15
79.88	97.13	96.55
79.48	90.92	88.84
79.06	82.96	80.59
78.58	73.07	70.37
78.09	61.98	59.16
77.26	35.56	34.01
77.02	26.00	25.01
76.87	17.62	16.90
76.78	5.05	4.97
76.76	6.02	5.93
76.77	4.67	4.62
76.77	3.60	3.58
76.81	3.39	3.35
76.80	2.47	2.41
76.84	1.54	1.54
76.81	0.65	0.65
76.79	0.00	0.00

SYSTEM ALCOHOL–BENZENE–CARBON TETRACHLORIDE

B. p., °C.	Liquid compn. Mole % C_6H_6	Liquid compn. Mole % CCl_4	Vapor compn. Mole % C_6H_6	Vapor compn. Mole % CCl_4
78.33	95.1	4.1	91.5	4.5
77.37	78.8	21.0	74.0	23.0
76.96	0.49	1.33	0.89	6.63
76.79	94.2	3.9	87.2	4.4
76.62	54.0	46.0	50.2	47.4
76.62	1.4	1.1	4.5	4.8
76.55	78.2	21.0	77.2	17.8
75.70	4.1	0.9	11.2	3.4
75.59	50.3	48.7	46.0	49.2
75.46	48.8	49.3	44.5	50.4
74.79	11.7	87.6	11.4	83.8
74.00	0.84	5.13	1.97	18.5
73.18	92.2	3.2	76.2	3.3
72.95	9.8	88.7	9.4	80.9
72.83	2.5	4.4	10.3	13.9
72.32	50.3	47.2	45.9	43.8
72.21	10.2	1.6	24.2	4.7
70.65	7.7	6.9	17.4	19.2
69.70	23.4	0.4	40.3	0.9
69.50	71.5	19.1	54.0	17.5
69.47	15.0	2.5	34.7	7.6
69.11	2.11	15.4	5.11	47.1
69.00	80.3	2.1	61.8	2.0
68.25	40.4	0.8	49.3	1.3
68.08	64.5	1.7	57.0	2.0
68.02	61.5	1.5	56.0	1.7
67.98	53.6	1.2	53.7	1.5
67.91	9.5	84.2	7.1	67.0
67.86	29.9	6.9	39.7	11.3
67.66	60.6	16.0	48.0	15.4
67.60	15.5	14.4	23.5	26.4
67.50	44.1	41.1	32.9	35.2
67.37	54.5	13.9	46.0	14.6
67.36	40.2	9.6	42.8	12.8
67.28	43.4	10.9	43.8	13.4
67.02	43.6	14.5	40.1	18.3
66.62	3.1	26.9	4.7	47.2
66.58	22.6	21.3	25.7	30.1
66.34	28.7	27.3	27.3	31.3
66.33	33.9	32.6	28.9	32.7
66.24	32.3	26.8	29.9	29.6
66.22	29.4	29.3	25.9	31.8
66.10	9.1	30.7	11.2	44.7
65.89	23.0	36.8	21.0	39.3
65.77	20.1	40.5	18.0	42.5
65.73	19.4	41.2	17.8	43.2
65.68	12.2	63.2	9.9	55.6
65.54	6.8	42.2	7.1	52.3
65.41	8.6	46.7	8.9	51.3
65.39	9.0	56.8	8.4	53.2
65.41	7.1	65.5	6.6	59.2
65.38	9.0	57.3	7.6	54.8

From the data of Table I, the distillation diagram (Fig. 4) has been deduced. The results of experimental distillations, conducted under laboratory pressure and without barostatic control, were in qualitative agreement with the predictions of Fig. 4.

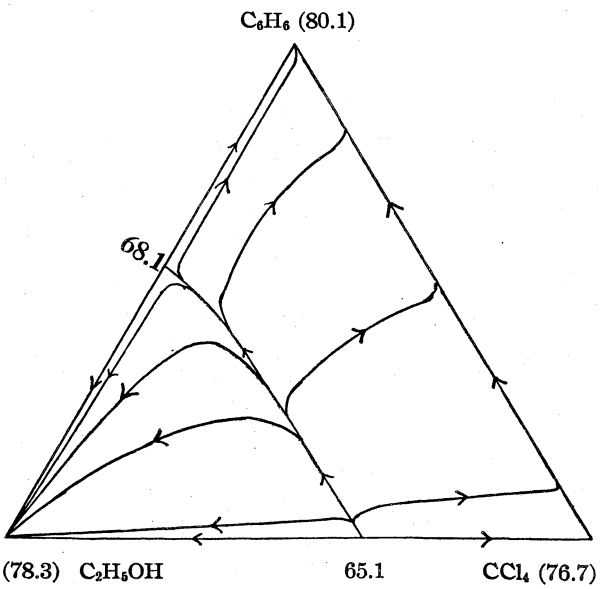


Fig. 4.—Course of the distillation: the arrows represent the direction of rising temperature.

Discussion

Nothing need be said about the binary systems: alcohol–benzene and alcohol–carbon tetrachloride except that our results were in good agreement

with published data and better than most in respect of composition, though not of temperature. The disputed system benzene–carbon tetrachloride does not show an azeotropic minimum on the boiling point curve, despite the fact that our own results appear to show a minimum temperature about 0.05° below the boiling point of carbon tetrachloride: this temperature difference is the error of measurement. The evidence against the minimum rests on our very accurate method of analysis. No matter how low the benzene content the tie-lines never reverse; that is, the vapor is a ways richer in carbon tetrachloride. It is admitted that if there were any azeotropic mixture it could not contain more than ten mole per cent. benzene, and from 10 to 2.47% benzene our results show a higher content of carbon tetrachloride in the vapor, while for 1.54 and 0.65 mole per cent. the vapor appears to have the same composition. This apparent identity is due to our inability to read the analytical curve to any higher degree of accuracy than, say, 0.02%; the density determinations themselves still indicated a higher carbon tetrachloride content in the vapor.

The ternary diagram shows the existence of a trough of minimum boiling point running across the diagram from 65.08° and about 39 mole per cent. alcohol, in the alcohol–carbon tetrachloride system, to 68.05° and about 45 mole per cent. alcohol, in the alcohol–benzene system. This trough has itself no minimum of temperature and therefore the liquid and vapor curves coincide only at its ends. The method of investigation actually used was to proceed across the diagram from the alcohol corner along lines of approximately constant benzene:carbon tetrachloride ratio. Proceeding in this way, the following behavior of the tie-lines is general over the diagram. At first, *i. e.*, for mixtures rich in alcohol, the vapor is much richer in benzene and carbon tetrachloride, the direction of the tie-line being symmetrical with respect to the sides of the triangle. As the content of alcohol decreases, the tie-line shortens and changes direction as it approaches the trough. A liquid mixture lying in the trough (which is almost, though not quite, a straight line) has a tie-line also lying almost in the trough, but the slightest change in liquid composition causes the tie-line to deviate considerably in one or the other direction. The experimentally determined tie-lines lying over the trough, of which there are several, were obtained by proceeding along the trough itself, a difficult procedure involving much trial and error. Proceeding along a line of constant benzene–carbon tetrachloride ratio, after crossing the trough, the tieline turns rapidly to assume a position at almost 180° to its former position; that is, the vapor is now richer in alcohol. In the solid model, the temperature slope from the trough to the benzene–carbon tetrachloride side is much steeper than the corresponding slope from the trough to the alcohol apex and, as Fig. 4 shows, the former slope increases very rapidly at the last. In agreement with this, it is found that the tie-line, which now slopes somewhat toward the carbon tetrachloride corner, retains this slope almost till the last and then, as the last trace of alcohol leaves the mixture, undergoes a sharp change to occupy its position in the binary surface benzene–carbon tetrachloride.

This detailed knowledge of the behavior of the tie-lines enables one to predict the course of distillation of any mixture. Referring to Fig. 4, consider a liquid mixture lying in the triangle to the left of the trough. The residue will move in the direction of the arrow, the temperature rising and the mixture becoming richer in alcohol, until pure alcohol is left in the boiler. The first distillate will be poorer in alcohol than the original mixture. Redistillation of distillates will eventually give a mixture lying in the trough: the trough can never be crossed. It might be supposed that a mixture on the trough, lying as it does in an (almost) pseudo-binary system, might be separated by distillation into a distillate of the low boiling azeotrope of the alcohol–carbon tetrachloride system, and a residue of the higher boiling azeotrope of the alcohol–benzene system. This is not true, however, because the projections of liquid and vapor compositions do not quite coincide in the trough of minimum boiling point. Hence, though the distillate will always approximate to the trough, the residue soon deviates from it, because the tie-lines change their direction rapidly on both sides of the trough. It would seem, then, that the final results of fractional distillation of any mixture in the triangle described above would be a residue of pure alcohol and a distillate of the low boiling azeotrope alcohol–carbon tetrachloride; but this obviously cannot describe the fate of the whole mass of the mixture, since the mixture as a whole contains benzene. The benzene is to be found in the middle fractions which approximate more and more to the trough and move up it in the direction of the higher boiling azeotrope To summarize, a mixture containing benzene, alcohol and carbon tetrachloride in such proportions that the mixture lies to the left of the trough can be separated by distillation into a residue of pure alcohol, a refined distillate of the low boiling azeotrope of the alcohol–carbon tetrachloride system and an intermediate mixture approximating in composition to the higher boiling azeotrope of the alcohol–benzene system. The same result could of course be obtained by using a fractionating column of suitable length and drawing off fractions at suitable heights.

In the quadrilateral area lying between the trough and the benzene and carbon tetrachloride corners, distillation eventually yields a distillate of the low boiling azeotrope, while the residue rapidly approaches in composition the binary system benzene–carbon tetrachloride. But shortly before the last trace of alcohol is removed from the res-

idue, the direction of change of composition of the residue alters abruptly in the direction of the benzene corner, so that when eventually the last trace of alcohol is removed, the binary mixture produced is much richer in benzene than the original mixture. From this binary mixture both benzene and carbon tetrachloride can (theoretically) be obtained by distillation, since the binary mixture benzene–carbon tetrachloride shows neither minimum nor maximum on the boiling point curve. It appears, therefore, that in the quadrilateral area pure benzene, pure carbon tetrachloride and the low boiling azeotrope can be obtained by fractionation. In addition, however, certain of the middle fractions would tend to approximate to the higher boiling azeotrope of benzene–alcohol but, as with the triangular area, it is doubtful whether in practice any of this binary azeotrope, uncontaminated by carbon tetrachloride, would be obtained, because of the strong curvature of the tie-lines around the trough.

The above predictions were borne out in practice by our distillation experiments.

Summary

The boiling temperatures, under constant pressure, of the binary systems alcohol–benzene, alcohol–carbon tetrachloride, and benzene–carbon tetrachloride, as well as those of the ternary system alcohol–benzene–carbon tetrachloride, have been investigated. The equilibrium concentrations of liquid and vapor for the above systems have been determined, with an accuracy of 0.3 weight per cent.

It is shown that the system benzene–carbon tetrachloride does not exhibit an azeotropic minimum on its boiling point curve. An improved barostat is described.

The liquid–vapor composition diagram is discussed and the course of distillation predicted. The course of distillation has been verified qualitatively by experiment.

WINNIPEG, CANADA RECEIVED OCTOBER 7, 1947

[CONTRIBUTION FROM THE BUREAU OF MINES, DEPARTMENT OF THE INTERIOR]

Modifications of the Brunauer, Emmett and Teller Equation II[1]

BY ROBERT B. ANDERSON[2] AND W. KEITH HALL[2]

The simple Brunauer, Emmett and Teller equation[3] (hereafter abbreviated to B.E.T.) has been useful in the estimation of surface areas from physical adsorption isotherms. This equation will fit satisfactorily experimental data for almost all isotherms except those of Type I of Brunauer, Deming, Deming and Teller[4] in the relative pressure range of 0.05 to 0.40. Several modifications of the simple B.E.T. equation have extended the range of applicability. In most cases the adsorbent structure is pictured as a series of parallel plates which will permit the adsorption of only n-layers from each side. An n-equation derived by B.E.T.[3] and Hill[5] extends the fit to higher relative pressures for most isotherms, but it is somewhat difficult to apply to experimental data.[6] Brunauer, Deming, Deming, and Teller[4] derived a more elaborate n-equation in which the heat of adsorption of the last layer adsorbed in a condenser plate capillary was higher than the heat of liquefaction. Although this equation can be fitted to the entire isotherm, its application is too difficult to be of any practical value as a method of characterizing isotherms.

Pickett[7] presented a simpler type of n-equation than that of B.E.T., one which is more easily applicable to adsorption data and probably fits over a greater range. The simplest derivation of this equation assumes that the volume of gas adsorbed in any layer is independent of the molecules adsorbed in higher layers; whereas, the n-equation of B.E.T.[3] implies that adsorption of molecules in higher layers stabilizes the molecules in underlying layers.

Recently, Anderson[8] suggested that the parallel plate type of pore structure is probably not a good physical picture of most porous adsorbents. A pore structure in which the area available to each subsequent layer is less than the area of the underlying layer is probably a better physical picture. In this paper it was also shown that for isotherms of finely divided, presumably non-porous solids such as carbon black, titania, etc., the modified B.E.T. equation could be fitted to the range of relative pressure of 0.05 to 0.7 by assuming the free energy of adsorption in the several layers after the first to be less than the free energy of liquefaction.

In the present paper, an equation embodying the same assumptions is derived in a manner similar to that of the B.E.T. equation. It can be satisfactorily fitted to isotherms of Type I and those approaching Type I by assuming the free energy of adsorption in the second and subsequent layers

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior, Washington, D. C. Article not copyrighted.

(2) Physical Chemist, Research and Development Division, Central Experiment Station, Bureau of Mines, Pittsburgh, Pa.

(3) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(4) Brunauer, Deming, Deming and Teller, *ibid.*, **62**, 1723 (1940).

(5) Hill, *J. Chem. Phys.*, **14**, 263 (1946).

(6) Joyner, Weinberger and Montgomery, THIS JOURNAL, **67**, 2182 (1945).

(7) Pickett, *ibid.*, **67**, 1958 (1945).

(8) Anderson, *ibid.*, **68**, 686 (1946).

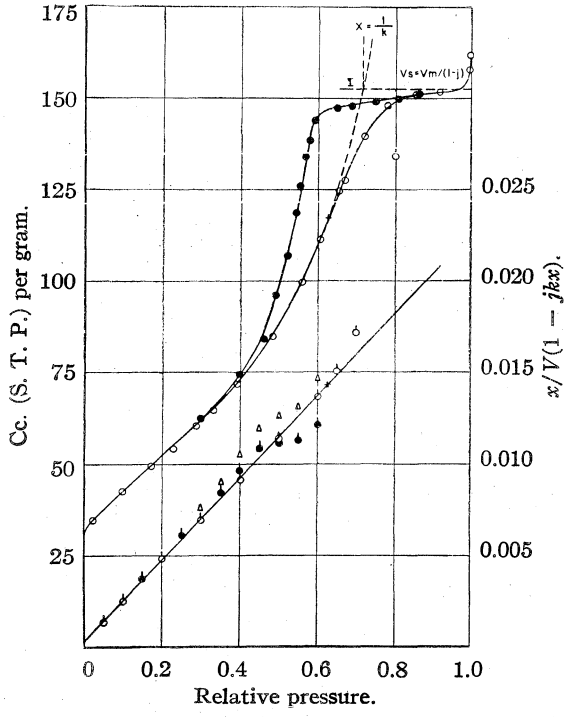


Fig. 1.—Adsorption isotherm and linear plot of equation 4 of nitrogen on iron oxide gel 47 C at −195°, where O and ● represent the adsorption and desorption isotherm, ⏀ represents the linear plot of the adsorption isotherm with $jk = 1$, and ⏀ and △ are linear plots of the desorption isotherm with $jk = 1.1$ and 1.2, respectively. The plus sign indicates where the data begin to deviate from the linear plot.

equal to that of liquefaction. The same equation can be fitted to Type IV isotherms,[4] which flatten below relative pressures of 0.85 by assuming the free energy of adsorption to be greater than that of liquefaction. This equation was used to integrate the equation of Kistler[9] for the latter type of isotherms. The areas computed with Kistler's equation were at least of the same order of magnitude as areas from the modified B.E.T. equation presented here or the simple B.E.T. equation.

In this paper adsorption in a capillary is assumed to occur in the same manner as on a free surface with capillary forces causing the pores to fill at relative pressures less than 1. Isotherms used as examples in this paper were determined by conventional volumetric and gravimetric methods, and either have been or will soon be described in the literature.

Derivation of a Modified B. E. T. Equation and Application to Type IV Isotherms.—The derivation follows that of the original B.E.T. equation[3] in which

$$V/V_m = \sum_0^\infty is_i / \sum_0^\infty s_i \qquad (1)$$

where V is the number of adsorbed gas molecules, V_m the number of molecules required to form a monolayer, and s_i is the number of sites covered with stacks i molecules high. In pore systems in which the area available to each layer is less than that of the layer underneath, it is assumed that at any relative pressure the volume adsorbed in the i-th layer is equal to the amount that would be adsorbed in this layer on a plane surface multiplied by A_n/V_m where A_n is the number of molecules required to fill the n-th layer. Although the relationship of A_n to V_m for any postulated type of pore is a function too complicated to give a simple summation of equation (1), it may be satisfactorily approximated in many cases by assuming $A_n/A_{n-1} = j$, where j is a constant less than 1. Since the surface area is defined as the area occupied by the first layer, the j correction will not be applied to it. This results in the relationship[10] that $s_i = s_0 c j^{i-1} x^i$. Thus

$$\frac{V}{V_m} = \frac{cs_0 \sum_1^\infty ij^{i-1}x^i}{s_0\left(1 + c\sum_1^\infty j^{i-1}x^i\right)} = \frac{cx}{(1 - jx)[1 + (c - j)x]} \qquad (2)$$

where, as in the simple B.E.T. equation, x is identified as p/p_0. At $x = 1$, almost all of the pores should be filled and since c is usually 5 to 100 and $1 > j > 0$

$$V/V_m = c/(1 - j)(1 - j + c) \cong 1/(1 - j) \cong V_s/V_m \qquad (3)$$

where V_s is the number of adsorbate molecules required to fill the pore system.

If the free energy of adsorption in the second and subsequent layers differs from the free energy of liquefaction by an equal amount d, then following the derivation by Anderson[8]

$$\frac{V}{V_m} = \frac{ckx}{(1 - jkx)[1 + (c - j)kx]} \qquad (4)$$

where $k = \exp d/RT$. The energy terms in the exponents of the equations for c and k are free energies of desorption and are opposite in sign to free energies of adsorption. Thus, if d is positive (k greater than 1), the free energy change in adsorption in the second and subsequent layers is more negative than the free energy of liquefaction, and the pores of the adsorbent should fill at relative pressures less than 1. In equation 4, almost all of the pores will be filled at $x = 1/k$. In systems of small pores the free energy of adsorption in second and subsequent layers may be expected to be less than that of liquefaction, since surface

(9) Kistler, Fischer and Freeman, *ibid.*, **65**, 1909 (1943).

(10) This relationship is not obvious but can be shown in the following manner: let V_i be the number of sites covered by i or more layers; then, for adsorption on a plane surface, $V_i = \sum_i^\infty s_i = s_i/(1-x)$, and $V_i/V_{i-1} = s_i/s_{i-1}$. For adsorption in a capillary the value of V_i/V_{i-1} should be multiplied by j, and hence the ratios s_i/s_{i-1} should also be multiplied by j. Thus, $s_i'/s_{i-1}' = js_i/s_{i-1} = jx$ where the primes indicate the values of s_i and s_{i-1} for adsorption in a capillary. In the rest of the derivation the primes will be omitted.

area decreases as the amount adsorbed increases. Equation 4 is similar to the equation derived previously[8] using the same assumptions as Pickett,[7] except that $(c - j)$ appears in the second term in the denominator instead of $(c - 1)$. The difference is negligible except for values of c near 1 and values of j near zero.

Equation (4) can be fitted to adsorption data by plotting $x/V(1 - jkx)$ against x with the constant jk varied to give the best straight line, and $1/V_m$ = slope + kj (intercept). To simplify computation, the volume adsorbed was read from the isotherms in intervals of 0.05 relative pressure unit. Tables of $x/(1 - jkx)$ were prepared, with corresponding values of x and for values of jk in intervals of 0.05 in the range of 0.00 to 1.40. Then, in making the modified B.E.T. plots, it was necessary only to divide the values in these tables by the volume adsorbed. Since fairly close approximations of j and k can be made from the isotherms, usually only one to three plots were necessary to establish the best value of the product jk. For evaluation of constant c, the adsorption equation was solved for c with $V = V_m$ in terms of x_m, the relative pressure at which $V = V_m$.

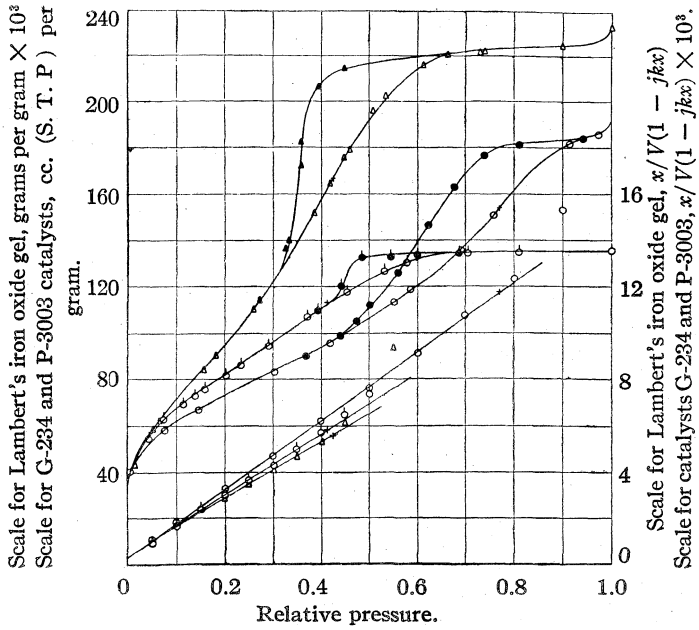


Fig. 2.—Isotherms and linear plots of benzene on Lambert's iron oxide gel at 50° with jk = 1.30; △, nitrogen on Fe_2O_3–CuO–K_2CO_3 Fischer–Tropsch catalyst P 3003 at −195° with jk = 0.90, ○, and nitrogen on Fe_2O_3–CuO–CaO–Kieselguhr Fischer–Tropsch catalysts G 234 with jk = 0.75, ○. Desorption points are solid, and the plus signs indicate where the data begin to deviate from the linear plot.

TABLE I

DATA FOR TYPE IV ISOTHERMS

Adsorbent Fe_2O_3 gels	Adsorbate	T, °C.	V_m[a]	Area sq. m./g.	V_s[a]	c	jk		k	Point +	$\bar{d}$[b] Å.	Area[c] sq. m./g.	$\bar{d}$[c] Å.
47C[d]	N_2	−195	44.1	193.0	152.5	42.2	1.00	0.711	1.41	0.63	49.0		
110C[e]	N_2	−195	39.3	172.1	124.7	54.4	1.05	.685	1.53	.55	44.9		
10K[d]	N_2	−195	38.5	168.9	129.0	56.6	1.00	.701	1.43	.65	47.4		
Lambert's[f]	C_6H_6	+ 40	0.0834	197.2	0.236	24.2	1.30	.647	2.01	.43	55.2		
	C_6H_6	+ 50	0.0773	185.3	0.221	17.3	1.30	.650	2.00	.43	55.9		
Fe_2O_3–CuO gels													
P 3003[g]	N_2	−195	74.8	327.5	134.0	17.6	0.90	.442	2.06	.43	25.4		
G 234[h]	N_2	−195	68.2	289.7	186.8	37.3	.75	.635	1.18	.77	38.8		
Porous glass[i]													
3	N_2	−195	49.7	217.7	120.5	125.8	.80	.587	1.39	.68	34.3		
3	A	−195	52.9	201.8	142.6	29.6	.95	.629	1.51	.62	35.3		
3	n-C_4H_{10}	0	14.5	125.8	40.0	5.7	1.00	.638	1.57	.55	54.4	237.9	31.1
5	N_2	−195	66.1	289.6	107.0	44.5	0.75	.382	1.96	.48	22.9		
5	n-C_4H_{10}	0	20.3	175.7	36.3	4.2	.95	.433	2.19	.43	34.8	307.9	19.9
7	N_2	−195	59.5	260.5	136.0	63.9	.85	.562	1.51	.65	32.3		
7	A	−195	57.9	221.0	159.3	25.2	1.00	.636	1.57	.65	36.0		
7	n-C_4H_{10}	0	15.2	131.6	48.9	6.3	1.20	.690	1.74	.55	63.6	230.5	36.3
Silica gels													
SiO_2 catalyst[j]	N_2	−195	79.7	349	590	95.8	0.90	.865	1.04	.63	105.0		
Aerogel[k]	N_2	−195	255.9	1120	1298	60.2	0.70	.804	0.87	.72	118.0		

[a] All data for V_m and V_s expressed as cc. (S. T. P.)/g. except Lambert's which are expressed as g. of adsorbate per gram. [b] Average pore diameter calculated from equation of Emmett and DeWitt[18] and equations (10) and (11) in the text. [c] Area and average pore diameter for n-butane isotherms assuming the cross-sectional area of butane to be 1.75 times the value of 32.1 Å.² [d] Ref. 11. [e] Unreduced iron Fischer–Tropsch catalyst similar to 10K. [f] Ref. 12. [g] P 3003, iron–copper–potassium carbonate (100:10:0.5) Fischer–Tropsch catalyst. [h] German iron Fischer–Tropsch catalyst (Fe:Cu:CaO:Kieselguhr = 100:2.5:10:15) prepared by Ruhrchemie. [i] Ref. 13. [j] Almost pure SiO_2 gel. [k] Sample from Prof. D. B. Keyes.

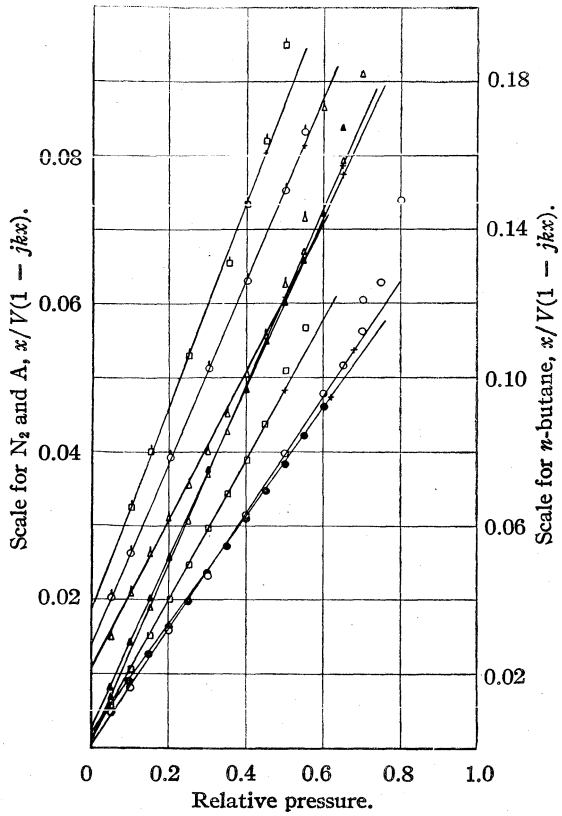


Fig. 3.—Linear plots of adsorption isotherms on porous glass where O, ● and ⏀ represent nitrogen, argon and n-butane on 0.253 g. of porous glass 3, □ and ⊟ represent nitrogen and n-butane on 0.157 g. of porous glass 5, and △, ▲ and ⧋ represent nitrogen, argon and n-butane on porous glass 7. The plus mark indicates the highest point at which the points fall on the straight line. Nitrogen and argon isotherms were determined at −195° and n-butane at 0°.

Application of equation (4) to the nitrogen adsorption and desorption isotherms of iron oxide gel catalyst 47C[11] is shown in Fig. 1. For the adsorption isotherm, the linear plot is satisfactory to the point marked +, which is about the point of inflection of the adsorption branch. The constants of the equation are V_m = 44.1 cc. and jk = 1, in this case the linear plot being identical to that of the simple B.E.T. equation. From equation (3) evaluated with V_s = 151.5, j = 0.7111 and thus k = 1.408. The isotherm calculated for relative pressures higher than the + mark is shown by the broken curve. This curve, which appears to be an extrapolation of the adsorption isotherm below +, intersects V_s at a relative pressure equal to $1/k$. This is useful in approximating the choice of jk, since j can be estimated from equation (3) assuming V_m to occur at x = 0.1.

In Fig. 1, equation (4) has also been applied to the desorption isotherm. The plots for the best choices of jk, 1.1 and 1.2, are not satisfactory, indicating the equation is not applicable to the desorption branch.

Equation (4) has been applied to the adsorption isotherms of nitrogen, argon, butane, and benzene on several ferric oxide gels and porous glasses with equal success. The equation has been fitted satisfactorily to all isotherms of this type which flatten below a relative pressure of 0.85. Isotherms of nitrogen on ferric oxide–copper oxide–potassium carbonate Fischer–Tropsch catalyst P3003, German ferric oxide–copper oxide–calcium oxide–kieselguhr catalyst 234, and benzene on ferric oxide gel of Lambert[12] and the corresponding plots of equation (4) are presented in Fig. 2. In Fig. 3 are linear plots of data for adsorption isotherms of nitrogen, argon, and butane on porous glasses 3, 5, and 7.[13] Data for the application of equation (4) to the isotherms shown in Figs. 1, 2, and 3 and several similar isotherms are summarized in Table I. Included in the table are data for two isotherms of nitrogen on silica gels which flatten above 0.85. These data, as well as data on average pore diameters, will be described in later sections. The value of V_m computed from equation (4) will vary slightly from the V_m computed from the simple B.E.T. equation, being higher for jk lower than 1 and lower for jk higher than 1. Since the difference is less than 10% in all cases, V_m from the simple B.E.T. equation has not been included. With the exception of the two silica gel isotherms, equation (4) could be satisfactorily fitted to the adsorption isotherm from relative pressures of 0.05 to the point of inflection, but the equation could not be fitted to the desorption isotherm.

The physical interpretation of equation (4) is that the capillary forces shift the p_0 value of the adsorbate from p_0 to p_0/k, and at a relative pressure of $1/k$ all, or almost all, of the pores are filled. The lack of fit above the point marked + may be due to the rather crude approximation of the assumptions of equation (4) to the pore structure of the adsorbent. Some isotherms such as those shown in Figs. 1 and 2 flatten and then rise again at high relative pressures. This is very probably due to a small fraction of very large pores. The value of V_s in these cases is taken as the point where the isotherm begins to rise again.

For isotherms which flatten above relative pressures of 0.8 or 0.85, equation (4) does not fit data satisfactorily to the point of inflection as in Fig. 4, although the data can usually be fitted to relative pressures of 0.7. This is interpreted as indicating that in systems of larger pores it is not permissible to assume the capillary forces effective in all layers, but that these forces become effective only in the third or higher layers. Equations embodying the assumption that the free energy of adsorption becomes less than that of

(11) Hofer, Peebles and Dieter, THIS JOURNAL, 68, 1953 (1946).

(12) Lambert and Clark, *Proc. Roy. Soc.* (*London*), **A122**, 497 (1929).

(13) Emmett and Cines, *J. Phys. Colloid Chem.*, **51**, 1248 (1947).

liquefaction in the third or higher and subsequent layers can be derived, but the difficulty in application to data is too great for them to be of interest as a simple method of characterizing isotherms with a few constants. Examples of isotherms of this type are those of the silica gel catalyst and a silica aerogel, as shown in Fig. 4. The values of k were 1.04 and 0.87, respectively, for these isotherms. This suggests a transition in systems of large pores of the values of k from greater than 1 as characteristic of small pores to values of k less than 1 as observed for non-porous solids. Kistler[9] has postulated the structure of aerogels to be a "felt" of fibers. Hence, when the surface is covered with only two or three layers it may act as a non-porous adsorbent.

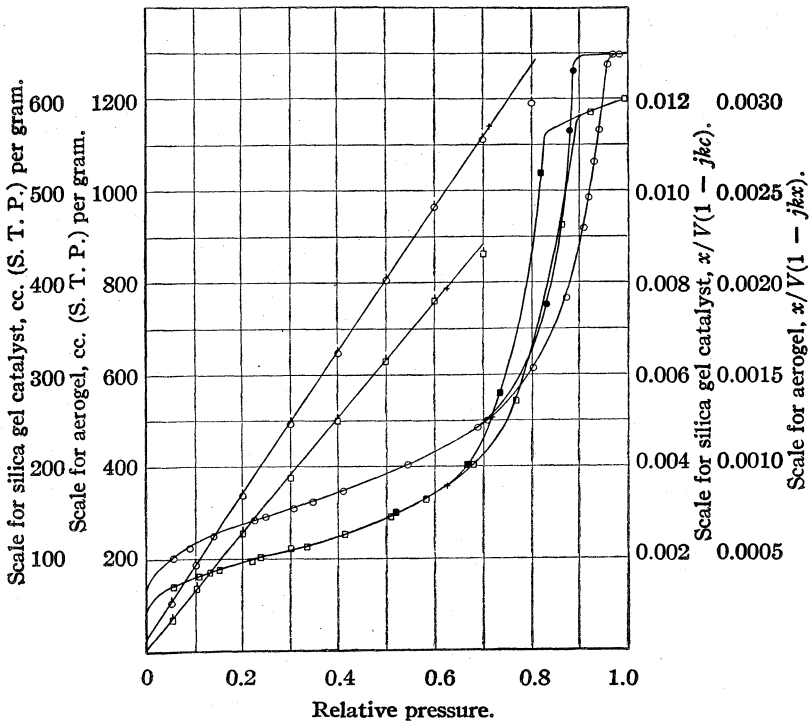


Fig. 4.—Adsorption isotherms and linear plots of nitrogen at −195° on silica catalyst □ and on aerogel O. Desorption points are solid and points of linear plot have tails. The plus sign indicates where data begin to deviate from linear plot.

Kistler[9] presented an equation for determining surface area without the assumption of an area per adsorbed molecule. In this equation, the free energy change in completely filling a system of capillaries covered by a monolayer (as computed from the adsorption isotherm) was equated to the decrease in surface area per gram, ΔA, times the normal surface tension of the liquid, σ. That is

$$\Delta A = -(RT/M\sigma)\int_0^{W(x=1)} \ln x \, dW \qquad (5)$$

where W is the total weight adsorbed minus the weight of adsorbate in the first layer in grams per gram of adsorbent. W was computed by subtracting a Langmuir-type isotherm fitted to points at low relative pressures from the adsorption isotherm, and the integral was evaluated graphically. It should be noted that: (a) equation 5 is only applicable to porous adsorbents in which all of the pores are completely filled at $x = 1$, (b) identification of the surface free energy of the first layer with the normal surface tension of the liquid may be a poor assumption, and (c) this equation does not confirm or deny multilayer adsorption.

Equation 5 may be written as

$$\Delta A = \Delta F_n'/\gamma \qquad (6)$$

where $\Delta F_n'$ is the free energy change in the process of going from a system of pores covered with a monolayer to a completely filled capillary system, and γ is the surface free energy, which is not necessarily equal to the normal surface tension. In equation 7, $\Delta F_n'$ is expressed in terms of ΔV, the volume of gas adsorbed in the second and subsequent layers in cc. (S.T.P.) per gram, that is, $\Delta V = V - V_1$, where V_1 is the volume adsorbed in the first layer. The variables of the integration have also been changed.[14]

$$\Delta F_n' = -\frac{RT}{22{,}400}\int_0^{V(x=1)} \ln x \, d\Delta V = \frac{RT}{22{,}400}\int_0^1 \Delta V \, d \ln x \qquad (7)$$

Thus for Type IV isotherms which flatten below relative pressures of 0.85 (isotherms to which equation (4) is applicable), equation (7) may be evaluated with

$$\frac{V_1}{V_m} = \frac{\sum_1^\infty s_i}{\sum_0^\infty s_i} = \frac{ckx}{1 + (c - j)kx} \qquad (8)$$

Equations (4) and (8) may be substituted into the last term of equation (7), and the integral evaluated to point I of Fig. 1 ($x = 1/k$) with $\Delta V = V - V_i$ and from $x = 1/k$ to $x = 1$ with $\Delta V =$

(14) This transformation is made as follows

$$\int_0^{V(x=1)} \ln x \, d\Delta V = -\int_0^1 \Delta V \, d \ln x + \Delta V \ln x \Big|_{x=0}^{x=1}$$

The upper limit of the second term of the right side of the equation is zero, and since at very low relative pressures $\Delta V = ckx$,[2] equation 4 minus equation 8, the indeterminate lower limit can be shown to be zero.

TABLE II

DATA FOR KISTLER'S EQUATION

Adsorbent[a]	Adsorbate	$T.$, °C.	$\Delta F_n'$[b] ergs $\times 10^{-7}$	Area, sq. m./g. $\frac{\Delta F_n'}{\sigma}$	Area, sq. m./g. from V_m S	Area, sq. m./g. from V_m $S(1+j)/2$	σ[c]	γ[d]
Fe_2O_3 gels								
47C	N_2	−195	2.58	307.9	193.0	165.0	8.4	15.6
110C	N_2	−195	2.31	275.7	172.1	145.0	8.4	15.9
10K	N_2	−195	2.28	265.0	168.9	143.5	8.4	15.9
Lambert's	C_6H_6	40	6.10	232.7	197.2	162.4	26.3	37.5
		50	5.90	235.0	185.3	152.6	25.1	38.6
Fe_2O_3–CuO gels								
P-3003	N_2	−195	2.32	276.0	327.5	236.0	8.4	9.8
G-234	N_2	−195	2.44	290.8	298.7	244.1	8.4	10.0
Porous glasses								
3	N_2	−195	1.91	227.2	217.7	172.7	8.4	11.1
3	A	−195	2.48	166.5	201.8	164.3	14.9	15.1
3	n-C_4H_{10}	0	2.49	166.4	(237.9	194.7)	14.9	(12.8)
					(125.8	103.0		(19.8)
5	N_2	−195	1.66	197.4	289.6	200.0	8.4	8.3
5	n-C_4H_{10}	0	2.24	149.6	(307.9	220.5)	14.9	(10.2)
					(175.6	125.8)		(17.8)
7	N_2	−195	2.29	272.0	260.5	203.2	8.4	11.3
7	A	−195	2.88	193.0	227.0	184.5	14.9	15.5
7	n-C_4H_{10}	0	3.50	234.3	(230.5	194.6)	14.9	(18.0)
					(131.6	111.1)		(31.5)

[a] Adsorbents described in Table I. [b] Computed from equation 9. [c] Normal surface tension of liquid in ergs/sq. cm. [d] Surface free energy of the first layer of adsorbate in ergs/sq. cm., computed by dividing $\Delta F_n'$ by $S(1+j)/2$.

$V_s - V_m$. This gives

$$\Delta F_n' = \frac{2.3\ RT\ V_m}{22{,}400}\left\{\frac{j}{c-j}\log_{10}(1+c-j)+\log_{10}(1-j)-\frac{j}{1-j}\log_{10}k\right\} \quad (9)$$

Data for the application of equation (9) to isotherms of Table I are given in Table II. Surface areas, ΔA, computed from the free energy divided by normal surface tension were usually larger than S, the area computed from V_m. The decrease in area, ΔA, is the area of the interface between the first and second layer. As an approximation this can be taken as half the sum of the areas of the first and second layers, which is $S(1+j)/2$; however, this area gives poorer agreement with ΔA than S. A small part of the discrepancy is due to the fact that equation (4) predicts a larger volume adsorbed than that of the actual isotherm in the vicinity of point I as shown in Fig. 1. In all cases the areas predicted from equations (4) and (9) are of the same order of magnitude.

The surface free energy, γ, was computed by

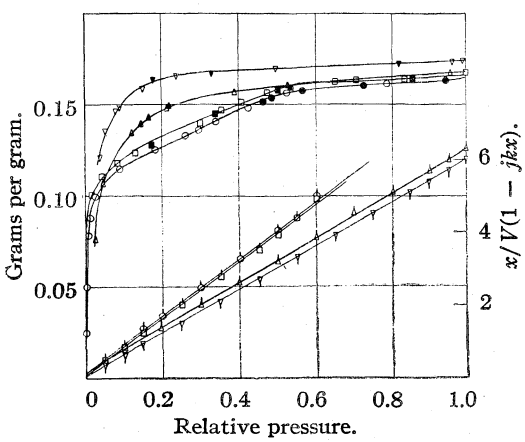


Fig. 5.—Adsorption isotherms and linear plots of ethanol and benzene on Lambert's silica gel, where □ and O indicate ethanol at 50 and 60°, respectively, and ▽ and △ benzene at 15.2 and 70°, respectively. Solid points indicate desorption, and points on linear plots have tails.

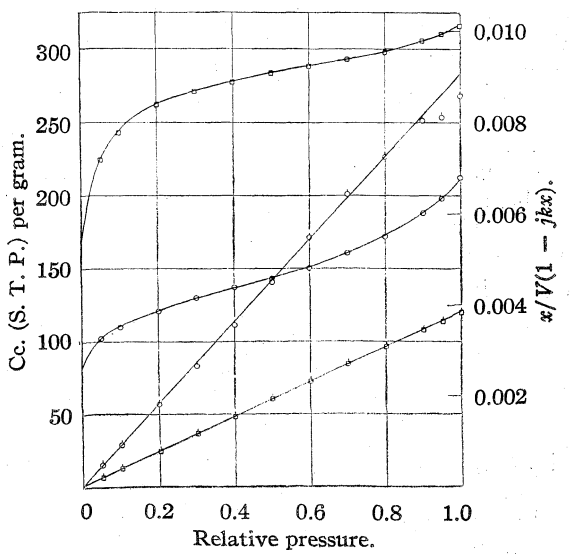


Fig. 6.—Adsorption isotherms and linear plots of nitrogen on charcoals PC1-1042, □, and PC1-1042 degassed O. Points of linear plots have tails.

TABLE III

DATA FOR TYPE I ISOTHERMS

Adsorbent	Adsorbate	T, °C.	V_m[a]	Area sq. m./g.	V_s[a]	jk	j	$\bar{d}$ Å.[b]
Lambert's silica gel[c]	C_6H_6	15	0.1680	391.3	0.1744	0.05	0.038	20.3
		40	.1661	394.1	.1732	.05	.041	20.3
		50	.1645	394.1	.1730	.05	.051	20.6
		70	.1616	394.1	.1680	.05	.038	20.5
	C_2H_5OH[e]	50	.1285	393.0	.1662	.4	.232	22.0
		60	.1260	386.5	.1662	.4	.242	22.5
Charcoal[d]								
PCI-1042	N_2	−195	269.0	1180	316.0	.17	.14	16.5
PCI-1042 (degassed)	N_2	−195	110.5	484	212.0	.45	.48	27.3
NS_5	N_2	−195	413.5	1810	418.0	.00	.01	14.2
NS_5 (degassed)	N_2	−195	266.0	1165	293.0	.10	.09	15.9

[a] Data of V_m and V_s expressed as grams adsorbate per gram for isotherms of Lambert[13] and cc. (S. T. P.)/g. for isotherms of Anderson and Emmett.[15] [b] Average pore diameter calculated from equation of Emmett and DeWitt,[16] equations (10) and (11) in text. [c] Ref. 13. [d] Ref. 15. [e] These isotherms are of Type IV, but without hysteresis.

assuming the values of surface area from $S(1 + j)/2$ and the free energies from equation (9) to be correct. These computed surface free energies given in the last column of Table II are usually always larger than the normal surface tension, in some cases being nearly twice as large. The data for the isotherms of *n*-butane are computed for both of the surface areas given in Table I.

Application of Equation (4) to Type I Isotherms.—Equation (4) is useful in characterizing Type I isotherms[4] as shown in Figs. 5 and 6 for silica gels and charcoals. The data for these and similar isotherms are given in Table III. Lambert's isotherms of benzene on silica gel are definitely of Type I, while the ethanol isotherms as shown in Fig. 5 appear similar to those of some iron gels. Although the values of j and k vary considerably, the surface areas calculated from benzene and ethanol isotherms are nearly identical. Recently, Emmett and Anderson[15] presented isotherms showing the effect of high temperature evacuation on charcoals. In charcoal PCI-1042 (Fig. 6) the evacuation caused sintering and enlargement of pores indicated by a decrease in V_m and an increase in the value of j, as shown in Table III. With charcoal NS_5 less sintering and relatively less pore size alteration occurred as indicated by the changes in V_m and j.

Relation of j to Average Pore Diameter.—Emmett and DeWitt[16] presented a useful method of estimating the average pore diameter, based on cylindrical pores

$$\bar{d} = 4V_L/A \qquad (10)$$

where V_L is the volume of adsorbate necessary to fill pores computed as normal liquid and A the surface area. Introducing equation (3) into equation (10)

$$\bar{d} = 6.56 \frac{M}{\rho a} \frac{1}{1 - j} \qquad (11)$$

where d is the average pore diameter in Å., M and ρ the molecular weight and density of adsorbate, respectively, and a the cross-sectional area of the adsorbate molecule in sq. Å.

Equation (11) has been used to compute average pore diameters from the isotherms of Tables I and III. The average pore diameters from the nitrogen and argon isotherms agreed quite satisfactorily, but the diameters from the butane isotherms were considerably larger. It has been pointed out in the literature that the cross-sectional area of molecules as computed by the method of B.E.T.[3] may not be correct, especially with long molecules like *n*-butane. If the cross-sectional area of butane is taken 1.75 (the average of the ratios of the areas from nitrogen and argon to areas from butane, computed by the usual B.E.T. methods) times the value of 32.1 Å.,[2] the average pore diameters computed from isotherms of the three gases are in fairly good agreement as shown in Table I. For pores that are the order of several molecular diameters, equation (11) does not hold, the diameter calculated being larger than the actual diameter. For the limiting case when the only one molecule fits into the capillary, $\bar{d} = 4V_L/\pi A$. For values of j less than 0.16 (the value of j for a pore of 3 molecular diameters), the constant in equation (11) should be less than 6.56 and greater than 2.09. Since in equation (9) $\bar{d} = \Sigma d^2/\Sigma d$, this average pore diameter will be larger than the arithmetic mean if there is a wide distribution of pore diameters; therefore, any diameter computed by equations (10) and (11) may be regarded as an upper limit of the pore diameter.

Discussion

Constant k of equation (4) is an average value of the k's for all of the adsorbed layers in the capillary system. Since d in the expression $k = \exp d/RT$ is equal to the change in surface area times the surface free energy, the values of k for a given pore system should be greater in higher layers than in those near the surface. Similarly for the same adsorbate on different adsorbents k should be nearly equal to 1 for large pores and

(15) Emmett and Anderson, *J. Phys. Colloid Chem.*, **51**, 1308 (1947).

(16) Emmett and DeWitt, THIS JOURNAL, **65**, 1253 (1943).

have higher values for small pores. Should the adsorbent offer considerable convex surface to adsorption in the first several layers, the value of k may be expected to be less than 1. This is shown in the data of Table I. It is difficult to explain the values of $k = 1$ observed for isotherms approaching Type I. There is no objection to $k = 1$ for isotherms that are strictly of Type I in which all of the adsorption occurs in the first layer. However, for the isotherms of the two PCI-1042 charcoals the values of k might be expected to be considerably larger than 1, since the isotherms indicate multilayer adsorption and since the average pore diameters are smaller than those of the Type IV isotherms of Table I. It is possible that these charcoals are composed of small pores plus a fraction of larger pores that cause the adsorption at higher relative pressures. In this case equation (4) may be regarded as somewhat empirical; however, V_m from this equation and the values of j probably have their usual significance.

With most isotherms the simple B.E.T. equation usually predicts larger adsorption above relative pressures of 0.35 than the actual isotherm, and deviation in this direction is usually considered to occur with all isotherms. It is interesting to note that the isotherms in Table I for which jk is greater than 1 deviate from the simple B.E.T. equation in the opposite direction.

In a previous section adsorption was postulated to occur in the same manner as multilayer adsorption with the decreased free energy of adsorption due to capillary forces causing the pores to fill at a lower relative pressure than 1. Equation (4) was found to satisfactorily fit the data for the adsorption branch of the isotherms, but could not be fitted to the desorption branch. This may indicate that desorption occurs in a different manner. In the authors' opinion desorption occurs from menisci of filled pores to leave the pores covered with the number of layers predicted by equation (4) remaining on the surface. This is similar to the picture of adsorption and desorption given by Cohan[17] except that he postulated that the pore will empty completely on capillary evaporation.

Equation (4) provides a systematic method of determining V_m for isotherms to which the simple B.E.T. equation cannot be fitted. This is also true of isotherms which appear to be a composite of several types of simple isotherms such as those of the porous carbon blacks previously described,[8] and some of the isotherms of active magnesia of Zettlemoyer and Walker.[18] In the latter case equation (4) can be applied satisfactorily to relative pressures of 0.4 by taking jk greater than 1.

Acknowledgment.—The authors wish to thank Dr. P. H. Emmett for his constructive criticisms of the manuscript and for permission to use the isotherms of porous glasses and silica aerogel.

Summary

1. A modified B.E.T. equation similar to that of Anderson[8] has been derived and applied to physical adsorption isotherms of Types I and IV.[4]

2. With Type I isotherms satisfactory fit of this equation can be obtained if the free energy of adsorption in the second and subsequent layers is taken to be equal to the heat of liquefaction.

3. For isotherms of Type IV which flatten below relative pressures of 0.85, the equation satisfactorily fits the data, if the free energy of adsorption was taken less than that of liquefaction. For this kind of Type IV isotherm the equation was used to integrate the equation of Kistler,[9] and the resulting expression gave surface areas of the same order of magnitude as the B.E.T. areas.

4. The equation is believed to be a simple method of characterizing isotherms with four constants.

(17) Cohan, *ibid.*, **66**, 98 (1944).

(18) Zettlemoyer and Walker, *Ind. Eng. Chem.*, **39**, 69 (1947).

PITTSBURGH, PA. RECEIVED JULY 23, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION]

The Sorption of Gases on a Plane Surface of Two Stainless Iron–Chromium–Nickel Alloys at 20, −78 and −183°[1]

BY MARION H. ARMBRUSTER

The resistance to corrosion and other properties of the stainless iron alloy containing approximately 18% chromium and 8% nickel suggest that the surface of the alloy may differ considerably from that of ordinary steels. As it seemed likely that the sorption of gases on such an alloy might yield a clue to the character of the surface and, by comparison with data for steels, might indicate differences in the nature of the surface, the sorption of hydrogen, neon, argon, nitrogen, carbon monoxide and oxygen has been measured at 20, −78 and −183° and at pressures up to 0.1 cm. mercury. The sorption of carbon dioxide has been determined at −78 and −183°.

The apparatus used, its calibration and method of operation have previously been described.[2] The gases were likewise those used in an earlier study of sorption on mild carbon steel.[3]

(1) Presented in part before the Chemical Research Conference on Catalysis sponsored by the American Association for the Advancement of Science, at New London, N. H., June 23–28, 1947.

(2) Armbruster and Austin, THIS JOURNAL, **60**, 467 (1938); **61**, 1117 (1939).

(3) Armbruster and Austin, *ibid.*, **66**, 159 (1944).

Samples.—Two samples of the alloy were used. The first (no. 25262), hereafter referred to as Alloy A, is the same sample used in an earlier determination of the solubility of hydrogen[4]; its composition was: C, 0.07; Mn, 0.37; P, 0.006; S, 0.005; Si, 0.47; Ni, 9.92; Cr, 18.30. After measurements with carbon monoxide and carbon dioxide at 400° on this alloy, the surface showed a very faint straw color which the usual reduction procedure with pure hydrogen at 450° did not appear to alter. The second sample (no. 25276), hereafter called Alloy B, is the same sample used in earlier measurements of the sorption of water vapor[5]; its composition was: C, 0.12; Mn, 0.37; P, 0.016; S, 0.005; Si, 0.44; Ni, 9.48; Cr, 18.48. Data collated by Maier[6] indicate that an alloy of this type is covered by an invisible yet protective oxide film not reducible by pure hydrogen. Both samples were commercial materials and are considered representative of this class of alloy within the regular tolerances. The sorbing surface in each case was a bundle of thin strips, each strip approximately 11.0 × 1.9 × 0.009 cm., with a geometric area, determined by summing the areas of the individual strips, of 11,130 sq. cm., the same as that of mild steel samples 1 (no. 25261) and 2 (no. 25277).[3]

Treatment of Samples.—The surface was degreased with absolute alcohol and anhydrous ether distilled over sodium, care being taken not to touch the surface with the fingers. Before each run the sample was reduced in place for about eight hours at 450° in a stream of hydrogen freed from traces of oxygen or water vapor; it was then outgassed for sixteen hours at 450° under a pressure of less than 10^{-6} mm., and finally was brought to the temperature at which the measurement was to be made in an atmosphere of hydrogen, which direct measurement has shown is not measurably adsorbed on this surface. The hydrogen was then pumped off and the pressure reduced to 10^{-6} mm. before the start of the run. In one series of measurements with Alloy A, the hydrogen reduction was omitted.

Orientation of Grains.—Microscopic examination showed that the grains are practically equiaxed. The X-ray pole figures of the two samples showed that there may be a slight preferred orientation of the grains with the (112) planes in the rolling plane.[7]

Microscopic Examination of Samples.—Examination of a polished but unetched section of each sample under the microscope showed that the amount of non-metallic inclusions was very small, less than 0.1%, these being of the same rounded type. Photomicrographs of the samples in the etched condition showed a shower precipitation of carbides mostly at the grain boundaries and to a lesser degree within the grains, mostly at crystallographic planes. The type of precipitation and sub-microscopic size of the individual particles make it impossible to specify the amount of carbides, or possibly nitrides, or to state positively that there is more carbide precipitate in Alloy B. The remainder of the surface is metallic, a solid solution of iron, chromium and nickel.

Results

The sorption of each gas was determined by building up the pressure in several increments, allowing sufficient time at each step for equilibrium to be attained. Several independent runs were made with each gas, the result being reproducible within the limit of measurement; moreover, the results for the two samples showed satisfactory agreement. Neon and hydrogen are not sorbed at any temperature, that is, the sorption, if any, is less than 3×10^{-4} cc. or less than 1% surface coverage.

Reduced Surface −183°.—Typical isotherms selected from concordant runs are shown for the several gases in Fig. 1, in which the amount of sorbed gas, expressed as a volume at 20° and 76 cm., is plotted for various pressures. Argon is

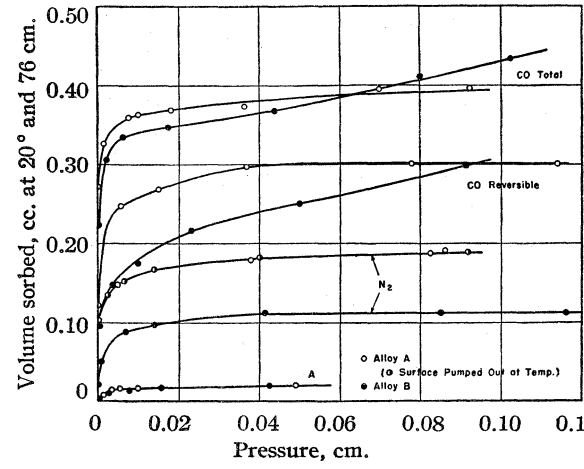


Fig. 1.—Typical adsorption isotherms of the several gases on reduced surface of stainless alloys at −183°.

sorbed very slightly and the gas taken up cannot be removed by pumping at this temperature. The rate of sorption of argon is virtually instantaneous. Nitrogen is sorbed in appreciable quantity and the sorption is completely reversible. The rate of adsorption is practically instantaneous, 99.7% being taken up within the time of measurement, two minutes, and the final increment slowly. Carbon monoxide is sorbed to a much greater extent. Approximately two-thirds of the sorbed carbon monoxide can be removed by evacuating the system at temperature, but the remaining one-third cannot be so removed. The rate of sorption is almost instantaneous, 99% being sorbed in a minute or two, the remainder very slowly, a drift being observed. Typical isotherms at all temperatures for oxygen are shown separately in Fig. 4: about one-tenth of the total oxygen can be removed by evacuating the system, the remainder is strongly held. The initial sorption is very rapid but is followed by a slow process of measurable rate.

Reduced Surface, −78°.—Argon and nitrogen are not measurably sorbed on either surface at this temperature. Typical isotherms for carbon monoxide and carbon dioxide are shown in Fig. 2. Carbon monoxide is slightly sorbed and cannot be removed by pumping at −78°; this chemisorption is appreciably less than that at −183°. The amount of carbon dioxide sorbed is relatively large and not completely reversible so that it is possible to differentiate two kinds: one

(4) Armbruster, *ibid.*, **65**, 1043 (1943).

(5) Armbruster, *ibid.*, **68**, 1342 (1946).

(6) C. G. Maier, U. S. Bur. Mines, Bulletin 436, 1942, p. 17.

(7) The density of packing is believed less for the (112) plane than the average of that calculated for the other crystallographic planes. On the basis that in these alloys the iron is of the face centered cubic form, and that the distance between the centers of two iron atoms is a_0 = 3.55 Å. the areas per iron atom for the several planes are:

plane	(100)	(111)	(110)	(112)
area (sq. Å./iron atom)	6.3	5.5	8.9	15.4

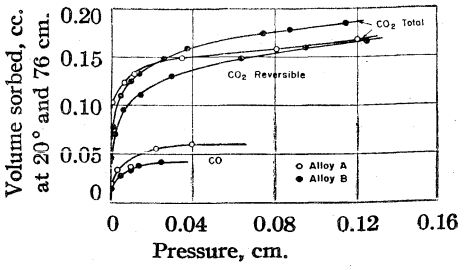


Fig. 2.—Typical isotherms for CO and CO_2 on reduced surface of stainless alloys at −78°.

in which 6% of the surface is covered by strongly held molecules; the other in which one-half of the surface is covered by weakly-held molecules. The sorption of oxygen (Fig. 4) is 30% greater than at −183°, apparently independent of pressure and too strongly held to be removed except by reducing with hydrogen and evacuating at 450°.

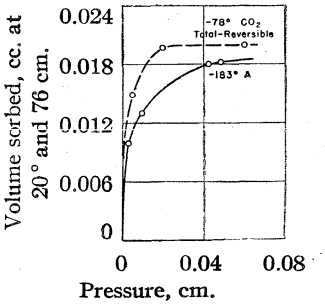


Fig. 3.—Sorption of argon at −183° and irreversible carbon dioxide at −78° on reduced surface of stainless alloy B.

Reduced Surface, 20°.—At room temperature the only gas sorbed to greater extent than the limit of error of measurement is oxygen, as is shown in Fig. 4. The amount of oxygen, which, as at −78°, appears to be independent of pressure, is almost twice as great as that sorbed at −183° and about 50% greater than at −78°.

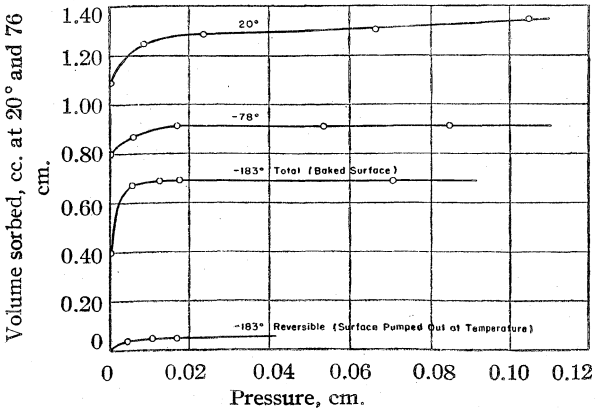


Fig. 4.—Typical isotherms for oxygen on reduced surface of stainless alloy A.

Unreduced Surface, −78°.—Measurements on the unreduced surface were limited to Alloy A at −78°, and typical isotherms are given in Fig. 5. The sorption of carbon monoxide is appreciable and, contrary to usual observation with this gas at −78° on steel, all of the sorbed gas is not strongly held. Only about 25% of the sorbed molecules are strongly held and the remainder can be pumped off at temperature. The total sorption of carbon dioxide is made up of a reversible sorption which corresponds to about 75% and a strongly held sorption which corresponds to about 25%.

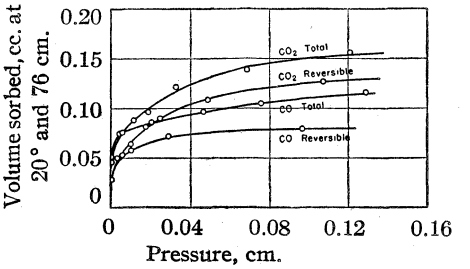


Fig. 5.—Typical isotherms for CO and CO_2 on unreduced surface of stainless alloy A at −78°.

Calculations and Discussion

Form of Isotherms.—The isotherms in Figs. 1, 2, 4 and 5 so greatly resemble in form those obtained for the same gases on mild steel as to suggest application of the Freundlich and Langmuir isotherms.

Freundlich Isotherm.—For initial comparison the data are expressed in the form of the exponential relation of Freundlich, $v = ap^{1/n}$, in which v is the volume sorbed at pressure p; a and n are constants. At lowest pressures this purely empirical expression had more satisfactorily represented the data for mild steels[3] than did the Langmuir equation. Typical Freundlich isotherms for several reversibly sorbed gases on these alloys are given in Fig. 6 in which the sorbed volume is plotted against pressure on double logarithmic coördinates and a straight line is obtained over a pressure range of a hundred fold or more.

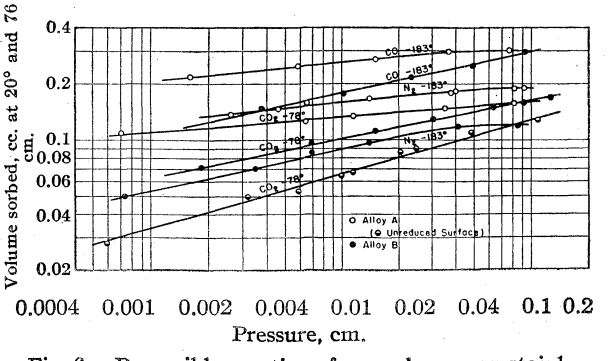


Fig. 6.—Reversible sorption of several gases on stainless alloys plotted on double logarithmic coördinates to illustrate application of parabolic or Freundlich relation.

The slope of the line corresponds to the exponent $1/n$ in the above equation. On the reduced Alloy B these slopes yield values of n which correspond with those for the same gases on mild steel surfaces.[3,5] For example nitrogen is 3, carbon monoxide 4 to 5 at −183°, and water is 3 at 20°. It is of interest to note that for carbon dioxide at −78° on Alloy B (reduced) n is 5. Generally in the case of Alloy A the slopes are less and the values of n are about twice as great as those for Alloy B. This point deserves further consideration in light of the interpretation of n as a measure of the departure of the sorbed film from that of an ideal two dimensional gas.

Langmuir Isotherm.—The Langmuir equation more satisfactorily represents the data over the whole range except at lowest pressures where the deviation is in the direction of greater volume sorbed than that required by the relation. This is shown in Fig. 7 in which typical isotherms are plotted as p/v against p and a linear relation is obtained down to about 0.01 cm. pressure. It is of

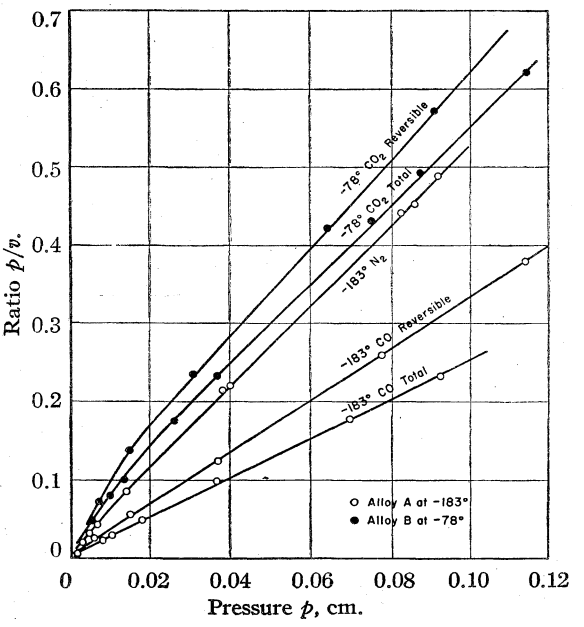


Fig. 7.—Typical isotherms for several gases on stainless alloys plotted as p/v against p.

significant interest to note that for the particular gas carbon monoxide on Alloy A this deviation at lowest pressure is least marked but for the same gas on Alloy B very marked deviation is evident below about 0.015 cm. as shown in a separate p/v against p plot given in Fig. 8. More marked deviation in this pressure range has generally been observed as characteristic of a reduced and not of an unreduced surface in the study of mild steels.[5] Possibly this may be interpreted as indicating more free metal or less oxide on alloy B than on Alloy A. If the Langmuir isotherms for carbon monoxide at −183° shown in Fig. 8 are considered further, the curves for Alloys B and A seem analo-

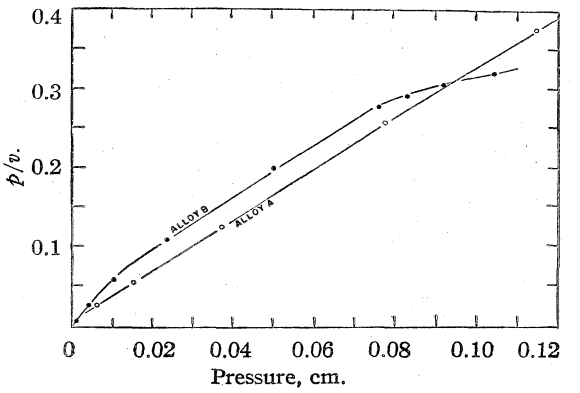


Fig. 8.—Isotherms for reversible sorption of CO at −183° plotted to show deviation from Langmuir relation.

gous in form to those for ethyl iodide on a reduced and unreduced surface of iron, respectively,[8] where there is evidence of a second layer forming on the reduced surface. The curve for Alloy B not only shows more marked deviation at lowest pressures but at higher pressures intersects the curve for Alloy A at about 0.095 cm. indicating that above this pressure the concentration of adsorbed carbon monoxide is greater on Alloy B than on Alloy A. In the intermediate pressure range the two curves are linear and have the same slope which shows that the same amount of gas is required as the limiting volume sorbed to complete a monolayer on the two surfaces. Then the increased adsorption at highest pressure for Alloy B may represent the beginning of a second layer and this behavior, by analogy with the increased adsorption of ethyl iodide on reduced but not on unreduced iron, suggests that the surface of Alloy B may be reduced to a higher degree than that of Alloy A. This deduction supports the earlier conclusion drawn from the adsorption behavior at lowest pressure that there may be less oxide or a lower oxide on Alloy B than on Alloy A.

Combined Form of Equation.—The isotherms may be represented over the entire range by a combined form of the Freundlich and Langmuir equations, namely,

$$v = v_s \sqrt[n]{ap/(1 + ap)}$$

in which a and n are constants, n corresponding to the value determined from the slope of the Freundlich plot for a particular temperature and system.

Comparison of Data

Reduced Surface.—The applicability of the Langmuir equation makes it possible to compare the results in terms of v_s, the so-called limiting volume sorbed, as obtained from such a plot. This comparison is made in Table I which contains: (a) the values of v_s derived from the Langmuir plot; (b) the per cent. surface coverage

(8) Armbruster and Austin, THIS JOURNAL, **61**, 1119 (1939), Fig. 3.

TABLE I

VALUES OF THE LIMITING VOLUME SORBED (v_s), OF THE RATIO OF v_s TO THAT FOR REVERSIBLE CARBON MONOXIDE AT −183°, AND OF THE APPARENT COVERAGE OF THE REDUCED SURFACE

Temp., °C.	Gas	Type of sorption	v_s (cc. at 20°, 76 cm.) Alloy A	v_s (cc. at 20°, 76 cm.) Alloy B	Apparent surface coverage, % Alloy A	Apparent surface coverage, % Alloy B	v_s (gas at temp.)[a] / v_s (rev. CO −183°) Alloy A	v_s (gas at temp.)[a] / v_s (rev. CO −183°) Alloy B
−183	A	Strongly held	0.020	0.017	6	4	0.07	0.05
	N_2	Total (reversible)	.197	.122	68	42	.65	.40
	CO	Total	.394	.455	135	155	1.30	1.43
	CO	Reversible	.304	.315	104	108	1.00	1.00
	CO	Chemisorbed	.090	.136	31	47	0.30	0.43
− 78	CO	Total (chemisorbed)	.070	.045	24	15	.23	.14
	CO_2	Total	.165	.199	61	74	.54	.63
	CO_2	Reversible	.146	.178	54	66	.48	.57
	CO_2	Strongly held	.019	.021	7	8	.06	.06

[a] Corresponding ratios with nitrogen at −183° as standard for comparison may be obtained by multiplying the factor for Alloy A and B by 1.54 and 2.58, respectively.

derived from v_s, the known geometric area and cross sectional area of the molecule[9]; and (c) the ratio v_s/v_s (reversible CO −183°), the relative number of molecules sorbed per unit area, a ratio in which it may be assumed that v_s is a measure of the concentration of molecules in a close packed monolayer and that v_s (reversible CO −183°) is a measure of the specific area of the surface. Whereas the per cent. coverage in the middle two columns is merely an apparent coverage, the ratio in the last two columns shows, on the basis of these assumptions, the extent to which the surface is covered by a monolayer and reduces the data to constant specific area.

Several deductions are possible from this comparison, together with our experience with mild steels at low pressure and the investigations of Emmett and Brunauer of iron catalysts, pure and promoted[10,11] at considerably higher pressure: (1) Argon is very slightly sorbed and so strongly held that it cannot be removed by pumping at temperature. Furthermore the amount of argon sorbed at −183° is practically the same as that of the chemisorbed carbon dioxide at −78°, namely, 5–7 and 6% surface coverage, respectively, for the two alloys. This is shown in Fig. 3 in which the chemisorbed carbon dioxide curve is the difference between the total and the reversible sorption data. These gases may, therefore, be sorbed on the same places, such as cracks, grain boundaries and virtual depressions on the surface. Similar strong adsorption has been reported in earlier study: for example, of argon and carbon monoxide on mica[12] in which the sorbed molecules appeared to be held in positions vacated by potassium ions during cleavage. Likewise argon, carbon monoxide and nitrogen strongly held on unreduced iron surfaces may be held on certain positions on the surface, resulting from the structure of the oxide film, on which the sorbed gas comes so close to oxygen atoms that the van der Waals forces are stronger. The existence of such sites on stainless alloy surface could explain the constant fraction (about 6 per cent.) of the surface covered by argon at −183° and chemisorbed carbon dioxide at −78°.

(2) All sorption, except for carbon monoxide, is less than a monolayer, even that of argon and nitrogen. Argon does not give a measure of surface area and one cannot be sure of nitrogen, since the limiting volume of nitrogen sorbed is only one-half that of reversibly sorbed carbon monoxide. If nitrogen were taken as a standard, as can readily be done by multiplying the values in the last two columns of Table I by the factor 1.54 and 2.58, respectively, and the limiting volume be assumed to correspond to a monolayer, it yields a true surface area only one-half that of the known geometric area, which is not reasonable. Also, reversible carbon dioxide at −78° as a measure of surface area is certainly in question. Hence the significant result follows that for a stainless alloy only the reversible sorption of carbon monoxide at −183° is a reliable measure of the surface area in the low pressure range studied. In contrast, Emmett and Brunauer[10] find for pure iron catalysts the same surface area is given by nitrogen −183°, carbon monoxide reversible −183° and carbon dioxide reversible −78°. Their work is at considerably higher pressure and applies an equation derived for multimolecular adsorption which, at low pressure, is formally identical to the Langmuir equation. Our experience with mild steels, reduced and unreduced, shows that nitrogen (−183°), carbon monoxide reversible (−183°) and argon reversible (−183°) may form a complete monolayer but that carbon dioxide reversible (−78°) is certainly in question.

(3) The following points deal with the sorption of carbon monoxide: (a) In all the reduced samples studied the total sorption of carbon monoxide at −78° is strongly held; there is no reversible sorption of this gas at −78° although this occurs at −183°. (b) Comparing carbon monoxide chemisorbed at −183° and at −78°, it is seen that

(9) The values for the cross sectional areas of the molecules are the same as cited previously in reference 3.

(10) Emmett and Brunauer, THIS JOURNAL, **59**, 1553 (1937).

(11) Emmett and Brunauer, *ibid.*, **59**, 310 (1937).

(12) Armbruster and Austin, *ibid.*, **60**, 467 (1938).

for Alloy A, carbon monoxide chemisorbed (−183°) is only slightly greater than at −78°, whereas for Alloy B, the chemisorption at −183° is three times greater than at −78°. In the work with mild steels, reduced, the chemisorbed carbon monoxide at −78° varied in amount from none to the same as that at −183°. Emmett and Brunauer[10] state that the chemisorption of this gas at the two temperatures is the same, though Brunauer[13] later mentions that with strongly sintered iron surfaces this chemisorption of carbon monoxide may be decreased and the binding forces of gas to iron may be weakened. (c) On Alloy B, carbon monoxide is chemisorbed at −183° in greater amount than on Alloy A. If carbon monoxide is considered sorbed on free metal, the fact that this corresponds to 30% and 43% for Alloys A and B, respectively, indicates that there is proportionally more free metal on Alloy B. Evidence afforded by the form of the isotherms supports further this conclusion. (d) It has been suggested that carbon monoxide chemisorbed at −183° may be not only a direct measure of the free metal present but also an indirect measure of the amount of oxide. Emmett and Brunauer[10] concluded that carbon monoxide chemisorbed at −183° is equivalent to van der Waals adsorption (a monolayer) if no oxide exists, but that if oxide is present chemisorbed carbon monoxide at −183° is less than a monolayer by an amount corresponding to the oxide. On this basis, if the chemisorbed carbon monoxide at −183° on Alloys A and B is 30 and 43%, respectively, which is less than a monolayer and indicates oxide exists, the corresponding oxide is 70 and 57%.

(4) Nitrogen may perhaps be sorbed on the non-metallic part of the surface of these alloys. The fact that sorption of nitrogen appears to be unreliable at the low pressures used in the present work as a measure of total surface area on these alloys, suggests that it is sorbed on some definite portion of the surface. For Alloys A and B the coverage is 65 and 40%, respectively, so that possibly the nitrogen-sorbing portion of the surface of Alloy B is less. Direct comparison of the ratio of nitrogen sorbed on Alloy A to that on Alloy B at definite pressure over the range studied can be made from the data presented in Fig. 1. This ratio varies from 1.76 to 1.64 over the pressure range 0.005 to 0.1 cm. which suggests, by its constancy, that the difference in nitrogen sorption on the two alloys is due to a difference in area of the nitrogen-sorbing portion of the surface and, by its value, that this portion of the surface is 60% greater for Alloy A. Lastly, if for Alloys A and B it is assumed that nitrogen is sorbed on metal, one would expect (*cf.* 3c and d) 30 and 43% coverage, respectively; but, if it is assumed that nitrogen is not sorbed on metal, one would expect 70 and 57% coverage, respectively, which is in better agreement with observation.

(13) Brunauer, private communication to Beebe and Stevens, THIS JOURNAL, 62, 2134 (1940), footnote 14.

Sorption of Oxygen, −183°.—Typical data for the sorption of oxygen at the several temperatures are shown graphically in Fig. 4 to facilitate separate consideration. The surface of Alloy A in the reduced condition chemisorbs oxygen equivalent to a film two molecules thick; it also sorbs physically about one-fifth of a monolayer of oxygen. The concentration of oxygen sorbed reversibly is less than that of the other gases sorbed physically at this temperature: 80% less than reversible carbon monoxide which is considered as corresponding to a monolayer; 70% less than nitrogen which corresponds to one-half monolayer. In the case of a reduced mild steel the concentration of oxygen sorbed reversibly is the same as nitrogen and is equivalent to a monolayer. The relatively larger amount of chemisorption as compared to physical sorption is characteristic of a reduced rather than an unreduced steel surface.

Of this sorption a large amount is taken up instantaneously and the remainder over a period of hours. For instance, when the freshly reduced surface of Alloy A was exposed to oxygen at a pressure of 0.0325 cm. a volume of 0.394 cc. was sorbed instantaneously followed by a slower sorption in which 0.397 cc. had been sorbed at the end of an hour and the oxygen pressure had fallen to 3×10^{-5} cm. The instantaneous sorption is equivalent to a concentration of 0.892×10^{-15} molecules/sq.cm. which corresponds to a complete monolayer of sorbed oxygen atoms upon which the slower sorption may take place.

The rate of adsorption is initially very rapid and subsequently falls off gradually. The rate of the slow sorption which follows the instantaneous one obeys the equation for a first order reaction, expressed as

$$\log v_e/(v_e - v) = kt$$

v being the volume sorbed at time t, v_e that sorbed at equilibrium and k the rate constant. Values of k thus calculated are given in Table II and approximate 8.1×10^{-5} sec.$^{-1}$, that is, about 0.008% of the oxygen present is sorbed per second.

TABLE II

REACTION VELOCITY CONSTANT FOR SORPTION OF OXYGEN AT −183° ON REDUCED ALLOY A

(v_e = 0.273 cc.)

t, sec.	v, cc.	$v_e - v$, cc.	$k = \log(v_e/v_e - v)/$
90	0.008	0.265	14.2×10^{-5}
300	.020	.253	11.0
600	.029	.244	8.12
1200	.055	.218	8.13
2100	.089	.184	8.17
3660	.135	.138	8.09
4800	.161	.112	8.13
7200	.201	.072	8.04
9600	.227	.046	8.05
12300	.245	.028	8.03
15300	.256	.017	7.98
23520	.269	.004	7.70

This is not appreciably greater than the rate observed with mild steel where $k = 1.4 \times 10^{-5}$ sec.$^{-1}$ for the reduced and the unreduced surface.

The energy of activation, E, has been estimated from the rate data by means of the relation

$$\frac{\text{no. of molecules sorbed/sq. cm./sec.}}{\text{no. of molecules striking/unit surface/sec.}} = e^{-E/RT}$$

in which $R = 1.987$ cal./deg./mole and T is the absolute temperature; it is also assumed that the adsorbed gas behaves ideally and forms a mobile layer.[14] For example, at about 0.1 mm. pressure the numerator and denominator become 1.23×10^{11} and 6.54×10^{19} molecules/sq. cm./sec., respectively, so that E is 3600 cal.

Sorption of Oxygen, −78° and 20°.—At −78° the oxygen chemisorbed on reduced Alloy A corresponds to about three layers and at 20° to about five layers. In each case, a large sorption, too rapid for measurement of its rate, occurs. The amount of oxygen instantly sorbed varies with the initial oxygen pressure: if this is less than about 0.001 cm., the sorption is instantaneous; if greater, part of the sorption is instantaneous and part slow. As illustration, 0.80 cc. was instantly sorbed at −78° and 1.0 cc. at 20°, which represents a sorbed layer two and three molecules thick if the specific area of the surface is considered unity. At these temperatures the rate of the slow reaction, after making correction for the instantaneous one, does not follow the first order reaction equation but is a logarithmic function of time as shown in Fig. 9 for oxygen at 20°.

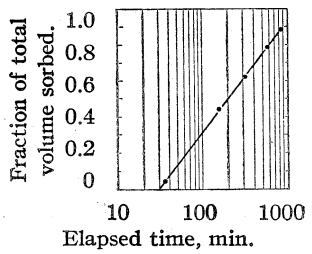


Fig. 9.—Logarithmic rate of formation of oxide film at 20° on reduced surface of alloy A.

All of these observations are quite similar to those reported for mild steel[15] and support the conclusion that the mechanism of the oxidation process of the stainless alloy as well as of iron is determined by the temperature.

The relative number of molecular layers of oxygen sorbed on stainless Alloy A and mild steel #1[3] are arbitrarily compared in Table III. For each sample, the coverage was estimated in the two ways used to obtain the middle two and last two columns of Table I, namely (a) from the limiting volume of nitrogen sorbed, the cross sectional area of the oxygen molecule, and the geometric area of the surface, and (b) from the ratio of the limiting volume of oxygen sorbed at a given temperature to that of carbon monoxide reversibly sorbed at −183°, the latter being assumed to correspond to a close packed monolayer. These two ways of estimating the coverage or thickness of the sorbed oxygen layer show good agreement. The samples are similar in that the total sorption at all temperatures is large, and the chemisorption is relatively much larger than the physical sorption at −183°. The sorption on the stainless alloy, however, is always less than on the mild steel; at −183° the reversible and chemisorption are one-third and two-thirds, respectively, of that on the mild steel and at −78 and 20° about one-half. This difference is one of degree and may well be attributed to the replacement of iron atoms by chromium and nickel, the presence and distribution of which on the surface of a crystal of solid solution may alter the structure, and nature of the oxygen film.

TABLE III

COMPARISON OF NUMBER OF LAYERS OF OXYGEN SORBED ON STAINLESS ALLOY A AND MILD STEEL 1[a]

Temp., °C.	Type of sorption	Stainless alloy A number of layers: Comparison with CO rev.	Stainless alloy A number of layers: From known area	Mild steel 1 number of layers: Comparison with CO rev.	Mild steel 1 number of layers: From known area
−183	Total	2.3	2.1	3.1	3.8
	Reversible	0.18	0.16	0.9	1.1
	Strongly held	2.1	1.9	2.2	2.7
− 78	Total (chemisorbed)	2.8	3.1	5.1	6.0
20	Total (chemisorbed)	4.0	4.5	8.6	10

[a] Complete data for this steel are reported in previous papers.[3,5]

Unreduced Surface −78°.—The data for the sorption of carbon monoxide and carbon dioxide at −78° on reduced Alloy A are compared with the results for the same alloy in the unreduced condition in Table IV. The chemisorption of carbon monoxide at −78° is more than twice as great on the reduced surface as the ratio shows, a fact which supports the assumption that carbon monoxide is chemisorbed on free metal. A noticeable difference in the case of the unreduced surface is that a large part of the sorption of carbon monoxide is reversible. As to carbon dioxide, the

TABLE IV

RATIO OF LIMITING VOLUME v_s (RELATIVE NUMBER OF MOLECULES) OF THE GASES SORBED AT −78° ON REDUCED SURFACE TO THAT ON UNREDUCED SURFACE OF ALLOY A

Gas	Type of sorption	v_s red.	v_s unred.	Ratio, red./unred.
CO_2	Reversible	0.146	0.138	1.04
CO_2	Total	.165	.170	0.97
CO_2	Chemisorbed	.019	.032	.59
CO	Reversible	0	.094	..
CO	Total	.070	.124	.56
CO	Chemisorbed	.070	.030	2.33

(14) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, ref. 16, p. 351.

(15) Armbruster and Austin, THIS JOURNAL, 68, 1347 (1946).

ratio of 1.04 for the reversibly sorbed gas indicates that the concentration of molecules in this layer is the same for reduced and unreduced alloy. The number of strongly held molecules of carbon dioxide is about twice as great for the unreduced surface. The greater chemisorption for the unreduced surface, which should be rougher, is in agreement with the earlier supposition that this gas may be held on cracks and grain boundaries.

Heat of Adsorption.—The "average heat of adsorption" on the less active part of the surface has been calculated for gases which are reversibly sorbed at −183° and −78° by the method of Brunauer, Emmett and Teller[16] from the linear, higher pressure, region of the isotherms plotted in Fig. 7. Although this method is usually applied to a higher range of relative pressure (p/p_0, p_0 being the saturation pressure of the gas) the results derived by it are given in Table V for comparison. The heat effects at −183° are 3.2 (±0.2) kcal. per mole for the several gases on these surfaces which is in close agreement with those for the same gases on other metals.[3,5] Such correspondence within the error of calculation for the same gases at a given temperature on surfaces as chemically different in nature as a mild carbon steel and a stainless chromium nickel alloy points to a greater dependence of this heat on the physical state of the surface than its chemical composition or on that of the gas. The heat of sorption for oxygen agrees with that calculated by an independent method from rate data. At −78° this heat quantity for carbon dioxide is about 8 kcal. and is twice as great as the heat of liquefaction of the gas at the same temperature obtained from extrapolation of data.

TABLE V

AVERAGE HEAT OF REVERSIBLE ADSORPTION OF GASES ON STAINLESS ALLOYS AS DERIVED BY THE METHOD OF BRUNAUER, EMMETT AND TELLER

Gas	Temp., °C.	Heat of liquefaction at temp., kcal./mole	Heat of adsorption, kcal./mole Alloy A	Alloy B
N_2	−183	1.33	3.3	3.4
CO	−183	1.41	3.6	3.2
O_2	−183	1.63	3.5	...
CO_2[a]	− 78	3.94	8.3	7.6
CO_2[b]	− 78	3.94	7.5	...
CO_2	− 78	3.94	...	7.4

[a] This adsorption is on the unreduced surface of Alloy A whereas all other data are for the reduced surface. [b] The heat effect on a reduced mild steel (no. 3)[3] is included for comparison of the same gas at the same temperature on a chemically different surface.

Force–Area Curves.—Force–area curves for the sorption of the several gases have been derived by the method of Innes and Rowley[17] and in general are smooth over the whole range of measurement and are displaced from the curve for an ideal two-dimensional gas to an extent characterized by the exponent n of the Freundlich or parabolic equation which represents the isotherm. The force–area curve for the reversible sorption of carbon monoxide at −183° on the reduced surface of Alloy B is shown in Fig. 10. The curve lies well above that for an ideal two-dimensional gas and close to the curve represented by $FA = 4kT$, as might be expected since its isotherm follows the Freundlich relation $v = ap^{1/4}$. In this instance the curve is not smooth but shows a suggestion of a plateau. This behavior was previously observed to be characteristic of a film on a surface which already holds strongly, either physically or chemically, some molecules attached to definite sites; for example, reversible carbon monoxide on reduced mild steel at −183 and −195°, also nitrogen on unreduced mild steel at −195°.[3] In the reversible sorption of carbon monoxide on this stainless alloy the surface already has on it chemisorbed molecules of carbon monoxide; in the adsorption of nitrogen on the same surface no molecules are already strongly held and the curve is smooth. The discontinuity may represent a phase change of the first order resulting from the influence of the strongly held molecules on the more mobile molecules of the reversibly adsorbed layer, showing close resemblance of the phase formed by the condensation of the reversibly sorbed monolayer on a metal or solid to the expanded phase of an insoluble liquid film on water.[18]

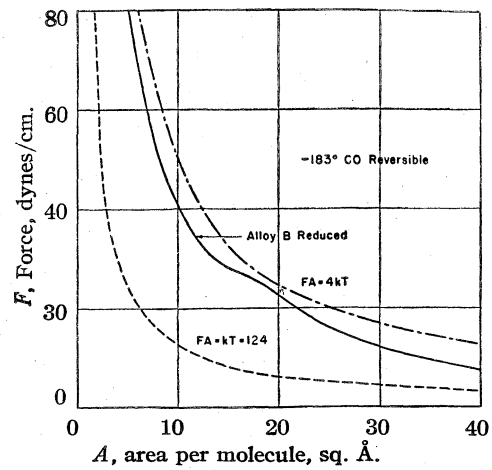


Fig. 10.—Typical force–area curves for film of carbon monoxide sorbed reversibly at −183° on reduced surface of stainless alloy B derived from data plotted as ln (p/v) *versus* v by method of Innes and Rowley.

Summary and Conclusions

The sorption of argon, neon, hydrogen, nitrogen, carbon monoxide, oxygen and carbon dioxide on two stainless iron–chromium–nickel alloys has been measured at −183, −78 and 20° and at pressures up to 0.1 cm. These determinations were made on a surface which had been degreased,

(16) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).
(17) Innes and Rowley, *J. Phys. Chem.*, **45**, 158 (1941).
(18) Harkins, *et al.*, *J. Chem. Phys.*, **10**, 272 (1942); **13**, 535 (1945); **14**, 117 (1946).

outgassed and reduced by hydrogen, and subsequently outgassed; a few measurements were made on the degreased, outgassed surface. The surface was more readily conditioned to reproducibility of the sorption within the error of measurement than for mild steel.

Neon and hydrogen are not measurably sorbed in the range of temperature and pressure studied. Argon is very slightly sorbed at −183° and cannot be removed by pumping at temperature; the magnitude of the sorption is about the same as that of strongly held carbon dioxide at −78°. Nitrogen is sorbed to a greater extent at −183°, sufficient at apparent saturation to cover about one-half of the measured geometric surface and the sorption is completely reversible.

Carbon monoxide is the only gas which is physically adsorbed to as great an extent as a complete monolayer; furthermore the reversible sorption of this gas confirms the measured geometric area of the surface. Hence, it is concluded that at the low pressures used in this work only the reversible sorption of carbon monoxide at −183° is a reasonably reliable criterion of surface area in the case of stainless alloys whereas on mild steels nitrogen and argon are also satisfactory.

The agreement of the sorption data for the two alloys indicates that the surfaces are of the same specific area and this appears to approximate unity.

There is evidence of a tendency to form a second adsorbed layer in the case of Alloy B. Sorption data for Alloy B also show more marked deviation from the Langmuir equation in the lowest pressure region. These observations suggest that the surface of Alloy B is in a more reduced condition than that of Alloy A. Furthermore the proportionally greater chemisorption of carbon monoxide at −183° on Alloy B leads to the conclusion that there is more free metal on this surface.

The sorption of oxygen at −183° consists of a fraction of a monolayer reversibly held and about two monolayers which are chemisorbed. At −78 and 20° three and four layers, respectively, of oxygen are chemisorbed.

KEARNEY, NEW JERSEY RECEIVED NOVEMBER 29, 1947

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Isomerization of Saturated Hydrocarbons. V.[1] The Effect of Cyclohexene upon the Isomerization of Methylcyclopentane and Cyclohexane

BY HERMAN PINES, B. M. ABRAHAM[2] AND V. N. IPATIEFF

It was shown previously[1,3] that under certain carefully controlled conditions aluminum bromide–hydrogen bromide or aluminum chloride–hydrogen chloride did not cause the isomerization of *n*-butane to isobutane unless traces of olefins were present. This study has now been extended to the investigation of the reversible isomerization of methylcyclopentane to cyclohexane using aluminum bromide–hydrogen bromide as the catalyst. A high vacuum technique was used for the purification of materials, and for charging and discharging of the products.

It was found that methylcyclopentane did not undergo isomerization when shaken in a sealed tube for nineteen hours at 25° in the presence of as much as 9 mole per cent. of aluminum bromide[4] and 1 mole per cent. of hydrogen bromide. When the hydrogen bromide concentration was increased to 3.2 mole per cent., the yield of cyclohexane produced was 2%. However, when 0.05 mole per cent. of olefin such as cyclohexene was added to the reaction mixture, 28 mole per cent. of the methylcyclopentane was converted to cyclohexane. By increasing the molal ratio of the cyclohexene from 0.05 to 0.07 and to 0.1 mole per cent. the amount of cyclohexane formed increased to 30 to 38 mole per cent., respectively. The results are summarized in Table I. The amount of methylcyclopentane listed in the above table and in subsequent experiments was 8.00 to 10.00 g. ± 0.001 g.

TABLE I

THE EFFECT OF OLEFINS ON ISOMERIZATION

Reaction time 19 hrs. The amount of methylcyclopentane used in the various experiments varied from 8–10 g.

	Reagents: moles/100 moles methylcyclopentane			
No.	$AlBr_3$	HBr		Analysis mole % cyclohexane
1	1.0	1.0	0.0	0
2	9.0	1.0	.0	0
3	9.0	3.2	.0	2
4	9.0	1.0	.05	28
5	9.0	1.1	.07	30
6	9.0	1.0	.10	38
7	1.0	1.0	.20	58

A 58% yield of cyclohexane was obtained when the concentration of cyclohexene added was 0.2 mole per cent.; in this particular experiment the

(1) The previous paper of this series was marked as "Isomerization of Alkanes. IV," see H. Pines and R. C. Wackher, THIS JOURNAL, **68**, 2518 (1946).

(2) Universal Oil Products Company Postdoctoral Fellow 1946–1947. Present address Argonne National Laboratory, Chicago, Illinois.

(3) H. Pines and R. C. Wackher, THIS JOURNAL, **68**, 595 (1946).

(4) Throughout this paper for the purpose of calculation the aluminum bromide was considered to be monomeric.

concentration of aluminum bromide was 1 mole per cent. instead of the usual 9 mole per cent. In the absence of hydrogen bromide, aluminum bromide does not isomerize methylcyclopentane even in the presence of olefins.

Cyclohexane reacted in the presence of an aluminum bromide–hydrogen bromide catalyst in a manner similar to methylcyclopentane. Isomerization did not occur when a solution consisting of 100 mole per cent. of cyclohexane was treated for nineteen hours at 25 ± 0.1° with 2.00 mole per cent. of aluminum bromide and 0.99 mole per cent. of hydrogen bromide. In the presence, however, of 0.107 mole per cent. of cyclohexene, 9% of cyclohexane isomerized to methylcyclopentane.

In order to determine the effect of the different variables upon the degree of isomerization of methylcyclopentane, the effect of hydrogen bromide and aluminum bromide concentration was investigated.

By maintaining the molal ratio of methylcyclopentane to aluminum bromide and to cyclohexene (cyclohexyl bromide) constant at about 100:9.0:0.08 and by varying the concentration of hydrogen bromide a definite trend in the degree of isomerization was observed. This effect was most pronounced when the concentration of hydrogen bromide was raised from 1.1 to 3 mole per cent.; in this case the degree of isomerization increased from 30 to 78%. Under similar conditions but in the absence of hydrogen bromide and cyclohexyl bromide no isomerization of methylcyclopentane was observed; this definitely establishes that the initiator is the alkyl halide or its equivalent. The results are summarized in Table II.

TABLE II

THE EFFECT OF HBr CONCENTRATION ON ISOMERIZATION

No.	Reaction time, hours	Reagents: moles/100 moles hydrocarbon $AlBr_3$	HBr		Analysis mole % cyclohexane
8	19	9.1		0.08[a]	17
9	19	8.9	0.02	.08[a]	25
10	19	9.1	0.28	.08	20
11	19	9.0	1.1	.07	30
12	19	9.1	3.0	.08	78
13	1	1.6	1.0	.1	19
14	1	1.0	3.1	.1	36
15	1	1.0	1.0	.1[a]	21
16	1	1.0	0	.1	0

[a] Olefin added as cyclohexyl bromide.

An increase in the isomerization of methylcyclopentane with an increase of hydrogen bromide concentration was also noticed when the aluminum bromide was maintained at lower concentrations and the contact time was one hour instead of the usual nineteen hours.

It was found that by decreasing the aluminum bromide concentration from 9 to 1 mole per cent. based on methylcyclopentane present and maintaining the molal concentration of hydrogen bromide at 1 and of cyclohexene at 0.1 mole per cent., the degree of isomerization within the experimental error was unchanged (Table III, Experiments 6 and 21). These results show that even 1 mole per cent. of aluminum bromide under the experimental conditions used seems to be in excess of that required to catalyze the isomerization. At about 9 mole per cent. concentration aluminum bromide is near the saturation point at 25°.

TABLE III

THE EXTENT OF ISOMERIZATION WITH TIME

No.	Reaction time, hours	Reagents: moles/100 moles hydrocarbon $AlBr_3$	HBr		Analysis mole % cyclohexane
17	0.5	1.0	1.0	0.10	12
18	1.0	1.0	1.0	.10	21
13	1.0	1.6	1.0	.10	19
19	1.25	9.0	0.9	.10	23
20	2.0	2.0	1.0	.10	34
21	19	1.0	1.1	.10	40
6	19	9.0	1.1	.10	38

The isomerization catalyst comprised of aluminum bromide–hydrogen bromide and promoted by cyclohexene loses its activity with time. This was shown in Experiment 22 (Table IV) in which methylcyclopentane was treated by this catalyst for a period of nineteen hours; a sample was then withdrawn for analysis and the contents of the reaction tube were diluted with an equal volume of methylcyclopentane; the tube was agitated for an additional nineteen hours at 25°. It was found that no additional isomerization occurred. These results suggested that the isomerization reaction must have stopped before the first nineteen-hour period was ended. This was shown more clearly in Experiment 20 (Table IV) in which the reaction was carried out for only two hours; the hydrocarbons were then withdrawn and the reaction tube was recharged with fresh methylcyclopentane and with the recovered hydrogen bromide. The tube was then agitated for two hours at 25°. From the results obtained it is seen that the reaction was almost complete during the first two hours.

On the basis of the above-described experiments it was believed that the loss of the catalyst activity was due primarily to the disappearance of the promoter through secondary reactions. This was demonstrated more clearly in Experiment 23 in which methylcyclopentane was treated with aluminum bromide–hydrogen bromide promoted by 0.11% of cyclohexene. After nineteen hours a small sample was withdrawn for analysis; it contained 38% of cyclohexane. In order to be certain that the catalyst had lost its activity, the reaction tube was resealed and shaken in the constant temperature bath for an additional nineteen

TABLE IV

THE STUDY OF CATALYTIC ACTIVITY AS A FUNCTION OF TIME AND INITIATOR: THE CHANGE IN CATALYST ACTIVITY WITH TIME

	Reagents: initial charge, moles/100 mole of methylcyclopentane							
	First period					Second period		
Expt.	Reaction time, hours	$AlBr_3$	HBr		Analysis, mole % cyclohexane	Reaction time, hours	Second charge, moles hydrocarbon	Analyses mole % cyclohexane
22	19	2.0	0.9	0.09	28	19	93[a]	14
20	2	2.0	1.0	.10	34	2	100[b]	9
23	19	1.0	1.0	.11	38[c]	19	0.12[d]	80

[a] Removed equivalent of 7 moles for analysis; diluted with an equivalent of 93 moles of methylcyclopentane. [b] Replaced first batch of hydrocarbon. The hydrocarbons from the first period of reaction were removed and replaced with 100 mole equivalent of fresh methylcyclopentane. [c] The reaction was continued for an additional nineteen hours between first and second period. No additional isomerization occurred. [d] Cyclohexene was added to the reaction mixture.

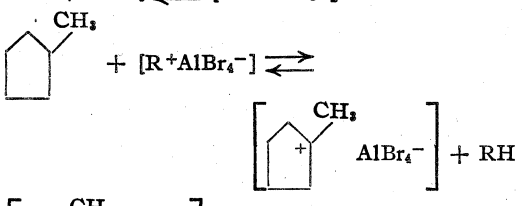
hours and then retested; it was found that no further isomerization occurred. The introduction, however, of 0.12% of cyclohexene restored and increased the activity of the catalyst; the reaction mixture after this treatment consisted of 80% cyclohexane.

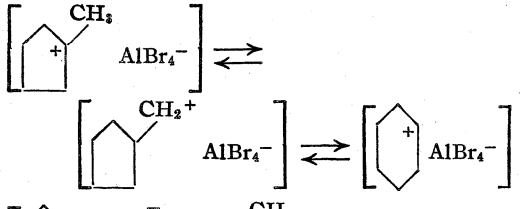
Discussion of Results

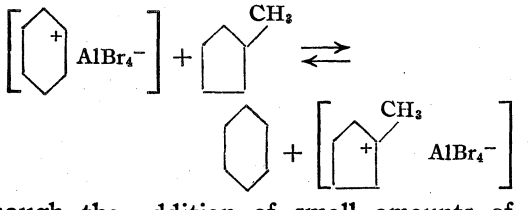
The experimental data given above indicate that under controlled conditions methylcyclopentane does not undergo isomerization in the presence of aluminum bromide–hydrogen bromide catalyst unless traces of cyclohexene or cyclohexyl bromide are present. These results are in accordance with a similar observation made when isomerizing *n*-butane[3] and can be explained by the following chain mechanism similar to that suggested for *n*-butane.[5]

Eq. 1 R^0 (olefins) + HBr $\rightleftharpoons$ RBr

Eq. 2 RBr + $AlBr_3$ $\rightleftharpoons$ $[R^+ AlBr_4^-]$

Eq. 3 

Eq. 4 

Eq. 5 

Although the addition of small amounts of cyclohexene or cyclohexyl bromide causes the isomerization to proceed, in no case was an equilibrium mixture of methylcyclopentane and cyclohexane obtained,[6] this is probably due to a chain-breaking reaction in which the carbonium ion of either of the original additives is involved or the one formed through a hydrogen transfer reaction as exemplified by Equation 3. The chain-breaking can be caused by such reactions as conjunct polymerization,[7] cycloalkylation, or condensation which involves a transfer of hydrogen.[8] The conjunct polymerization involves the transformation of the olefins into saturated hydrocarbons of the same or higher molecular weight and the formation of highly unsaturated hydrocarbons which form a complex with the catalyst which is insoluble in hydrocarbons. This might explain the formation of an oily film during isomerization which can be detected on the walls of the reaction tube. The conjunct polymerization is probably one of the chief reactions causing the destruction of the carbonium ions; this reaction is relatively rapid and pronounced when the concentration of the olefins is relatively high. For that reason, in order to obtain the most benefit from the olefins added, it is preferred that the olefins be not added at once but at intervals and in small quantities. This is brought up in Table IV.

Experimental

A high vacuum apparatus similar to that reported previously[3] was constructed (Fig. 1); all liquid reactants once purified in this apparatus were kept out of contact with air or moisture.

The aluminum bromide was a resublimed commercial grade which was further purified by a vacuum sublimation through a series of constrictions into a receiver. This receiver contained several weighed and numbered capsules. To fill these capsules the following procedure was adopted: A few millimeters pressure of dry air was admitted to the line and the aluminum bromide was heated to the melting point; as soon as the salt became molten an atmosphere of dry gas was admitted thus forcing the molten salt into the capsule. After the material had solidified the capsules were removed from the line, sealed and reweighed. Each capsule contained from 1.7–2.2 g. of aluminum bromide. In Fig. 2 is illustrated the reaction tube with an aluminum bromide capsule in place.

(5) H. S. Bloch, H. Pines and L. Schmerling, THIS JOURNAL, **68**, 153 (1946).

(6) The equilibrium mixture at 25° consists of 88% of methylcyclopentane and 12% of cyclohexane.

(7) V. N. Ipatieff and H. Pines, *J. Org. Chem.*, **1**, 464 (1946).

(8) H. Pines and V. N. Ipatieff, *ibid.*, **6**, 242 (1941); THIS JOURNAL, **70**, 531 (1948).

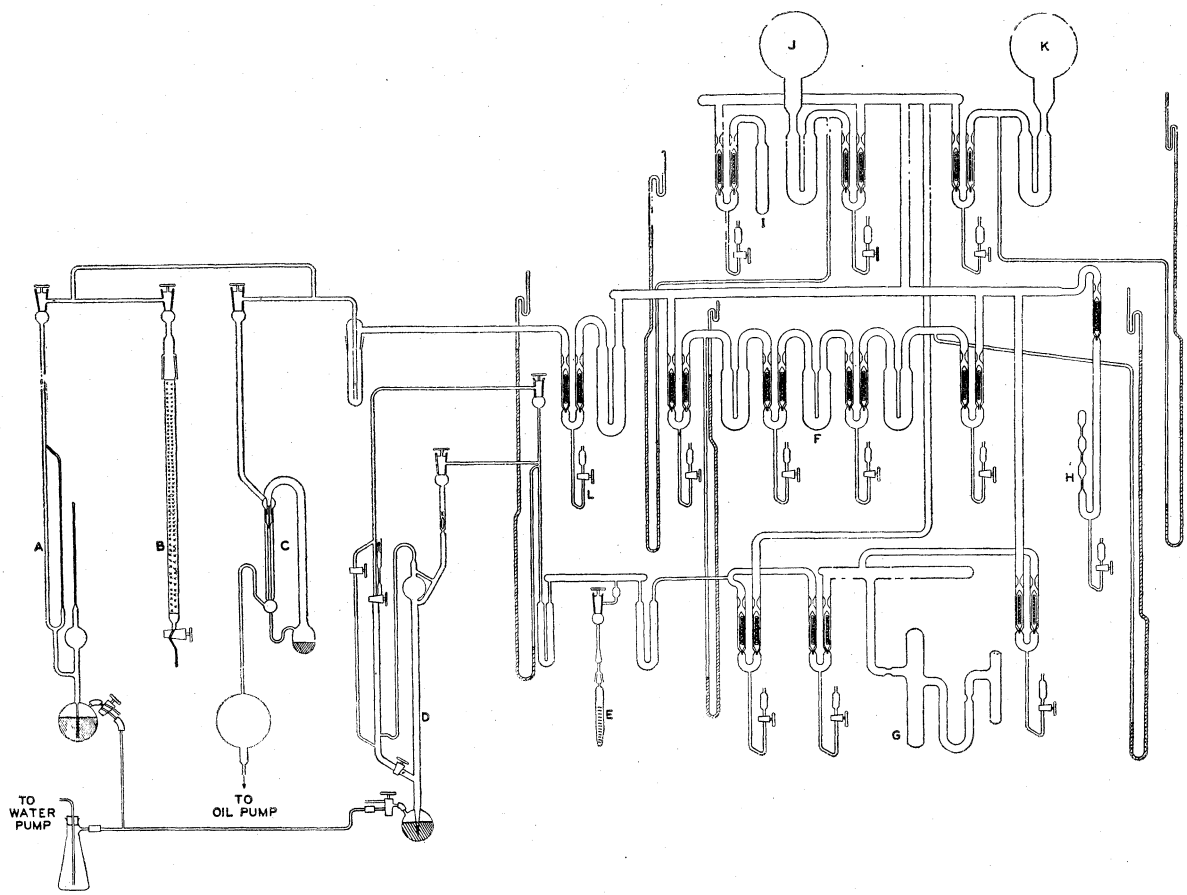


Fig. 1.—Isomerization apparatus: A, McLeod gage; B, phosphorus pentoxide drying tower; C, mercury diffusion pump; D, Toepler pump; E, sample inlet; F, fractionation system; G, reaction tube; H, small volume aliquoting tube; I, cyclohexene storage; J, gaseous olefins storage; K, hydrogen bromide storage; L, stock valve.

The methylcyclopentane used in this work was prepared from cyclohexane by catalytic isomerization; this was accomplished by refluxing the cyclohexane in the presence of aluminum chloride activated by the addition of about 2–3% of water. The methylcyclopentane thus formed, boiling lower than its isomer, was continuously removed on a 50-plate column. The distillate which contained 85–90% methylcyclopentane was washed with alkali, dried, and redistilled on a 100-plate column. The methylcyclopentane fraction used in these experiments did not show any impurities as determined by index of refraction, $n^{20}D$ 1.4100, or by infrared or ultraviolet spectroscopy. The methylcyclopentane thus obtained was weighed out to give the proper molal ratio for a given aluminum bromide capsule. The liquid was then distilled into a numbered tube which contained liquid sodium–potassium alloy and stored until used (Fig. 3).

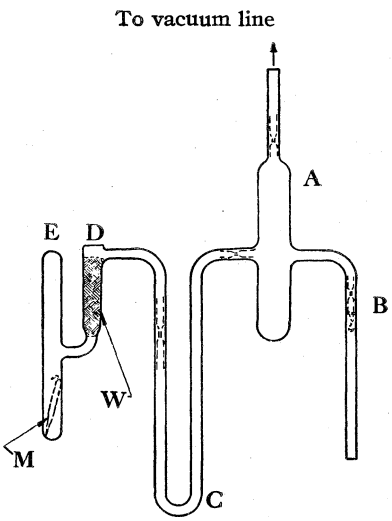


Fig. 2.—Reaction tube: W, glass wool; M, aluminum bromide.

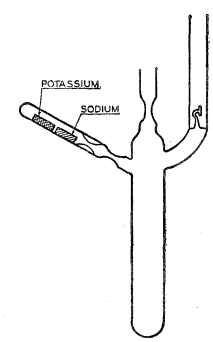


Fig. 3.—Hydrocarbon purification tube.

The cyclohexene was stored *in vacuo* over sodium–potassium alloy and removed as needed. The olefin was measured as a gas in one of the calibrated U tubes on the apparatus (Section F, Fig. 1).

Hydrogen bromide was prepared by dropping bromine on tetralin. The material was fractionated on the line, discarding generous first and last fractions. The middle fraction which had a dry-ice–ether vapor tension of 400

mm. ("International Critical Tables" value 401 mm.) was stored in a 5-liter bulb (Section K, Fig. 1).

The experimental technique used was as follows: A reaction tube (Fig. 2) was sealed on the line (Section G, Fig. 1), evacuated and degassed. Dry air was then admitted through a phosphorus pentoxide drying column and a small hole was blown in the side tube (Section E, Fig. 2). An aluminum bromide capsule was then dropped into the side-arm after the tip had been broken. The hole was sealed and the tube re-evacuated. When the pressure had dropped to *ca.* 10^{-3} mm. of mercury the aluminum bromide was sublimed through the glass wool, into the U-tube (Section C, Fig. 2); Sections E and D were sealed off. The aluminum bromide was then sublimed into the reaction tube proper and Section C was sealed off. In later experiments the glass wool in D was eliminated. The oily film which is put on the glass during fabrication was difficult to remove and seemed to influence the results. The methylcyclopentane was next added, then the olefin, and finally the hydrogen bromide. The reaction tube was sealed off the line at A and warmed to room temperature. The tube was then placed in the constant temperature bath and agitated for the period of the experiment.

If no olefin or alkyl halide had been added the solution was clear; however, if either of these compounds was present in the reaction mixture, droplets of light yellow oil—insoluble in the hydrocarbon—were always noticed to be formed on the glass. When cyclohexyl bromide was used, cyclohexene was mixed with hydrogen bromide in equimolal amounts in a small capsule. The sealed capsule was then placed in the reaction tube. In this case all reagents except cyclohexene were added as previously described. After the aluminum bromide had dissolved in the methylcyclopentane, the tip of the capsule was broken by shaking the reaction tube. Immediately the whole solution became turbid and yellow; in a short while the oil separated on the glass. In the light of the variation in the experimental results mixing is a very serious problem with these rapid reactions.

After the agitation period, the tubes were attached to the line by sealing a ground joint on tube B, Fig. 2, and inserting this joint at E, Fig. 1. The tube was opened by dropping an iron weight enclosed in glass on the break-off in tube B, Fig. 2. The volatile gases were tested for the presence of non-condensables such as hydrogen or methane. In no case was more than 0.04 cc. S. T. P. of gas recovered (*ca.* 0.0001 mole per cent.). The value was determined with the aid of the Toepler pump (Section D, Fig. 1). The hydrogen bromide was difficult to separate quantitatively from methylcyclopentane so no analysis was attempted here. The hydrocarbon was analyzed by index of refraction and infrared spectroscopy. In no case did the infrared analysis reveal the presence of constituents other than cyclohexane and/or methylcyclopentane.

Summary

The reversible isomerization of methylcyclopentane to cyclohexane in the presence of aluminum bromide–hydrogen bromide catalyst has been studied using high vacuum technique. It was found that under certain controlled conditions methylcyclopentane does not undergo isomerization to cyclohexane unless cyclohexene or cyclohexyl bromide in amounts of about 0.05 mole per cent. or higher are present.

The effect of olefins, hydrogen bromide, and aluminum bromide concentrations upon the isomerization of methylcyclopentane has been studied.

A mechanism of isomerization has been proposed.

EVANSTON, ILLINOIS RECEIVED DECEMBER 11, 1947

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Synthesis of Syringaldehyde[1]

BY IRWIN A. PEARL

In a study of the separation of guaiacyl from syringyl compounds in fractions obtained from lignin oxidations it was necessary to use large amounts of syringaldehyde. A review of the literature revealed numerous reported syntheses of syringaldehyde,[2-8] but yields were all negligible or low, and syringaldehyde has remained more or less of a laboratory curiosity. However, one obvious synthesis of syringaldehyde has been overlooked by other investigators and that is the series of reactions analogous to the synthesis of vanillin from eugenol.

For years vanillin has been manufactured on a large scale from eugenol (the chief constituent of oil of cloves and cinnamon leaf oil) by two general methods. In the first, eugenol is treated with alkali to isomerize it to isoeugenol which, in turn, is oxidized to vanillin by some mild oxidizing agent, such as nitrobenzene and alkali. In the second method, eugenol is acetylated to protect the hydroxyl group, and the acetyleugenol is oxidized by a strong oxidizing agent, such as dichromate and acid or permanganate. The resulting acetylvanillin is then hydrolyzed to vanillin. The present paper describes a synthesis of syringaldehyde analogous to the first of these vanillin syntheses.

Although the syringyl analog of eugenol is not an easily obtained natural product or article of commerce, its preparation from pyrogallol 1,3-dimethyl ether in good yield has been recorded.[9,10] Pyrogallol 1,3-dimethyl ether is easily prepared by the controlled methylation of pyrogallol according to Krauss and Crede.[11]

(1) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(2) Graebe and Martz, *Ber.*, **36**, 1031 (1903).

(3) Guyot, *Compt. rend.*, **149**, 788 (1909).

(4) Mauthner, *Ann.*, **395**, 273 (1913).

(5) Späth, *Monatsh.*, **41**, 278 (1920).

(6) Pauly and Strassberger, *Ber.*, **62**, 2277 (1929).

(7) McCord, THIS JOURNAL, **53**, 4181 (1931).

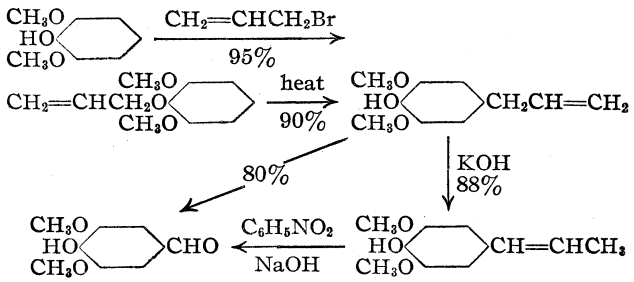
(8) Manske, Ledingham and Holmes, *Can. J. Research*, **23B**, 100 (1945).

(9) Mauthner, *Ann.*, **414**, 252 (1917).

(10) Hahn and Wassmuth, *Ber.*, **67**, 702 (1934).

(11) Krauss and Crede, THIS JOURNAL, **39**, 1433 (1917).

Pyrogallol 1,3-dimethyl ether was treated with allyl bromide in anhydrous acetone in the presence of anhydrous potassium carbonate and yielded 95% of 2-allyloxy-1,3-dimethoxybenzene; this underwent the Claisen rearrangement to 4-hydroxy-3,5-dimethoxyallylbenzene by boiling under reflux at 75 mm. pressure in a yield of 90%. Isomerization of 4-hydroxy-3,5-dimethoxyallylbenzene to 4-hydroxy-3,5-dimethoxypropenylbenzene by the action of alkali proved to be a more difficult problem. The methods ordinarily employed for isomerizing eugenol to isoeugenol were inoperative because the alkali metal salts of 4-hydroxy-3,5-dimethoxyallylbenzene are only slightly soluble in water. The use of aniline as a solvent solved the problem and a high yield of 4-hydroxy-3,5-dimethoxypropenylbenzene and of syringaldehyde was obtained by an adoption of the process described by Bots[12] for preparing vanillin from eugenol. 4-Hydroxy-3,5-dimethoxyallylbenzene was isomerized to 4-hydroxy-3,5-dimethoxypropenylbenzene by boiling with potassium hydroxide in aniline solution. The propenyl derivative could be isolated in 88% yield. Without separation of the propenyl compound, the entire reaction mixture was treated with more alkali and nitrobenzene and heated to yield 80% of syringaldehyde. The reactions involved are shown by the following formulas.



The ultraviolet absorption spectra of these compounds were determined in anhydrous dioxane with a Beckman spectrophotometer at minimum slit width. These spectra are shown in Fig. 1. The curve for syringaldehyde agrees fairly well with that reported by Patterson and Hibbert,[13] who determined their curve in ethanol. However, the present curve shows the fine structure of the principal 3050 Å. band.

The curves for the isomers—2-allyloxy-1,3-dimethoxybenzene, 4-hydroxy-3,5-dimethoxyallylbenzene and 4-hydroxy-3,5-dimethoxypropenylbenzene—illustrate the effect of structure on the ultraviolet absorption spectra and emphasize the difference between a conjugated and unconjugated unsaturated side chain. The double bond only becomes a strong resonator in this portion of the ultraviolet when it is conjugated with the ring. Change from an oxygen–allyl linkage to a carbon–allyl linkage results only in slight bathochromic and hyperchromic shifts. These data concur with those of Patterson and Hibbert for eugenol and isoeugenol.

(12) Bots, U. S. Patent 1,643,805 (Sept. 27, 1927).

(13) Patterson and Hibbert, THIS JOURNAL, **65**, 1862 (1943).

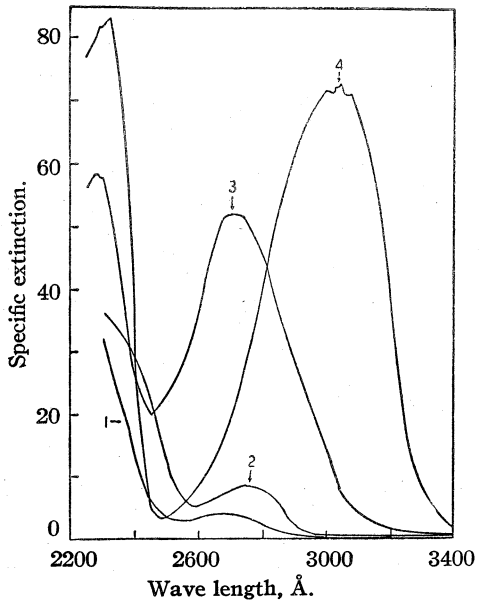


Fig. 1.—1, 2-Allyloxy-1,3-dimethoxybenzene; 2, 4-hydroxy-3,5-dimethoxyallylbenzene; 3, 4-hydroxy-3,5-dimethoxypropenylbenzene; 4, syringaldehyde.

Experimental

All melting points and boiling points are uncorrected.

2-Allyloxy-1,3-dimethoxybenzene.—Pyrogallol 1,3-dimethyl ether (154 g., 1.0 mole) was treated with 121 g. (1.1 mole) of allyl bromide and 180 g. (1.3 moles) of finely powdered anhydrous potassium carbonate in 400 ml. of anhydrous acetone according to the general procedure described by Hahn and Wassmuth.[10] 2-Allyloxy-1,3-dimethoxybenzene was obtained in 184 g. (95%) yield as a colorless fluid oil, b. p. 102° at 2 mm., refractive index $n^{22}D$ 1.5301.

4-Hydroxy-3,5-dimethoxyallylbenzene.—2-Allyloxy-1,3-dimethoxybenzene was boiled under reflux at 75 mm. pressure according to Hahn and Wassmuth[10] to yield 90% of 4-hydroxy-3,5-dimethoxyallylbenzene as a colorless viscous oil, b. p. 123–125° at 2 mm., refractive index $n^{22}D$ 1.5478.

4-Hydroxy-3,5-dimethoxypropenylbenzene.—Into a one-liter flask was placed a mixture of 100 g. of 4-hydroxy-3,5-dimethoxyallylbenzene and 50 g. of potassium hydroxide dissolved in 200 g. of water. The flask was connected to a distillation assembly and heated to boiling. After approximately 75 cc. of water had distilled, the boiling temperature began to rise. When the temperature of the mixture reached 110°, 450 g. of aniline was added and the mixture was distilled again. After about 100 ml. of distillate was collected, the boiling solution became thick with precipitate, but all precipitate dissolved when the last traces of water distilled and the temperature of the mixture began to rise. Approximately 150 ml. of distillate had been collected at this point. The distillation was continued until approximately 100 ml. of aniline was collected. The temperature at this point was 179–180°. The mixture was allowed to cool, and the solid material was treated with an excess of water and extracted with ether. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ether extract was thoroughly washed with dilute hydrochloric acid, and then with water, and finally dried with sodium sulfate and distilled. The residual oil was distilled under vacuum

to yield 22 g. (88%) of 4-hydroxy-3,5-dimethoxypropenylbenzene as a yellow oil, b. p. 107–108° at 0.05 mm., refractive index $n^{27}D$ 1.5741.

Anal. Calcd. for $C_{11}H_{14}O_3$: CH_3O, 31.9. Found: CH_3O, 31.9.

Syringaldehyde.—The above reaction was carried through the cooling stage before the treatment with water. The solidified mixture was covered with 400 g. of nitrobenzene and 135 g. of 50% sodium hydroxide solution, and with vigorous stirring it was boiled under reflux for three hours. The reaction mixture was distilled with steam until almost no oil distilled with the steam. The mixture was then cooled, diluted with water, and extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was extracted with 21% sodium bisulfite solution. The bisulfite extract was acidified with 50% sulfuric acid and aspirated with air while heating on the steam-bath. After all traces of sulfur dioxide were removed, the solution was allowed to cool. The heavy crystals which separated were filtered, washed with water and air dried to yield 53.5 g. (52%) of syringaldehyde melting at 109–110°. Recrystallization from petroleum ether (b. p. 65–110°) yielded very pale yellow needles melting at 109–110°.

Anal. Calcd. for $C_9H_{10}O_4$: CH_3O, 34.07. Found: CH_3O, 34.01.

The aqueous filtrate was extracted with ether, and the ether was dried with sodium sulfate and distilled, leaving an additional 16 g. (23%) of crude syringaldehyde melting at 108–110°. Recrystallization from petroleum ether raised the melting point to 109–110°.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were determined with a Beckman model DU quartz spectrophotometer employing 1.0-cm. quartz cells and minimum slit widths. Measurements were made on freshly and accurately prepared solutions containing approximately 0.02 g. per liter in specially purified dioxane.

Acknowledgment.—The author is indebted to the Analytical Department of The Institute of Paper Chemistry for the analyses and ultraviolet absorption spectra reported in this paper.

Summary

Syringaldehyde has been synthesized from 4-hydroxy-3,5-dimethoxyallylbenzene by nitrobenzene oxidation in aniline solution. The intermediate 4-hydroxy-3,5-dimethoxypropenylbenzene has been isolated and characterized. This method affords a simple procedure for obtaining syringaldehyde from pyrogallol or pyrogallol 1,3-dimethyl ether. All steps in the synthesis give high yields. The ultraviolet absorption spectra of the intermediates have been determined.

APPLETON, WISCONSIN RECEIVED JANUARY 22, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ALBERTA]

Some Derivatives of Dibenzothiophene

BY ROBERT K. BROWN, ROBERT G. CHRISTIANSEN AND REUBEN B. SANDIN

The discovery of the carcinogenic action of the versatile 2-acetaminofluorene (VII) by Wilson, DeEds and Cox[1] has suggested the possibility that 3-acetaminodibenzothiophene might show similar activity. In this communication is described the preparation of this substance and some related compounds.

The orientation and derivatives of dibenzothiophene have been studied extensively by Gilman and co-workers.[2]

Recently Gilman and Nobis[3] have shown that 4-iododibenzothiophene undergoes an interesting rearrangement when treated with sodamide in liquid ammonia to give 3-aminodibenzothiophene.

In the present work it has been found that by using the sulfoxide of dibenzothiophene in which the oxygen is susceptible to reducing agents, a conversion of dibenzothiophene into 3-aminodibenzothiophene in an over-all yield of 45% can be accomplished. The preparation of dibenzothiophene-5-oxide from dibenzothiophene proceeds without difficulty and in high yields. Subsequent mono-nitration and reduction with stannous chloride and concentrated hydrochloric acid also proceed without difficulty and both reactions afford satisfactory yields of the desired products. The step-wise reduction of 3-nitrodibenzothiophene-5-oxide with stannous chloride and dilute hydrochloric acid has also been carried out, and has afforded 3-aminodibenzothiophene-5-oxide in good yield.

(1) Wilson, DeEds and Cox, *Cancer Research*, **1**, 595 (1941).

(2) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); Gilman, Jacoby and Pacevitz, *ibid.*, **3**, 120 (1938).

(3) Gilman and Nobis, THIS JOURNAL, **67**, 1479 (1945).

Experimental[4]

Dibenzothiophene-5-oxide (II).—Dibenzothiophene (I) was prepared by the excellent method of Gilman and Jacoby.[2] For the preparation of the sulfoxide the procedure of Fries and Vogt[5] was used. A solution of 15 g. of I in carbon tetrachloride (150 ml.) was treated at 0–5° with chlorine until 6 g. had been added. The solution became red and the addition compound which was produced was hydrolyzed by vigorously shaking the reaction mixture with ice and water. The solid was filtered off and washed with water. The yield of dibenzothiophene-5-oxide melting at 174–180° was 15.8 g. (97%). It was crystallized from benzene and the yield of pure compound was 12.5 g. (77%); m. p. 185–187°.

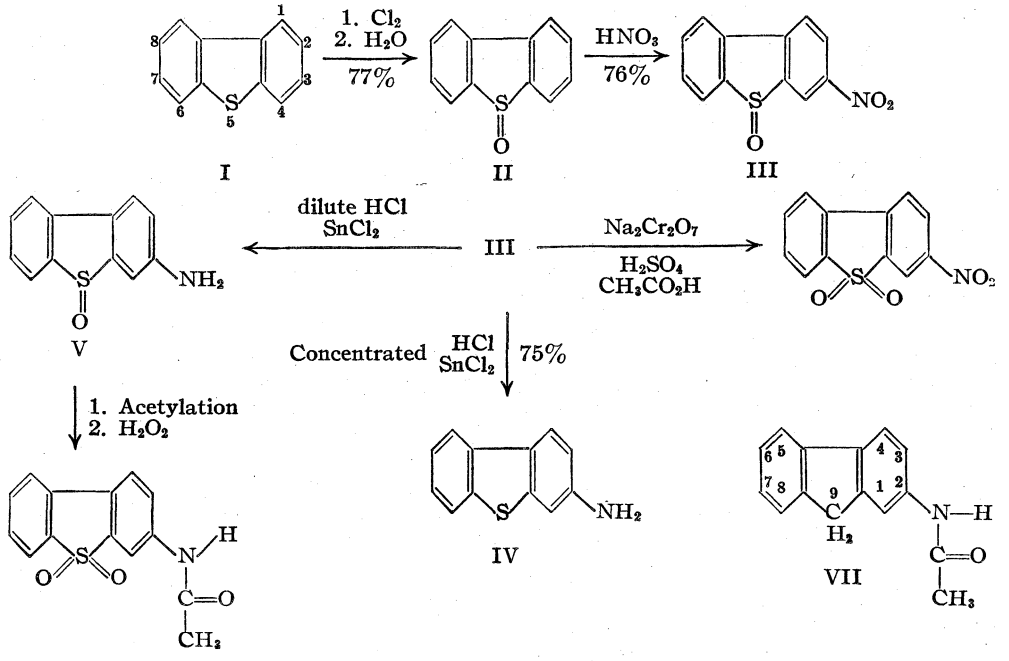
Anal. Calcd. for $C_{12}H_8OS$: S, 16.0. Found: S, 16.15.

The reduction of dibenzothiophene-5-oxide with stannous chloride and concentrated hydrochloric acid afforded an 85% yield of pure dibenzothiophene.

3-Nitrodibenzothiophene-5-oxide (III).—The nitration of II was carried out by the procedure developed by Gilman and Jacoby[2] for the nitration of the corresponding dioxide. To an ice-cold mixture of 15 g. of II, 33 ml. of glacial acetic acid and 33 ml. of concentrated sulfuric acid, was added with stirring 36 ml. of fuming nitric acid (sp. gr. 1.5) during a period of fifteen minutes. After the resulting clear solution had stood at 0–5° for thirty

(4) All melting points are uncorrected.

(5) Fries and Vogt, *Ann.*, **381**, 341 (1911).



minutes, it was poured into 200 g. of cracked ice. The gummy solid which was formed soon hardened and was filtered off and washed with water. The crude material weighed 16.5 g. (87%) and melted at 201–205°. After crystallization from ethyl alcohol the pure 3-nitrodibenzothiophene-5-oxide weighed 14 g. (76%) and melted at 209.5–210.5°.

Anal. Calcd. for $C_{12}H_7O_3NS$: S, 13.06. Found: S, 13.15.

3-Nitrodibenzothiophene-5-oxide was oxidized with a mixture of sodium dichromate, acetic acid and dilute sulfuric acid (1:1). The product after crystallization from acetone was shown to be identical with an authentic sample of 3-nitrodibenzothiophene-5-dioxide.[2]

3-Aminodibenzothiophene (IV).—To a solution of 10 g. of III in 100 ml. of glacial acetic acid was added a solution of 51 g. of hydrated stannous chloride in 65 ml. of concentrated hydrochloric acid. The reaction was exothermic and a solid was formed. After standing at room temperature for twelve hours the solid was filtered off and washed with a mixture of equal parts of glacial acetic and concentrated hydrochloric acid. The amine was liberated with dilute sodium hydroxide solution and the weight of crude material, melting at 113–117°, was 8.1 g. (99%). The pure compound after crystallization from dilute ethyl alcohol weighed 6.1 g. (75%), and melted at 121–122.5°. A mixed melting point with the above amine and the amine prepared by the action of sodamide in liquid ammonia on 4-iododibenzothiophene (kindly furnished by Drs. Gilman and Nobis), was not depressed.

The acetylation of 3-aminodibenzothiophene was readily accomplished by the procedure of Gilman and Nobis.[3] After purification from ethyl alcohol it melted at 196–197°.

3-Aminodibenzothiophene-5-oxide (V).—To a solution of 5 g. of III in 60 ml. of glacial acetic acid was added 26 g. of hydrated stannous chloride in 40 ml. of dilute (6 *N*) hydrochloric acid. The reaction mixture was kept at 40° for thirty minutes and then allowed to stand at room temperature for three hours, after which it was cooled to 0° and the yellow solid was then filtered off. The amine was liberated with sodium hydroxide solution and afforded 4 g. (91%) of compound melting at 206–207.5°. The light yellow compound slowly darkened on exposure to air. For analytical purposes it was crystallized from dilute alcohol, m. p. 208–209°.

Anal. Calcd. for $C_{12}H_9ONS$: S, 14.87. Found: S, 15.05.

The amino sulfoxide is sensitive to heat and for that reason a temperature below 60° during the process of crystallization is desirable.

3-Acetaminodibenzothiophene-5-oxide (VI).—To a solution of 1.8 g. of V in 30 ml. of benzene was added 4 ml. of acetic anhydride. The reaction mixture was allowed to stand for twelve hours. The light yellow solid which was formed melted at 262–264°; yield, 95%. It was crystallized from absolute alcohol; m. p. 265–267°.

Anal. Calcd. for $C_{14}H_{11}O_2NS$: S, 12.44. Found: S, 12.47.

The oxidation of VI in glacial acetic acid with 30% hydrogen peroxide afforded 3-acetaminodibenzothiophene-5-dioxide, m. p. 308–310° (cor. m. p. 322–324°). A mixed melting point carried out with an authentic sample of 3-acetaminodibenzothiophene-5-dioxide[3] was not depressed.

Acknowledgment.—The authors are very grateful to the Alberta Branch of the Canadian Cancer Society for financial aid in support of this work. We are also grateful to Drs. J. A. Miller and E. C. Miller of the McArdle Memorial Laboratory, Madison, Wisconsin, for determining the carcinogenic properties of 3-acetaminodibenzothiophene. Their results will be published elsewhere.

Summary

The reduction of 3-nitrodibenzothiophene-5-oxide with stannous chloride and concentrated hydrochloric acid affords 3-aminodibenzothiophene. With stannous chloride and dilute hydrochloric acid reduction to 3-aminodibenzothiophene-5-oxide can be accomplished. Some new derivatives of dibenzothiophene have been prepared.

EDMONTON, ALBERTA, CANADA

RECEIVED NOVEMBER 28, 1947

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORY OF GENERAL ANILINE & FILM CORPORATION]

Reaction of Diazo Compounds with Sulfamic Acid

BY H. W. GRIMMEL AND JACK F. MORGAN

Sulfamic acid has long been used both in industry and in the laboratory to remove excess nitrous acid following diazotization of amines. Obviously, it has been generally assumed that the diazo compounds were unaffected by sulfamic acid under the conditions employed. It has been demonstrated in this Laboratory that a number of diazo compounds do react with sulfamic acid even in strongly acid solution. In fact, in certain cases this reaction is a rapid and quantitative one yielding the products shown in the net equation

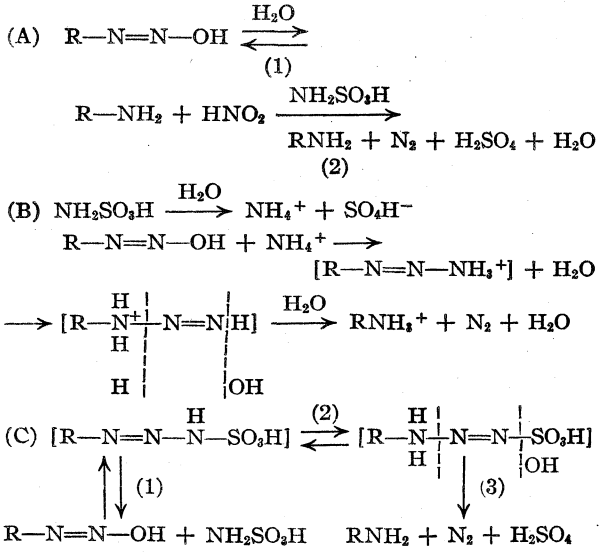
$$R{-}N{=}N{-}OH + NH_2SO_3H \longrightarrow RNH_2 + H_2SO_4 + N_2$$

Scope of the Reaction

Only the most reactive diazo compounds are capable of reacting with sulfamic acid in mineral acid solution. For example, diazo compounds derived from *p*-chloroaniline, aniline or *p*-toluidine do not react with sulfamic acid in strong acid solution. 2,5-Dichloroaniline and *p*-nitroaniline yield diazo compounds which react very slowly with sulfamic acid while the diazo compounds from 2,4-dinitroaniline and 2,6-dichloro-4-nitroaniline react quite rapidly. Most reactive of all are the diazo compounds derived from 5-aminotetrazole and 5-amino-1,2,4-triazole-3-carboxylic acid.

Mechanism

Three explanations of the reaction are listed. Evidence will be presented to show that the first two, A and B, are untenable and that C is probably a true picture of what takes place.



Explanation A is incorrect. If equilibrium (1) existed and the sulfamic acid were merely reacting with nitrous acid, it is obvious that the role of sulfamic acid in (2) could be played by urea. However, it was shown by experiment that urea did not react at all to reverse the diazotization reaction.

Explanation B breaks down on at least two counts. First of all the hydrolysis of sulfamic acid in cold strongly acid solution is at least ten thousand fold too slow to account for the reaction. The reaction of excess sulfamic acid with the diazo compound derived from 5-amino-1,2,4-triazole-3-carboxylic acid at 0–5° is complete within five minutes. However, no barium sulfate precipitate results when an aqueous solution of sulfamic acid, hydrochloric acid, and barium chloride is kept at 5° for a week. Secondly, the 5-diazo-1,2,4-triazole-3-carboxylic acid did not react at all with ammonium chloride in dilute hydrochloric acid.

Explanation C is proposed as the correct mechanism for the reaction. Since the first stage of the reaction does not involve hydrolysis of either of the two reactants (mechanisms A or B) it follows that the first step in the reaction directly involves the diazo compound and the sulfamic acid *per se*. Step (1) of mechanism C appears to be the only logical way for the reaction to start if the final products are to include nitrogen and the original amine.

Experimental

5-Diazo-1,2,4-triazole-3-carboxylic Acid.[1]—5-Amino-1,2,4-triazole-3-carboxylic acid (50 g.) was dissolved by warming in water (400 ml.) and concentrated hydrochloric acid (200 ml.). Diazotization was effected at −5° by addition of a slight excess of sodium nitrite solution. The white solid diazo compound was separated by filtration, washed thoroughly with ice water and pressed on the funnel. One gram of this stable presscake was titrated in cold acid solution with 0.05 *N* 2-naphthylamine hydrochloride solution to determine its strength. The yield of isolated diazo compound usually amounted to 75% of the theoretical.

(a) **Reaction with Sulfamic Acid.**—The filter cake of the diazo compound (0.05 mole) was slurried in 1 *N* hydrochloric acid solution (200 ml.) and treated with a solution (100 ml.) of sulfamic acid (0.15 mole). Nitrogen was evolved rapidly and the diazo compound was entirely destroyed within five minutes as shown by failure to couple with β-naphthylamine. When acidic solutions of ammonium chloride or urea replaced the sulfamic acid solution, no reaction took place even in several days.

In a second experiment a suspension of the diazo compound was "reversed" to the amine with a slight excess of sulfamic acid, rediazotized, and the newly formed precipitate removed by filtration. This precipitate proved to be identical with the original diazo compound by identical X-ray diffraction patterns.

In a third experiment aliquots of a dilute solution of diazotized 5-amino-1,2,4-triazole-3-carboxylic acid were (a) titrated with 0.05 *N* 2-naphthylamine hydrochloride and (b) "reversed" to the amine with sulfamic acid, rediazotized, and titrated with 2-naphthylamine. The results of these titrations gave a minimum of 94% yield for the "reversal" and rediazotization.

(1) W. Manchot and R. Noll, *Ann.*, **343**, 1 (1905).

Comparison of Reaction Rates of Various Diazo Compounds with Sulfamic Acid.—Tenth normal solutions of diazo compounds were prepared by known procedures and 50-ml. aliquots (0.005 mole) employed in each experiment. For each diazo compound the 50-ml. aliquots were treated with solutions (50 ml.) containing 0, 1, 10, or 20 equivalent amounts of sulfamic acid and the nitrogen gas evolved measured continuously by means of a rate nitrometer.[2] In all cases the *p*H was <1 and the temperature 25° except in the case of diazotetrazole which was run at 0–5°.

The original amine was isolated and identified as the primary reaction product except in the case of 2-chloro-4-nitroaniline. In this latter case, the diazoamino compound was isolated in good yield with the expected (50%) amount of N_2 liberated. Typical reaction rate curves are shown in Fig. 1.

2,5-Dichloroaniline and *p*-Nitroaniline.—The diazo compounds of these two amines were not sufficiently reactive for study with the rate nitrometer. Consequently, 0.05 *N* solutions of these diazo compounds were treated with 0, 1 and 10 equivalent amounts of sulfamic acid and stored at 5° for ten days. At the end of this time the solutions were filtered and the amounts of solid diazoamino compounds determined. Yields are given in Table I.

TABLE I

YIELD OF DIAZOAMINO COMPOUNDS

Sulfamic acid	% Yield from diazotized *p*-nitroaniline	% Yield from diazotized 2,5-dichloroaniline
None	..	..
1 equiv.	3.6	6.2
10 equiv.	12.0	19.0

Summary

1. Certain diazo compounds were shown to react with sulfamic acid in acid solution to yield the original amine from which the diazo compound was derived together with nitrogen and sulfuric acid.

2. A mechanism has been proposed to explain the reaction.

3. Relative reaction rates of various diazo compounds with sulfamic acid were compared by means of a rate nitrometer.

EASTON, PENNSYLVANIA RECEIVED AUGUST 16, 1947

(2) M. L. Crossley, R. H. Kienle and C. H. Benbrook, *Ind. Eng. Chem., Anal. Ed.*, **12**, 216 (1940).

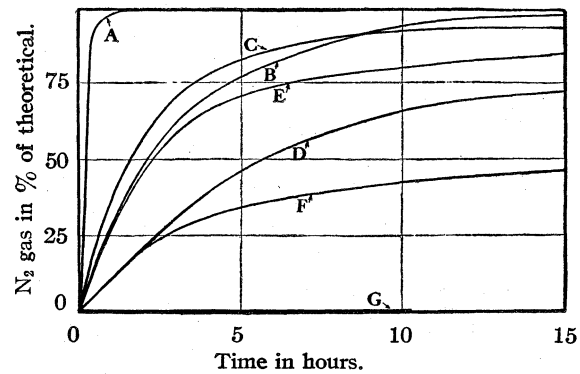


Fig. 1.—Rates of reaction of the diazo compounds of the following amines with sulfamic acid at the indicated concentration: A, 5-aminotetrazole, 20 equivalents of sulfamic acid; B, 2,4-dinitroaniline, 10 equivalents of sulfamic acid; C, 2,6-dichloro-4-nitroaniline, 20 equivalents of sulfamic acid; D, 2,6-dichloro-4-nitroaniline, 1 equivalent of sulfamic acid; E, 2-amino-5-nitro-N-ethylbenzenesulfonanilide, 20 equivalents of sulfamic acid; F, 2-chloro-4-nitroaniline, 20 equivalents of sulfamic acid; G, blank.

[CONTRIBUTION FROM THE DIVISION OF PLANT NUTRITION, COLLEGE OF AGRICULTURE, THE DEPARTMENT OF BACTERIOLOGY, UNIVERSITY OF CALIFORNIA, AND THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

α-L-Glucose-1-phosphate

BY A. L. POTTER, JOHN C. SOWDEN, W. Z. HASSID AND M. DOUDOROFF

An enzyme obtained from the bacterium *Pseudomonas saccharophila* has been named sucrose phosphorylase because it catalyzes the reversible reaction between fructose and α-D-glucose-1-phosphate to form sucrose. This enzyme is also capable of catalyzing the reaction between other monosaccharides and the same ester, thus forming a number of disaccharides, namely, D-glucosido-L-sorboside, D-glucosido-D-xyloketoside, D-glucosido-L-araboketoside, and D-glucosido-L-arabinose.[1] The formation of these disaccharides demonstrates the versatility of the enzyme with regard to the non-glucose substrates which act as "glucose acceptors" in the synthetic reactions. However, the enzyme appears to be specific toward the glucose portion of its substrate. It has been found that the sucrose phosphorylase will not form compound sugars when α-maltose-1-phosphate, α-D-galactose-1-phosphate, or α-D-xylose-1-phosphate is substituted for α-D-glucose-1-phosphate. Similarly, potato and muscle phosphorylases will not form polysaccharides when these phosphorylated sugars are substituted for α-D-glucose-1-phosphate.

In this connection, it was of interest to test whether or not α-L-glucose-1-phosphate could be substituted for its optical isomer, α-D-glucose-1-phosphate in the enzymatic reaction with potato phosphorylase for polysaccharide synthesis or with sucrose phosphorylase for disaccharide formation.

In the present work the preparation of α-L-glucose-1-phosphate from L-glucose is described and

(1) M. Doudoroff, W. Z. Hassid and H. A. Barker, *J. Biol. Chem.*, **168**, 733 (1947); W. Z. Hassid, M. Doudoroff, A. L. Potter and H. A. Barker, THIS JOURNAL, **70**, 306 (1948).

its behavior as a substrate in these enzymatic reactions is determined.

Experimental

Preparation of α-L-Glucose-1-(barium phosphate).—L-Glucose was synthesized by the method previously described.[2] β-Pentaacetyl-L-glucose was prepared by heating 15 g. of L-glucose with 75 g. of acetic anhydride and 7.2 g. of powdered anhydrous sodium acetate according to the method of Fischer.[3] The yield of the acetylated derivative was 23.4 g. or 72%.

α-Bromotetraacetyl-L-glucose[4] was prepared as follows: fourteen grams of β-pentaacetyl-L-glucose was treated with 9.1 ml. of 30 to 32% solution of hydrogen bromide in glacial acetic acid and the mixture allowed to stand at room temperature for two hours. The solution was diluted with 60 ml. of chloroform, poured into 200 ml. of ice water and stirred rapidly. The chloroform layer was separated and the aqueous phase extracted once more with 15 ml. of chloroform. The chloroform extracts were washed twice with ice water, dried with calcium chloride and evaporated *in vacuo* at 40° to a thick sirup. The sirup was taken up with 35 ml. of anhydrous ether and petroleum ether was added until a second liquid phase began to appear. Crystallization was then allowed to take place. The yield of the crystalline acetobromo-L-glucose was 13.5 g. (91.6%).

α-L-Glucose-1-(barium phosphate) was prepared by treating 13.5 g. of α-bromotetraacetyl-L-glucose with trisilver phosphate, then partially hydrolyzing the intermediate product, presumably tri-(tetraacetyl-L-glucose-1)-phosphate, for twelve hours in 0.2 *N* hydrochloric acid in methanol at 23°, and neutralization with barium hydroxide.[5] A yield of 1.09 g. of the barium salt was obtained (22.2%). Analysis of the salt shows that it contains three molecules of water of crystallization. It is an amorphous, non-hygroscopic white powder, which is easily soluble in water and insoluble in 50% alcohol.

Anal. Calcd. for $C_6H_{11}O_5 \cdot O \cdot PO_3Ba \cdot 3H_2O$: P, 6.9. Found: P, 7.1; specific rotation, $[\alpha]_D$ −73.2° (*c*, 1.01, anhydrous barium salt, in water). Cori, Colowick and Cori's[5] value for the D-form of the barium salt, $[\alpha]_D$ +75°.

Preparation of α-L-Glucose-1-(dipotassium phosphate).—A portion of the barium salt (0.8 g.) was dissolved in 12 ml. of warm water and treated with an equivalent amount (0.31 g.) of potassium sulfate. The precipitated barium sulfate was removed through a precoated diatomaceous silica filter and absolute ethanol was added to the filtrate until a slight cloudiness appeared. The solution was allowed to remain at room temperature, and 1.7 volumes of absolute alcohol was added gradually. Crystallization was then allowed to take place. The crystals were filtered, washed with 65% ethanol and recrystallized from water by addition of an equal volume of ethanol. A yield of 0.48 g. was obtained (73%).

The L-glucose-1-(dipotassium phosphate) thus prepared is a white non-hygroscopic crystalline product, containing two molecules of water of crystallization and, except for its negative rotation, is similar in its physical and chemical properties to the D-form of the hexosephosphate.

Anal. Calcd. for $C_6H_{11}O_5 \cdot O \cdot PO_3K_2 \cdot 2H_2O$: C, 19.35; H, 4.06; P, 8.33; aldose, 48.4. Found: C, 19.19; H, 4.03; P, 8.40; aldose, 48.7. Specific rotation, $[\alpha]_D$ −78.2° (in water, *c*, 1.01). Hanes'[6] value for the D-form of the dipotassium salt, $[\alpha]_D$ +78.5° (in water, *c*, 1.24).

The L-glucose-1-phosphate is readily hydrolyzed with dilute acid, is stable in alkali, and shows no Fehling reduction on prolonged boiling. The ester is completely hydrolyzed to glucose and inorganic phosphate when heated for seven minutes in 1 *N* hydrochloric acid in a boiling water-bath. Upon hydrolysis of the ester the reducing sugar produced was identified as glucose by the preparation of glucosazone.

Oxidation of α-L-Glucose-1-(dipotassium phosphate) with Sodium Periodate.—In oxidizing the L-glucose-1-phosphate Wolfrom and Pletcher's[7] procedure for oxidation of the D form of this ester was used. The results showed that in the oxidation of one mole of dipotassium dihydrate L-glucose-1-phosphate 2.0 moles of periodate were consumed with the production of 1.1 moles of formic acid. These data closely agree with the theoretical requirements of two moles of periodate and one mole of formic acid, assuming that the L-glucose of this ester exists in the pyranose configuration.

Action of Potato Phosphorylase and Sucrose Phosphorylase from *P. saccharophila* on α-L-Glucose-1-(dipotassium phosphate).—A solution of α-L-glucose-1-phosphate was adjusted with acetic acid to *p*H 6.0 and treated with potato phosphorylase. The mixture was analyzed for inorganic phosphorus at several thirty-minute intervals. No inorganic phosphate was liberated, except for a small amount which was attributed to hydrolytic decomposition of the ester. In a control experiment with D-glucose-1-phosphate, inorganic phosphate was rapidly liberated.

A similar experiment was performed with a mixture of α-L-glucose-1-phosphate, D-fructose and sucrose phosphorylase extracted from *P. saccharophila*. No liberation of inorganic phosphate could be observed. Neither was inorganic phosphate liberated when L-fructose[8] was substituted for D-fructose in the mixture. In a control experiment with D-glucose-1-phosphate, D-fructose and the same enzyme, inorganic phosphate was liberated under these conditions.

Acknowledgments.—The work reported in this paper was supported in part by a grant from the Corn Industries Research Foundation.

Summary

The barium salt of α-L-glucose-1-phosphoric acid has been synthesized and converted into the dipotassium salt. An elementary analysis and data obtained from oxidation with sodium periodate of the potassium salt of this ester agree with the composition $C_6H_{11}O_5 \cdot O \cdot PO_3K_2 \cdot 2H_2O$. Except for the negative rotation, $[\alpha]_D$ −78.2°, of the α-L-glucose-1-phosphate, its physical and chemical properties agree with those of its optical isomer, α-D-glucose-1-phosphate.

α-L-Glucose-1-phosphate is not converted by potato phosphorylase to polysaccharide. Neither can it be used as substrate by sucrose phosphorylase from *P. saccharophila* with either D- or L-fructose to form a disaccharide.

BERKELEY 4, CALIFORNIA RECEIVED SEPTEMBER 29, 1947

(2) John C. Sowden and H. O. L. Fischer, THIS JOURNAL, **69**, 1963 (1947).

(3) E. Fischer, *Ber.*, **49**, 584 (1916).

(4) P. Karrer, E. Nageli and A. P. Smirnoff, *Helv. Chim. Acta*, **5**, 141 (1922); H. Ohle, W. Marecek and W. Bourjau, *Ber.*, **62**, 849 (1929).

(5) C. F. Cori, S. P. Colowick and Gerty T. Cori, *J. Biol. Chem.*, **121**, 465 (1937).

(6) C. S. Hanes, *Proc. Roy. Soc.* (*London*), **B129**, 174 (1940).

(7) M. L. Wolfrom and D. E. Pletcher, THIS JOURNAL, **63**, 1050 (1941).

(8) The authors wish to thank Dr. M. L. Wolfrom for supplying a sample of L-fructose.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

The Synthesis of 5-Halogeno-2-thiouracil and 6-Methyl-5-halogeno-2-thiouracil Derivatives[1]

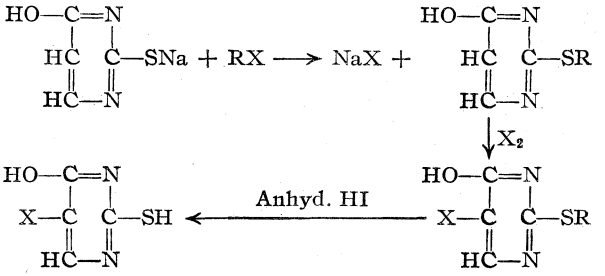
BY HAROLD W. BARRETT,[2] IRVING GOODMAN AND KARL DITTMER

Following Astwood's discovery in 1943 of the relatively high antithyroid activity and low toxicity of 2-thiouracil,[3] numerous derivatives of this compound were prepared and tested for physiological activity.[4-6] In general, it has been found that substitution on either the sulfur[4] or the nitrogen[5] of the molecule decreased or destroyed the antithyroid potency of the parent compound, while substitution of a small alkyl group in either the 5- or the 6-position enhanced such activity, as did substitution of a benzyl, phenethyl or thenyl group in the 6 position.[4,6] A large variety of other substituents in either of these positions, including saturation of the 5,6-double bond, diminished the activity so that the resulting compound was no longer useful as an antithyroid agent.

Clinically, the more highly active derivatives have not corrected the basic defects of 2-thiouracil itself; they frequently provoke toxic reactions which limit or preclude their use, and also induce thyroid hyperemia and friability consequent to blocking hormone synthesis. Attempts to overcome these defects by simultaneous administration of iodine,[7,8] thyroxine,[8] folic acid,[9,10] or various other vitamins[11] have not been uniformly successful; hence there has been a continuing search for new types of derivatives for both research and clinical purposes.

In view of the effect of 5-substitution on the activity of thiouracil, it seemed of interest to prepare the 5-halogeno-2-thiouracils, and to test their physiological action. It seemed especially desirable to obtain the 5-iodo derivative which would permit the simultaneous administration of an organic iodide and a possible antithyroid compound. In this paper, we wish to report the synthesis of 5-chloro, 5-bromo, and 5-iodo-2-thiouracil, and the corresponding halogeno derivatives of 6-methyl-2-thiouracil. The antithyroid potency of three of these halogenated derivatives was compared with that of 2-thiouracil using the rat as the assay animal. Assigning an arbitrary value of 100% to 2-thiouracil, the relative potencies of the 5-chloro-, 5-bromo-, and 5-iodo compounds in producing increased thyroid weights were +125, −2 and +35%, respectively. The relative potencies in producing decreased thyroid iodine levels were 86, 68 and 66%, respectively. The detailed results of these physiological tests will be reported later.

The synthesis of these derivatives is summarized by the following steps



5-Halogeno-2-thiouracil

Although Johnson and Johns[12] prepared the 5-bromo derivative of 6-amino-4-oxy-2-mercaptopyrimidine by direct bromination of the pyrimidine in glacial acetic acid, it appears that 2-thiouracil can be halogenated only when the sulfur is blocked by an alkyl or aryl group. Attempts to obtain the halogenated derivatives by condensation methods or by halogenation of the unsubstituted molecule failed; and, although 2-thiouracil will react with 7.7 equivalents of iodine in neutral or alkaline solution,[13] no iodine can be found in the product following purification. The 2-thiocyanate (m. p. 148–149° with decomposition) was formed by adding an alcoholic solution of cyanogen bromide to an aqueous solution of sodium thiouracil, but this derivative could not be brominated in the ring. Attempts were made to form the S-benzoyl and the S-sulfonyl derivatives by the Schotten–Baumann method, but the products were too unstable to isolate.

In preliminary work with the S-alkyl derivatives, a sample of 5-bromo-2-ethylthiouracil was prepared by the method of Wheeler and Johnson,[14] and treated with dry hydrogen chloride to remove the ethyl group.[15] However, this compound slowly decomposed at the melting point, and when the hydrogen chloride was passed through for a few minutes, only a red tar remained. The same result was obtained with the analogous methyl

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) Present address: Department of Chemistry, Colorado A. & M. College, Fort Collins, Colorado.

(3) Astwood, *J. Pharmacol. Exptl. Therap.*, **78**, 79 (1943).

(4) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

(5) Bywater, McGinty and Jenessel, *J. Pharmacol. Exptl. Therap.*, **85**, 14 (1945).

(6) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(7) Christian, *Med. Clinics N. Am.*, **30**, 283 (1946); from "Yearbook of General Therapeutics," 1946, p. 350.

(8) Danowski, Mann and Winkler, *Am. J. Med. Sci.*, **210**, 777 (1945).

(9) Goldsmith, Gordon, Finkelstein and Charipper, *J. Am. Med. Assoc.*, **125**, 847 (1944).

(10) Newman and Jones, *ibid.*, **132**, 77 (1946).

(11) Fishberg and Vorzimer, *ibid.*, **128**, 915 (1945).

(12) Johnson and Johns, *Am. Chem. J.*, **34**, 186 (1905).

(13) Miller, Roblin and Astwood, THIS JOURNAL, **67**, 2201 (1945).

(14) Wheeler and Johnson, *Am. Chem. J.*, **31**, 591 (1904).

(15) Wheeler and Liddle, *ibid.*, **40**, 537 (1908).

derivative. A quantity of 2-benzylthiouracil was prepared[15] and brominated in the same manner as the ethyl derivative to yield 5-bromo-2-benzylthiouracil (m. p. 184–185° with decomposition). This compound could be partially debenzylated, but with considerable decomposition, by passing dry hydrogen chloride through a tube of the crystals at 120° or by dissolving the compound in glacial acetic acid and passing dry hydrogen bromide through the solution which was kept near the boiling point. An attempt was made to split this derivative with cyanogen bromide[16] in glacial acetic acid, but little reaction took place even when the mixture was heated to 90–100° in a sealed tube.

Finally it was determined that 5-bromo-2-benzylthiouracil, as well as the corresponding S-alkyl derivatives, could be split to give fair yields of the desired 5-halogeno-2-thiouracils by dissolving the intermediate in glacial acetic acid and treating the solution with dry hydrogen iodide at the appropriate temperature. Since a controlled flow of hydrogen iodide gas was difficult to obtain, the splitting was originally carried out by adding 50% hydriodic acid to a large excess of acetic acid–acetic anhydride mixture, and adding the resulting solution dropwise to the hot glacial acetic acid solution of the pyrimidine. Upon subsequent cooling, a part of the final product precipitated out, and the remainder was obtained by evaporating the excess solvent under reduced pressure. During the preparation of a larger quantity of 5-iodo-2-thiouracil the splitting reaction with anhydrous hydrogen iodide was greatly improved by carrying out this reaction in the apparatus illustrated in Fig. 1. This apparatus provides a convenient method for the preparation of anhydrous hydrogen iodide from 50% hydriodic acid without the possibility of introducing water into the reaction mixture, and also permits working with much less solvent. This technique was used in the preparation of 5-iodo-2-thiouracil and 6-methyl-5-iodo-2-thiouracil in better yields than was obtained by the method employed for the other halogeno compounds.

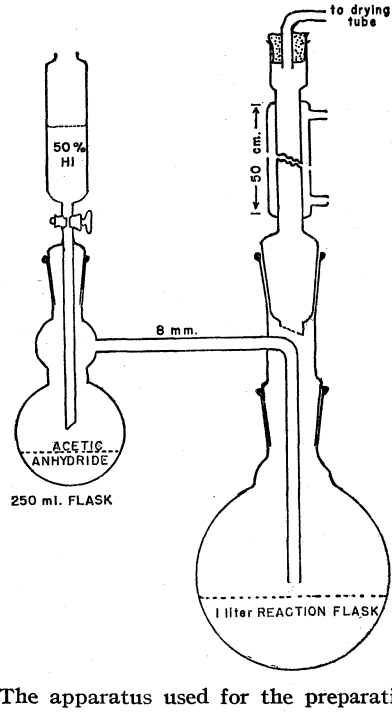


Fig. 1.—The apparatus used for the preparation of anhydrous hydrogen iodide.

(16) Braun and Englebertz, *Ber.*, **56**, 1573 (1923).

Although bromine was very readily introduced in the 5 position of the S-alkyl derivatives of 2-thiouracil, the same was not true of chlorine. When an acetic acid solution of the pyrimidine was treated with chlorine, it appeared that either a hydrochloride salt[14] or a sulfonium chloride was formed,[17] and when the product was taken up in water it decomposed to form uracil and a mercaptan. It was found necessary to use a ferric chloride catalyst with heating to introduce the chlorine into the 5-position. The product was then taken up in a water–pyridine mixture to avoid decomposition.

Experimental[18]

2-Methylthiouracil.—Wheeler and McFarland[19] prepared 2-methylthiouracil by the action of methyl iodide on 2-thiouracil in a solution of absolute alcohol and sodium alcoholate. It was found more convenient to prepare the intermediate in the manner described here.

A mixture of 12.8 g. of 2-thiouracil and 4.3 g. of sodium hydroxide was placed in a 500-ml. Erlenmeyer flask, and dissolved on the steam-bath with a minimum amount of water. Twice the volume of 95% alcohol was then added, the solution cooled to about 30°, and 6.3 ml. of methyl iodide added. The solution was reheated to 50–60° for twenty minutes, then cooled to room temperature. The precipitate was filtered off, and, after acidifying the filtrate with acetic acid, the excess solvent was removed *in vacuo*. The combined precipitates were thoroughly washed with water and recrystallized from alcohol to give a final yield of 9.0 g. (63% of the theoretical yield) of 2-methylthiouracil, capillary m. p. 198°.

5-Chloro-2-methylthiouracil.—Nine grams of 2-methylthiouracil was dissolved in an excess of glacial acetic acid containing 5% acetic anhydride to remove any moisture. A trace of ferric chloride was added as catalyst. The solution was then treated with a 20% excess of chlorine in carbon tetrachloride. The solution became warm and the temperature was maintained at 50–60° until most of the hydrogen chloride fumes were evolved. After cooling, a small amount of precipitate formed; more was obtained when the filtrate was evaporated *in vacuo* to a small volume. The combined precipitates were taken up in excess aqueous pyridine, and the solvent allowed to evaporate at room temperature. The residue was taken up in water, acidified with glacial acetic acid, filtered, and washed several times with water. After several recrystallizations from alcohol the final yield of 5-chloro-2-methylthiouracil was 2.2 g. (20%), m. p. 258–260°.

Anal. Calcd. for $C_5H_5N_2OSCl$: Cl, 20.08. Found: Cl, 20.02.

5-Chloro-2-methylthiouracil was obtained in the same yield when the chlorination was carried out by adding a

(17) Fromm and Raiziss, *Ann.*, **374**, 90 (1910).

(18) All melting points reported in this paper, unless otherwise indicated, were determined on a Dennis melting point bar.

(19) Wheeler and McFarland, *Am. Chem. J.*, **42**, 101 (1909).

20% excess of sulfuryl chloride to the acetic acid–acetic anhydride solution of 2-methylthiouracil, with ferric chloride as the catalyst.

5-Chloro-2-thiouracil.—Two and two-tenths grams of 5-chloro-2-methylthiouracil was dissolved in 100 ml. of glacial acetic acid containing 20% acetic anhydride. This solution was placed in a round bottom flask provided with a ground glass joint and reflux condenser with a funnel at the top. While the solution was kept at its boiling temperature, a mixture consisting of 3.5 ml. of 50% hydriodic acid (specific gravity 1.5), 60 ml. of glacial acetic acid, and 20 ml. of acetic anhydride was added dropwise through a reflux condenser. Heating was continued for an hour after all the hydriodic acid was added. Crude 5-chloro-2-thiouracil precipitated on cooling, and more was obtained when the remaining solution was concentrated to a small volume. The combined precipitates were taken up in dilute ammonium hydroxide and heated until solution was complete. The hot solution was acidified with acetic acid, cooled and the 5-chloro-2-thiouracil collected on the filter. It was recrystallized first from alcohol and then from water to yield 1.5 g. (72%) of pure 5-chloro-2-thiouracil, m. p. 264–270° with decomposition.

Anal. Calcd. for $C_4H_3N_2OSCl$: Cl, 21.80; N, 17.23; S, 19.71. Found: Cl, 21.90; N, 17.54; S, 19.52.

6-Methyl-5-chloro-2-ethylthiouracil.—A sample of 6-methyl-2-ethylthiouracil was prepared by the method of Johns,[20] and chlorinated in glacial acetic acid and acetic anhydride as described for the preparation of 5-chloro-2-methylthiouracil. A 10-g. sample of 6-methyl-2-ethylthiouracil was chlorinated and the product recrystallized from alcohol. A 24% yield of 6-methyl-5-chloro-2-ethylthiouracil, m. p. 188–190°, was obtained.

Anal. Calcd. for $C_7H_9N_2OSCl$: Cl, 17.32. Found: Cl, 17.20.

6-Methyl-5-chloro-2-thiouracil.—The 6-methyl-5-chloro-2-ethylthiouracil was split and the product isolated in the same manner as has been described for the preparation of 5-chloro-2-thiouracil, except that after all the hydriodic acid was added the reaction mixture was vigorously boiled for two hours. The yield from 10 g. of 6-methyl-5-chloro-2-thiouracil was 50–60%. The 6-methyl-5-chloro-2-thiouracil had a m. p. of 265–270° with decomposition.

Anal. Calcd. for $C_5H_5N_2OSCl$: Cl, 20.08; N, 15.86. Found: Cl, 20.18; N, 15.52.

6-Methyl-5-chloro-2-isopropylthiouracil.—6-Methyl-2-isopropylthiouracil, m. p. 155°, was prepared in the same manner as the S-ethyl analog, and upon chlorination gave a 36% yield of 6-methyl-5-chloro-2-isopropylthiouracil, m. p. 162–163°.

Anal. Calcd. for $C_8H_{11}N_2OSCl$: Cl, 16.21. Found: Cl, 16.39.

Unfortunately, the isopropyl group was so difficult to remove that this derivative was not used further.

5-Bromo-2-methylthiouracil.—The intermediate 5-bromo-2-methylthiouracil was prepared by the method described by Wheeler and Johnson[14] for the preparation of the S-ethyl analog. It is best to repeat the bromination, since some unreacted material precipitates out during the first bromination. Fourteen grams of 2-methylthiouracil was dissolved in glacial acetic acid containing 5% acetic anhydride. To this solution was added 7.3 ml. of bromine in 15 ml. of glacial acetic acid. The precipitated product was filtered off, washed with glacial acetic acid and suspended in hot glacial acetic acid. To this suspension was added 1 ml. of bromine in 5 ml. of glacial acetic acid. The product was collected on the filter, washed with glacial acetic acid and recrystallized from ethyl alcohol. The yield of 5-bromo-2-methylthiouracil was 17.4 g. (80%), m. p. 255°. When heated in a capillary it turned yellow at 205°, red at 217°, and decomposed completely to a red liquid at 219°.

Anal. Calcd. for $C_5H_5N_2OSBr$: Br, 36.15. Found: Br, 36.07.

5-Bromo-2-thiouracil from the S-Methyl Intermediate.—The methyl group was removed by hydriodic acid, and the 5-bromo-2-thiouracil isolated, in the same way as described for the chlorinated derivative. Yields obtained, when 10 g. of 5-bromo-2-methylthiouracil was split, varied from 30–49%. The 5-bromo-2-thiouracil crystallized out of either water or alcohol as long, colorless prisms, m. p. 270° with decomposition; when heated slowly in a capillary it turned brown around 170° and decomposed to a red liquid near 200°. As with the chloro derivative, it is necessary to identify this compound and verify its purity by analysis.

Anal. Calcd. for $C_4H_3N_2OSBr$: Br, 38.59; N, 13.53; S, 15.48. Found: Br, 38.70; N, 13.44; S, 15.30.

5-Bromo-2-thiouracil from the S-Benzyl Intermediate.—5-Bromo-2-thiouracil was prepared from 5-bromo-2-benzylthiouracil in the same manner as from the S-methyl derivative but at a temperature of 100°. This preparation, however, was not employed because 2-benzylthiouracil decomposed appreciably during bromination. The 5-bromo-2-benzylthiouracil, m. p. 184° with decomposition, was usually obtained in yields of 40 to 50%.

Anal. Calcd. for $C_{11}H_9N_2OSBr$: Br, 26.9. Found: Br, 26.8.

6-Methyl-5-bromo-2-methylthiouracil.—Ten grams of 6-methyl-2-methylthiouracil was brominated and isolated in the same manner as 5-bromo-2-methylthiouracil to yield 13 g. (91%) of 6-methyl-5-bromo-2-methylthiouracil, m. p. 255–256° with decomposition.

Anal. Calcd. for $C_6H_7N_2OSBr$: Br, 34.00. Found: Br, 34.08.

6-Methyl-5-bromo-2-thiouracil.—Eleven grams of 6-methyl-5-bromo-2-methylthiouracil was treated with hydriodic acid in acetic acid–acetic anhydride solution according to the above described directions to yield 1.8 g. of 6-methyl-5-bromo-2-thiouracil, m. p. 268–272° with decomposition; capillary melting point was 230° with decomposition.

Anal. Calcd. for $C_5H_5N_2OSBr$: Br, 36.15. Found: Br, 36.28.

5-Iodo-2-benzylthiouracil.—This compound was made by iodinating 2-benzylthiouracil according to the method of Johnson and Johns[21] for the preparation of 5-iodo-2-ethylthiouracil. When a quantity of 10.5 g. of 2-benzylthiouracil was iodinated, a yield was obtained of 9.3 g. (56%) of 5-iodo-2-benzylthiouracil, m. p. 178–180°.

Anal. Calcd. for $C_{11}H_9N_2OSI$: I, 36.87. Found: I, 36.83.

5-Iodo-2-thiouracil.—A sample of 5-iodo-2-ethylthiouracil was prepared according to the method of Johnson and Johns,[21] but in attempting to de-ethylate the compound with hydriodic acid as previously described, it was found that practically all the iodine was lost from the ring, while little splitting occurred. Essentially the same result was obtained with the S-methyl derivative. For this reason the 5-iodo-2-benzylthiouracil was used, since it could be satisfactorily split by keeping the temperature between 90 and 100° while adding anhydrous hydrogen iodide by the use of the apparatus illustrated in Fig. 1.

Sixty-five and four-tenths grams of 5-iodo-2-benzylthiouracil was dissolved in 400 ml. of glacial acetic acid containing 10 ml. of acetic anhydride and placed in the reaction vessel. In the side flask was placed 95 ml. of acetic anhydride, and in the dropping funnel 75 ml. of 50% hydriodic acid. While maintaining the temperature of the reaction flask at approximately 100° with a boiling water-bath, the hydriodic acid was added dropwise to the acetic anhydride in the side flask. This mixture became hot, and the hydrogen iodide as it was liberated was conducted into the reaction flask. As the hydrogen iodide came in contact with the solution of the S-benzyl deriva-

(20) Johns, *Am. Chem. J.*, **40**, 348 (1908).

(21) Johnson and Johns, *J. Biol. Chem.*, **1**, 305 (1905).

tive, a ring of precipitate of the split product formed under the inlet tube. When all the hydriodic acid was added to the acetic anhydride, the remaining hydrogen iodide was forced over by heating the hydrogen iodide generator with a small flame. The reaction was considered complete when no more precipitate formed in the reaction flask. After the reaction mixture was cool and the precipitation complete, the supernatant liquid was poured off and the 5-iodo-2-thiouracil was washed on the Buchner funnel with peroxide-free ether to remove the residual iodine. It was then twice extracted with hot glacial acetic acid to remove unreacted material, then washed alternately with water and alcohol to remove the acetic acid. The almost pure product was purified by dissolving in dilute sodium hydroxide with gentle warming; the addition of acetic acid precipitated 27 g. of 5-iodo-2-thiouracil (57%).

The supernatant liquid from the reaction mixture was concentrated *in vacuo* and 7.4 g. of unreacted 5-iodo-2-benzylthiouracil was recovered.

When the 5-iodo-2-thiouracil was heated in a capillary the product became discernibly yellow at 190°; slowly darkened to brown at 210°; and decomposed to a black tar at 214–215°. On the Dennis melting point bar it decomposed slowly with melting at 231–236° and melted instantaneously with decomposition at 278–280°.

Anal. Calcd. for $C_4H_3N_2OSI$: I, 49.95; N, 11.03; S, 12.62. Found: I, 50.08; N, 10.9; S, 12.77.

5-Iodo-2-thiouracil and 5-iodo-2-benzylthiouracil are light sensitive and are best dried over phosphorus pentoxide *in vacuo*.

6-Methyl-5-iodo-2-benzylthiouracil.—Twelve grams of 6-methyl-2-benzylthiouracil was iodinated as described above but, since some of the material escaped iodination, the product was washed thoroughly with water, and reiodinated. Eleven grams (58%) of 6-methyl-5-iodo-2-benzylthiouracil was obtained, m. p. 180–181° with decomposition.

Anal. Calcd. for $C_{12}H_{11}N_2OSI$: I, 35.44. Found: I, 35.65.

6-Methyl-5-iodo-2-thiouracil.—Ten grams of 6-methyl-2-benzylthiouracil was split as described for the preparation of 5-iodo-2-thiouracil. The yield was 3 g. (40%). On the Dennis melting point bar it decomposed slowly above 220°; it melted instantly at 285–289° with decomposition. When heated slowly in the capillary 6-methyl-5-iodo-2-thiouracil began to darken at 175°, progressively decomposed with loss of iodine, and decomposed completely at 195° without melting.

Anal. Calcd. for $C_5H_5N_2OSI$: I, 47.34. Found: I, 47.10.

Acknowledgment.—The authors wish to thank Dr. Noel E. Foss of the Calco Chemical Division of the American Cyanamid Company for generous supplies of thiouracil.

Summary

Methods are described for the preparation of 5-iodo-, 5-bromo- and 5-chloro-2-thiouracil, and the 5-iodo-, 5-bromo-, and 5-chloro-6-methyl-2-thiouracil. These compounds were prepared by the direct halogenation of either the S-methyl or S-benzyl derivatives followed by splitting with anhydrous hydrogen iodide.

An apparatus is illustrated for the convenient preparation of anhydrous hydrogen iodide.

BOULDER, COLORADO RECEIVED DECEMBER 27, 1947

[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS, AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH SCHOOL OF MEDICINE]

The Preparation of D- and L-Homoserine[1]

BY MARVIN D. ARMSTRONG

In the course of the synthesis of some biologically interesting compounds, it became necessary to prepare a considerable amount of pure L-homoserine (α-amino-γ-hydroxybutyric acid). A review of the literature revealed that little work had been accomplished on homoserine since its first preparation by Fischer and Blumenthal[1a] in 1907. Kitagawa's discovery of canavanine[2] and his demonstration that it was α-amino-γ-guanidinoxy-*n*-butyric acid[3–6] was the beginning of an increasing number of references to homoserine in the later literature. The main emphasis in such reports has been in connection with both syntheses and degradations of methionine.[7–12]

The previously reported O-phenylhomoserine[1a] provided a suitable intermediate for the preparation of the optically active homoserines. The N-formyl derivative was easily prepared and was found to give a crystalline strychnine salt; the use of 50% aqueous methanol as a solvent gave a good separation of the two diastereoisomers in one step, the salt of the D-isomer being more insoluble.

That the more soluble strychnine salt was of the L-configuration was shown by an application of the rule of Lutz and Jirgensons[13] to the crude (+)-O-phenylhomoserine obtained by decomposition of the mother liquors from the first crystallization of the strychnine salt. A definite negative maxi-

(1) This research was supported by a grant from the United States Public Health Service. Presented in part before the Division of Biological Chemistry at the 112th meeting of the American Chemical Society, New York, September 16, 1947.

(1a) E. Fischer and H. Blumenthal, *Ber.*, **40**, 106 (1907).

(2) M. Kitagawa and S. Monobe, *J. Biochem. Japan*, **18**, 333 (1933); *C. A.*, **28**, 1021[9] (1934).

(3) M. Kitagawa and S. Monobe, *J. Agr. Chem. Soc. Japan*, **9**, 845 (1933); *C. A.*, **28**, 2678[7] (1934).

(4) M. Kitagawa, *ibid.*, **12**, 871 (1937); *C. A.*, **31**, 1362[2] (1937).

(5) M. Kitagawa and A. Takani, *J. Biochem. Japan*, **23**, 181 (1936); *C. A.*, **30**, 4818[2] (1936).

(6) M. Kitagawa, *ibid.*, **24**, 107 (1936); *C. A.*, **30**, 8162[4] (1936).

(7) L. W. Butz and V. du Vigneaud, *J. Biol. Chem.*, **99**, 135 (1932).

(8) E. M. Hill and W. Robson, *Biochem. J.*, **30**, 248 (1936).

(9) H. R. Snyder, J. H. Andreen, G. W. Cannon and C. F. Peters, THIS JOURNAL, **64**, 2082 (1942).

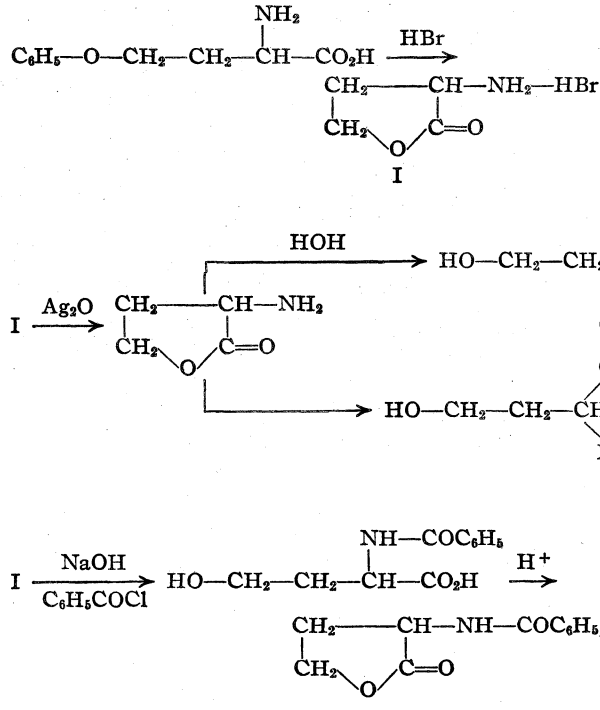
(10) J. E. Livak, E. C. Britton, J. C. VanderWeele and M. F. Murray, *ibid.*, **67**, 2218 (1945).

(11) G. Toennies and J. J. Kolb, *ibid.*, **67**, 1141 (1945).

(12) W. H. Stein and S. Moore, *J. Org. Chem.*, **11**, 681 (1946).

(13) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931).

mum of rotation at the isoelectric point was shown when its rotation was measured in solutions containing different concentrations of acid and alkali (Fig. 1). Further confirmation was found when the free homoserine was obtained by hydrolysis of this isomer; its properties checked those reported by Kitagawa[3,4] for the homoserine obtained upon degradation of canavanine. Canavanine, itself, had earlier been shown to possess the L configuration by a study of the effect of acid concentration on its rotation.[14]



As indicated in the equations the active O-phenylhomoserines were readily converted to the active lactone hydrobromides of homoserine; other derivatives were prepared in the manner described by Fischer and Blumenthal in their original description of DL-homoserine.

Relatively poor yields of the active lactone hydrobromides were obtained as compared with the yield of the racemic compound. This was due to a significant amount of racemization (10–20%) under the conditions employed for the hydrolysis of the active O-phenylhomoserines. Fortunately the optically active derivatives could be easily obtained by recrystallization of the crude product from the hydrolysis; usually one recrystallization from aqueous ethanol sufficed to produce an optically pure compound.

Unsatisfactory yields were also obtained in the conversion of the isomers of α-aminobutyrolactone hydrobromide to the corresponding isomers of homoserine. However, by evaporating the mother liquors from the first recrystallization of the free homoserine to dryness, refluxing the residue for a short time with 48% hydrobromic acid and reworking the solution, most of the lost homoserine could be reisolated as the lactone hydrobromide. It is probable that formation of the diketopiperazines under the conditions for the preparation of homoserine caused the low yields.

Experimental

O-Phenyl-DL-homoserine.—This compound was prepared according to the method of Painter.[15] From 340 g. of ethyl acetamidomalonate and 350 g. of β-bromoethylphenyl ether 235 g. (76% yield) of product, m. p. 235–236° dec., was obtained.

This product is sufficiently pure for formylation and subsequent resolution. For analysis a small sample was recrystallized from hot water, m. p. 236–237° dec.

Anal. Calcd. for $C_{10}H_{13}O_3N$: N, 7.17. Found: N, 7.03.

N-Formyl-O-phenyl-DL-homoserine.—A solution of 200 g. of O-phenylhomoserine in 1700 ml. of 88% formic acid was warmed to 50° and 600 ml. of acetic anhydride was added dropwise at such a rate that the temperature remained at 50–60°. After the addition was completed the solution was allowed to stand for six hours at room temperature, at the end of which time 500 ml. of water was added and the reaction mixture was allowed to stand overnight. It was then concentrated to dryness *in vacuo*, keeping the bath temperature below 50°, and the last traces of water, formic acid and acetic acid were removed by repeated additions of 500 ml. portions of benzene followed by reconcentration to dryness. This treatment was repeated until the residue was dry and almost odorless.

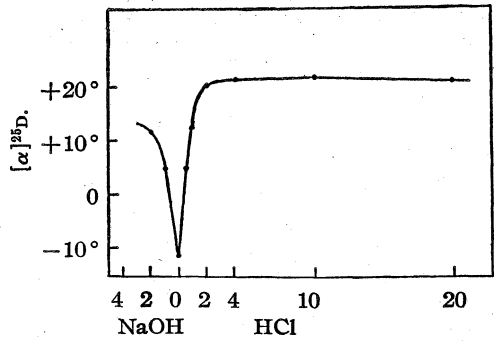


Fig. 1.—The effect of acid and alkali on the rotation of (+)-O-phenylhomoserine. The abscissa gives the ratio of the number of moles of acid and alkali, respectively, to the number of moles of amino acid in solution. A 1% aq. solution of the compound was used.

The dry residue was suspended in 800 ml. of boiling 95% ethanol and the suspension was filtered while hot. The residue was resuspended in 400 ml. of hot ethanol and filtered; the residue of recovered impure O-phenylhomoserine (48 g., m. p. 195–199° dec.) is suitable for reformylation. The combined filtrates were cooled overnight in a refrigerator and filtered; 95 g., m. p. 137–154° dec., of crude formyl derivative was obtained. The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from 130 ml. of hot ethanol

(14) J. F. Cadden, *Proc. Soc. Exptl. Biol. Med.*, **45**, 224 (1940).

(15) E. P. Painter, THIS JOURNAL, **69**, 233 (1947).

(5 g. of crude O-phenylhomoserine was separated by filtering the hot solution); an additional 57 g. of crude N-formyl derivative was obtained. The crude N-formyl-O-phenylhomoserine (152 g.) was recrystallized from 200 ml. of hot 95% ethanol; 126 g., m. p. 135–143°, suitable for resolution, was obtained.

By concentrating the combined mother liquors to dryness and refluxing the residue with 1 *N* HCl an almost quantitative recovery of unformylated O-phenylhomoserine may be made.

For analysis a sample of the N-formyl-O-phenylhomoserine was recrystallized two times from aqueous ethanol; m. p. 137–137.5°.

Anal. Calcd. for $C_{11}H_{13}O_4N$: N, 6.27. Found: N, 6.45.

Resolution of N-Formyl-O-phenyl-DL-homoserine.—To a dry mixture of 112 g. (0.5 mole) of N-formyl-O-phenylhomoserine and 170 g. (0.5 mole) of powdered strychnine was added 5 liters of hot 50% methanol and the suspension was swirled and heated in a water-bath until almost all of the solids had dissolved. The solution was filtered while hot and was allowed to stand overnight at room temperature. The crystalline strychnine salt of N-formyl-O-phenyl-D-homoserine was collected on a filter, washed with a small amount of cold water, and dried; yield, 152 g.; $[\alpha]^{27}D$ −28° (1% in HOAc). One recrystallization from 4 liters of hot 50% methanol yielded 128 g.; $[\alpha]^{26}D$ −27° (1% in HOAc). Four more recrystallizations of the salt from aqueous methanol produced a pure strychnine salt, $[\alpha]^{27}D$ −25° (1% in HOAc), but in practice the best method of obtaining the pure isomer proved to be recrystallization of the free O-phenyl-D-homoserine resulting from the decomposition of the once recrystallized strychnine salt.

O-Phenyl-L-homoserine.—The original mother liquors from the crystalline strychnine salt were concentrated to a volume of approximately 2.5 liters, made alkaline by the addition of 20 ml. of concd. ammonia, cooled and filtered; the strychnine may be dried and reused. The filtrate was concentrated to a volume of about 1500 ml., made 1 *N* in hydrochloric acid by the addition of the proper amount of concd. hydrochloric acid and refluxed for two hours. The solution was then concentrated to dryness under reduced pressure and the residue was dissolved in 200 ml. of hot water; the hot solution was made neutral to congo red by the careful addition of concd. sodium hydroxide solution, the suspension was cooled and filtered. The residue was recrystallized from 500 ml. of hot water; yield, 35 g., m. p. 210–211° dec., $[\alpha]^{25}D$ +21.5° (1% in 1 *N* HCl). The combined mother liquors were concentrated to a volume of approximately 500 ml., cooled and filtered, yielding an additional 13 g. of impure product; m. p. 196–204° dec.; $[\alpha]^{26}D$ +5° (1% in 1 *N* HCl).

Two more recrystallizations of the pure derivative from 400-ml. portions of hot water yielded 22.0 g. of pure O-phenyl-L-homoserine; m. p. 241–242° dec., $[\alpha]^{26}D$ +23.5° (1% in 1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}O_3N$: N, 7.17. Found: N, 7.21.

O-Phenyl-D-homoserine.—A solution of 125 g. of the strychnine salt of N-formyl-O-phenyl-D-homoserine in 4 liters of hot 50% methanol was made alkaline by the addition of 20 ml. of concd. ammonia. The solution was cooled overnight in a refrigerator, the strychnine was removed by filtration, and the crude O-phenyl-D-homoserine was prepared in the same manner as previously described for the L-isomer; yield 38.5 g., m. p. 216–219° dec., $[\alpha]^{24}D$ −19° (1% in 1 *N* HCl). By reworking the mother liquors 6 g. of impure compound was obtained; m. p. 214–216° dec., $[\alpha]^{26}D$ −10° (1% in 1 *N* HCl).

Two recrystallizations of the first crop from 300 ml. portions of hot water yielded 26.5 g., m. p. 218–220° dec., $[\alpha]^{26}D$ −22.0° (1% in 1 *N* HCl). One more recrystallization from 500 ml. of hot water yielded 22 g., m. p. 241° dec., $[\alpha]^{24}D$ −23.5° (1% in 1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}O_3N$: N, 7.17. Found: N, 7.32.

In spite of its low solubility the D isomer possesses a definitely sweet taste, whereas the L isomer is tasteless or nearly so.

Preparation of DL-α-Aminobutyrolactone Hydrobromide.—A solution of 10 g. of O-phenyl-DL-homoserine in 100 ml. of 48% hydrobromic acid was refluxed for twenty hours[16] and was then concentrated to dryness *in vacuo*. The contents of the flask were dissolved in 50 ml. of distilled water and the solution was heated to boiling, treated with Norit, and filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was suspended in 20 ml. of cold absolute ethanol and filtered; the solid residue was washed once with a 10 ml. portion of cold alcohol. The combined alcoholic filtrates were again concentrated to dryness, and the procedure was repeated. The weight of pure white α-aminobutyrolactone hydrobromide obtained was 7.5 g. (81% yield), m. p. 225–228° dec. It was recrystallized by dissolving it in a mixture of 3 ml. of water and 3 ml. of absolute ethanol, the hot solution was diluted with 54 ml. of warm absolute alcohol and allowed to stand in a refrigerator overnight. Only 65–70% recovery can be made upon recrystallization of the compound but the remainder can be obtained by reworking the mother liquors; m. p. 226–228° dec. (F. and B., 227° dec.).

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.69. Found: N, 7.89.

L-α-Aminobutyrolactone Hydrobromide.—A solution of 10 g. of O-phenyl-L-homoserine ($[\alpha]^{25}D$ +23.5°) in 100 ml. of 48% hydrobromic acid was refluxed for twenty hours and was worked up as described for the DL-α-aminobutyrolactone hydrobromide. After one recrystallization, 4.1 g. (44% yield) was obtained; m. p. 242–244° dec., $[\alpha]^{27}D$ −21.0° (1% in water).

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.69. Found: N, 7.63.

D-α-Aminobutyrolactone Hydrobromide.—Ten grams of O-phenyl-D-homoserine ($[\alpha]^{25}D$ −23.5°) was hydrolyzed and worked up in the same manner as described for the L compound; yield, 2.8 g. (41% yield); m. p. 242–244° dec., $[\alpha]^{27}D$ +21.0° (1% in water).

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.69. Found: N, 7.68.

N-Benzoyl-DL-homoserine.—Prepared from α-aminobutyrolactone hydrobromide according to the directions of Fischer and Blumenthal[16]; m. p. 126–127° (F. and B., 121°).

Anal. Calcd. for $C_{11}H_{13}O_4N$: N, 6.27. Found: N, 6.18.

DL-α-Benzamidobutyrolactone.—The benzoyl derivative was dissolved in a small amount of hot water containing a trace of hydrochloric acid, the solution was heated a few minutes and was then cooled. The α-benzamidobutyrolactone that crystallized was collected and was recrystallized from hot water; m. p. 140–141° (F. and B., 142°).

Anal. Calcd. for $C_{11}H_{17}O_4N$: N, 6.82. Found: N, 6.96.

L-α-Benzamidobutyrolactone.—A solution of 1.0 g. of L-α-aminobutyrolactone hydrobromide in 11 ml. of 1 *N* NaOH was cooled to 0° and benzoylation was carried out in the customary manner using 0.85 g. of benzoyl chloride and 2 ml. of 3 *N* NaOH. The reaction mixture was worked up by making the solution just acid to congo red, extracting the excess benzoic acid with ether, and recrystallizing the precipitate of crude N-benzoyl-L-homoserine by warming the mixture just enough to dissolve the solid and then

(16) Fischer and Blumenthal report complete hydrolysis after seven hours refluxing. This laboratory is located at an elevation of 5000 ft. with a usual barometric perssure of approximately 630 mm. of mercury, hence many of the reaction times in refluxing solutions or amounts of solvents needed for recrystallization may vary considerably at ordinary elevations from those reported herein. In this particular experiment it was found that fifteen hours of refluxing was not sufficient for complete hydrolysis.

quickly cooling the solution. It was collected on a filter, washed with water and dried: N-benzoyl-L-homoserine[17]; m. p. 139–141°.

The N-benzoyl-L-homoserine obtained was dissolved in 20 ml. of hot water containing two drops of concd. hydrochloric acid, the solution was boiled for two minutes and cooled. Beautifully formed needles of L-α-benzamidobutyrolactone crystallized and were collected; m. p. 139°, $[\alpha]^{20}D$ −21.5° (1.25% in 95% EtOH).[18]

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.82. Found: N, 6.80.

D-α-Benzamidobutyrolactone.—Prepared from D-α-aminobutyrolactone hydrobromide in the same manner as described for the L compound; N-benzoyl-D-homoserine, m. p. 139–141°; D-α-benzamidobutyrolactone m. p. 139–140°, $[\alpha]^{23}D$ +22.5° (1% in 95% EtOH).[18a]

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.82. Found: N, 6.93.

DL-Homoserine.—To a solution of 1.0 g. of DL-α-aminobutyrolactone hydrobromide in 5 ml. of water was added 0.7 g. of silver oxide and the suspension was shaken at room temperature for five minutes. The silver bromide was removed at the centrifuge, the clear supernatant solution was treated with hydrogen sulfide, again centrifuged, and the clear colorless solution was evaporated to dryness on a steam-bath. The residue was dissolved in 2 ml. of water, filtered, and the filtrate was diluted with 10 ml. of warm absolute ethanol and allowed to stand overnight in a refrigerator. The crystalline product was collected on a filter, washed with 95% ethanol and dried; yield 0.30 g., (46% yield); m. p. 186–187° dec.

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.98.

(17) Kitagawa and Monobe, refs. 3, 4, reported the following physical properties for homoserine and its derivatives as obtained by the degradation of canavanine: (1) homoserine, m. p., 201–202° dec.; $[\alpha]^{16}D$ −8.20, (2) N-benzoylhomoserine, m. p., 140–144°, (3) α-benzamidobuytrolactone, m. p. 139°, $[\alpha]^{17}D$ −27.99° (in EtOH).

(18) $[\alpha]^{20}D$ −27.0° (1% w/v in 95% EtOH).

(18a) $[\alpha]^{23}D$ +28.0° (1% w./v. in 95% EtOH).

L-Homoserine.—Prepared from 1.0 g. of L-α-aminobutyrolactone hydrobromide as described above for the DL compound; yield, 0.28 g. (43% yield); m. p. 203° dec., $[\alpha]^{23}D$ −8.0° (1% in water).

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.98.

D-Homoserine.—Prepared from 1.0 g. of D-α-aminobutyrolactone hydrobromide as described above; yield 0.30 g. (46% yield); m. p. 203° dec., $[\alpha]^{23}D$ +8.0° (1% in water).

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 12.00.

3,6-bis-(β-Hydroxyethyl)-2,5-diketopiperazine.—Prepared from 3.34 g. of DL-α-aminobutyrolactone hydrobromide according to the directions of Livak, *et al.*[10]; yield, 1.10 g. (60% yield); m. p. 189–191° dec.

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 14.22.

L-3,6-bis-(β-Hydroxyethyl)-2,5-diketopiperazine.—The above reaction was repeated using 3.34 g. of L-α-aminobutyrolactone hydrobromide; yield, 1.25 g. (67% yield); m. p. 190.5–191° dec.; $[\alpha]^{27}D$ −30.0° (1% in water).

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.79.

Acknowledgment.—The author wishes to thank Marie S. Hanson for performing the nitrogen analyses reported in this paper.

Summary

D- and L-homoserine have been prepared by the acid hydrolysis of the corresponding O-phenylhomoserines. The properties of L-homoserine were shown to agree with those reported for the optically active α-amino-γ-hydroxybutyric acid obtained by the degradation of canavanine.

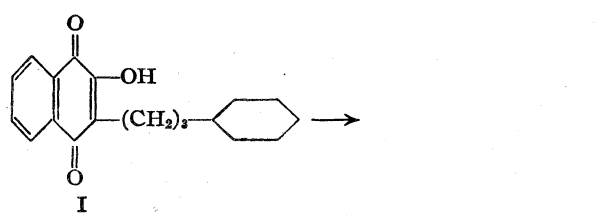
SALT LAKE CITY, UTAH RECEIVED OCTOBER 18, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Synthesis of 2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone

BY WILLIAM G. DAUBEN AND RAYLENE E. ADAMS

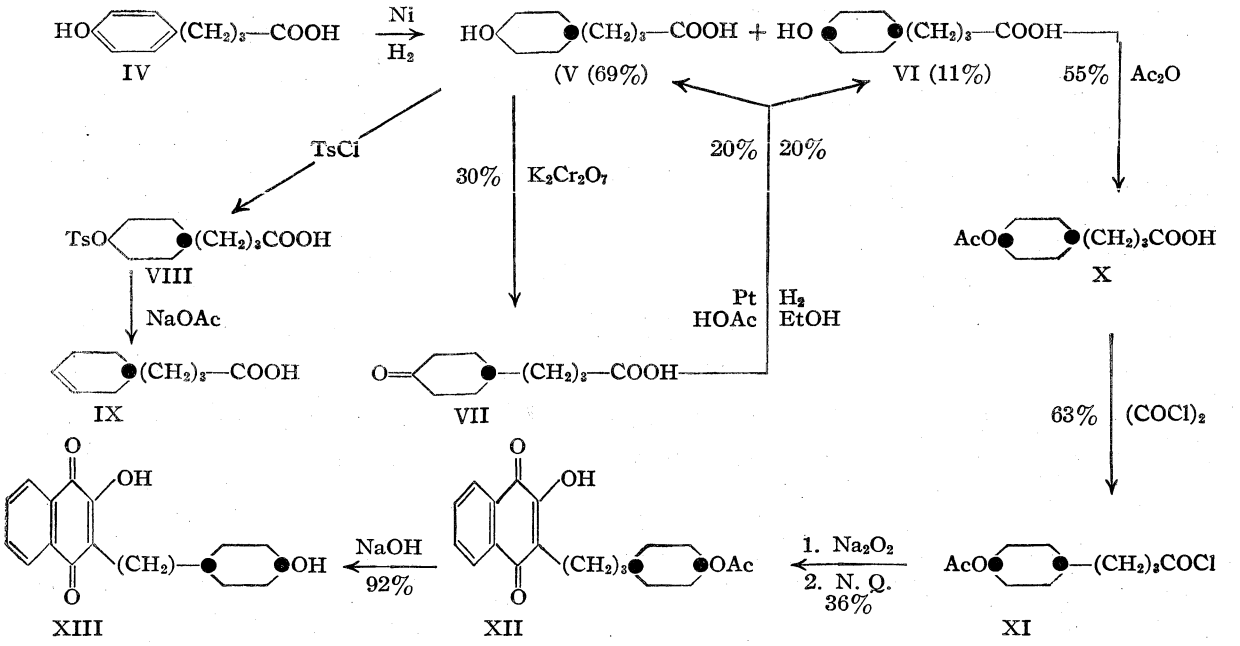
It has recently been reported by Fieser[1] that various [2-hydroxy-3-alkyl-1,4-naphthoquinones when administered to humans undergo degradation. It was found that when the alkyl group was 3-cyclohexylpropyl (I), two hydroxylated quinones (II and III) could be isolated. Compound II, which melts at 155°, was shown to be 2-hydroxy-3-[3′-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone by synthesis from γ-(*p*-hydroxycyclohexyl)-butyric acid (V). This series of compounds can be assumed to be of the *trans* configuration since the starting acid (V) was obtained by the hydrogenation of γ-(*p*-hydroxyphenyl)-butyric acid (IV) in basic solution over Raney nickel catalyst.[2] Compound III was shown to be optically inactive, to contain a secondary hydroxyl group, and to melt at 112°. In view of these facts it was thought that this degradation product might be the *cis*-isomer of compound II and the synthesis of this isomer is reported in this paper.



R = 2-Hydroxy-1,4-naphthoquinone-3-yl

(1) Fieser and co-workers, THIS JOURNAL, in preparation.

(2) (a) Macbeth and Mills, *J. Chem. Soc.*, 709 (1945); (b) Skita, *Ber.*, **53**, 1792 (1920), and later papers.



It was found that fractionation of the hydrogenation product of γ-(*p*-hydroxyphenyl)-butyric acid (IV) gave, in addition to the *trans* acid (V), 11% of the *cis* isomer (VI). However, since a large amount of the *trans* compound was formed in the hydrogenation, a study was made of the possible methods for conversion of it to the *cis* isomer.

It is well-known that alcohols can be inverted by the process of tosylation and subsequent displacement with acetate ion.[3] For example, Kenyon and co-workers have inverted *trans*-4-methoxycyclohexanol in a yield of 30% by this method. However, the major reaction product was 4-methyl-1-cyclohexene. When the *trans* acid (V) was tosylated in pyridine solution and then treated with an alcoholic solution of sodium acetate only the unsaturated acid (IX) was obtained.

Another mode of preparation of *cis–trans*-isomers in the cyclohexanol series is the hydrogenation of the corresponding ketone.[2a] MacBeth and Mills have found that when *trans*-3-methylcyclohexanol was oxidized to 3-methyl-1-cyclohexanone and the ketone hydrogenated at room temperature over Adams catalyst in acetic acid solution the *cis*-3-methylcyclohexanol was obtained in 69% yield.

Various methods were tried in order to prepare γ-(*p*-cyclohexanone)-butyric acid (VII). Numerous Oppenauer oxidations were conducted on the methyl ester of the *trans* acid using either acetone or cyclohexanone as the hydrogen acceptor. No ketone or ketone derivative could be isolated. A dark red oil was always obtained and it is believed that an aldol-type condensation may have occurred under the conditions of the reaction. The catalyst, aluminum *t*-butoxide, was checked for its activity by oxidizing cyclohexanol. High yields of cyclohexanone were always obtained.

Various chemical methods are described in the literature for the oxidation of analogous secondary alcohols to ketones. However, with the *trans*-acid (V) very low yields were obtained by almost all the methods. It was found that the keto-acid (VII) could be prepared in a yield of 30–45% by means of potassium dichromate, acetic acid, sulfuric acid, and water at room temperature.

The hydrogenation of the keto-acid (VII) was attempted with various catalysts and solvents, but the amount of *cis* isomer isolated was invariably low (0–20%). A mixture containing small amounts of the *cis* and *trans*-hydroxycyclohexylbutyric acids, a large amount of the cyclohexylbutyric acid, and often a little unreacted ketone was usually received. The best results were obtained when platinum oxide was used as the catalyst and ethanol containing one drop of acetic acid or hydrochloric acid as the solvent. The various unsuccessful methods were platinum oxide in water or absolute ethanol, platinum black in ethanol and Raney nickel in ethanol or water. No reduction occurred when barium sulfate containing ten per cent. palladium was used as the catalyst and ethanol or acetic acid as the solvent.

The results of these experiments are quite similar to those obtained recently by Hardegger, Heusser and Blank.[4] These workers have reported that the hydrogenation of α-hydroxy-β-(*p*-cyclohexanone)-butanolide in aqueous acetic acid over Adams catalyst gave mainly the hydrogenolysis product. The small amount of the desired hydroxyl compound obtained was a mixture of the

(3) Gough, Hunter and Kenyon, *J. Chem. Soc.*, 2052 (1926).

(4) Hardegger, Heusser and Blank, *Helv. Chim. Acta*, **29**, 477 (1946).

cis and *trans* isomers. Gauthier[5] also has reported that 4-propylcyclohexanone is hydrogenated in acetic acid in the presence of hydrochloric acid and platinum catalyst to a mixture of *cis* and *trans* isomers.

The *cis* isomer of the naphthoquinone (XIII) was prepared following the usual methods.[1] The *cis*-γ-(*p*-acetoxycyclohexyl)-butyric acid (X) was obtained in a yield of 55% by treating the *cis*-hydroxy acid (VI) with acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid. This acid was then converted to the acid chloride with oxalyl chloride in 63% yield. The acid chloride was allowed to react with sodium peroxide following the general procedure of Fieser and Oxford[6] to give the peroxide which in turn was decomposed in an acetic acid solution of 2-hydroxy-1,4-naphthoquinone. The 2-hydroxy-3-[3′-*cis*-(4-acetoxycyclohexyl)-propyl]-1,4-naphthoquinone (XII) was isolated in 36% yield and then deactylated to give *cis*-hydroxy compound (XIII). This latter compound melts at 136–137°. Hence the compound III isolated in the metabolism studies is not the *cis* isomer of compound II. L. F. Fieser has reported in a private communication that the *cis* compound, XIII, is completely inactive when assayed by the antirespiration method previously described by him.[1] The isolated degradation products, II and III, however, show definite activity.

Acknowledgment.—The authors wish to express their appreciation to Professor L. F. Fieser for his interest in this work, and to the Abbott Laboratories for their financial aid.

Experimental[7]

β-(*p*-Anisoyl)-propionic Acid.—The acid was prepared from anisole and succinic anhydride according to the procedure of Rosemund and Shapiro[8] using nitrobenzene as the solvent. The yield was 75–85%. When nitroethane was employed as the solvent the yield was slightly less but this method was more convenient since anhydrous aluminum chloride is soluble in this solvent and could be added in the form of a solution.

γ-(*p*-Methoxyphenyl)-butyric Acid.—The reduced acid was prepared from the above keto-acid either by the Martin modification[9] of the Clemmensen reduction or by the Huang-Minlon[10] modification of the Wolff–Kishner reaction. This latter method was more convenient and the product was obtained in 75% yield.

γ-(*p*-Hydroxyphenyl)-butyric Acid.—The methoxy-acid was demethylated by heating under reflux with 48% hydrobromic acid. The crude acid was recrystallized from benzene and the pure acid melts at 107–108°.

γ-(*p*-Hydroxycyclohexyl)-butyric Acid (V and VI).—This acid was prepared following the procedure described by Fieser and co-workers.[1] From 45 g. (0.25 mole) of γ-(*p*-hydroxyphenyl)-butyric acid, 40 g. (86%) of crude product, which sinters from 80° and melts by 114°, was obtained. This material was added to 300 cc. of ether and the mixture heated under reflux for fifteen minutes. The solid which did not dissolve was filtered and it melts from 118–122°. After recrystallization from aqueous acetic acid, the pure acid melts from 123–124°, yield 32 g. (68.9%). This compound is presumably the *trans* isomer.

The above ethereal extract was concentrated and then petroleum ether was added until turbidity. On cooling, white crystals (6.1 g.) which sinter at 80° and melt from 84–89° were obtained. This solid was fractionally crystallized from a mixture of ether and petroleum ether. The first small fraction was impure *trans* isomer. The second fraction contained 5.0 g. (10.7%) of the pure *cis* acid, m. p. 83–84°. *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.77; H, 9.95.

***cis*-γ-(*p*-Acetoxycyclohexyl)-butyric Acid (X).**—*cis*-γ-(*p*-Hydroxycyclohexyl)-butyric acid (1.0 g., 0.006 mole) was mixed with 6 cc. of acetic anhydride and three drops of concentrated sulfuric acid, allowed to stand at room temperature for eighteen hours, and then poured into 250 cc. of water. The aqueous mixture was extracted with three 25-cc. portions of ether. The water layer then was concentrated, saturated with sodium chloride, and extracted again with ether.

The combined ethereal extracts were washed, dried, and the solvent evaporated. The residual liquid was distilled in a sublimation-type still at a block temperature of 125° and a pressure of 2 mm. The yield was 0.55 g. (44.7%).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.40; H, 8.57.

***cis*-γ-(*p*-Acetoxycyclohexyl)-butyryl Chloride (XI).**—A mixture of 7.2 g. (0.032 mole) of the *cis*-acetoxy acid and 12.2 g. (8.2 cc., 0.01 mole) of oxalyl chloride was warmed at 70° for a period of four hours. The excess oxalyl chloride was then removed and the product distilled, b. p. 139–141° (1 mm.), yield 4.9 g. (63%).

Di-[*cis*-γ-(*p*-acetoxycyclohexyl)-butyryl] Peroxide.—The peroxide was prepared following the procedure of Fieser and Oxford[6] using 4.9 g. (0.02 mole) of acid chloride. A yield of 88% was indicated by titration of an aliquot.[11]

2-Hydroxy-3-[3′-*cis*-(4-acetoxycyclohexyl)-propyl]-1,4-naphthoquinone (XII).—The alkylation was conducted in the flash-off manner[1] using 1.50 g. (0.086 mole) of 2-hydroxy-1,4-naphthoquinone, the peroxide prepared above and 35 cc. of acetic acid. After the evolution of carbon dioxide had ceased, the mixture was refluxed for one hour and the acetic acid removed under reduced pressure. The residual sirup was dissolved in ether and the ethereal solution extracted with dilute, freshly-prepared, aqueous sodium bicarbonate until only a faint pink color was discernible in the aqueous layer. After removal of the ether, the residue was crystallized from aqueous methanol. After several recrystallizations, the yellow solid sinters slightly from 79–99° and melts from 99–100°. When a sample was immersed in a bath at 94°, it melted completely. The yield of the dimorphic compound was 1.1 g. (35.7%) and no single form of dimorph could be isolated.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.46; H, 6.58.

2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone (XIII).—A solution of 0.43 g. (0.0012 mole) of the acetyl compound, 0.1 g. (0.018 mole) of potassium hydroxide and 30 cc. of water was refluxed for one hour. The solution was acidified and a small volume of ethanol was added to effect solution. The product crystallized slowly from this mixture. The yellow solid was best recrystallized by long standing in a large volume of ethanol highly diluted with water containing a trace of acetic acid. The yield was 0.35 g. (92.2%), m. p. 136–137°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.71; H, 7.10.

(5) Gauthier, *Ann. chim.*, **20**, 581 (1945).

(6) Fieser and Oxford, THIS JOURNAL, **64**, 2061 (1942).

(7) Microanalyses by Mr. C. W. Koch. All melting points are uncorrected.

(8) Rosemund and Shapiro, *Arch. Pharm.*, **272**, 313 (1934).

(9) Martin, THIS JOURNAL, **58**, 1438 (1936).

(10) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(11) Kokatnur and Jelling, *ibid.*, **63**, 1432 (1941).

γ-(*p*-Cyclohexanone)-butyric Acid (VII).—A mixture of 3.5 g. of γ-(*p*-hydroxycyclohexyl)-butyric acid (0.019 mole), 10 cc. of acetic acid and 40 cc. of water was placed in a flask equipped with a mechanical stirrer, a dropping funnel and a thermometer which was immersed in the liquid and warmed to 60°. After the acid had dissolved, the solution was cooled to 35° and kept at that temperature for the rest of the reaction.

An oxidizing mixture of 1.9 g. (0.0065 mole) of potassium dichromate, 6 cc. of concentrated sulfuric acid and 14 cc. of water was added over a period of fifteen minutes to the stirred solution. The reaction mixture was stirred for an additional thirty minutes and then it was allowed to stand until all of the oxidizing agent had been consumed. This usually required eight to ten hours. The mixture was then diluted with 200 cc. of water, saturated with sodium chloride and was extracted with ether. Upon evaporation of the ether, a yellow sirup remained which on cooling and scratching crystallized. The product was recrystallized from a mixture of ether and ligroin, yield 1.05 g. (30%), m. p. 81–82°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.91; H, 8.74.

The semicarbazone melts at 183–184°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94. Found: C, 54.99; H, 7.82.

Summary

1. 2-Hydroxy-3-[3′-*cis*-(4-hydroxycyclohexyl)-propyl]-1,4-naphthoquinone has been prepared and has been shown to be different from the low melting metabolite of 2-hydroxy-3-(3′-cyclohexyl-propyl)-1,4-naphthoquinone isolated by Fieser and associates.

2. The hydrogenation of γ-(*p*-cyclohexanone)-butyric acid has been studied.

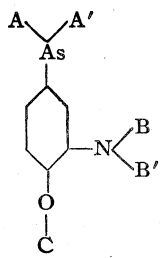
BERKELEY 4, CALIFORNIA RECEIVED DECEMBER 10, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

3-Amino-4-hydroxybenzenearsonous Acid. II. Derivatives

BY C. K. BANKS, JOHN CONTROULIS, D. F. WALKER, E. W. TILLITSON,[1] L. A. SWEET AND O. M. GRUHZIT

The amine salts and arsenite hemiesters of 3-amino-4-hydroxybenzenearsonous acid (I, oxophenarsine) were described in the first paper of this series.[2] All of these compounds, as well as the dihalo derivatives, equilibrate readily in solution to a common ion, postulated to be 3-ammonium-4-hydroxybenzenearsonite. Since this nucleus has been unique in therapeutic agents for the treatment of spirochetal diseases, further variations of the general structure II have been made.

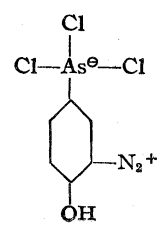


II

Previously reported compounds of this type include the aforementioned salts, hemiesters and acid adducts,[2] mercaptan derivatives in which A and A′ were mercaptoacetic acid, mercaptoacetamide and cysteine,[3] the acetyl derivative (B = $COCH_3$)[4] and compounds in which C was replaced by hydroxyalkyl[5–7] and alkyl groups.[8] Since variations in C appeared to be explored adequately, the principal variants studied were those of A and B. Since 3-amino-4-β-hydroxyethoxybenzenearsonous acid (III)[5] has been found to have practically the same *in vivo* spirochetal activity as I, the β-hydroxyethyl group was selected as the C variant for the study of multiple substitution.

The mercaptol derivatives of I were extended to include mercaptoacetone, octyl mercaptoacetate, thiomalic acid and unsubstituted sulfides. Hydrogen sulfide reacted with I to yield compounds having —$As(SH)_2$, —As(SH)(OH) and —AsS structures, depending on the conditions employed. The mercaptoacetic acid, octyl mercaptoacetate and mercaptoacetamide derivatives of III were also formed. The octyl mercaptoacetates were of interest in that they are soluble in oils.

The amine group was modified by substituting B and B′ with the acid succinamide, benzal, formaldehyde bisulfite and glucose bisulfite groups. Attempts to prepare the analogous formaldehyde sulfoxylate resulted in neoarsphenamine types. Similar amine derivatives were prepared in which A and A′ were replaced by thiols and where C was the hydroxyethyl group. The formaldehyde sul-



IV

(1) Present address, Department of Chemical Engineering, Wayne University, Detroit, Michigan.

(2) Banks, *et al.*, THIS JOURNAL, **69**, 5 (1947).

(3) Barber, *J. Chem. Soc.*, 1020 (1929).

(4) Newbery and Phillips, *ibid.*, 2375 (1928).

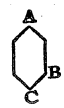
(5) Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).

(6) Bare and Hamilton, *ibid.*, **59**, 2444 (1937).

(7) Holcomb and Hamilton, *ibid.*, **61**, 1236 (1939).

(8) Doak, Steinman and Eagle, *ibid.*, **63**, 99 (1941).

TABLE I



	A	B	Yield, %	Empirical formula[a]	Analysis,[b] % Calcd.	Found	Toxicity[c] I. V.-white rats Compound mg./kg. LD_{50}	As, mg./kg. LD_5	As, mg./kg. LD_{50}	Trypanocidal activity[c] *T. equiperdum*-white rats M. Th. D. mg./kg.	M. C. D. mg./kg.	Th. I.	C. I.
1	As(OH)$_2$	NH$_2$	[d]	$C_6H_8AsNO_3$	34.51	34.47	19.5	17.5	6.73	0.6	2.0	32.5	9.7
2	As(OH)$_2$	NH$_3$Cl	[d]	$C_6H_9AsClNO_3$	29.54	29.62	21.0	16.0	6.21	.7	2.6	30.0	8.1
3	As(OH)(Cl)	NH$_2$	[d]	$C_6H_7AsClNO_2$	31.81	31.74	17.5	16.0	5.57	.6	2.2	29.1	8.0
4	AsO[e]	NH$_3$Cl	[d]	$C_6H_7AsClNO_2$	31.81	31.85	18.5	15.0	5.88	.6	2.5	30.8	7.4
5	[f]	NH$_3$Cl	[d]	$C_{14}H_{20}As_2Cl_2N_2O_5$	28.98	29.11	18.0	14.0	5.22	.4	2.0	45.0	9.0
6	AsO	NH$_2$·1/$_2$SO$_4$	[d]	$C_{12}H_{14}As_2N_2O_8S$	30.20	30.08	17.5	14.0	5.29	.6	3.0	29.1	5.9
7	AsO	NH$_2$·$C_6H_9O_7$[g]	[d]	$C_{12}H_{16}AsNO_9$	19.05	18.98	33.0	20.0	6.29	2.0	4.0	17.5	8.3
8	AsO	NH$_2$·$C_6H_7O_7$[h]	[d]	$C_{12}H_{14}AsNO_9$	19.15	19.17	28.7	25.0	5.50	1.5	4.0	19.0	7.2
9	AsCl$_2$	NH$_3$Cl	[i]	$C_6H_7AsCl_2NO$	25.79	25.82	21.8	15.0	5.62	1.0	3.6	21.8	6.1
10	AsBr$_2$	NH$_3$Br	[j]	$C_6H_7AsBr_2NO$	17.68	17.71	32.5	20.0	4.78	1.5	5.0	21.6	6.5
11	As(SH)(OH)	NH$_2$	78	$C_6H_8AsNO_2S$	32.14	32.02[k]	...	..	...	..	..	..	...
12	As(SH)$_2$	NH$_2$	67	$C_6H_8AsNOS_2$	30.06	30.06	...	..	...	..	..	..	...
13	AsS	NH$_2$	55	C_6H_6AsNOS	34.83	34.58[l]	...	..	...	..	..	..	...
14	As(SH)(OH)	NH$_3$Cl	63	$C_6H_9AsClNO_2S$	27.79	27.74[m]	22.0	18.0	6.11	2.5	4.0	8.8	5.5
15	AsS	NH$_3$Cl	78	$C_6H_7AsClNOS$	29.77	29.98[n]	18.5	15.0	5.55	2.5	3.6	7.4	5.1
16	As(SCH$_2$CO$_2$H)$_2$	NH$_2$	92	$C_{10}H_{12}AsNO_6S_2$	20.51	20.48	...	..	...	..	..	..	...
17	As(SCH$_2$CO$_2$Na)$_2$	NH$_2$	87	$C_{10}H_{10}AsNNa_2O_6S_2$	18.31	18.46	18.0	16.0	3.30	0.8	3.0	22.5	6.0
18	As(SCH CONH$_2$)$_2$	NH$_2$	92	$C_{10}H_{14}AsN_3O_4S_2$	20.62	20.28[p]	...	..	...	..	..	..	...
19	As(SCH$_2$CONH$_2$)$_2$	NH$_3$Cl	90	$C_{10}H_{15}AsClN_3O_3S_2$	18.74	18.48[q]	32.5	20.0	3.75	3.0	4.0	10.8	8.2
20	As(SC$_4$H$_8$O$_4$)$_2$[r]	NH$_2$	68	$C_{14}H_{18}AsNO_9S_2$	15.56	15.38	...	..	...	..	..	..	...
21	As(SC$_{10}$H$_{19}$O$_2$)$_2$	NH$_2$	72	$C_{26}H_{44}AsNO_5S_2$	12.70	13.01	50.0	35.0	6.35	9.0	..	5.5	...
22	As(SCH$_2$COCH$_3$)$_2$	NH$_3$Cl	65	$C_{12}H_{17}AsClNO_3S_2$	18.83	19.01	...	..	...	..	..	..	...
23	AsO[s]	NO$_2$	78	$C_6H_4AsNO_4$	32.71	32.52	5.0	4.0	1.63	> 2.0	..	..	...
24	AsO	NC$_8$H$_8$O$_2$[u]	85	$C_{14}H_{11}AsNO_4$	22.55	22.40	25.0	20.0	5.64	2.0	8.0	12.5	3.1
25	AsO	NHCOCH$_3$	70	$C_8H_{10}AsNO_4$	28.91	28.75	5.0	4.0	1.45	3.0	> 3.0	1.7	...
26	AsO	NHCH$_2$SO$_3$Na[v]	90	$C_7H_9AsNNaO_6S$	22.49	22.25	20.0	12.5	4.50	10.0	15.0	2.0	1.3
27	As(OH)$_2$	NHC$_6$H$_{11}$O$_6$[w]	54	$C_{12}H_{18}AsNO_8$	19.76	19.52	...	..	...	..	..	..	...
28	As(OH)$_2$	NHC$_6$H$_{12}$NaO$_8$S[x]	55	$C_{12}H_{19}AsNNaO_{11}S$	15.50	15.21	70.0	60.0	10.85	>10.0	..	..	...
29	AsO	NHC$_4$H$_6$O$_3$[y]	82	$C_{10}H_{10}AsNO_6$	25.05	24.80	4.5	4.0	1.13	2.0	> 2.0	2.2	...
30	AsCl$_3$$^-$	N$_2$$^+$	92	$C_6H_4AsCl_3N_2O$	24.85	24.86	17.5	15.0	4.35	1.2	> 5.0	14.5	...
31	AsCl$_2$(OH)$^-$	N$_2$$^+$	54	$C_6H_5AsCl_2N_2O_2$	26.48	26.50[z]	...	..	...	..	..	..	...
32	As(SCH$_2$CO$_2$Na)$_2$	NHCH$_2$SO$_2$Na[aa]	70	$C_{11}H_{11}AsNNa_4O_7S_2$	14.71	14.78	30.0	25.0	4.41	5.0	10.0	6.0	3.0
33	As(SCH$_2$CO$_2$Na)$_2$	NHCH$_2$SO$_3$Na[v]	85	$C_{11}H_{11}AsNNa_4O_8S_2$	14.26	14.10	58.0	52.0	8.27	12.0	20.0	4.8	2.9
34	As(SCH$_2$CO$_2$Na)$_2$	NHC$_6$H$_{12}$NaO$_8$S[x]	68	$C_{16}H_{21}AsNNa_3O_{14}S_2$	11.09	10.84	101.0	93.0	11.20	12.0	15.0	8.4	6.7
35	As(SCH$_2$CONH$_2$)$_2$	NHC$_6$H$_{12}$NaO$_8$S[x]		[cc]			45.0	35.0	5.00	> 8.0	..	..	...
	C=OCH$_2$CH$_2$OH												
36	As(OH)$_2$	NH$_2$		[bb]			16.5	10.0	4.75	0.8	3.5	20.6	4.7
37	As(SCH$_2$CO$_2$H)$_2$	NH$_2$	82	$C_{12}H_{16}AsNO_6S_2$	18.30	18.25	...	..	...	..	..	..	...
38	As(SCH$_2$CO$_2$Na)$_2$	NH$_2$	90	$C_{12}H_{14}AsNNa_2O_6S_2$	16.53	16.48	27.5	25.0	4.55	2.5	3.5	11.0	7.9
39	As(SCH$_2$CONH$_2$)$_2$	NH$_2$	82	$C_{12}H_{18}AsN_3O_4S_2$	18.39	18.32	...	..	...	..	..	..	...
40	As(SCH$_2$CONH$_2$)$_2$	NH$_3$Cl	88	$C_{12}H_{19}AsClN_3O_4S_2$	16.88	16.70	60.0	40.0	10.13	3.0	8.0	20.0	7.5
41	As(SC$_{10}$H$_{19}$O$_2$)$_2$[s]	NH$_2$	78	$C_{28}H_{48}AsNO_6S_2$	11.82	11.43	40.0	30.0	4.73	8.0	>20.0	5.0	...
42	As(OH)$_2$	NHCH$_2$SO$_3$Na[v]	85	$C_9H_{12}AsNNaO_7S$	19.86	19.72	50.0	30.0	9.93	15.0	20.0	3.3	2.5
43	As(SCH$_2$CO$_2$Na)$_2$	NHCH$_2$SO$_3$Na[v]	75	$C_{13}H_{15}AsNNa_2O_9S_2$	13.16	13.10	70.0	55.0	9.21	20.0	>30.0	3.5	...
44	As(SCH$_2$CONH$_2$)$_2$	NHCH$_2$SO$_3$Na[v]	67	$C_{13}H_{19}AsN_3NaO_7S_3$	14.31	14.20	27.5	25.0	3.84	3.0	7.0	9.2	4.0
45	As(SCH$_2$CO$_2$Na)$_2$	NHC$_6$H$_{12}$NaO$_8$S[x]		[cc]			75.0	60.0	7.50	8.0	30.0	9.4	2.5
	C=—OCH$_2$CHOHCH$_3$												
46	As(OH)$_2$	NH$_2$		[dd]			15.0	12.0	4.10	0.5	2.0	30.0	7.5
	C=—OCH$_2$C(OH)(CH$_3$)$_2$												
47	As(OH)$_2$	NH$_2$		[ee]			14.0	10.0	3.71	4.0	..	3.5	...

[a] No attempt has been made to indicate degree of polymerization but all —AsO and —AsS compounds are at least dimeric, see ref. 2. [b] By Banks and Sultzaberger, THIS JOURNAL, **69**, 1 (1947), when possible, otherwise by methods A or D, Banks, Sultzaberger, Maurina and Hamilton, *J. Am. Pharm. Assocn., Sci. Ed.*, **37**, 13 (1948). [c] See text for details. [d] Ref. 2. [e] Oxophenarsine hydrochloride, U. S. P. [f] Hydrochloride hemialcoholate of Ehrlich and Bertheim. *Ber.*, **45**, 756 (1912), in which the arsenic portion has the structure, HOAs(R)—O—As(R)OC$_2$H$_5$, see Ref. 2. [g] Ascorbate. [h] Citrate. [i] Dichlorophenarsine hydrochloride, U. S. P., Binz and Bauer, *Z. angew. Chem.*, **34**, 261 (1921). [j] U. S. Patent 2,222,384 (1940). [k] S, calcd.: 13.75%; found: 13.80%. [l] S, calcd.: 14.90%; found: 14.78%. [m] S, calcd.: 11.88%; found: 11.96%. [n] S, calcd.: 12.74%; found: 12.46%. [p] N, calcd.: 11.57%; found: 11.43%. [q] N, Calcd.: 10.51%; found: 10.30%. [r] From α-mercaptosuccinic (thiomalic) acid. [s] From octyl mercaptoacetate. [t] Christiansen, *et al.*, THIS JOURNAL, **47**, 2716 (1925). [u] Anil from vanillin. [v] Formaldehyde bisulfite. [w] Glucosyl. [x] Sodium glucosebisulfite. [y] Succinyl. [z] N, calcd.: 9.91%; found: 10.14%. [aa] Formaldehyde sulfoxylate. [bb] Sweet and Hamilton, *ibid.*, **56**, 2409 (1934). [cc] Used in solution without isolation. [dd] Stevenson and Hamilton, *ibid.*, **57**, 1600 (1935). [ee] Holcomb and Hamilton, *ibid.*, **61**, 1236 (1939).

foxylates of the thiol substituted arsenicals were prepared without difficulty.

I was also diazotized and 3-diazonium-4-hydroxybenzenetrichloroarsonite (IV) isolated on strong acidification. This proved to be identical with the reduction product of 3-diazonium-4-hydroxybenzenearsonate described by Schmidt and Hoffmann.[9] However, decomposition of this compound in methanol followed by precipitation

(9) Schmidt and Hoffmann, *Ber.*, **59**, 560 (1926).

with ether did not result in 3-diazido-3,4-quinone-1-dichloroarsine as they report but in 3-diazonium-4-hydroxybenzenedichloroarsonite. This was confirmed by elemental analysis for C, H, N, As and Cl, and by the reactions of the substance. The compounds prepared, their toxicity and trypanocidal activity are listed in Table I. The treponemacidal effect of selected compounds is given in Table II.

TABLE II

RELATIVE TREPONEMACIDAL ACTIVITY

No. in Table I	CD_{50}, mg./kg. × 3, I. V. rabbits	No. in Table I	CD_{50}, mg./kg. × 3, I. V. rabbits
1	1.5	17	1.5
2	1.0	33	4.0
3	1.0	35	5.25
5	1.5	36	1.5
9	1.5	46	1.75

Experimental

3-Amino-4-hydroxybenzenearsonous acid and 3-amino-4-β-hydroxybenzenearsonous acid were prepared according to previously published methods.[2,5]

Sulfides.—A solution of 3-amino-4-hydroxybenzenearsonous acid (0.1 mole), prepared by dissolving the acid in 100 ml. of water with an excess of hydrochloric acid and then neutralizing the solution to *p*H 6, was saturated with hydrogen sulfide. On standing in the refrigerator, the —As(SH)(OH) compound separated. When the addition of hydrogen sulfide was made in the presence of two equivalents of hydrochloric acid, the corresponding *hydrochloride* separated. On drying at 0.5 mm. and 37° over phosphorus pentoxide, the analogous —AsS compounds were formed. Addition of ammonium sulfide to the original solution precipitated the $As(SH)_2$ compound.

Mercapto Products.—Mercaptoacetic acid (0.2 mole) was added to a solution of the arsonous acid (0.1 mole) and the *p*H adjusted to 7 with sodium hydroxide. Seven volumes of alcohol were added to crystallize the *sodium salts*. The free *mercaptoacetic acid derivatives* were formed by acidification of aqueous solutions of their sodium salts with hydrochloric acid. Other mercapto derivatives were prepared by the reaction of an alcohol solution of the mercaptan with an alcohol solution of the arsonous acid. The *hydrochlorides* were crystallized by the addition of dry hydrogen chloride gas, with cooling, and the *free bases* liberated from aqueous solutions of the hydrochlorides by neutralization with sodium hydroxide.

Formaldehyde and Glucose Bisulfites.—Water (40 ml.) was heated to boiling for a few minutes, then allowed to cool. At 90° the sodium aldehyde bisulfite (0.1 mole) was added and when cooled to 70°, the arsonous acid, or other arylamino arsenical, was added (0.1 mole) and stirred until solution occurred. The solution was clarified with charcoal, filtered and cooled to 30° and 600 ml. of ethanol added. On standing in an ice-bath, the products crystallized.

Formaldehyde Sulfoxylates.—Water (40 ml.), previously boiled and cooled under nitrogen, was used to dissolve sodium formaldehyde-sulfoxylate (0.1 mole) and the arylaminoarsenical (0.1 mole). When the reaction was complete, the solution was clarified with charcoal and the product crystallized by the addition of six volumes of ethanol.

Acyl Derivatives.—The corresponding arsonic acids were reduced by previously described techniques.[2]

3-Diazonium-4-hydroxybenzenetrichloroarsonite.—3-Amino-4-hydroxybenzenearsonous acid (217 g.) was suspended in 60.0 ml. of 3 *N* hydrochloric acid. The solution was cooled externally and a mole of sodium nitrite, dissolved in water, added slowly. As soon as the diazotization was complete, the resulting solution was filtered and a liter of cold concentrated hydrochloric acid added slowly with cooling. The crystalline product was filtered off and washed with glacial acetic acid and ether.

The compound is a pale yellow powder, soluble in water, alcohols, acetone, and dioxane but insoluble in benzene, ether and petrolic ether. The compound exploded on heating. Solutions of the substance in water coupled with β-naphthol and α-dimethylaminonaphthalene to yield deeply colored dyes.

3-Diazonium-4-hydroxybenzenedichloroarsonite.—Ten grams of the trichloroarsonite was dissolved in a minimum of absolute methanol, allowed to stand a few minutes until gas evolution ceased and an excess of anhydrous ether added. A bright yellow product separated. It was filtered off, and dried in a vacuum desiccator. It has the same solubilities and reactions as the trichloro compounds.

Pharmacological Evaluations

Toxicity.—The intravenous toxicity of each compound was determined in albino male rats as previously described.[10] The dose which was lethal for 50% of the animals (LD_{50}) was calculated by the method of Dragstedt and Lang.[11] The LD_{50} and LD_5 are given in Table I in terms of mg. compound per kg. body weight of animal. The LD_{50} values in terms of compound administered also were converted to LD_{50} figures in terms of mg. As per kg. for purposes of comparison.

It can be seen that all of the simple salts and haloarsine derivatives of compound 1 have approximately the same toxicity in terms of arsenic administered (compound 10 may be considered an exception). This is compatible with the hypothesis that all derivatives of this type (1–10 incl.) are converted in aqueous solution to the same form.

The substitution of mercapto groups on arsenic (14, 15, 17, 19, 21, 32, 33, 34, 35) either did not affect or increased the relative toxicity. No general postulations can be made as to the result of substituting hydrogens of the amino group.

Trypanocidal Activity.—The compounds were administered to albino male rats previously infected with a standardized strain of *Trypanosoma equiperdum*. The techniques have been described previously.[10] The minimum therapeutic dose (M.Th.D.) is designated as the minimal dose of drug which entirely eliminated trypanosomes from the peripheral blood forty-eight hours after treatment and the minimum curative dose (M.C.D.) as that dose which prevented relapse of the infection for four weeks. The therapeutic index (Th.I.) is taken as the ratio LD_{50}/M.Th.D. and the curative index (C.I.) as the ratio LD_{50}/M.C.D. The results are given in Table I. Those compounds which can generate No. 1 on solution and neutralization all have comparable activities (2–10 incl.). Sulfhydryl derivatives were of the same or lower order of activity. In general, the trypanocidal effect was lessened when the amino group was substituted. While the substitution of the hydroxyl by a β-hydroxyalkoxyl group did not appreciably affect activity, further substitution on arsenic or nitrogen had approximately the same effect as was noted in the analogous hydroxyl compounds.

Treponemacidal Activity.[12]—Healthy normal rabbits of different breeds were infected with a virulent Nichols strain of *Treponema pallidum* and held until lesions became well developed. The rabbits were treated intravenously with selected compounds three times on alternate days. They were observed for regression of the lesions and by microscopic darkfield examination for the disappearance of spirochetes. The popliteal lymph glands of those rabbits showing no lesions three months after treatment were excised and implanted intratesticularly in normal

(10) Banks, Controulis, Tillitson and Gruhzit, THIS JOURNAL, **66**, 1771 (1944).

(11) Dragstedt and Lang, *J. Pharm. Exptl. Therap.*, **32**, 215 (1927–1928).

(12) A more complete discussion of procedures may be found in Gruhzit, O.M., *Arch. Derm. Syph.*, **32**, 848 (1935).

animals. Absence of syphilitic lesions in the transfer animals over a period of three months was taken as the criterion of cure. The results are given in Table II. In general, compounds which revert to 1 in solution had approximately equal activity, mercapto derivatives being about equally active. Substitution of hydroxyalkoxyl groups for hydroxyl may have decreased the activity slightly but substitution of amino hydrogen resulted in marked reduction of activity.

Summary

1. A number of new derivatives of 3-amino-4-hydroxybenzenearsonous acid have been prepared for trypanocidal and treponemacidal studies. These consisted of variations in which easily and difficultly hydrolyzable groups were attached to the arsenic, nitrogen and phenolic oxygen atoms.

2. Animal studies indicated that none of the compounds was more active than the parent compound and that only those compounds having readily hydrolyzed groups retained any appreciable activity.

DETROIT, MICHIGAN RECEIVED NOVEMBER 15, 1947

[CONTRIBUTION FROM THE INSTITUTE OF MATERIA MEDICA, NATIONAL ACADEMY OF PEIPING, SHANGHAI, AND THE PHARMACOLOGICAL LABORATORY, NATIONAL INSTITUTE OF HEALTH, NANKING]

Antimalarial Constituents of Chinese Drug, Ch'ang Shan, *Dichroa febrifuga* Lour

BY T. Q. CHOU, F. Y. FU AND Y. S. KAO

A brief account on the isolation of an antimalarial alkaloid named dichroine from the Chinese drug, Ch'ang Shan, identified as *Dichroa febrifuga* Lour., has been reported.[1] Mention should be made that the name dichroine has been used previously by Hartwich[2] to indicate a carbohydrate of an indefinite nature isolated from the same plant. The alkaloid dichroine has the composition $C_{16}H_{21}O_3N_3$ and easily undergoes isomeric change under the action of heat, acids, and alkalies, and even with different solvents used. Three isomerides, which are provisionally named, α-, β- and γ-dichroines, have been obtained, melting, respectively, at 136, 145 and 160°, and being convertible into each other under suitable conditions. Oxidized with potassium permanganate, dichroine yields 4-quinazolone and some other products not yet identified. Hydrolysis with sodium hydroxide gives easily the decomposition products, anthranilic acid, formic acid, and ammonia, together with a compound which behaves like a pyrrole derivative. Benzoylation with benzoyl chloride furnishes most probably a tribenzoyl derivative of dichroine according to its nitrogen content. No presence of carboxyl-, methoxyl- and methylenedioxy- groups could be detected in the molecule of dichroine. Dichroine forms both normal and acid salts and a nitroso compound. Besides dichroine, 4-quinazolone, a base with the composition $C_{18}H_{23}N_3O_3$, and umbelliferon have also been isolated from the roots of Ch'ang Shan; the first one may be originally present in the plant or resulted during chemical manipulation. Synthetic quinazoline derivatives used as antimalarials have recently been investigated extensively by Magidson and Yolovchinskaya[3] and others. The isolation of 4-quinazolone from a natural plant affords a remarkable coincidence with the chemical research along this line, although the quinazolone nucleus has already been found in certain alkaloids.[4] Regarding the antimalarial activity of dichroines, the γ-isomeride shows the greatest, and α-isomeride the least; the curative dose for chicken malaria being found to be 4 mg. of γ-isomer per kg.[5]

Experimental

The finely powdered root of Ch'ang Shan is percolated with 90% alcohol at room temperature for two days and the extract evaporated in a vacuum. The residue is taken up with dilute hydrochloric acid, filtered, and extracted repeatedly with ether, which constitutes fraction A. The acid solution is rendered slightly alkaline with sodium bicarbonate and shaken well with ether containing about 20% of chloroform (fraction B). The aqueous solution is then made strongly alkaline with potassium carbonate and extracted several times with chloroform (fraction C).

Umbelliferon, $C_9H_6O_3$.—The residue obtained from fraction A, by distilling off ether, crystallizes from alcohol in colorless needles, m. p. 224–227°, sparingly soluble in water, but easily soluble in chloroform, alcohol, and alkaline solutions, the last possessing an intense blue fluorescence. Its properties and analysis correspond well to umbelliferon (7-hydroxycoumarine). *Anal.* Calcd. for $C_9H_6O_3$: C, 66.6; H, 3.7. Found: C, 66.6; H, 3.9.

4-Quinazolone.—Fraction B, on evaporation of ether–chloroform mixture, gives a product which crystallizes from alcohol in silky long needles, m. p. 212–213°. It is identical in all respects with a sample of 4-quinazolone prepared by heating 2 g. of anthranilic acid and 1 g. of formamide for two hours at 120–130° and crystallizing the resulting products from alcohol. Its analysis as well as those of its hydrochloride and platinum salt confirms its composition $C_8H_6ON_2$. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.8; H, 4.1; N, 19.1. Found: C, 65.6; H, 4.4; N, 19.1.

Hydrochloride.—It is obtained by treating an alcoholic solution of 4-quinazolone with hydrochloric acid gas dissolved in alcohol and adding a sufficient quantity of ether; needles, m. p. 247°. Its aqueous solution is acid to litmus paper. *Anal.* Calcd. for $C_8H_6ON_2 \cdot HCl$: N, 15.3; Cl, 19.4. Found: N, 15.0; Cl, 19.2.

Platinum Salt.—It is obtained by treating an alcoholic solution of 4-quinazolone with an aqueous solution of platinum chloride in the presence of hydrochloric acid and

(1) Chou, Jang, Fu, Kao and Huang, *Science (Chinese)*, **29**, No. 2, 49 (1947).

(2) Hartwich, *Neue Arzneidrog*, 127 (1897).

(3) Magidson and Yolovchinskaya, *J. Gen. Chem. (U. S. S. R.)*, **8**, 1797 (1938).

(4) Asahina, Manske and Robinson, *J. Chem. Soc.*, 1708 (1927).

(5) Jang and co-workers, private communication.

Table I

Analytical Results of Three Dichroines, their Salts, and Derivatives Described in This Paper

	Formula	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
α-Dichroine	$C_{16}H_{21}O_3N_3$	136	63.3	63.5 63.4	7.0	7.3 6.7	13.9	14.1		
α-Dichroine monohydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	210	56.6	56.3	6.5	6.4	12.4	12.2	10.4	10.4
α-Dichroine sulfate	$(C_{16}H_{21}O_3N_3)_2 \cdot H_2SO_4$	220	54.5	54.8 54.3	6.3	5.9 6.1	11.9	11.5		..
Nitroso-α-dichroine	$C_{16}H_{20}O_4N_4$	182	..	..		...	16.9	17.2		..
β-Dichroine	$C_{16}H_{21}O_3N_3$	145	63.3	63.3 63.1	7.0	6.9 6.5	13.9	14.0 13.8		..
β-Dichroine monohydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	220	56.5	56.4 56.8	6.5	6.2 6.5	12.4	12.2 12.3	10.4	10.4
β-Dichroine dihydrochloride	$C_{16}H_{21}O_3N_3 \cdot 2HCl$	236	51.5	51.1	6.2	6.2	11.2	11.3	18.9	19.1
β-Dichroine sulfate	$(C_{16}H_{21}O_3N_3)_2 \cdot H_2SO_4$	224	54.5	54.61	6.3	6.5		..		..
Tribenzoyl-β-dichroine	$C_{16}H_{18}O_3N_3(C_6H_5CO)_3$			..		...	6.8	7.2		..
Nitroso-β-dichroine	$C_{16}H_{20}O_4N_4$	170		..		...	16.9	17.0		..
γ-Dichroine	$C_{16}H_{21}O_3N_3$	160	63.3	63.4	7.0	6.7	13.9	13.9		..
γ-Dichroine monohydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	220		..		...		..	10.4	10.4
Nitroso-γ-dichroine	$C_{16}H_{20}O_4N_4$	170		..		...	16.9	16.9		..

recrystallizing the resulting precipitate from aqueous alcohol; yellowish prisms, m. p. above 250°. *Anal.* Calcd. for $(C_8H_6ON_2 \cdot HCl)_2 \cdot PtCl_4$: Pt, 27.8. Found: Pt, 28.0.

Alkaloid, $C_{18}H_{23}O_3N_3$.—It is isolated from the mother liquor of 4-quinazolone by fractional crystallization with alcohol. When crystallized pure from acetone, it forms small prisms, m. p. 212–213°. *Anal.* Calcd. for $C_{18}H_{23}O_3N_3$: C, 65.6; H, 7.0; N, 12.7. Found: C, 65.6; H, 6.7; N, 12.6.

Dichroines.—Three isomerides, which are named α-, β- and γ-dichroines, are isolated as follows: the chloroform extract (fraction C) is evaporated and the residue taken up with about five times its volume of absolute alcohol. On neutralizing with hydrochloric acid gas in alcohol, a mixture of hydrochlorides, chiefly of β- and γ-dichroines, crystallizes rapidly. The alcoholic mother liquor is evaporated in a vacuum, and the residue taken up with water and filtered. On alkalinization with sodium carbonate, the liberated base is extracted with chloroform, distilled, and neutralized with sulfuric acid in alcohol, at which time α-dichroine sulfate crystallizes out in almost a pure state, being soluble in alcohol or cold water with difficulty.

α-Dichroine can be prepared easily by dissolving its sulfate as described above in warm water, making alkaline with sodium carbonate, and extracting the liberated base with chloroform. It crystallizes from alcohol in colorless hard prisms, m. p. 136°, being soluble in chloroform, alcohol, or acetone and much less so in cold water. When heated to its melting point and maintained at that temperature for a few minutes, or its aqueous solution is warmed on the water-bath for an hour or so, it is converted into β-dichroine, m. p. 145°. It forms a hydrochloride, prismatic needles from alcohol, m. p. 210°; a sulfate, silky needles from alcohol, m. p. 220°; and a nitroso compound, needles from alcohol or acetone, m. p. 182°. Its dihydrochloride and acid sulfate can also be prepared when excess of respective acids is used (all analyses are given in Table I).

β-Dichroine.—When the crude dichroine bases are crystallized from an organic solvent such as chloroform, it is always the β-dichroine which crystallizes out slowly on standing; needles, m. p. 145°. It is much more soluble in cold water than α-dichroine. It forms a hydrochloride, prisms, m. p. 220°, easily soluble in methyl alcohol or water; a dihydrochloride, needles, m. p. 236°; a neutral sulfate, needles, m. p. 224°; and a nitroso derivative, rhombic prisms, m. p. 170°; alcohol being used for crystallization of either the salts or nitroso compound (see Table I for analyses).

γ-Dichroine is prepared by heating α- or β-dichroine to a temperature of about 145° for ten to twenty minutes and crystallizing the resulting product rapidly from a small amount of acetone. It forms silky needles, m. p. 160°. When crystallized slowly from alcohol or chloroform, it converts back to β-dichroine, m. p. 145°. Its hydrochloride, dihydrochloride, sulfate, and nitroso compound are found to be the same as those of β-dichroine, possessing the same physical and chemical properties (Table I).

Benzoylation.—A solution of 0.5 g. of β-dichroine in 3 cc. of 10% sodium hydroxide is treated with 1.5 cc. of benzoyl chloride with vigorous shaking. The resulting semi-solid mass is taken up with ether and the ethereal solution washed with dilute sodium carbonate solution, dried with anhydrous sodium sulfate, and distilled. The residue refuses to crystallize from any of the usual organic solvents tried. Its nitrogen content corresponds to that of the tribenzoyl derivative when analyzed (Table I). Similar results are obtained with either α- or γ-dichroine.

Oxidation with Potassium Permanganate.—To a solution of 0.2 g. of α-dichroine in 20 cc. of water is added 10 cc. of a 5% potassium permanganate solution. After being allowed to stand at room temperature for two hours, the aqueous solution is filtered, decolorized with a few drops of sodium thiosulfate solution, mixed with some sodium bicarbonate, and extracted with ether. The ethereal solution is dried and distilled, and the residue taken up with a little alcohol, whereupon 4-quinazolone crystallizes in needles, m. p. 212–213°. When mixed with a pure specimen of 4-quinazolone isolated from the plant or prepared synthetically, as above described, its melting point remains unchanged.

Hydrolysis with Sodium Hydroxide.—A solution of 2 g. of α-dichroine in 40 cc. of water with addition of 20 cc. of 15% sodium hydroxide solution is refluxed on the water-bath for an hour and then steam distilled. The distillate smells of ammonia. When neutralized with hydrochloric acid and evaporated to dryness, the residue crystallizes from dilute alcohol in needles, subliming when heated, and being identical to ammonium chloride. The alkaline solution, after steam distillation, is acidified with acetic acid and extracted with ether. The ethereal solution is distilled and the residue crystallized from hot water, small prisms, m. p. 145°; when mixed with pure anthranilic acid, its melting point remains unchanged. *Anal.* Calcd. for anthranilic acid, $C_7H_7O_2N$: C, 61.3;

H, 5.2; N, 10.2. Found: C, 61.3; H, 5.4; N, 10.5. After removal of anthranilic acid, as above, the acid solution is made alkaline with sodium bicarbonate and extracted with ether. The ethereal solution, when evaporated, leaves behind an oily basic residue which behaves like a pyrrole derivative, imparting a red color to a pine shaving moistened with hydrochloric acid. The alkaline solution is again acidified with sulfuric acid and steam distilled. The steam distillate is acid to congo paper, and after neutralization with sodium hydroxide and evaporation, leaves behind a salt identical to sodium formate. *Anal.* Calcd. for HCOONa: Na, 33.3. Found: Na, 31.8.

Summary

From the Chinese drug, Ch'ang Shan, identified as *Dichroa febrifuga* Lour., there have been isolated umbelliferon, 4-quinazolone, a base with the composition $C_{18}H_{23}O_3N_3$, and a water soluble alkaloid named dichroine. The last compound has the composition $C_{16}H_{21}O_3N_3$ and undergoes easily isomeric change with the formation of three isomerides, which are provisionally named α-, β- and γ-dichroines, being convertible into each other under suitable conditions. Regarding their antimalarial activity, the γ-isomeride shows the greatest, and the α-isomeride the least. Based on the results of oxidation and alkaline hydrolysis, dichroine appears to be composed of 4-quinazolone and a pyrrole derivative which requires further investigation. Dichroine forms both normal and acid salts and a nitroso compound. The isolation of 4-quinazolone from a natural plant, Ch'ang Shan, affords a remarkable coincidence with the chemical research for antimalarials along this line.

RECEIVED JUNE 21, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

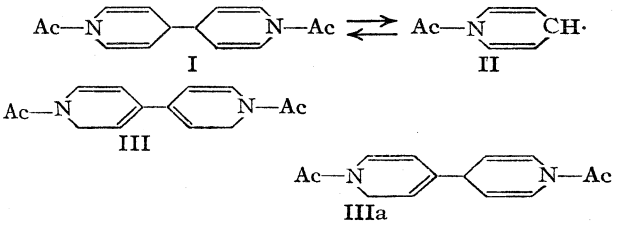
Pyridines. II. The Dissociation of N,N'-Diacetyltetrahydro-4,4'-dipyridyl[1]

BY ROBERT L. FRANK, FLOYD PELLETIER AND FRED W. STARKS

The reductive acetylation of pyridine by means of zinc and acetic anhydride was first reported by Dimroth and Heene[2] to yield the bimolecular product N,N'-diacetyltetrahydro-4,4'-dipyridyl (I). They observed that the compound exists in two interconvertible modifications, one white, the other yellow. Dimroth and Frister[3] later suggested that the yellow color might be due to an impurity, N,N'-diacetyldihydro-4,4'-dipyridyl.

It has occurred to us that either of two phenomena might be responsible for the existence of the two forms of this compound. The easy cleavage of the 4,4' valence bond between the rings in compounds of this type[2-6] suggests that the yellow color is connected with dissociation of the colorless form (I) into radicals (II).[7] On the other hand the work of Mumm and co-workers[5] on N-alkylated tetrahydrodipyridyls and the fact that α-dihydropyridines are yellow while the γ-isomers are colorless[8] presents the alternative proposition that the white and yellow forms may be represented by Structures I and III (or IIIa), respectively, owing to isomerism of double bonds.

The evidence presented herein favors the dissociation theory and renders unlikely the rearrangement of double bonds.



The interconversion of the two modifications depends on the solvent and on the temperature. If the white form is dissolved in methanol, ethanol, acetone or dioxane, it stays white until heated, then turns yellow. On cooling it again becomes colorless. In acetic acid or chloroform the white form turns yellow on standing at room temperature, or more quickly on heating.

Both forms have been reported to have the same m. p.[2] The reason for this is that the white crystals can be observed to turn yellow before melting. This change is first evident at about 105° and the material is bright yellow just before melting at 130–131°. This thermal conversion from white to yellow conforms with the idea that the yellow form contains radicals, since dissociation should be more likely at elevated temperatures.

Further, the yellow color in solutions is dispelled by small amounts of air. This is to be expected of radicals,[9] and may signify the formation of a peroxide from the dissociated form. No peroxide has been found, however, and complete air oxidation either of solutions or of the crystalline forms, yields 4,4'-dipyridyl.[2]

Measurements of the magnetic susceptibility of the two crystalline forms further indicate the presence of radicals in the yellow modification. The

(1) For the previous communication on pyridine chemistry, see Frank, Blegen, Dearborn, Myers and Woodward, THIS JOURNAL, **68**, 1368 (1946).

(2) Dimroth and Heene, *Ber.*, **54**, 2934 (1921).

(3) Dimroth and Frister, *ibid.*, **55**, 1223 (1922).

(4) Emmert, *ibid.*, **53**, 370 (1920).

(5) Mumm, Roder and Ludwig, *ibid.*, **57**, 865 (1924); Mumm and Ludwig, *ibid.*, **59**, 1605 (1926).

(6) Wibaut and Arens, *Rec. trav. chim.*, **60**, 119 (1941).

(7) Structure II represents only one of the several possible resonance forms for such a radical.

(8) Karrer, Schwarzenbach, Benz and Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(9) Gomberg and Cone, *Ber.*, **37**, 3538 (1904).

yellow form was found to be paramagnetic ($K = +0.437 \times 10^{-6}$), while the white is diamagnetic ($K = -0.199 \times 10^{-6}$).

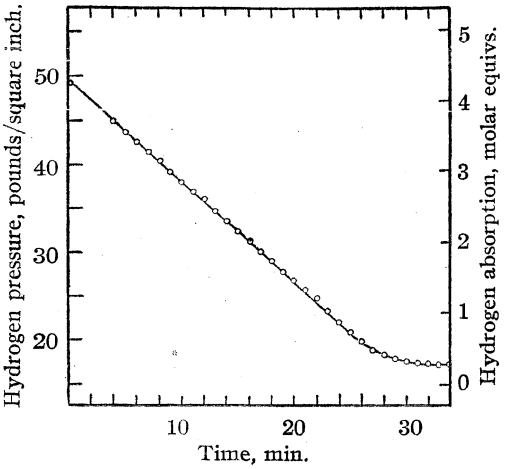


Fig. 1.—Rate of hydrogenation of N,N′-diacetyltetrahydro-4,4′-dipyridyl.

Considering now the data which rule out Structure III (or IIIa) for the yellow form, the rate of complete hydrogenation of yellow N,N′-diacetyltetrahydro-4,4′-dipyridyl over platinum oxide in acetic acid showed that all four double bonds absorb hydrogen at the same rate (Fig. 1). This indicates four unconjugated double bonds, as in Structure I. Structure III would be expected to absorb the last mole of hydrogen more slowly than the first three.

tetrahydro-4,4′-dipyridyl gave succinic acid as the only isolable product. Succinic acid would be expected from Structure I, but is not possible from Structures III or IIIa.

Although the above evidence is best interpreted by dissociation of Structure I into free radicals, the amount of dissociation at room temperature is probably slight, since the catalytic hydrogenation of the yellow form gave only N,N′-diacetyl-4,4′-dipiperidyl. No N-acetylpiperidine, the expected reduction product of the radical (II), was found.

One further experiment was considered, the effect of the white and yellow forms on the polymerization of styrene. When a trace of either form was added to styrene and the styrene heated in a sealed viscosimeter at 58°, the solution containing the white form turned yellow, and in either case polymerization of the styrene was completely inhibited.

Experimental

N,N′-Diacetyltetrahydro-4,4′-dipyridyl (I).—A yield of 23.6 g. (20%) of the yellow form was obtained using the directions of Wibaut and Arens[9] from 50.0 g. (0.632 mole) of freshly-distilled pyridine. From this was obtained in 75% yield the colorless modification by means of 0.5% methanolic potassium hydroxide.[6,11] The b. p. of 10.00 ml. of chloroform was raised 0.128° by 0.10995 g. of the compound (yellow in boiling chloroform); mol. wt. 224 (calcd. for undissociated molecule 244).

Behavior in Solutions and in Air.—Small amounts (0.1–1.0%) of colorless N,N′-diacetyltetrahydro-4,4′-dipyridyl dissolved in methanol, ethanol, acetone or dioxane become yellow on warming in a stoppered flask. On cooling, the solution becomes colorless. If the heated flask is opened to the air and shaken, the solution becomes colorless, but gradually turns yellow again if restoppered. The

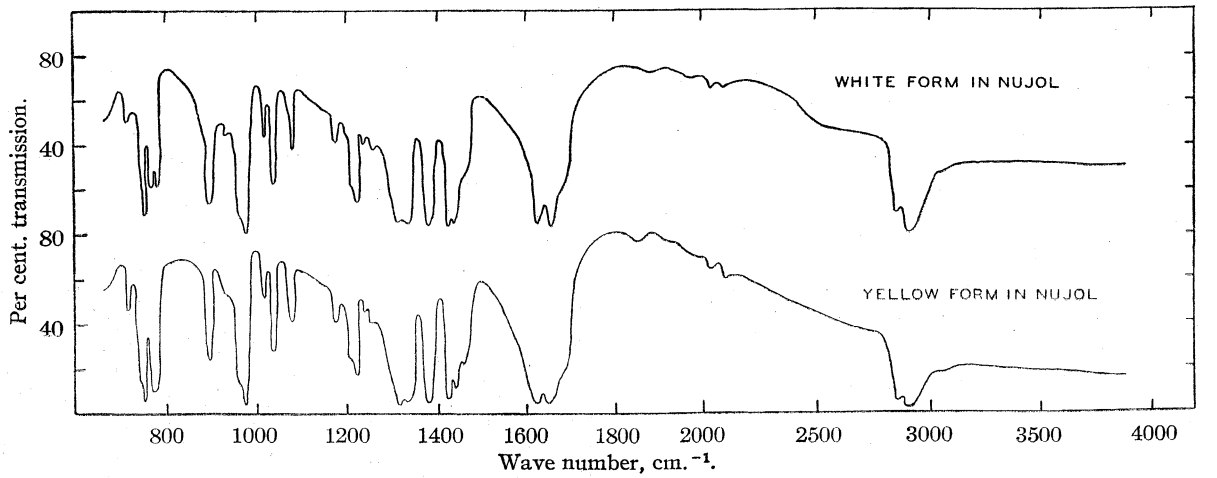


Fig. 2.—Infrared spectra of solid, N,N′-diacetyltetrahydro-4,4′-dipyridyl.

Infrared (Fig. 2) and ultraviolet (maximum at 239 mμ (log ε = 3.73)) absorption spectra of both white and yellow forms are essentially identical, which would not be expected if the forms differed in the manner of Structure I and III (or IIIa).[10]

Ozonolysis of the yellow form of N,N′-diacetyl

yellow crystalline modification, dissolved (0.1%) in any of these solvents open to the atmosphere at room temperature, becomes colorless in five to ten minutes.

The same properties are exhibited in glacial acetic acid or chloroform, except that in these solvents the yellow

(10) Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Corp., New York, N. Y., 1944, pp. 1–25.

(11) This "conversion" of the yellow to the white form is probably not a conversion at all, but rather the oxidative destruction of the small amount of yellow dissociated material present, with subsequent recovery of the remaining undissociated compound.

color predominates at room temperature as well as at higher temperatures.

Prolonged heating of the yellow acetic acid (or ethanol) solution gives rise to the deep blue color observed and studied by Dimroth and co-workers.[2,3]

In the crystalline form both modifications decompose on standing in air (the yellow form apparently more readily) to give a brown oil having the odor of pyridine. From one such sample was isolated a small quantity of 4,4′-dipyridyl as its crystalline hydrate, m. p. 105–106°; m. p. of picrate 252–254° (Dimroth and Heene[2] have reported the isolation of 4,4′-dipyridyl from air-oxidized ethanolic solutions).

Magnetic Susceptibility.—The measurements were kindly carried out by Mr. Clayton Callis using the apparatus described by Driggs and Hopkins.[12] All measurements were taken at 25° on the two solid forms of N,N′-diacetyltetrahydro-4,4′-dipyridyl and the magnetic susceptibility (K) calculated in units per gram.

Quantitative Catalytic Hydrogenation.—Eight and six-tenths grams (0.035 mole) of yellow N,N′-diacetyltetrahydro-4,4′-dipyridyl dissolved in 130 ml. of glacial acetic acid was hydrogenated over 0.2 g. of platinum oxide at room temperature and 50 pounds per square inch initial pressure. Hydrogen was absorbed as shown in Fig. 1. Removal of the solvent under reduced pressure gave a white residue which yielded on recrystallization from dioxane 6.3 g. (74%) of shiny colorless plates of N,N′-diacetyl-4,4′-dipiperidyl, m. p. 173.5–174.5° (reported,[13] 174°). Attempts to hydrogenate N,N′-diacetyltetrahydro-4,4′-dipyridyl using Raney nickel in dioxane or methanol under pressures of 50–1400 pounds per square inch and temperatures of 25–70° generally failed to reduce the compound. Zinc and methanolic sodium hydroxide also failed to effect reduction.

Absorption Spectra.—Infrared determinations were kindly carried out by Mrs. J. L. Johnson using the crystalline white and yellow forms in Nujol. The instrument was a Perkin-Elmer Model 12B infrared spectrometer with rock salt optics.

Ultraviolet determinations were kindly made by Mr. John C. Brantley using a Model D Beckman spectrophotometer with 95% ethanolic solutions of the white (5.22 mg. per liter of solution) and yellow (12.1 mg. per liter of solution) forms.

Ozonolysis.—Five and five-tenths grams (0.025 mole) of yellow N,N′-diacetyltetrahydro-4,4′-dipyridyl dissolved in 40 ml. of glacial acetic acid was ozonized for forty-eight hours at 20° with 3% ozone flowing at a rate of 2.2 ml. per minute. The acetic acid solution was then added dropwise at 0° to 300 ml. of water and 30 ml. of 30% hydrogen peroxide. The mixture was allowed to stand overnight, then heated to 90° for ten minutes. The solvent was removed by distillation, leaving a residue of 3.5 g. of crude yellowish succinic acid, m. p. 160–178°. From this was prepared a *p*-bromophenacyl ester by the method of Shriner and Fuson,[14] m. p. 210–212°. Succinamide was also prepared in 43% yield through the methyl ester from 0.692 g. of the crude acid, using the method of Morrell.[15] The colorless needles, recrystallized from water, melted at 260–261°. A mixed m. p. with an authentic sample was not depressed.

Effect on Polymerization of Styrene.—The flow times of solutions of 0.10 g. of the white and yellow forms of N,N′-diacetyltetrahydro-4,4′-dipyridyl in 13.3 ml. of freshly-distilled styrene were periodically compared with those of pure styrene in Foord-type viscosimeters[16] maintained at 58°. The viscosity of the pure styrene increased steadily, until after two days the liquid was too thick to flow. The flow times of the solutions were unchanged after two days at 58°, and still unchanged after five months at room temperature.

Summary

Evidence is presented to suggest that N,N′-diacetyltetrahydro-4,4′-dipyridyl dissociates into free radicals which give rise to the yellow modification of the compound.

(12) Driggs and Hopkins, THIS JOURNAL, **47**, 363 (1925).

(13) Emmert and Wolpert, *Ber.*, **74**, 1015 (1941).

(14) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 132.

(15) Morrell, *J. Chem. Soc.*, **105**, 2698 (1914).

(16) Foord, *ibid.*, 48 (1940).

URBANA, ILLINOIS RECEIVED FEBRUARY 16, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

The Reaction of Azlactones with Secondary Amines

BY DAVID K. BARNES,[1] E. CAMPAIGNE AND R. L. SHRINER[2]

No systematic study has been made of the reaction of secondary amines with azlactones.[3] Only a few scattered examples of the reaction have been reported in the literature.[4–8] In view of this fact, it was considered desirable to investigate the reactions of 2-phenyl-4-benzal-5-oxazolone (an unsaturated azlactone) and 2-phenyl-4-benzyl-5-oxazolone (a saturated azlactone) with the following series of secondary amines: piperidine, morpholine, dimethylamine, diethylamine, methylaniline, ethylaniline, diphenylamine, indole and carbazole. These amines were chosen because they represented different degrees of basicity.

Erlenmeyer[4] reported that 2-phenyl-4-benzal-5-oxazolone (I) reacted with piperidine to produce α-benzoylaminocinnamapiperidide with a melting point of 178°. In the present work, it has been found that two isomeric products may be isolated from the reaction of 2-phenyl-4-benzal-5-oxazolone[9] with piperidine. When equivalent amounts of the reactants were employed, Piperidide A,

(1) Taken from part of a thesis submitted by David K. Barnes to the Faculty of the Graduate School in partial fulfillment of the requirements for the Degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University. Present address, Stanolind Oil and Gas Co., Tulsa, Oklahoma.

(2) Present address: Chemistry Department, University of Iowa, Iowa City, Iowa.

(3) Carter, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, 1946, p. 198.

(4) Erlenmeyer, *Ber.*, **33**, 3035 (1900).

(5) Erlenmeyer and Wittenberg, *Ann.*, **337**, 294 (1904).

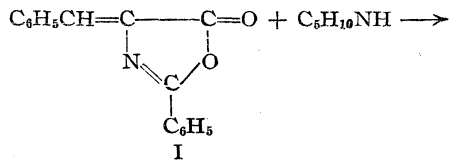
(6) Erlenmeyer and Stadlin, *ibid.*, **337**, 283 (1904).

(7) Lettre and Fernholz, *Z. physiol. Chem.*, **266**, 37 (1940).

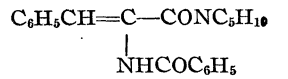
(8) Doherty, Tietzman and Bergmann, *J. Biol. Chem.*, **147**, 617 (1943).

(9) Two isomeric forms, (*cis* and *trans*) of this azlactone have been described by Carter and Risser, *J. Biol. Chem.*, **139**, 255 (1941). Only the readily available higher melting isomer was used by Erlenmeyer and also in the present work.

melting at 161–162.5° was obtained. The use of a large excess of piperidine in the reaction resulted in the formation and isolation of Piperidide B, melting at 187–188°.



I

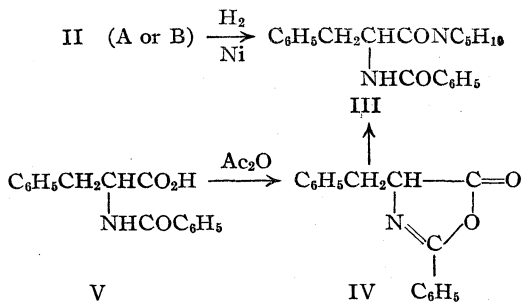


Piperidine-A, m. p. 161–162°
Piperidide-B, m. p. 187–188°

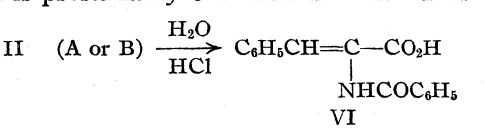
II

Analyses showed that both of these compounds were formed from one mole of the azlactone and one mole of piperidine. No compound corresponding to the addition of a second mole of amine to the unsaturated amide was found in spite of changes in mole ratio of reactants and time, temperature and solvents.

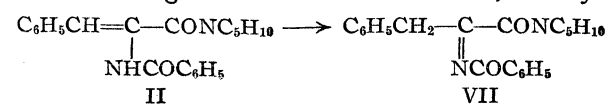
A study of the reactions of these isomers showed that they possessed the same chemical properties. For example, catalytic reduction of both piperidides (II, A and B) produced α-benzoylaminocinnamapiperidide (III) which was identical with a sample of this compound obtained by treatment of 2-phenyl-4-benzyl-5-oxazolone (IV) with piperidine. The saturated azlactone (IV) was made by the action of acetic anhydride on *dl*-benzoylphenylalanine (V).



Hydrolysis of both piperidides with dilute hydrochloric acid gave piperidine and the same α-benzoylaminocinnamic acid (VI) m. p. 229–230°, which is presumably the *trans*-isomer. This was somewhat surprising since, if the two piperidides are *cis–trans* isomers, it might be expected that the *cis*- and *trans*-forms of VI would be formed. It is of course possible that interconversion occurred during the hydrolysis.



Both piperidides were converted to the original oxazolone (I) and piperidine when heated in tetralin or glacial acetic acid. Although the isomerism of the two compounds might be due to the shift of the double bond and proton (Formulas II, VII), the above regeneration of the oxazolone, and hydrolysis to VI favor the possibility that they are *cis* and *trans* isomers. It was also found that the lower melting isomer (IIA) was converted to the higher melting form (IIB) by heating with piperidine or pyridine; reagents which have previously been shown to cause conversion of *cis* to *trans* isomers.[9,10]



II VII

Similarly, two isomeric products were obtained from the reaction of morpholine with 2-phenyl-4-benzal-5-oxazolone. Catalytic reduction of each isomer resulted in the formation of α-benzoylaminohydrocinnamamorpholide, and acid hydrolysis yielded α-benzoylaminocinnamic acid (VI) and morpholine.

Isomeric products were not obtained with the other amines, although there may have been small amounts of the lower melting forms present. Table I in the Experimental Part summarizes the products obtained from secondary amines and 2-phenyl-4-benzyl-5-oxazolone, and Table II, the substituted amides obtained from 2-phenyl-4-benzal-5-oxazolone. The weakly basic amines, diphenylamine, indole and carbazole failed to open the azlactone ring.

Experimental

2-Phenyl-4-benzal-5-oxazolone.—The 2-phenyl-4-benzal-5-oxazolone used in this work was prepared according to the method of Gillespie and Snyder.[11] The product was obtained in 53–73% yield, melting at 165–166° without recrystallization.

N-Benzoyl-*dl*-phenylalanine.—Reduction of 2-phenyl-4-benzal-5-oxazolone with phosphorus and hydriodic acid, according to the method of Gillespie and Snyder[11] afforded *dl*-phenylalanine in 50–60% yields. Treatment of this product with benzoyl chloride and sodium hydroxide[12] resulted in the preparation of N-benzoyl-*dl*-phenylalanine melting at 184–186° in 70–75% yields.

2-Phenyl-4-benzyl-5-oxazolone.—N-Benzoyl-*dl*-phenylalanine was converted to 2-phenyl-4-benzyl-5-oxazolone by dehydration in acetic anhydride, according to the method of Mohr and Stroschein.[13] The yields ranged from 58–63% of the azlactone which melted at 70–71°. Due to the ease of hydrolysis of the saturated azlactone, the pure material was stored in a vacuum desiccator over phosphorus pentoxide prior to use.

The Reaction of Piperidine with 2-Phenyl-4-benzyl-5-oxazolone.—In a 25-ml. Erlenmeyer flask, 10 ml. (0.1 mole) of piperidine was added to 1.0 g. (0.004 mole) of 2-phenyl-4-benzyl-5-oxazolone. Heat was evolved as the solid azlactone dissolved. The reaction mixture was heated in a boiling water-bath for ten minutes. After cooling, the white, crystalline precipitate was filtered with suction and washed on the filter with petroleum ether. The α-benzoylaminohydrocinnamapiperidide was

(10) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945); Clemo and Graham, *J. Chem. Soc.*, 213 (1930); Pollard, Bain and Adelson, THIS JOURNAL, **57**, 199 (1935).

(11) Gillespie and Snyder, "Org. Syntheses," Coll. Vol. II, 1943, p. 489.

(12) Steiger, *J. Org. Chem.*, **9**, 396 (1944).

(13) Mohr and Stroschein, *Ber.*, **42**, 2521 (1909).

recrystallized from dilute ethanol; the weight, after drying, was 1.3 g. (98%) of white crystals which melted at 162–162.5°.

The same procedure was used for the reaction of morpholine, methylaniline and ethylaniline with 2-phenyl-4-benzyl-5-oxazolone. Dimethylamine, diethylamine and di-*n*-butylamine gave satisfactory yields when the reaction was carried out in dry solvents such as ligroin or chloroform. The melting points and analyses of the products are given in Table I.

TABLE I

N,N-SUBSTITUTED α-BENZOYLAMINOHYDROCINNAMAMIDES

Amide group	M. p. of product, °C.	Formula	Nitrogen, % Calcd.	Found
Piperidide	162–162.5	$C_{21}H_{24}O_2N_2$	8.33	8.21
Morpholide	171–172	$C_{20}H_{22}O_3N_2$	8.28	8.34
Dimethylamide	148.5–149	$C_{18}H_{20}O_2N_2$	9.46	9.27
Diethylamide	121.5–122.5	$C_{20}H_{24}O_2N_2$	8.64	8.57
Methylanilide	163–164	$C_{23}H_{22}O_2N_2$	7.82	7.59
Ethylanilide	184.5–185	$C_{24}H_{24}O_2N_2$	7.52	7.33

Diphenylamine, indole and carbazole did not form substituted cinnamides. A by-product melting at 269° was formed in the reaction of the aliphatic amines with the saturated azlactone. This may be a condensation product of the azlactone with itself (see ref. 3).

The Reaction of Piperidine with 2-Phenyl-4-benzal-5-oxazolone. Method A.—In a 125-ml. Erlenmeyer flask fitted with a reflux condenser, 12.5 g. (0.05 mole) of 2-phenyl-4-benzal-5-oxazolone was suspended in 50 ml. of dry benzene, and 4.25 g. (0.05 mole) of freshly distilled piperidine was added. The reaction mixture warmed spontaneously, and was further heated for thirty minutes in a boiling water-bath. During this time the reaction mixture became homogeneous. Approximately two-thirds of the solvent was removed under reduced pressure, the product precipitating when the concentrated solution was allowed to cool. The white, powdery solid was filtered with suction and washed on the filter with petroleum ether. The weight of crude Piperidide A was 14.6 g. (86.5%) m. p. 151–153°. After recrystallization from 300 ml. of 95% ethanol, the product weighed 13.9 g. (83%) m. p. 161–162.5°. This melting point is the same as that of α-benzoylaminohydrocinnamapiperidide but the melting point of a mixture of the two was markedly lowered.

This method was utilized for the preparation of the corresponding Morpholide A from the reaction of 2-phenyl-4-benzal-5-oxazolone with an equivalent amount of morpholine.

Method B.—To 5.0 g. (0.02 mole) of 2-phenyl-4-benzal-5-oxazolone was added 25 ml. (0.25 mole) of piperidine. The azlactone dissolved rapidly with the evolution of heat. The homogeneous, yellow solution was heated in a boiling water-bath for ten minutes, during which time a white solid began to precipitate. The reaction mixture was allowed to cool, and the product was filtered with suction and washed with cold acetone. The weight of crude Piperidide B was 5.0 g., m. p. 181–183°. After recrystallization from benzene, the weight was 4.2 g. (63%), m. p. 187–188°.

This method was utilized for the preparation of Morpholide B from the reaction of 2-phenyl-4-benzal-5-oxazolone with morpholine. These two general methods were used in the reaction of dimethylamine, diethylamine, methylaniline, and ethylaniline, with 2-phenyl-4-benzal-5-oxazolone. Isomers were not obtained from these amines but may have been present. Examination of the mother liquors from the crystallization of the reaction products gave small amounts of unchanged azlactone but no definite pure isomers could be separated. The melting points and analyses of the products are given in Table II.

Diphenylamine, indole and carbazole failed to react with the unsaturated azlactone. The reactants were recovered unchanged except when Method A was employed with carbazole. In this case, the recovered azlactone melted at 148–149°. When it was treated with pyridine it changed to the higher melting isomer, m. p. 165–166°. This corresponds to the isomerization reported by Carter and Risser.[9]

TABLE II

N,N-SUBSTITUTED α-BENZOYLAMINOCINNAMAMIDES

Amide group	M. p. of product, °C.	Formula	Analyses, % Calcd.	Found
Piperidide (A)	161–162.5	$C_{21}H_{22}O_2N_2$	N, 8.38	8.43
			C, 75.45	76.14
			H, 6.56	6.80
Piperidide (B)	187–188	$C_{21}H_{22}O_2N_2$	N, 8.38	8.19
			C, 75.45	75.63
			H, 6.56	6.77
Morpholide (A)	135.5–137	$C_{20}H_{20}O_3N_2$	N, 8.33	8.17
			C, 71.43	71.65
			H, 5.95	6.06
Morpholide (B)	180.5–181	$C_{20}H_{20}O_3N_2$	N, 8.33	8.26
			C, 71.43	71.14
			H, 5.95	5.80
Dimethylamide	166.5–167	$C_{18}H_{18}O_2N_2$	N, 9.52	9.43
Diethylamide	172–173	$C_{20}H_{22}O_2N_2$	N, 8.70	8.70
Methylanilide	193–194	$C_{23}H_{20}O_2N_2$	N, 7.87	7.29
Ethylanilide	174–175	$C_{24}H_{22}O_2N_2$	N, 7.57	7.39

Reduction of N,N-Substituted α-Benzoylaminocinnamamides.—In a 500-ml. hydrogenation bottle were placed 0.005 mole of the N,N-substituted α-benzoylaminocinnamamide, 100 ml. of absolute ethanol and 2–3 g. of Raney nickel.[14] The bottle was placed on a Parr hydrogenation apparatus and the solution shaken with hydrogen at a pressure of 45 lb. The calculated pressure drop occurred in about five minutes, but the mixture was allowed to shake for fifteen minutes to ensure complete reduction. After removing the Raney nickel by filtration, the filtrate was concentrated to approximately one-fourth the original volume under reduced pressure. Upon cooling the solution to room temperature, a white, crystalline product precipitated which was filtered with suction and dried. The reduced products were identified by comparison with the corresponding hydrocinnamamides prepared from the reaction of 2-phenyl-4-benzyl-5-oxazolone with secondary amines (see Table I).

Acid Hydrolysis of N,N-Substituted α-Benzoylaminocinnamamides.—The following method was used for the hydrolysis of each of the isomeric piperidides and morpholides. In a 200-ml. round-bottomed flask fitted with a reflux condenser, 0.003 mole of the N-substituted-α-benzoylaminocinnamamide was boiled in 100 ml. of dilute (3:1) hydrochloric acid for three hours. The white, crystalline, acid-insoluble material was filtered with suction and washed on the filter with water. When dry, this product melted at 228–230° and was readily soluble in 10% sodium hydroxide. A mixed melting point with α-benzoylaminocinnamic acid showed no depression.

The acidic filtrate was cooled in an ice–water-bath, and made alkaline to litmus by the addition of 30% sodium hydroxide. A strong amine-like odor was usually noticeable. Five milliliters of benzenesulfonyl chloride and 5 ml. of 30% sodium hydroxide were added to the reaction mixture; the flask was corked tightly and shaken vigorously for thirty minutes. The white, flocculent sulfonamide was filtered with suction and washed thoroughly with water. The benzene sulfonamides were recrystallized from dilute ethanol and compared with authentic samples.

Conversion of Piperidide A to Piperidide B.—In a 50-ml. round-bottomed flask fitted with a reflux condenser were placed 2.5 g. (0.006 mole) of α-benzoylaminocinnamapiperidide (Piperidide A), 10 ml. (0.1 mole) of piperidine and 10 ml. of benzene. The flask was immersed in a boiling water-bath and the mixture refluxed for thirty minutes. The solution became homogeneous, but after cooling, a white, crystalline precipitate was obtained. The solid was filtered with suction and washed on the filter with several small portions of petroleum ether.

(14) R. Mozingo, "Org. Syntheses," **21**, 15 (1941).

The dry material weighed 1.2 g. and melted at 166–167°. An additional 1.0 g. was obtained by evaporating the filtrate to dryness under reduced pressure. The two fractions were combined and recrystallized from benzene. The yield of pure Piperidide B was 2.0 g., melting at 187–188°. Boiling pyridine also converted the low melting isomer to the higher melting compound. In a similar way the low melting Morpholide A was converted to the higher melting Morpholide B.

Summary

1. A series of α-benzoylamino-N,N-disubstituted hydrocinnamamides has been prepared by the reaction of 2-phenyl-4-benzyl-5-oxazolone with dimethylamine, diethylamine, methylaniline, ethylaniline, piperidine and morpholine.

2. A series of α-benzoylamino-N,N-disubstituted cinnamamides has been prepared by the reaction of 2-phenyl-4-benzal-5-oxazolone with the same secondary amines. Each of these compounds was catalytically hydrogenated to the corresponding hydrocinnamamide.

3. Piperidine and morpholine were found to react with 2-phenyl-4-benzal-5-oxazolone to yield two isomeric products in each case. The isomeric piperidides were both hydrolyzed to the same α-benzoylaminocinnamic acid, and reduced to α-benzoylaminohydrocinnamapiperidide and morpholide, respectively.

4. Diphenylamine, indole and carbazole failed to react with 2-phenyl-4-benzyl-5-oxazolone or 2-phenyl-4-benzal-5-oxazolone under the conditions employed in this work.

BLOOMINGTON, INDIANA
IOWA CITY, IOWA RECEIVED NOVEMBER 10, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Monomers and Polymers. III. A New Synthesis for α-Methylstyrenes[1,2]

BY G. BRYANT BACHMAN AND HENRY M. HELLMAN

Most α-methylstyrenes so far described have been prepared by two general types of syntheses. The first involves the conversion of carbonyl or carbalkoxyl groups to isopropenyl groups, *e. g.*

(1) $R—COCH_3 \xrightarrow[(2)\ \text{acid}]{(1)\ CH_3MgX} R—C(CH_3)_2OH \xrightarrow{-H_2O} R—C(CH_3)=CH_2$

(2) $R—CO_2CH_3$

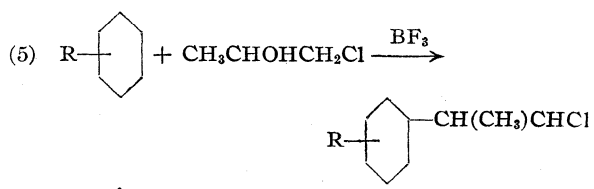
The method is limited to intermediates which contain no other groups affected by Grignard reagents and is impractical for large scale production. The second type involves the conversion of isopropyl groups to isopropenyl groups, *e. g.*

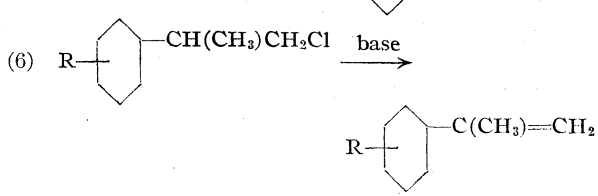
(3) $R—CH(CH_3)_2 \xrightarrow{Al_2O_3} R—C(CH_3)=CH_2 + H_2$

(4) $R—CH(CH_3)_2 \xrightarrow{Cl_2} R—C(CH_3)_2Cl \xrightarrow[\text{base}]{} RC(CH_3)=CH_2$

It is better suited for commercial production but is also limited as to other groups which may be present. Thus alkyl substituents are especially troublesome because of their indiscriminant attack by the dehydrogenation catalyst or by the halogen. Furthermore, the tertiary halides produced (Equation 4) tend to dehydrohalogenate during distillation giving difficulty separable mixtures.

We have sought for and found a synthesis which can be applied more or less generally to substitute α-methylstyrenes, especially of the types difficultly obtainable by previously known methods, and which might be adapted to large scale production. The synthesis is illustrated by the following equations in which R represents one or more nuclear substituents.

(5) 

(6) 

Aromatic compounds have been alkylated before with alcohols and with alkyl halides[3] but never apparently with halohydrins. We have found that secondary alcohols react so much more readily than primary halides in this synthesis that condensation with two aryl nuclei to form diarylpropanes may be made of minor importance. Positional isomers are formed but the para derivative (with monosubstituted benzenes) is the chief product.

In Table I are shown the haloalkylation products of a number of substituted benzenes. The method appears to work especially well with alkylated benzenes, probably because the alkyl group activates the nucleus to further substitution.

(1) From the Ph.D. thesis of H. M. Hellman, Purdue University, June, 1947. Present address: Department of Chemistry, New York University, New York.

(2) For previous papers in this series see THIS JOURNAL, **69**, 2022 (1947); **70**, 622 (1948), and others to be published.

(3) For a general review see C. C. Price, "The Alkylation of Aromatic Compounds by the Friedel–Crafts Method," in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1946, Vol. III, Chapter 1.

TABLE I

HALOALKYLATED BENZENES

Reactants		Yield, %[a]	Products B. p. °C.	Mm.	d^{25}_{25}	$n^{25}D$	Analyses Calcd.	Found
$CH_3CHOHCH_2Cl$	Benzene[b]	37	79–80	9	1.047	1.5210	Cl, 23.0	23.3
$CH_3CHOHCH_2Cl$	Toluene[c]	36	80–82	5	1.028	1.5205	Cl, 21.0	20.9
$CH_3CHOHCH_2Cl$	Chlorobenzene[b]	29	116–122	15	1.181	1.5384	Cl, 37.5	37.5
$CH_3CHOHCH_2Cl$	Cumene	48	103–109	3	0.995	1.5130	Cl, 18.0	18.0
$CH_3CHOHCH_2Cl$	*o*-Xylene	27	78–79	2	1.027	1.5260	Cl, 19.4	19.6
$CH_3CHOHCH_2Cl$	*o*-Chlorotoluene	30	95–97	2	1.164	1.5392	Cl, 34.9	34.9
$CH_3CHOHCH_2Cl$	*o*-Bromotoluene	30	109–112	1	1.389	1.5595	Cl, 14.4	14.2
							Br, 32.3	32.0
$CH_3CHOHCH_2Cl$	*o*-Dichlorobenzene	7	116–120	2	1.304	1.5556	Cl, 47.7	46.9
$CH_3CHOHCH_2Cl$	Anisole	5	108–110	5	1.095	1.5281	Cl, 19.2	18.7
$CH_3CHOHCH_2Cl$	2,6-Dichlorotoluene	4	110–112	1	1.265	1.5553	Cl, 44.8	43.4
$CH_3CHOHCH_2Cl$	1-Chloronaphthalene	20	130–135	1	1.232	1.6168	Cl, 29.7	29.4
$CH_3CHOHCH_2Br$	Cumene	32	98–99	1	1.192	1.5290	Br, 33.2	33.3
$CH_3CHOHCH_2Br$	*o*-Fluorotoluene	17	72–74	2	1.334	1.5233	Br, 34.6	34.4
							F, 8.2	8.1
$C_2H_5CHOHCH_2Cl$	Toluene	41	80–83	3	1.011	1.5140	Cl, 19.4	19.4
$C_2H_5CHOHCH_2Br$	Toluene	51	89–90	1	1.224	1.5332	Br, 35.2	35.0

[a] Based on halohydrin. [b] Truffault, *Compt. rend.*, **202**, 1286 (1936). [c] Truffault, *Bull. soc. chim.*, **6**, 726 (1939).

TABLE II

α-METHYLSTYRENES

Substituents	Yield, %	B. p. °C.	Mm.	d^{25}_{25}	$n^{25}D$	Br. No.	Percentage composition E[e]	Calcd.	Found	E[e]	Calcd.	Found
None[a]	77	72–72	30	0.910	1.5350	...	..	..	..	..	..	..
4-CH_3[a]	60	76–78	19	0.898	1.5290	...	..	..	..	..	..	..
4-Cl[a,b]	16	80–83	10	1.079	1.5529	106	Cl	23.3	23.4	..	..	..
4-$CH(CH_3)_2$	73	76–77	5	0.889	1.5204	98	C	90.0	89.5	H	10.0	9.9
2,3-di-CH_3	8	54–55	3	0.895	1.5170	111	C	90.4	90.5	H	9.6	9.8
3,4-di-CH_3	72	72–73	4	0.908	1.5362	109	C	90.4	90.0	H	9.6	9.6
3-Cl-2-CH_3	26	64–65	4	1.043	1.5340	106	Cl	21.3	21.4	..	..	..
3-Cl-4-CH_3	48	73–74	4	1.056	1.5520	99	Cl	21.3	21.3	..	..	..
3-Br-2-CH_3	18	89–90	7	1.295	1.5555	76	Br	37.8	38.0	..	..	..
3-Br-4-CH_3	45	102–103	7	1.311	1.5757	77	Br	37.8	38.1	..	..	..
Chlorobenzo[c]	10	119–121	1	1.150	1.6210	78	Cl	17.5	17.8	..	..	..
3-F-2-CH_3+					1.5128–							
3-F-4-CH_3	83	72–90	10	0.996	1.5187	100	C	80.0	80.0	F	12.6	12.4
4-CH_3[a,d]	18	78–81	10	0.890	1.5202	110	C	90.4	90.0	H	9.6	10.0

[a] Known compound, *cf.* Beilstein or indicated reference. [b] Reported recently by Mowry, Huber and Ringwald, THIS JOURNAL, **69**, 851 (1947), b. p. 88–89° (15); $n^{25}D$ 1.5543. [c] From chloroisopropylated α-chloronaphthalene. [d] An α-ethylstyrene, *cf.* Griskevich–Trokhimovskii, *C. A.*, **5**, 3799 (1911). [e] E represents element analyzed for.

Boron trifluoride alone as catalyst is satisfactory, but the yields of condensation products are often improved (5–10%) by the addition of dehydrating agents such as sulfuric acid or phosphorus pentoxide. The low yields with anisole may be attributed to combination between the ether oxygen and the boron trifluoride molecule creating a group-complex ($-\overset{+}{O}R \rightarrow \bar{B}F_3$) whose dipolar character is such as to deactivate the nucleus. Haloalkylation of thiophene was unsuccessful, probably for similar reasons, and because of cleavage of the thiophene ring.

In attempting to extend the utility of the reaction to homologs of propylene halohydrins it was found that the halohydrin of 1-butene (1-bromo-2-butanol) reacted very satisfactorily with toluene. There appears to be no reason why α-alkylstyrenes generally should not be readily available by this synthesis.

The α-methylstyrenes prepared by dehydrohalogenation (Table II) showed evidence of being mixtures of positional isomers not completely separated by distillation through a 42-cm. glass helices packed column. The products boiled over a range and showed varying refractive indices, but the several cuts gave correct bromine numbers and correct analyses. The styrenes were therefore redistilled through a 3-foot, 1/4 inch tantalum spiral column with an efficiency of about 10 theoretical plates. The separated isomers were then oxidized with 6 molar nitric acid to the corresponding substituted benzoic acids. Comparison of the m. p.'s of these acids with values reported in the literature led to a determination of the structures of the original styrenes.

An advantage of this synthesis is that the haloisopropylated benzene obtained as an intermediate may easily be further substituted nuclearly before

TABLE III

1,2-DIPHENYLPROPANES

Phenyl substituents	Yield	B. p. °C.	Mm.	$n^{25}D$	d^{25}_{25}	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
None[a]	4.3	90–91	1	1.5593	0.989	91.8	8.2	91.68	8.36
4-CH_3	35.5	106–110	1	1.5525	.970	91.0	9.0	91.00	8.94
4-CH_3[b]	16.0	115–117	1	1.5476	.960	90.7	9.3	90.4	9.2
3,4-di-CH_3	30.0	150–155	2	1.5560	.971	90.4	9.6	90.1	9.5
4-$CH(CH_3)_2$	2.0	104–106	0.5	1.5238	.979	90.0	10.0	89.52	9.66

[a] Reported by Klages and Heilmann, *Ber.*, **37** 1450 (1904), b. p. 285–286°; d^{17}_4 0.9857; $n^{17}D$ 1.5635. [b] 1,2-ditolylbutane.

dehydrohalogenation. Thus *p*-(chloroisopropyl)-toluene was brominated and then dehydrohalogenated to give 3-bromo-4-methyl-α-methylstyrene. In this way products with substituents in the meta and para positions rather than in the ortho positions are obtained, and even deactivating (electron-withdrawing) groups may be introduced without interfering with the subsequent styrene formation.

All of the styrenes prepared except those with ortho substituents copolymerized satisfactorily with butadiene in emulsion systems to give rubber-like materials similar to GR-S in appearance. They also copolymerized with styrene, methyl methacrylate and maleic anhydride, but they did not polymerize alone with peroxide catalysts.

Acknowledgment.—The authors are indebted to the General Tire and Rubber Company and the Purdue Research Foundation for financial assistance in the form of a fellowship.

Experimental[4,5]

1-Halo-2-arylpropanes.—The chloroalkylation of *o*-chlorotoluene is typical for all of the compounds in this series. A cooled, stirred solution of 1920 g. (15 moles) of *o*-chlorotoluene and 520 g. (5.5 moles) of freshly distilled propylene chlorohydrin was saturated with boron trifluoride at temperatures below 10°, and then 196 g. (1.4 moles) of phosphorus pentoxide was added. The resulting two phase mixture was heated at 75° for four hours. During the heating period boron trifluoride was evolved and vented into a water trap. The layers were separated after cooling, the top layer was washed several times with water, dried, and rectified through a 43-cm. Fenske column; yield 358 g. (32%), b. p. (2 mm.) 95–97°, d^{25}_{25} 1.164, $n^{25}D$ 1.5392. It is interesting to note that the narrow b. p. range and constant n_D values give no evidence of the presence of isomers, although the styrenes later obtained by dehydrohalogenation separated into fractions on distillation and were definitely shown to contain positional isomers by oxidation to known isomeric benzoic acids. In Table I are listed the haloalkylated aromatic compounds together with their physical constants and analyses.

1,2-Diarylalkanes.—The chloroalkylation of benzene, isopropylbenzene, *o*-xylene, and toluene led to 1,2-diarylalkanes as by-products. The yields and properties of these compounds are shown in Table III.

Bromination of Chloroisopropylated Toluene.—Chloroisopropylated toluene (250 g., 1.5 moles) was mixed with 0.6 g. of iodine, and 76 ml. (1.5 moles) of bromine was added dropwise to the cooled, stirred mixture which was shielded from light. After twenty-four hours, the color of bromine was still apparent; hence, about 0.1 g. of iron filings was added and the mixture was allowed to stand at room temperature for an additional twenty-four hours, after which it was washed with water, dilute sodium hydroxide, twice again with water, distilled, washed with sodium thiosulfate solution, and rectified. There was obtained 257 g. of product b. p. (2 mm.) 108–113°; $n^{25}D$ 1.5590; d^{25}_{25} 1.3896. It is interesting to compare these properties with those of chloroisopropylated *o*-bromotoluene which were: $n^{25}D$ 1.5592; d^{25}_{25} 1.3893; b. p. (1–2 mm.) 109–112°. The yield on the bromination was 70%.

Substituted α-Methylstyrenes.—The preparation of 3-chloro-2-methyl- and 3-chloro-4-methyl-α-methylstyrenes is typical. Chloroisopropylated *o*-chlorotoluene (2 moles) was refluxed with a filtered solution of 466 g. (7 moles) of 85% potassium hydroxide in 1850 ml. of methanol. Most of the methanol was removed by distillation and the residual liquid was washed with water, dried with calcium chloride, and rectified through an efficient column giving 90 g. (26%) of 3-chloro-2-methyl-α-methylstyrene (I) (b. p. (4 mm.) 64–65°; $n^{25}D$ 1.5340; d^{25}_{25} 1.043) and 152 g. (48%) of 3-chloro-4-methyl-α-methylstyrene (II) (b. p. (4 mm.) 73–74°; $n^{25}D$ 1.5520; d^{25}_{25} 1.056).

Anal. Calcd. for $C_{10}H_{11}Cl$: Cl, 21.3; bromine number, 96. Found: (I) Cl, 21.4; bromine number, 96. Found: (II) Cl, 21.3; bromine number, 99.

Oxidation of (I) and (II) with dilute nitric acid gave respectively 3-chloro-2-methylbenzoic acid (m. p. 152–153°; neutral equivalent 172)[6] and 3-chloro-4-methylbenzoic acid (m. p. 205–206°; neutral equivalent 171).[7]

In Table II are listed the substituted α-methylstyrenes together with their physical constants and analyses.

Preparation of Copolymers.—Copolymers of the substituted α-methylstyrenes with methyl methacrylate, maleic anhydride and styrene were made at 65–70° in small stoppered test-tubes, using 0.5% benzoyl peroxide as catalyst. Copolymers with butadiene[8] were made at 40° in small sealed tubes, using the following formula: butadiene 7.5 parts, substituted α-methylstyrene 2.5 parts, water 18 parts, soap 0.5 part, a peroxide 0.03 part and lauryl mercaptan 0.06 part. Copolymers were obtained from all of the alpha-methylstyrenes except those with ortho substituents (*e. g.* 3-chloro-2-methyl-alpha-methylstyrene). None of the alpha-methylstyrenes copolymerized with vinyl acetate.

Summary

A new synthesis of α-methylstyrenes has been developed which involves the catalytic condensation of aromatic compounds with propylene chlorohydrin and the dehydrohalogenation of the resulting halopropylated derivatives. Several new α-methylstyrenes have been prepared and copolymerized with butadiene, methyl methacrylate, styrene and maleic anhydride.

LAFAYETTE, INDIANA RECEIVED DECEMBER 13, 1947

(4) All melting points and boiling points are corrected.

(5) Analyses by Mr. A. M. Ribley and Miss L. Roth of the Purdue Department of Chemistry.

(6) Kruger, *Ber.*, **18**, 1758 (1885), reports m. p. 154°.

(7) Von Gerichten, *Ber.*, **11**, 365 (1878), reports m. p. 199–201°.

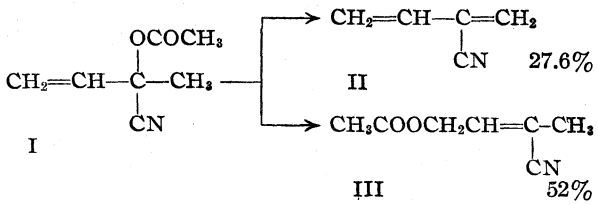
(8) These copolymers were made by Dr. L. J. Filar of the Purdue Department of Chemistry.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Allylic Rearrangement in the Pyrolysis of 3-Acetoxy-3-cyano-1-butene[1]

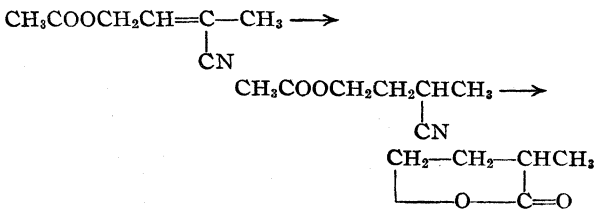
BY C. S. MARVEL AND NEAL O. BRACE

2-Cyano-1,3-butadiene (II) has been prepared by Carter and Johnson[2] by the pyrolysis of 3-acetoxy-3-cyano-1-butene (I) but details on the yields or side reactions involved have not been reported. In repeating this preparation we have found that the main reaction is the allylic rearrangement of the acetoxy group to give 1-acetoxy-3-cyano-2-butene (III); only a small part of the original material is converted to 2-cyano-1,3-butadiene. When the rearrangement product (III) was recycled through the pyrolysis chamber it was recovered unchanged. This rearrangement



is related to that reported by Heilbron, James, McCombie and Weedon[3] for 3-acetoxy-1,4-hexadiene.

The structure of the 1-acetoxy-3-cyano-2-butene was established by reduction of the olefin group and subsequent hydrolysis of the nitrile to yield α-methylbutyrolactone, which was identified by its physical properties and those of its hydrazide.[4]



The benzoate of the cyanohydrin of methyl vinyl ketone was also prepared and pyrolyzed. In this case only 10% yield of 2-cyano-1,3-butadiene was obtained and the major product was a rearranged ester isomeric with the starting material. This undoubtedly is also the result of an allylic shift of the benzoxyl group.

Experimental

Methyl Vinyl Ketone Cyanohydrin.—This was prepared by the procedure of Leupold and Vollmann[5] with potassium cyanide as the alkaline catalyst. It was necessary to control the temperature of the reaction mixture very carefully since little addition occurred below 5° and above 10° the product of addition was levulinonitrile.[6] It was also important to remove the phosphoric acid layer promptly at the end of the reaction. When these precautions were followed the yields of cyanohydrin were consistently between 60 and 70% when 200–400 g. of ketone was used. The product boiled at 60° under 5 mm. pressure, $n^{20}D$ 1.4264 (lit.[5] $n^{17.5}D$ 1.4264).

Acetate of Methyl Vinyl Ketone Cyanohydrin.—In a 1-liter, round-bottom flask were placed 428 g. (4.2 moles) of acetic anhydride and 5 g. of acetyl chloride. The flask was equipped with a Y-adapter fitted with a reflux condenser and dropping funnel. To the boiling mixture 388 g. (4.0 moles) of methyl vinyl ketone cyanohydrin was added slowly, and sufficient heat was applied to maintain gentle reflux. About two hours were required for the addition. Heating was continued for one-half hour. Distillation through a 10-in., helix-packed, electrically-heated column yielded 536 g. (96%) of 3-acetoxy-3-cyano-1-butene, b. p. 89–90° at 19 mm., $n^{20}D$ 1.4270, d^{20}_4 1.0070. The literature reports[3] b. p. 89–90° at 17 mm.

Anal.[7] Calcd. for $C_7H_9O_2N$: C, 60.27; H, 6.50; N, 10.04; *MR*, 35.47. Found: C, 60.53; H, 6.31; N, 10.24; *MR*, 35.48.

Benzoate of Methyl Vinyl Ketone Cyanohydrin.—To a mixture of 31.7 g. (0.3 mole) of methyl vinyl ketone cyanohydrin and 42 g. (0.3 mole) of benzoyl chloride in a 600-ml. beaker cooled in an ice–salt-bath was added slowly with stirring 40 g. (0.5 mole) of pyridine, so that the temperature was maintained between 8–15°. Care was taken to keep the mass that forms broken up, in order to aid in control of the temperature. After the pyridine had been added, the lumps were broken up and 500 ml. of water added with stirring. The suspended solid was collected on a Buchner funnel and washed with three 500-ml. portions of water. Recrystallization from a water–ethanol mixture yielded 47.5 g. (79%) of the benzoate of methyl vinyl ketone cyanohydrin, m. p. 49–50°. A small sample was recrystallized from a dioxane–water mixture, m. p. 53.5° and submitted for analysis.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.44; H, 5.24; N, 6.75.

Pyrolysis of the Acetate of Methyl Vinyl Ketone Cyanohydrin.—Pyrolysis of the acetate of methyl vinyl ketone cyanohydrin was accomplished by passing the ester dropwise through a Pyrex tube (outside diameter 19 mm.) packed for a distance of 12 inches with 4-mm. glass beads and heated to 475° by means of an electrically-heated combustion furnace. The acetate was added at a rate of one drop every three seconds and a diluting stream of purified nitrogen gas was passed through the hot tube during pyrolysis. The pyrolysate was collected in a 500-ml. suction flask cooled by a Dry Ice-bath and connected with a vapor trap cooled with Dry Ice. The liquid pyrolysate was washed with four 100-ml. portions of an aqueous sodium chloride solution, and the organic material separated and dried over anhydrous sodium sulfate. About 0.1 g. of picric acid was added to prevent polymerization and the material was distilled through a 4-in., helix-packed column. From 219 g. (1.56 moles) of the acetate there was obtained 34 g. (27.6%) of 2-cyano-1,3-butadiene, b. p. 30–40° (4 mm.), $n^{20}D$ 1.4450 and 114.0 g. of an ester, b. p. 95° (10 mm.), $n^{20}D$ 1.4500, d^{20}_4 1.0280 that was not the acetate of methyl vinyl ketone cyanohydrin. This represents 52% of the original ester.

(1) The work described in this communication was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Carter and Johnson, U. S. Patent 2,205,239 (June 18, 1940).

(3) Heilbron, James, McCombie and Weedon, *J. Chem. Soc.*, 88 (1945).

(4) (a) Adams and Rogers, THIS JOURNAL, **63**, 228 (1941); (b) Cavallito and Haskell, *ibid.*, **68**, 2332 (1946).

(5) Leupold and Vollmann, U. S. Patent 2,166,600 (July 18, 1939).

(6) Dykstra, U. S. Patent 2,188,340 (January 30, 1940).

(7) The microanalyses reported in this work were done by Mr. Howard Clark of the Illinois State Geological Survey.

Anal. Calcd. for $C_7H_9O_2N$: C, 60.27; H, 6.50; N, 10.04; *MR*, 35.47. Found: C, 60.53; H, 6.66; N, 10.29; *MR*, 36.36 (exaltation of 0.9).

Identification of the Ester Produced in the Pyrolysis.—Hydrogenation of 13.9 g. of the recovered ester dissolved in 100 ml. of absolute ethanol was accomplished in an Adams hydrogenation apparatus at room temperature using as catalyst 1 g. of 10% palladium on charcoal. The compound absorbed 82% of the theoretical amount of hydrogen. The catalyst was removed by filtration and the ethanol removed by distillation. Distillation of the residue through a 10-in., helix-packed column yielded 8 g. of a saturated derivative, b. p. 110° (18 mm.), $n^{20}D$ 1.4280.

Anal. Calcd. for $C_7H_{11}O_2N$: C, 59.56; H, 7.86; N, 9.92. Found: C, 58.89; H, 7.21; N, 9.65.

Six grams of the compound was added to a solution of 5 g. of sodium hydroxide in 20 ml. of distilled water in a 100-ml. round-bottom flask fitted with a reflux condenser. The mixture was refluxed for two hours, after which it was cooled in an ice-bath and 9 ml. of 50% sulfuric acid slowly added. The acidified solution was again refluxed for two hours. The organic layer was separated, and the aqueous layer extracted with two 15-ml. portions of benzene. The combined extracts and the original layer were dried over anhydrous magnesium sulfate, the drying agent removed by filtration, and the residue distilled through a 6-in. Vigreux column, giving 2.5 g. of a clear liquid, b. p. 197°, $n^{20}D$ 1.4320, d^{20}_4 1.0570.

Anal. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.70; H, 7.73.

Adams and Rogers[4a] report the following constants for α-methylbutyrolactone: b. p. 200–201°, $n^{24}D$ 1.4282, d^{26}_4 1.047. A hydrazide of this material was prepared by treating 1.0 g. with 0.5 g. of 85% hydrazine hydrate in 10 ml. of absolute ethanol. The mixture was refluxed for eight hours and the hydrazide isolated by distillation,[8] b. p. 72–75° (12 mm.). Recrystallization of this material from ethyl acetate yielded white crystals, m. p. 90–91°. This corresponds to the melting point reported by Cavallito and Haskell,[4b] for the hydrazide of α-methylbutyrolactone.

Anal. Calcd. for $C_5H_{12}O_2N_2$: C, 45.43; H, 9.15; N, 21.20. Found: C, 45.70; H, 9.00; N, 20.78.

Pyrolysis of Benzoate of Methyl Vinyl Ketone Cyanohydrin.—Into the hot tube heated to 550° was dropped 169.5 g. of melted benzoate at a rate of one drop every two seconds using some nitrogen gas as a diluent. There was obtained by distillation of the pyrolysis mixture 7 g. (10%) of impure 2-cyanobutadiene, b. p. 24–31° (30 mm.). The remaining residue was washed several times with 5% sodium bicarbonate solution, and then twice with 100 cc. of 5% sodium hydroxide solution. The acid-free material was dried over anhydrous sodium sulfate and distilled from an oil-bath at high vacuum. A small amount of oil with an ester-like odor, b. p. 73–81° (5 mm.), came over first and then 12 g. of liquid, b. p. 150° (1 mm.), $n^{20}D$ 1.5315. This compound is nearly odorless and remained a liquid. It is isomeric with the original benzoate.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 70.69; H, 5.28; N, 7.37.

Summary

Pyrolysis of the acetate of methyl vinyl ketone cyanohydrin gives a 27% yield of 2-cyano-1,3-butadiene but the major portion of the ester undergoes an allylic rearrangement to yield 1-acetoxy-3-cyano-2-butene. A similar rearrangement has been observed with the corresponding benzoate.

(8) Darapsky, Beyer and Neuhaus, *J. prakt. Chem.*, **255**, 145 (1936).

URBANA, ILL. RECEIVED JANUARY 9, 1948

[CONTRIBUTION FROM THE INDUSTRIAL RESEARCH INSTITUTE, UNIVERSITY OF CHATTANOOGA]

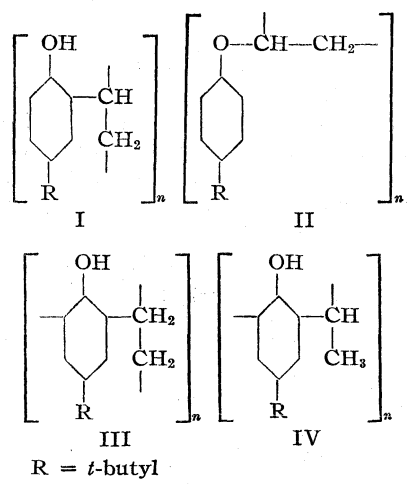
The Pyrolysis of Koresin[1]

BY J. W. LEMAISTRE AND R. B. SEYMOUR

Koresin, a synthetic resin used as a tackefier for synthetic rubber, is made[2,3] by condensation of acetylene with 4-*t*-butylphenol. Probable formulations for this resin include structures I–IV.[4]

The possibility of the polymeric material having structure I led us to study the pyrolysis of Koresin as a source of hydroxybutylstyrene. It has been shown[5,6] that vinyl polymers are thermally decomposed into the corresponding monomers or low polymers.

The pyrolysis of Koresin at 300–400° did not produce a substituted styrene but gave 55% (by weight) of 4-*t*-butylphenol, 20% of alkali-insoluble distillate and 25% of tarry non-volatile residue. The yield of 4-*t*-butylphenol was thus 65% of the theoretical.[4]



R = *t*-butyl

(1) Presented at the Meeting-in-Miniature of the Chattanooga Section of the American Chemical Society, October 11, 1947.

(2) G. M. Kline, *Modern Plastics*, **23** [11], 151 (1946).

(3) A. O. Zoss, W. E. Hanford and C. E. Schildknecht, paper presented at the Sept. 1947 A. C. S. meeting, New York.

(4) Actually an excess of acetylene over the 1:1 molar ratio indicated by these structures is used in manufacture. The 1:1 ratio was, however, assumed for calculations of yields and analyses.

(5) R. B. Seymour, *Ind. Eng. Chem.* **40**, 524 (1948).

(6) G. B. Bachman, *et al.*, *J. Org. Chem.*, **12**, 108 (1947).

Since this result did not conform to structure I, some other reactions of Koresin were studied. In carbon tetrachloride solution, Koresin reacted with 0.94 mole of bromine per structural unit of the resin with evolution of hydrogen bromide. The product was a brittle, mahogany-colored resin which lost 60% of its bromine on refluxing for one and one-half hours with 1 *N* alcoholic potassium hydroxide. The brominated resin also lost hydrogen bromide on heating above 180° and, on further heating, gave an alkali-soluble distillate from which 4-*t*-butylphenol was isolated.

The presence of free hydroxyl groups in Koresin was confirmed by acetylation. The saponification equivalent of the ester indicated an acetyl content of 87% of that calculated.[4] This ester was fairly stable to pyrolysis but broke down at 340–400° to give a distillate which was partly soluble in alkali. While the alkali-soluble portion could not be crystallized, 4-*t*-butylphenol was isolated from the distillate by saponification of the alkali-insoluble portion.

The data obtained for acetylation and the degree of bromination are not in accord with structure II nor does the lability of the bromine introduced agree with either I or III The ease of bromination is thought to accord better with structure IV which contains a tertiary carbon atom than with III which was proposed by Kline.[2] Structure II would probably produce the alkylphenol on pyrolysis if its decomposition was similar to simple alkyl aryl ethers[7] but pyrolysis of the brominated product should yield a bromophenol. From an analogy with bibenzyl, structure III would be expected to yield a *t*-butylphenol having methyl groups *ortho* to the hydroxyl group.[8] While structure IV which has also been proposed by Zoss, *et al.*,[3] appears most probable for Koresin, the resin may not be homogeneous and it is not excluded that the other structures may occur to some extent. Structure IV also resembles the formulation of aldehyde-alkyl phenol resins[9] which are likewise said to be effective tackefiers for synthetic rubber. This structure is also in accord with that proposed by Nieuwland and Vogt[10] for the product obtained by the condensation of benzene and acetylene.

Experimental

Pyrolysis of Koresin.—Koresin[11] (20.0 g.) was heated rapidly over a free flame in a distilling flask. Significant formation of volatile material began at a pot temperature of 300°. In the course of one hour the temperature was raised from 300 to 400°. During this time there was steady distillation of an amber oil. Little uncondensable gas was formed. The residue was viscous and froze on cooling to a brittle, black solid, 4.9 g. The distillate was extracted with 5% sodium hydroxide solution, leaving an insoluble amber oil, 4.0 g. On acidification of the alkaline wash a pale yellow oil separated and soon crystallized, 11.0 g. The latter product was recrystallized from *n*-heptane and identified as 4-*t*-butylphenol (yield, 64%) by melting point, 97–98°, as well as by conversion to the benzoate, m. p. 81°, mixed with an authentic sample, 81°.

Bromination of Koresin.—To 1.76 g. of Koresin dissolved in 15 g. of carbon tetrachloride was added a solution of 2.40 g. of bromine (0.0150 mole) in 50 g. of carbon tetrachloride. The mixture soon gave off colorless fumes. After two hours at room temperature, the solution was washed with excess potassium iodide solution. Titration of the latter with standard thiosulfate showed 0.0056 mole of unreacted bromine to have been present, corresponding to a consumption of 0.0094 mole. The carbon tetrachloride solution was evaporated on a water-bath to a mahogany-colored brittle resin which was taken up in dioxane and evaporated again to remove carbon tetrachloride. The residue dried at 100° weighed 2.5 g. (98%). A weighed sample was hydrolyzed by refluxing for 1.5 hours with 1 *N* potassium hydroxide in ethanol and the solution was titrated with standard acid. Alkali consumption was 0.0023 mole per gram of brominated Koresin, calcd. 0.00376 if all the bromine were removed by alkali.

Pyrolysis of Brominated Koresin.—To a solution of 17.6 g. of Koresin in 150 g. of carbon tetrachloride was added dropwise 16.0 g. of bromine. The solution was let stand overnight and then washed successively with water, sodium sulfite solution and water. The solvent was distilled and the residue destructively distilled. When the still temperature reached 180–190°, evolution of hydrogen bromide began and continued as the temperature was raised. Between 270 and 400° an amber liquid distilled, 6.5 g. The residue was a spongy black tar, 9.9 g. The gas absorbed in a water trap was shown by titration with silver nitrate to contain 0.048 mole hydrogen bromide. The liquid distillate was nearly all soluble in 5% sodium hydroxide and the oil separated by acidification of the alkaline solution partly crystallized on standing. The crystals were identified as 4-*t*-butylphenol after recrystallization from *n*-heptane by melting point, 97–98°, and mixed melting point, 97–99°.

Acetylation of Koresin.—Koresin (17.6 g.) was dissolved in 50 g. of acetic anhydride containing 0.5 g. of anhydrous sodium acetate. The mixture was refluxed for two hours and then poured into cold water. The precipitated resin was taken up in 100 ml. of ethyl ether and washed well with sodium hydroxide solution and then with water. The ether layer was dried over anhydrous calcium sulfate and evaporated to yield a brittle, yellow resin, 21 g. (96%); saponification equivalent (by refluxing with 1 *N* potassium hydroxide in ethanol for one hour), 251, calcd., 218.

Pyrolysis of Acetylated Koresin.—Acetylated Koresin (15 g.) was heated in a distilling flask. Decomposition began at a still temperature of 340° and continued slowly as the temperature was raised to 400°. The residue was a black tar, 6 g. The oily distillate, 6.5 g., smelled of acetic acid. The distillate was washed with sodium hydroxide solution and the insoluble portion, 4.5 g., was refluxed for one-half hour with 25 ml. of 10% potassium hydroxide in ethanol. Water was added, the ethanol distilled off and the residual solution acidified. The separated oil slowly crystallized and, after recrystallization from *n*-heptane, was identified as 4-*t*-butylphenol by melting point, 96–97°, and mixed melting point, 97°.

Summary

1. The principal product of pyrolysis of Koresin is 4-*t*-butylphenol.

(7) Meyer and Hofmann, *Monatsh.*, **38**, 343 (1917).

(8) Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., Inc. (Reinhold Publ. Corp.), New York, N. Y., 1929, p. 30.

(9) G. E. P. Smith, Jr., J. C. Ambelang and G. W. Gottschalk, *Ind. Eng. Chem.*, **38**, 1166 (1946).

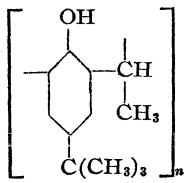
(10) J. A. Nieuwland and R. R. Vogt "The Chemistry of Acetylene," Reinhold Publishing Corp., New York, N. Y., Chap. 5, p. 154.

(11) Obtained from General Aniline and Film Corporation.

2. Koresin reacts with approximately one mole of bromine per structural unit of the resin. The bromine introduced is labile toward heat and toward alkali.

3. Acetylation of Koresin indicates approximately one free hydroxyl group per structural unit.

4. The probable structure of Koresin is



CHATTANOOGA, TENN. RECEIVED DECEMBER 1, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Mechanism of the Methane Fermentation

BY A. M. BUSWELL AND F. W. SOLLO, JR.[1]

Three possible mechanisms for the methane fermentation of acetic acid are suggested by the findings and reasoning of previous workers in this field. From the work of Omelianskii[2,3] and Söhngen[4,5] we would expect a preliminary decomposition of the acetic acid to hydrogen and carbon dioxide, with subsequent reduction of carbon dioxide to methane by the hydrogen. Barker's work[6] indicates that carbon dioxide would be directly reduced to methane and the acetic acid thereby oxidized to carbon dioxide. The reasoning of Buswell and Neave[7] leads to simple decarboxylation as the mechanism.

The first mechanism was based on the similarity of the hydrogen and methane fermentations, but the low concentration of hydrogen found in the gas from the methane fermentation of acetic acid is evidence against this mechanism. If we examine the data of Symons and Buswell[8] we find that only 3.5 liters of methane was formed over a period of one hundred days with regular circulation of hydrogen and carbon dioxide through a culture of 2.0 liters total volume. In the same time, such a culture fermenting acetic acid could be expected to form 75[8,9] liters of methane.

The second mechanism avoids this weakness by implying a direct reduction of the carbon dioxide, without the intermediate stage of free hydrogen. This mechanism seems rather indirect and involved, but parallels that found by Barker in the oxidation of alcohols.

The last mechanism appears to be the simplest and most direct. A similar reaction *in vitro* is the chemical decarboxylation of sodium acetate with sodium hydroxide. The internal oxidation reduction could be effected by the transfer of the hydrogen atom from the carboxyl to the methyl group. Evidence against this mechanism is found in Thayer's work.[10] He reasoned that this reaction was a decarboxylation, and that the fermentation of propionic and butyric acids should yield ethane and propane. However, his results were entirely negative, for no hydrocarbon other than methane was found. This has been confirmed in all work where the gas was analyzed. Therefore, if we are to accept this mechanism of simple decarboxylation for acetic acid, it must be as a special case, not applicable to the higher fatty acids.

Barker, Ruben and Kamen[11] found evidence for the reduction of carbon dioxide in the fermentation of acetic acid through the use of $C^{11}O_2$, but they stated that the radioactive methane found might have been due to the presence of methanol carried over with the inoculum. It should also be mentioned that these workers were using a pure culture of *Methanosarcina methanica*, and that even if methane should be formed by reduction of carbon dioxide in that case, that might not be the predominant mechanism in the general methane fermentation where a mixed culture is used.

This question of the mechanism of fermentation of acetic acid is of more than academic interest. Culture failure is almost invariably accompanied by, or preceded by, the accumulation of high concentrations of volatile organic acids, largely acetic. Thus any information concerning this mechanism might lead to methods of treatment or operation which would alleviate or prevent this accumulation of acids and possibly the failure of many cultures.

It may be seen at once that if the carbon of the carbon dioxide were marked isotopically, this question of mechanism could be settled. If either of the mechanisms involving reduction of carbon dioxide were involved, the methane produced should be similarly marked. If the reaction were a simple decarboxylation, the methane should not be so marked.

(1) Present address: National Aluminate Corporation, 6216 W. 66th Place, Chicago, Illinois.

(2) W. Omelianskii, *Zentr. Bakt.*, II Abt., **8**, 193, 225, 257, 289, 321, 353, 385 (1902).

(3) W. Omelianskii, *ibid.*, II Abt., **11**, 369 (1904).

(4) N. L. Söhngen, *Rec. trav. chim.*, **29**, 238 (1910).

(5) N. L. Söhngen, *Proc. Roy. Acad. Amsterdam*, **8**, 327 (1905).

(6) H. A. Barker, *Arch. Mikrobiol.*, **7**, 404 (1936).

(7) A. M. Buswell and S. L. Neave, Ill. State Water Survey, Bull. No. 30, 1930.

(8) Ill. State Water Survey, Bull. No. 32, 1936, p. 47.

(9) D. Tarvin and A. M. Buswell, THIS JOURNAL, **56**, 1751 (1934), p. 1752, Table I.

(10) L. A. Thayer, *Bull. Am. Assoc. Petroleum Geol.*, **15**, 441 (1931).

(11) H. A. Barker, S. Ruben and M. D. Kamen, *Proc. Natl. Acad. Sci.*, **26**, 426 (1940).

Radioactive C^{14} was chosen as the most easily handled of the carbon isotopes which could be used for this purpose.

Experimental

The radioactive carbon was obtained through the Manhattan district in the form of barium carbonate. This material was converted to sodium carbonate by acidification with perchloric acid and absorption of the carbon dioxide in a solution of sodium hydroxide. The solution resulting was found to yield 3.24×10^5 counts per minute per ml. One ml. of this solution was added to each culture before feeding and incubating.

The fermentations were carried out in 30-ml. round-bottomed flasks, connected to brine displacement gas collectors. Fifteen ml. of inoculum was taken from a digester which had been fermenting acetic acid for several months. To this was added 1.00 ml. of the radioactive sodium carbonate solution, and 1.0 ml. of 1.0% acetic acid. To the first three cultures, similar portions of acetic acid were added after two days of incubation, and again after the third day. The fourth culture was fed only once and analyzed after two days.

The first culture was analyzed after four days of incubation. The other two were kept in the incubator until they were analyzed, total incubation time being six days for the second and twelve days for the third.

The culture to be analyzed was acidified and boiled to free the dissolved carbon dioxide and to drive the gas over into the gas collector. Oxygen was added and after mixing, the sample was drawn through a train in which the carbon dioxide was first absorbed on carbon dioxide free Mikobite. A catalyst[12] of copper and cobalt oxides impregnated on porcelain, kept at 550°, effected the oxidation of the methane to carbon dioxide and water. This carbon dioxide was similarly absorbed. The carbonate was washed off the respective portions of Mikobite with hot water and precipitated with barium nitrate.

These operations were carried out in a carbon dioxide free atmosphere.

The precipitated barium carbonate was suspended in ethanol and deposited on an aluminum sample pan, by transferring to a brass tube, at the bottom of which was fastened the sample pan. The alcohol was evaporated under an electric heat lamp.

The samples thus prepared were counted with a conventional type Geiger–Mueller counter. The tube used was a pressure seal type mica window counter (Radiation Counter Laboratories, Mark 1, Model 2A, window thickness 2.19 mg. per sq. cm.). Background counts averaged from 40 to 45 counts per minute.

Correction for geometry was unnecessary, since only one geometry was used, and no correction for absorption by the window was made since the same tube was used throughout. The data of Yankwich, Rollefson and Norris[13] were used to calculate the correction of self absorption.

The specific activity of the methane was calculated by dividing the total counts by the weight of barium carbonate derived therefrom. The average specific activity of the carbon dioxide was calculated by dividing the average of the initial and final counts by the average of the initial and final equivalent weights of barium carbonate. From these, the activity ratio between the methane and the carbon dioxide, on the basis of the activity of the barium carbonate resulting, was calculated.

The activity ratio was found to vary with the time of incubation. It was for this reason that the additional sample with short incubation time was analyzed. The results are listed in Table I below.

TABLE I

Culture number	1	2	3	4
Days incubated	4	6	12	2
Acetic acid fed (g.)	0.0315	0.0315	0.0315	0.0105
CO_2 at start (mg. $BaCO_3$)	102.5	103.2	110.4	95.2
CO_2 at end (mg. $BaCO_3$)	197.4	215.5	226.4	136.8
Total counts per minute added	3.24×10^5	3.24×10^5	3.24×10^5	3.24×10^5
Activity of CO_2 at end (total counts per min.)	.....	2.58×10^5	2.48×10^5	2.50×10^5
Average activity of CO_2 (counts/min./mg. $BaCO_3$)	1913	1805	1705	2474
Methane produced (mg. $BaCO_3$)	94.9	112.3	116.0	41.6
Total activity of CH_4 (counts/min.)	3415	6324	9903	549
Activity of CH_4 (counts/min./mg. $BaCO_3$)	36	56.3	85.4	13.2
Activity of CH_4/activity of CO_2	0.0188	0.0312	0.0501	0.0053

Discussion

If the mechanism of the fermentation of acetic acid involved the reduction of carbon dioxide to methane, the barium carbonate derived from the methane should have the same specific activity as the carbon dioxide had during the fermentation. The data show that the activity of the methane is only a few hundredths of that of the carbon dioxide, which makes it immediately apparent that the methane is derived from the acetic acid itself.

Calculation of the average activity of the carbon dioxide is an approximation, since we do not have an accurate measure of the activity at the various stages of methane production. The average figure used for this activity was thought to be the nearest estimate possible with the data obtained. It must be noted though, that even if we assumed the lowest possible activity, that found at the end of the incubation period, the ratio of the activities would be only slightly raised. For example, in culture no. 2, where the ratio found was 0.0312, use of the lower total activity would raise this figure to only 0.0358.

In Fig. 1, the ratio of activities is plotted against time of incubation. This curve indicates that there is a lag period, with a subsequent gradual rise in the activity ratio. It seems likely that from this we can assume that very little carbon dioxide is directly reduced to methane in this fermentation, and that the source of the radioactive methane is an indirect fixation of carbon dioxide, with subsequent decomposition of the material formed therefrom. Whether we assume fixation into cell

(12) I. F. Walker and B. E. Christensen, *Ind. Eng. Chem., Anal. Ed.*, **7**, 9 (1935).

(13) P. E. Yankwich, G. K. Rollefson and T. H. Norris, *J. Chem. Phys.*, **14**, 131 (1946).

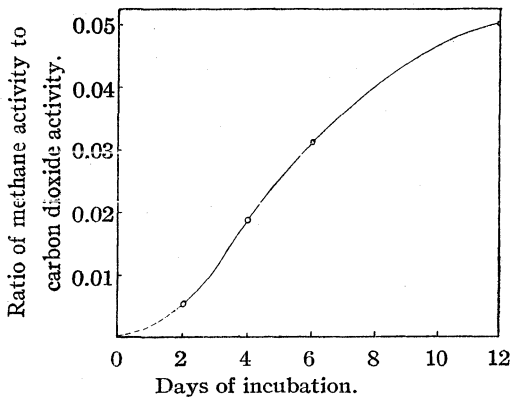


Fig. 1.—Relation of activity ratio to time of incubation.

material with later autolysis, or the formation of endogenous compounds, makes little difference. In any case we must conclude that the predominant reaction in the methane fermentation of acetic acid does not involve reduction of carbon dioxide.

This work indicates that the methane is produced by some mechanism other than the reduction of carbon dioxide, and must therefore be derived from the acetic acid. A simple decarboxylation seems to be the most likely mechanism, but is not definitely established. It is still possible that some preliminary condensation might take place, with subsequent decomposition of the condensation product, but this point cannot be proved by this method of attack.

Summary

It was suggested by previous workers that the methane fermentation of acetic acid might proceed by reduction of carbon dioxide to methane, as was shown to be the case for several alcohols.

In order to determine whether or not this was the case, radioactive C^{14} was used to mark the carbon atom of the carbon dioxide. The gases resulting from the fermentation were separated and converted to barium carbonate for measurement of the radioactivity.

By comparing the activity of the methane and the carbon dioxide, it was shown that only a very small portion of the methane was derived from the carbon dioxide. By studying the relation of the amount of methane formed by reduction of carbon dioxide to the time of incubation, a correlation was found which was interpreted as indicating a slow reduction unassociated with the general fermentation, such as the formation of cell substance and subsequent autolysis. From this it was concluded that the acetic acid was fermented entirely, or very nearly so, without reduction of carbon dioxide, and that the methane is predominantly derived from the acetic acid and not from carbon dioxide.

URBANA, ILLINOIS RECEIVED OCTOBER 27, 1947

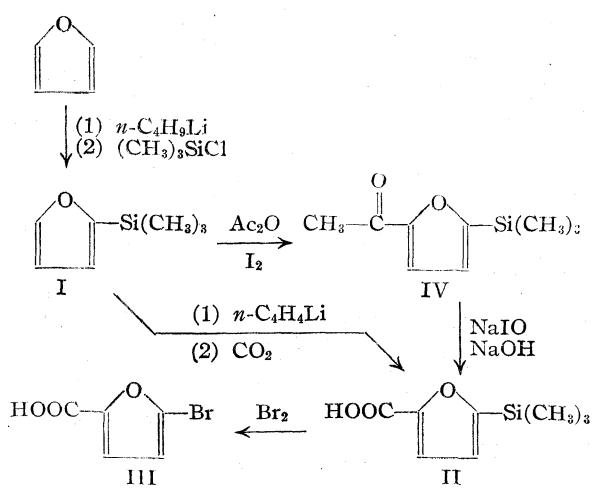
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PURDUE UNIVERSITY]

Acylation Reactions with Organosilicon Compounds[1]

BY ROBERT A. BENKESER AND ROBERT B. CURRIE[2]

Apparently, the only attempt to carry out a Friedel–Crafts reaction involving an organosilicon compound is the work of Kipping.[3] He reported that if a compound like tetraphenylsilane is heated with aluminum chloride the only product isolated is silicon tetrachloride (80% yield). Viewed from the generalized Lewis concept of acids[4] this is not surprising since it has long been known that the aromatic carbon–silicon bond is readily cleaved by acidic reagents.[5–7] The electropositive silicon atom tends to combine with a more electronegative element than carbon when given the opportunity.

It has now been found that using the mild catalyst iodine, an acylation reaction can be carried out with certain organosilicon compounds. In the experiments herein reported, 2-thienyltrimethylsilane and 2-furyltrimethylsilane were acetylated with acetic anhydride at 50°. The yields were of the order of 20–25%. The equations indicate the general sequence of reactions with furan



(1) A portion of this work is abstracted from the thesis submitted by Robert B. Currie to Purdue University in partial fulfilment of the requirements for the degree of Master of Science, August, 1947.

(2) Present address: Merck and Company, Rahway, New Jersey.

(3) Evison and Kipping, *J. Chem. Soc.*, 2774 (1931).

(4) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(5) Ladenburg, *Ann.*, **173**, 143 (1874).

(6) Kipping and Lloyd, *J. Chem. Soc.*, **79**, 449 (1901).

(7) Kipping, *ibid.*, **91**, 223 (1907).

The proof of structure of 2-acetyl-5-trimethylsilylfuran (IV) was accomplished by the hypoiodite degradation to the corresponding acid. This acid was identical with that obtained by the metalation of 2-furyltrimethylsilane (I) with *n*-butyllithium. Finally this acid (II) was converted to the known 5-bromo-2-furoic acid by treatment with bromine.

The thiophene sequence was essentially the same as that indicated above for furan except that metalation of thiophene with *n*-butyllithium is known to occur in the 2-position.[8] This established the structure of 2-thienyltrimethylsilane. The acid obtained from the metalation of this compound with *n*-butyllithium and from the hypoiodite degradation of 2-acetyl-5-trimethylsilylthiophene was shown to be 5-trimethylsilyl-2-thiophenecarboxylic acid by cleaving it with hydrogen chloride to the known 2-thiophenecarboxylic acid.

Experimental

2-Thienyltrimethylsilane.—To 84 g. (1.0 mole) of thiophene[9] was added 325 ml. of an ethereal solution of *n*-butyllithium[10] containing 0.98 mole of the organometallic.[11] The addition was made as rapidly as the evolved butane would allow. The mixture was refluxed three hours and then permitted to stand overnight at room temperature. Eighty grams (0.74 mole) of trimethylchlorosilane was added slowly and when the addition was complete the mixture was refluxed an additional three hours. After hydrolyzing with 10% sulfuric acid, the ether layer was separated and shaken with 10% sodium hydroxide. After drying over Drierite the ether was removed, and the residue was fractionated through a short, glass-spiral column. Eighty-six grams (75%) of a colorless oil was collected boiling at 159–160° (748 mm.), $n^{20}D$ 1.4966, d^{20}_4 0.945.

Anal. Calcd. for $C_7H_{12}SSi$: C, 53.8; H, 7.70. Found: C, 53.3; H, 7.78.

If the thienyllithium prepared above is carbonated the acid can be shown to be 2-thiophenecarboxylic acid[8] thus establishing the position of the trimethylsilyl group.

2-Acetyl-5-trimethylsilylthiophene.—A mixture of 30 g. (0.19 mole) of 2-thienyltrimethylsilane, 30 g. (0.29 mole) of acetic anhydride, and 0.25 g. of iodine[12] was heated for one hour at 50°. The dark solution was shaken with 10% potassium hydroxide until the washings were basic. Ether was added; the residue was washed several times with water and then with a concentrated solution of sodium thiosulfate. After drying over anhydrous sodium sulfate, the ether was removed and the residue was fractionated through a small glass-spiral column. Five grams (13%) of a yellow oil boiling at 104–105° (4 mm.) was collected, $n^{20}D$ 1.5289, d^{20}_4 1.028.

Anal. Calcd. for $C_9H_{14}OSSi$: Si, 14.1; C, 54.5; H, 7.07. Found: Si, 13.7; C, 54.3; H, 7.08.

The semicarbazone of this ketone was prepared in the conventional manner and it melted with decomposition at 217–220°.

Anal, Calcd. for $C_{10}H_{17}ON_3SSi$: N, 16.46. Found: N, 16.30 and 16.47.

5-Trimethylsilyl-2-thiophenecarboxylic Acid.—To 8 g. (0.05 mole) of 2-thienyltrimethylsilane was added 54 ml. of an ethereal solution of *n*-butyllithium[10] containing 0.05 mole of the organometallic.[11] The mixture was refluxed four hours and then carbonated by pouring jet-wise onto powdered Dry Ice. After allowing the mixture to warm to room temperature, water was added with vigorous stirring. The clear ether layer was discarded and, upon acidifying the basic water layer with concentrated hydrochloric acid, 6.3 g. (62%) of 5-trimethylsilyl-2-thiophenecarboxylic acid separated and after crystallization from dilute ethanol it melted at 134–135°.

Anal. Calcd. for $C_8H_{12}O_2SSi$: Si, 14.0. Found: Si, 13.7.

This same acid was isolated (mixed m. p.) when 2-acetyl-5-trimethylsilylthiophene was treated with sodium hydroxide and iodine in a typical iodoform reaction.

2-Thiophenecarboxylic Acid.—Approximately 0.5 g. of 5-trimethylsilyl-2-thiophenecarboxylic acid was dissolved in 15 ml. of benzene, and while refluxing the solution, hydrogen chloride was bubbled through for one hour. Extraction with 10% sodium hydroxide, followed by acidification of the water layer gave a crystalline solid melting at 126–127° which showed no depression with an authentic sample of 2-thiophenecarboxylic acid. This establishes the position of both the carboxyl and acetyl group.

2-Furyltrimethylsilane.—To 68 g. (1.0 mole) of furan[13] was added 325 ml. of an ethereal solution of *n*-butyllithium[10] containing 0.98 mole of the organometallic.[11] The remainder of the directions are identical with those described above for 2-thienyltrimethylsilane. Rectification of the residue gave 53 g. (52%) of a colorless oil boiling at 124–125° (750 mm.), $n^{20}D$ 1.4470, d^{20}_4 0.880.

Anal. Calcd. for $C_7H_{12}OSi$: C, 60.0; H, 8.58. Found: C, 59.5; H, 8.71.

2-Acetyl-5-trimethylsilylfuran.—A mixture of 35 g. (0.25 mole) of 2-furyltrimethylsilane, 28.4 g. (0.27 mole) of acetic anhydride and 0.3 g. of iodine[12] was heated with stirring to an internal temperature of about 50°. At this point the reaction became exothermic and some cooling and later heating was necessary to keep the temperature between 45–55° for one hour. At the end of this time 15 ml. of water was added, and after stirring for a few minutes the dark solution was shaken with small quantities of 10% potassium hydroxide until the washings were basic. It was washed once with water and again with a concentrated solution of sodium thiosulfate. Upon removal of the solvent and rectification of the residue there was obtained 11.3 g. (25%) of a yellow oil (darkens rapidly on standing) boiling at 78.5–79° (3–4 mm.), $n^{20}D$ 1.4925, d^{20}_4 0.978.

Anal. Calcd. for $C_9H_{14}O_2Si$: Si, 15.4. Found: Si, 15.0.

The semicarbazone of this ketone, prepared in the usual way, melted at 200–201°.

Anal. Calcd. for $C_{10}H_{17}O_2N_3Si$: N, 17.56. Found: N, 17.72 and 17.59.

5-Trimethylsilyl-2-furoic Acid.—To 10 g. (0.07 mole) of 2-furyltrimethylsilane was added 67 ml. of an ethereal solution of *n*-butyllithium[10] containing 0.07 mole of the organometallic.[11] The mixture was refluxed four hours, and then allowed to stand overnight at room temperature. The mixture was carbonated and worked up in a manner similar to that described for 5-trimethylsilyl-2-thiophenecarboxylic acid. After reprecipitating the acid from 10% potassium hydroxide and crystallizing it twice from dilute ethanol, 8 g. (62%) of a light tan solid was obtained melting at 110–111°.

Anal. Calcd. for $C_8H_{12}O_3Si$: Si, 15.2. Found: Si, 14.9.

This same acid was isolated (mixed m. p.) when 2-acetyl-5-trimethylsilylfuran was treated with sodium hydroxide and iodine.

5-Bromo-2-furoic Acid.—A mixture of 1 g. (0.005 mole) of 5-trimethylsilyl-2-furoic acid and 1.5 g. (0.009 g. atom) of bromine in 15 ml. of dry carbon tetrachloride was refluxed one hour. The solid which had separated was

(8) Private communication from Dr. Henry Gilman.

(9) Purchased from Socony-Vacuum Oil Company.

(10) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

(11) Gilman and Haubein, *ibid.*, **66**, 1515 (1944).

(12) See Hartough and Kosak, *ibid.*, **68**, 2639 (1946).

(13) Kindly supplied by the E. I. du Pont Company.

filtered off and crystallized from hot water. It melted at 185.5–187° and was shown to be identical (mixed m. p.) with an authentic specimen of 5-bromo-2-furoic acid prepared according to the method of Whittaker.[14]

Summary

2-Furyltrimethylsilane and 2-thienyltrimethylsilane were synthesized from 2-furyllithium and 2-thienyllithium. The reaction of acetic anhydride with the above organosilicon compouunds, using iodine as the catalyst, gave 2-acetyl-5-trimethylsilylfuran and 2-acetyl-5-trimethylsilylthiophene, respectively.

(14) Whittaker, *Rec. trav. chim.*, **52**, 352 (1933).

LAFAYETTE, INDIANA RECEIVED DECEMBER 4, 1947

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Mechanism of the Nitration of Anisole

BY R. M. SCHRAMM AND F. H. WESTHEIMER

In the course of an investigation of the oxynitration of benzene,[1] the nitration of several phenols and of anisole was studied. The nitration of anisole leads to the formation of a mixture of nitroanisoles[2] and of nitrophenols[3] in proportions which depend upon experimental conditions. It is here shown that the nitration of anisole in dilute nitric acid solution is nitrite-catalyzed and that the nitrosoanisoles are probably intermediates in the reaction. These facts are of current interest because Bunton, Hughes, Ingold and Reed[4] have recently found that, under certain conditions, nitrosophenols are likewise intermediates in the nitration of phenols to nitrophenols.

More precisely, anisole has been found to react rapidly with 40 or 50% nitric acid containing a little nitrous acid, but fails during many hours to react with nitric acid containing urea.[5] When anisole is nitrated with 40% nitric acid (containing nitrous acid), the principal products are nitrophenols; when more concentrated (*e. g.* 60%) nitric acid is used, the principal products are nitroanisoles. The quantitative results of several experiments are reported in Table I.

TABLE I

THE REACTION OF ANISOLE WITH NITRIC ACID AND NITRITE

Conc. HNO_3, %	Conc. HNO_2, m./l.	Time of addition of anisole in minutes	Yield of nitroanisoles, % of theoretical	Yield of 2,4-dinitrophenol, % of theoretical
40	0.04	60	25	51
40	.18	60	18	63
50	.18	70	56	21
60	.18	60	71	Trace

(1) Westheimer, Segel and Schramm, THIS JOURNAL, **69**, 773 (1947).

(2) Brunck, *Z. Chemie*, 205 (1867); see also Holleman, *Rec. trav. chim.*, **22**, 263 (1903); Martinsen, *Z. physik. Chem.*, **59**, 605 (1907); Griffiths, Walkey and Watson, *J. Chem. Soc.*, 631 (1934); Buttle and Hewitt, *ibid.*, **95**, 1755 (1909).

(3) J. J. Hoffman, Dissertation, University of Chicago, 1931. For similar results with other aromatic ethers see K. Meyer, *Ann.*, **398**, 661 (1913); Ryan and Drum, *Sci. Proc. Roy. Dubin Soc.*, **17**, 313 (1924); Reilley, *ibid.*, **19**, 461 (1930).

(4) Bunton, Hughes, Ingold and Reed, *Nature*, **158**, 514 (1946).

(5) This nitration is thus similar to that of phenol; see Martinsen, *Z. physik. Chem.*, **50**, 385 (1905).

p-Nitroanisole cannot be an intermediate in the nitrite-catalyzed nitration of anisole to nitrophenols because, if this substance is added to a nitrating mixture which reacts rapidly with anisole, it may be quantitatively recovered. On the other hand, experiments with *p*-nitrosoanisole show that it reacts readily with the same nitrating mixture.[6] The products obtained by the nitration of *p*-nitrosoanisole under a wide variety of conditions parallel those obtained from anisole under corresponding conditions (see Table II). Thus it appears that nitrosoanisole is an intermediate in the nitrite-catalyzed nitration of anisole.

TABLE II

THE REACTION OF *p*-NITROSOANISOLE WITH NITRIC ACID AND NITRITE

Conc. HNO_3, %	Conc. HNO_2, m./l.	Time of addition of anisole in minutes	Yield of nitroanisoles, % of theoretical	Yield of 2,4-dinitrophenol, % of theoretical
40	0.04	60	14	73
40	.18	60	11	76
50	.18	1	62	29
50	.18	10	54	36
50	.18	70	60	30
60	.18	60	91	5

Although the proportions of the two products (nitroanisoles and nitrophenols) obtained from *p*-nitrosoanisole are about the same as those obtained from anisole, there is no exact correspondence between the two nitrations. Several reasons for this discrepancy may be suggested. In the first place, anisole, when nitrated with nitric acid and nitrite, must yield a certain amount of *o*-nitrosoanisole[2] as an intermediate, and this isomer would not necessarily give further reaction products in the same proportions as does *p*-nitrosoanisole. In the second place, the actual nitrite concentrations are not exactly those given in the two tables, because, during the reaction, anisole and nitrosoanisole produced different amounts of oxides of nitrogen. Thirdly, the addition of gross quantities of *p*-nitrosoanisole to the reaction mixture rather than the formation of this compound

(6) *Cf.* Bayer and Knorr, *Ber.*, **35**, 3034 (1902).

in situ (as in the reaction of anisole with nitric acid and nitrite) may have some effect on the course of the reaction. However, this effect is probably unimportant, since the period of addition of *p*-nitrosoanisole may be varied from one to seventy minutes without materially affecting the proportions of the reaction products.

Experimental

The Effect of Nitrite on the Reaction of Anisole with Nitric Acid.—(1) Anisole (20 g.) was added dropwise to 400 cc. of 40% nitric acid containing approximately 0.04 m./l. of nitrous acid. The addition required about half an hour; the reaction mixture was held at 30° and stirred for forty-eight hours. This long reaction time was necessary to convert all the mononitrophenols first formed into the more readily isolated dinitrophenol.[1] The mixture was then chilled in ice and filtered. The crude product obtained weighed 26.5 g. and melted at 100–108°. By recrystallization of this material from alcohol, 20 g. (59%) of pure dinitrophenol (m. p. 112–114°) was obtained. The identity of this compound was established by its melting point, the melting point of its mixture with an authentic sample of 2,4-dinitrophenol, and by the preparation of 6-bromo-2,4-dinitrophenol, m. p. 117–118°. In this experiment, the reaction mixture was not worked up for nitroanisoles; the product or products which arise from the methyl group of anisole have not been determined.

(2) In a second experiment, anisole (20 g.) was added dropwise over a period of one-half hour to 400 cc. of 40% nitric acid to which (one hour previously) 4 g. of urea had been added. After the mixture had been stirred for eighteen hours at about 30°, the reaction mixture was transferred to a separatory funnel and extracted with three successive 50 cc. portions of benzene. The benzene extract was washed with 60 cc. of water and dried over anhydrous sodium sulfate. Distillation from a small Claisen flask yielded 16.3 g. of anisole (81% of that used) boiling in the range 153–155°. There was no high-boiling residue.

(3) Seventy-five cc. of 50% nitric acid was allowed to stand with 1 g. of urea for three hours. Then anisole (about three g.) was added. The reaction mixture, after standing at room temperature for twelve hours was decidedly colored. The cause of the color was not determined; however, the extent of reaction was slight, since a three-drop sample of the mixture, when dissolved in a large excess sodium hydroxide solution, gave only a negligible yellow color. This test for nitrophenols is quite sensitive; and will easily reveal the presence of five parts per million of these compounds.

(4) One-hundred cc. of 50% nitric acid containing 0.1 m./l. of nitrous acid was mixed with three grams of anisole. The reaction mixture, after standing for two minutes at room temperature, was very dark. A three-drop sample of this reaction mixture, when dissolved in excess sodium hydroxide, gave a strong yellow color. The color was identified as that of nitrophenols, since (a) it was much more intense than that of a similarly diluted but neutral sample of the reaction mixture and (b) the coloring material had the indicator properties of nitrophenols.

(5) One-hundred cc. of 60% nitric acid containing 0.1 m./l. of nitrous acid was mixed with 0° with 1 g. of anisole. Reaction occurred instantly and proceeded autocatalytically. These conditions are probably not very different from those which were used for the preparation nitration of anisole to a mixture of ortho and para nitroanisoles.[2]

(6) Five-hundred cc. of 60% nitric acid was allowed to stand for an hour with 8 g. of urea; the solution was cooled to 0°, where urea nitrate crystallized. Three grams of anisole was then added. After two hours at 0°, 200 cc. of water was added and the mixture extracted with three 50-cc. portions of benzene. The benzene extract was washed and then fractionated through a short (10″) distilling column (tantalum-wire spiral type). After all the benzene was removed, the residue was distilled from a small Claisen flask. Anisole (1.9 g. distilling at 152–155°) was recovered. A small high boiling residue presumably contained nitro anisoles. At room temperature, 60% nitric acid containing urea gives no evidence of reaction for several minutes; then vigorous and autocatalytic nitration (with evolution of oxides of nitrogen) occurs.

The Reaction of *p*-Nitroanisole with Nitric Acid in the Presence of Nitrite.—Nine grams of *p*-nitroanisole was stirred at 50° for four and a half hours with 200 cc. of 50% nitric acid which contained 0.017 m./l. of sodium nitrite. When the mixture was filtered, 8.5 g. of *p*-nitroanisole, m. p. 50–52°, was recovered.

In a second experiment, *p*-nitroanisole (8.0 g.) was stirred at 50° for four and one-half hours with 200 cc. of 70% nitric acid containing 0.034 m./l. of nitrous acid. The reaction mixture in this case was homogeneous, whereas a slurry was obtained in the first experiment. When the mixture was cooled, diluted with water and filtered, 7.5 g. of *p*-nitroanisole, (identified by melting point and by the melting point of a mixture with an authentic sample) was recovered.

The Products of the Reaction of Anisole and of *p*-Nitrosoanisole with Nitric Acid and Nitrite.—Anisole (or *p*-nitrosoanisole) was added dropwise to about 200 cc. of a reaction mixture composed of nitric and nitrous acids (see Table I and II). During the addition, the reaction mixture was stirred vigorously and maintained at 50°. The amount of anisole or *p*-nitrosoanisole added was in each case between 3 and 4 g. After the addition was complete, the reaction mixture was heated long enough[1] to convert any mononitrophenols which had been formed into the more readily isolated 2,4-dinitrophenol. The mixture was then cooled and extracted with four successive 100-cc. portions of benzene. The benzene extract was concentrated to a volume of about 100 cc., and was then extracted with about 100 cc. of aqueous triethanolamine solution. Acidification of the aqueous extract threw down a precipitate of 2,4-dinitrophenol, which was filtered off, dried in a vacuum desiccator and weighed. The nitroanisole fraction was obtained from the residual benzene solution by removing the benzene under reduced pressure at room temperature.

In several instances, the above procedure was slightly varied. When the yield of nitroanisoles was relatively high, practically pure *p*-nitroanisole crystallized from the reaction mixture when it was cooled, and was recovered by filtration. This product was identified by its melting point and by the melting point of a mixture with an authentic sample of *p*-nitroanisole. In the reaction with *p*-nitrosoanisole, the nitroanisole isolated from the benzene extract was also practically pure *p*-nitroanisole. In the reactions with anisole, however, the product similarly isolated was an oil, probably a mixture of *o*- and *p*-nitroanisoles. These mixtures were usually worked up for *p*-nitroanisole, but were tested for the presence of nitrophenols only by their color reaction with alkali. In no case was an appreciable amount of nitrophenol found. The presumption that these oils were actually mixtures of *o*- and *p*-nitroanisoles was based first on the comparison with similar preparations previously reported.[2] In addition (in one instance), 1.40 g. of pure *p*-nitroanisole was isolated from 3.13 g. of the oil by recrystallization from aqueous alcohol. In another experiment, where the reaction with anisole gave a high yield of nitroanisoles, the initial yield of crystals from the reaction mixture was collected and found to be practically pure *p*-nitroanisole. In this case, 2.00 g. of *p*-nitroanisole was obtained from a total yield of 2.96 g. of crude oil.

Summary

The nitration of anisole in 40, 50 and 60% nitric acid is nitrite-catalyzed. The reaction product is a mixture of nitroanisoles and nitrophenols, in which the former compounds predominate when

60% acid is used and the latter when 40% acid is used. Under the same experimental conditions the same products can be obtained in roughly the same proportions from both nitrosoanisole and from anisole. This fact strongly indicates that the nitrosoanisoles are intermediates in the nitrite-catalyzed nitration of anisole.

CHICAGO, ILLINOIS RECEIVED DECEMBER 13, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

The Vapor Pressures and Some Related Quantities of Pentene-1 from 0 to 200°

BY H. O. DAY AND D. E. NICHOLSON WITH W. A. FELSING

Introduction

The determination of the thermodynamic properties of hydrocarbons has been a part of the research program of this laboratory for a number of years. Thus, heat capacities, heats of vaporization, and compressibilities for a number of hydrocarbons have been determined and reported.[1] The increasing importance of olefinic hydrocarbons has indicated a study of the pentenes and this report covers a portion of the work on pentene-1. In determining *p–v–t* data on both gaseous and liquid pentene-1, it was found that adequate data on vapor pressures over the range of temperatures from room temperature to the vicinity of its critical temperatures were lacking. This paper, hence, reports the experimentally determined vapor pressures for the range 0 to 200°.

Previous Investigations

The existing vapor pressure data have been examined critically by Stull[2] and he has reported the most probable values for the temperature range of −80.4 to 30.1°.

The normal boiling points, as recorded in the literature, differ considerably, due probably to differences in the purity of the samples of pentene-1 used. The most probable value, as selected by Stull[2] and as reported by Sherrill and Walter[3] is 30.1°, though the value of 29.97° was chosen by the A.P.I. Project No. 44.[4]

Methods and Apparatus

The dead-weight piston gage apparatus used in this Laboratory in *p–v–t* investigations was limited to a low pressure value of about 5 atmospheres, as determined by the weight of the piston and scale pan. Hence, vapor pressures up to 7.5 atmospheres were determined by means of a glass-contained compound mercury manometer, as described by Wilson,[5] attached to a static vapor pressure determining apparatus used by Felsing and Thomas.[6] The loading device employed by Felsing and Durban[7] was used to introduce pure, air-free pentene-1 into the piezometer at about −65°. A reasonable fraction, usually one-third, of the liquid was then evaporated out of the piezometer into the vacuum system to insure complete freedom from dissolved gases. An internal stirrer, actuated by a solenoid and metronome, served to prevent temperature gradients in the liquid. The entire apparatus was constructed of Pyrex glass. Mercury levels in the manometer were determined by means of a Gaertner cathetometer which could easily be read to 0.05 mm. Temperatures within the Dewar-flask bath were measured by short range mercurial thermometers calibrated by the National Bureau of Standards. The overall precision of these measurements was ±0.3%.

For vapor pressures from about 6 to 40 atmospheres, a dead-weight piston gage previously described,[8] was employed. Thermostat temperatures were controlled to ±0.005° by means of a platinum resistance thermometer in conjunction with a Mueller bridge and a photoelectric cell relay. The actual thermostat temperature was simultaneously determined by the resistance thermometer (calibrated by the National Bureau of Standards). In determining the vapor pressures, the volume of the vapor phase was varied from 0.2 to 15 cc.; this change in vapor volume had no effect on the observed pressures, indicating a high purity of the pentene-1. Three separate runs on three separate fillings gave closely agreeing values; the precision of the measurements was within ±0.1%.

The region above 200° is *not* considered in this paper, since the critical pressure is in the neighborhood of 201°; this critical region and liquid and vapor compressibilities will be reported in a later paper.

Material Used

The pentene-1 for this investigation was obtained from the Phillips Petroleum Company. The National Bureau of Standards, from freezing point data on representative samples of this lot, reported a purity of 99.34 ± 0.40 mole per cent. The most probable impurity was isopentane. The densities of the liquid under its own vapor pressure as a function of the temperature over the range 0–50° are represented by the equation

$$d(\text{g./cc.}) = 0.6630 - 0.001034t$$

where t is in degrees centigrade. The normal boiling point, as calculated from the vapor pressure equation, was found to be 30.07 ± 0.02°.

Treatment of Data

The experimental data were plotted to large scale as log p (mm.) against the reciprocal of the absolute temperature. Three linear equations were fitted by the method of least squares to separate portions of the line

(1) 0– 35°: $\log_{10} p$ (mm.) $= 7.40607 - 1372.194/T$
(2) 40– 95°: $= 7.31561 - 1342.407/T$
(3) 100–170°: $= 7.26782 - 1324.730/T$

The ice-point was taken as 273.16°K.

(1) (a) Lemons with Felsing, THIS JOURNAL, **65**, 46 (1943); (b) Dailey with Felsing, *ibid.*, **65**, 42 (1943); (c) Felsing and Watson, *ibid.*, **64**, 1822 (1942); **65**, 1889 (1943); **65**, 780 (1943); (d) Templeton and Davies with Felsing, *ibid.*, **66**, 2033 (1944); (e) Felsing, Cuellar and Newton, *ibid.*, **69**, 1972 (1947).

(2) Stull, *J. Ind. Eng. Chem.*, **39**, 517 (1947).

(3) Sherrill and Walter, THIS JOURNAL, **58**, 742 (1936).

(4) A.P.I. Res. Project 44 at NBS; "Selected Values of Properties of Hydrocarbons" Table 8a, dated May 31, 1947.

(5) Wilson, *Univ. of Illinois Eng. Exp. Sta. Bull.*, No. 146 (1925).

(6) Felsing and Thomas, *J. Ind. Eng. Chem.*, **21**, 1269 (1929).

(7) Felsing and Durban, THIS JOURNAL, **48**, 2885 (1926).

(8) Kelso with Felsing, *ibid.*, **62**, 3132 (1940).

From 170 to 200°, as the critical region was approached, the logarithm of the vapor pressure no longer could be represented by a linear function of the reciprocal of the absolute temperature. The equation, derived by aid of a central difference table, was found to be

(4) 170–200°: $\log_{10} p$ (mm.) = $-2089.553682 + 233{,}084.9289/T + 7034.8267 \times 10^{-3} T - 1049.16605 \times 10^{-5} T^2 + 5868.8889 \times 10^{-3} T^3$

Equations (1) and (2) reproduce the data to within ±0.3%, while equations (3) and (4) are reliable to a mean deviation of ±0.1 per cent.

The vapor pressures calculated by means of these equations at a few selected rounded temperatures are given in Table I.

The latent heats of vaporization were calculated for 0 and 30.07° by means of the exact Clapeyron equation; the vapor volume was calculated by means of the van der Waals equation, the constants of which for pentene-1 were derived from critical data. These values are 6225 and 6117 calories per gram mole for 0 and 30.07°.

TABLE I

SOME VAPOR PRESSURES OF PENTENE-1 FROM 0 TO 200°

Temp., °C.	Vapor pressure, mm.	Temp., °C.	Vapor pressure, mm.
0	241.3	100	5,221
5	297.1	120	7,913
10	363.1	150	13,717
20	531.3	170	19,055
30.07[a]	760	180	22,233
40	1069	190	25,850
60	1933	195	27,902
80	3269	200	30,203

[a] Normal boiling point.

Summary

1. The densities of liquid pentene-1 under its vapor pressure were determined from 0 to 50°.

2. The vapor pressures of pentene-1 were determined from 0 to 200°;

3. Calculated heats of vaporization are reported at 0 and 30.07°.

AUSTIN, TEXAS RECEIVED JANUARY 14, 1948

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Densities and Liquid–Vapor Equilibria of the System Ethanol–Isoöctane (2,2,4-Trimethylpentane) between 0 and 50°

BY CARL B. KRETSCHMER, JANINA NOWAKOWSKA AND RICHARD WIEBE

The present investigation is part of a systematic program in progress at this Laboratory to determine certain physical properties of ethanol–hydrocarbon systems. A considerable amount of experimental and theoretical material on solutions of aliphatic alcohols in non-polar solvents has been published and will be referred to in its proper place.

Density Measurements

Commercial absolute ethanol was fractionated in a 5-foot column packed with glass helices and then treated with magnesium ethylate.[2] The final product of d^{25}_4 0.78506 was kept under its own vapor pressure in a sealed container over magnesium ethylate and samples were withdrawn by vacuum distillation. Certified isoöctane (2,2,4-trimethylpentane) was fractionated in the same column. The middle fraction taken was filtered through a column of silica gel to remove the small content of olefins.[3] The final density was found to be d^{25}_4 0.68777.

The 13-ml. pycnometer shown in Fig. 1A was used for measuring the densities of the air-saturated liquids and solutions at 25°. No noticeable loss of liquid through evaporation was experienced during weighing because of the smallness of the capillaries (0.3 mm.). By applying gentle suction at the top, filling was accomplished by means of a device shown in Fig. 1B, and the turned-down tip[4] greatly facilitated the adjustment of volume. The accuracy of measurement was estimated to be 2×10^{-5} g./ml. or better.

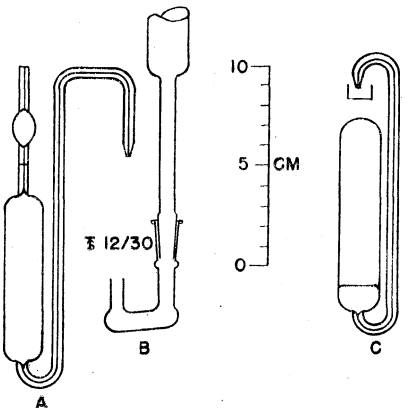


Fig. 1.—A, pycnometer; B, filling device; C, weight dilatometer.

The densities of the two pure liquids at 0 and 50° relative to their values at 25° were measured in a 14-ml. Pyrex weight dilatometer (Fig. 1C). Both apparatus and method were similar to those

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

(2) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(3) B. J. Mair and A. F. Forziati, *J. Research Nat. Bur. Standards*, **32**, 151, 165 (1944).

(4) G. F. Hennion, *Ind. Eng. Chem., Anal. Ed.*, **9**, 479 (1937).

described by Burlew.[5] Temperatures were measured by means of a standard platinum resistance thermometer and were not in error by more than 0.003°. The correction for the exposed portion of the capillary amounted to 5×10^{-6} g./ml.

The values obtained for ethanol are given in the last column of Table I. For isoöctane the values obtained were 0.708120, 0.687773 and 0.666855 g./ml. at 0, 25, and 50°, respectively. These values are the means of two or three determinations which differed by amounts indicating a precision of 4×10^{-6} g./ml. in the change of density over each 25° interval. In addition, the densities at all three temperatures are affected equally by the uncertainty of 2×10^{-5} g./ml. in the pycnometer measurements at 25° which were used to calculate the weight of liquid in the dilatometer. The densities given refer to liquids containing enough dissolved air to saturate them at 25°.

In Table I values recorded in the literature for the density of ethanol between 0° and 50° are compared with those obtained in this work. Osborne's[6] values from 10° to 40° are generally believed to be very reliable. At room temperature, our value and that of Riiber[7] are in good agreement with them. Tyrer's[8] densities are higher than the others, probably because of water in his sample. His value of thermal expansion from 0° to 25° is lower than ours, while the reverse is true for the interval 25–50°, the difference in each case being of the order of 10^{-4} ml./g. Our value of the density at 0° is slightly higher than those of Young,[9] Klason and Norlin,[10] and of Merriman,[11] while our value at 50° is appreciably lower than that of Young.

TABLE I

RECORDED VALUES FOR DENSITY OF ETHANOL, 0 TO 50°, G./ML.

Temp. °C.	Osborne[a]	Young[b]	Klason[c]	Tyrer[d]	Merriman[e] 0° Riiber[f] 20°	Authors' values obtained
0		0.80627	0.80628	0.80645	0.80628	0.806306
10	0.79784		.79792	.79803		
20	.78934	.7894	.78938		.78933	
25	.78506			.78532		0.785063
30	.78075		.78080			
40	.77203	.7722		.77224		
50		.7633		.76331		0.763137

[a] N. S. Osborne, E. C. McKelvy and H. W. Bearce.[6] [b] S. Young.[9] [c] P. Klason and E. Norlin.[10] [d] D. Tyrer.[8] [e] R. W. Merriman.[11] [f] C. N. Riiber.[7]

Brooks, Howard and Crafton[12] have measured the density of isoöctane at 20 and 25°, and our value at 25° is in excellent agreement with theirs.

(5) J. S. Burlew, THIS JOURNAL, **62**, 690 (1940).

(6) N. S. Osborne, E. C. McKelvy and H. W. Bearce, *Bull. Bur. Standards*, **9**, 327 (1913).

(7) C. N. Riiber, *Z. Elektrochem.*, **29**, 335 (1923).

(8) D. Tyrer, *J. Chem. Soc.*, 2534 (1914).

(9) S. Young, *ibid.*, 707 (1902); *Sci. Proc. Roy. Dublin Soc.*, **12**, 374 (1910).

(10) P. Klason and E. Norlin, *Arkiv Kemi Mineral. Geol.*, **2**, No. 24, 1 (1906).

(11) R. W. Merriman, *J. Chem. Soc.*, 628 (1913).

(12) D. B. Brooks, F. L. Howard and H. C. Crafton, *J. Research Nat. Bur. Standards*, **24**, 33 (1940).

The following equations fit the data for ethanol and isoöctane, respectively, for the range 0 to 50°

Ethanol

$$d^t_4 = 0.806306 - 8.4456 \times 10^{-4}t - 3.52 \times 10^{-6}t^2 - 6.82 \times 10^{-9}t^3$$

Isoöctane

$$d^t_4 = 0.708120 - 8.0481 \times 10^{-4}t - 3.168 \times 10^{-7}t^2 - 1.87 \times 10^{-9}t^3$$

The cubic terms were chosen to make the equation for ethanol agree with Osborne's figures, and to make the equation for isoöctane agree with Brooks, Howard and Crafton's value at 20°, all to within 1×10^{-5} g./ml.

Solutions were prepared by distilling the individual components into an evacuated bulb, and the amounts determined by weighing. In this way any loss, as well as any correction for the displacement of air, was avoided. Transfer to the pycnometer (Fig. 1A) was effected through displacement by mercury. The results shown in Table II were used in subsequent work for converting densities to compositions.

TABLE II

DENSITIES AT 25°

Ethanol Wt. fract.	Ethanol Mol. fract.[a]	d^{25}_4	$1000\,(V/V_0 - 1)$
0	0	0.68777	0
0.0130	0.0316	.68834	0.786
.0163	.0394	.68857	0.861
.0431	.1005	.69041	1.532
.0499	.1152	.69088	1.686
.1432	.2930	.69823	2.820
.2960	.5104	.71140	3.602
.4680	.6856	.72735	3.806
.6313	.8093	.74358	3.448
.8057	.9114	.76227	2.348
.8962	.9554	.77261	1.407
1	1	.78506	0

[a] Molecular weights: ethanol 46.07; isoöctane 114.22.

Densities of solutions at 0 and 50°, referred to the density of air-saturated solutions at 25°, were measured with a pycnometer similar to the one

TABLE III

DENSITIES OF SOLUTIONS AT 0 AND 50°

Ethanol Wt. fract.	Ethanol Mol. fract.	d^0_4	d^{50}_4	$1000\,(V/V_0 - 1)$ 0°	50°
0	0	0.70812	0.66686	0	0
0.0544	0.1248	.71207	.66959	1.09	2.81
.1120	.2382	.71676	.67378	1.60	3.92
.2332	.4299	.72705	.68368	2.43	4.96
.3232	.5421	.73508	.69158	2.79	5.25
.4166	.6390	.74371	.70018	3.03	5.25
.5307	.7371	.75464	.71119	3.18	4.95
.5397	.7440	.75554	.71212	3.17	4.86
.6409	.8157	.76573	.72243	3.05	4.28
.6968	.8507	.77160	.72831	2.83	3.87
.8042	.9106	.78330	.74009	2.16	2.80
.9195	.9659	.79658	.75342	1.04	1.26
.9332	.9719	.79823	.75503	0.85	1.08
1	1	.80631	.76314	0	0

shown in Fig. 1A, with an estimated accuracy of 7×10^{-5} g./ml. Results are given in Table III.

Discussion

Data of relative expansion of mixing, $(V/V_0) - 1$, where V is the volume of the solution and V_0 the sum of the volumes of the components, given in Tables II and III, are plotted in Fig. 2. Harms,[13] using the mass law, calculated this volume increase on mixing for several aliphatic alcohols in cyclohexane on the basis of dissociation of complexes containing from two to an infinite number of alcohol molecules. On this basis he obtained excellent agreement between experimental and calculated values for ethanol–cyclohexane solutions, whose volumetric behavior closely resembles that of the system ethanol–isoöctane. We feel, however, that the discussion is based on an oversimplified physical picture, and that the agreement is partly due to the fact that Harms' treatment contains two adjustable constants.

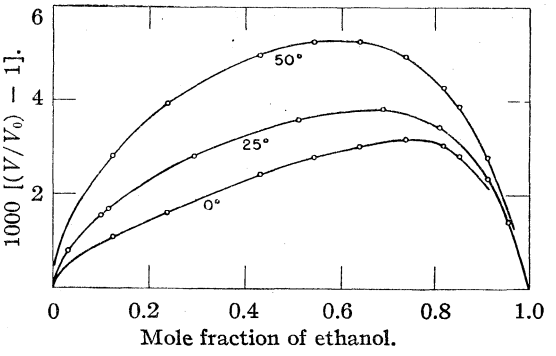


Fig. 2.—Relative expansion of mixing.

Liquid–Vapor Equilibrium Measurements

After a thorough consideration of existing methods, including actual trials, which emphasized the desirability of generating vapor in a separate boiler rather than depending on the boiling process itself to give equilibrium, the equilibrium still of Scatchard and co-workers[14] was selected as a basis.

Purification and density of the ethanol and isooctane used have been described previously. Figure 3 shows the equilibrium still. A water-bath was substituted for the vapor jacket used by Scatchard, which simplified construction and tended to maintain A at a more uniform temperature. Vapor was generated in boiler D and passed into the vapor-lift tube B where liquid was entrained and lifted to the top of chamber A. The mixture of liquid and vapor descended through the annular space packed with 3-mm. glass helices surrounding the thermometer well, and the vapor which separated passed through tube E to a condenser and finally to trap F. A heater located at the bend prevented any condensation during the passage. Bulb J was used to remove any possible traces of water as the ternary azeotrope. When a steady state was reached, the composition of the vapor in A was the same as that of the liquid in F, and the liquid and vapor samples were taken by means of evacuated sampling containers G. The tubes connecting the sampling containers G to the apparatus were full of air for all practical purposes and the error due to liquid holdup from this cause was negligible. No trouble was experienced using Apiezon grease L on stopcocks and joints when suitable precautions were taken.

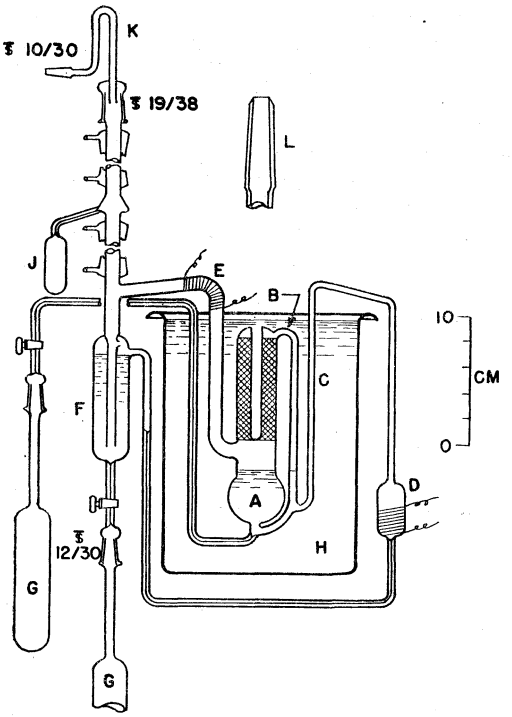


Fig. 3.—Equilibrium still: L, detail of sample bulb.

A platinum resistance thermometer and Mueller bridge, both recently calibrated, were used for temperature measurement. The condenser above trap F was connected to a 20-liter ballast and a manometer through trap K, an inverted U-tube surrounded by solid carbon dioxide. The manometer of 12 mm. i. d. tubing had provision for evacuating the vacuum arm when necessary. It was read with a Gaertner cathetometer (model M901) at a distance of 250 mm. Readings could easily be estimated to 0.02 mm., and no errors of this magnitude were found when the cathetometer was checked at the same working distance against a Gaertner standard meter calibrated by the Bureau of Standards. The vapor pressures are given in International mm. of mercury and have an estimated accuracy of 0.05 mm.

After complete evacuation, dry air was admitted and approximately 52 ml. of solution was introduced into the apparatus. Distillation rates were about 35 ml./hr. at 25° and 100 ml./hr. at

(13) H. Harms, *Z. physik. Chem.*, **53B**, 280 (1943).

(14) G. Scatchard, *et al.*, THIS JOURNAL, **60**, 1275, 1278 (1938); **61**, 3206 (1939); **62**, 712 (1940); and **68**, 1957, 1960 (1946).

50°. The pressure was regulated manually to keep the resistance thermometer reading exactly at 25.00° or 50.00°. The bath temperature was regulated to keep a constant amount of liquid (about 3 ml.) in boiler D, which required that the bath be several hundredths of a degree above the temperature in A. During initial operation a small amount was distilled into J to eliminate any possible traces of water, as explained previously. The steady state was maintained for considerable time after which temperature and pressure were measured in quick succession, heaters turned off, the apparatus was brought to atmospheric pressure, and samples were taken.

In addition, static measurements were made of the total vapor pressure of the solutions at 0 and 25°, by use of a vapor-pressure cell equipped with a magnetic stirrer and connected directly to the manometer. The solutions were freed of dissolved gases and traces of water by slowly distilling off part of the sample while the stirrer was in operation. This process was continued until McLeod gage readings on the portion of distillate uncondensed at −78° showed no more gases were being evolved. Vapor pressure and density of the remaining solution were then measured.

Results

Static vapor pressures at 0 and 25° and liquid–vapor equilibrium measurements at 25 and 50° are presented in Tables IV and V, respectively. The good agreement between static and dynamic vapor pressure measurements at 25° is indicated in Fig. 4; the actual agreement is within 0.2 mm.

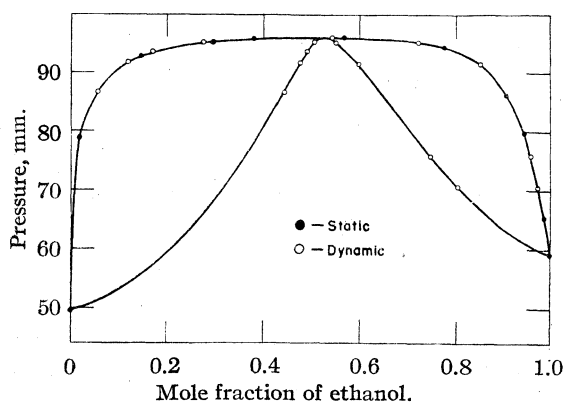


Fig. 4.—Vapor pressure at 25°.

The vapor curve below 0.4 mole fraction ethanol is conjectural. The data for 50° give curves of similar shape The azeotropic mole fraction of ethanol at 25° is 0.5270 and at 50° is 0.5941; the corresponding vapor pressures are 96.1 and 318.8 mm.

Vapor pressures for isoöctane reported here are in good agreement with the ones calculated from the equation published by Willingham and coworkers,[15] as shown in the following comparison at 0, 25 and 50° with their values in parentheses: 13.04 (12.99), 49.31 (49.34) and 146.47 (146.51). Since the value quoted by Willingham, *et al.*, for 0° represents an extrapolation from their lowest experimental point of nearly 25°, the agreement demonstrates the suitability of the Antoine equation used by them.

A comparison of the vapor pressures of ethanol at 0, 25 and 50° reported here with those of Merriman[11] in parentheses: 11.95 (12.0), 59.02 (59.0) and 220.94 (222.2) shows a good agreement except at 50°. Recorded values for the vapor pressure at 50° range from 219.8 mm.[16] to Merriman's

TABLE IV

STATIC VAPOR PRESSURE MEASUREMENTS

Mole fract. C_2H_5OH	P, mm. 0°	P, mm. 25°	Mole fract. C_2H_5OH	P, mm. 0°	P, mm. 25°
0.0000	13.03	49.29	0.5684	22.65	96.05
.0000	13.06	49.33	.7749	22.18	94.41
.0000 Av.	13.04	49.31	.9077	19.94	86.31
.0186	19.95	78.83	.9458	17.99	79.64
.1470	22.30	92.81	.9882	13.81	65.28
.2967	22.61	95.32	1.0000	11.96	59.01
.3795	22.68	95.83	1.0000	11.94	59.04
			1.0000 Av.	11.95	59.02

TABLE V

EQUILIBRIUM-STILL MEASUREMENTS

Liquid, mole fract. C_2H_5OH	Vapor, mole fract. C_2H_5OH	P, mm.	$10^4 \Delta \log P$
	25°		
0.0000	0.0000	49.31[a]	0
.0565	.4441	86.56	− 34
.1182	.4762	91.81	10
.1700	.4910	93.57	4
.2748	.5073	95.22	1
.3773	.5153	95.85	2
.5416	.5285	96.14	6
.7225	.5501	95.25	6
.8511	.5994	91.49	27
.9603	.7471	75.71	− 70
.9757	.8023	70.41	−120
1.0000	1.0000	59.03[a]	− 16
	50°		
0.0000	0.0000	146.47	0
.0113	.2938	207.31	32
.0340	.4238	250.15	16
.0579	.4752	271.87	13
.1240	.5254	296.29	21
.3428	.5701	315.21	21
.5176	.5863	318.26	27
.5943	.5941	318.75	29
.6144	.5969	318.82	29
.7713	.6279	315.10	30
.8799	.6881	301.38	43
.9319	.7526	282.86	30
.9516	.7942	271.27	22
.9829	.9008	242.85	− 23
1.0000	1.0000	220.94	− 50

[a] Static measurements.

(15) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Nat. Bur. Standards*, **35**, 219 (1945).

(16) W. Ramsay and S. Young, *Phil. Trans. Roy. Soc. London*, **A177**, 123 (1886).

222.2 mm. and the value given here is in reasonable agreement with the one of Scatchard and Raymond,[17] *viz.*, 221.17 mm.

Discussion

The partial molal free energy equation for binary solutions

$$x_1 \frac{d\bar{F}_1}{dx_1} + x_2 \frac{d\bar{F}_2}{dx_1} = 0$$

has been used extensively in the form of the Duhem–Margules equation

$$x_1 \frac{d \ln P_1}{dx_1} + x_2 \frac{d \ln P_2}{dx_1} = 0$$

or substituting total pressure times the corresponding mole fraction in the vapor phase Py and $P(1-y)$ for the partial pressures, the equation becomes[18]

$$d \ln P = \frac{y - x}{1 - y} d \ln y,$$

where deviations from ideal behavior of the vapor phase are neglected. This equation was integrated numerically, using our experimental values of mole fraction of ethanol in the liquid, x, and in the vapor, y. The differences $\Delta \log P$ between observed values of $\log P$ and those resulting from the integration are given in Table V. These deviations are made up of the experimental error plus the correction for vapor imperfections. The latter correction is proportional to the vapor pressure; at the low pressures involved in this work it is comparable in magnitude to the contribution of experimental errors to the integral. Hence, no significant evaluation of the parameters in the equation of state of the vapor can be obtained from the listed values of $\Delta \log P$. The agreement between calculated and observed pressures is reasonably satisfactory, however, since only two values of $\Delta \log P$ exceed 0.005.

Liquid–vapor compositions at 0° given in Table VI were calculated from the data in Table V on the assumption of additive specific heats. Using the same assumption, the differences $F - F_i = F^E$ and $S - S_i = S^E$ as well as H^M were computed, where F^E and S^E are the amounts of free energy and entropy above that of the ideal solution as indicated and H^M is the heat of mixing. They are shown in Table VII and Fig. 5. Detailed exposition of the method is given by Scatchard.[14] No correction was made for the imperfection of the vapor since it was found insignificant. The system carbon tetrachloride–methanol[14] shows a practically identical shape of curve for S^E *vs.* x as well as negative values for TS^E over the entire range. As pointed out, this must be due, in part at least, to the strong interaction of the two components. The entropy of mixing was discussed recently by Wood[19] at some length and it was stated that the orientational distribution is the principal factor. The negative values of S^E obtained in this investigation, as well as those obtained by Scatchard and co-workers for solutions of methanol in carbon tetrachloride and benzene,[14] would then be explained by increased orientation of the non-polar solvent molecules caused by the presence of alcohol molecules. Such an interaction is fairly plausible for carbon tetrachloride which contains chlorine atoms that can interact with the hydroxyl hydrogen, but it is somewhat surprising for the hydrocarbons, benzene and isooctane.

TABLE VI

CALCULATED LIQUID–VAPOR EQUILIBRIUM AT 0°

Mole fraction ethanol			
Liquid	Vapor	Liquid	Vapor
0.01	0.2673	0.40	0.4491
.025	.3626	.50	.4527
.05	.4062	.60	.4592
.10	.4219	.70	.4698
.15	.4291	.80	.4952
.20	.4374	.90	.5511
.30	.4447	.95	.6206
		Azeotrope	.451

TABLE VII

SMOOTHED VALUES OF THERMODYNAMIC FUNCTIONS IN CAL./MOLE AT 25°

Mole fract. ethanol	F^E	$-TS^E$	H^M
0.05	93	28	65
.1	159	53	106
.2	250	100	150
.3	307	138	169
.4	335	166	169
.5	342	183	159
.6	325	183	142
.7	287	168	119
.8	225	138	87
.9	136	87	49
.95	76	49	27

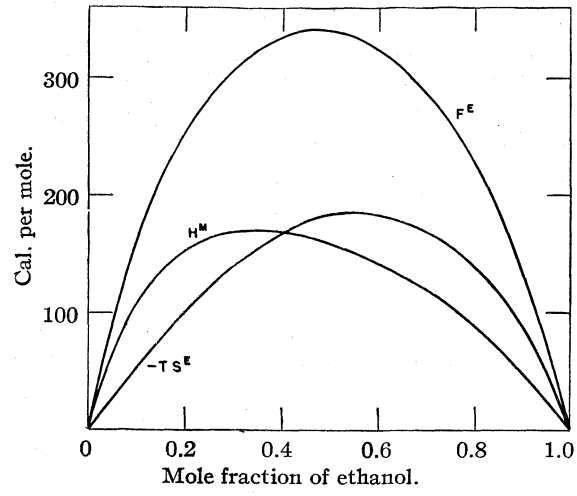


Fig. 5.—Thermodynamic functions at 25°.

(17) G. Scatchard and C. L. Raymond, THIS JOURNAL, **60**, 3099 (1938).

(18) W. K. Lewis and E. V. Murphree, *ibid.*, **46**, 1 (1924).

(19) S. E. Wood, *J. Chem. Phys.*, **15**, 358 (1947).

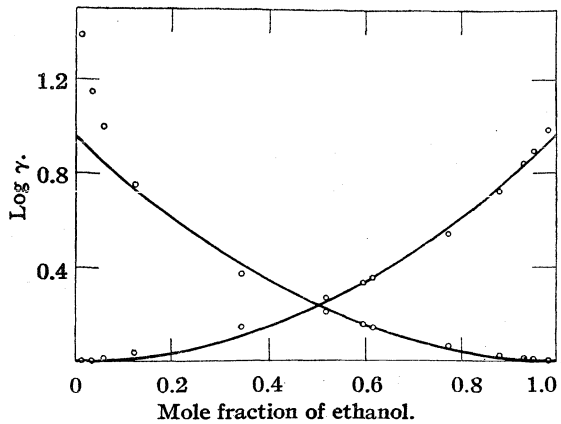


Fig. 6.—Logarithms of activity coefficients at 50°: circles, experimental values; curves, calculated from Van Laar equations.

Figure 6 shows the experimental activity coefficients at 50° compared with curves calculated from the Van Laar equations[20] fitted to the azeotropic composition and pressure. The two-constant Margules equations would give nearly identical curves since the terminal activity coefficients are nearly equal.[20] The agreement is seen to be fairly close except below 0.1 mole fraction where the equations fail to reproduce the rapidly increasing activity coefficient of ethanol. A better fit can be obtained only by using equations with more than two adjustable constants. However, the Van Laar equations would be useful in extending data on other hydrocarbon–alcohol systems, provided the peculiar behavior at low alcohol concentrations were kept in mind.

(20) H. C. Carlson and A. P. Colburn, *Ind. Eng. Chem.*, **34**, 581 (1942).

Summary

Densities of ethanol, isoöctane and of isoöctane–ethanol solutions were measured at 0, 25 and 50°. Equations giving the density of ethanol and isoöctane as a function of temperature are presented. The volume expansion on mixing increases rapidly with temperature.

Static vapor pressures at 0 and 25° and liquid–vapor equilibria at 25 and 50° were determined. Good agreement was obtained between the two sets of measurements at 25°. Satisfactory agreement was also obtained when calculating vapor pressures by means of the Duhem–Margules equation without corrections for imperfection of the vapor.

The excess thermodynamic functions F^E, TS^E and H^M were computed. Activity coefficients were calculated using the Van Laar equation and approximate reproduction of the experimental data were obtained.

PEORIA 5, ILLINOIS RECEIVED NOVEMBER 13, 1947

[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

Melting Point Curves of Optical Isomers

BY CHARLES L. BICKEL AND ALFRED T. PEASLEE, JR.[1]

The problem of the melting points of mixtures of optical isomers was placed on a sound theoretical basis by Roozeboom[2] who showed that three types of melting point curves might be expected. Several of the substances studied[3,4] give the mixed-crystal curve predicted by Roozeboom, a continuous curve joining the melting points of the two optical isomers and a straight line in its simplest form. Most of the compounds investigated[3,4,5] give a curve with two minima and a maximum, indicating the formation of a racemic compound. Ross and Somerville[4] reported that pinene gave the third type of curve, characteristic of a simple mixture and consisting of two parts with a minimum at the point of intersection. However, Timmermans[6] stated that the "dextro" pinene used by Ross and Somerville was a mixture of the two isomers of α-pinene, so that these investigators were working with a ternary mixture and not with optical opposites.

The present study of the dextro and levo forms of β-benzoylhydratropic acid indicates that these optical opposites give a simple mixture. The identity of the isomers appears to be definitely established[7,8,9] so that the question involved in the case of pinene should not be raised in this case.[10] The experimental data for the acids are presented graphically in Fig. 1.

This study has been extended to include the methyl esters of the above acids. Figure 2 indicates that a racemic compound is formed. The behavior of the methyl esters therefore resembles that of most of the acids and esters previously investigated.

(1) A senior in the Phillips Exeter Academy during the school year, 1947–1948.

(2) Roozeboom, *Z. physik. Chem.*, **28**, 494 (1899).

(3) Adriani, *ibid.*, **33**, 467 (1900).

(4) Ross and Somerville, *J. Chem. Soc.*, 2770 (1926).

(5) Ross, *ibid.*, 718 (1936).

(6) Timmermans, *Bull. soc. chim., Belg.*, **39**, 243 (1930).

(7) Bickel, THIS JOURNAL, **60**, 927 (1938).

(8) Kohler and Bickel, *ibid.*, **63**, 1531 (1941).

(9) Bickel, *ibid.*, **68**, 941 (1946).

(10) Since the submission of this manuscript the observations of Singh and Tewari [*Proc. Indian Acad. Sci.*, **25A**, 389 (1947)] regarding 3-nitro-*p*-toluidinomethylenecamphor have come to our attention. The *d* and *l* isomers of this substance appear to form a simple mixture, the melting point of the eutectic being only 1.8° below the melting point of each pure isomer.

This investigation was assisted by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

Experimental

A previous paper from this Laboratory[7] adequately described the preparation of the dextro and levo forms of β-benzoylhydratropic acid as well as their methyl esters. Each of these compounds was repeatedly crystallized to ensure purity, the acids from acetone and the esters from a mixture of ether and petroleum ether. The racemic methyl ester, prepared directly from the hydrogen cyanide addition product of benzylideneacetophenone by the action of methanol and concentrated sulfuric acid, was purified by repeated crystallization from methanol.

Each sample, weighing one-half gram and weighed to the nearest half milligram, was placed in an 8 by 75 mm. Pyrex test-tube which was centered in a sulfuric acid-bath equipped with an efficient motor stirrer and heated by a small burner with chimney. A calibrated tenth-degree thermometer was used, all temperature readings being corrected for emergent stem. The temperature rise of the bath did not exceed one-tenth degree per minute in the region of the melting point of each sample.

Each sample was melted, allowed to solidify, remelted, solidified, and melted at least once more. The original melting points were disregarded in the case of the mixtures. The values for the melting points of each acid mixture agreed to the nearest tenth degree; the tabulated values for the melting points of the ester mixtures are average values, the maximum deviation being one half degree for the mixture containing 90 per cent. of the dextro ester. There was no evidence of racemization or decomposition for either the acids or the esters.

The experimental data are collected below in tabular form.

Acids		Esters	
% Dextro[a]	M. p. in °C.	% Dextro[b]	M. p. in °C.
100	182.1	100	50.3
90	177.8	97	49.2
80	173.3	95	48.8
70	167.1	90	75.7
60	160.2	85	85.9
56	157.3	80	92.5
53	155.5	70	99.7
50	153.9	60	104.3
		55	105.4
		50	106.0

[a] These mixtures were prepared from the dextro and levo acids. The 50% mixture was also realized by using the inactive acid directly. [b] These mixtures were prepared from the dextro and racemic esters. The 50% mixture was also prepared from the dextro and levo esters.

The hope of obtaining reliable freezing point curves[11] for these mixtures could not be realized because of marked supercooling of the melts. For example, a five-gram sample of the fifty per cent. acid mixture, melting at 153.9°, showed an initial halt in the freezing point curve at 134° and then at 139° when the experiment was repeated with the same sample. Moreover, the ester mixtures containing a high proportion of either dextro or levo ester remained liquid for several hours in some cases and for several days in others.

(11) Bickel, THIS JOURNAL, 68, 866 (1946).

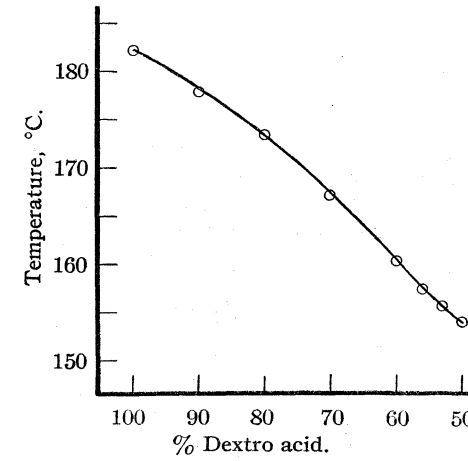


Fig. 1.

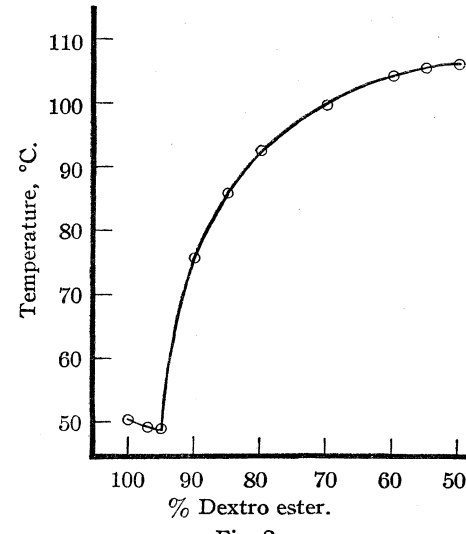


Fig. 2.

Summary

The melting point curve of the dextro and levo forms of β-benzoylhydratropic acid indicates that these isomers give a simple mixture.

The methyl esters of these acids, however, form a racemic compound.

EXETER, NEW HAMPSHIRE RECEIVED JANUARY 2, 1948

[CONTRIBUTION FROM THE TEXAS GULF SULPHUR COMPANY, INC.]

The Surface Tension of Chloroform

BY R. FANELLI

The surface tension of chloroform has been determined previously by numerous investigators using various methods. With few exceptions, the determined values fall on two straight lines which differ by less than one dyne per cm.[1] as shown in Fig. 1.

With the exception of Akhamatov's[2] value, all of the earlier data on the lower curve are due to Ramsay and Aston[5] while the upper curve encompasses almost all other values save that of Tyler[8] which obviously is too high. Because of the novel and less well established methods employed by Akhamatov and Tyler, their values may be justifiably disregarded.

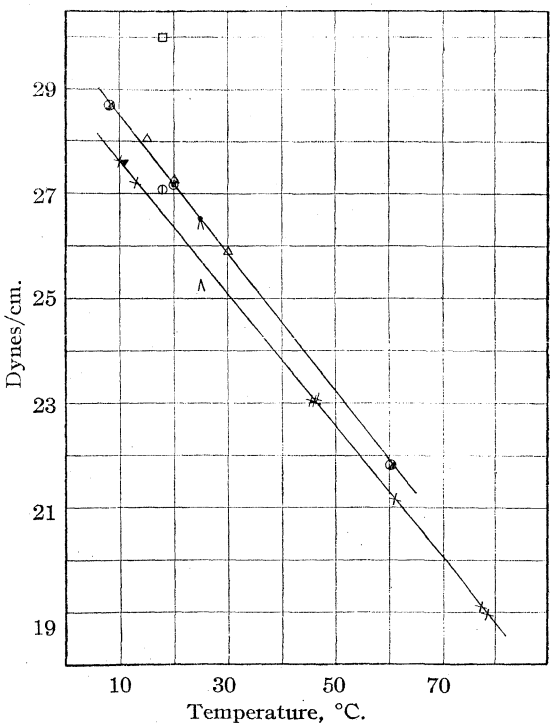


Fig. 1.—Surface tension of chloroform determined by various investigators: O, Richards and Carver[3] (capillary rise); △, Hennaut-Roland and Lek[4] (capillary rise); ×, Ramsay and Aston[5] (capillary rise); ◑, Schiff[6] (differential capillary rise); ▼, Akhamatov[2] (differential pressure corresponding to differential capillary rise); O, Harkins, Clark and Roberts[7] (drop weight); □, Tyler[8] (ripple); O, Addison[9] (vibrating jet); ⊕, Whatmough[10] (maximum bubble pressure, single capillary); ∧, Cupples[11] (maximum bubble pressure, single capillary); ●, Fanelli (maximum bubble pressure, Sugden's double capillary).

Explanation of Ramsay and Aston's low values probably lies in their failure to correct for the capillary rise in the wide tube (bore not given) and in other errors inherent in the method followed in 1894. Ramsay and Shields[12] using the same method and procedure (bore of wide tube, 1 cm.) and correcting for capillary rise in the wide tube in the case of water, obtained four values in the range 10 to 40°. They are 2.3 to 2.1 (av. 2.2) dynes per cm. too low, indicating that the method and procedure in that period tended to give low results. A correction factor for Ramsay and Aston's values may be approximated by multiplying the ratio of their chloroform value at 25° (25.7 dynes per cm.) to Ramsay and Shield's result for water at 25° (69.9 dynes per cm.) by the above average, 2.2. This factor, 0.8 dyne per cm., is equivalent to the discrepancy shown by the curves in Fig. 1. Richards and Coombs[13] using the capillary rise method attribute the low values of the early investigators to failure to correct all factors which tend to give low results.

At the time Cupple's paper appeared, Sugden's[14,15] form of maximum bubble pressure apparatus employing two capillaries was being standardized against chloroform. Therefore, the effect of saturating the inlet gas with chloroform vapor before entering the capillaries was determined.

Experimental

The apparatus and method of calculation employed have been described by Sugden.[15] The bore of the fine capillary was close to 0.2 mm.; the wider capillary was 3.66 mm. A Meriam Micromanometer reading directly to 0.001 in. (±0.001 in.) with water as the gage liquid measured pressure. Dried nitrogen gas forced through the capillaries was used for bubble formation. The bubble rate was varied between 60 per min. and 60 per 140 sec. In the main each result represents a different bubble rate. The constant temperature bath was kept well within 0.1° of the operating temperature.

The instrument was calibrated against benzene at 20 and 25°. Eastman Kodak Co. thiophene-free benzene,

(1) Dr. Cupples discussed these data in a recent article (11) but he was misled by plotting Richards and Carver's data for 20° incorrectly at 25°. This was confirmed by a private communication from Dr. Cupples.

Ramsay's and Aston's value of 19.98 dynes per cm. at 77.6° is misprinted in the original paper. Recalculation of their data gives the corrected value of 19.08 dynes per cm.

(2) A. Akhamatov, *Kolloid Z.*, **66**, 266 (1934).

(3) T. W. Richards and E. K. Carver, THIS JOURNAL, **43**, 827 (1921).

(4) Hennaut-Roland and M. Lek, *Bull. soc. chem. Belg.*, **40**, 177 (1931).

(5) W. Ramsay and E. Aston, *Proc. Roy. Soc. (London)*, **56**, 182 (1894); *Trans. Roy. Irish Acad.*, **32A**, 93 (1902).

(6) R. Schiff, *Ann.*, **223**, 47 (1884).

(7) W. D. Harkins, G. L. Clark and L. E. Roberts, THIS JOURNAL, **42**, 700 (1920).

(8) E. Tyler, *Phil. Mag.*, [7] **31**, 209 (1941).

(9) C. C. Addison, *J. Chem. Soc.*, 535 (1943).

(10) W. H. Whatmough, *Z. physik. Chem.*, **39**, 129 (1901).

(11) H. L. Cupples, *J. Phys. Chem.*, **50**, 412 (1946).

(12) Ramsay and Shields, *J. Chem. Soc.*, **63**, 1089 (1893).

(13) T. W. Richards and L. B. Coombs, THIS JOURNAL, **37**, 1656 (1915).

(14) S. Sugden, *J. Chem. Soc.*, **121**, 858 (1922).

(15) S. Sugden, *ibid.*, **125**, 27 (1924).

m. p. 5°, was fractionally distilled and the middle fraction boiling close to 80° was used. Six determinations were made at varying bubble rates with an average deviation from the mean of less than one part in a thousand. Saturating the nitrogen gas with benzene vapor before entering the capillaries had no effect whatever on the values. Values given by the original unpurified benzene differed but slightly from those given by the purified product.

The chloroform used was prepared from the C. P. analyzed grade by washing with water, drying over calcium chloride, and finally fractionally distilling. The portion boiling close to 61° was used.

The surface tension values obtained at 25.0° using dried nitrogen were: 26.47, 26.49, 26.52, 26.57, 26.56, 26.54; average 26.53 dynes per cm., average deviation from the mean <1/1000.

At 25.0°, using dried nitrogen saturated with chloroform vapor, the following values were obtained: 26.37, 26.47, 26.47, 26.52; average 26.46 dynes per cm., average deviation, <3/2000.

The above values show that saturating the inlet gas with chloroform vapor has little effect upon the surface tension values obtained by using the dried gas alone in Sugden's apparatus.

The values obtained at 20.0° using dried nitrogen were: 27.20, 27.15, 27.16, 27.14, 27.17, 27.14; average, 27.16 dynes per cm., average deviation, <1/1000. These values are very close to Richards and Carver's[3] and with those obtained at 25° fall squarely on the upper curve.

Like benzene, the unpurified chloroform gave essentially the same values as the purified liquid. This confirms Sugden's observation that the normal impurities in water and benzene have but slight effect on their respective surface tension values when the maximum bubble pressure method is used.

Summary

The surface tension of chloroform has been determined at 20 and 25° using Sugden's form of maximum bubble pressure apparatus. The values obtained check Richards and Carver's[3] results very closely.

Using Sugden's apparatus, saturation of the inlet gas with chloroform vapor before entering the capillaries has very little effect on the surface tension values. This confirms Whatmough's[10] observation, contrary to Cupples' findings. The probable explanation for the low values of Ramsay and Aston is reiterated.

75 EAST 45TH STREET
NEW YORK, N. Y.

RECEIVED MAY 15, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANITOBA]

The Systems Chromic Ammonium Sulfate–Ferric Ammonium Sulfate–Water and Chromic Ammonium Sulfate–Aluminum Ammonium Sulfate–Water at 25°

BY NORMAN O. SMITH AND CHARLES S. LENNOX

In a summary of the results of a series of isothermal investigations of ternary systems consisting of pairs of isomorphous salts and water Hill, Durham and Ricci[1] showed that the distribution of the salts between liquid and solid solutions obeys the semi-empirical relation

$$\log R_1 = \log K + m \log R_s \qquad (1)$$

where R_1 is the mole ratio of the salts in the liquid, R_s that in the coexisting solid solution, and m and K are constants for a particular system. The distribution constant K was shown to equal $(S_1\gamma_1^0/S_2\gamma_2^0)^{\nu/b}$, where S_1 and S_2 are the aqueous molal solubilities of the component salts, γ_1^0 and γ_2^0 the respective mean ion activity coefficients at these concentrations, ν the total number of ions per molecule of salt and b the number of ions per molecule of the ion which is being interchanged. Originally applied to alums and picromerites equation (1) has since been found to hold also for other isomorphous salt pairs.[2] In the case of alums m, in general, is unity, implying that solid solutions of alums are ideal. Of the five alum pairs reported, however, the ferric ammonium–aluminum ammonium pair did not obey the above relation satisfactorily. It was concluded[1] that this was the result of experimental error, but at the same time it was pointed out that this pair differed fundamentally from the other four in involving an interchange of the trivalent instead of the univalent cation. In order to examine further the effect of interchanging the trivalent cation the distribution studies of the present paper were undertaken.

(1) Hill, Durham and Ricci, THIS JOURNAL, **62**, 2723 (1940).

(2) See, for example, Ricci and Smiley, *ibid.*, **66**, 1011 (1944), and Simons and Ricci, *ibid.*, **68**, 2194 (1946).

Experimental

The technique employed was that of the previous alum studies: Complexes of known composition were made up in duplicate from the two alums and water in glass-stoppered test-tubes, glass marbles were added and the tubes rotated in a thermostat at 25 ± 0.03° for many weeks, at the end of which time both the liquid and solid phases were analyzed, the latter after being filtered from the liquid, centrifuged and air-dried for a few minutes. In the chromium–iron system two marbles were used but in the chromium–aluminum system one marble. In most cases the tubes contained about 35 g. of material but in regions of low chromium this was increased to 60 g. The members of each duplicate pair differed only in the order of addition of the components, one alum being dissolved in the water (by slight warming where necessary) before the other was added. In this way each point in the system was approached from two directions thereby establishing the attainment of equilibrium. The fact that a chrome alum was a component of both systems suggested that no less than three months of rotation would be required as it had been shown[3] that well over two months of time is required merely to attain the simple solubility equilibrium of a chrome alum in water. It was found, however, that for the chromium–iron system only nine weeks gave agreement of the duplicates. In

(3) Hill, Smith and Ricci, *ibid.*, **62**, 858 (1940).

TABLE I

SYSTEM $NH_4Cr(SO_4)_2$–$NH_4Fe(SO_4)_2$–H_2O AT 25°

	Complex, wt. % $NH_4Cr(SO_4)_2$	Complex, wt. % $NH_4Fe(SO_4)_2$	Liquid solution, wt. % $NH_4Cr(SO_4)_2$	Liquid solution, wt. % $NH_4Fe(SO_4)_2$	Solid solution, wt. % $NH_4Cr(SO_4)_2$	Solid solution, wt. % $NH_4Fe(SO_4)_2$	Log R_1 (mean of A & B)	Log R_2 (mean of A & B)	Log (R_1/R_2)
1	0.000	....	0.000	31.20	0.000	55.17			
2A	1.000	34.00	.332	29.53	3.799	50.43			
B	1.000	34.00	.332	29.56	3.778	50.49	1.943	1.181	0.762
3A	2.000	32.00	.743	28.76	8.019	47.16			
B	2.000	32.00	.747	28.66	7.964	47.11	1.580	0.764	.816
4A	3.000	30.00	1.151	27.58	11.97	41.95			
B	3.000	30.00	1.154	27.57	10.93	40.46	1.373	.550	.823
5A	5.000	28.00	1.785	25.64	17.07	37.56			
B	5.000	28.00	1.790	25.60	17.45	36.84	1.150	.327	.823
6A	7.50	25.00	2.713	23.29	23.58	31.29			
B	7.50	25.00	2.671	23.29	23.52	31.39	0.931	.118	.813
7A	9.00	19.00	4.555	19.03	33.26	21.36			
B	9.00	19.00	4.537	19.00	33.51	19.00[a]	.615	− .225	.840
8A	11.00	12.00	7.401	12.08	44.25	10.47			
B	11.00	12.00	7.403	12.10	44.26	10.31	.207	− .636	.843
9A	12.40	6.000	10.29	6.086	49.09	4.655			
B	12.40	6.000	10.30	6.075	50.27	4.469	− .235	−1.043	.808
10	....	0.000	13.66	0.000	54.81	0.000			

[a] By algebraic extrapolation.

TABLE II

SYSTEM $NH_4Cr(SO_4)_2$–$NH_4Al(SO_4)_2$–H_2O AT 25°

	Complex, wt. % $NH_4Cr(SO_4)_2$	Complex, wt. % $NH_4Al(SO_4)_2$	Liquid solution, wt. % $NH_4Cr(SO_4)_2$	Liquid solution, wt. % $NH_4Al(SO_4)_2$	Solid solution, wt. % $NH_4Cr(SO_4)_2$	Solid solution, wt. % $NH_4Al(SO_4)_2$	Log R_1 (mean of A & B)	Log R_2 (mean of A & B)	Log (R_1/R_2)
1	0.000	...	0.000	6.15	0.00	52.31			
2A	3.000	8.000	2.760	4.821	6.54	46.24			
B	3.000	8.000	2.762	4.830	6.34	46.29	−0.286	−0.900	0.614
3A	6.000	5.500	5.389	3.333	15.13[a]	37.87[a]			
B	6.000	5.500	5.246	3.622	16.20	36.23	+ .141	− .417	.558
4A	10.00	5.000	8.04	2.308	25.83	27.15			
B	10.00	5.000	7.95	2.440	26.05	27.46	+ .484	− .066	.550
5A	12.90	3.000	10.19	0.967	37.14	19.61	+ .979	+ .234	.745
6A	17.00	2.000	11.94	.659	44.02	9.29			
B	17.00	2.000	12.01	.560	43.96	8.69	+1.249	+ .646	.603
7	....	0.000	13.66	.000	54.81	0.00			

[a] By algebraic extrapolation.

the chromium-aluminum system about three months of rotation was allowed.

Materials.—The aluminum ammonium and chromic ammonium alums were recrystallized Baker Analyzed chemicals and the ferric ammonium alum was recrystallized British Drug Houses Analar product. These three alums will henceforth be referred to as the aluminum, chrome and iron alums, respectively. The first-mentioned retained its theoretical composition indefinitely; the other two effloresced slightly so that their analytical composition at the time of using was employed in calculating the compositions of the complexes.

Analysis.—In both systems the liquids and solids were analyzed for total ammonium and chromium. Ammonium was determined by alkaline distillation in steam of the ammonia into excess boric acid and titration of the excess of the latter with standard hydrochloric acid.[4] Chromium was determined by oxidation with persulfate in the presence of silver nitrate, precipitation of silver with hydrochloric acid, addition of a measured excess of standard ferrous sulfate and titration of the excess of the latter with standard dichromate in the presence of phosphoric acid using barium diphenylamine sulfonate as internal indicator. By preliminary trials these analytical methods were found to give an accuracy of better than 0.2% even for low proportions of chromium.

(4) Wagner, *Ind. Eng. Chem., Anal. Ed.*, **12**, 771 (1940).

Results and Discussion

Tables I and II give the analytical compositions of the liquid and solid phases for the chrome–iron and chrome–aluminum systems, respectively. In Table I the A data are for those tubes in which the chrome alum, and the B data the iron alum, was present as the initial solid phase. In Table II chrome alum was the initial solid for the A data and aluminum alum for the B data. The single solubilities of the alums are those of a previous paper.[3]

The agreement of the duplicates indicates satisfactory approach to equilibrium. To test the consistency of the analyses the per cent. of chromic ammonium sulfate in each solid was calculated by algebraic extrapolation from the compositions of

the liquid and complex to the analytical water content of the solid and compared with the observed per cent. In the first system the average absolute deviation for all the tubes was only 0.48% and in the second 0.71%.

The plots of the data are shown in Figs. 1 and 2. It is seen that in both systems there is a complete series of solid solutions as found (with one exception[5]) in all previous alum studies. The points for the liquid lie on a smoother curve for the first than for the second system suggesting a less complete attainment of equilibrium in the latter in spite of the longer period of rotation—the result, doubtless, of a less effective grinding of the solids during rotation (only one marble used).

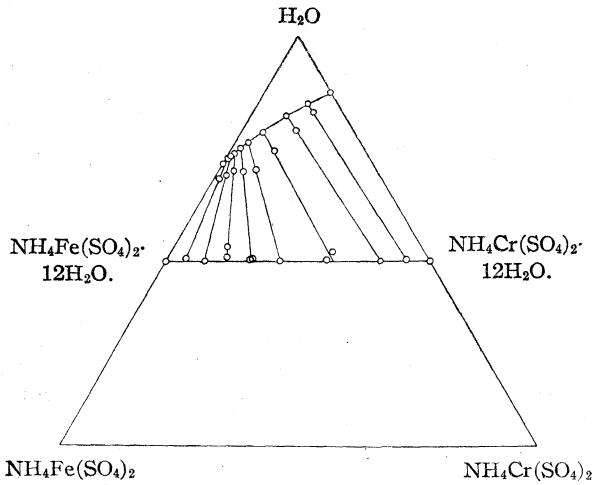


Fig. 1.—The system $NH_4Cr(SO_4)_2$–$NH_4Fe(SO_4)_2$–H_2O at 25°.

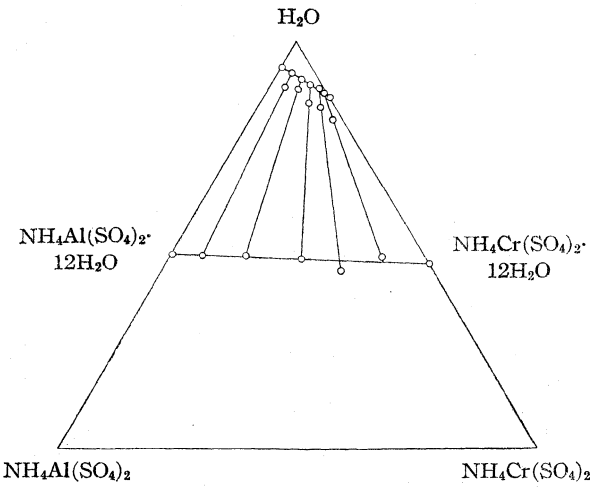


Fig. 2.—The system $NH_4Cr(SO_4)_2$–$NH_4Al(SO_4)_2$–H_2O at 25°.

In order to test the applicability of the distribution relation (1) log R_1 is plotted against log R_s in Fig. 3 from the values listed in Tables I and II. These are the logarithms of the ratios, in liquid

(5) Hill and Kaplan, THIS JOURNAL, **60**, 550 (1938).

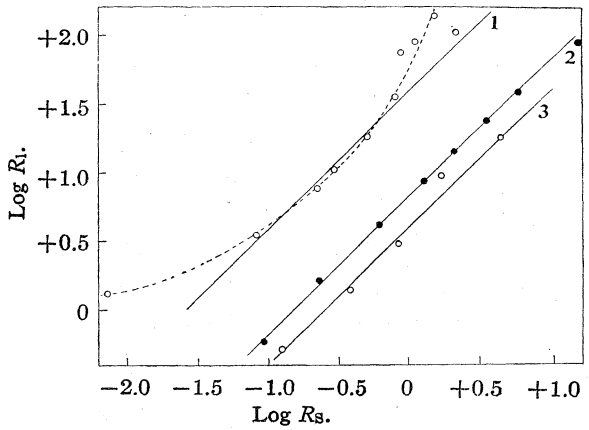


Fig. 3.—Distribution in alum systems: (1) $NH_4Fe(SO_4)_2$–$NH_4Al(SO_4)_2$–H_2O, (2) $NH_4Fe(SO_4)_2$–$NH_4Cr(SO_4)_2$–H_2O, (3) $NH_4Cr(SO_4)_2$–$NH_4Al(SO_4)_2$–H_2O.

and coexisting solid, respectively, of the molal concentration of the alum with the greater molal solubility to that of the alum with the lower. It is evident that the present systems, particularly the chrome–iron pair where more complete equilibrium was attained, give, within the limits of experimental error, a linear relation between log R_1 and log R_s and furthermore that the slope is unity. The data, therefore, obey equation (1) where m is unity, and the intercepts on the vertical axis, namely, 0.82 for the chrome–iron and 0.59 for the chrome–aluminum pair, should give the value of log K defined earlier. Because of lack of data on activity coefficients of alums these intercepts can, as yet, only be tested by the approximation[1]

$$K = (S_1/S_2)^{\nu/2b} \qquad (2)$$

based on the observation that for bi-bivalent sulfates $\gamma \cong A + B/\sqrt{\mu}$ over a limited concentration range, where μ is ionic strength, A is a very small constant and B a constant for most of the sulfates for which data were then available. It may be noted here that recent measurements in this Laboratory[6] show that this is also nearly true for chromic potassium and chromic ammonium sulfates from $\sqrt{\mu} = 0.9$ to $\sqrt{\mu} = 2.3$. Similarly, available data on chromic,[7] aluminum[7] and indium[8] sulfates suggest that these too satisfy the relation approximately, except that B is half as large. Thus the assumed applicability[1] of the relation to higher valence types is to some extent confirmed. Calculation of log K from (2) for the chrome–iron system gives 0.90 and for the chrome–aluminum system 0.68 in satisfactory agreement with the observed intercepts.

Another consequence of the linear relationships of Fig. 3 is that both systems can be assigned to Type I of the Roozeboom classification,[9] for the slope of each line is unity.

(6) Smith, *ibid.*, **69**, 91 (1947).
(7) Robinson, *ibid.*, **59**, 84 (1937).
(8) Hattox and DeVries, *ibid.*, **58**, 2126 (1936).
(9) Roozeboom, *Z. physik. Chem.*, **8**, 521 (1891).

Included in Fig. 3 for purposes of comparison are the data of Hill and Kaplan[5] for the ferric ammonium–aluminum ammonium system. The suggestion of Hill, Durham and Ricci that the distribution in this system is also a linear one in spite of the fact that the points tend to lie on a curve is therefore further supported by the two analogous systems here reported.

The relation

$$\log R_1 = \text{constant} + \log R_s \qquad (3)$$

thus found valid in all alum systems so far studied has been shown[1] to have a theoretical basis as a special case of

$$\log R_1 = \log K + \log (f_B/f_{B'}) - \log (\gamma_B/\gamma_{B'}) + \log R_s \qquad (4)$$

where f_B and $f_{B'}$ are the rational activity coefficients of the interchanging ions in the solid solution and γ_B and $\gamma_{B'}$ their practical activity coefficients in the coexisting liquid solution. To reduce this to (3) requires that $f_B/f_{B'}$ and $\gamma_B/\gamma_{B'}$ shall be constant at all points across the diagram and Hill, Durham and Ricci propose that in systems where m is unity both ratios are not only constant but unity. This assumption is, of course, necessary if the intercepts of Fig. 3 are to be identified with $\log K$.

It is possible to raise an objection to the identification of the intercepts with $\log K$ in the light of data of ref. 6 as applied to the chromic potassium–chromic ammonium alum pair.[3] The values of the molal solubilities of these alums are 0.817 and 0.603, respectively, in which solutions the respective mean ion activity coefficients are 0.0358 and 0.0465. This gives $\log K = \log (0.817 \times 0.0358/0.603 \times 0.0465)^4 = 0.07$. The intercept on the $\log R_1$ *vs.* $\log R_s$ plot is given[1] as 0.20 which equals the sum of the first three terms on the right side of (4). This means that $\log (f_K/f_{NH_4}) - \log (\gamma_K/\gamma_{NH_4}) = 0.13$, a finite constant for all proportions of the two alums. It is very unlikely that as one passes across the diagram the f and γ ratios both alter in such a way that the difference of their logarithms is constant; it is more reasonable to suppose that they are both constant, but then both could not be unity. It is interesting to note that if f_K/f_{NH_4} is regarded as unity then $\log (\gamma_K/\gamma_{NH_4})$, becomes -0.13 which may be compared with that estimated as follows: The ratio of the mean ion activity coefficient of chromic potassium sulfate to that of chromic ammonium sulfate is reasonably constant (about 0.88) over the range of ionic strengths of the isotherm. If the activity coefficients of chromic and sulfate ions are assumed to be the same in solutions of single alums as they are in mixed alums of the same ionic strength then $\log (\gamma_K/\gamma_{NH_4})$ should be given roughly by $\log (0.88)^4 = -0.22$. On the other hand, the uncertainties involved in the evaluation of the activity coefficients of the alums may have combined to produce a large error in $\log K$ thus invalidating the above argument.

Summary

1. The systems chromic ammonium sulfate–ferric ammonium sulfate–water and chromic ammonium sulfate–aluminum ammonium sulfate–water have been investigated at 25°.

2. Both systems exhibit a complete series of solid solutions at this temperature, and, as the distribution of the components follows the relation $\log R_1 = \text{constant} + \log R_s$, they are assigned to Type I of the Roozeboom classification. The values of the constant for each system compare favorably with the values estimated from the individual solubilities of the component alums.

3. A possible objection is raised to the assumption of a value of unity for the ratio of the activity coefficients of the interchanging ions in the liquid.

WINNIPEG, CANADA RECEIVED NOVEMBER 12, 1947

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

The System Ammonium Nitrate–Ammonium Sulfamate[1]

BY JACK H. THELIN[2] AND P. A. VAN DER MEULEN

The present research represents the initial investigation of the phase equilibria in the reciprocal salt pair system sodium nitrate–ammonium sulfamate. This included the phase diagram of the binary system ammonium nitrate–ammonium sulfamate.

Ammonium nitrate is known to exist in five crystalline modifications. Early and Lowry[3] have re-examined the transition temperatures of the various modifications and have summarized the results. Two of the transition points are of importance in the present investigation. They are the transition temperatures of 125.2° at which the cubic changes to the tetragonal and 84.2° at which the tetragonal changes to the monoclinic modification. There are no published records concerning possible polymorphism of ammonium sulfamate.

Experimental Method

Purification of Materials.—Merck ammonium nitrate was crystallized twice from distilled water and dried under

(1) Based on a thesis submitted by Jack H. Thelin to the graduate faculty of Rutgers University in partial fullfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: American Cyanamid Co., Calco Chemical Division, Bound Brook, N. J.

(3) R. G. Early and T. M. Lowry, *J. Chem. Soc.*, **115**, 1387 (1919).

vacuum with phosphorus pentoxide at 40° with frequent grinding. Heating was found to be necessary to obtain the accepted freezing point of 169.6° as given by Early and Lowry.[3] Samples dried for two months at room temperature under vacuum with phosphorus pentoxide gave a freezing point of only 169.2°. In all experiments the ammonium nitrate used in this research had a freezing point of 169.5–169.6° (cor.).

The ammonium sulfamate was obtained from E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware, and was their technical grade. It was recrystallized twice from distilled water with care taken not to heat above 60°. An odor of ammonia was plainly noticeable at 80°. The freezing point obtained by us after two crystallizations from water and drying under vacuum with phosphorus pentoxide with intermittent heating to 100° on a water-bath was 132.9° (cor.). Gordon and Cupery[4] report a melting point of 131°. The purity was established by reaction of the ammonium sulfamate with potassium nitrite to form the sulfate and subsequent determination as barium sulfate. Two determinations gave 28.17 and 28.15% sulfur (calcd. 28.07). Dilatometric measurements using a high boiling kerosene fraction as medium showed no transition within the temperature range of 47° and the melting point.

Apparatus Used.—The freezing point apparatus is shown in Fig. 1. The oil-bath consisted of a one-liter Griffin-type beaker filled with Nujol in which the jacketed freezing point tube was placed. The inner tube which held the melted salts was made from a small Pyrex test-tube (13 × 100 mm.). The platinum wire used to agitate the melt was driven by a suitable mechanism at 120 strokes per minute. A loop of glass tubing through which water could be circulated was suspended in the oil-bath to aid cooling at temperatures below 100°. When the flame under the oil-bath was adjusted so that no variation of the oil-bath temperature was noted, the flowing of a few milliliters of water through the coil lowered the temperature of the melt as little as 0.05° a minute. Such slow cooling was advantageous in treating melts which had a strong tendency to supercool.

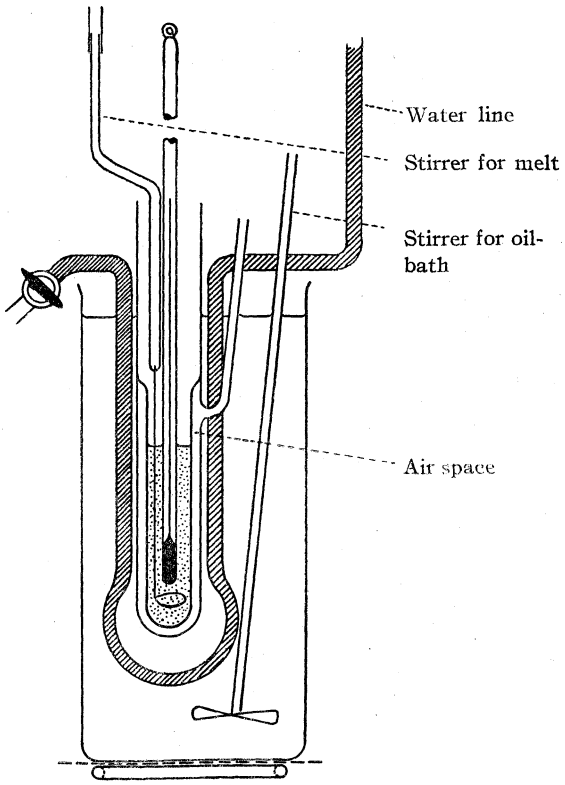


Fig. 1.

The thermometers were graduated in fifths of a degree and were standardized against thermometers recently checked by the Bureau of Standards. Corrections for emergent stem were made.

Technique.—The salt charge of approximately 4 g. was weighed by difference, placed in the aluminum boat of the apparatus shown in Fig. 2, and dried under vacuum at 56° (boiling acetone) for one to two hours with phosphorus pentoxide. In this way any moisture absorbed while weighing was removed. After drying, the mixtures were quickly transferred to the freezing point tube and placed in the previously heated oil-bath.

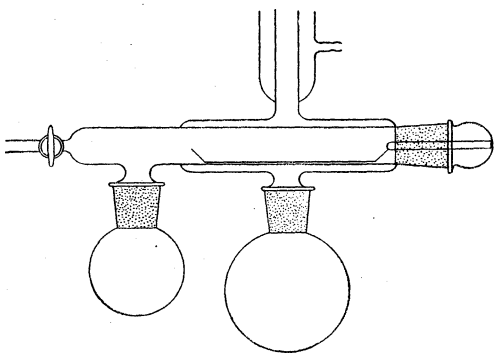


Fig. 2.—Modified Abderhalden drying pistol.

The drying apparatus of Fig. 2 is a modification of the Abderhalden drying pistol. In the conventional type the vacuum pump connection, the phosphorus pentoxide bulb and the sample itself are all attached at the front of the apparatus. In the present modification the drying chamber is extended through to the rear and the vacuum connection and the phosphorus pentoxide bulb are attached at the back out of the way. The boat is fastened to the glass stopper by a short piece of glass rod.

The usual cooling rate was 0.2–0.4° per minute. Seeding was accomplished by dipping a platinum wire into the melt at one-minute intervals and allowing the melt clinging to the tip to solidify. Enough of the melt adhered to the wire to "seed" the melt on the next trial. All recorded temperatures represent visual observation of initial crystal formation.

Experimental.—The data given in Table I were obtained as described under Experimental Method. Each recorded temperature represents a freshly prepared melt.

Figure 3 is a plot of the data with temperature as ordinates and composition as abscissas. The composition indicated by the intersection of the liquidus curves is 54.8% $NH_4SO_3NH_2$. Supercooling effects were observed, however, so that the eutectic temperature of 75.3° finally obtained with all mixtures is higher than the temperatures indicated by the intersection of the two liquidus curves. This leaves the precise composition of the eutectic mixture in doubt to the extent of about 1% of ammonium sulfamate. An enlarged plot of the curve gave 125.7° for the transition temperature of $NH_4NO_3(I) \rightleftarrows NH_4NO_3(II)$. Early and Lowry give 125.2° as the transition point for pure ammonium nitrate. Holmes and Revinson[5]

(4) W. E. Gordon and M. E. Cupery, *Ind. Eng. Chem.*, **31**, 1237 (1939).

(5) E. C. Holmes, Jr., and D. Revinson, THIS JOURNAL, **66**, 453 (1944).

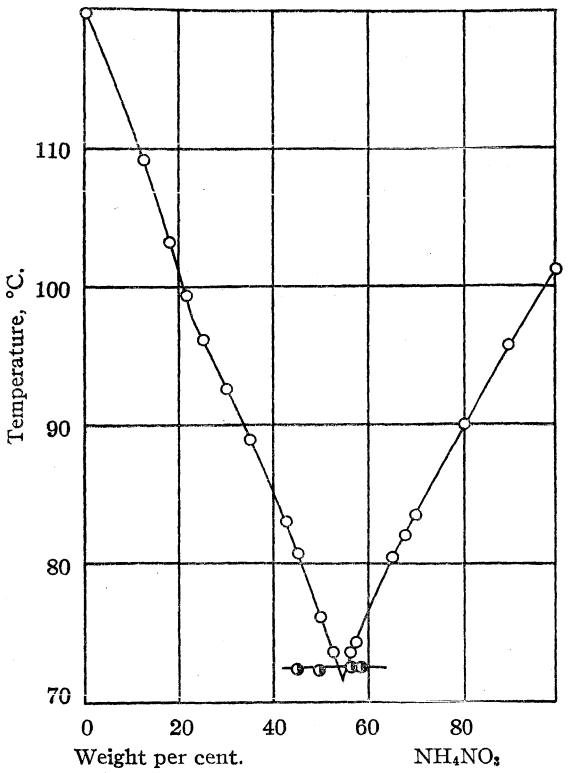


Fig. 3.—Freezing point of mixtures of $NH_4SO_3NH_2$ and NH_4NO_3

report 126.2° from a reinvestigation of the system ammonium nitrate–sodium nitrate. Perman and Harrison[6] report the transition temperature as 122° from a study of the system lithium and ammonium nitrates. The absence of the inversion point at 84.2° has been reported previously[7] in a study of the solubility of ammonium nitrate in water.

Howells,[8] on the basis of a study of the system urea–ammonium nitrate also states that no inversion point was obtained at 83°.

(6) E. P. Perman and W. R. Harrison, *J. Chem. Soc.*, **125**, 1709 (1924).

(7) A. Findlay, "The Phase Rule," Longmans, Green and Co., New York, N. Y., 1938, p. 174.

(8) W. J. Howells, *J. Chem. Soc.*, 910 (1929).

TABLE I

FREEZING POINTS OF MIXTURES OF AMMONIUM NITRATE (A) AND AMMONIUM SULFAMATE (B)

	% B by weight	F. p., °C.	Eutectic, °C.
Solid phase A	0.0	169.6	..
	12.5	148.3	..
	17.5	136.4	..
	18.0	135.5	..
	20.0	131.2	..
	21.0	128.9	..
	25.0	122.1	..
	30.0	115.4	..
	35.0	107.8	..
	42.5	96.0	..
	45.0	91.4	75.0
	50.0	82.1	74.5
	52.5	77.2	75.4
	53.8	75.4	75.4
Solid phase B	56.2	76.6	75.3
	57.5	78.7	75.3
	60.0	83.2	..
	65.0	91.0	..
	67.5	93.9	..
	70.0	97.0	..
	80.0	110.1	..
	90.1	121.4	..
	100.0	132.9	..

Summary

1. The freezing point of ammonium sulfamate is 132.9°.

2. Dilatometric measurements indicate that ammonium sulfamate exists in only one crystalline modification in the temperature range from 47° up to the melting point.

3. The binary system NH_4NO_3–$NH_4SO_3NH_2$ has a eutectic point at 75.3° and *ca.* 54.8% ammonium sulfamate with NH_4NO_3 and $NH_4SO_3NH_2$ as the solid phases.

4. The transition from NH_4NO_3(I) to NH_4NO_3(II) takes place at 125.7°.

NEW BRUNSWICK, N. J. RECEIVED JANUARY 19, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

The Systems Ammonium Sulfamate–Sodium Sulfamate and Sodium Sulfamate–Sodium Nitrate

BY STEPHEN H. LANING[1] AND P. A. VAN DER MEULEN

The present paper describes the binary systems ammonium sulfamate–sodium sulfamate and sodium sulfamate–sodium nitrate.

Preparation and Purification of Materials.—The method used in the purification of ammonium sulfamate was described in the previous paper.

Merck sodium nitrate C. P. was crystallized twice from distilled water and dried under vacuum with phosphorus pentoxide.

Sodium sulfamate was prepared by the method described by Laning and van der Meulen.[2]

The Binary System Ammonium Sulfamate–Sodium Sulfamate.—Mixtures of weighed quantities of the components were prepared and placed in the melting point apparatus described in the previous paper. They were melted and allowed to crystallize slowly. The initial freezing point was taken, and then the melt was slowly warmed and the temperature at which the last crystals disappeared was also taken. In most cases the two temperatures were not more than a half degree apart. The mean of the temperatures at which crystals were just formed and at which the last crystal disappeared was taken as the freezing point. This procedure was necessary because the high viscosity of most of the melts led to extensive supercooling and exceedingly slow crystallization even when the melt was seeded.

The results of these determinations are given in Table I, and represented graphically in Fig. 1.

TABLE I

FREEZING POINTS OF MIXTURES OF AMMONIUM SULFAMATE (B) AND SODIUM SULFAMATE (C)

$NaSO_3NH_2$ (C), % by wt.	F. p., °C.	Eutectic point, °C.	Solid phase
0.0	132.85		B
5.0	128.80		
10.0	124.75		
15.0	120.70	118.7	
16.2	119.80	118.8	
16.8	119.20	118.8	
17.0	119.0	118.8	B_2C_5
17.5	121.0	118.8	
18.0	122.9	118.8	
20.0	130.2		
25.0	144.7		
30.0	157.9		
35.0	168.5		
40.0	177.0		
50.0	193.0		
60.0	204.4		
65.0	209.0		
70.0	212.3		
72.5	212.9		
73.0	212.6		C
75.0	215.0		
77.5	218.0		
80.0	221.5		
100.0	250.5		

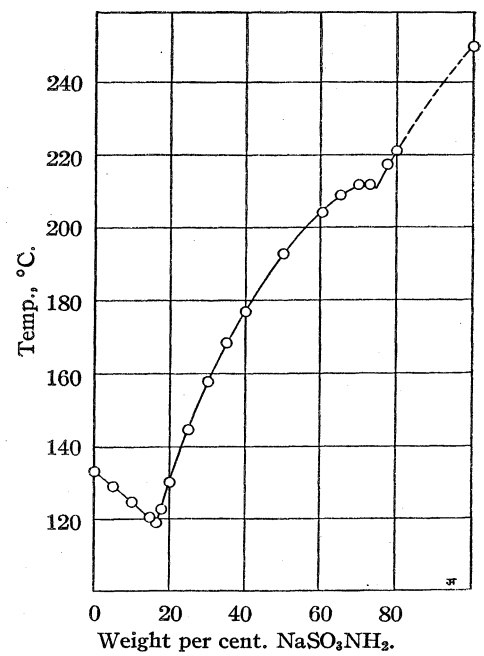


Fig. 1.—Freezing points of mixtures of $NH_4SO_3NH_2$ and $NaSO_3NH_2$.

The curve shows two eutectics. The lower occurs at a composition of 16.95% sodium sulfamate, and a temperature of 118.8°. The solid phases at this point are ammonium sulfamate and a compound $2NH_4SO_3NH_2 \cdot 5NaSO_3NH_2$. The latter compound melts congruently at 213 ± 1°. Since at temperatures above 170° decomposition of ammonium sulfamate occurs, it was necessary to work rapidly, especially at temperatures above 200°. An accurate determination of the upper eutectic point was not possible, but it lies near a temperature of 212° and a composition of 73.0% sodium sulfamate. From melts containing more sodium sulfamate, the solid which separates is pure sodium sulfamate.

The Binary System Sodium Sulfamate–Sodium Nitrate.—A preliminary investigation indicated that only a limited range of compositions could be studied. Mixtures containing

(1) Based on a thesis submitted by Stephen H. Laning to the graduate faculty of Rutgers University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Laning and van der Meulen, THIS JOURNAL, **69**, 1828 (1947).

less that 15% or more than 60% of sodium nitrate have melting points at which decomposition is sufficiently rapid to prevent accurate determinations of melting points.

The melting points of mixtures in the range in which decomposition does not occur are given in Table II and are shown graphically in Fig. 2.

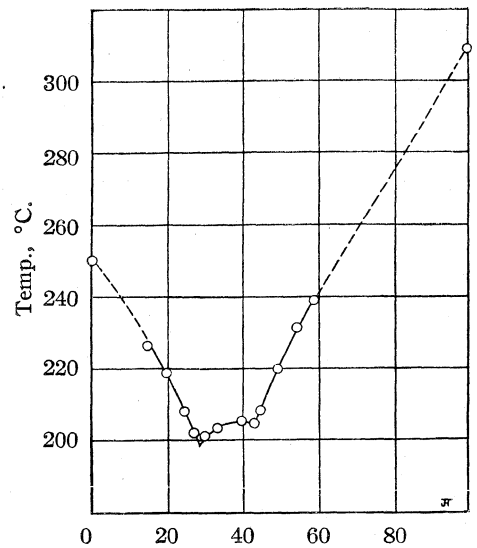


Fig. 2.—Freezing point of mixtures of $NaSO_3NH_2$ and $NaNO_3$.

From melts containing less than 28.5% sodium nitrate, the first crystals which separate are sodium sulfamate. The lower eutectic mixture contains 28.5% sodium nitrate, and melts at 199°. The other eutectic mixture contains 43.4% sodium nitrate and melts at a temperature of 205.0°. There is a compound $NaSO_3NH_2 \cdot NaNO_3$ with a melting point of 205.7°. It contains 41.68% sodium nitrate. From melts containing more than 43.4% sodium nitrate, the first crystals which separate on cooling are sodium nitrate.

TABLE II

FREEZING POINTS OF MIXTURES OF SODIUM SULFAMATE (C) AND SODIUM NITRATE (D)

$NaSO_3NH_2$ % (D) by wt.	F. p., °C.	Eutectic point, °C.	Solid phase
0.0	250.0		C
15.0	226.5		
20.0	219.0		
25.0	208.3	198.3	
27.5	202.5	198.8	
30.0	201.6	199.0	
33.3	203.8		
35.0	204.7		
40.0	205.3		
41.65	205.7		CD
41.67	205.3		
42.50	205.2		
43.33	205.2	205.0	
45.0	208.6	205.0	D
50.0	220.0		
55.0	231.6		
55.6	232.0		
59.8	238.8		
100.0	307.5		

Summary

1. Ammonium sulfamate and sodium sulfamate form a compound, $2NH_4SO_3NH_2 \cdot 5NaSO_3NH_2$, which melts congruently at 213 ± 1°.

2. The eutectic point between ammonium sulfamate and the 2:5 compound is at 118.8° with a melt containing 16.95% sodium sulfamate; the eutectic point between sodium sulfamate and the 2:5 compound is at a temperature near 212° with a melt containing 73.0% sodium sulfamate.

3. Sodium sulfamate and sodium nitrate form a compound $NaSO_3NH_2 \cdot NaNO_3$ with a melting point of 205.7°.

4. The eutectic point between sodium sulfamate and the 1:1 compound is at 199° with a melt containing 28.5% sodium nitrate; the eutectic point between sodium nitrate and the 1:1 compound is at 205° with a melt containing 43.4% sodium nitrate.

NEW BRUNSWICK, N. J. RECEIVED JANUARY 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

Dimethylgermanium Sulfide and Dimethylgermanium Oxide

BY EUGENE G. ROCHOW*

Organogermanium oxides of varying degree of complexity have been prepared,[1,2,3] some of them closely analogous to the organosilicon condensation products prepared by Kipping.[4] The ready availability of dimethylgermanium dichloride[5] suggests the preparation of dimethylgermanium oxide to determine whether it has polymeric forms and whether such forms resemble the corresponding methylpolysiloxanes or silicones.

It also is of interest to note that aqueous solutions of germanium dioxide and related inorganic compounds of germanium have been shown to stimulate the production of red blood cells in mammals.[6] New organogermanium oxides or related compounds may provide more suitable reagents for such studies.

Experimental

Preliminary.—Methyl silicones may be prepared by hydrolyzing the corresponding chlorosilanes, separating the water-insoluble methyl siloxane, and processing it to produce the desired polymer. It soon was found that the behavior of the germanium analogs was entirely different. Dimethylgermanium dichloride did not produce a water-repellent film on solids as does dimethyldichlorosilane[7]; instead it dissolved completely in 100 volumes of water. When this solution was evaporated to dryness, no residue was left. When the dimethylgermanium dichloride was hydrolyzed in dilute ammonium hydroxide and the resulting clear solution was evaporated, only ammonium chloride remained. This behavior suggests either volatile hydrolysis products or a readily reversible reaction

$$(CH_3)_2GeCl_2 + 2H_2O \rightleftarrows (CH_3)_2Ge(OH)_2 + 2HCl$$

4.44 g. of dimethylgermanium dichloride was refluxed with two equivalents (0.92 g.) of water for fifteen minutes and allowed to stand overnight. Samples of the aqueous layer then were withdrawn and titrated, and were found to be 3.19 *N* to hydrochloric acid, showing that the reaction equilibrium was far to the left.

Other techniques of direct hydrolysis, including repeated extraction of the dichloride with small portions of cold water, produced some resinous products in poor yield but were ineffective in producing a pure dimethylgermanium oxide. A pure preparation was achieved only by conversion of the sulfide.

Dimethylgermanium Sulfide.—When dimethylgermanium dichloride was dissolved in 6 *N* sulfuric acid and treated with hydrogen sulfide as in the determination of germanium,[8] there was precipitated a waxy white solid which was soluble in acetone (which GeS_2 is not) and insoluble in dilute ammonium hydroxide (which dissolves GeS_2). This precipitate was found to be dimethylgermanium sulfide, $(CH_3)_2GeS$.

100 g. of dimethylgermanium dichloride was stirred with 1000 g. of water[9] and treated with hydrogen sulfide over a period of several days. The precipitate was washed, dissolved in 100 ml. of warm alcohol, and reprecipitated by the addition of four volumes of cold water.[10] The mixture was chilled and saturated with hydrogen sulfide to prevent hydrolysis, and then filtered with suction. The crystals were washed on the filter with water containing hydrogen sulfide, and dried in a desiccator; yield, 73.4 g., or 94.5% of theoretical.

Anal. Calcd.: C, 17.83; H, 4.49; Ge, 53.9; S, 23.80. Found: C, 17.92, 17.77; H, 4.52, 4.46; Ge, 51.6, 52.0[11]; S, 23.42, 24.07, 23.80.[12]

The dimethylgermanium sulfide so prepared crystallizes in flat plates which melt at 55.5° and boil at 302°. These have a peculiar pepper-and-onions odor, and hydrolyze very slowly in moist air to liberate hydrogen sulfide. Hydrolysis also is slow in boiling water, but more rapid in dilute acids or dilute solutions of hydrogen peroxide.

Dimethylgermanium Oxide.—The hydrolysis of dimethylgermanium sulfide in a 10% aqueous solution of hydrogen peroxide yields a clear water solution of methylgermanium oxides or hydroxides, from which resinous and crystalline substances may be obtained upon evaporation. If the original dimethylgermanium dichloride contained some methylgermanium trichloride, or if the treatment with hydrogen peroxide is sufficiently vigorous to oxidize a minor fraction of the methyl groups, there is obtained a sirupy mass which becomes resinous when chilled. The resin is soluble in hot water, in benzene, and in alcohol. Upon long standing, white crystals (presumably of hydroxide) slowly grow in the mass but dissolve upon reheating. A resinous sample which had an average of but 1.2 methyl groups per germanium atom by analysis did not crystallize on standing and was found to be infusible though slightly soluble in water.

The effect of hydrogen peroxide in accelerating the hydrolysis of dimethylgermanium sulfide might be interpreted as the oxidation of a small amount of sulfide ion to sulfate, following by acid hydrolysis of the remainder of the organogermanium sulfide. If so, dilute sulfuric acid would be preferable to hydrogen peroxide as a hydrolytic

* Present address: Chemical Laboratories of Harvard University, Cambridge, Mass.

(1) Orndorff, Tabern and Dennis, THIS JOURNAL, **49**, 2512 (1927).

(2) Kraus and Brown, *ibid.*, **52**, 3690 (1930).

(3) Burschkies, *Ber.*, **65**, 956 (1932).

(4) See Morgan and Drew, *J. Chem. Soc.*, **127**, 1760 (1925).

(5) Rochow, THIS JOURNAL, **69**, 1729 (1947).

(6) Beard, Myers, Baker and Rafferty, *J. Biol. Chem.*, **94**, 71 (1931), and *J. Am. Med. Assn.*, **93**, 1210 (1929); Hueper, *Am. J. Med. Sci.*, **181**, 820 (1931); Parr, *Trans. Ill. Acad. Sci.*, **21**, 194 (1928) and U. S. Patent 1,909,070; Lenker, *Penn. Med. J.*, **26**, 86 (1922); Kast, Croll and Schmitz, *J. Lab. Clin. Med.*, **7**, 643 (1922); Harrold, Meek and McCord, *Ind. Med.*, **23**, 236 (1944).

(7) Patnode, U. S. Patent 2,306,222; Norton, *Gen. Elec. Rev.*, **47**, No. 8, p. 6 (1944).

(8) Johnson and Dennis, THIS JOURNAL, **47**, 790 (1925).

(9) Six normal sulfuric acid was used in the preliminary experiments because the initial observation came out of attempts to analyze dimethylgermanium dichloride. Later experiments showed that the same crystalline sulfide is precipitated from a water solution or suspension of the dichloride. The products from water and 6 *N* H_2SO_4 had the same melting point and the same mixed melting point. Lacking an investigation of the crystal structure, it is not known whether the structural units are monomeric $(CH_3)_2GeS$ or some association of several monomeric units.

(10) Well-formed crystals may be obtained merely by cooling the alcohol, but better separation from residual chlorine is obtained by precipitating tiny crystals by the water dilution method.

(11) Germanium was determined by wet oxidation with fuming nitric acid and ammonium persulfate (THIS JOURNAL, **69**, 1730, (1947)), but volatilization of GeO was encountered repeatedly at the beginning of ignition of the residues. Oxidation in a Parr bomb followed by precipitation of the germanium as GeS_2 is being studied.

(12) Sulfur was determined by Dr. L. P. Pepkowitz, using a new method which he has developed for the analysis of microgram samples.

medium for making a pure dimethylgermanium oxide because it has been shown that it does not affect the methyl groups. Accordingly, 7.63 g. of pure distilled $(CH_3)_2GeS$ was refluxed with 20 ml. of water and 0.5 ml. of concentrated sulfuric acid for seven hours, or until there no longer was a rapid evolution of hydrogen sulfide. A solution of barium hydroxide then was added dropwise until the solution was just alkaline to phenolphthalein, and the barium sulfate was filtered off.[13] The clear filtrated was evaporated under reduced pressure to a sirup. The remaining water was distilled off, along with some volatile dimethylgermanium oxide or hydroxide, in the range 100 to 105°, and then the boiling point rose rapidly to over 200° and a polymer of dimethylgermanium oxide distilled. The empirical composition was shown to correspond to $(CH_3)_2GeO$.

Anal. Calcd.: C, 20.24; H, 5.10; Ge, 61.2. Found: C, 20.34, 20.52; H, 5.25, 5.16; Ge, 60.96, 60.28.

The dimethylgermanium oxide so prepared melts at 133.4°[14] and boils at 211°. It does not dissolve readily in water, benzene or cyclohexane. It dissolves in alcohol, and upon addition of water is not precipitated but reverts to the water-soluble form encountered during the preparation. Cryoscopic determinations of the molecular weight of the solid in cyclohexane were inconclusive, probably because of the very limited solubility of the substance. Camphor was found to be a good solvent, however, and determinations of molecular weight (found, 491; calcd. for $(CH_3)_2GeO$, 118.7) indicate that the substance is a tetramer.[15] However, upon repeated melting of the camphor solutions in sealed tubes the depression of the freezing point was found to increase in a way that suggests an (as yet unknown) alteration of the polymeric state of the oxide.

(13) The weight of dried barium sulfate was slightly under the weight expected from the amount of sulfuric acid originally used, showing that there was no oxidation of sulfide to sulfate during the hydrolysis.

(14) Melted samples solidify to a glassy phase which then melts at about 125°.

Summary

1. The hydrolysis of dimethylgermanium dichloride is shown to be reversible to an extent which makes impractical the preparation of dimethylgermanium oxide by the techniques used for preparing silicones.

2. Dimethylgermanium sulfide (m. p. 55.5°, b. p. 302°) has been prepared.

3. Dimethylgermanium oxide has been obtained in a crystalline polymeric form (m. p. 133.4°, b. p. 211°) by hydrolysis of the sulfide.

(15) Probably cyclic, see related tetramer of $(C_6H_5)_2GeO$ in Morgan and Drew, ref. 4.

RESEARCH LABORATORY
GENERAL ELECTRIC CO.
SCHENECTADY, N. Y.

RECEIVED NOVEMBER 6, 1947

[CONTRIBUTION FROM THE CHEMICAL CORPS TECHNICAL COMMAND]

Alcoholysis of Ethyl Phosphate. The Preparation of Mixed Ethyl Butyl Phosphates

BY WALTER H. C. RUEGGEBERG AND JACOB CHERNACK

Examples of the alcoholysis of esters derived from inorganic acids are not nearly so plentiful in the chemical literature as are those of the organic acid esters. Recently, the alcoholysis of alkyl silicates was studied by Peppard, Brown and Johnson,[1] who found that in some cases the alcoholysis of silicates proceeded without the addition of catalysts to yield mixed silicic acid esters, while, in other instances, hydrogen chloride or silicon tetrachloride was needed to catalyze the reaction. A similar transalkylation reaction between butyl silicate and ethyl silicate under the catalytic influence of aluminum chloride or the alkoxides of aluminum, antimony or magnesium was also found by these same authors[2] to produce mixed alkyl silicates.

Morel and Friedel[3] have shown that under the influence of sodium ethylate, a mixture of ethanol and phenyl phosphate will yield mixed ethyl phenyl phosphates as well as phenetole. The latter property of alkylation is an interesting feature in this reaction and has been extended by Noller and Dutton.[4] Toy[5] has found that methyl alkyl ethers can be prepared by refluxing a mixture of trimethyl phosphate and alcohols whose boiling points are greater than 160°. The residue products in this reaction are described by Toy to be alkali soluble mixtures of alkyl acid phosphates.

The reaction between *n*-butanol and ethyl phosphate was studied in this Laboratory with the view of obtaining diethyl *n*-butyl and ethyl di-*n*-butyl phosphates. It was observed that an equimolar mixture of ethyl phosphate and *n*-butanol would not undergo appreciable reaction even at temperatures of about 160°. In the presence of small amounts of sodium butylate, however, alcoholysis proceeded rapidly at temperatures between 90 and 120°. In Table I, it can be seen that the relative amounts of diethyl *n*-butyl phosphate and ethyl di-*n*-butyl phosphate depend upon the relative amounts of sodium butylate present in the reaction mixture and also upon the mole ratio of ethyl phosphate to *n*-butanol. Some physical properties of the mixed esters are presented in Table II.

(1) Peppard, Brown and Johnson, THIS JOURNAL, **68**, 73 (1946).

(2) Peppard, Brown and Johnson, *ibid.*, **68**, 77 (1946).

(3) Morel and Friedel, *Compt. rend.*, **128**, 507 (1899).

(4) Noller and Dutton, THIS JOURNAL, **55**, 424 (1933).

(5) Toy, *ibid.*, **66**, 409 (1944).

TABLE I

ALCOHOLYSIS AND ETHER FORMATION WITH ETHYL PHOSPHATE

Reagents, moles			Products, moles						Residue,
n-BuOH	Na	Et_3PO_4	EtOH[a]	Ether[a,b]	*n*-BuOH	Et_3PO_4	$BuEt_2PO_4$	Bu_2EtPO_4	g.
1.0	0.03	0.5	0.18	0.02	0.81	0.32	0.12	..	12.3
1.0	.07	.5	.50	.06	0.51	.14	.19	0.06	24.1
1.0	.13	.5	.55	.08	0.37	.10	.16	.08	36.9
2.0	.13	.5	.76	.11	1.09	.04	.12	.15	..
3.0	.13	.5	.77	.09	2.16	.02	.13	.15	43.9
3.0	.22	.5	.90	.14	1.98	.01	.06	.12	..

[a] The total ethanol–ether cut from the distillation was subjected to a separate analysis for per cent. alcohol using acetic anhydride and pyridine followed by titration for acid in the usual manner. [b] This is chiefly ethyl *n*-butyl ether, containing less than 2% of a material boiling between 33 and 35° which possesses the characteristics of ethyl ether.

TABLE II

SOME PHYSICAL CONSTANTS OF MIXED ETHYL BUTYL PHOSPHATES

	Et_2BuPO_4[a]			$EtBu_2PO_4$[b]		
T, °C.	d*T*/4, g./ml.	n_D	Viscosity, centistokes	d*T*/4, g./ml.	n_D	Viscosity, centistokes
9.8	....	....	2.73	....	....	3.76
10.0	1.0380	1.4170	..	1.0112	1.4215	..
20.0	....	1.4131	..	....	1.4182	..
24.7	....	....	1.97	....	....	..
25.0	1.0243	....	..	0.9984	....	2.54
30.0	....	1.4091	..	....	1.4148	..
35.0	1.0151	....	1.61	0.9897	....	2.05

[a] Surface tension at 27.0° = 28.8 dynes/cm.; parachor, calcd. 480.7; found 476.3. [b] Surface tension at 29.2° = 28.0 dynes/cm.; parachor, calcd. 560.7; found 553.4.

In addition to the products of alcoholysis, there were obtained other products which proved to be ethers of which ethyl *n*-butyl ether predominated.

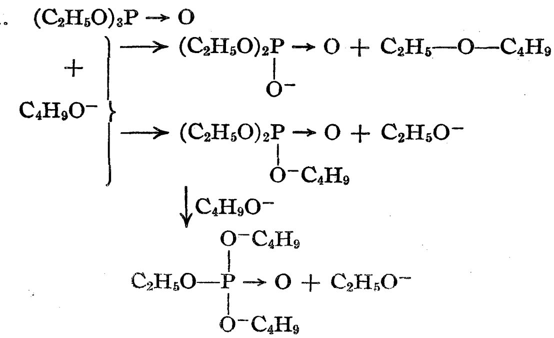
The mole ratio of ether to mixed butyl esters formed (calculated as difference between moles butanol in products and residue and moles butanol originally used) is about 1 to 7. This indicates that sodium butylate acts catalytically in the alcoholysis but is destroyed through ether formation.

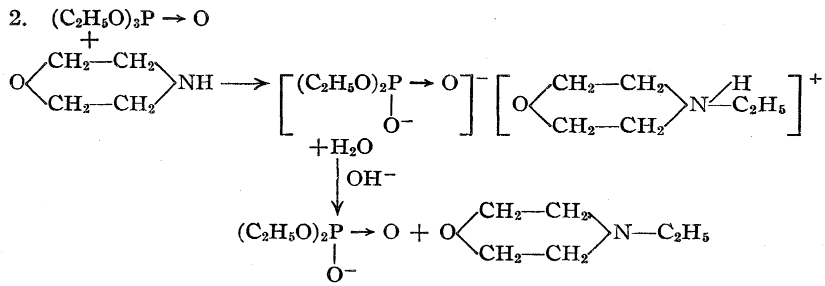
The alkylation of butylate ion by ethyl phosphate is in many respects similar to the alkylation of aromatic amines studied by Billman, Radike and Mundy.[6] In order to establish the similarity between the alkylation of amines and of butylate ion, the reaction of an equimolar mixture of morpholine and ethyl phosphate was investigated. It was found that upon heating an oily, non-volatile substance, presumably an ammonium salt, was formed which upon hydrolysis with aqueous caustic yielded pure N-ethylmorpholine. Although amidation of the phosphoric acid ester, similar to alcoholysis, was not detected, this reaction may be of value in the de-alkylation of phosphoric acid esters.[7]

(6) Billman, Radike and Mundy, THIS JOURNAL, **64**, 2977 (1942).

(7) Similar work is being considered at Cambridge University, England, and was learned by one of us (WHCR) through a personal communication with Prof. A. R. Todd of Cambridge.

These reactions may be summarized by the equations

1.


2.


It is obvious from reaction 1, above, that small amounts of diethyl as well as dibutyl ether are to be expected through further reaction of the ethylate and butylate ions on the phosphates, and indeed these substances are found.

Experimental

Alcoholysis of Ethyl Phosphate.—*n*-Butanol, clean metallic sodium and ethyl phosphate were placed in the kettle of an all-glass, fifteen-plate column still in the order indicated. The amounts of reagents used in each particular run are given in Table I. Ethyl phosphate was not added to the other components until all of the sodium had dissolved in the butanol. The complete reaction mixture was heated by means of a Glas-Col heating mantle. Boiling of the reagents occurred when the kettle temperature reached about 115°. The still head was set to constant reflux until boiling and the reflux rate became steady. Then, a low boiling fraction (about 0.5 g., n^{20}_D 1.3655, probably diethyl ether) was removed. The fraction boiling from 36 to 93° was collected and found to be a mixture of ethanol and chiefly ethyl *n*-butyl ether, containing from 75–80% ethanol as found by acetylation with acetic anhydride. The refractive index of these cuts varied between n^{20}_D 1.365 to 1.368 and the densities, d^{20}_4, from 0.780 to 0.788 g./ml. During the removal of this fraction, the kettle temperature rose slowly to 140°

and on occasions the temperature was allowed to climb to 160° in order to remove all of this fraction at atmospheric pressure.

The pressure was subsequently reduced to 50 to 60 mm. and *n*-butanol ($n^{20}D$ 1.390 to 1.398) was removed. After removing unreacted ethyl phosphate at pressures varying between 3 and 10 mm. of mercury (b. p. 66–69° at 3 to 4 mm.; $n^{20}D$ 1.404–1.4055), diethyl *n*-butyl phosphate (b. p. 82–87° at 3 to 4 mm.) and ethyl di-*n*-butyl phosphate (b. p. 95–96° at 3 to 4 mm.) were fractionated out of the reaction mixture.

Anal. Calcd. for $C_8H_{19}PO_4$: P, 14.7; M_R 51.1.[8] Found: P, 14.9; M_R 51.5. Calcd. for $C_{10}H_{23}PO_4$; P, 13.0; M_R 60.5. Found: P, 13.2; M_R 59.8.[8]

The material balances in all runs including residues amounted to 97 to 99%.

Isolation of Ethyl *n*-Butyl Ether.—Fifty grams of the ethanol–ether fraction (b. p. 36–93°) was added to 180 ml. of water. The upper layer, amounting to 8.9 g., was separated, dried over activated silica gel and distilled. The main fraction boiled at 90–93° and was found to have the following constants: d^{20}_4, 0.752; $n^{20}D$ 1.3818; M_R calcd., 31.6; found, 31.6.

Anal. Calcd. for $C_6H_{14}O$: C, 70.5; H, 13.8. Found: C, 70.6; H, 13.9.

Treatment of the ether with hydriodic acid yielded ethyl and *n*-butyl iodides.

Alkylation of Morpholine.—An equimolar mixture of morpholine and ethyl phosphate was charged to a round-bottomed flask equipped with a water-cooled reflux condenser. The mixture was heated by means of a Glas-Col mantle and brought to 150° in fifteen to twenty minutes. At this temperature, vigorous refluxing took place due to heat of reaction, and the mixture changed from a water white to a reddish brown color. If too well insulated, the reaction temperature may rise to 190°. It was found, however, that by maintaining the reaction temperature between 157 and 159° good results can be obtained. The product was poured into 500 ml. of water and heated with 10% excess (44 g.) of sodium hydroxide. The basic aqueous solution was charged to a still and the amine distilled with water as an azeotrope over the range 95–99.8°. The azeotropic distillate was saturated with potassium carbonate whereupon the amine was salted out. After separating from the aqueous layer, the amine was dried over sodium sulfate, filtered and distilled; b. p. 137–138°, d^{20}_4 0.919, $n^{20}D$ 1.4418; yield 70%.

Anal. Calcd. for $C_6H_{13}NO$: C, 62.2; H, 11.4; N, 12.2. Found: C, 62.3; H, 11.5; N, 11.9.

All physical constants given for known compounds agree satisfactorily with those previously published.

Acknowledgment.—The authors are indebted to Messrs. N. Beitsch, S. Sass and B. Zeffert of this Laboratory for having performed the necessary analytical and physical determinations.

Summary

Sodium butylate behaves catalytically on a mixture of *n*-butanol and ethyl phosphate yielding diethyl *n*-butyl phosphate and ethyl di-*n*-butyl phosphate. This alcoholysis is accompanied by a side reaction which causes the alkylation of the butylate ion to ethyl *n*-butyl ether.

This behavior indicates that ethyl phosphate under the conditions employed behaves both as a true ester undergoing alcoholysis and as an alkylating agent. The degree to which each of the products of reaction is produced depends upon the concentration of sodium butylate as well as upon the mole ratio of *n*-butanol to ethyl phosphate.

The alkylation of morpholine to N-ethylmorpholine by means of ethyl phosphate is also described.

ARMY CHEMICAL CENTER, MD.

RECEIVED DECEMBER 15, 1947

(8) The molecular refractivities were calculated from that of ethyl phosphate by adding the proper value for the required number of methylene groups to that molecule.

[CONTRIBUTION FROM THE ESSO LABORATORIES, CHEMICAL DIVISION, STANDARD OIL DEVELOPMENT COMPANY]

Study of the Reaction of Buna Rubbers with Aliphatic Mercaptans[1]

BY G. E. SERNIUK, F. W. BANES AND M. W. SWANEY

Introduction

The relative proportion of 1,4- *versus* 1,2-addition of diene units and the elucidation of the partial structure of polymers and copolymers of butadiene have been investigated by various chemical and physical methods such as ozonolysis,[2–5] perbenzoic acid oxidation,[6,7] potassium permanganate oxidation,[6] and infrared absorption.[8] The work presented in this paper was undertaken in an attempt to obtain further information regarding the structure of butadiene polymers and copolymers by studying the reaction of these polymers with aliphatic mercaptans.

The reaction of mercaptans with unsaturated compounds including natural and synthetic rubbers is not new. Posner,[9] Gunnar, Axberg and Holmberg,[10] Hoag and Eichwald,[11] Kharasch, Read and Mayo,[12] Jones and Reid,[13] Cunneen,[14] and others have treated mercaptans with various types of unsaturated compounds. Holmberg[15] treated natural pale crepe rubber with thiogly-

(1) This paper was presented before the Division of Rubber Chemistry at the American Chemical Society Meeting in Chicago, 1946.

(2) Hill, Lewis and Simonsen, *Trans. Faraday Soc.*, **35**, 1067 (1939).

(3) Yakubchik, Vasiliev and Zhabina, *Rubber Chem. and Tech.*, **18**, 780 (1945).

(4) Alekseeva and Belitzkaya, *ibid.*, **15**, 693 (1942).

(5) Rabjohn, Bryan, Inskeep, Johnson and Lawson, THIS JOURNAL, **69**, 314 (1947).

(6) Weidlein, Jr., *Chem. Eng. News*, **24**, 772 (1946).

(7) Kolthoff, Lee and Mairs, *J. Polymer Science*, **2**, 220 (1947).

(8) Rasmussen and Brattain, private communication.

(9) Posner, *Ber.*, **38**, 646 (1905).

(10) Gunnar, Axberg and Holmberg, *ibid.*, **66B**, 1193 (1933).

(11) Hoag and Eichwald, *Rec. trav. chim.*, **58**, 481 (1939).

(12) Kharasch, Read and Mayo, *Chem. and Ind.*, **57**, 752 (1938).

(13) Jones and Reid, THIS JOURNAL, **60**, 2452 (1938).

(14) Cunneen, *J. Chem. Soc.*, 36, 134 (1947).

(15) Holmberg, *Ber.*, **65**, 1349 (1932).

colic acid, and more recently, Kolthoff and co-workers,[16] and Marvel and co-workers[17] studied the reaction of aliphatic mercaptans with butadiene polymers and copolymers in latex form.

From a preliminary study of the reaction of mercaptans with model compounds it was found that ethylenic bonds in conjugated, vinyl, terminal butenyl, and in closed ring structures added mercaptans readily, while internal, non-conjugated ethylenic bonds reacted at a relatively slower rate. Thioglycolic acid added to simple olefins more vigorously than *n*-aliphatic mercaptans. Since this paper was originally submitted, Cunneen[14] reported the reactions of unsaturated hydrocarbons and various thiols. An apparent order of reactivity was found to be cyclohexene > dihydromyrcene > squalene > rubber; and for the thiols, thioglycolic acid > thiophenol ~ isopentanethiol. It is evident that the ease with which an ethylenic bond can add thiols is dependent, in part, upon the structural unit retaining the double bond.

It is quite probable that diene polymers contain several types of ethylenic bonds, but from ozonolysis data[2-5] it must be concluded that a major portion of these bonds results from either 1,2- or 1,4-addition of butadiene units to the polymer chains. These two types of ethylenic bonds should exhibit different rates of mercaptan addition and the determination of the proportion of mercaptan-reactive units in the polymer chains should represent a measure of the per cent. of ethylenic bonds present as side vinyl groups. Ethylenic bonds in structures formed by intramolecular cyclization reactions should likewise be mercaptan reactive. Obviously mercaptan addition reactions will not show complete selectivity for side vinyl groups but it is quite probable that mercaptan-reactive structures other than the side vinyl groups will represent only a very minor portion of the total unsaturation of the butadiene polymers.

This paper records the reaction of thioglycolic acid and *n*-aliphatic mercaptans of C_2 to C_{16} chain length with diene polymers, and the reaction of thioglycolic acid and a *n*-C_{12} mercaptan with model compounds. Polymer-mercaptan reactions were effected in solution, mass and in latex form at various temperatures, in the presence of air, or in the presence of additives which were evaluated as catalysts. The experimental data indicate a pronounced difference in the rate and extent of mercaptan addition by the various diene polymers, and the difference in rate and extent of addition has been utilized in estimating the relative proportion of external and internal ethylenic bonds in the polymer chains.

Experimental

Materials

Polymers.—The polymers used in studying the polymer–mercaptan reactions were natural rubber, polyisoprene, polybutadiene, and copolymers of butadiene and acrylonitrile, butadiene and styrene, and butadiene and alpha methyl para-methylstyrene. Both emulsion and sodium catalyzed polymers of butadiene were used, but in all other cases, emulsion polymers and copolymers were employed. The emulsion polymers were prepared by the standard technique. The polymerization reactions were discontinued when 75% of the monomers were converted to polymer. The latices were freed of unconverted monomers by steam stripping under a pressure of 50–60 mm. Polymers required for solution and mass reactions were obtained by coagulating the stripped latices with 99% isopropyl alcohol, followed by water washing and drying at 175° F. No attempt was made to fractionate the resulting polymers, or to free them of any developed peroxide materials.

Mercaptans.—Mercaptans of C_2 to C_4 chain length were obtained from Eastman Kodak and were used after distillation. Thioglycolic acid was first dried by removing the water as a benzene azeotrope before distilling under vacuum. Normal mercaptans of C_8 to C_{16} chain length were of research grade from the Connecticut Hard Rubber Company. These mercaptans were used directly without further purification. Sharples 3B mercaptan was used after distillation.

Procedure.—A modification of the procedure used by Holmberg[15] was used in effecting the reaction of various polymers with thioglycolic acid. A 5% solution of polymer in benzene was placed in a flask and agitated while a calculated amount of dry thioglycolic acid was added slowly to the solution at room temperature. The reactants were allowed free access to air throughout the course of the reaction. With butadiene polymers and copolymers the reaction was exothermic, and after a short time the solution became cloudy and an insoluble layer separated. The separated product was solubilized by the addition of *n*-hexanol and the reaction continued. Samples were withdrawn periodically for analysis. The polymer–thioglycolic acid reaction products were purified by water washing the benzene–*n*-hexanol solutions until no further test for free thioglycolic acid could be obtained by titration with 0.1 *N* iodine solution. The solvents were then removed by heating the solutions on a steam-bath under high vacuum. The reaction products were further dried in a vacuum oven at 70°. Sulfur analyses of the products were obtained by combustion in a Parr bomb.

Polymers in latex form were treated with mercaptans in 2 oz. and one quart glass reactors which were charged to varying levels and then agitated in a thermostated bath at 50° for varying periods of time. The amount of mercaptan employed corresponded to a 100% excess over the amount theoretically required for complete double bond saturation. Several conditions were employed wherein the free space of the reactors was flushed either with nitrogen, air, or pure oxygen; and the amount of persulfate in the systems was varied. The polymer–mercaptan reaction products were isolated from the emulsions by coagulating in an excess of 99% isopropyl alcohol. The products were thoroughly washed in fresh portions of alcohol and then dried in a vacuum oven at 70°.

Mass reactions of dry polymers and mercaptans were carried out under essentially the same conditions employed by Jones and Reid[13] in their study of the reaction of mercaptans with unsaturated compounds. The dry polymer was dissolved in the desired mercaptan, two mols of mercaptan being used per mol of diene in the polymer. The solutions were agitated in a glass reactor, sealed from the atmosphere without displacing the air in the reactor, at 180–200° for varying periods of time. Samples of the reaction mixture were removed at intervals for purification and analysis. The polymer–mercaptan reaction products were isolated by coagulating the reaction mixture with a large volume of 99% isopropyl alcohol followed by repeated dissolution of the mass in petroleum ether and coagulation until the mixed solvents showed no trace of free mercaptan as determined by titration with 0.1 *N* iodine solution. The purified reaction mass was stripped of solvents and moisture under vacuum at 80°.

(16) Kolthoff and co-workers, private communication.
(17) Marvel and co-workers, private communication.

Calculations.—The calculation of the per cent. of double bonds saturated by a particular mercaptan is based on the sulfur content of the reaction product, molecular weight of the mercaptan, and the unsaturation value of the polymer expressed as Wijs number. It is assumed that the total sulfur of the reaction product minus the sulfur value of the original polymer represents the total sulfur introduced into the polymer by the additive fixation of the mercaptan. The percentage of double bonds saturated was calculated from the expression

$$\% \text{ D.B. saturated} = \frac{2.54 \times 10^6 (\% \text{ Sa} - \% \text{ Sp})}{[3200 - (\% \text{ Sa} - \% \text{ Sp})(\text{Mol. wt. RSH})]I_{2p}}$$

where

Sa = % Sulfur of the reaction product
Sp = % Sulfur of the original polymer
I_{2p} = Wijs number of original polymer

Results and Discussion

Reactions of Mercaptans and Unsaturated Compounds.—In determining the relative reactivities of various types of ethylenic bonds with aliphatic mercaptans, model compounds were employed which possessed either terminal or internal unsaturation. The results of these experiments are given below and indicate that compounds possessing terminal methylene groups or double bonds in closed ring structures add mercaptans vigorously while internally located double bonds react very slowly with mercaptans.

Oleic acid (0.1 mole), free of linoleic and linolenic acids, and thioglycolic acid (0.1 mole) when combined in benzene (50 cc.) at room temperature did not produce an exothermic reaction. The product isolated from the reaction mixture after standing at room temperature for ten days with access to air, contained 6.60% S (calcd. for $C_{20}H_{38}O_4S$: S, 8.53%). By treating linoleic acid (0.1 mole) and thioglycolic (0.2 mole) in the manner described above, a yield of 40.3 g. of adduct and unreacted linoleic acid was obtained after 29 days' reaction time at room temperature (calcd. amount of adduct 46.44 g.). On the other hand, when one-tenth molar proportions of 10-undecylenic acid and thioglycolic acid were combined as above, a highly exothermic reaction resulted. The solid, crude product, isolated from the water-washed benzene solution, contained 12.36% S (calcd. for $C_{13}H_{24}O_4S$: S, 11.58%).

Cyclohexene (0.1 mole), and thioglycolic acid (0.1 mole) also reacted exothermally in benzene in the presence of air. The product, after being water washed and dried under vacuum and undistilled, showed a sulfur content of 20% (calcd. for $C_8H_{14}O_2S$: S, 18.4%). This reaction was described by Cunneen.[14]

Molar proportions of 10-undecylenic acid and *n*-dodecyl mercaptan reacted exothermally in benzene solution in the presence of air. This reaction was less vigorous than when thioglycolic acid was used. The solid reaction product after a single crystallization from benzene showed a sulfur content of 8.20% (calcd. for $C_{23}H_{46}O_2S$: S, 8.30%).

Reaction of Polymers.—An emulsion copolymer of butadiene and styrene, prepared from an initial feed ratio of 78 parts of butadiene and 22 parts of styrene by weight, reacted exothermally with thioglycolic acid after a few minutes of contact. Reaction products isolated after 3, 25, 45, 70 and 144 hours, showed 47, 42, 38, 43 and 42% double bond saturation values, respectively. These data indicate that the reaction is exceedingly rapid and apparently reaches a saturation value corresponding to about 38–47% double bond saturation. Under the same conditions a copolymer prepared from an initial feed of 74 parts of butadiene and 26 parts of acrylonitrile, and a polybutadiene prepared by sodium catalysis, reacted exothermally with thioglycolic acid and after twenty-five hours the products were isolated and showed 42 and 39% double bond saturation values, respectively. Natural smoked sheet, purified by acetone extraction, solution, and precipitation showed no exothermic reaction with thioglycolic acid in benzene solution under the same conditions. After one month the isolated product showed a sulfur content of 7.04% which corresponds to 18.8% double bond saturation. Cunneen[14] found but a slight reaction between natural rubber and thioglycolic acid under peroxidic conditions and high vacuum. The above experiments emphasize a pronounced difference in the reaction rate between mercaptans and butadiene polymers and natural rubber. The difference in reaction rates is undoubtedly due to the presence of different double bond structures in the respective polymers.

The double bond saturation values obtained for butadiene polymers and natural rubber, treated in latex form with mercaptans, also indicate a pronounced difference in the reaction rate and the extent of reaction. Emulsion polymer latices, containing equivalent amounts of residual potassium persulfate catalyst, when sealed in reactor vessels with an excess of ethyl mercaptan in such a manner that the vessel was flushed with nitrogen and mercaptan vapor, reacted with a definite and reproducible amount of mercaptan. This addition proceeded rapidly during the first three to six hours of reaction time at 50°, and reached a limiting value which was unique for the type of polymer being treated. These observations are illustrated by the data of Table I. It will be noted that polymers and copolymers of butadiene showed a relatively greater proportion of double bonds reacted than emulsion polyisoprene or natural rubber in air-free systems containing equivalent amounts of persulfate catalyst.

The effect of oxygen and peroxides on the rate and extent of ethyl mercaptan addition to Buna N polymers was followed by effecting the reactions in vessels charged to varying levels. The charged reactors were flushed with air prior to sealing. It will be noted from the results presented in Table II that when the reactors were completely filled, the amount of ethyl mercaptan which added to the polymer double bonds was the same as when oxy-

TABLE I

REACTION OF ETHYL MERCAPTAN WITH EMULSION POLYMERS IN AIR-FREE SYSTEMS

Latex	Reaction time, hrs. at 50°	% double bond saturated
Buna-S	23	25
Sample A(1)	46	27
Sample B(2)	45	23
Buna-N (3)	2	9
	6	12
	48	12
Polybutadiene	3	10
	19	13
	65	14
Polyisoprene	3	3
	47	4
Natural rubber	20	2
	64	2

Weight per cent. monomers in polymerization charge:
(1) Butadiene, 78; styrene, 22
(2) Butadiene, 75; styrene, 25
(3) Butadiene, 72; acrylonitrile, 28.

gen had been flushed from the systems. However, when the amount of free air space of the reactors was increased, the amount of mercaptan reacting with the polymer also increased, apparently approaching a limiting value of 35–45% double bond saturation. This saturation value did not change appreciably as a result of a prolonged reaction time, increased or decreased potassium persulfate concentrations used in the original polymerization charge, or by substituting *n*-propyl or *n*-butyl for ethyl mercaptan. Further, it was observed that flushing the reactors with oxygen instead of air, or the addition to the reaction charge of 0.05 part of benzoyl peroxide, based on the polymer, did not affect the extent of mercaptan addition to the polymer. These data indicate that the reaction of mercaptans with Buna rubbers in latex form is catalyzed by oxygen, and the extent of double bond saturation is of the same order of magnitude as was found when this polymer reacted with thioglycolic acid.

TABLE II

REACTION OF BUNA LATICES WITH C_2–C_4 MERCAPTANS IN THE PRESENCE OF AIR

Latex	Charging volume[a]	RSH	Reaction time, hrs. at 50°	% double bonds saturated
Buna-N[b]	20	Ethyl	20	39
Sample A[c]	28	Ethyl	3	27
	28	Ethyl	17	40
	28	Ethyl	43	40
	35	Ethyl	20	36
	63	Ethyl	20	31
	87	Ethyl	20	17
	100	Ethyl	20	12
Sample B[d]	28	Ethyl	20	40
	100	Ethyl	20	13
Sample C[e]	28	Ethyl	20	40
	100	Ethyl	20	12
Buna-S[f]	30	Ethyl	48	45
	30	*n*-Propyl	48	35
	30	*n*-Butyl	48	41

[a] Per cent. of volume of 2-oz. reactor occupied by latex and mercaptan. [b] Monomer feed ratio, wt. %: butadiene, 74; acrylonitrile, 26. [c] Contained 0.30 parts $K_2S_2O_8$ on monomers in charge. [d] Contained 0.15 parts $K_2S_2O_8$ on monomers in charge. [e] Contained 0.60 parts $K_2S_2O_8$ on monomers in charge. [f] Monomer feed ratio, weight %: butadiene, 75; styrene, 25.

The data presented in Table III relate to the C_8 to C_{16} chain length mercaptan saturation values for polybutadiene, butadiene–styrene, and butadiene–α - methyl–p - methylstyrene copolymers. The reactions were effected in mass at high temperatures. The data do not include the reaction rates, but only summarize the values obtained during reaction times in which reaction apparently ceased. Although it was observed that the rate of mercaptan addition varied, the final polymer double bond saturation values were of about the same order of magnitude. Sharples 3B mercaptan gave rise to gel polymers of low sulfur content under the same reaction conditions.

TABLE III

MASS REACTIONS

RSH	% Double bonds saturated for polymer A	B	C
n-C_8	41	..	52
n-C_{10}	44	..	56
n-C_{12}	47	42	42
n-C_{14}	35	42	36
n-C_{16}	40	41	48
3B	Gelled	Gelled	..

A, Polybutadiene. B, Butadiene, 50; styrene, 50; wt. % composition. C, Butadiene, 43.5; α-methyl-p-methylstyrene, 63.5; wt. % composition. 3B, Sharples 3B (tertiary) mercaptan.

The selectivity of the mass reaction at elevated temperatures appears to be overcome when a continuous stream of air is passed through the reaction mixture. Under such conditions 75% of the double bonds in a butadiene–styrene copolymer were saturated by a normal mercaptan of C_{14} chain length. The presence of volatile reaction products possessing an odor suggestive of aldehydes would indicate that under such drastic conditions the polymer was degraded.

In further experiments polybutadiene reacted in mass with Lorol mercaptan in the presence of possible activating agents at various temperatures in order to determine whether the time of the reaction could be decreased, and whether activating agents have any effect upon the selectivity of the reaction. Piperidine, zinc dibutyldithiocarbamate, anthraquinone, benzoyl disulfide, sulfur, and benzoyl peroxide were evaluated in concentrations of 2 to 10%, based on the polymer, at temperatures of 75 to 180° for varying periods of time. Piperidine and anthraquinone exhibited an activating effect, but the extent of polymer double bond saturation was unaltered.

Based on the partially known structure of buta-

diene polymers and copolymers and upon the vast difference in the rate at which vinyl and internal ethylenic bonds add mercaptans, it would appear that the 38 to 47% of ethylenic bonds which added mercaptans readily are probably those derived from 1,2-addition of butadiene units to the polymer chains, or those arising from 1,2-addition and intramolecular cyclization reactions.

The saturation values obtained by the reactions between various types of mercaptans and butadiene polymers are in fair agreement in spite of a wide range of reaction conditions.

If it is assumed that the polymer double bonds which added mercaptans readily are those present in side vinyl groups, then the mercaptan saturation values found are in fair agreement with the value of 48% for a butadiene–styrene copolymer as determined by potassium permanganate oxidation,[6] and 34.5 and 42.8% as determined by ozonolysis[3] for a butadiene–styrene and a sodium catalyzed polybutadiene, respectively. The mercaptan saturation values are not, however, in full agreement with those found by perbenzoic acid oxidation whereby emulsion butadiene–styrene copolymers showed 1,2-values of 27[6] and 20–22[7] per cent. while sodium catalyzed polybutadiene showed 58[7] per cent. side vinyl groups.

Summary

Thioglycolic acid added exothermally to butadiene polymers and copolymers in benzene solution under mild conditions to give apparent double bond saturation values of 38 to 47%. When the same polymers reacted with aliphatic mercaptans of C_2 to C_{16} chain length, in mass or latex reactions, saturation values were obtained which were in accord with those found by thioglycolic acid addition.

It is suggested that the double bonds in butadiene polymers and copolymers which were readily saturated by the above mercaptans are predominately those present in the polymer chains as vinyl side groups.

ELIZABETH, NEW JERSEY RECEIVED[18] DECEMBER 16, 1947

(18) Original manuscript received September 23, 1946.

[CONTRIBUTION FROM THE CHARLES F. KETTERING FOUNDATION FOR THE STUDY OF CHLOROPHYLL AND PHOTOSYNTHESIS, ANTIOCH COLLEGE, AND FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Porphyrin Studies. V.[1] The Metal Complex Salts of α,β,γ,δ-Tetraphenylporphine

BY PAUL ROTHEMUND AND AMEL R. MENOTTI[2,3]

In the preceding paper of this series[1] we reported the synthesis of α,β,γ,δ-tetraphenylporphine (hereafter to be abbreviated T.P.P.) on a preparative scale. Thus sufficient quantities of this porphyrin became available for the preparation and study of a large number of its metal complex salts, fifteen of which have been obtained in the present investigation in crystalline form and five in solution only.

This is probably the largest number of metal complex salts ever prepared from any one porphyrin, and the work was undertaken with the aim of furnishing reliable material for physico-chemical studies on the structure of porphyrin metal complexes, especially in connection with the study of chlorophyll. Spectrophotometric measurements on the above-mentioned series of compounds are in progress at the Charles F. Kettering Foundation in order to determine possible correlations between absorption and fluorescence spectra; some of the findings have already been published.[4]

The metal complex salts described are the derivatives of T.P.P. which shows the "etio type"[5] spectrum and has its first absorption band in ether solution at 648 mμ. Derivatives of isomers and of other polynuclear pyrrole pigments, by-products in the synthesis of T.P.P., will be described in a separate publication.

In the preparation of these metal complexes three general methods were employed which are described in detail in the experimental part.

General Properties of the Metal Complex Salts.—All of the salts isolated were well-crystallized compounds of high surface luster. They showed selective absorption in the visible region of the spectrum and had melting points ranging from 400 to 520°. On heating from 400 to 450° all but the manganese chloride and the gold salts sublimed. During this sublimation partial decomposition of the complex occurred.

The complexes varied markedly in stability. Thus, the potassium and one thallium complex decomposed when dissolved in neutral solvents such as benzene and ether; the magnesium, mercury, and lead complexes split when shaken with 50% acetic acid. The zinc and silver complexes were stable to 50% acetic acid but decomposed slowly in hydrochloric acid solutions. In every case of these decomposition conditions the presence of free porphyrin in the solution was ascertained. The iron chloride, manganese chloride, cobalt, nickel, copper, stannous chloride, and gold complexes were heated in the steam-bath with

(1) Paper IV, THIS JOURNAL, **63**, 267 (1941).

(2) From the dissertation submitted by Amel R. Menotti to the Faculty of the Graduate School of the Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1940.

(3) Present address: Bristol Laboratories, Inc., Syracuse 1, New York.

(4) Knorr and Albers, *J. Chem. Phys.*, **9**, 197 (1941).

(5) Stern and Wenderlein, *Z. physik. Chem.*, **A170**, 348 (1934).

TABLE I

SOLUBILITY OF α,β,γ,δ-TETRAPHENYLPORPHINE METAL COMPLEX SALTS

VS = very soluble; S = soluble; SS = slightly soluble; VSS = very slightly soluble; I = insoluble; D = decomposes

	Mg	Zn	Cd	Hg	Cu	Ag	Sn	Pb	MnCl	FeCl	Co	Ni	Tl
Acetone	S	SS	SS	VSS	VSS	VSS	I	I	S	SS	I	I	I
Benzene	S	S	VS	SS	SS	S	SS	SS	S	S	S	SS	VSS
Chloroform	VS	VS	VS	VS	S	S	VS	S	VS	VS	S	S	VSS
Ether	S	S	S	VSS	SS	SS	I	I	S	VSS	SS	VSS	I
Ethyl acetate	S	SS	SS	I	SS	SS	I	VSS	S	SS	SS	I	I
Glacial acetic acid	D	VSS	D	D	VSS	I	I	D	S	VSS	SS	I	I
Methanol	I	VSS	VSS	I	I	I	I	I	VS	SS	I	I	I
Petroleum ether	I	I	I	I	I	I	I	I	SS	I	I	I	I
Pyridine	VS	VS	VS	VS	S	S	S	S	VS	VS	S	SS	VSS

concentrated hydrochloric acid for hours without any sign of decomposition.

The complexes of lithium, sodium, potassium, rubidium and cesium decomposed rapidly when their solutions were exposed to strong light; the magnesium and thallium (stabile compound) complexes showed spectrum shifts under these conditions. Solutions of the magnesium salt first showed a decrease in the intensity of the absorption band in the red and then decomposed to a solution without porphyrin spectrum on further exposure. The solubility data of the complex salts are given in Table I.

Upon heating of magnesium phthalocyanin with commercial tetralin Helberger[6] observed a new case of chemiluminescence, and demonstrated that a number of metal complex salts of different types of porphyrin pigments exhibit this luminescence reaction. Later Helberger and Hevér[7] studied the mechanism of the reaction in detail and ascertained that the presence of tetralin peroxide in commercial tetralin was responsible for the positive result; with other solvents these authors arrived at similar findings and rendered it highly probable that in every case impurities of peroxide types are present in the solvent. It is to be hoped that they will succeed in elucidating the conditions for this reaction, which may be of great interest in the field of photosynthesis research. From this point of view it seems desirable to test all new porphyrin metal complex salts under the conditions of Helberger's chemiluminescence reaction and give the results as additional characteristics of the compounds discussed. Of the complex salts described above, the magnesium, zinc, and cadmium salts were tested thus far. Each of them exhibited bright red chemiluminescence when heated above 125° in tetralin, xylene, *p*-cymene, or bromocyclohexane. When freshly distilled tetralin was employed, only a faint glow of short duration was obtained. On adding to the hot solution a few drops of tetralin which had been standing for some time, however, the bright red glow reappeared.

Experimental

General Remarks.—Three methods of preparation of the metal complex salts were used; they will be referred to in the following text by number, and only quantities of reagents and variants from the general procedure will be indicated specially.

Method 1 (Acid Medium).—The porphyrin solution in acetic (or formic) acid was heated under reflux with the acetate of the metal. In the preparation of the silver complex the di-silver salt was formed under these conditions; the mono-silver complex was obtained by adding a chloroform solution of the porphyrin to the solution of silver acetate in glacial acetic acid and heating under reflux. This variant was also useful in those cases where the slight solubility of the porphyrin in glacial acetic acid alone would have required large quantities of solvent. The reaction mixture was examined spectroscopically from time to time; after completion of the reaction the solution was concentrated to a small volume and the crystalline product removed by filtration after cooling.

Method 2 (Weakly Alkaline Medium).—The metal salt was added to the hot solution of the porphyrin in pyridine; the reaction mixture was heated until conversion was complete and concentrated under reduced pressure on a steam-bath to obtain the crystalline product. Thallium yielded two complexes, one relatively labile one directly, and a stabile one when hydrogen peroxide had been added to the reaction mixture.

Method 3 (Strongly Alkaline Medium).—To a porphyrin solution in pyridine the required metal salt and 40% methanolic potassium hydroxide were added.

The acetates of the metals gave the best results in forming the complex salts. Gold chloride ($AuCl_3$) and tin chloride ($SnCl_2$) were used for the preparation of the gold and tin complex salts, respectively. It was best to obtain complete conversion of the free porphyrin into the complex metal salt before attempting to isolate the product. The separation of any free porphyrin remaining as an impurity was usually difficult. This point of complete conversion could be ascertained by diluting a few drops of the reaction mixture with ether (acetic acid present was removed with water) and examining the ether solution spectroscopically for the bands of free T.P.P. In case of their presence the solution had to be refluxed longer, occasionally with the addition of more inorganic salt. In Method 1 above it was sometimes necessary to distil off the chloroform and to reflux the remaining acetic acid solution to obtain complete conversion. In the preparation of the cadmium, lead and thallium complexes a small amount of free T.P.P. always remained in the pyridine mother liquid; however, since these complexes were insoluble in pyridine and crystallized out while the free porphyrin was quite soluble, a good separation was obtained.

Copper Complex Salt. Preparation, (a) Method 1.—T.P.P.,[8] 50 ml. of chloroform, 200 mg. of copper acetate in 50 ml. of glacial acetic acid; yield, quantitative. Recrystallized by extraction from Soxhlet thimble with benzene.

Elimination of Copper from the Complex.—The crystals were moistened with water, and phosphorus pentachloride

(6) Helberger, *Naturwiss.*, **26**, 316 (1938).

(7) Helberger and Hevér, *Ber.*, **72**, 11 (1939).

(8) 500 mg. T.P.P. was used in each experiment, except where a different amount is mentioned.

TABLE II

ANALYSES, %

Formula	Mol. weight	Calculated C	H	N	Cl	O	Metal	Py[a]	Found C	H	N	Cl	Metal	Py
$C_{44}H_{28}N_4Cu$	676.26	78.12	4.18	8.29			9.41		78.1	4.4	8.5		9.2	
$C_{44}H_{28}N_4Ag$	721.58	73.23	4.05	7.77			14.95		73.6	3.7	7.9		14.8	
$C_{44}H_{28}N_4Ag_2$	828.45	63.79	3.41	6.76			26.04		63.5	3.5	6.7		25.3	
$C_{44}H_{28}N_4Au_2Cl_4$	1148.92	45.99	2.45	4.89	12.34		34.33		46.4	2.5	4.9	12.8	34.0	
$C_{44}H_{28}N_4Mg$	637.01	82.94	4.43	8.80			3.83		80.4	4.4	8.6		3.8	
$C_{44}H_{30}N_4MgO$	655.03	80.67	4.62	8.56		2.44	3.71		80.4	4.4	8.6		3.8	
$C_{44}H_{28}H_4Zn$	678.07	77.93	4.16	8.27			8.64		77.7	4.3	8.4		10.0	
$C_{44}H_{28}Cd\cdot Py$	804.18	73.18	4.0	8.71			13.98	9.85	72.9	4.0	8.6			9.6
$C_{44}H_{28}N_4Cd$	725.10	72.88	3.89	7.73			15.50		72.9	3.9	7.8			
$C_{44}H_{28}N_4Hg$	813.30	64.97	3.47	6.89			24.67		64.9	3.5	7.0		24.0	
$C_{44}H_{28}N_4Tl$	817.08	64.67	3.45	6.86			25.02		64.0	3.7	6.3		21.0	
$C_{44}H_{28}N_4SnCl_2$	802.30	65.86	3.52	6.98	8.84		14.80		65.5	3.6	7.0	10.0		
$C_{44}H_{28}N_4PbPy$	899.00	65.46	3.70	7.79			23.05		65.3	3.6	7.5		22.3	
$C_{44}H_{28}N_4MnCl$	703.08	75.16	4.01	7.97	5.05		7.82		75.0	4.0	8.1	5.0	7.9	
$C_{44}H_{28}N_4FeCl$	703.99	75.06	7.01	7.96	5.04		7.93		75.1	4.1	8.0	5.1	7.8	
$C_{44}H_{28}N_4Co$	671.63	78.68	4.20	8.34			8.78		78.7	4.2	8.3		8.6	
$C_{44}H_{28}N_4Ni$	671.38	78.71	3.20	8.35			8.74		78.9	4.5	8.3		8.7	

[a] Pyridine.

was added until further addition caused no reaction. The solution was then poured into ether and neutralized with sodium carbonate solution. The ether layer contained the free porphyrin.

(b) **From Formic Acid Solution.**—Constant boiling formic acid, approximately 90% HCOOH, is a good solvent for the free porphyrin. From this solution a complex copper salt of the porphyrin could be obtained which differed from that prepared above, Method 1, in that it possessed an additional intense absorption band at 651.8. T.P.P.[8] was dissolved in 200 ml. of 90% formic acid, 400 mg. of copper acetate was added and the whole refluxed on a steam-bath for one hour. At the end of this time conversion was complete and the yield was quantitative. The analysis of this material, recrystallized from benzene, was identical with that of the copper complex salt prepared under (a).

Mono Silver Complex Salt. Preparation, Method 1.—T.P.P.,[8] 50 ml. of chloroform, 500 mg. of silver acetate, 50 ml. of glacial acetic acid. For analysis the material was recrystallized twice from benzene.

Di Silver Complex Salt.—A silver complex salt containing two atoms of silver in the molecule was obtained from glacial acetic acid solutions with silver acetate. Five hundred ml. of glacial acetic acid containing 150 mg. of the porphyrin was refluxed with 150 mg. of silver acetate for one-half hour; yield, 90 mg. blue violet crystals on cooling.

Gold Complex Salt. Preparation, Method 1.—Two hundred mg. of porphyrin, 50 ml. of chloroform, 200 mg. of gold chloride, 1 g. of sodium acetate, 50 ml. of glacial acetic acid. The chloroform was distilled off and the solution refluxed fifteen minutes, cooled and filtered. Three hundred mg. of blue crystals was obtained. They were recrystallized by extracting from a Soxhlet thimble with a mixture of 20 ml. of chloroform and 50 ml. of benzene; yield, 200 mg. blue-red crystals.

Magnesium Complex Salt, "Phyllin." Preparation, Method 3.—A sealing tube similar to that employed in the synthesis of the porphyrin[1] was filled with the following: 300 mg. of T.P.P. in 25 ml. of hot pyridine, 500 mg. of magnesium acetate, 60 ml. of 40% methanolic potassium hydroxide. The air in the tube was displaced by nitrogen to render sealing safer, and the sealed tube was supported in a large Carius furnace. For this experiment the furnace was tilted at an angle of 30° or more to prevent the porphyrin from creeping into the upper part of the tube not bathed in liquid. The furnace was left at 170° for sixteen hours, then the contents of the cooled tube were poured into approximately 100 g. of ice made from distilled water. When the ice had melted, the crystalline precipitate was filtered off, washed with water, and the crystals dried by suction. This dried material was then recrystallized by extracting from a thimble with 20–30 ml. of ether. The "phyllin" was very photolabile; the reaction mixture or solutions of the "phyllin" should not be exposed to light. The reaction tube was wrapped in towelling on removing from the furnace and the extraction apparatus for recrystallizing was wrapped in black paper, or better still, the extraction was carried on in a dark room. Solutions of the "phyllin" could be exposed for brief periods to diffuse light but a half hour exposure to daylight, not direct sunlight, caused a visible decrease in the intensity of the absorption band at 624.4 mμ. On exposing dilute ether solutions of the "phyllin" to daylight, northern exposure, the first visible change was a decrease in the intensity of the absorption band at 624.4 mμ. After two hours this band had usually disappeared completely. During this time the other absorption bands remained visibly unchanged. On further exposure the "phyllin" slowly decomposed to yield a pale yellow ether solution. Analysis of different batches of the "phyllin," prepared as described above, consistently yielded low values for carbon. Assuming hydrolytic cleavage of one bond from magnesium to nitrogen during the precipitation with ice of the "phyllin" from the reaction mixture and calculating for one hydroxyl group in the molecule, the analysis compares with the new theory as shown in Table II.

Zinc Complex Salt. Preparation, Method 1.—T.P.P.,[8] 50 ml. of chloroform, 250 mg. of zinc acetate, and 250 ml. of glacial acetic acid were refluxed for one hour on the steam-bath, and quantitative yield was obtained; the substance was recrystallized by extracting from a Soxhlet thimble with a mixture of 40 ml. of ether and 20 ml. of methanol.

Cadmium Complex Salt. Preparation, Method 2.—One gram of T.P.P. in 100 ml. of hot pyridine, 800 mg. of cadmium acetate, and 40 ml. of 40% methanolic potassium hydroxide were refluxed for two hours on the steam-bath. To this hot solution 240 ml. of hot water was added, and the contents allowed to cool; yield, 1.5 g. of very fine crystals which were washed several times with 2-ml. portions of cold water, dried and extracted from a Soxhlet thimble with 100 ml. of pure ether. For analysis the material was recrystallized once from ether and dried overnight in a phosphorus pentoxide desiccator; it contained 1 mole of pyridine of crystallization. When dried at 175° for eighteen hours to constant weight in a Pregl block, the substance lost 9.6%, corresponding to the pyridine value (see Table II).

TABLE III

ABSORPTION SPECTRA OF METAL COMPLEX SALTS OF α,β,γ,δ-TETRAPHENYLPORPHINE

The spectra were visually measured in the conventional manner by determining points of equal intensity at the edges of each absorption band which are given in mμ. The center of the band (absorption maximum) was for symmetrical bands calculated by averaging the two values measured. Unsymmetrical bands are indicated by dashes, *e. g.*, ---546.0 shows that the maximum of intensity is located at 546.0 with the more gradual increase of the intensity toward the red region of the spectrum. In recording the order of intensity (Int.:) marked differences in intensity have been separated by a semicolon.

All solutions of the metal complex salts showed red fluorescence; solutions of the cadmium, stabile thallium, iron chloride, manganese and cobalt complex exhibited it intensely. The red fluorescence was most conspicuous in the solutions of the alkali complexes and of the magnesium and zinc salt.

Name	Solvent	Color of solution	Absorption spectrum
Copper	Ether	Pink	I, 610.6; II, 574.7; III, 538.0; IV, 497.3; E. A. 446.6. Int.: III; I, IV, II
Mono Silver	Ether	Pink	I, 575.3; II, 539.3; III, 501.0; Shadow 477; E. A. 448.0. Int.: II; I, III; IV
Di Silver	Ether	Pink	I, 576.2; II, 539.3; III, 500.5; IV, 474.2; E. A. 448.0. Int.: II; I, III; IV
Gold	Ether	Orange-pink	I, 522.7; II, 485.2; Shadow 458; E. A. 436.5. Int.: I; II
Magnesium ("Phyllin")	Ether	Magenta	I, 651.5; II, 624.4; III, 602.6; IV, 562.3; V, 521.4; VI, 490.2; VII, 461.2; E. A. 441.6. Int.: IV; III; II, V, VII, I, VI
Zinc	Ether	Magenta	I, 595.5; II, 553.9; III, 515.0; IV, 485.3; E. A. 440.5. Int.: II, I; III, IV
Cadmium	Ether	Green	I, 613.4; II, 567.5---; III, 528.2; IV, 497.8; V, 472.7; E. A. 456.0. Int.: II, I; III, IV, V. In greater dilution: Ia, 623.9; Ib, 610.0; Ib > Ia. In very weak solution: VI, 431.5; E. A. 410[a]
Mercury	Benzene	Reddish with tinge of green	I, 653.9; II, 619.0; III, 559.3; IV, 513.9; Shadow 484.8; E. A. 455.3. Int.: III; IV, I, II
	Pyridine	Grass green	I, 629.9; II, 584.6; III, 545.1; Shadow 512; E. A. 482.8. Int.: I, II; III. III
Thallium (labile)	Pyridine	Green	I, 695.8; II, ---645.5---; III, 483.0; IV, 458.3---; E. A.---418.0. Int.: III, IV, I; II
Thallium (stabile)	Pyridine–ether (1:3)	Bluish-green	Shadow 651.0; I, 631.7; II, 606.2; III, 565.3; IV, 526.7; Shadow 495.6; E. A. 447.2. Int.: III, II; I, IV. After 3 hours exposure to bright light: I, 650.9; II, 610.4; III, 567.0; IV, ---518.5; E. A. 460. Int.: III, II; IV, I[b]
Tin Chloride	Pyridine–ether (1:3)	Purple	I, 627.4; II, 601.6---; III, 560.3; IV, 522.2---; V, 490.3; Shadow 460.5; E. A. 444.0. Int.: III, II; I=IV, V[c]
Lead	Ether	Bright Green	I, 657.0; II, ---606.2---; III, 555.8; Shadow 506; IV, 463.4; V, 438.4; E. A. 420. Int.: IV, V; I; II, III
Manganese	Ether	Green	I, 619.9; II, 579.9---; III, 532.0; E. A. 492.5. Int.: I, II, III. In greater dilution: IV, 473.7; E. A. Approx. 420
Iron Chloride ("Hemin")	Pyridine–ether or in benzene	Orange-brown	I, 687.9---; II, ---571.6---; III, ---506.6---; E. A. 465.2. Int.: III; II, I
Cobalt	Ether	Orange	I, 607.7; II, ---626.6---; E. A. ---447.0. Int.: II; I
Nickel	Pyridine–ether (1:4)	Pink	I, 652.1; II, ---614.1; III, 557.1; IV, ---526.3; V, 485.9; E. A. 455. Int.: IV; II, III, V
Lithium	Pyridine–methanol	Magenta	I, ---619.2; II, 575.5; III, 533.6; IV, 502; E. A. 456.3. Int.: I, II, III, IV
Sodium	Pyridine–methanol	Magenta	I, 626.3; II, 580.8; III, 539.7; Shadow 506; E. A. 462.8. Int.: I, II, III
Potassium	Pyridine–methanol	Magenta	I, 626.5; II, 580.2; III, 540.2; IV, 492.6; E. A. 458.2. Int.: I, II; IV, III
Rubidium	Pyridine–methanol	Green	I, ---634.0; II, 589.2; III, 549.6; E. A. 567.2. Int.: I, II; III
Cesium	Pyridine–methanol	Green	I, 651.7; II, 599.1; III, 554.4; IV, 516.4; E. A. 472.8. Int.: I, II; III, IV

[a] In pyridine solution the absorption bands are slightly shifted toward the red region. [b] This change did not occur in the dark. [c] In the pyridine mother liquid above remained a small amount of a substance of bluish lavender color in pyridine–ether solution. Spectroscopically it showed an additional absorption band at 651.4 and a more intense 627.4 band.

Mercury Complex Salt. Preparation, Method 2.—T.P.P.,[8] 50 ml. of pyridine and 500 mg. of mercuric acetate were refluxed for two and one-half hours on a steam-bath. The conversion was complete and yielded approximately

0.5 g. of blue needles from the solution after cooling. The substance was recrystallized twice from benzene by extracting from a Soxhlet thimble and air dried.

The spectra in benzene and in pyridine are recorded in Table III. In piperidine and quinoline the absorption spectrum was similar to that in pyridine, the only difference lying in a shift of the absorption bands toward the red, this shift being greatest for piperidine. The color and spectrum shifted to that observable in the organic base if a drop of the base was added to the benzene solution.

Labile Thallium Complex Salt. Preparation, Method 2.—Two hundred mg. of T.P.P., 20 ml. of pyridine and 200 mg. of thallous acetate were refluxed overnight on a steam-bath. One hundred mg. of dark green crystals was obtained from the cold solution. Addition of more thallous acetate to the mother liquid and repeating the refluxing yielded a second crop of complex salt. This thallium complex was very unstable in solution, the mother liquid always containing unchanged porphyrin. When the above green crystals were dissolved in pyridine, the free T.P.P. spectrum appeared immediately in the spectrum of the salt. A pure complex salt spectrum was obtained only in hot pyridine solution in the presence of thallous acetate. On standing the free porphyrin spectrum appeared in this solution also. The complex was easily split by water to form the free porphyrin.

Stable Thallium Complex Salt. Preparation, Method 2.—The thallous acetate used must be oxidized in order to prevent the formation of the unstable thallium complex described above. The thallous salt was oxidized in acetic acid with 30% hydrogen peroxide solution, and the crystals obtained on evaporating the solution were used, or 30% hydrogen peroxide was added directly to a pyridine solution of the porphyrin containing thallous acetate. Both methods were used, the latter being described below. A solution of T.P.P.,[8] 50 ml. of pyridine, 500 mg. of thallous acetate and 2 ml. of 30% hydrogen peroxide boiled down to a total volume of 30 ml. After addition of 20 ml. of pyridine and 1 ml. of 30% hydrogen peroxide solution and concentrating to 20 ml. by boiling, the conversion was complete. Forty ml. of hot methanol was poured into the hot solution. Five hundred mg. of lustrous blue crystals formed on cooling. The material was extracted from a Soxhlet thimble with benzene, filtered, the benzene solution concentrated to 20 ml., and 50 ml. of hot methanol added; yield, 450 mg.

Tin Chloride Complex Salt. Preparation, Method 2.—T.P.P.[8] in 50 ml. of pyridine and 400 mg. of stannous chloride: Refluxing for two hours yielded 500 mg. of fine lavender crystals on cooling, which were recrystallized by extracting from a thimble with a mixture of 15 ml. of chloroform and 40 ml. of benzene.

Lead Complex Salt. Formation, Method 2.—T.P.P.,[8] 50 ml. of pyridine, and 500 mg. of lead acetate were heated for one hour. On cooling approximately 500 mg. of dark blue-green crystals was obtained and recrystallized twice by extracting from a thimble with 40 ml. of benzene. The analytical results check for 1 mole of pyridine in the molecule. There was no loss in weight upon heating at 175° for eighteen hours.

Manganese Chloride Complex Salt. Formation, Method 1.—T.P.P.,[8] 50 ml. of chloroform, 70 ml. of glacial acetic acid, 500 mg. of manganous acetate and 100 mg. of sodium chloride were refluxed for six hours. The solvents were distilled off under vacuum and 50 ml. of glacial acetic acid was added to the dry residue and the resulting solution concentrated to approximately 15 ml. The crystals in the cooled solution were filtered off, washed with glacial acetic acid, air dried, and recrystallized by extracting from a Soxhlet thimble with ether; yield, approximately 300 mg. of dark green crystals of high luster. The manganese chloride complex was extremely soluble in methanol. Crystals could be obtained if the methanol solution was added to ligroin and the methanol evaporated. The spectrum of the resulting crystals in methanol differed little from that in ether, which is given in Table III.

Iron Chloride Complex Salt, "Hemin." Preparation, Method 1.—T.P.P.[8] was dissolved in 50 ml. of chloroform and 200 mg. of sodium chloride was added. Into this solution was filtered, hot, 150 ml. of glacial acetic acid saturated with ferrous acetate. This was prepared by dissolving pure iron filings in boiling glacial acetic acid and filtering the hot solution into the chloroform. After refluxing for two hours, concentrating to approximately 50 ml., cooling and filtering, approximately 500 mg. of impure crystals was obtained. The crystals were extracted from a thimble with chloroform, the solution concentrated to 10 ml. and approximately 80 ml. of hot methanol was added. Dark blue crystals formed on cooling. Prolonged heating had to be avoided since this caused the formation of a substance with spectrum differing from that given above for the "hemin." For analysis the material was recrystallized twice from chloroform–methanol.

Cobalt Complex Salt. Preparation, Method 1.—T.P.P.,[8] 50 ml. of chloroform, 250 mg. of cobaltous acetate, and 50 ml. of glacial acetic acid were refluxed for one-half hour. On cooling fine maroon crystals formed quantitatively and were recrystallized by extracting from a thimble with ether.

Nickel Complex Salt.—Nickel acetate was substituted for cobalt acetate in the above procedure and the solution was heated for one hour. Five hundred ten mg. of blue crystals, filtered from the cooled solution, were recrystallized by extracting from a thimble with benzene.

Lithium Complex Salt. Formation.—A methanolic solution of lithium hydroxide was added to a solution of the porphyrin in pyridine.

Sodium Complex Salt. Formation.—Same as above, substituting sodium hydroxide for the lithium salt.

Potassium Complex Salt. Preparation.—50 mg. of T.P.P. in 20 ml. pyridine was added to 20 ml. of 40% methanolic potassium hydroxide. After a few hours of standing the solution was filtered through a fritted glass filter. It was not possible to prepare the pure complex salt since it was unstable in solutions not containing dissolved potassium hydroxide.

Rubidium Complex Salt. Formation.—A methanolic solution of rubidium hydroxide was added to a solution of the porphyrin in pyridine. The hydroxide was obtained by shaking rubidium chloride with silver oxide in methanol.

Cesium Complex Salt. Formation.—Same as above, substituting cesium hydroxide for rubidium hydroxide.

Summary

1. The preparation of the complex salts of α,β,γ,δ-tetraphenylporphine with the following metals is reported: lithium, sodium, potassium, rubidium, cesium, copper, mono silver, di silver, gold chloride, magnesium ("phyllin"), zinc, cadmium, mercury, tin chloride, lead, thallium (stabile complex salt), thallium (labile complex salt), manganese chloride, ferric chloride ("hemin"), cobalt and nickel.

2. The data for the absorption spectra of these compounds in the visual region of the spectrum are presented.

3. The elementary analyses by microanalytical procedures show that most of these salts are normal complexes; the gold salt crystallizes from benzene with 1 mole of gold chloride, the "phyllin" as magnesium hydroxide, cadmium and lead salt with 1 mole of pyridine. The structure of the tin chloride complex remains to be investigated further. The isolation and analysis of the complexes of the alkali metals—for which the spectra only are given—have not been performed as yet.

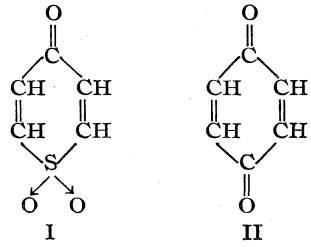
YELLOW SPRINGS, OHIO
COLUMBUS, OHIO RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Studies in the Thiapyran Series. The Preparation, Properties and Reactions of 1,4-Thiapyrone-1-dioxide

BY EDWARD A. FEHNEL[1] AND MARVIN CARMACK

A comparison of the structural formulas of 1,4-thiapyrone-1-dioxide (I) and *p*-benzoquinone (II) suggests that these two compounds might possess



I II

many chemical and pharmacological properties in common. Several investigators[2] have demonstrated the similarity in the behavior of α,β-unsaturated sulfones and α,β-unsaturated ketones in addition reactions involving both symmetrical and unsymmetrical reagents, and Kohler and Larsen[3] have shown that the addition reactions of α-phenylsulfonyl-β-benzoylethylene with unsymmetrical reagents are similar to those of β-benzoylacrylic esters, the mode of addition being controlled by the conjugated system —C=C—C=O. Although these and other investigations[4] have provided evidence for the temporary expansion of the valence shell of sulfur to accommodate ten electrons, the characteristic enolization of the initial 1,4-addition products of quinones to yield stable hydroquinones as the final products would not be expected to have a counterpart in the thiapyrone dioxide series.

The preparation of 1,4-thiapyrone-1-dioxide has been described by Arndt and Bekir,[5] who obtained a very small amount of the compound as the final product of a five-step synthesis starting with ethyl β-thiodipropionate.[6] In order to prepare the relatively large amounts of I required in the present work, we have re-investigated each step in the original procedure and by applying various modifications have succeeded in obtaining a greatly improved over-all yield of the desired product.

(1) American Chemical Society Postdoctoral Fellow, 1946–1948.

(2) (a) Kohler and Potter, THIS JOURNAL, **57**, 1316 (1935); (b) Alexander and McCombie, *J. Chem. Soc.*, 1913 (1931); (c) Kretov, *J. Russ. Phys.-Chem. Soc.*, **62**, 1 (1930); *C. A.*, **24**, 4257 (1930).

(3) Kohler and Larsen, THIS JOURNAL, **57**, 1448 (1935).

(4) (a) Rothstein, *J. Chem. Soc.*, 309 (1937); 1550, 1553, 1558 (1940); (b) Fehnel and Carmack, "The Ultraviolet Absorption Spectra of Organic Sulfur Compounds," presented before the Division of Organic Chemistry of the American Chemical Society at the Chicago meeting, April, 1948.

(5) Arndt and Bekir, *Ber.*, **63**, 2393 (1930).

(6) The earlier steps in this synthesis were first carried out by (a) Bennett and Scorah, *J. Chem. Soc.*, 194 (1927); (b) Bennett and Waddington, *ibid.*, 2829 (1929).

1,4-Thiapyrone-1-dioxide, like its carbonyl analog, *p*-benzoquinone, is a sternutator, stains the skin yellow, and is decomposed by aqueous alkali with the formation of a deep red color. The ultraviolet absorption spectra of *p*-benzoquinone, 1,4-thiapyrone-1-dioxide, and 2,3-dihydro-1,4-thiapyrone-1-dioxide are compared in Fig. 1.

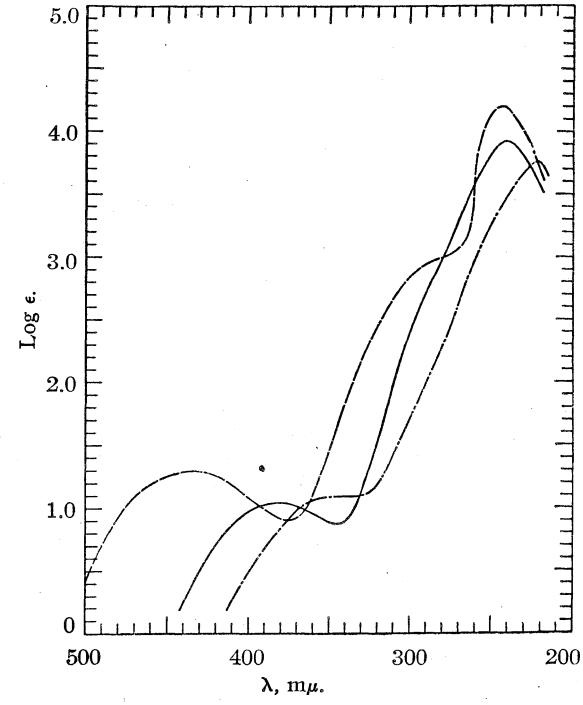
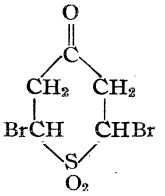


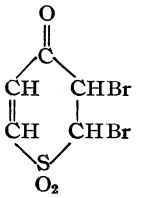
Fig. 1.—Absorption spectra of 1,4-thiapyrone-1-dioxide, ——; 2,3-dihydro-1,4-thiapyrone-1-dioxide, —·—·—; *p*-benzoquinone, — — —.

On treatment with zinc and acetic acid, 1,4-thiapyrone-1-dioxide is smoothly reduced to the corresponding saturated heterocycle, tetrahydro-1,4-thiapyrone-1-dioxide. Two molecules of hydrogen bromide may be added to I in the presence of a large excess of the reagent in acetic acid solution, but the reaction appears to be reversible and the dibromo compound readily loses hydrogen bromide on warming in aqueous or acetic acid solution. This rather unstable addition product (m. p. 130–133° dec.) has quite different properties from the stable isomer, 3,5-dibromotetrahydro-1,4-thiapyrone-1-dioxide (m. p. 220–222° dec.) obtained by bromination of tetrahydrothiapyrone dioxide,[5] and has been assigned structure III on the basis of Kohler and Larsen's observations[3] regarding the mode of addition of unsymmetrical addenda to unsaturated ketosulfones.

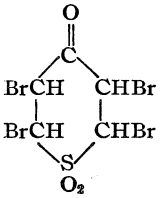


III

The addition of either one or two molecules of bromine to I proceeds readily at room temperature, giving as the initial products the dibromide IV and the tetrabromide V. The isolation of

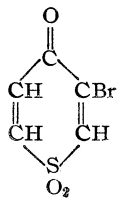


IV

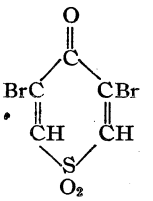


V

these compounds proved to be rather difficult, since, like the corresponding quinone bromides,[7] they readily lose hydrogen bromide on warming and are gradually converted into the mono- and dibromothiapyrone dioxides, VI and VII. The structures assigned to the latter compounds, which



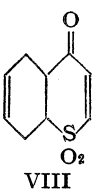
VI



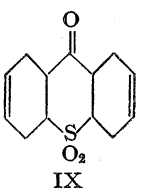
VII

are the only isolable products of bromination when no special precautions are taken to prevent the dehydrobromination of the initial adducts, follow from a consideration of the relative ease of dehydrobromination of the 3,5- and 2,6-dibromotetrahydrothiapyrone dioxides.

The stepwise addition of butadiene to I occurs slowly at room temperature and more rapidly at elevated temperatures, yielding mono- and di-adducts (VIII and IX) analogous to the products obtained in a similar manner from *p*-benzoquinone.[8]

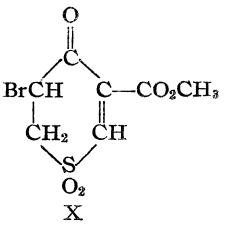


VIII

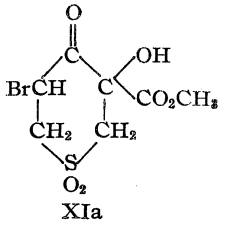


IX

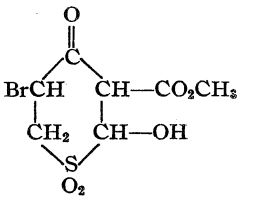
3,5-Dibromo-3-carbomethoxytetrahydro-1,4-thiapyrone-1-dioxide, prepared in the course of this investigation by the bromination of 3-carbomethoxytetrahydro - 1,4 - thiapyrone - 1 - dioxide, was found to lose one molecule of hydrogen bromide so readily that a good yield of a monobromocarbomethoxydihydrothiapyrone dioxide



X



XIa



XIb

was obtained merely by refluxing the dibromo compound with aqueous acetic acid. The product is undoubtedly the 2,3-dihydro compound X. In one similar experiment, however, the product isolated appeared, on the basis of the analytical data, to be a bromohydroxycarbomethoxytetrahydrothiapyrone dioxide. Either structure XIa or XIb might be assigned to this compound, depending on whether the bromine atom was replaced directly by a hydroxyl group or, as is more probable, hydrogen bromide was first split out to give X, which then added a molecule of water, the hydroxyl becoming attached to the carbon *beta* to the carbonyl function. All attempts to repeat the preparation of this compound, starting with either the dibromo derivative or with X, were unsuccessful, and its structure was not further investigated.

Experimental[9]

Improved Preparation of 1,4-Thiapyrone-1-dioxide (I).—A mixture of 289 g. (1.4 moles) of methyl β-thiodipropionate,[10] 2.8 moles of alcohol-free sodium methoxide (freshly prepared from 64.3 g. of sodium), and 1 liter of anhydrous ether was stirred and refluxed for three hours. The mixture was cooled quickly to room temperature and poured into an ice-cold solution of 178 ml. of acetic acid in 1 liter of water. After vigorous agitation, the layers were separated and the aqueous layer was extracted repeatedly with small portions of ether until the extracts no longer gave a violet color with ferric chloride solution. The extracts were added to the original ether layer, and the combined solution was washed with aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. After removal of the ether, the residual oil was distilled under diminished pressure to yield 158.8 g. (65%) of **3-carbomethoxytetrahydro-1,4-thiapyrone** as a colorless oil, b. p. 120–125° at 5 mm. The analytical sample was obtained by redistillation of a small portion of this material; b. p. 120° at 5 mm., $n^{20}D$ 1.5234.

Anal. Calcd. for $C_7H_{10}O_5S$: C, 48.26; H, 5.79. Found: C, 48.31; H, 5.79.

Hydrolysis and decarboxylation of the cyclic ketoester was accomplished in a single step by treatment with 10%

(7) Nef, *J. prakt. Chem.*, [2] **42**, 161 (1890).

(8) Diene additions of quinones have been studied by Diels, *et al.*, *Ber.*, **62B**, 2337 (1929), and by Alder and Stein, *Ann.*, **501**, 247 (1933).

(9) Microanalyses were performed by Miss Sarah H. Miles. All melting points are corrected.

(10) Gershbein and Hurd, THIS JOURNAL, **69**, 241 (1947).

sulfuric acid according to the method of Bennett and Scorah.[6a] A reflux period of two hours sufficed to complete the reaction in the case of the methyl ester. Evaporation of the dried ether extract afforded colorless crystals of crude tetrahydro-1,4-thiapyrone melting at 58–62° (reported[6a] m. p., 65–66°); yield, 84%.

To a solution of 56.0 g. (0.48 mole) of tetrahydrothiapyrone in 500 ml. of glacial acetic acid, 114 ml. (1.00 mole) of 30% hydrogen peroxide was added in small portions while the mixture was cooled under the tap to moderate the reaction. After the strongly exothermic reaction had subsided, 400 ml. of the solvent was distilled from the mixture and the residue was cooled to crystallize out the major portion of the product as almost colorless needles melting at 164–167° (reported[6b] m. p., 170°). A further small quantity of crude product was obtained by evaporation of the filtrate to dryness on the steam-bath and recrystallization of the residue from acetic acid; total yield of tetrahydro-1,4-thiapyrone-1-dioxide, 54.7 g. (77%).

A warm solution of 38.3 g. (0.26 mole) of the crude dioxide in 450 ml. of glacial acetic acid was shaken with 83.2 g. (0.52 mole) of bromine for several minutes and was then cooled to room temperature and filtered. 3,5-Dibromotetrahydro-1,4-thiapyrone-1-dioxide was thus obtained as colorless needles, m. p. 220–222° dec. (reported[5] m. p., 220° dec.); yield, 71.9 g. (91%).

Attempts to dehydrobrominate this material by treatment with pyridine according to the original method of Arndt and Bekir[5] led to the formation of considerable tarry material and only small amounts of the desired product. Almost quantitative yields of pure product were obtained, however, when the dibromo compound was treated briefly with sodium acetate in refluxing acetone. In a typical experiment, a suspension of 12.2 g. (0.04 mole) of the dibromo compound in 150 ml. of hot acetone was added gradually over a fifteen-minute period to a mechanically stirred, refluxing suspension of 27.2 g. (0.20 mole) of powdered sodium acetate trihydrate in 150 ml. of acetone. Stirring and refluxing were continued for another ten minutes, and the dark red mixture was cooled and filtered. Concentrated hydrochloric acid was added dropwise to the filtrate until the color of the solution changed from red to yellow, and the mixture was refiltered to remove the precipitate of sodium chloride. The clear yellow filtrate was evaporated to dryness on the steam-bath, leaving a yellow-brown crystalline residue which was recrystallized from glacial acetic acid (Norit) to yield 3.9 g. of yellow crystals, m. p. 173–174° (reported[5] m. p., 174°). The mother liquor was worked up to provide a second crop of crystals, which was recrystallized and added to the original product to give a combined yield of 1,4-thiapyrone-1-dioxide (I) of 5.5 g. (96%). This compound is readily soluble in water, ethanol, and acetone; slightly soluble in cold acetic acid; and insoluble in hydrocarbon solvents. It sublimes as long yellow needles at temperatures somewhat below its melting point. Purified samples appear to be entirely stable when stored in contact with air.

The **oxime** was obtained as colorless needles which, after recrystallization from water, decomposed violently without melting at 196°.

Anal. Calcd. for $C_5H_5NO_3S$: C, 37.72; H, 3.17. Found: C, 37.77; H, 2.93.

The **semicarbazone** was obtained as a pale yellow microcrystalline powder, m. p. 237–239° dec., after recrystallization from water (Norit).

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.81; H, 3.51. Found: C, 35.67, 35.86; H, 3.76, 3.35.

Reduction of 1,4-Thiapyrone-1-dioxide.—A mixture of 1.00 g. of I, 2.0 g. of zinc dust, and 15 ml. of glacial acetic acid was refluxed for one hour, after which the yellow color of the solution had disappeared. The unreacted zinc was filtered off, and the filtrate was saturated with hydrogen sulfide and refiltered. Evaporation of the clear filtrate to dryness on the steam-bath afforded 0.89 g. (87%) of almost colorless crystals which melted at 167–169° after recrystallization from acetic acid and exhibited no melting-point depression when mixed with authentic tetrahydro-1,4-thiapyrone-1-dioxide.

2,6-Dibromotetrahydro-1,4-thiapyrone-1-dioxide (III).—One gram of I was dissolved in 6 ml. of glacial acetic acid saturated with dry hydrogen bromide, and more hydrogen bromide was passed into the solution until precipitation was complete. The crystalline precipitate was collected and dried at room temperature to yield 0.9 g. of 2,6-dibromotetrahydro-1,4-thiapyrone-1-dioxide as brownish needles, m. p. 126–131° dec. Although this material appeared to be only slightly soluble in cold acetic acid, all attempts to recrystallize it from this solvent resulted in the formation of yellow solutions from which only negligible amounts of the dibromo compound could be recovered on cooling; m. p. 130–133° dec.

Anal. Calcd. for $C_5H_6Br_2O_3S$: C, 19.62; H, 1.99. Found: C, 20.06; H, 1.99.

When a sample of this compound was boiled with water for a few seconds, and was then cooled, acidified with dilute nitric acid, and treated with aqueous silver nitrate, a copious precipitate of silver bromide formed at once.

3-Bromo-1,4-thiapyrone-1-dioxide (VI).—To a solution of 1.00 g. (0.007 mole) of I in 25 ml. of glacial acetic acid there was added 1.11 g. (0.007 mole) of bromine, and the mixture was allowed to stand for four hours at 5°. After removal of the solvent by evaporation *in vacuo* at room temperature, the dark-colored, semicrystalline residue was recrystallized from methanol (Norit) to yield 0.50 g. (32%) of pale yellow crystals, m. p. 173–174° dec. with previous sintering. Another recrystallization from methanol gave the pure compound melting at 189–190° dec., when immersed in a bath at 185° and heated rapidly; considerable decomposition occurred above 150° when the compound was heated slowly from room temperature.

Anal. Calcd. for $C_5H_3BrO_3S$: C, 26.92; H, 1.36. Found: C, 26.96; H, 1.29.

3,5-Dibromo-1,4-thiapyrone-1-dioxide (VII).—A mixture of 1.44 g. (0.01 mole) of I, 3.20 g. (0.02 mole) of bromine, and 30 ml. of glacial acetic acid was allowed to stand at 5° until all the solid had dissolved and the color of the solution had faded to pale yellow. The mixture was poured into 60 ml. of ice-water and the resultant yellow precipitate was collected, washed with water, and dried; m. p. 157–161°; yield, 1.87 g. (62%). Recrystallization from methanol (Norit) gave pale yellow needles, m. p. 160–162°.

Anal. Calcd. for $C_5H_2Br_2O_3S$: C, 19.88; H, 0.67. Found: C, 19.79; H, 0.67.

2,3-Dibromo-2,3-dihydro-1,4-thiapyrone-1-dioxide (IV).—A solution of 1.44 g. (0.01 mole) of I in 50 ml. of hot chloroform was cooled to precipitate the thiapyrone dioxide as a microcrystalline suspension. A solution of 1.60 g. (0.01 mole) of bromine in 10 ml. of chloroform was added to this suspension in small portions over a thirty-minute period with vigorous agitation after each addition. The solvent was removed by evaporation under reduced pressure at room temperature, leaving a dark-colored sirup which slowly solidified on standing for several days. This product was digested with a little hot benzene, care being taken not to prolong the period of heating any longer than absolutely necessary, and the benzene extract was cooled to precipitate 0.6 g. of colorless powder, m. p. 133–135° dec. Cautious recrystallization of this material from benzene gave the dibromide as colorless crystals, m. p. 138–139° dec.

Anal. Calcd. for $C_5H_4Br_2O_3S$: C, 19.75; H, 1.33. Found: C, 20.74; H, 1.25.

This compound lost hydrogen bromide so readily that further purification could not be effected by repeated recrystallization. Analytical and melting-point data obtained for the same sample on different dates also indicate that the compound gradually undergoes dehydrobromination on standing at room temperature.

2,3,5,6-Tetrabromotetrahydro-1,4-thiapyrone-1-dioxide (V).—A mixture of 1.44 g. (0.01 mole) of I, 3.20 g. (0.02

mole) of bromine, and 65 ml. of chloroform was allowed to stand for one hour at room temperature with occasional agitation, and the solvent was then removed by evaporation under reduced pressure. The dark-colored residue was heated for a few minutes with a little acetic acid and the suspension was cooled and filtered. The insoluble portion was washed with a little cold acetic acid and dried *in vacuo* to yield 0.4 g. of colorless powder, m. p. 195–198° dec. with previous sintering and blackening. This compound dissolved slowly in hot acetic acid, water, and methanol with the production of a yellow color.

Anal. Calcd. for $C_5H_4Br_4O_3S$: C, 12.95; H, 0.87. Found: C, 13.20; H, 0.85.

The acetic acid filtrate from the isolation of the tetrabromide was evaporated and the residue was worked up with methanol to yield 1.6 g. of pale yellow needles. After repeated recrystallization from methanol, this material melted at 158–160° and failed to depress the melting point of the 3,5-dibromo-1,4-thiapyrone-1-dioxide described above.

3-Bromotetrahydro-1,4-thiapyrone-1-dioxide.—To a microcrystalline suspension obtained by cooling a hot solution of 7.40 g. (0.05 mole) of tetrahydro-1,4-thiapyrone-1-dioxide in 100 ml. of glacial acetic acid, 8.00 g. (0.05 mole) of bromine was added dropwise over a twenty-minute period. The mixture was agitated vigorously after each addition, and after all the bromine had been added the precipitate was filtered off and dried *in vacuo* over potassium hydroxide to yield 8.39 g. (74%) of colorless silky needles, m. p. 176–179°. Recrystallization from acetic acid raised the melting point to 182–183°.

Anal. Calcd. for $C_5H_7BrO_3S$: Br, 35.19. Found: Br, 35.66.

2,3-Dihydro-1,4-thiapyrone-1-dioxide.—3-Bromotetrahydro-1,4-thiapyrone-1-dioxide (6.81 g., 0.03 mole) was dehydrobrominated by treatment with sodium acetate trihydrate (9.5 g., 0.07 mole) in boiling acetone (100 ml.) exactly as in the case of the 3,5-dibromo compound. The first crystallization of the crude product from acetic acid (Norit) afforded 3.41 g. (78%) of very pale yellow needles, m. p. 144–146°. Several further recrystallizations from this solvent raised the melting point to 147–148°. This compound gave a deep red color on treatment with aqueous alkali.

Anal. Calcd. for $C_5H_6O_3S$: C, 41.07; H, 4.14. Found: C, 41.11; H, 4.11.

The **oxime** was obtained as colorless needles which melted at 178–179°, dec., after recrystallization from water.

Anal. Calcd. for $C_5H_7NO_3S$: C, 37.24; H, 4.38. Found: C, 37.01; H, 4.53.

$\Delta^{2,7}$-Octahydrothiaxanthone-5-dioxide (IX).—Twenty-five milliliters of purified dioxane[11] was saturated with butadiene (*ca.* 3.8 g., 0.070 mole) at room temperature, 2.0 g. (0.014 mole) of I was added, and the mixture was heated in an autoclave at 140–150° for four hours. On cooling, most of the product crystallized out of the solution in a nearly pure condition; yield, 2.5 g. (72%) of almost colorless plates, m. p. 228–234°, dec., when immersed in a bath previously heated to above 200°. Recrystallization from acetic acid afforded colorless needles, m. p. 235–236°, dec. This compound gave no color on treatment with aqueous sodium hydroxide.

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.78; H, 6.21.

Δ^{6}-Tetrahydro-1,4-benzothiapyrone-1-dioxide (VIII).—A mixture of 2.00 g. (0.014 mole) of I, 3.8 g. (0.070 mole) of butadiene, and 25 ml. of purified dioxane was heated in an autoclave at 100° for four hours, after which the solvent was distilled off and the semicrystalline residue was extracted repeatedly with boiling water. On cooling, the combined aqueous extracts deposited 1.10 g. (40%) of colorless needles, m. p. 146–156°. After several recrystallizations from ethanol, this compound melted at 157–159° and gave a deep yellow color with aqueous sodium hydroxide.

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.54; H, 5.09. Found: C, 54.57; H, 4.85.

A small amount (*ca.* 0.3 g.) of the di-addition product was isolated from the water-insoluble residue by extraction with hot acetic acid. On dilution with several volumes of water, the acetic acid extract slowly deposited a white solid which melted at 229–231° dec. after recrystallization from acetic acid and which failed to depress the melting point of the di-adduct described above.

In an experiment in which a suspension of I in an ethanol solution of butadiene was allowed to stand at room temperature for seven days, a small amount of crystalline material melting at 153–156° was isolated and identified as the mono-adduct by the method of mixed melting points.

3-Carbomethoxytetrahydro-1,4-thiapyrone-1-dioxide.—Oxidation of 1.74 g. (0.01 mole) of 3-carbomethoxytetrahydro-1,4-thiapyrone with 2.5 ml. (0.022 mole) of 30% hydrogen peroxide in 12 ml. of glacial acetic acid afforded 1.35 g. (65%) of colorless crystals melting at 115–116° after recrystallization from water. This compound gave a blood-red color with ferric chloride solution.

Anal. Calcd. for $C_7H_{10}O_5S$: C, 40.75; H, 4.89. Found: C, 40.84; H, 5.01.

3,5-Dibromo-3-carbomethoxytetrahydro-1,4-thiapyrone-1-dioxide.—Bromine (2.72 g., 0.017 mole) was added to a suspension of 1.75 g. (0.0085 mole) of the above ketoester in 10 ml. of glacial acetic acid, and the mixture was agitated until all the solid had dissolved. The clear red solution was placed in a vacuum desiccator over potassium hydroxide and allowed to stand for two weeks. At the end of this time all of the solvent had evaporated and 2.90 g. (94%) of a pale yellow crystalline solid, m. p. 155–165° dec., remained. After repeated recrystallization from ethyl acetate, the pure product was obtained as colorless needles melting at 182–183° dec.

Anal. Calcd. for $C_7H_8Br_2O_5S$: C, 23.10; H, 2.22. Found: C, 23.26, 23.27; H, 2.38, 2.24.

3-Bromo-5-carbomethoxy-2,3-dihydro-1,4-thiapyrone-1-dioxide (X).—A solution of 2.00 g. of the above dibromo compound in 50 ml. of 50% aqueous acetic acid was refluxed for ten minutes, and the crystalline precipitate obtained on cooling was recrystallized from ethyl acetate to yield 1.10 g. (71%) of colorless plates, m. p. 156–157° with previous sintering. This compound gave a positive Beilstein test for halogen.

Anal. Calcd. for $C_7H_7BrO_5S$: C, 29.70; H, 2.49. Found: C, 29.50; H, 2.29.

5-Bromo-3(or 2?)-hydroxy-3-carbomethoxytetrahydro-1,4-thiapyrone-1-dioxide (XI).—In one experiment in which 3,5-dibromo-3-carbomethoxytetrahydro-1,4-thiapyrone-1-dioxide was heated briefly with aqueous acetic acid as above, a colorless crystalline compound melting at 175–177°, dec., after recrystallization from ethyl acetate was obtained. Subsequent attempts to repeat

TABLE I

ULTRAVIOLET ABSORPTION DATA

Compound	$\lambda_{max.}$,[a] mμ	Log ε
1,4-Thiapyrone-1-dioxide	380	1.04
	240	3.93
2,3-Dihydro-1,4-thiapyrone-1-dioxide	(340)	1.10
	221	3.74
p-Benzoquinone[b]	433	1.31
	(275)	3.03
	243	4.21

[a] The wave lengths in parentheses refer to prominent inflection points. [b] *Cf.* Anderson and Yanko, THIS JOURNAL, 56, 732 (1934); Light, *Z. physik. Chem.*, 122, 414 (1926); Hartley and Leonard, *J. Chem. Soc.*, 95, 34 (1909).

(11) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 369.

the preparation of this compound afforded only the dihydro compound X or unchanged starting material.

Anal. Calcd. for $C_7H_9BrO_6S$: C, 27.92; H, 3.01. Found: C, 27.86, 28.10, 27.88; H, 3.21, 3.12, 3.25.

Ultraviolet Absorption Spectra.—The spectra were determined in purified dioxane with a Beckman Quartz Spectrophotometer, Model DU, using an approximately constant spectral band width of *ca.* 1 mμ. *p*-Benzoquinone (Eastman practical grade) was purified by recrystallization from water and subsequent sublimation at 100°; m. p. 114–115°. 1,4-Thiapyrone-1-dioxide and 2,3-dihydro-1,4-thiapyrone-1-dioxide were both recrystallized from acetic acid and then sublimed *in vacuo* at temperatures slightly below their melting points; the sublimed samples melted at 174–175° and 147–148°, respectively. The wave lengths and extinction coefficients at the absorption maxima are summarized in Table I.

Summary

An improved procedure for the synthesis of 1,4-thiapyrone-1-dioxide, a sulfonyl analog of *p*-benzoquinone, has been described, and the addition reactions of this compound with hydrogen, hydrogen bromide, bromine and butadiene have been investigated. A number of new thiapyrone derivatives have been prepared and characterized. The ultraviolet absorption spectra of 1,4-thiapyrone-1-dioxide and 2,3-dihydro-1,4-thiapyrone-1-dioxide have been determined and compared with the spectrum of *p*-benzoquinone.

PHILADELPHIA, PENNSYLVANIA
RECEIVED DECEMBER 19, 1947

[A CONTRIBUTION OF THE CHEMICAL LABORATORY OF CLARK UNIVERSITY]

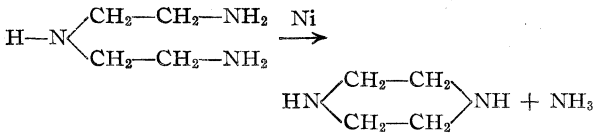
Preparation of Piperazine[1]

BY WILLIAM B. MARTIN AND ARTHUR E. MARTELL

The formation of secondary amines from primary amines by catalytic deamination has been mentioned by Adkins in the case of the formation of dibenzylamine from benzylamine. Also, C. W. Hoerr, *et al.*,[2] have recently prepared secondary aliphatic amines by the same method.

Kyrides[3] has described the preparation of piperazine from ethylenediamine and diethylenetriamine by the same method. The reaction was carried out without solvent at high temperatures (about 235°) in an autoclave. No yields were reported. This reaction has been subjected to considerable investigation in this Laboratory, and it seemed desirable at this time to report on the investigation to supplement the disclosures of the Kyrides patent.

Diethylenetriamine was heated with Raney nickel under various experimental conditions. The results of these experiments are tabulated below. In all cases ammonia was evolved and piperazine was formed according to the reaction



A temperature of about 150° or somewhat higher was found to be most suitable for the reaction. When a low-boiling solvent such as xylene or toluene was used at atmospheric pressure, the reaction proceeded very slowly and little piperazine was obtained. The reaction seemed to be endothermic, and an increase of the rate of heating at atmospheric pressure merely resulted in a more rapid evolution of ammonia. After the reaction had proceeded for a while the temperature would gradually rise to the reflux point of the solvent.

Allowing the ammonia to escape from the reaction mixture does not tend to improve the yield of piperazine. The yields are in general somewhat higher when the reaction is carried out in an autoclave. This may have been due in part to the loss of piperazine through volatilization in the escaping ammonia, since the vapor pressure of piperazine, even at room temperature, is fairly high. At any rate, the reaction does not approach a state of equilibrium. In all cases in which the ammonia was not allowed to escape, very little unreacted diethylenetriamine was isolated. As a further test, piperazine was treated with several molar proportions of alcoholic ammonia in an autoclave at 150° for ten hours in the presence of Raney nickel catalyst. No diethylenetriamine or ethylenediamine was obtained, and substantially all the piperazine was recovered by fractional distillation.

In all the reactions attempted some high-boiling fractions and viscous high molecular weight residues were obtained. These were evidently mixtures of higher "polyalkylene polyamines" which probably resulted from linear deamination of diethylenetriamine to form tetraethylenepentamine and higher homologs. The use of solvent is important in cutting down intermolecular condensation and in improving the yield of piperazine. This was also found to be the case by Pollard, *et al.*,[4] in the preparation of piperazine by the catalytic dehydration of hydroxyethylethylenediamine. In general, the use of a solvent decreased the formation of high boiling tarry residues. Of the solvents employed, moderately high boiling hydrocarbons gave the best results.

Similar results were obtained when the experi-

(1) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wis., 1937, p. 55.

(2) C. W. Hoerr, *et al.*, *J. Org Chem.*, **9**, 201–210 (1944).

(3) Kyrides, U. S. Patent 2,267,686, December 23, 1941.

(4) Pollard, *et al.*, U. S. Patent 2,400,022, May 7, 1946.

TABLE I

YIELDS OF PIPERAZINE UNDER VARIOUS REACTION CONDITIONS

Reagent	G.	Solvent	Temperature, °C.	Time, hr.	Yield of piperazine, g.	Yield %
Diethylenetriamine	103	None	Reflux	10	46	53
Diethylenetriamine		Tetrahydronaphthalene	Reflux	12	53	62
Diethylenetriamine		None	150, autoclave	8	33	38
Diethylenetriamine		Dipentene	160, autoclave	8	63	73
Diethylenetriamine		Xylene	Reflux	7	15	17
Diethylenetriamine		Dioxane	160, autoclave	7	28	32
Ethylenediamine	60	Tetrahydronaphthalene	150, autoclave	6	17	39

ments were repeated using ethylenediamine instead of diethylenetriamine. The formation of piperazine from ethylenediamine probably resulted through preliminary formation of diethylenetriamine which then condensed to form piperazine as described above.

$$2H_2NCH_2CH_2NH_2 \longrightarrow H{-}N\begin{matrix}CH_2{-}CH_2{-}NH_2\\ CH_2{-}CH_2{-}NH_2\end{matrix} + NH_3$$

The piperazine was isolated as white crystals upon distillation and was identified in each case as the dibenzoyl derivative.

Experimental

The experimental conditions are summarized in Table I. Ethylenediamine and diethylenetriamine were purified by drying the commercial material over potassium hydroxide pellets and subsequent fractional distillation. Ethylenediamine was collected between 117 and 119°, while the diethylenetriamine used distilled from 83 to 86° at 3 mm. pressure. All solvents were dried and purified by distillation with the exception of dioxane which was first refluxed with sodium and aniline and then distilled. In each of the reactions listed in Table I, 10 g. of Raney nickel was used.

The reaction mixture was fractionally distilled in each case to remove solvent and separate the products. The piperazine was isolated as colorless prisms, all samples melting within a few degrees of 100°. In each case the dibenzoyl derivative was prepared. The melting points of the dibenzoyl derivatives of each reaction product ranged from 193 to 195°. In all cases, a mixed melting point with an authentic sample of dibenzoylpiperazine showed no depression.

Acknowledgment.—The authors express their appreciation to the F. C. Bersworth Laboratories of Framingham, Massachusetts, for supplying the materials used in this investigation.

Summary

Experimental conditions for the preparation of piperazine by catalytic deamination of diethylenetriamine and of ethylenediamine are described.

WORCESTER 3, MASS. RECEIVED OCTOBER 2, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidine. II. Amino Alcohols Derived from Pyrimidine[1]

BY RAY A. CLARKE AND BERT E. CHRISTENSEN

This laboratory has previously synthesized[2] a number of amino alcohols with this substituent in the 5 position of pyrimidine nucleus, by the application of the Mannich reaction to various 5-acetylpyrimidines.

The usual methods for the preparation of such compounds involve the Mannich reaction on the acetyl derivative or the coupling of the bromomethyl ketone with the desired amine. The bromomethyl ketones are prepared either by direct bromination of the acetyl derivative or by means of the Arndt–Eistert reaction. Whenever possible, this latter method is preferable since it utilizes the acid rather than the less common acetyl derivative of the desired nucleus. Furthermore, there is less possibility of brominating other positions in the molecule and hence fewer separations and characterization problems.

Several 4-pyrimidinecarboxylic acid derivatives have been reported.[3,4,5] In this laboratory, 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid was prepared in 50 to 60% yield from sodio diethyloxalpropionate and benzamidine. The acid in this instance was obtained directly in contrast to the diethyl oxalacetate condensation described by both Pinner[3] and Rappeport.[4]

5 - Methyl - 6 - oxo - 2 - phenyl - 4 - pyrimidinecarboxylic acid I was readily converted through the series of intermediates, 6-chloro-5-methyl-2-phenylpyrimidine-4-carbonyl chloride II → 4-bromoacetyl - 6 - chloro - 5 - methyl - 2 - phenylpyrimidine III → 4-(2-diethylamino-1-oxoethyl)-6-chloro-5-methyl-2-phenylpyrimidine hydrochloride IV to the amino alcohol, 4-(2-diethylamino-

(1) The work described in this paper was made possible by a grant in aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 121, School of Science, Department of Chemistry.

(2) Bruce Graham, A. M. Griffith, C. S. Pease and B. E. Christensen, THIS JOURNAL, **67**, 1294 (1945).

(3) A. Pinner, *Ber.*, **22**, 2615 (1889).

(4) T. Rappeport, *Ber.*, **34**, 1986 (1901).

(5) T. B. Johnson and K. G. Mackenzie, *Am. Chem. J.*, **42**, 365 (1909).

1 - hydroxyethyl) - 6 - chloro - 5 - methyl - 2-phenylpyrimidine hydrochloride V. These reactions were all straight-forward, giving good yields of crystalline intermediates. The free base of the amino ketone as is frequently the case was rather unstable.

Experimental

5-Methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic Acid (I).—An aqueous solution of sodio diethyloxalpropionate was prepared according to the directions of Johnson and Mackenzie[5] except that benzene was substituted for ether as the solvent. To the aqueous solution was added 34.8 g. (0.22 mole) of benzamidine hydrochloride and a solution containing 21 g. (0.445 mole, assuming 85% purity) of sodium hydroxide. The mixture was allowed to stand for one hour. A small amount of solid material was filtered off. The filtrate was acidified with concentrated hydrochloric acid causing a precipitate to form. After cooling in the refrigerator the white- to tan-colored solid was filtered by suction, washed with water, and dried. The yield of acid was 27 g. (53%). This acid was purified for analysis by dissolving in dilute alkali, decolorizing with charcoal, and reprecipitating with hydrochloric acid. The acid melted at 274° with decomposition.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.18; neutral equivalent, 230. Found: C, 62.35; H, 4.24; N, 12.29; neutral equivalent, 228.

6-Chloro-5-methyl-2-phenylpyrimidine-4-carbonyl Chloride (II).—Sixteen grams of I (0.07 mole) and 85.5 g. (0.42 mole) of phosphorus pentachloride were mixed and heated in an oil-bath at 130° for one hour. The mixture on cooling solidified to a solid mass. The acid chloride was extracted from the excess phosphorus pentachloride with warm dry ether. By partial evaporation and cooling of the ether, the acid chloride crystallized and was removed by filtration. The yield of very nearly pure acid chloride was 16 g. (86%). Thirteen and one-half grams of pure product was obtained by recrystallization from 50 ml. of heptane, m. p. 99–101°.

Anal. Calcd. for $C_{12}H_8Cl_2N_2O$: C, 54.0; H, 3.00; N, 10.49; Cl, 26.6. Found: C, 53.5; H, 3.36; N, 10.53; Cl, 26.4.

4-Bromoacetyl-6-chloro-5-methyl-2-phenylpyrimidine (III).—A solution of 12 g. of II (0.045 mole) in 60 ml. of dry benzene was added dropwise with stirring to 200 ml. of a cold benzene solution of diazomethane (0.135 mole). The reaction appeared to take place rapidly as evidenced by the vigorous evolution of nitrogen. The solution was allowed to warm up to room temperature and after standing for about one hour, the benzene was evaporated under reduced pressure. The solid residue was suspended in ether and 25 ml. of 48% hydrobromic acid was added slowly with stirring. The bromomethyl ketone precipitated and nitrogen was evolved. The crude product (13.0 g.) was removed by filtration. Some additional material was obtained by evaporation of the ether. This residue and crude product when combined and recrystallized from heptane, gave 12.6 g. (86% yield) of slightly yellow needles. For analysis a portion of this product was recrystallized twice from heptane after decolorizing with charcoal (m. p. 139–141°).

Anal. Calcd. for $C_{13}H_{10}BrClN_2O$: C, 47.93; H, 3.08; total halogen, 35.4. Found: C, 48.38; H, 3.39; total halogen, 35.4.

6-Chloro-4-chloroacetyl-5-methyl-2-phenylpyrimidine.—The chloromethyl ketone was prepared in a manner similar to the bromomethyl ketone. From 4.00 g. of the acid chloride was obtained 3.48 g. of the crystalline chloromethyl ketone, m. p. 155–156°. This was purified for analysis by recrystallization from heptane.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: N, 9.96; Cl, 25.2. Found: N, 10.02; Cl, 24.8.

6-Chloro-4-(2-diethylamino-1-oxoethyl)-5-methyl-2-phenylpyrimidine Hydrochloride (IV).—Two grams (0.00615 mole) of III was dissolved in 20 ml. of dry benzene and 1.26 ml. (0.0123 mole) of diethylamine were added dropwise. The formation of crystalline diethylamine hydrobromide was very rapid. After standing for fifteen minutes, the mixture was diluted with dry ether and the crystalline solid (0.82 g.) was filtered with suction and washed with dry ether.

Dry hydrogen chloride was passed into the filtrate to precipitate the condensate as the hydrochloride. The solid was filtered with suction and washed with dry ether. The weight of crude product was 2.15 g. This material after purification by three recrystallizations from isopropyl alcohol gave 0.61 g. of crystalline product, m. p. 170–178° (red melt).

Anal. Calcd. for $C_{17}H_{21}Cl_2N_3O$: N, 11.86; total Cl, 20.0; ionizable Cl, 10.0. Found: N, 12.10; total Cl, 20.0; ionizable Cl, 9.84.

6-Chloro-4-(2-diethylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine Hydrochloride (V).—The amino ketone (0.50 g.) was dissolved in 20 ml. of methanol and reduced in a low pressure hydrogenation apparatus at 34 pounds pressure using 30 mg. of platinum oxide catalyst. After about two hours the catalyst was removed by filtration and the solvent evaporated. The residue was taken up in 10 ml. of warm isopropyl alcohol and upon cooling deposited 0.29 g. of white solid. This product partially melted at 160°, resolidified and finally melted at 170–172°.

Anal. Calcd. for $C_{17}H_{23}Cl_2N_3O$: N, 11.80; total Cl, 19.9; ionizable Cl, 9.82. Found: N, 12.15; total Cl, 19.5; ionizable Cl, 9.95.

6-Chloro-4-(2-di-*n*-propylamino-1-oxoethyl)-5-methyl-2-phenylpyrimidine Hydrochloride.—The condensation of the bromomethyl ketone with di-*n*-propylamine was carried out in the same manner as that with diethylamine. From 2.00 g. (0.00615 mole) of the bromomethyl ketone, 1.85 g. of crude amino ketone hydrochloride was obtained. This was recrystallized twice from a minimum amount of isopropyl alcohol yielding 0.85 g. of product, m. p. 170–178° (red melt).

Anal. Calcd. for $C_{19}H_{25}Cl_2N_3O$: N, 11.00; total Cl, 18.6; ionizable Cl, 9.28. Found: N, 11.06; total Cl, 18.3; ionizable Cl, 9.45.

6-Chloro-4-(2-di-*n*-propylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine Hydrochloride.—The reduction to the di-*n*-propylamino alcohol was carried out in the same way as that given for the preparation of the diethylamino alcohol. This amino alcohol crystallized very slowly with low recovery from a minimum of isopropyl alcohol; from 0.50 g. of the amino ketone was obtained 0.20 g. of solid product, m. p. 180–181°.

Anal. Calcd. for $C_{19}H_{27}Cl_2N_3O$: N, 10.94; total Cl, 18.5; ionizable Cl, 9.23. Found: N, 11.33; total Cl, 18.3; ionizable Cl, 9.18.

Summary

4-Bromo(and chloro)-acetyl-6-chloro-5-methyl-2-phenylpyrimidine were prepared by application of the diazomethane synthesis to the acid chloride prepared from 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid.

The amino alcohols, 6-chloro-4-(2-di-*n*-propylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine hydrochloride, 6-chloro-4-(2-diethylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine hydrochloride, were prepared by coupling the bromoacetylpyrimidine with the appropriate secondary amine and subsequent reducing of the amino ketones.

CORVALLIS, OREGON RECEIVED AUGUST 7, 1947

[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Piperidine Derivatives. XVIII. The Condensation of Aromatic Aldehydes with 1-Methyl-4-piperidone

By S. M. McElvain and Kurt Rorig[1]

The preparation of 3-substituted-4-piperidones via the condensation of aromatic aldehydes with 1-methyl-4-piperidone (I) was the purpose of the work here reported. Only two examples of such a condensation appear in the literature: benzaldehyde with 4-piperidone[2] and 1-methyl-4-piperidone.[3] Both of these condensations, however, yielded only the corresponding 3,5-dibenzal-4-piperidones.[4]

When 1-methyl-4-piperidone was treated with benzaldehyde in a 4% solution of potassium hydroxide in 40% ethanol–water (which was just sufficient alcohol to keep the reaction mixture homogeneous) a rapid reaction occurred, but none of the monobenzal derivative (IV) was found among the several reaction products. The main reaction product was 1-methyl-3,5-dibenzal-4-piperidone (VIII) which precipitated from the reaction mixture; in addition to this compound phenyl - bis - 3 - (1 - methyl - 4 - ketopiperidyl)-methane (X) and two apparently similar products with wide melting ranges, which were separated by their solubility differences in dilute ethanol, were obtained by dilution of the reaction mixture with water. In contrast to the dibenzalpiperidone (VIII), the ethylenic bonds of which are rapidly and completely hydrogenated over Adams platinum oxide catalyst, these latter two products absorb hydrogen slowly and incompletely for one ethylenic bond per molecule. Elemental analyses indicate that one of these products, A, is a mixture of the monobenzalpiperidone (IV) and the carbinol (III) and that the other product, B, is a mixture of the monobenzalpiperidone (IV) and the dicarbinol (VI) *or* a mixture of the carbinol (III) and the benzalcarbinol (VII).

In one of the first experiments with this procedure two products, having elemental analyses corresponding to the carbinol (III), were isolated at the point where mixtures A and B appeared in subsequent experiments. These were, undoubtedly, the two racemic forms of III, but neither could be isolated completely free of the other.

When benzaldehyde was allowed to react with 1-methyl-4-piperidone in a 4% solution of potassium hydroxide in 55–60% ethanol–water solvent, 1-methyl-3-benzal-4-piperidone (IV) *slowly* precipitated from the solution.[5] It was the sole product of the reaction and was obtained in 61% yield.

Since the dibenzalpiperidone (VIII) was rapidly precipitated from a 40% ethanol–water solvent in which it is insoluble and not formed in the 60% ethanol–water solvent in which it is quite soluble, it appears that the reaction of the piperidone (I) with benzaldehyde in the presence of alkali is best represented by a series of equilibria from which either the mono- or dibenzal derivative may be obtained, depending on the solubility of the product in the reaction solvent. This conclusion is further indicated by the fact that either of the carbinol mixtures A and B, the two racemic forms of III, as well as the dibenzal derivative (VIII), which were formed in 40% ethanol–water solvent, were converted to the monobenzal derivative (IV) when allowed to stand in a 4% potassium hydroxide solution in 60% ethanol–water. The conversion of VIII to IV amounts to 78%.

It is a curious fact that the monobenzal derivative IV does not precipitate from the 40% ethanol–water solvent in which it is as insoluble as is the dibenzal derivative VIII. The most obvious explanation of this fact is that the series of equilibria involved in the transformation of II (or IIa) → VIII are attained more rapidly than that of II → IV. This is indicated by the rapid (see Table I) precipitation of VIII from the 40% ethanol–water solvent and the consequent shift of the reaction in this direction; when VIII is kept in solution by the 60% ethanol–water solvent, there is opportunity for the slower change of II (or IIa) into IV and the latter compound precipitates over a period of several days (see Table I). The mixtures of IV with the carbinols, which are present in the 40% ethanol–water solvent and are precipitated by dilution with water, may be molecular complexes that prevent the precipitation of IV.

It seems likely that the benzal derivatives IV and VIII are formed from the ions IIa and VIIa rather than from the direct dehydration of the carbinols III and VI. The carbinol mixtures were completely resistant to dehydration with hydrogen chloride in absolute ethanol, and when refluxed with acetic anhydride in pyridine, or with acetic anhydride containing *p*-toluenesulfonic acid, were converted to a product, the analyses and molecular weight of which approximates the structure IX, and which corresponds to the dodecahydrotriphenylene formed from cyclohexanone[6]

(1) Eli Lilly and Company Fellow, 1945–1947.

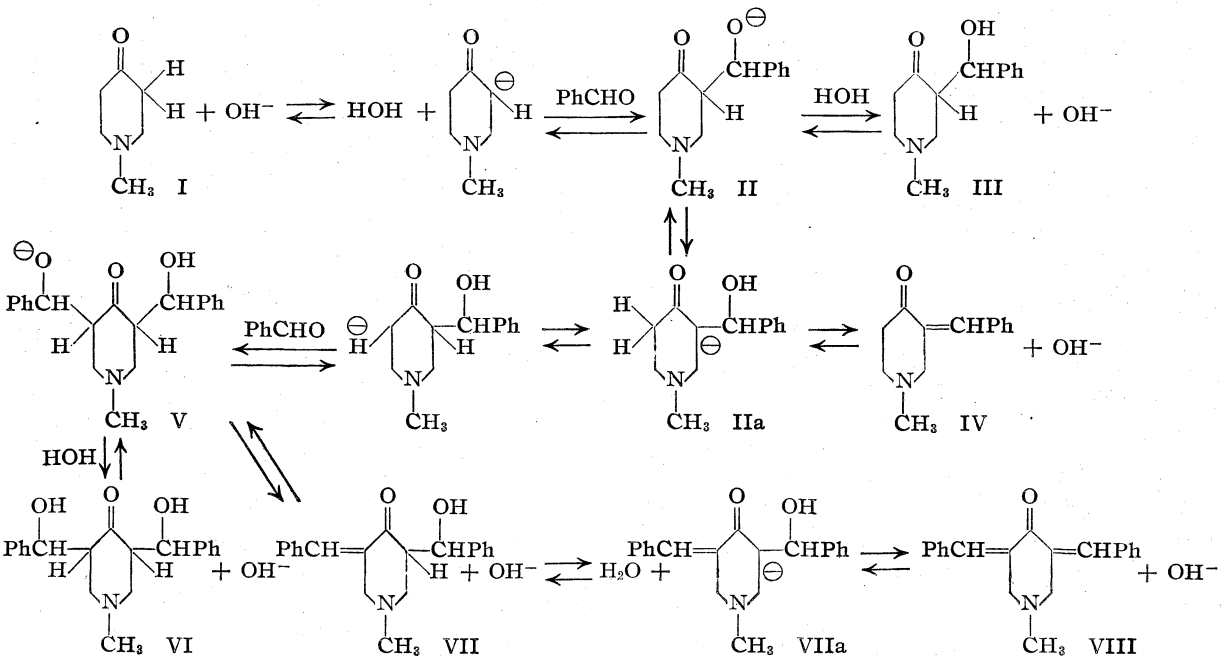
(2) Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920); Kuettel and McElvain, This Journal, **53**, 2692 (1931).

(3) Howton, *J. Org. Chem.*, **10**, 279 (1945).

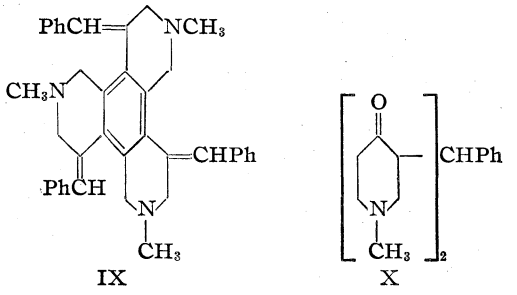
(4) Similarly tropinone has yielded the dipiperonal derivative [Robinson, *J. Chem. Soc.*, **111**, 762 (1917)] and the dibenzal derivative despite numerous attempts to prepare the monobenzal derivative [Willstätter, *Ber.*, **30**, 731, 2681, 2716 (1897)].

(5) Poggi and Gaustella, *Gazz. chim. ital.*, **61**, 405 (1931), have reported the formation of 2-benzalcyclohexanone from benzaldehyde and cyclohexanone in a 4% aqueous solution of potassium hydroxide.

(6) Mannich, *Ber.*, **40**, 154 (1907); Kunze, *ibid.*, **59**, 2086 (1926); Triebs, *ibid.*, **61**, 684 (1928).



and to the *sym*-tris-2,3-thiocoumaronobenzene formed from thioindoxyl by the action of acetic anhydride with zinc chloride.[7]



The fourth product X isolated from the base-catalyzed condensation of benzaldehyde with the piperidone I is the result of the condensation of two moles of the piperidone with one of the aldehyde. The yields of X vary with the ratio of reactants as may be seen from Table I, which summarizes the results of typical runs in a 4% potassium hydroxide solution in various solvents.

TABLE I

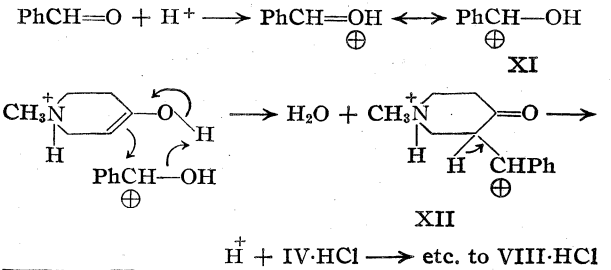
BASE-CATALYZED REACTION OF BENZALDEHYDE WITH 1-METHYL-4-PIPERIDONE (I)

PhCHO/I, moles	Solvent	Yield of VIII, %	Yield of mixtures A + B, %	Yield of IV, %	Yield of X, %
1.0	40% EtOH	44[a]	36	...	8
2.0	40% EtOH	66	28	...	0.3
1.0	60% EtOH	...	..	61[b]	..
0.12	12% EtOH	45	16	...	11
1.0	Water[c]	25	30	...	19

[a] Precipitated in fifteen minutes; the weaker base, sodium bicarbonate, gave similar yields but required several days to produce them. [b] About five days required for this amount of IV to precipitate. [c] Benzaldehyde added dropwise over a period of 2.5 hours to an aqueous solution of potassium hydroxide and the piperidone.

(7) Dalgliesh and Mann, *J. Chem. Soc.*, 910 (1945).

The condensation of benzaldehyde with the piperidone (I) may also be effected by acid catalysis. This reaction was carried out in absolute ethanol saturated with hydrogen chloride and the sole product was the hydrochloride of VIII, which precipitated in 86% yield over a period of three days. In this case it seems certain that the carbinols III or VI *are not* intermediates in the formation of VIII, because the mixtures (A and B from the base-catalyzed reaction) containing these carbinols remain unchanged in the medium used for the acid-catalyzed reaction. The reaction mechanism, therefore, cannot permit the formation of a carbinol. The simultaneous coupling and loss of water between the enolic form[8] of the piperidone and the carbonium ion (XI) to produce the car-



(8) Although the amount of the enolic form of the ketone as well as the rate of its formation may be increased by the acidic medium [*cf.* Hauser and Breslow, THIS JOURNAL, **62**, 2391 (1940)]; Schwarzenbach and Wittwer, *Helv. Chim. Acta*, **30**, 659 (1947); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, p. 237], the concentration of the enolic form may well be the limiting factor that determines the over-all rate of reaction.

bonium ion XII, which then passes into a benzal derivative, would seem to rationalize the acid-catalyzed condensation of benzaldehyde with I.

The solubilities of the hydrochlorides of IV and VIII in absolute ethanol are the reverse of those of IV and VIII in the 60% ethanol–water medium used in the base-catalyzed reaction. The hydrochloride of IV is soluble in absolute ethanol while the hydrochloride of VIII is quite insoluble. If a solvent in which the hydrochloride of I is soluble and the hydrochloride of IV is insoluble could be found, it might be possible to prepare IV by an acid-catalyzed reaction; as yet such a solvent has not been found.

Condensation of Other Aldehydes with I.—The study of the condensation of benzaldehyde with I was intended to serve as a model for the determination of the proper conditions for the condensation of other aldehydes, particularly the quinoline aldehydes, with this piperidone. Actually the benzaldehyde condensation proved to be the most complex from the standpoint of the number of reaction products. With the other aldehydes only those products corresponding to the mono- and dibenzal derivatives IV and VIII were obtained; none of the carbinols or the bispiperidylarylmethanes, corresponding to X, were found.

The course of the condensation of quinoline-2 and 4-aldehydes with I showed a curious dependence on the amount of alkali used to catalyze the reaction. In a 4% solution of potassium hydroxide in ethanol–water, in which the molar ratio of alkali to I was 3.5:1, the 2-aldehyde gave a dark oil from which only a 9% yield of the diquinolinal derivative could be isolated. However, when a 0.25% solution of the alkali, containing an alkali to piperidone ratio of 0.54 was used, a 39% yield of the diquinolinol derivative and a trace of the monoquinolinol derivative were obtained. The quinoline-4-aldehyde yielded either the mono- or diquinolinol derivative depending on the amount of alkali used. Both of these quinoline aldehydes gave useless brown tars when hydrogen chloride in absolute ethanol was used as the reaction medium.

Table II

Condensation of Certain Aldehydes, ArCHO, with 1-Methyl-4-piperidone (I)

Ar is	ArCHO/I, moles	KOH/I, moles	Yield of mono—al, %	Yield of di—al, %[b]
2-Quinolyl	2	3.55	0	9
2-Quinolyl	2	0.54	Some[a]	39
4-Quinolyl	1	1.37	95	..
4-Quinolyl	2	0.73	Some[a]	79
α-Naphthyl	1	1.78	Some[a]	80
α-Naphthyl	1	0.27	Some[a]	88
o-Chlorophenyl	1	1.42	Some[a]	74
o-Chlorophenyl	2	1.78	0	90
o-Chlorophenyl	1	0.27	Some[a]	82

[a] Percentage yield not given since this product was not obtained pure; analyses indicated it to be mainly the mono—al derivative. [b] Yield based on amount of aldehyde used.

Neither benzaldehyde, o-chlorobenzaldehyde or α-naphthaldehyde showed any variations in reaction products with variations in the amount of alkali used to effect the condensations.

The condensations of these aldehydes with I in the presence of varying amounts of potassium hydroxide are summarized in Table II. In each case water containing sufficient ethanol to make the initial reaction mixture homogenous was used as the solvent.

Experimental

Methyl-di-(β-carbethoxyethyl)-amine.—A cooled one-liter reaction bomb was filled with 432 ml. (400 g.) of ethyl acrylate (containing 0.25% hydroquinone inhibitor) and 86 ml. (62 g.) of liquefied methylamine. Crystallization occurred upon stirring these chilled reactants. The cover was quickly secured since the temperature rose to around 80° within five minutes. The reaction vessel was heated in a water-bath at 60–70° for one hour. The bomb was cooled, opened, and the reaction mixture distilled. The fraction boiling at 110–119° (mainly at 118–119°) at 0.5 mm. was methyl-di(β-carbethoxyethyl)-amine; it weighed 367 g.

1-Methyl-3-carbethoxy-4-piperidone Hydrochloride.—Although this compound could be prepared in good yields (80%) by the cyclization of methyl-di-(β-carbethoxyethyl)-amine with sodium ethoxide,[9] the following procedure using sodium hydride was found more satisfactory.

Into a three-liter, three-necked flask equipped with a Hershberg stirrer, dropping funnel, and a reflux condenser, were placed 800 ml. of dry thiophene-free benzene and 54 g. of sodium hydride. After flushing the apparatus with nitrogen, 30 g. of methyl-di-(β-carbethoxyethyl)-amine was added to the vigorously stirred suspension of sodium hydride in benzene.

Five minutes after adding two milliliters of absolute ethanol the reaction started as evidenced by the evolution of hydrogen. When, after five minutes more, the reaction mixture was noticeably warm, 201 g. of methyl-di-(β-carbethoxyethyl)-amine was added at such a rate as to keep the mixture refluxing briskly. During this addition of the di-ester the appearance of the reaction mixture gradually changed from a dark-gray fluid to an almost white paste. To facilitate stirring an additional 250 ml. of benzene was added after addition of the di-ester was completed. The mixture then was stirred and refluxed with external heating until no more hydrogen was evolved.

A crock of crushed ice was placed under the reaction flask to cool the mixture while 135 g. of glacial acetic acid was added. To this very slightly acid solution, cooled to 5°, 123 ml. of water was added to precipitate sodium acetate trihydrate. This salt was filtered off and washed with 350 ml. of benzene.

The combined filtrates were distilled to remove ethanol and water. After 600 ml. of distillate had been collected, a refractive index showed that pure benzene was distilling over. The residual solution of 1-methyl-3-carbethoxy-4-piperidone in benzene was diluted with 500 ml. of absolute ether. This solution then was cooled in an ice-salt-bath and treated with dry hydrogen chloride until the 1-methyl-3-carbethoxy-4-piperidone hydrochloride had precipitated. The yield of product softening at 115°, melting at 125–128°, was 201 g. (91%).

1-Methyl-4-piperidone (I).—To a one-liter flask containing 350 ml. of 20% hydrochloric acid was added 86.0 g. of 1-methyl-3-carbethoxy-4-piperidone hydrochloride. After refluxing for one hour, the ferric chloride reagent gave no coloration. The solution was evaporated to dryness on a steam-bath at 10 mm. pressure. The solid product, heated at 100° for four hours at 0.1 mm. and further dried over solid potassium hydroxide for twenty-four hours, weighed 57.7 g., m. p. 80–120°. Although this

(9) Prill and McElvain, This Journal, 55, 1233 (1933).

melting range goes above that of the pure compound, 0.45 g. of crude material dissolved in 90 ml. of hot acetone gave 0.40 g. of pure compound melting at 93–95°. Other samples of the crude piperidone hydrochloride showed even higher upper limits of the melting points than that mentioned above, yet this apparently impure material always gave good yields of sharp melting product when recrystallized. Thus the crude material can be used successfully for further work without recrystallization.

To 37.0 g. of crude 1-methyl-4-piperidone hydrochloride dissolved in 50 ml. water was added 14 g. of solid potassium hydroxide. Then 20 g. of potassium carbonate was added to salt out the free amine. This basic solution was extracted with seven 100-ml. portions of ether. The ethereal solution was dried overnight with anhydrous sodium sulfate and the ether distilled. The higher boiling residue was distilled at 19 mm. pressure. A forerun weighing 1.7 g. was collected to 67°. The 1-methyl-4-piperidone fraction boiled from 67–69° and weighed 18.7 g.

The phenylhydrazone of this piperidone melted at 100–104°.[10]

The semicarbazone, prepared in the usual manner, did not precipitate from the reaction medium until salted out with potassium carbonate. After filtering and washing with a small amount of ice water it melted at 182–184°; recrystallization from ethyl acetate did not raise this m. p.

Anal. Calcd. for $C_7H_{14}N_4O$: C, 49.39; H, 8.29. Found: C, 48.85; H, 8.04.

The 2,4-dinitrophenylhydrazone hydrochloride was also made, m. p. 249° d. The free base was obtained by dissolving 1.0 g. of the hydrochloride in 75 ml. water, neutralizing with sodium bicarbonate, filtering, and recrystallizing from ethyl acetate. The orange prisms melted 172.0–173.5°.

Anal. Calcd. for $C_{12}H_{15}N_5O_4$: N, 23.88. Found: N, 24.0.

The Condensation of Benzaldehyde with the Piperidone (I) in 40% Ethanol.—To a solution of 7.5 g. of 1-methyl-4-piperidone and 7.0 g. of freshly distilled benzaldehyde in 69 ml. of 40% ethanol was added 3.0 g. of potassium hydroxide. The flask was then stoppered and shaken for fifteen minutes. The yellow solid that precipitated then was filtered off and the filtrate diluted with 75 ml. water. The white precipitate from the diluted reaction medium was labeled mixture A. It weighed 1.31 g. and melted at 115–150° dec.

Anal. Found: C, 76.42; H, 7.15; N, 6.59.

These analytical data indicate mixture A to be composed of the carbinol (III) and the monobenzal derivative (IV) (see below for the elemental content of these compounds).

The yellow solid which had been filtered from the 40% ethanol solution was dissolved in 250 ml. of hot 5% hydrochloric acid. Upon cooling 4.93 g. of fine yellow needles of **1-methyl-3,5-dibenzal-4-piperidone hydrochloride,** m. p. 243.5–244.5°, was obtained. This compound has been reported to melt at 240–241°.[3]

Anal. Calcd. for $C_{20}H_{20}ClNO$: Cl, 10.9. Found: Cl, 10.8.

The 1-methyl-3,5-dibenzal-4-piperidone was obtained in quantitative yield from its hydrochloride by dissolving the salt in hot 50% ethanol, adding sufficient sodium bicarbonate solution to neutralize the hydrogen chloride, cooling and filtering. After two recrystallizations from dilute alcohol, the canary-yellow **1-methyl-3,5-dibenzal-4-piperidone** melted at 116.5–117.5°.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.04; H, 6.39; N, 4.76.

This compound has been previously reported by Howton[3,11] to melt 117.2–118.2°.

The acidic filtrate from which the dibenzal piperidone hydrochloride had been obtained was neutralized with sodium bicarbonate to precipitate 2.92 g. of the white mixture B, m. p. 115–160° dec.

Anal. Found: C, 75.16; H, 6.93; N, 5.85.

These analytical data indicate mixture B to be composed of IV (see below) and the dicarbinol (VI) (calcd. C, 73.9%; H, 7.1%; N, 4.3%) *or* of the carbinol (III) (see below) and the benzalcarbinol (VII) (calcd. C, 78.3%; H, 6.88%; N, 4.53%).

The dilute alkaline reaction mixture from which mixture A had been obtained deposited massive white rosettes on standing three days.[12] The amount increased until after two weeks 0.82 g. of **phenyl-bis-3-(1-methyl-4-keto-piperidyl)-methane,** m. p. 221–225°, was filtered off. After two recrystallizations from dilute ethanol an analytical sample melted 233–234°.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34. Found: C, 72.23; H, 7.95.

Phenyl-3-(1-methyl-4-keto-piperidyl)-carbinol (III).—One of the first reactions carried out as described above yielded a product the analysis of which corresponded to phenyl-3-(1-methyl-4-keto-piperidyl)-carbinol. Instead of mixture A, 1.90 g. of white solid, m. p. 115–126°, was obtained. On attempted recrystallization from dilute ethanol, it repeatedly precipitated as an oil.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.03; H, 7.42.

The hydrochloride of this compound was made by dissolving it in a small quantity of absolute ethanol, diluting with absolute ether, and treating the solution with hydrogen chloride. After decanting the supernatant liquid from the precipitated salt, it was redissolved in ethanol and reprecipitated with ether. This was repeated twice to obtain an analytical sample melting at 230–235° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: Cl, 13.9. Found: Cl, 14.1.

At the place where mixture B was obtained in the previously described reaction, 3.09 g. of a product melting at 90–120° d. precipitated. The hydrochloride, made as described above, melted at 243–245° dec.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; Cl, 13.9. Found: C, 60.80; H, 7.14; Cl, 14.0.

The melting point of a mixture of the carbinol hydrochloride melting at 243–245° with that melting at 230–235° was 110–160° dec. It was concluded that these carbinols are the two racemic forms, each contaminated with a small amount of the other.

None of the later experiments yielded either of these carbinols; only the mixtures A and B, with analyses approximating those given above, were obtained.

Neither of these carbinols were affected when allowed to stand in solution in absolute ethanol saturated with hydrogen chloride. Both yielded the same product, m. p. 187–189° d., with acetic anhydride as that obtained in the following experiment with mixture B.

A solution of 4.83 g. of mixture B in 32 ml. of pyridine and 35 ml. of acetic anhydride was refluxed five hours. The brown solution then was poured into 400 ml. of ice-water to hydrolyze the acetic anhydride. Upon neutralization with sodium bicarbonate a dark, tacky oil precipitated. After standing four days, the oil solidified so that it could be filtered off. The crystalline material weighed 1.07 g. It was recrystallized four times from dilute ethanol to give 0.81 g. of a white solid, m. p. 187–189° dec. This compound rapidly darkened on exposure to light and air.

The elemental content and molecular weight of this product approximated that of the cyclic dehydration trimer (IX) of the benzalpiperidone.

(10) *Cf.* Cook and Reed, *J. Chem. Soc.*, 401 (1945).

(11) Although Howton reported correct nitrogen and hydrogen analyses for his 1-methyl-3,5-dibenzal-4-piperidone, the carbon values were consistently 2% lower than the theoretical value.

(12) On the two occasions that a very small amount of 1-methyl-3-benzal-4-piperidone was obtained from such a reaction, it crystallized from the dilute alkaline reaction medium one day after filtering off mixture A. The monobenzal derivative was thus removed before the dipiperidyl methane started to precipitate.

Anal. Calcd. for $C_{39}H_{39}N_3$: C, 85.21; H, 7.15; mol. wt., 550. Found: C, 84.87; H, 6.72; mol. wt., 504 (Rast).

Mixture A, when refluxed with acetic anhydride and pyridine as described above, gave a 15% yield of this product, m. p. 187–189° dec.

The Condensation of Benzaldehyde with the Piperidone (I) in 60% Ethanol. 1-Methyl 3-benzal-4-piperidone (IV).—To a solution of 1.06 g. (0.01 mole) of benzaldehyde and 1.13 g. (0.01 mole) of 1-methyl-4-piperidone in 45 ml. of 60% ethanol was added 0.3 g. of potassium hydroxide. The solution became yellow almost at once. After standing one day a very small quantity of oil appeared. The solution was heated slightly to dissolve this oil which did not reappear on cooling. No further visible reaction occurred until a seed of 1-methyl-3-benzal-4-piperidone was added. Two days after adding this seed 0.78 g. of 1-methyl-3-benzal-4-piperidone, m. p. 213–215°, was filtered off. On successive days three additional crops totaling 0.27 g., and melting at 214–217° were obtained. The mother liquor then was diluted with 18 ml. of water and decanted from 0.16 g. of oil. This oil, when it solidified, melted at 85–105° and could not be recrystallized from dilute ethanol. One day after the oil had been removed from the diluted reaction mixture another 0.17 g. of product, m. p. 216–219° was obtained. The total yield of crystalline product was 1.32 g. (61%). An analytical sample, twice recrystallized from water–ethanol solvent, m. p. 224–225°, had a faint yellow color.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.30; H, 7.38.

The benzalpiperidone (IV) was also obtained from mixtures A and B, and from the dibenzalpiperidone (VIII) in the following manner.

To 0.36 g. of mixture A in 17.5 ml. of 54% ethanol was added 0.2 g. of potassium hydroxide. Within one day crystals began to deposit. After standing for two weeks at room temperature 0.18 g. (53%) of IV, m. p. 215–218°, was obtained.

A solution of 0.50 g. of mixture B and 0.2 g. of potassium hydroxide in 17.5 ml. 60% ethanol stood for one week at room temperature without precipitating the monobenzal piperidone. The solution was then heated at reflux for ten minutes and allowed to stand at room temperature again. A week after heating the mixture, crystals of IV began to separate. After one month 0.13 g. (28%) of monobenzalpiperidone, m. p. 214–216°, was obtained.

A solution of 0.48 g. of pure 1-methyl-3,5-dibenzal-4-piperidone (VIII), 0.19 g. of 1-methyl-4-piperidone and 1.0 g. of potassium hydroxide in 26 ml. of 60% ethanol was prepared. After standing for three days the solution was refluxed for five minutes while 4.0 ml. of hot water was added. After seventeen days of standing at room temperature 0.23 g. of IV, m. p. 211–215°, was filtered off. A second crop weighing 0.07 g. was obtained eighteen days after the first crop was filtered off. The total yield was 45% of that theoretically possible from the dibenzalpiperidone and the added 1-methyl-4-piperidone. However, the yield is 78% of theoretical, if based on the decomposition of dibenzalpiperidone only.

The Condensation of Benzaldehyde with the Piperidone I with Ethanolic Hydrogen Chloride.—Benzaldehyde (1.06 g.) and 1-methyl-4-piperidone (1.13 g.) were dissolved in 15 ml. of absolute alcohol. Anhydrous hydrogen chloride was passed in until the solution was saturated. The flask was allowed to stand at room temperature for two days during which time a crystalline deposit slowly formed. The hydrochloride of the dibenzal derivative so obtained melted 234–240° and weighed 1.40 g. (86%) (see above for analytical data of this salt).

1-Methyl-3,5-dibenzyl-4-piperidone.—In an apparatus for hydrogenation at atmospheric pressure[13] 5.14 g. of 1-methyl-3,5-dibenzal-4-piperidone hydrochloride in 60 ml. of ethanol was hydrogenated over 0.48 g. of Adams platinum oxide catalyst. Although the dibenzalpiperidone was not completely soluble in the ethanol, the hydrogenated product was and, consequently, the insoluble material disappeared, as the hydrogenation proceeded. After the theoretical amount of hydrogen was taken up (fifteen minutes), the catalyst was filtered off, the solvent evaporated, and the product neutralized with sodium bicarbonate. The brown, oily product did not crystallize and was dissolved in petroleum ether (b. p. 60–68°)–benzene solution (three volumes of benzene to two volumes of petroleum ether) and filtered through a twenty-five centimeter column of activated aluminum oxide. Upon evaporation of the filtrate 2.45 g. of oily, white crystals was obtained. Since these crystals were soluble at room temperature in all common organic solvents, they were triturated with 10 ml. of ice-cold petroleum ether (b. p. 40–60°) to give 1.31 g. of product m. p. 76–79°. An analytical sample was obtained by dissolving the crystals in a minimum amount of petroleum ether (b. p. 40–60°), then cooling the solution to −10°. After three such recrystallizations the melting point of 1-methyl-3,5-dibenzyl-4-piperidone was 84.0–85.5°.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 82.12; H, 7.62.

The Condensation of Other Aldehydes with I. Quinoline-2-aldehyde.—To 1.58 g. (0.01 mole) of quinoline-2-aldehyde[14] and 0.56 g. (0.005 mole) of 1-methyl-4-piperidone dissolved in 51 ml. of 30% aqueous ethanol, 0.15 g. (0.002 mole) of potassium hydroxide was added. The solution became yellow immediately and a precipitate appeared within one minute. After shaking the solution for twenty-five minutes, a single lump of semi-solid product was removed. When dried this yellow material weighed 1.87 g. and melted at 143–147°. The residual reaction liquid was diluted with 60 ml. of water to obtain a second crop (0.04 g.) of yellow solid, m. p. 140–146°. This reaction product was recrystallized from 80 ml. of 95% ethanol to give 0.72 g.[15] of long slender yellow needles of **1-methyl-3,5-di-(2-quinolinal)-4-piperidone,** m. p. 153–154°. A thrice recrystallized sample, m. p. 158–159°, was used for analyses.

Anal. Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41. Found: C, 79.72; H, 5.24.

The filtrate from this recrystallization was evaporated to dryness and the residue redissolved in 30 ml. of benzene. Hot petroleum ether (b. p. 60–68°) was added to the boiling benzene and the solution was cooled. In this manner 0.54 g. of tan powder, m. p. 150–160°, was obtained. The purity of this product was not improved by recrystallization, since the contaminant seemed to be as soluble in various solvents as the main portion. Furthermore, recrystallization was discouraged by the heat-sensitivity of the product. An elemental analysis suggested that it was mainly a mono-quinolinal piperidone.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.32; H, 5.28.

Quinoline-4-aldehyde.—To 5.73 g. (0.03 mole) of quinoline-4-aldehyde hydrate[16] and 3.70 (0.03 mole) of 1-methyl-4-piperidone, dissolved in 75 ml. of 67% aqueous ethanol, 2.5 g. (0.05 mole) of solid potassium hydroxide was added. This solution was shaken for fifteen minutes, diluted with 200 ml. of water, then shaken for twenty minutes and diluted with another 200 ml. of water. After a final ten minutes of shaking the light-tan solid was filtered and dried. It weighed 7.36 g. (95%) and melted at 190–203°. A 6.05-g. sample of this crude product was triturated with a few ml. of cold benzene,

(13) Fieser and Hershberg, This Journal, **60**, 944 (1938).

(14) Kaplan, *ibid.*, **63**, 2654 (1941).

(15) This large loss on recrystallization is due partly to decomposition. For example, when 0.58 g. of pure 1-methyl-4,5-di-(2-quinolinal)-4-piperidone was recrystallized from 45 ml. of 95% ethanol only 0.46 g. was recovered. The filtrate, when evaporated to dryness, gave 0.09 g. of a brown powder which was much more ethanol-soluble and higher-melting than the di-quinolinalpiperidone.

(16) Kwartler and Lindwall, This Journal, **59**, 524 (1937).

filtered, and dried. The **1-methyl-3-(4-quinolinal)-4-piperidone** thus obtained weighed 5.96 g. and melted 222–225° dec. For an analytical sample this triturated product was recrystallized from 95% ethanol. It melted at 250–252° dec. when heated from room temperature; when introduced at a bath temperature of 240°, however, it melted at 252–253°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 76.06; H, 6.04.

A mixture of 0.42 g. (0.0037 mole) of 1-methyl-4-piperidone, 1.30 g. (0.0074 mole) of quinoline-4-aldehyde, and 0.15 g. (0.002 mole) of potassium hydroxide in 50 ml. of 30% aqueous ethanol was shaken for twenty minutes. The yellow solid which formed was filtered off and recrystallized from hot methanol. The first crop of long yellow needles of **1-methyl-3,5-di-(4-quinolinal)-4-piperidone** weighed 0.94 g., m. p. 198–200°. A second crop (0.20 g.) of this same product, m. p. 193–196°, was obtained by diluting the ethanol filtrate with a few ml. of water. On further dilution a third crop of crystals weighing 0.09 g. was obtained. The latter product softened at 190° but the major portion did not melt until 245°. This behavior indicates this product to be mainly the mono-4-quinolinal derivative described above.

An analytical sample of **1-methyl-3,5-di-(4-quinolinal)-4-piperidone**, m. p. 199–200°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41. Found: C, 79.85; H, 5.41.

***o*-Chlorobenzaldehyde.**—To 1.75 g. (0.01 mole) of freshly distilled *o*-chlorobenzaldehyde and 1.40 g. (0.012 mole) of 1-methyl-4-piperidone in 26 ml. of 62% aqueous ethanol was added 1.0 g. of solid potassium hydroxide. After shaking for fifteen minutes the crude, yellow **1-methyl-3,5-di-(*o*-chlorobenzal)-4-piperidone** was filtered off. Recrystallization from ethanol gave 1.63 g. (73%) of yellow needles, m. p. 152–155°. A thrice recrystallized sample, m. p. 152–154°, was used for analytical purposes.

Anal. Calcd. for $C_{20}H_{17}Cl_2NO$: C, 67.04; H, 4.78. Found: C, 67.25; H, 4.73.

The **hydrochloride** of 1-methyl-3,5-di-(*o*-chlorobenzal)-4-piperidone, after recrystallization from an ethanol–ether mixture, melted at 227–229° d.

Anal. Calcd. for $C_{20}H_{17}Cl_2NO \cdot HCl$: ionic Cl, 9.0. Found: ionic Cl, 9.0.

The reaction mixture from which the dibenzal derivative had been filtered was diluted with 60 ml. of water to precipitate 0.764 g. of an almost white powder, m. p. 120–135°. After five recrystallizations from ethanol–water, this product melted at 150–155°. An elemental analysis indicated that this somewhat impure sample was mainly **1-methyl-3-(*o*-chlorobenzal)-4-piperidone.**

Anal. Calcd. for $C_{18}H_{14}ClNO$: C, 66.24; H, 5.99. Found: C, 65.93; H, 5.34.

α-Naphthaldehyde.—The condensation of this aldehyde with the piperidone I was carried out in a manner similar to that of *o*-chlorobenzaldehyde. The crude, yellow dinaphthal derivative, m. p. 160–170°, was obtained in 80% yield. Recrystallization from ethanol gave an analytical sample of **1-methyl-3,5-di-(α-naphthal)-4-piperidone**, m. p. 173–175°.

Anal. Calcd. for $C_{28}H_{23}NO$: C, 86.34; H, 6.09. Found: C, 86.74; H, 6.22.

A small amount of an ivory-colored powder, m. p. 177–181°, the analyses of which indicated it to be an impure mononaphthal derivative, also was obtained. Variations in the relative amounts of potassium hydroxide used in the condensations of *o*-chlorobenzaldehyde and α-naphthaldehyde did not materially affect the nature of the reaction products (see Table II).

Summary

The base-catalyzed condensation of benzaldehyde with 1-methyl-4-piperidone has been found to yield either the mono or the dibenzal derivative depending on the nature of the solvent used for the reaction. In addition to these products, other materials corresponding to the phenylpiperidyl carbinols and mixtures of these types with the benzal derivative, as well as bis-dipiperidylphenylmethane, have been isolated.

The base-catalyzed condensation is shown to be reversible by the conversion of the carbinol-containing mixtures, as well as the dibenzal derivative, into the monobenzal derivative.

The acid-catalyzed condensation of benzaldehyde and the piperidone yields only the dibenzal derivative. The carbinol is shown not to be an intermediate in this condensation.

Quinoline-4-aldehyde yields either the mono- or diquinolinal derivative of the piperidone depending on the amount of alkali used to effect the condensation. *o*-Chlorobenzaldehyde and α-naphthaldehyde yields only the dibenzal derivative regardless of the amount of alkali used. Similarly quinoline-2-aldehyde yields mainly a rather unstable diquinolinal derivative.

MADISON, WISCONSIN RECEIVED JANUARY 2, 1948

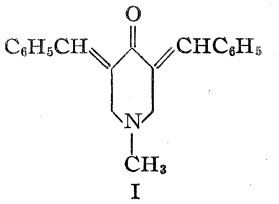
[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Piperidine Derivatives. XIX. Esters of Substituted 4-Piperidinols

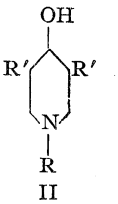
By S. M. McElvain and Kurt Rorig[1]

In the seventh paper of this series the benzoates and *p*-aminobenzoates of a series of 1-alkyl-4-piperidinols (II, R′ = H) were described.[2] The piperidinols were not isolated but were directly acylated in the form of their hydrochlorides, which were obtained by the hydrogenation of the corresponding 1-alkyl-4-piperidone hydrochlorides over Adams platinum oxide catalyst. In the present paper the preparation of 1-methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidinol and the three inactive stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols and certain of their esters are described.

The 1-alkyl-4-piperidinols were obtained in excellent yields by the hydrogenation of the corresponding piperidones over Raney nickel. These piperidinols were converted to the diphenylacetates and 1-methyl-4-piperidinol to the N-phenylcarbamate for pharmacological testing. The benzilic esters could not be prepared either by the direct interaction of benzilic acid with the piperidinol or with the corresponding 4-chloropiperidine according to the procedure of Horenstein and Pählicke.[3]



I



II

There are four theoretically possible stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols (II, R = CH_3; R′ = $C_6H_5CH_2$): *d*, *l*, and two *meso* forms. The hydrogenation of 1-methyl-3,5-dibenzal-4-piperidone[4] (I) under various conditions with platinum, nickel and copper chromite catalysts has yielded three different dibenzylpiperidinols, corresponding to the racemic and the two meso forms, as well as a product in which both benzene nuclei are hydrogenated. The separation of these hydrogenation products was difficult and recrystallization losses were high. The proportion of products from any one hydrogenation varied with the temperature, but in no case was the yield of any one more than 68% of the theoretical. The melting points and analyses of these piperidinols together with the catalysts and conditions under which they were produced are summarized in Table I.

Table I

Hydrogenation Products of 1-Methyl-3,5-dibenzal-4-piperidone (I)

Compound	M. p., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H	Catalyst
1-Methyl-3,5-dibenzyl	155–157	$C_{20}H_{25}NO$	81.31	8.33	81.30	8.60	Ni,[a] $CuCrO_3$[b]
4-piperidinol	183–184	$C_{20}H_{25}NO$	81.31	8.33	81.21	8.12	Pt,[c] Ni[d]
	177–178	$C_{20}H_{25}NO$	81.31	8.33	80.97	8.35	$CuCrO_3$[e]
1-Methyl-3,5-di-(hexahydrobenzyl)-4-piperidinol	176–178	$C_{20}H_{37}NO$	78.11	12.13	78.36	12.03	Ni[f]

[a] At 80° under 160 atmospheres of hydrogen for 5 hours. [b] At 200° under 160 atmospheres for 2.5 hours. [c] At 20–25° under 1 atmosphere for 1.5 hours. [d] At 60° under 105 atmospheres for 1 hour. [e] At 215° under 145 atmospheres for 5 hours. [f] At 80° under 160 atmospheres for 5 hours, followed by 180° for 3.5 hours.

With the platinum catalyst the carbon to carbon double bonds were hydrogenated in ten to fifteen minutes; the carbonyl group required an additional one to two hours. Hydrogenation over platinum was never very satisfactory, however, because a colored, oily product resulted and from this oily material pure crystalline compounds were obtained only with considerable difficulty. The nickel and copper chromite catalysts, on the other hand, gave white products that readily crystallized.

The diphenylacetate was prepared from the most abundant 1-methyl-3,5-dibenzyl-4-piperidinol (m. p. 177–178°). The salts of this ester are remarkably insoluble in water; in fact, none were found with sufficient solubility to permit pharmacological testing.

The properties and analyses of the hydrochlorides of the substituted piperidinol esters prepared in this work are summarized in Table II.

The 1-methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidyl diphenylacetate hydrochlorides were tested for antispasmodic activity by Dr. K. K. Chen and associates of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. On the isolated guinea pig ileum, the 1-methyl-4-piperidyl ester showed about 50% of the activity of atropine sulfate; the higher homologs showed only about 1% of this activity.

Experimental

Alkyl-di-(β-carbethoxyethyl)-amines.—These tertiary amines were prepared by the addition of the appropriate primary amine to ethyl acrylate. Methylamine adds to the acrylate in six hours at 65° to give an 80% yield of the

(1) Eli Lilly and Company Fellow, 1945–1947.
(2) Bolyard and McElvain, This Journal, **51**, 922 (1929).
(3) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).
(4) McElvain and Rorig, This Journal, **70**, 1820 (1948).

TABLE II

HYDROCHLORIDES OF SUBSTITUTED-4-PIPERIDINOL ESTERS

$RNCH_2CHR'CHOCOR''CHR'CH_2$

R is	R′ is	R″ is	Formula	M. p., °C.	Analyses, % Cl Calcd.	Found
CH_3	H	$(C_6H_5)_2CH$	$C_{20}H_{24}ClNO_2$	115–120[a]	10.2	10.3
$(CH_3)_2CH$	H	$(C_6H_5)_2CH$	$C_{22}H_{28}ClNO_2$	174–176	9.5	9.8
n-C_4H_9	H	$(C_6H_5)_2CH$	$C_{23}H_{30}ClNO_2$	181–184	9.2	9.3
CH_3	H	C_6H_5NH	$C_{13}H_{19}ClN_2O_2$	228–229	13.1	13.5
CH_3	$C_6H_5CH_2$[b]	$(C_6H_5)_2CH$	$C_{34}H_{36}ClNO$	205–207	6.8	6.8

[a] Burtner and Cusic, THIS JOURNAL, **65**, 263 (1943), report this compound to be too hygroscopic for a melting point determination. [b] The piperidinol isomer melting at 177–178° was used to prepare this ester.

TABLE III

1-ALKYL-4-PIPERIDONES

Alkyl	Formula	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl[4]	.....	67–69	19	....	....	...	...	...	...
Isopropyl	$C_8H_{15}NO$	100–101	27	1.4627	0.9495	68.04	10.71	67.98	10.83
n-Butyl	$C_{19}H_{17}NO$	106–108	22	1.4595	0.9292	69.63	11.04	69.37	11.04

TABLE IV

1-ALKYL-4-PIPERIDINOLS

Alkyl	Formula	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl	.....	95–98	16[a]	....	....	...	...	...	...
Isopropyl	$C_8H_{17}NO$	113–114	23	1.4750	0.9529	67.09	11.97	67.14	12.11
n-Butyl	$C_9H_{19}NO$	127–129	22	1.4734	0.9411	68.72	12.18	68.42	12.00

[a] M. p. 24–27°; this compound has been prepared from chelidonic acid and reported to melt at 28° [Mills, Parkin and Ward, *J. Chem. Soc.*, 2622 (1927)]; its preparation from chelidonic acid also has been reported by Emmert, German Patent 292,871 [*Chem. Zentr.*, **87**, II, 116 (1916)]; Riegel and Reinhard, THIS JOURNAL, **48**, 1344 (1926); Burtner and Cusic, *ibid.*, **65**, 266 (1943).

tertiary amine[4]; isopropylamine requires ten hours at 175° to produce a 56% yield[5]; and n-butylamine requires ten hours at 125° to give a 73% yield of the tertiary amine. The properties of these tertiary amines corresponds to those previously reported.[6]

1-Alkyl-4-piperidones.—These piperidones were obtained by decarboxylation of the 1-alkyl-3-carbethoxy-4-piperidones, resulting from the Dieckmann cyclization of the above tertiary amino-esters, in the same manner as described for 1-methyl-4-piperidone.[4] The properties of these piperidones are listed in Table III.

1-Alkyl-4-piperidinols.—These compounds were obtained in 80–95% yields by the hydrogenation of the 1-alkyl-4-piperidones over Raney nickel at 140 atmospheres and 125° for two hours. The properties and analyses of these piperidinols are summarized in Table IV.

Hydrogenation of I to the 1-Methyl-3,5-dibenzyl-4-piperidinols. (a) Adams Platinum Oxide Catalyst.—A 2.00-g. sample of 1-methyl-3,5-dibenzal-4-piperidone hydrochloride in 33 ml. of 95% ethanol was hydrogenated over 0.20 g. of Adams platinum oxide catalyst. The amount of hydrogen necessary for saturation of the olefinic bonds was taken up in ten minutes. However, hydrogenation of the carbonyl group was so much slower that ninety-two minutes were required for completion. The free basic product was obtained by neutralization and crystallized from an aqueous ethanolic medium. The first crop of crystals, weighing 0.29 g., melted at 176.5–178.0°. Three lower-melting crops, totaling 0.20 g., were obtained by diluting the ethanolic mother liquors.

The first crop was recrystallized once from aqueous ethanol and twice from benzene–petroleum ether (b. p. 60–68°) solvent to give an analytical sample melting at 183.5–184.0°.

(b) Raney Nickel Catalyst.—The 183.5–184° isomer was also obtained by high pressure hydrogenation over Raney nickel. To 2.57 g. of 1-methyl-3,5-dibenzal-4-piperidone and 40 ml. of ethanol in a 270-ml. steel hydrogenation bomb was added 0.4 g. of Raney nickel catalyst prepared according to the directions of Pavlic and Adkins.[7] The bomb was filled with hydrogen to an initial pressure of 105 atmospheres and hydrogenated at 60° for fifty minutes. After filtering off the catalyst and removing the ethanol, the residue was taken up in hot petroleum ether (b. p. 60–68°). On cooling this solution 0.30 g. of material melting at 160–167° was obtained. Three recrystallizations from benzene–petroleum ether mixture raised the melting point to 182–183°. There was no depression of melting point when this sample was mixed with the one previously obtained by hydrogenation over Adams platinum oxide catalyst.

The above hydrogenation was repeated with 7 g. of I in 25 ml. of ethanol over 3 g. of the nickel catalyst at 80° and 160 atmospheres for five hours. After removal of the catalyst and solvent, the product was crystallized from a mixture of two volumes petroleum ether (b. p. 60–68°) and one volume benzene to give 2.4 g. of crude product melting 153–159°. This was recrystallized three times from the benzene–petroleum ether solvent to remove a higher melting impurity. The analytical sample thus obtained melted 155.0–156.0°.

(c) Copper–Chromite Catalyst.—The lower melting 1-methyl-3,5-dibenzyl-4-piperidinol was also obtained by the hydrogenation of a 2.0-g. sample of the dibenzal-piperidone over 1.0 g. of copper–chromite catalyst which

(5) Ziering, Berger, Heineman and Lee, *J. Org. Chem.*, **12**, 901 (1947), recently reported the preparation of this tertiary amine by allowing the reactants to stand in alcohol solution for one week at room temperature.

(6) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926).

(7) Adkins and Pavlic, *ibid*, **68**, 1471 (1946).

was prepared according to Adkins' directions.[8] The bomb was filled initially to a hydrogen pressure of 160 atmospheres, and the hydrogenation run at 200° for two and one-half hours. The recrystallized product (1.36 g.) melted 155–157°. A mixture of this product with that obtained from the Raney nickel hydrogenation melted at 154.5–157°.

When 5.0 g. of 1-methyl-3,5-dibenzal-4-piperidone in ethanol and 2.0 g. of copper chromite catalyst in a bomb containing 145 atmospheres of hydrogen were heated for five hours at 215°, 1.76 g. of white crystals melting at 175–177° was obtained by allowing the hydrogenation product to crystallize from a benzene–petroleum ether (b. p. 60–68°) mixture. This product then was recrystallized from the same solvent mixture to give an analytical sample of 1-methyl-3,5-dibenzyl-4-piperidinol melting at 177.0–178.5°. A mixture of a sample of this material with the 1-methyl-3,5-dibenzyl-4-piperidinol, m. p. 183.5–184.0°, was 153–170°.

1-Methyl-3,5-di-(hexahydrobenzyl)-4-piperidinol.—When the 1-methyl-3,5-dibenzyl-4-piperidinol, melting at 155–157°, was prepared by hydrogenation over Raney nickel the yields were low. A substantial portion of the crude product was much more soluble in petroleum ether (b. p. 60–68°) than the 155–157° melting product. The solubility suggested that the benzene rings had been hydrogenated in the reaction. However, no such product could be isolated from the crude mixture. Accordingly this petroleum ether soluble residue (4.20 g.) was rehydrogenated over fresh Raney nickel (4 g.) for three and one-half hours at 180° and 165 atmospheres hydrogen pressure. After removal of catalyst and solvent, the oily residue was caused to crystallize by rubbing with a few drops of petroleum ether. The resultant semi-crystalline mass then was dissolved in 25 ml. of petroleum ether (b. p. 60–68°) and cooled to −10° to precipitate a crop (1.08 g.) of white, fluffy needles melting 160–167°. These were recrystallized from 50 ml. of petroleum ether to give 0.80 g. of analytically pure product melting at 176.5–178.0°.

The analytical data for these 3,5-substituted N-methylpiperidinols are listed in Table I.

1-Methyl-4-chloropiperidine.—A solution of 7.0 g. of thionyl chloride in 25 ml. of dry benzene was added slowly to 4.15 g. of 1-methyl-4-piperidinol in 25 ml. of dry benzene. An oily precipitate formed almost immediately. This mixture was refluxed for one hour and cooled overnight. The solid, when filtered and dried, weighed 5.5 g., melted at 145–155°, and contained 42.7% chlorine (calcd. for $C_6H_{13}Cl_2N$: Cl, 41.7). When this salt was twice recrystallized from isopropanol and ether, the melting point was raised to 163–165°.

A solution of 4.65 g. of 1-methyl-4-chloropiperidine hydrochloride in 15 ml. of water was neutralized with an excess of potassium carbonate to salt out the free base. This was taken up in ether, dried, and distilled to give 2.81 g. of a liquid with a pungent, ammoniacal odor, b. p. 160–162° (733 mm.). Elementary analyses gave consistent but slightly high results for carbon and hydrogen. This may well be due to the presence of a small amount of the tetrahydropyridine, formed by dehydrohalogenation of the chloropiperidine during distillation. Accordingly the 1-methyl-4-chloropiperidine was redistilled at reduced pressure and three fractions collected. The middle cut, on analysis was found to contain less carbon and hydrogen than before but more than required by theory. There was insufficient material to redistil further.

Anal. Calcd. for $C_6H_{12}ClN$: C, 53.93; H, 9.06. Found: C, 54.87; H, 9.18.

After several days of standing, a brown gum began to deposit from this redistilled 1-methyl-4-chloropiperidine.

Hydrochlorides of Certain 1-Alkyl-4-piperidinol Esters.—The hydrochlorides of the various piperidyl diphenylacetates were obtained from the reaction of diphenylacetyl chloride with the piperidinol in refluxing benzene solution. On cooling the salt separated and was further purified by recrystallization from benzene. 1-Methyl-4-piperidyl N-phenylcarbamate was prepared from the piperidinol and phenyl isocyanate. The free base melted at 125–126°[9]; the hydrochloride was prepared by treatment of an ether solution of the free base with hydrogen chloride. The melting points and analyses of these hydrochlorides are listed in Table II.

In an attempt to prepare 1-methyl-4-piperidylbenzilate by the method of Horenstein and Pählicke,[3] 1.13 g. of freshly distilled 1-methyl-4-chloropiperidine was added to 1.94 g. of benzilic acid in 20 ml. of anhydrous isopropanol. After refluxing for thirteen hours, the solvent was removed by distillation *in vacuo*, and the residue was extracted with ether. From this ethereal extract 1.10 g. of benzilic acid was recovered. The ether-insoluble residue, which should have contained the 1-methyl-4-piperidyl-benzilate hydrochloride, was a water insoluble, brown gum from which no pure product could be isolated.

Summary

All of the possible inactive stereoisomeric 1-methyl-3,5-dibenzyl-4-piperidinols and one of the 1-methyl-3,5-dihexahydrobenzyl-4-piperidinols have been isolated from the hydrogenation of 1-methyl-3,5-dibenzal-4-piperidone.

1-Methyl-, 1-isopropyl- and 1-*n*-butyl-4-piperidinol have been prepared by the hydrogenation of the corresponding 4-piperidones.

Certain esters of these piperidinols have been prepared for pharmacological testing.

Madison, Wisconsin Received January 2, 1948

(8) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wis., 1937, p. 13.

(9) Emmert, German Patent 292,871 [*Chem. Zentr.*, **87**, II, 116 (1916)] reported this compound to melt at 120°.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. VIII. The Synthesis of 1-(Cyclohexen-1′-yl)-3-methyl-3-epoxybutyne-1 and Related Products[1]

BY NICHOLAS A. MILAS, NORMAN S. MACDONALD[2] AND DONALD M. BLACK[3]

The availability of a reliable method for the synthesis of biologically active vitamin A products[4] made it desirable to investigate the effect of various substituents in the cyclohexene ring on the biological activity of the final products. For example, one could synthesize a vitamin A analog without any substituents in the cyclohexene ring, or even substitute a benzene ring for the latter. In order to effect these changes, several new key intermediates have been synthesized and are herein reported.

In the synthesis of the epoxides (VI) and (VII) four different series were studied. In the first series cyclohexanone was acetylenated in liquid ammonia with sodium acetylide and the 1-ethynylcyclohexanol-1 (II, $R_1 = R_2 = R_3 = H$) formed dehydrated at 290–300° using aluminum phosphate as the dehydrating catalyst. This dehydration has been previously studied using alumina[5] and aluminum sulfate[6] catalysts but no analytical data beyond a series of widely different physical constants have been reported. The same holds true with the results of other investigators who prepared this enyne by other procedures.[7,8] The lack of chemical evidence for the existence of the pure enyne is perhaps significant, since even in our case all low boiling fractions were found to possess values for active hydrogen ranging from less than 0.1 to 0.9, in spite of the fact that hydrogenation values and other properties were almost identical to those of the pure enyne.

In the second series, 2-methyl-1-ethynylcyclohexanol-1 was prepared in liquid ammonia from 2-methylcyclohexanone and sodium acetylide. When this ethynylcyclohexanol was allowed to stand at 0° for sixteen hours, it separated into two forms: a solid and a liquid form of approximately equal weight. Since the addition of acetylene to the carbonyl group of the 2-methylcyclohexanone introduces a second asymmetric carbon atom, one would expect two pairs of enantiomorphs, a fact which has been overlooked by earlier investigators[9,10] although Wang and Hu[11] reported both the solid and the liquid forms. Dehydration of both the liquid and the solid forms over aluminum phosphate at 290–295° produced the same ethynylcyclohexene in yields of 52 and 27%, respectively. Ozonization of the enyne, produced from either the solid or the liquid form, yielded the same keto acid, namely, 6-ketoheptoic acid. The 2,4-dinitrophenylhydrazone of this acid from either ozonization product had the same m. p., and mixed m. p. showed no depression. Furthermore, the semicarbazone of the keto-acid from either ozonization product had essentially the same m. p. which was identical with the m. p. of the semicarbazone of 6-ketoheptoic acid reported by Wallach.[12] Therefore, we are forced to conclude that both enynes must have essentially the same structure.

That the solid carbinol presumably corresponds to the *cis* form and the liquid to the *trans* form may be deduced from the tendency of each to dehydrate. It is well known[13] that *trans* elimination of water or halogen acids proceeds more smoothly than the corresponding *cis* elimination, and the low yields of the enyne obtained from the solid carbinol are in accord with these facts.

In the third series 2,6,6-trimethyl-1-ethynylcyclohexanol-1 was prepared in liquid ammonia from 2,6,6-trimethylcyclohexanone and sodium acetylide. Although two pairs of enantiomorphs were also expected in this case, only one product was obtained and attempts to separate it into two forms were not successful. The dehydration of this acetylene carbinol to produce the corresponding enyne in good yields was difficult to accomplish.[14] Methods which were known to yield good results with other acetylene carbinols were either too drastic or too ineffective in producing the proper dehydration. Small yields of the desired enyne were obtained when the acetylene carbinol was dehydrated at 270–290° using aluminum phosphate on pumice as catalyst or when heated with either succinic anhydride in dibutyl phthalate or with a mixture of succinic anhydride and small amounts of glacial metaphosphoric acid. Perhaps

(1) Paper No. VII, "Vitamins and Hormones," **5**, 1 (1947), Academic Press, Inc., New York, N. Y.

(2) Research Associate, 1942–1943. Present address: Occidental College, Los Angeles, Cal.

(3) Present address: Monsanto Chemical Company, Everett, Mass.

(4) (a) Milas, U. S. Patents, 2,369,156–2,369,168 inclusive, Feb. 13 (1945); 2,382,085–2,382,086, Aug. 14 (1945); *Science*, **103**, 581 (1946); (b) Milas, *et al.*, THIS JOURNAL, **70**, 1597 (1948); (c) Isler, Kofler, Huber and Ronco, *Experimentia*, **2**, 31 (1946); Jubilee Volume to Emil C. Barell, Hoffman-LaRoche and Co., Basle, 1946, p. 31.

(5) Friedr. Farbenfab. von Baeyer and Co., German Patent 290,558; *Chem. Zentr.*, **87**, I, 644 (1916).

(6) Carothers and Coffman, THIS JOURNAL, **54**, 4071 (1932).

(7) Mousseron, *Compt. rend.*, **217**, 155 (1943).

(8) Azerbaev, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 412 (1945).

(9) Cook and Lawrence, *J. Chem. Soc.*, 58 (1938).

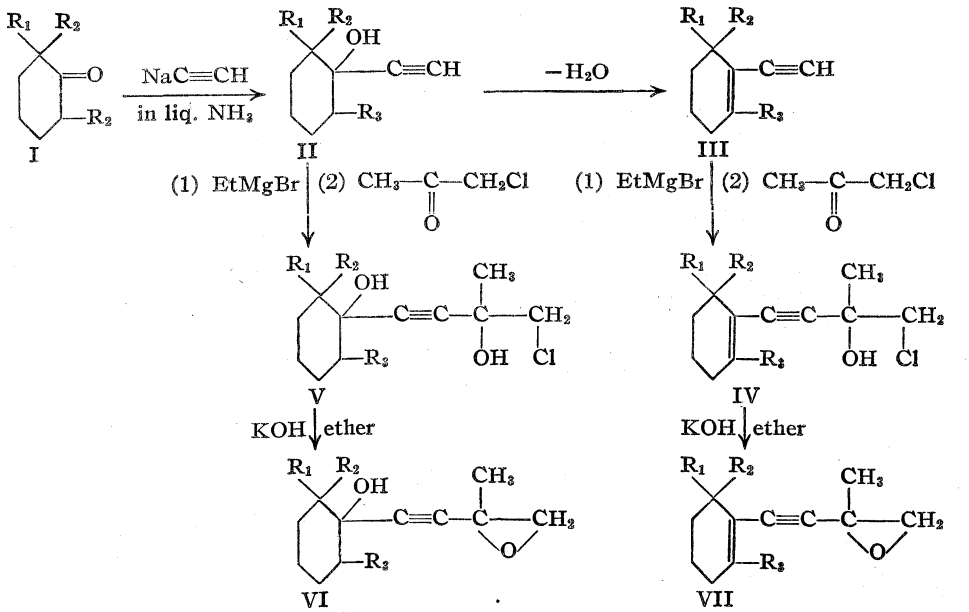
(10) Marvel, Mozingo and White, THIS JOURNAL, **62**, 1880 (1940).

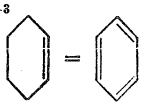
(11) Wang and Hu, *J. Chinese Chem. Soc.*, **10**, 1 (1943).

(12) Wallach [*Ann.*, **329**, 376 (1903)] reports the m. p. of the semicarbazone of 6-ketoheptoic acid as 144–145°.

(13) (a) Michael, *J. prakt. Chem.*, **46**, 210 (1892); (b) Bartlett and Rosenwald, THIS JOURNAL, **56**, 1990 (1934); (c) Winstein, Pressman and Young, *ibid.*, **61**, 1645 (1939); (d) Huckel, Tappe and Legutke, *Ann.*, **543**, 191 (1940).

(14) Since this enyne is an important intermediate in the synthesis of vitamin A itself, work is being continued to study the mechanism of its formation.



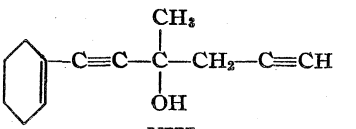
I, $R_1 = R_2 = R_3 = H$
II, $R_1 = R_2 = H$; $R_3 = CH_3$
III, $R_1 = R_2 = R_3 = CH_3$
IV, $R_1 = R_2 = R_3 = H$;  =

the reason for our difficulty in obtaining good yields of the enyne in this case is due to the possibility of the hydroxyl group being hindered by the methyl groups. A similar case has been reported recently[15] with 1-(2,4-dimethylphenyl)-2,6-dimethylcyclohexanol which could not be dehydrated with potassium acid sulfate at 190–200°, or with boiling acetic anhydride. However, when it was refluxed with anhydrous oxalic acid at 200–220°, a yield of 81% of the corresponding cyclohexene derivative was obtained.[16] When this method was applied to our acetylene carbinol only small amounts (3%) of the pure enyne were obtained.

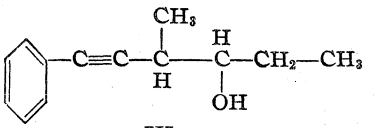
In the subsequent step of the synthesis of the epoxides either the enynes (III) or the carbinols (II) were allowed to react via their Grignard reagents with chloroacetone to form the corresponding chlorohydrins (V or VI).[17] In this step phenylacetylene was added to the list to afford comparison of the benzene ring with the cyclohexene ring.

Dehydrochlorination of the chlorohydrins was effected with powdered potassium hydroxide in quantities two to three times that of the theoretical. Sodamide was found equally effective, but an organic base such as triethylamine was completely ineffective. All the epoxides prepared in this investigation responded slowly to the fuchsin-aldehyde test, and in acid solution they yielded crystalline 2,4-dinitrophenylhydrazones.

In the vitamin A synthesis cited in the early part of this paper, 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylbuten-1-al-4 was the key intermediate. This was either acetylenated in liquid ammonia or allowed to react with a Grignard of an ethynyl compound of the proper structure. Both of these reactions were tested with some of our epoxides. For example, when 1-(cyclohexen-1′-yl)-3-methyl-3-epoxybutyne-1 was allowed to react in liquid ammonia with lithium acetylide, 1-(cyclohexen-1′-yl)-3-methyl-3-hydroxy hexadiyne-1,5 (VIII) was formed. Similarly, when 1-phenyl-3-methyl-3-epoxybutyne-1 was treated with ethylmagnesium bromide the carbinol (IX) was presumably formed, since it is well known[18]



VIII



IX

(15) Carlin, THIS JOURNAL, **67**, 928 (1945).

(16) Carlin and Constantine, *ibid.*, **69**, 50 (1947).

(17) (a) Lespieau, *Compt. rend.*, **180**, 442, 557 (1925); *Bull. soc. chim.*, **43**, 199, 657 (1928); (b) Favorsky and Tikhomolov, *Compt. rend.*, **203**, 726 (1936); *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1501 (1940); (c) Herschstein, *ibid.*, **12**, 132 (1942).

(18) (a) Fourneau and Tiffeneau, *Bull. soc. chim.*, **33**, 741 (1905); *Compt. rend.*, **145**, 437 (1907); (b) Henry, *Bull. acad. roy. Belg.*, 162 (1907); *Compt. rend.*, **145**, 21 (1907); (c) Hess, *Ber.*, **46**, 3117 (1913).

that a Grignard reagent reacts with an unsymmetrically substituted epoxide to form secondary rather than tertiary alcohols. The structure of (VIII) and (IX) are only provisionally proposed and further work is being done to establish the structure of this type of compounds.

It is therefore seen that the success of the synthesis of vitamin A itself or its analogs, in which the methyl groups of the cyclohexene ring may be changed or left out entirely, can be achieved by by-passing β-ionone.

Experimental

1-Ethynylcyclohexanol-1.—Five hundred grams of pure cyclohexanone was added dropwise with stirring to a mixture of sodium acetylide (from 117 g. of sodium) and liquid ammonia (3 l.) at −50° in the course of three hours. Stirring was continued overnight while a slow stream of dry acetylene was allowed to pass through the solution. The ammonia was then allowed to evaporate and the residue acidified with 200 g. of tartaric acid in 500 cc. of water and extracted with ether. After the ether solution was dried and the ether removed, the residue was fractionated through a four-foot packed column and the fraction (518 g., 82%) boiling at 74–77° (15 mm.) or 79–81° (21 mm.) collected and analyzed. The supercooled liquid had an $n^{20}D$ 1.4823. On standing the liquid solidified completely; m. p. 31–32°. Marvel, *et al.*,[19] gave a m. p. of 31–32°.

Anal. Calcd. for $C_8H_{12}O$: active hydrogen, 2.00. Found: A. H. (Zerewitinoff), 1.97, 2.02.

2-Methyl-1-ethynylcyclohexanol-1.—This acetylene carbinol was prepared in exactly the same way as the previous one in liquid ammonia from 560 g. of 2-methylcyclohexanone (b. p. 160.5–161°, $n^{25}D$ 1.4465) and sodium acetylide (from 130 g. of sodium). The product was fractionated through a four-foot packed column and the fraction (464 g., 67%) boiling at 98–105° (45 mm.) collected and allowed to stand at 0° for sixteen hours, whereby it separated into two fractions: a solid fraction (227 g.) and a liquid portion (225 g.). The solid was recrystallized from petroleum ether, m. p. 61.0–61.5° (cor.). The liquid portion was redistilled; b. p. 84° (17 mm.). Further attempts to obtain crystals from the liquid portion were unsuccessful. Wang and Hu[20] gave 60 and 85° (18 mm.), respectively.

Anal. Calcd. for $C_9H_{14}O$: A. H., 2.00. Found (crystalline): A. H. (Zerewitinoff), 2.0, 1.97. Found (liquid): A. H. (Zerewitinoff), 2.0, 2.0.

2,6,6-Trimethyl-1-ethynylcyclohexanol-1.—In a similar manner this acetylene carbinol was prepared in liquid ammonia from 560 g. of 2,6,6-trimethylcyclohexanone [b. p. 177–178.5° (758 mm.), or 69–71.5° (20 mm.); $n^{25}D$ 1.4465][21] and sodium acetylide (from 92 g. of sodium). The final product was fractionated through a four-foot packed column and the fraction (524 g., 79%) boiling at 212–212.4° (760 mm.) or 88–90° (20 mm.) collected and analyzed; $n^{25}D$ 1.4740; d^{25}_4 0.9300; MR_D (calcd.), 50.32; MR_D (obsd.), 50.25.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; unsaturation, 2.0 ⌐¬; A. H. (Zerewitinoff), 2.0. Found: C, 79.51, 79.45, 79.31; H, 10.86, 11.23, 11.21; unsaturation, 2.11 (Pt), 2.02 (Pd) ⌐¬; A. H. (Zerewitinoff), 2.0, 2.04.

1-Ethynylcyclohexene-1.—1-Ethynylcyclohexanol-1 was dehydrated by passing it upwards at the rate of 75 g. per hour under a slightly reduced pressure (175–180 mm.) through a glass tube 2.5 × 24 cm. packed with a 5:1 mixture of pumice and aluminum phosphate and maintained at a temperature of 290–300°. The vapors were condensed and fractionated through a four-foot packed column and the fraction (52% per pass) boiling at 47° (13 mm.) was collected and analyzed. Although this product showed the correct hydrogenation value, its Zerewitinoff value was between 0.6 and 0.8. It was therefore purified further via its silver derivative which was decomposed either with hydrogen sulfide or ammonium thiocyanate and the pure enyne recovered. For example, from 9 g. of crude 1-ethynylcyclohexene-1 6 g. of pure enyne was obtained boiling at 52–53° (30 mm.) or 63–64° (52 mm.) or 137–138° (760 mm.); $n^{25}D$ 1.4934; d^{25}_4 0.8843; MR_D (calcd.), 34.48; MR_D (obsd.), 34.90. It also showed a maximum in the ultraviolet at 224 mμ, log $\epsilon_{mol.}$ 4.13.

Anal. Calcd. for C_8H_{10}: C, 90.50; H, 9.50; unsaturation, 3.0 ⌐¬; A. H., 1.0. Found: C, 90.44; H, 9.52; unsaturation, 3.19 ⌐¬; A. H. (Zerewitinoff), 1.01, 1.0, 1.03.

2-Methyl-1-ethynylcyclohexene-1.—(a) From liquid 2-methyl-1-ethynylcyclohexanol-1. When 250 g. of this ethynylcarbinol was dehydrated under the same conditions as in the previous case and the crude product fractionated, a fraction (103 g., 47% per pass) was obtained which boiled at 55° (20 mm.) and had a Zerewitinoff value of 0.9. This was further purified through its silver derivative and the recovered enyne had a b. p. of 63–65° (30 mm.) and gave correct analytical values; $n^{25}D$ 1.4895; d^{25}_4 0.8827; MR_D (calcd.), 39.09; MR_D (obsd.), 39.41. It also showed a maximum in the ultraviolet at 229 mμ, log $\epsilon_{mol.}$ 4.0.

Anal. Calcd. for C_9H_{12}: C, 89.93; H, 10.07; A. H., 1.0. Found: C, 89.71; H, 10.16; A. H. (Zerewitinoff), 1.0, 0.97.

(b) From solid 2-methyl-1-ethynylcyclohexanol-1: From 180 g. of solid 2-methyl-1-ethynylcyclohexanol-1, 84 g. of an enyne was obtained which had a b. p. of 57° (30 mm.) and a Zerewitinoff value of 0.5. This corresponds to a 27% yield per pass. This crude enyne was purified through its silver derivative and the pure product had a b. p. of 63.5–64° (30 mm.) and gave correct analytical values; $n^{25}D$ 1.4883; d^{25}_4 0.8820; MR_D (calcd.), 39.09; MR_D (obsd.), 39.26. It also showed a maximum in the ultraviolet at 229 mμ, log $\epsilon_{mol.}$ 4.06.

Anal. Calcd. for C_9H_{12}: C, 89.93; H, 10.07; A. H., 1.0. Found: C, 89.75; H, 10.20; A. H. (Zerewitinoff), 1.0.

Ozonization of the Two 2-Methyl-1-ethynylcyclohexenes.—Using the method developed by Strain,[22] 2 g. of each anyne was ozonized and the 2,4-dinitrophenylhydrazones precipitated and recrystallized from aqueous acetic acid solution.

From the enyne obtained by the dehydration of the solid 2-methyl-1-ethynylcyclohexanol-1, a pure 2,4-dinitrophenylhydrazone was obtained, m. p. 132.6–133.1° (cor.).

Anal. Calcd. for $C_{13}H_{16}O_6N_4$: C, 48.14; H, 4.97; N, 17.28; neut. equiv., 324. Found: C, 47.97; H, 4.89; N, 16.96; neut. equiv., 327.

From the enyne obtained from the liquid 2-methyl-1-ethynylcyclohexanol-1, the pure 2,4-dinitrophenylhydrazone melted at 132.6–133° (cor.) and mixed m. p. with the previous sample showed no depression. A neutralization equivalent was taken and gave a value of 326.

Since the 2,4-dinitrophenylhydrazone of 2-ketoheptoic acid was not known, the acid was prepared by the method of Wallach[23] and this derivative prepared from it and purified; m. p. 132.5° (cor.). Mixed m. p. with the two derivatives mentioned above showed no depression.

The semicarbazone was also prepared from each ozonized product and found to have a m. p. of 145–146° (cor.) from the enyne obtained from the solid acetylene carbinol and 144–145° (cor.) from the enyne obtained from the

(19) Marvel, Pinkney, Nesty and Wiley, THIS JOURNAL, **58**, 972 (1936).

(20) Wang and Hu, *J. Chinese Chem. Soc.*, **10**, 1 (1943).

(21) The preparation of this cyclohexanone from *m*-xylene and from 2-methylcyclohexanone will be described elsewhere.

(22) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

(23) Wallach, *Ann.*, **329**, 376 (1903).

liquid acetylene carbinol. Mixed m. p. of the two showed no depression. Wallach[23] gives a m. p. of 144–145° for this derivative.

2,6,6-Trimethyl-1-ethynylcyclohexene-1.—This enyne was made by the dehydration of 2,6,6-trimethyl-1-ethynylcyclohexanol-1. The following dehydrating agents were tried usually at temperatures above the b. p. of the carbinol and in an atmosphere of nitrogen: fused potassium hydrogen sulfate, aluminum oxide on pumice, calcined ammonium alum on pumice, a 50–50 mixture of aluminum oxide–aluminum sulfate on pumice, thorium oxide on pumice, barium oxide, *p*-toluenesulfonic acid, molten succinic anhydride, succinic anhydride and sulfuric acid, succinic anhydride and glacial metaphosphoric acid, succinic anhydride in dibutyl phthalate, anhydrous oxalic acid, aluminum phosphate on pumice and anhydrous magnesium sulfate. Acidic dehydrating agents gave small amounts of the enyne while basic dehydrating agents gave mostly decomposition products. Of all the combinations tried, aluminum phosphate (20 g.) on pumice (30 g.) at 270–290° gave yields of 18–20% of the enyne per pass with only 50–60% of the carbinol recovered unchanged. When 22.6 g. of the acetylenecarbinol was added dropwise to a molten mixture of succinic anhydride (25 g.) and glacial metaphosphoric acid (0.4 g.) at 240–260° and under a slightly reduced nitrogen pressure (400 mm.), a product was obtained which when fractionated gave a fraction (6.7 g.) b. p. 60–80° (18 mm.). On the basis of its Zerewitinoff value, a yield of 26% of the enyne was obtained. However, on account of a large amount of tar formation, very little or no unchanged carbinol was recovered. When a similar dehydration was done in dibutyl phthalate (150 cc.) containing succinic anhydride (16 g.) under similar pressure and temperature conditions, yields of 12–15% of the enyne were obtained with slightly over 80% of the carbinol recovered unchanged. Similarly when 80 g. of the carbinol was heated with 61 g. of anhydrous oxalic acid[16] at 170° under a slightly reduced pressure a product was obtained which when fractionated gave a fraction (26 g.) b. p. 75° (30 mm.). The Zerewininoff value was only 0.3 corresponding to a yield of 10% of the enyne.

Since the silver derivative of this enyne precipitates instantly from an alcoholic ammoniacal silver nitrate solution, and the acetylene carbinol fails to give a precipitate even after one to two hours, the enyne was purified by this method as in the previous cases. The recovered pure enyne was found to boil at 56–57° (18 mm.) or 72–74° (30 mm.) and to give good analytical values; $n^{25}D$ 1.4745; $d^{25}D$ 0.8574; MR_D (calcd.) 48.33; MR_D (obsd.), 48.55.

Anal. Calcd. for $C_{11}H_{16}$: C, 89.11; H, 10.89; unsaturation, 3.0 ⌐¬; A. H., 1.0. Found: C, 89.20, 89.10; H, 10.82, 10.75; unsaturation, 3.28 (Pt); A. H. (Zerewitinoff), 0.90, 1.01.

Phenylacetylene.—This acetylene was prepared by the dehydrobromination of styrene dibromide (m. p. 74–75°) with sodamide in liquid ammonia.[24] A product was obtained which had a b. p. of 139.5–140.5° and an $n^{25}D$ 1.5459.

1-[Cyclohexan-1′-ol-yl]-3-methyl-3-hydroxy-4-chlorobutyne-1.—Using the usual Grignard technique, 372 g. of 1-ethynylcyclohexanol-1 was converted to the corresponding magnesio salt acetylene Grignard by allowing it to react in 3 l. of anhydrous ether with ethylmagnesium bromide prepared from 146 g. of magnesium and 719 g. of ethyl bromide. The acetylene Grignard was then allowed to react with 277.5 g. of freshly distilled chloroacetone. The mixture was then hydrolyzed with an ice–ammonium chloride solution and the product obtained fractionated under a reduced pressure; b. p., 155–157° (4–5 mm.) or 115–116° (10^{-3} mm.); yield 400 g. (62%). When this was allowed to stand at 0° overnight, it solidified and was recrystallized from petroleum ether into colorless prisms; m. p., 58–60°.

Anal. Calcd. for $C_{11}H_{17}O_2Cl$: C, 60.95; H, 7.90; Cl, 16.32; unsaturation, 2.0 ⌐¬; A. H., 2.0. Found: C, 59.90, 60.13; H, 7.76, 7.38; Cl, 16.99, 17.16; unsaturation, 3.55 (Pt), 3.5 (Pd) ⌐¬; A. H. (Zerewitinoff), 1.88, 2.03.

1-[2′,6′,6′-Trimethylcyclohexan-1′-ol-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—A Grignard was prepared from 30 g. of magnesium and 138 g. of ethyl bromide in 1500 cc. of anhydrous ether. To this was added in the course of two hours 100 g. of 2,6,6-trimethyl-1-ethynylcyclohexanol-1. After the Grignard of the acetylene carbinol was formed, 55.7 g. of chloroacetone was added slowly at 0° then the mixture stirred overnight at room temperature. The mixture was then hydrolyzed with an ice–ammonium chloride solution and the product obtained fractionated; b. p. 65–67° (10^{-4} mm.). The highly viscous distillate (69 g.) was allowed to stand at 0° for three weeks whereby it solidified. This was recrystallized from petroleum ether into colorless needles; m. p., 41–42°.

Anal. Calcd. for $C_{14}H_{23}O_2Cl$: Cl, 13.72; unsaturation, 2.0 ⌐¬; A. H., 2.0. Found: Cl, 14.04, 14.13; unsaturation, 3.47 (Pt), 2.1 (Pd) ⌐¬; A. H. (Zerewitinoff), 2.24.

1-[Cyclohexen-1′-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—Ethylmagnesium bromide (0.5 mol) was made in 500 cc. of anhydrous ether and cooled in nitrogen with an ice–salt mixture. To this was added dropwise with stirring in the course of two hours 60 g. of 1-ethynylcyclohexene-1 (A. H., 0.9) in 200 cc. of ether. The mixture was stirred in nitrogen at room temperature for twenty-four hours, then cooled with an ice–salt mixture and to it added 47.2 g. of chloroacetone in 200 cc. of ether. The solution was stirred at room temperature for six hours then hydrolyzed with 200 cc. of cold saturated ammonium chloride solution. A product was obtained which when fractionated yielded 40 g. (40% yield) of a light orange colored liquid; b. p. 110–116° (4 mm.) or 60–63° (10^{-3} mm.); $n^{25}D$ 1.5259; d^{25}_4 1.1090; MR_D (calcd.), 54.72; MR_D (obsd.), 54.96.

Anal. Calcd. for $C_{11}H_{15}OCl$: C, 66.4; H, 7.56; Cl, 17.9; unsaturation, 3.0 ⌐¬; A. H., 1.0. Found: C, 66.15; H, 7.61; Cl, 18.2; unsaturation, 3.3 (Pt) ⌐¬; A. H. (Zerewitinoff), 1.0.

1-[2′-Methylcyclohexen-1′-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—Using a similar technique as in the previous case, a chlorohydrin was obtained in 54% yield from 2-methyl-1-ethynylcyclohexene-1 and chloroacetone. The product obtained had a b. p. of 115–130° (4 mm.) and gave good analytical results; $n^{25}D$ 1.5360; d^{25}_4 1.111; MR_D (calcd.), 59.34; MR_D (obsd.), 59.63. It also had an absorption band in the ultraviolet at 2270 Å., log $\epsilon_{mol.}$ 4.072.

Anal. Calcd. for $C_{12}H_{17}OCl$: C, 67.75; H, 8.06; Cl, 16.77; unsaturation, 3.0 ⌐¬; A. H., 1.0. Found: C, 67.98; H, 8.04; Cl, 16.81; unsaturation, 3.3 (Pt) ⌐¬; A. H. (Zerewitinoff), 1.0.

3-Methyl-1-phenyl-4-chloro-1-but-1-yn-ol-3.—In a similar manner a chlorohydrin was obtained in a yield of 52.5% from phenylacetylene and chloroacetone. This chlorohydrin was found to boil at 94–96° (1 mm.); $n^{25}D$ 1.5624.

Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.86; H, 5.70; Cl, 18.22. Found: C, 66.91; H, 5.92; Cl, 19.86.

The purification of this chlorohydrin was found to be more difficult than that of the others in view of the presence of small quantities of diphenyldiacetylene which was isolated and identified.[25]

1-[Cyclohexan-1′-ol-yl-]-3-methyl-3-epoxybutyne-1.—A solution of 181 g. of 1-[cyclohexan-1′-ol-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3 in 500 cc. of dry ether was added dropwise in the course of two hours to a well-stirred suspension in nitrogen of 100 g. of freshly powdered potassium hydroxide in 750 cc. of ether. The mixture turned brick-red. Stirring was continued for two hours longer than the mixture treated with 500 cc. of cold water. A product

(24) Nieuwland, Vaughn and Vogt, THIS JOURNAL, **56**, 2121 (1934).

(25) Black, Ph.D. Thesis, M. I. T., July, 1947.

was isolated from the ethereal layer which was fractionated and the fraction (120 g.) boiling at 90–94° (10^{-3} mm.) collected. When allowed to stand at 0° overnight, this product solidified and was recrystallized from petroleum ether; m. p. 47–48°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89; unsaturation, 2.0 ⌐¬; A. H., 1.0. Found: C, 73.03, 73.07; H, 8.89, 8.67; unsaturation, 4.4 (Pt), 3.9 (Pd) ⌐¬; A. H. (Zerewitinoff), 0.93.

This epoxide gave a positive test with the fuchsin aldehyde reagent and formed a 2,4-dinitrophenylhydrazone in dilute hydrochloric acid solution; m. p., 160–164°. It exhibited no band in the ultraviolet; only end absorption.

1-[2',6',6'-Trimethylcyclohexan-1'-ol-yl]-3-methyl-3-epoxybutyne-1.—This epoxide was made from the corresponding chlorohydrin by the usual dehydrochlorina ion technique using powdered potassium hydroxide. A product was obtained which was fractionated under a high vacuum; b. p. 55–58° (10^{-4} mm.). This product was induced to crystallize, then was recrystallized from petroleum ether; m. p., 81–82°.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; unsaturation, 2.0 ⌐¬; A. H., 1.0. Found: C, 75.36, 75.62; H, 10.14, 10.17; unsaturation, 3.3 (Pt), 2.4 (Pd) ⌐¬; A. H. (Zerewitinoff), 1.04.

Although this epoxide gave a negative fuchsin–aldehyde test, it formed a 2,4-dinitrophenyldhydrazone with Lund's reagent; m. p., 185–187°. This phenylhydrazone had an ultraviolet absorption spectrum (alcohol) with a well-defined maximum at 400 mμ, log $\epsilon_{mol.}$ 4.70. This epoxide also showed an end absorption.

1-[Cyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1.—Employing the usual technique this epoxide was prepared by the dehydrochlorination of the corresponding chlorohydrin with powdered potassium hydroxide or sodamide. Purification of this epoxide was rendered more difficult by its instability toward air oxidation, and frequently several fractionations were essential before a pure product was obtained. Physical constants and other analytical data had to be obtained immediately upon final fractionation. A yield of 33.5% of the pure epoxide was obtained; b. p. 64–64.5° (1 mm.); $n^{25}D$ 1.5145; d^{25}_4 0.9960; MR_D (calcd.), 47.77; MR_D (obsd.), 49.01. It showed a maximum in the ultraviolet at 232 mμ, log $\epsilon_{mol.}$ 4.32.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70; unsaturation, 3.0 ⌐¬. Found: C, 80.81; H, 8.63; unsaturation, 3.3 (Pt) ⌐¬.

This epoxide gave a positive test (slow) with the fuchsin–aldehyde reagent and formed an orange 2,4-dinitrophenylhydrazone with Lund's reagent (hot); m. p., 157–158° (cor.).

Anal. Calcd. for $C_{17}H_{18}O_4N_4$: C, 59.61; H, 5.30; N, 16.37. Found: C, 59.49; H, 5.99; N, 16.28.

Its absorption spectrum (alcohol) showed two well-defined maxima at 369 mμ (log $\epsilon_{mol.}$ 4.53) and 258 mμ (log $\epsilon_{mol.}$ 4.44), respectively.

1-[2'-Methylcyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1.—Similarly this epoxide was prepared in 31% yield by the technique given above, and was found to have similar properties as the previous epoxide; b. p., 64–66° (1 mm.); $n^{25}D$ 1.5058; d^{25}_4 0.9942; MR_D (calcd.), 52.39; MR_D (obsd.), 52.70. It also showed a maximum in the ultraviolet at 232 mμ, log $\epsilon_{mol.}$ 4.19.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.76; H, 9.15; unsaturation, 3.0 ⌐¬. Found: C, 81.33; H, 9.24; unsaturation, 3.2 (Pt) ⌐¬.

This epoxide gave a positive test (slow) with the fuchsin–aldehyde reagent and formed an orange 2,4-dinitrophenylhydrazone; m. p., 158–159° (cor.).

Anal. Calcd. for $C_{19}H_{20}O_4N_4$: C, 60.66; H, 6.65. Found: C, 60.52; H, 6.34.

The absorption spectrum (alcohol) of this phenylhydrazone showed also two well-defined maxima at 377 mμ (log $\epsilon_{mol.}$ 4.35) and 260 mμ (log $\epsilon_{mol.}$ 4.38), respectively.

3-Methyl-1-phenyl-3-epoxybutyne-1.—This epoxide was also prepared by the usual technique in 43.5% yield (using powdered potassium hydroxide) or 40% yield (using sodamide). It boiled at 65–67° (1 mm.); $n^{25}D$ 1.5570; d^{25}_4 0.9968; MR_D (calcd.), 46.84; MR_D (obsd.), 51.02. It also showed a maximum in the ultraviolet at 243 mμ, log $\epsilon_{mol.}$ 4.29.

Anal. Calcd. for $C_{11}H_{10}O$: C, 83.50; H, 6.37; unsaturation, 5.0 ⌐¬. Found: C, 82.84; H, 6.42; unsaturation, 5.2 (Pt) ⌐¬.

A reddish-orange 2,4-dinitrophenylhydrazone was also prepared, m. p., 96–97° (cor.).

Anal. Calcd. for $C_{17}H_{15}O_4N_4$: C, 60.17; H, 4.46; N, 16.52. Found: C, 60.10; H, 4.34; N, 15.65.

1-[Cyclohexen-1'-yl-]-3-methyl-1,5-hexadiyn-3-ol (VIII).—Using lithium acetylide (from 0.8 g. lithium) in liquid ammonia (1.5 liters), 16.4 g. of 1-[cyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1 was converted into the crude carbinol (VIII). The product was fractionated from a pot molecular still and the fraction (7 g.) boiling at bath temperature 100° (10^{-4} mm.) collected and crystallized from petroleum ether; m. p. 63–67°. This product is rather unstable and after a few days it turns dark yellow. With alcoholic ammoniacal silver nitrate it gives a yellowish-white precipitate showing the presence of an acetylene group.

Anal. Calcd. for $C_{13}H_{16}O$: unsaturation, 5 ⌐¬; A. H., 2.0. Found: unsaturation, 4.76 ⌐¬; A. H. (Zerewitinoff), 1.93.

3-Methyl-1-phenyl-1-hexyn-4-ol (IX).—A Grignard reagent was prepared from 3.2 g. of magnesium and 14.6 g. of ethyl bromide in 100 cc. of anhydrous ether. The solution was cooled to 0° and to it was added dropwise 17.5 g. of 3-methyl-1-phenyl-3-epoxybutyne-1 in 40 cc. of ether. The mixture was then stirred in nitrogen at room temperature for three hours then hydrolyzed at 0° with 8 g. of ammonium chloride in 50 cc. of water. A product was obtained which was fractionated and the fraction (12 g., 57.7% yield) boiling at 90–94° (1 mm.) collected and analyzed; $n^{25}D$ 1.5458; d^{25}_4 0.9865; MR_D (calcd.), 58.16; MR_D (obsd.), 60.34.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57; unsaturation, 5.0 ⌐¬. Found: C, 82.95; H, 8.55; unsaturation 5.0 (Pt) ⌐¬; A. H. (Zerewitinoff), 1.0.

3-Methyl-1-phenylhexanol-4.—Seven and a half grams of the foregoing unsaturated carbinol was partially hydrogenated in a mixture of 100 cc. of absolute ethanol and 2 cc. of glacial acetic acid using platinum oxide as catalyst. A product was obtained which was fractionated under a reduced pressure and the fraction (4.3 g., 54.7% yield) boiling at 90–92° (1 mm.) collected and analyzed; $n^{25}D$ 1.5020; d^{25}_4 0.9522; MR_D (calcd.), 60.16; MR_D (obsd.), 61.66.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.24; H, 10.49; unsaturation, 3.0 ⌐¬; A. H., 1.0. Found: C, 81.20; H, 10.82; unsaturation, 3.0 (Pt) ⌐¬; A. H. (Zerewitinoff), 1.0.

Acknowledgment.—The authors are indebted to Mrs. Silvia P. Solar and Mr. S. M. Nagy for the analyses given in this paper, to Miss Therese M. Harrington for the spectroscopic determinations, to Drs. Emile Sakal and John T. Plati and to Mr. Frank X. Grossi for some of the early experiments in this field. This article is a part of a research program on the synthesis of vitamins A and D, support of which was derived in part through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Parke, Davis and Company, The Upjohn Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

Summary

1. Several intermediates for the synthesis of vitamin A and vitamin A analogs have been synthesized and characterized.

2. 1-[Cyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1 and related epoxides have been synthesized and their physical and chemical properties studied.

CAMBRIDGE 39, MASSACHUSETTS
RECEIVED DECEMBER 27, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. V. The *i*-Cholesterylamines

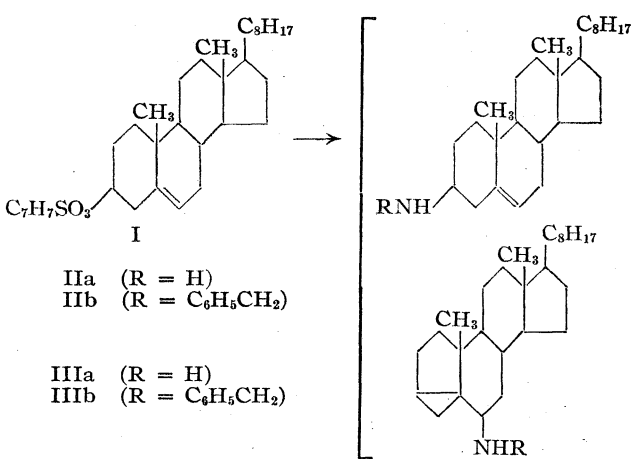
BY PERCY L. JULIAN, ARTHUR MAGNANI, EDWIN W. MEYER AND WAYNE COLE

In connection with transformations involving replacement reactions at the C_3 position of $\Delta^{5,6}$ unsaturated steroids, it was decided to explore carefully the possible role of *i*-steroids as intermediates in such conversions. The formation of an *i*-steroid has been shown to take place readily when the 3-*p*-toluenesulfonate of a $\Delta^{5,6}$-steroid is treated with an appropriate reagent in the presence of a proton acceptor[1]; however, in the absence of the latter a simple replacement seems to occur.

Our attempts to replace the 3-*p*-toluenesulfonate group by amino groups resulted in varying yields of 3-amino steroids, the relative basicity of the reagent employed strongly influencing the course of the reaction. It seemed logical to assume that we might be encountering the hitherto unknown *i*-steroid amines.

The unexpected ether solubility of the hydrochlorides of the *i*-steroid amines obscured at first their presence among the reaction products. Advantage was taken, however, of this property for their separation and characterization. This communication reports a study of certain *i*-cholesterylamines.

When cholesteryl *p*-toluenesulfonate (I) was



IIa (R = H)
IIb (R = $C_6H_5CH_2$)

IIIa (R = H)
IIIb (R = $C_6H_5CH_2$)

heated with ammonia at about 98°, there was obtained not only cholesterylamine (IIa)[2] but an isomeric amine, *i*-cholesterylamine (IIIa), which was the predominant product. The separation of the isomeric cholesterylamines was greatly facilitated by the ether solubility of *i*-cholesterylamine hydrochloride. This hydrochloride, which melted at 212–214°, gave the crystalline *i*-cholesterylamine (IIIa), m. p. 77–79°. Both the *i*-amine and its hydrochloride were dextrorotatory, possessing specific rotations of +34° and +20°, respectively, in contrast to the negative rotation of cholesterylamine and its hydrochloride.

The reaction of cholesteryl *p*-toluenesulfonate (I) and benzylamine was found to proceed in an analogous fashion. Here again two isomeric amines were formed. The reaction mixture was separated into two fractions on the basis of the ether solubilities of the amine hydrochlorides. From the ether-insoluble hydrochloride, there was isolated benzylcholesterylamine (IIb), a levorotatory crystalline solid which melted at 115–117°. The purified ether-soluble hydrochloride which melted at 217–218° and possessed a specific rotation of −27° gave benzyl-*i*-cholesterylamine (IIIb), a viscous liquid which could not be crystallized. Unlike the hydrochloride, the free base was dextrorotatory, $[\alpha]D$ + 12°.

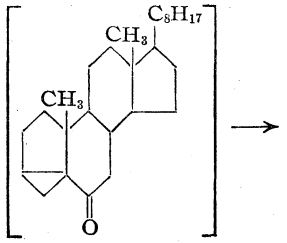
In order to prove the constitution of benzylcholesterylamine, benzyl-*i*-cholesterylamine and *i*-cholesterylamine, these amines were degraded by alkaline decomposition of the respective chloroamines followed by acid hydrolysis.[3] Upon treatment with an ethereal solution of hypochlorous acid, benzylcholesterylamine formed an N-chloro derivative which when decomposed with sodium ethoxide followed by acid hydrolysis gave cholesterylamine, identified as the acetyl derivative.[2] In a similar fashion benzyl-*i*-cholesterylamine was degraded. The product of this degradation, *i*-cholesterylamine, was identified as the crystalline hydrochloride. Further degradation of this hydrochloride via the N-chloro derivative gave a neutral product which, in spite of the inability to crystallize it, was *i*-cholestenone (IV), for upon treatment with hydrochloric acid in acetic acid in the known way,[4] it readily yielded 3(β)-chlorocholestane-6-one. Thus the position

(1) (a) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); (b) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); (c) Wallis, Fernholz and Gephardt, THIS JOURNAL, **59**, 137 (1937).

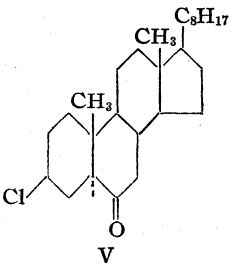
(2) Windaus and Adamla, *Ber.*, **44**, 3051 (1911).

(3) *Cf.* Hellerman and Sanders, THIS JOURNAL, **49**, 1742 (1927).

(4) Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938).

IIIb ⟶ IIIa ⟶ 

IV



V

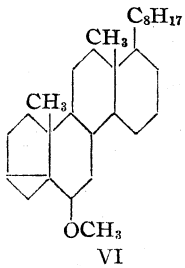
of the substituent amino group is adequately demonstrated in each instance.

During the investigation of the formation of benzylcholesterylamine and benzyl-*i*-cholesterylamine it was noted that as the reaction time increased the yield of benzyl-*i*-cholesterylamine decreased while that of benzylcholesterylamine increased. This suggested that the *i*-steroid amine was either the precursor of the C_3 substituted amine or the source of a common intermediate. The validity of this hypothesis was proved by the conversion of benzyl-*i*-cholesterylamine into benzylcholesterylamine with benzylamine in the presence of benzylammonium *p*-toluenesulfonate. Furthermore, reaction of benzyl-*i*-cholesterylamine hydrochloride with aniline gave cholesterylaniline (VII). Both of these transformations failed to proceed in the absence of an ammonium salt. This type of acid catalysis is in harmony with the conditions necessary for the "rearrangement" of *i*-steroid ethers.[5] The analogy of the *i*-steroid amines to the *i*-steroid ethers is strengthened by the nature of the reaction of *i*-cholesteryl methyl ether (VI) with benzylamine or aniline. In the presence of an ammonium salt, these reagents gave benzylcholesterylamine (IIb) and cholesterylaniline (VII), respectively. The attempted conversions failed in the absence of the ammonium salt. It is important to note that benzyl-*i*-cholesterylamine and *i*-cholesteryl methyl ether, in the presence of the proton donor, react more sluggishly with benzylamine than with aniline, an amine with a smaller basic dissociation constant. This may be explained through consideration of the following equilibria

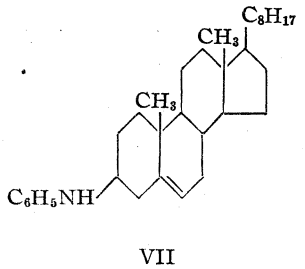
$$RNH_3^+ + i\text{-CholNHCH}_2C_6H_5 \rightleftharpoons RNH_2 + i\text{-Chol}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}\overset{H^+}{H}\text{CH}_2C_6H_5$$

$$RNH_3^+ + i\text{-CholOCH}_3 \rightleftharpoons RNH_2 + i\text{-Chol}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}\overset{H^+}{H}\text{CH}_3$$

As the basic strength of RNH_2 decreases, the concentration of the steroid ammonium and steroid oxonium ions should increase. Thus if these ions underwent conversion to the C_3 substituted amines, which appears plausible, the "rearrangement" should be more readily effected with amines of low basic strength. In any given instance, the equilibrium may be shifted to the right by an increase in concentration of RNH_3. This fact has been of value in effecting the reactions of benzyl-*i*-cholesterylamine and *i*-cholesteryl methyl ether with benzylamine.



VI



VII

(5) Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

Experimental[6]

Cholesterylamine (IIa) and *i*-Cholesterylamine (IIIa).—A mixture of 15.0 g. of cholesteryl *p*-toluenesulfonate and 18.0 g. of liquid ammonia was placed in a glass-lined steel bomb and heated with steam at about 98° for fifteen hours. After cooling the bomb to room temperature, the excess ammonia was allowed to evaporate and the residue was shaken with ether and 10% sodium hydroxide solution. Upon shaking the ethereal layer with excess 5% hydrochloric acid there separated a white, gelatinous hydrochloride which was centrifuged, washed with ether and dried. (The ether layer and washings which contained the *i*-amine hydrochloride was saved.) The crude, insoluble hydrochloride (4.0 g.) was shaken with 10% sodium hydroxide and ether. The water-washed ether layer gave, upon removal of solvent, 2.6 g. (23%) of white, waxy crystals of cholesterylamine which melted at 89–94°; $[\alpha]^{29}D$ −26° (115 mg. made up to 10 ml. with chloroform, α −0.30°, *l*, 1 dm.). For identification, a sample was converted to N-cholesterylacetamide,[3] m. p. 238–242°.

The ether solution which was separated from the insoluble cholesterylamine hydrochloride was washed with 5% hydrochloric acid and with water, and then concentrated to about 25 ml. After dilution with 50 ml. of acetone, the *i*-cholesterylamine hydrochloride slowly crystallized. The acetone-washed and dried hydrochloride weighed 7.6 g. (64%), m. p. 176–182°. Two crystallizations from ether–acetone raised the melting point to 212–214°; $[\alpha]^{29}D$ +20° (151.9 mg. made up to 5.1 ml. with chloroform, α +0.60°, *l*, 1 dm.).

Anal. Calcd. for $C_{27}H_{47}N\cdot HCl$: N, 3.32; Cl, 8.40. Found: N, 3.20; Cl, 8.13.

This hydrochloride was soluble in ether, benzene or methanol, but relatively insoluble in water or acetone.

The free amine was prepared from the salt by shaking a mixture of 1.0 g. of *i*-cholesterylamine hydrochloride, 100 ml. of ether and 10 ml. of 10% sodium carbonate solution. The clear ether layer was washed twice with sodium carbonate solution, four times with distilled water and then dried and concentrated to a white wax which could be crystallized directly from pentane or sublimed *in vacuo*. At about 1×10^{-2} mm., the amine vaporized

(6) Analyses by Mr. R. Schroeder of this Laboratory, Dr. T. S. Ma of the University of Chicago and Mr. C. W. Beazley of Micro-Tech Laboratories, Skokie, Illinois.

from a bath held at 115° and crystallized in the receiver as white rosettes, m. p. 77–79°. Recrystallization from pentane did not change the melting point; $[\alpha]^{30}D$ +34° (371 mg. made up to 3.64 ml. with chloroform, α +3.42°, l, 1 dm.).

Anal. Calcd. for $C_{27}H_{47}N$: C, 84.08; H, 12.28; N, 3.63. Found: C, 84.10; H, 12.00; N, 3.44.

A sample of the *i*-cholesterylamine was reconverted to the hydrochloride, m. p. 212–214°. The amine failed to give a crystalline derivative with benzaldehyde, but with acetic anhydride in pyridine it gave N-*i*-cholesterylacetamide which crystallized from ether as white prisms, m. p. 142–143°.

Anal. Calcd. for $C_{29}H_{49}ON$: C, 81.43; H, 11.55; N, 3.27. Found: C, 81.35; H, 10.87; N, 3.16.

Benzycholesterylamine (IIb) and Benzyl-*i*-cholesterylamine (IIIb).—A solution of 100 g. of cholesteryl-*p*-toluenesulfonate in 200 ml. of benzylamine was refluxed for two hours, chilled and poured into ether. The benzylammonium *p*-toluenesulfonate (48.7 g.) was filtered and washed with ether. The combined ethereal filtrate was concentrated, steam distilled and the residue was dissolved in ether. The white, gelatinous precipitate which formed upon shaking the water-washed ether solution with 10% hydrochloric acid was separated by centrifugation. The hydrochloride, after dissolving in a small volume of ethanol, was decomposed with 10% sodium hydroxide solution. The free base was then extracted with ether, washed free of alkali and dried. The solid remaining after removal of ether crystallized from acetone yielding 19.6 g. of crude benzylcholesterylamine melting at 110–115°. Several recrystallizations from acetone gave colorless prisms melting at 115.5–117°; $[\alpha]^{33}D$ −25° (164.2 mg. made up to 5 ml. with chloroform, α −0.83°, l, 1 dm.).

Anal. Calcd. for $C_{34}H_{53}N$: C, 85.83; H, 11.22. Found: C, 86.02; H, 10.88.

The amine formed an acetyl derivative melting at 153–154°, a picrate melting at 195–198° (dec.) and a benzenesulfonamide melting at 151–153°.

The ether solution and washings separated from the gelatinous hydrochloride were washed with water, dried and concentrated to a solid residue (40.9 g.). The residue when crystallized from chloroform–acetone gave 34.5 g. (40%) of benzyl-*i*-cholesterylamine hydrochloride melting at 217–218° (dec.), $[\alpha]D$ −27° (126 mg. made up to 5 ml. with chloroform, αD −0.68°, l, 1 dm.).

Anal. Calcd. for $C_{34}H_{53}N$: C, 85.83; H, 11.23. Found: C, 85.42, 85.51; H, 11.34, 10.98.

Upon refluxing the solution of cholesteryl *p*-toluenesulfonate in benzylamine for twenty-two hours, the yield of benzylcholesterylamine was increased to 52%; however, the yield of benzyl-*i*-cholesterylamine was decreased to 10%. A further increase in reflux time (forty-six hours) complicated matters with the formation of considerable tribenzylamine,[7] an amine which also forms an ether and water insoluble hydrochloride.

Degradation of Benzylcholesterylamine.—A 4.75-g. sample of benzylcholesterylamine was dissolved in 100 ml. of dry ether, cooled to −5° and treated with 50 ml. of an ethereal solution of hypochlorous acid[8] (0.0152 g./ml.). The amine which had separated from solution on chilling, dissolved and soon a solid separated. After five minutes at room temperature (solid dissolved on warming) the ether solution was washed with 20 ml. of cold 8% aqueous sulfuric acid, 20 ml. of cold 5% sodium hydroxide solution and finally water until free of alkali. (A small quantity of the N-chloramine was separated as a white solid, m. p. 119–124°.) The dried ether solution was treated with a solution of 1.0 g. of sodium in 100 ml. of ethanol. Sodium chloride separated. The ether was removed by distillation and the remaining solution was refluxed for thirty minutes. The mixture was then steam distilled after the addition of 60 ml. of 1:5 hydrochloric acid. Benzaldehyde was evident in the distillate (gave 1.62 g. of the 2,4-dinitrophenylhydrazone, m. p. 237–238°). The residue was made basic with 50 ml. of 10% sodium hydroxide and extracted with ether. The water-washed ether layer was shaken with an aqueous solution of *p*-toluenesulfonic acid and the resulting precipitate was filtered, washed with ether and dried. The dry cholesterylammonium *p*-toluenesulfonate weighed 4.4 g. and melted at 276–278°.

One gram of this salt was decomposed in ethanol with dilute sodium hydroxide. The amine was taken up in ether, washed with water, dried and concentrated. It was then treated with 1 ml. of acetic anhydride in 20 ml. of ether to yield 0.7 g. of once-recrystallized (ethanol) N-cholesterylacetamide, m. p. 238–240° which gave no depression with that previously described.

Degradation of Benzyl-*i*-cholesterylamine.—A solution of 5.12 g. of benzyl-*i*-cholesterylamine hydrochloride in 100 ml. of ether was shaken with 10% sodium hydroxide, washed with water and dried. This solution was then treated with 50 ml. of hypochlorous acid solution as described above. After treatment with sodium ethoxide, the ethanol solution was refluxed for seventy-five minutes (it no longer liberated iodine from an acidified potassium iodide solution). After the addition of 60 ml. of 1:5 hydrochloric acid, the mixture was refluxed for forty-five minutes and steam distilled (benzaldehyde). The residue, a brown gum, was taken up in ether and washed with 10% sodium hydroxide solution, 10% hydrochloric acid and water. The gum remaining after removal of solvent from the dried ether solution was crystallized from acetone; 2.7 g. of white solid. A 2.2-g. sample recrystallized from chloroform–acetone gave 2.0 g. of material melting at 201–205°. Several recrystallizations from the same solvent mixture and one from ether–acetone raised the melting point to 212–215°. This substance gave no depression in melting point when mixed with a sample of *i*-cholesterylamine hydrochloride.

Degradation of *i*-Cholesterylamine.—A solution of 1.05 g. of *i*-cholesterylamine hydrochloride (material prepared from the *i*-benzyl compound as described above) in ether was shaken with 10% sodium hydroxide solution, washed with water and dried. It was then treated at −10° with 6.2 ml. of an ether solution of hypochlorous acid (0.021 g./ml.). After five minutes, the solution was washed with 5% sodium hydroxide solution, water and dried. Titration of the iodine liberated by 1.0 ml. of the ether solution from acidified potassium iodide indicated that the conversion to the N-chloramine had taken place in 84% yield. The ether solution was then poured into a solution of 0.5 g. of sodium in 25 ml. of ethanol, the ether removed by distillation, and the remainder refluxed for thirty minutes. The mixture was then diluted with 100 ml. of cold water and acidified with dilute hydrochloric acid. After standing overnight, the mixture was extracted with ether. The residue remaining after removal of ether from the washed and dried solution could not be crystallized from methanol or acetone even after seeding with *i*-cholestenone. Thus it was taken up in 10 ml. of warm glacial acetic acid, chilled and treated with 2 ml. of concentrated hydrochloric acid. The solid which crystallized upon scratching was filtered, washed with methanol and dried; 0.5 g., m. p. 126–131°. Recrystallization from methanol raised the melting point to 130–133°. A mixture of this material with an authentic specimen of 3(β)-chlorocholestane-6-one[9] showed no depression in melting point.

Rearrangement of Benzyl-*i*-cholesterylamine to Benzylcholesterylamine.—A solution of 7.5 g. of benzyl-*i*-cholesterylamine and 5.0 g. of benzylammonium *p*-toluenesulfonate in 20 ml. of benzylamine was refluxed for twenty-three hours. The golden-yellow solution was poured into ether and the benzylammonium *p*-toluenesulfonate (5.0 g.) was separated and washed with ether. The ether filtrate was concentrated and steam distilled.

(7) *Cf.* Nozaki, THIS JOURNAL, **64**, 2920 (1942).

(8) Goldschmidt, *Ber.*, **46**, 2728 (1913).

(9) Windaus and Dalmer, *ibid.*, **52**, 162 (1919).

Upon shaking an ethereal solution of the residue with 10% hydrochloric acid, a gelatinous precipitate formed. The hydrochloride was separated by centrifugation, washed three times with ether and decomposed in ethanol solution with 10% sodium hydroxide solution. The amine was extracted with ether and washed with water. The residue remaining after removal of solvent from the dried solution was crystallized from acetone yielding 3.4 g. (56.5%) of fine, white crystals melting at 115–117°. These gave no depression in melting point when mixed with a sample of benzylcholesterylamine.

The ether washings of the gelatinous hydrochloride gave 1.5 g. of unchanged benzyl-*i*-cholesterylamine hydrochloride melting at 216–218° (dec.).

Reaction of Benzyl-*i*-cholesterylamine Hydrochloride with Aniline.—A solution of 3.0 g. of benzyl-*i*-cholesterylamine hydrochloride in 15 ml. of aniline was refluxed for four hours. Upon cooling, the mixture set to a semi-solid mass. It was then digested with ethanol and chilled. The solid was separated, washed with ethanol and dried. The dry material, 2.3 g. (85%) of white plates, melted at 189–191°. A sample of the compound gave no depression in melting point when mixed with cholesterylaniline.[10]

In a similar experiment in which the free amine, benzyl-*i*-cholesterylamine, was employed, the amine was recovered unchanged.

Reaction of *i*-Cholesteryl Methyl Ether with Benzylamine.—A solution of 3.0 g. of *i*-cholesteryl methyl ether[1a] and 3.0 g. of benzylammonium *p*-toluenesulfonate in 20 ml. of benzylamine was refluxed for twenty-two hours. The solution was poured into water and extracted with ether. Upon shaking the ethereal layer with dilute hydrochloric acid an insoluble hydrochloride separated. The hydrochloride was centrifuged, washed three times with ether and then decomposed in ethanol with 10% sodium hydroxide. An ether extract of the free amine was washed with water, dried and concentrated. Upon crystallization from acetone, the yellow residue yielded 1.5 g. of white prisms melting at 115–118°. This material showed no depression in melting point when mixed with a sample of benzylcholesterylamine.

Upon heating a 1.0-g. sample of the *i*-ether with 5 ml. of benzylamine in a closed tube at 240° for eighteen hours, the *i*-ether was recovered unchanged.

Reaction of *i*-Cholesteryl Methyl Ether with Aniline.—A mixture of 0.6 g. of carefully purified *i*-cholesteryl methyl ether and 5 ml. of freshly distilled aniline containing a few mg. of *p*-toluenesulfonic acid was refluxed from an oil-bath at 190° for two hours and then allowed to cool. The semi-solid mass was slurried with 10 ml. of methanol, filtered, washed with methanol and dried. The resulting cholesterylaniline, 0.65 g. of white flakes, melted at 190°. This gave no depression in melting point when mixed with a sample of cholesterylaniline prepared in the known manner.[10]

In a similar experiment, in which the *p*-toluenesulfonic acid was omitted, the *i*-ether was recovered unchanged.

(10) Lieb, Winkelmann and Koeppl, *Ann.*, **509**, 214 (1934).

Summary

1. Cholesteryl *p*-toluenesulfonate reacts with ammonia and with primary aliphatic amines to give 6-amino-*i*-cholestenes accompanied by some 3-amino-5-cholestenes.

2. *i*-Cholesterylamine and benzyl-*i*-cholesterylamine are described and their structures proved by stepwise degradation to the known 3(β)-chlorocholestan-6-one.

3. Benzyl-*i*-cholesterylamine can be transformed into benzylcholesterylamine by treatment with benzylamine and benzylammonium toluenesulfonate. The necessity of the presence of the salt in this reaction points to an ionic mechanism for the conversion of the *i*-steroid into the normal steroid and further corroborates the known acid-catalyzed reactivity of the *i*-steroids.

CHICAGO, ILLINOIS RECEIVED NOVEMBER 28, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY OF THE UNIVERSITY OF CHICAGO]

Preparation of 17-Ketosteroids from Enol Acetates of 20-Ketosteroids[1a]

BY CHARLES W. MARSHALL, THEODORE H. KRITCHEVSKY, SEYMOUR LIEBERMAN[1b] AND T. F. GALLAGHER[1b]

The 20-ketosteroids are obtainable in good yield from accessible natural products. It appeared to us that oxidation of the enol acetates might offer a promising procedure for the preparation of 17-ketosteroids from these substances and we have accordingly investigated this problem using four different 20-ketosteroids. The general reactions are summarized in the partial formulations of Fig. 1. The enol acetates were prepared by the method of Bedoukian[2] and from the three pregnane derivatives studied, only one enol acetate was obtained. The structure of the product was proved by ozonolysis to the corresponding 17-ketosteroid. From 3(β)-hydroxy-20-ketoallopregnane, two stereoisomeric enol acetates were obtained which must be regarded as *cis* and *trans* isomers about the double bond from C-17 to C-20, since both compounds upon ozonolysis followed by saponification yielded isoandrosterone. The compound with higher melting point has been arbitrarily designated as the *trans*-form. For preparative purposes, isolation of the enol acetate is

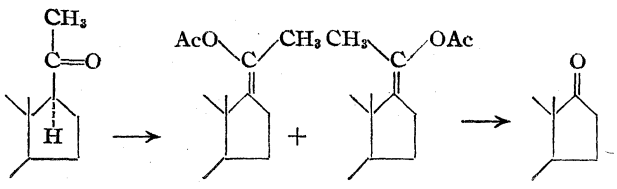


Fig. 1.

(1a) The work described in this paper was supported in part by a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council and in part by grants from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago. Presented before the Midwest Regional Meeting of the American Chemical Society, June, 1947.

(1b) Present address: Sloan–Kettering Institute for Cancer Research, New York 21, N. Y.

(2) Bedoukian, THIS JOURNAL, **67**, 1430 (1945).

TABLE I

ENOL ACETATES OF 20-KETOSTEROIDS

No.	Derivatives of Δ^{17}-pregnene	Cryst. form	M. p.[a] °C.	$[\alpha]_D$[b]	Formula	Composition, % Calcd. C	Found C	Calcd. H	Found H
1	3(α),20-Diacetoxy	Prisms	141.5–142	+ 60	$C_{25}H_{38}O_4$	74.59	74.56	9.51	9.44
2	3(α),11(α),20-Triacetoxy	Needles	218 –220	– 19	$C_{27}H_{40}O_6$	70.40	70.65	8.75	8.61
3	3(α),12(α),20-Triacetoxy	Prisms	174 –175.5	+165[c]	$C_{27}H_{40}O_6$	70.40	70.47	8.75	8.73
4	3(α),12(α),20-Triacetoxy-21-benzal	Prisms	261 –263[d]	+118	$C_{34}H_{44}O_6$	74.42	74.41	8.08	8.07
5	3(β),20-Diacetoxy-Δ^{17}-allopregnene (*cis*)	Plates	121.5–122.5	+ 21	$C_{25}H_{38}O_4$	74.59	74.45	9.51	9.56
6	3(β),20-Diacetoxy-Δ^{17}-allopregnene (*trans*)	Ndls.	172.5–173.5	+ 12	$C_{25}H_{38}O_4$	74.59	74.53	9.51	9.47

[a] All melting points are corrected. [b] In $CHCl_3$. [c] +173° in acetone. [d] Sinter 257°.

unnecessary and the sirupy enol acetate can be directly ozonized without further purification.

Ozonolysis of the enol acetate proceeded smoothly and in satisfactory yield except with 3(α),12(α)-20-triacetoxy-Δ^{17}-pregnene. When this compound was ozonized in the same manner used for the other four substances, two products were obtained in approximately equal amounts. One was the anticipated 17-keto derivative and the other was a crystalline substance of melting point 217–218.5° and $[\alpha]^{25}D$ +40° ($CHCl_3$) which will be reported in detail at a later time. None of the other compounds investigated yielded a comparable by-product.

The enol acetate of 3(α),12(α)-dihydroxy-20-keto-21-benzalpregnane was prepared and the ultraviolet absorption spectrum of this compound is shown in Fig. 2. When this enol acetate was oxidized with O_3 or with CrO_3, no recognizable product was obtained. This experience is similar to that of Koechlin and Reichstein,[3] who oxidized the enol chloride of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane without obtaining any detectable amount of the 17-keto derivative, although 3(β)-acetoxy-20-keto-21-benzalallopregnane was converted to isoandrosterone in 45% yield by the same reactions. Since the preparation of 17-ketosteroids over the benzal derivatives appeared to be less advantageous than the method already described, further work on these compounds was abandoned.

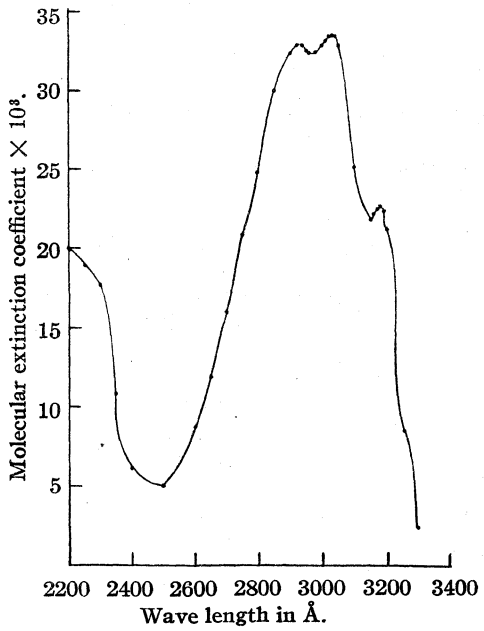


Fig. 2.—Absorption spectrum of the enol acetate of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane in 95% ethanol.

(3) Koechlin and Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

Experimental

Preparation of Enol Acetates of 20-Ketopregnane Derivatives.—A solution of 2 millimoles of the ketone and 2 millimoles of *p*-toluenesulfonic acid in 75 cc. of acetic anhydride was distilled slowly through a short unpacked column until most of the acetic anhydride had been removed (four to five hours). The residual solution was chilled, water was added, and after a short interval the product was extracted with ether, which was in turn washed with sodium hydroxide solution and with water, dried over sodium sulfate and the ether removed. The dark residue was dissolved in petroleum ether and purified by passage through a column of aluminum oxide. The colorless enol acetates were recovered in the petroluem ether eluates and were recrystallized from this solvent. The characteristics of the products are recorded in Table I. The yield of crystalline enol acetate was between 60 and 70%. The isomers 5 and 6 required extensive chromatography to effect separation, and for this reason the yield was much lower.

Ozonolysis of the Enol Acetates.—The preparation of 3(α),11(α)-diacetoxy-17-ketoetiocholane is typical. A solution of 490 mg. of the enol acetate in 400 cc. of a 1:1 mixture of anhydrous methanol and ethyl acetate was chilled to −40° and five mole equivalents of ozone in a 6% stream were passed through the solution. A 5% palladium–calcium carbonate catalyst (2.5 g.) was added and the mixture was shaken in an atmosphere of hydrogen until there was no further uptake (less than fifteen minutes). After removal of the catalyst and solvent, the product was purified by chromatographic fractionation on aluminum oxide. The yield of analytically pure material based on the enol acetate was 51%. The characteristics of the products are recorded in Table II.

Hydrolysis of Acetylated 17-Ketosteroids.—Partial hydrolysis of compounds number 8 and 11 was accomplished at room temperature with 0.15 *N* sodium hydroxide in 85% ethanol. The monoacetate from 11 was amorphous.[4] The monoacetates obtained from the ozonolysis of compounds number 1, 5 and 6 were also hydrolyzed in this manner. Complete hydrolysis of the diacetate no. 8 was accomplished by heating under a reflux in an atmosphere of nitrogen with 0.5 *N* sodium hydroxide in 75% ethanol for one-half hour; the diacetate no. 11 required heating with 1.0 *N* sodium hydroxide in 75% ethanol for one hour. The constants are recorded in Table II.

(4) Reich, *Helv. Chim. Acta*, **28**, 863 (1945).

TABLE II

17-KETOSTEROIDS FROM THE OZONIZATION OF 20-ENOL ACETATES

No.	Derivatives of 17-ketoetiocholane	Obt. from	Cryst. form	Solvent	M. p.[e] °C.	[α]D[g]	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
7	3(α)-Hydroxy[a]	1	Needles	C_6H_6-lig.	151 –152[f]	+109	$C_{19}H_{30}O_2$		[i]		
8	3(α),11(α)-Diacetoxy	2	Needles	Ligroin	170.5–172	+ 43	$C_{23}H_{34}O_5$	70.74	70.47	8.78	8.80
9	3(α)-Hydroxy-11(α)-acetoxy	8	Prisms	Ligroin	147 –148	+ 25	$C_{21}H_{32}O_4$	72.38	72.17	9.26	9.63
10	3(α),11(α)-Dihydroxy	8, 9	Prisms	Et acet.	170.5–171	+ 80	$C_{19}H_{30}O_3$	74.47	74.43	9.87	9.55
11	3(α),12(α)-Diacetoxy[b]	3	Prisms	Acetone–lig.	156 –157	+193[h]	$C_{23}H_{34}O_5$	70.74	70.71	8.78	8.75
12	3(α),12(α)-Dihydroxy[c]	11	Needles	Et acet.	164.5–165	+167	$C_{19}H_{30}O_3$	74.47	74.50	9.87	9.54
13	3(β)-Hydroxy-allo[d]	5, 6	Prisms	Et acet.-lig.	174 –175	+ 97	$C_{19}H_{30}O_2$		[i]		

[a] Reported values,[5] m. p. 150–151°;[6] m. p. 151–152°, transition point, 140–142°; [α]D +100°; $[\alpha]_{5461}$ +130° (ethanol). [b] Reported values,[7] m. p. 162–162.5°; [α]D +176°; $[\alpha]_{5461}$ +214° (acetone);[8] m. p. 157–158.5°; [α]D +179° (acetone). [c] Reported values,[4] m. p. 165.5–168°; m. p. 164–165°.[8] No rotation reported. [d] Reported values,[9] m. p. 174–174.5°; [α]D +87° (methanol). [e] All melting points are corrected. [f] Softens at 140°. [g] In $CHCl_3$. [h] +177° in acetone. [i] Identified by melting point of a mixture and comparison of the infrared spectrum with an authentic specimen. The infrared spectra were determined and compared by Dr. Konrad Dobriner, Sloan–Kettering Institute, New York 21, N. Y., to whom we extend our thanks.

Enol Acetate of 3(α),12(α)-Diacetoxy-20-keto-21-benzalpregnane.—This substance is obtained as one of the reaction products from the acetylation of the dihydroxy benzal derivative by heating twenty-four hours with acetic anhydride and pyridine. It is also obtained in small amounts from the acetylation catalyzed with perchloric acid according to the method of Whitman and Schwenk,[10] especially if the reaction mixture is permitted to stand at room temperature for forty-five minutes. It is most readily separated by chromatography upon aluminum oxide or by fractional crystallization of the acetylation product from acetone. It was recrystallized from glacial acetic acid, and its characteristics are recorded in Table I.

3(α)-Acetoxy-12(α)-hydroxy-20-keto-21-benzalpregnane.—When 3(α),12(α)-dihydroxy-20-keto-21-benzalpregnane is acetylated using milder conditions (pyridine–acetic anhydride at room temperature; acetic anhydride in the presence of low concentrations of perchloric acid at 5° for ten minutes), the 3-monoacetoxy derivative is obtained in good yield. The product was recrystallized from acetone as plates, m. p. 210–211°; $[\alpha]^{21}D$ +177° (ethanol).

Anal. Calcd. for $C_{30}H_{40}O_4$: C, 77.25; H, 8.69. Found: C, 77.57; H, 8.68.

Upon more vigorous acetylation with either pyridine and acetic anhydride or with acetic anhydride and sodium acetate, the monoacetate is converted to the known diacetate,[3] m. p. 123–126°.

(5) Ruzicka, Goldberg, Meyer, Brüngger and Eichenberger, *Helv. Chim. Acta*, **17**, 1395 (1934).

(6) Callow, *Biochem. J.*, **33**, 559 (1939).

(7) Reich and Reichstein, *Helv. Chim. Acta*, **26**, 2102 (1943).

(8) Ettlinger and Fieser, *J. Biol. Chem.*, **164**, 451 (1946).

(9) Ruzicka, Goldberg and Brüngger, *Helv. Chim. Acta*, **17**, 1389 (1934).

(10) Whitman and Schwenk, THIS JOURNAL, **68**, 1865 (1946).

Summary

1. The conversion of 20-ketosteroids to 17-ketosteroids was accomplished by preparation of the enol acetates followed by ozonolysis.

2. 3(α)-Hydroxy-17-ketoetiocholane, 3(β)-hydroxy-17-ketoetioallocholane, 3(α),12(α)-dihydroxy-17-ketoetiocholane, and 3(α),11(α)-dihydroxy-17-ketoetiocholane were prepared in this way.

3. The enol acetate of 3(β)-hydroxy-20-keto-allopregnane was obtained in two forms which were shown to be geometric isomers by ozonolysis to isoandrosterone.

4. The enol acetate of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane was prepared and its ultraviolet absorption spectrum is described.

RECEIVED NOVEMBER 12, 1947

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY][1]

4,4′-Dichlorodibutyl Ether and its Derivatives from Tetrahydrofuran

BY KLIEM ALEXANDER AND L. E. SCHNIEPP

Cleavage of the tetrahydrofuran ring by acyl halides to give halogen-substituted butyl esters has been reported by Goldfarb and Smorgonskii,[2] Cloke and Pilgrim[3] and Manchen and Schmidt.[4] The reaction of tetrahydrofuran with acetyl chloride, catalyzed with a small amount of anhydrous zinc chloride, gives a good yield of δ-chlorobutyl acetate plus small amounts of compounds of the formulas: $CH_3COO(CH_2)_4O(CH_2)_4Cl$ and $CH_3COO(CH_2)_4O(CH_2)_4O(CH_2)_4Cl$.[3]

Because of the apparent ease with which acyl halides cleave the hydrogenated furan ring, an investigation was undertaken to determine whether or not inorganic acid chlorides react similarly. Preliminary experiments showed that phosphorus oxychloride, thionyl chloride and silicon tetrachloride, when catalyzed with zinc or zinc chloride, reacted vigorously with tetrahydrofuran. In no case was it found possible to isolate the phosphate, sulfite, or silicate esters; however, decomposition

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Y. L. Goldfarb and L. M. Smorgonskii, *J. Gen. Chem. (USSR)*, **8**, 1516–1522 (1938).

(3) J. B. Cloke and F. J. Pilgrim, THIS JOURNAL, **61**, 2667 (1939).

(4) F. Manchen and W. Schmidt, U. S. Patent 2,314,454 (1943).

of the reaction mixtures with water, followed by vacuum distillation of the water-insoluble products, gave a fair yield of 4,4′-dichlorodibutyl ether, a high boiling liquid which has been previously prepared from 4-chlorobutanol by Trieschmann.[5]

During these investigations a number of reports on German technical developments became available through the Office of Technical Services. Several of these reports dealt directly with the reactions under investigation. Delfs[6] in his discussion of the polymerization of alkylene oxides shows that tetrahydrofuran is readily converted to polyalkylene ethers, with chlorine end-groups, by the action of thionyl chloride catalyzed with ferric chloride. Technical development of this reaction led to the production of synthetic lubricants.[7]

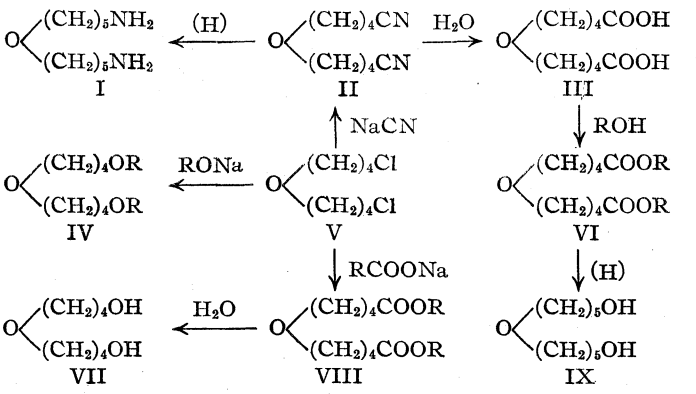
A report by Krzikalla and Maier[8] discusses the cleavage of cyclic ethers with thionyl chloride. The type of catalyst used was found to be of considerable importance. Zinc chloride favored the formation of 1,4-dichlorobutane from tetrahydrofuran, whereas with sulfuric acid as the catalyst high yields of 4,4′-dichlorodibutyl ether were obtained. The type of product was also found to be a direct function of the molar ratio of thionyl chloride to tetrahydrofuran. By varying that ratio, greater or lesser amounts of 1,4-dichlorobutane, 4,4′-dichlorodibutyl ether, and a trimeric ether of the formula $Cl(CH_2)_4O(CH_2)_4O(CH_2)_4Cl$ were obtained.

The superiority of sulfuric acid as a catalyst for the cleavage of tetrahydrofuran by phosphorus oxychloride was established in our subsequent investigations, and yields of 4,4′-dichlorodibutyl ether were improved up to 65–70% of the theoretical.

The conversion of tetrahydrofuran to 4,4′-dichlorodibutyl ether takes place by one of several possible mechanisms. Our failure to isolate chlorobutyl phosphate esters which might convert to the ether on heating, and the observed polymer formation when tetrahydrofuran was treated with thionyl chloride and ferric chloride at room temperature, indicate that the reaction is one of polymerization and depolymerization as discussed by Delfs.[6] This route of formation is also favored by the facts (1) that the high boiling residues from dichloroether distillations can be further converted to dichlorodibutyl ether by retreatment with phosphorus oxychloride, and (2) by the formation of the trimeric ether $Cl(CH_2)_4O(CH_2)_4O(CH_2)_4Cl$ when less than one-third mole of phosphorus oxychloride per mole of tetrahydrofuran is used in the reaction.

4,4′-Dichlorodibutyl ether is an interesting intermediate for the preparation of a variety of difunctional compounds. The halogens are readily replaced by cyano, alkoxy, acyloxy and similar groups. Oxydivaleric acid and its esters, 5,5′-diaminodiamyl ether, 4,4′-dihydroxydibutyl ether and 5,5′-dihydroxydiamyl ether have been prepared from such derivatives.

Derivation of these products may be illustrated as follows



Attempts to apply the same ring cleavage reaction to tetrahydropyran and tetrahydromethylfuran gave much lower yields of the expected dichlorodiamyl ethers. Tetrahydropyran apparently underwent side reactions involving dehydrohalogenation of the cleavage products and yielded a complex reaction product from which only a small yield of 5,5′-dichlorodiamyl ether could be isolated.

Experimental

4,4′-Dichlorodibutyl Ether (V).—A mixture of 72 g. (1.0 mole) of tetrahydrofuran and 51.2 g. (0.33 mole) of phosphorus oxychloride was placed in a 1-liter, three-necked flask equipped with stirrer, reflux condenser, and thermometer. The mixture was cooled in a water bath, and 10 cc. of concentrated sulfuric acid added gradually with stirring. The temperature was then slowly raised by heating in a bath. At about 80° a vigorous exothermic reaction occurred and cooling was necessary to keep the reaction under control. The temperature was controlled at 80–100° until the exothermic reaction subsided. This period usually lasted about forty minutes and was accompanied by refluxing, some evolution of hydrogen chloride, and the precipitation of a gelatinous, phosphorus-containing material. The reaction mixture was then held at 90–100° for an additional ten minutes after which 100 cc. of water was added and heating to reflux continued for thirty minutes longer.

The unchanged tetrahydrofuran and the by-product 1,4-dichlorobutane were removed by distilling their water azeotropes. The water and oil layers were separated after the residue from this distillation had cooled. The aqueous layer was extracted twice with ether, the ether and oil layers combined and water-washed. The ether was evaporated and the residue distilled under reduced pressure. The main fraction of distillate boiling at 83–87° (0.4–0.6 mm.) weighed 64.5 g. and was essentially pure 4,4′-dichlorodibutyl ether. The yield, based on tetrahydrofuran of which 5.5 g. was recovered, was 70% of the theoretical. Three grams of 1,4-dichlorobutane was isolated from the azeotropic distillates.

Refractionation of a composite of 250 g. of 4,4′-dichlorodibutyl ether gave 245 g. of a colorless, water-insoluble product having the following properties: b. p. 84–86° (0.5 mm.), d^{25}_4 1.069, $n^{25}D$ 1.4567. *Anal.* Calcd. for

(5) H. G. Trieschmann, U. S. Patent 2,245,509 (1941).

(6) Delfs, P. B. 717, O. T. S., U. S. Department of Commerce.

(7) F. H. Roberts, P. B. 898, O. T. S., U. S. Department of Commerce.

(8) Krzikalla and Maier, P. B. 631, O. T. S., U. S. Department of Commerce.

$C_8H_{16}OCl_2$: C, 48.2; H, 8.09; Cl, 35.6. Found: C, 48.6; H, 7.88; Cl, 35.5. Calcd. for $Cl(CH_2)_4O(CH_2)_4Cl$: M_D 50.52; M_D found 50.70.

The same product was obtained in lower yields by treating tetrahydrofuran with phosphorus trichloride, thionyl chloride, phosgene, and silicon tetrachloride, all catalyzed by sulfuric acid; and with phosphorus oxychloride catalyzed by zinc, zinc chloride, aluminum chloride, ferric chloride, chlorosulfonic acid and metaphosphoric acid.

The reaction was also run in solvents such as benzene, toluene and carbon tetrachloride, but in all cases the yield was lower than by the method described.

Polymerization of Tetrahydrofuran.—Tetrahydrofuran was polymerized by the method of Delfs[6] to determine whether such a polymeric material could be converted to 4,4′-dichlorodibutyl ether.

Tetrahydrofuran was mixed with thionyl chloride and anhydrous ferric chloride in a molar ratio of 85.5:12:2.5 and allowed to stand for eleven days at room temperature, in a flask protected against entry of atmospheric moisture. Water was then added and the unchanged tetrahydrofuran recovered by distillation. The water-insoluble oil layer was separated, washed with water, and heated to 140° under vacuum (0.35 mm.). No distillate other than water was collected. From 92.5 g. of original reaction mixture 46.5 g. of a brown, oily liquid was obtained. This material solidified to a waxy solid when cooled below 0°.

Anal. Found: C, 61.4; H, 10.26; Cl, 9.60.

The chlorine value indicates a molecular weight of 739 and x equal 8.5 for a polymer of the assumed structure $Cl[(CH_2)_4O]_x$-$(CH_2)_4Cl$.

Anhydrous aluminum chloride used in place of ferric chloride gave a comparable product in lower yield.

A 27.4 g. sample of this polymer was heated for two and one-half hours with 14.3 g. of phosphorus oxychloride and 0.25 g. of concentrated sulfuric acid. The reaction was only mildly exothermic at about 100° and the temperature of the reaction mixture was not allowed to exceed 125°. Addition of water, separation of the water-insoluble products, and distillation gave 14 g. (40%) of 4,4′-dichlorodibutyl ether, showing that partial depolymerization occurred on heating with inorganic acid halides.

Based on this observation, 157 g. of high-boiling and polymeric residues from earlier dichlorodibutyl ether preparations was heated with 71 g. of phosphorus oxychloride and 3 cc. of concentrated sulfuric acid. Workup and distillation of this reaction mixture gave 28 g. of 1,4-dichlorobutane, 35.4 g. of 4,4′-dichlorodibutyl ether, and 6.5 g. of a higher boiling [91–155° (0.5 mm.)] material.

4,4′-Dichlorodibutyl ether is partially destroyed under such reaction conditions, 50–75% being recovered, depending upon the severity of the conditions used.

1,4-Di-(δ-chlorobutoxy)-butane.—Tetrahydrofuran, 162 g. (2.25 moles), reacted with 77 g. (0.5 mole) of phosphorus oxychloride and 3 cc. of concentrated sulfuric acid. Distillation of the water-insoluble products of the reaction gave 85 g. (42.7%) of 4,4′-dichlorodibutyl ether, 39.4 g. of a distillate collected over the range of 120–160° at 1 mm., and 18.5 g. of a viscous liquid residue. Redistillation of the higher-boiling product gave a liquid having the following properties: b. p. 133° (0.6 mm.), $n^{23}D$ 1.4535, d^{23}_4 1.0444.

Anal. Calcd. for $C_{12}H_{24}O_2Cl_2$: Cl, 26.15. Found: Cl, 25.9.

This product is probably $Cl(CH_2)_4O(CH_2)_4O(CH_2)_4Cl$.[8]

5,5′-Dichlorodiamyl Ether.—Tetrahydropyran, 86 g. (1 mole), was mixed with 51.2 g. (0.33 mole) of phosphorus oxychloride and 2.5 cc. of concentrated sulfuric acid and the mixture stirred and heated to reflux for twelve hours. There was no evidence of an exothermic reaction such as was observed with tetrahydrofuran. Only a very gradual increase in boiling temperature, from 80 to 112°, occurred during the heating period. Hydrogen chloride was evolved throughout the refluxing period, the amount increasing with the increase in temperature. At the end of the heating period 100 cc. of water was added to the mixture and refluxing continued for one hour. Distillation of the water-insoluble reaction products gave 18 g. of 1,5-dichloropentane, 25 g. of a yellow liquid, b. p. 96–125° (0.5–0.8 mm.), and 26 g. of residue. Refractionation of the yellow liquid fraction gave 8.8 g. of a colorless liquid, b. p. 65–70° (3–4 μ); $n^{27}D$ 1.4580; d^{27}_4 1.0349; M_D calcd. for $Cl(CH_2)_5O(CH_2)_5Cl$, 59.76; M_D found 60.05.

Anal. Calcd. for $C_{10}H_{20}OCl_2$: Cl, 31.25. Found: Cl, 31.2.

No conditions were found whereby this compound could be prepared in better than 10–15% yields.

4,4′-Dichlorodiamyl Ether.—2-Methyltetrahydrofuran, 172 g. (2.0 moles) was mixed with 102.3 g. (0.67 mole) of phosphorus oxychloride and 1.3 g. of anhydrous zinc chloride. The mixture was heated to reflux for five hours during which the temperature gradually increased from 84 to 108°. The reaction mixture was diluted with water and heated to reflux for thirty minutes. The aqueous and oil layers were separated, the oil layer washed with water, and distilled. In addition to unchanged tetrahydromethylfuran, 1,4-dichloropentane and undistillable residue, 54 g. (23.8% yield) of 4,4′-dichlorodiamyl ether boiling at 69–75° (0.3 mm.) was obtained. Redistillation of this product yielded 38 g. of material having the following properties: b. p. 94–95° (0.88 mm.); $n^{25}D$ 1.4533; d^{25}_4 1.0191. M_D calcd., 59.76; found, 60.28.

Anal. Calcd. for $C_{10}H_{20}OCl_2$: C, 52.80; H, 8.87; Cl, 31.25. Found: C, 53.1; H, 8.85; Cl, 30.3.

No attempt was made to determine whether this product was a single compound or a mixture of the three possible isomeric 4,4′-dichlorodiamyl ethers.

Derivatives of 4,4′-Dichlorodibutyl Ether

4,4′-Dicyanodibutyl Ether (Oxydivaleronitrile) (II).—A mixture of 99.5 g. (0.5 mole) of 4,4′-dichlorodibutyl ether, 58 g. (1.18 moles) of pulverized sodium cyanide and 190 cc. of anhydrous methanol was charged into a steel hydrogenation bomb, shaken and heated to 150° for six hours. After the bomb had cooled, the reaction mixture was removed, filtered free of precipitated salt, and the methanol removed by evaporation on a steam-bath. The dark-colored residue was dissolved in ether, the solution filtered, and the filtrate washed with water. The ether was removed by evaporation and the residue heated to 200° at 0.7 mm. pressure. The small amount of distillate, 8 g., gave analytical and refractivity values for 4-methoxy-4′-cyanodibutyl ether.

Anal. Calcd. for $C_{10}H_{19}O_2N$: OCH_3, 16.74; N, 7.57; M_D 51.4. Found: OCH_3, 15.75; N, 7.78; M_D 51.6.

The undistilled material weighed 73 g., an 81% yield of oxydivaleronitrile. A sample of this dark-colored product was purified by distillation under high vacuum and had the following properties: b. p. 75–80° (10^{-4} mm.); $n^{26}D$ 1.4453; d^{26}_4 0.9627; M_D calcd. 49.54; found, 49.70.

Anal. Calcd. for $C_{10}H_{16}ON_2$: C, 66.6; H, 8.95; N, 15.55. Found: C, 66.55; H, 8.82; N, 15.29.

4,4′-Dicarboxydibutyl Ether (Oxydivaleric Acid) (III).—Oxydivaleronitrile, 45 g. (0.25 mole), was hydrolyzed by refluxing for five hours with a mixture consisting of 150 cc. of alcohol, 150 cc. of water, and 40 g. of sodium hydroxide. The alcohol was removed by distillation and the aqueous alkaline solution acidified with 9 N sulfuric acid. The product separated as a brown, crystalline solid. The yield was 49 g. or 90% of the theoretical. This crude product was dissolved in hot water, the solution treated with activated carbon, and filtered. The product crystallized as white leaflets, m. p. 88.5–89.5°.

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31; neut. equiv., 109.1. Found: C, 55.15; H, 8.13; neut. equiv., 110.4.

Both the crude and the distilled oxydivaleronitrile gave high yields of the desired acid.

A sample of this acid when heated with hydriodic acid

TABLE I

ESTERS OF OXYDIVALERIC ACID, ROOC—$(CH_2)_4$—O—$(CH_2)_4$—COOR

R	B. p., °C.	Pres., mm.	Yield, %	$n^{25}D$	d^{25}_4	Formula	Saponification equivalent Calcd.	Found
Ethyl	117–118	0.3	90	1.4356	0.9719	$C_{14}H_{26}O_5$	137.2	136.2
n-Butyl	172–174	1.0	75	1.4405	0.9622	$C_{18}H_{34}O_5$	165.2	166.1
Tetrahydrofurfuryl	220–221	0.66	67	1.4680	1.0883	$C_{20}H_{34}O_7$	193.2	195.2

TABLE II

4,4′-DIALKOXYDIBUTYL ETHERS, R—O—$(CH_2)_4$—O—$(CH_2)_4$—O—R

R	B. p., °C.	Pres., mm.	Yield, %	$n^{25}D$	d^{25}_4	M_D Calcd.	M_D Found	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
Methyl	67	0.55	86	1.4219	0.8972	53.32	53.88	$C_{10}H_{22}O_3$	63.1	62.4	11.66	11.3
Ethyl	76–77	.45	70	1.4230	.8761	62.56	63.46	$C_{12}H_{26}O_3$	66.01	65.3	12.00	11.65
n-Butyl	114–116	.45	60	1.4304	.8687	81.04	81.17	$C_{16}H_{34}O_3$	70.02	69.8	12.49	12.3
Isoamyl	125–126	.4	75	1.4322	.8609	90.28	91.14	$C_{18}H_{38}O_3$	71.47	71.4	12.66	12.30

was converted in high yield to δ-iodovaleric acid, m. p. 56–57°.

Esterification with ethyl, *n*-butyl, and tetrahydrofurfuryl alcohols gave good yields of the normal oxydivalerates (VI). The properties of these are listed in Table I.

5,5′-Dihydroxydiamyl Ether (IX).—Diethyl oxydivalerate, 41.2 g. (0.15 mole), was reduced with sodium and alcohol by the procedure described by Manske[9] for the reduction of diethyl sebacate. The product, 20.3 g. (71% yield), had the following properties: m. p. 16–18°, b. p. 141–142° (0.5 mm.); $n^{25}D$ 1.4570; d^{25}_4 0.9727; M_D calcd., 53.08; found, 53.26; soluble in water and ether, insoluble in benzene.

Anal. Calcd. for $C_{10}H_{22}O_3$: C, 63.18; H, 11.66. Found: C, 62.3; H, 11.8.

5,5′-Diaminodiamyl Ether (I).—Oxydivaleronitrile, 30 g. (0.166 mole), was dissolved in 350 cc. of absolute ethanol and the solution heated to boiling. Sodium, 31 g., was added in small pieces to the boiling solution over a period of forty-five minutes. Boiling was continued until all of the sodium had reacted. Most of the alcohol was then removed by distillation and the residue acidified with hydrochloric acid. The acidified mixture was evaporated to dryness and the amine hydrochloride extracted from the sodium chloride with anhydrous ethanol. Addition of ether to the alcoholic extract precipitated the diamine dihydrochloride as a white crystalline solid; yield 30.5 g., 70% of theoretical.

Anal. Calcd. for $C_{10}H_{24}ON_2 \cdot 2HCl$: Cl, 27.1. Found: Cl, 27.6.

A portion of this dihydrochloride was mixed with an excess of 50% potassium hydroxide and the insoluble oil separated by extraction with ether. Evaporation of the ether left a colorless, strongly basic liquid which absorbed carbon dioxide from the air to form a stable carbonate. The free diamine had the following properties: $n^{22}D$ 1.4602; $d^{22}D$ 0.907.

Anal. Calcd. for $C_{10}H_{24}ON_2$: N, 14.87. Found: N, 14.57.

Dibenzoyl derivative, m. p. 84°. (*Anal.* Calcd.: N, 7.07. Found: N, 6.99.)

(9) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 154.

4,4′-Diacetoxydibutyl Ether (VIII).—4,4′-Dichlorodibutyl ether, 60 g. (0.3 mole), was mixed with 98 g. (1 mole) of fused potassium acetate and 60 cc. of glacial acetic acid. The mixture was refluxed for fifteen hours with occasional stirring to break up incrustations of insoluble salts. The reaction mixture was then cooled, diluted with 600 cc. of water, and the product separated by extraction with ether. Distillation of the residue from ether evaporation gave 60 g. (81% yield) of a colorless liquid, b. p. 115–118° (0.6 mm.); $n^{28}D$ 1.4330; d^{28}_4 1.018.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.5; H, 9.00; acetyl, 34.94; sapn. equiv., 123.1. Found: C, 58.6; H, 8.93; acetyl, 34.92; sapn. equiv., 122.7.

4,4′-Dihydroxydibutyl Ether (VII).—Methyl alcoholysis of 4,4′-diacetoxydibutyl ether gave a quantitative yield of 4,4′-dihydroxydibutyl ether, b. p. 115–116° (0.3 mm.); $n^{26}D$ 1.4544; d^{26}_4 0.9999; M_D calcd., 43.82; found, 43.93. Di-α-naphthylurethan, m. p. 124–125° (*Anal.* Calcd.: N, 5.60. Found: N, 5.56).

4,4′-Dialkoxydibutyl Ethers (IV).—4,4′-Dichlorodibutyl ether was converted to dialkoxydibutyl ethers by refluxing for eight hours with the sodium alkoxides in solutions of the respective alcohols. These dialkoxy products were obtained in yields of 70–80% as colorless mobile liquids (see Table II).

Acknowledgment.—The tetrahydrofuran used in this investigation was generously supplied by the Electrochemicals Department, E. I. du Pont de Nemours and Company. C. H. Van Etten of this Laboratory performed the analyses.

Summary

A method is described for the conversion of tetrahydrofuran to 4,4′-dichlorodibutyl ether in 65–70% yields. Application of the method to tetrahydropyran and tetrahydromethylfuran gave poor yields of the expected dichlorodiamyl ethers.

A number of derivatives of 4,4′-dichlorodibutyl ether, not previously reported, are described.

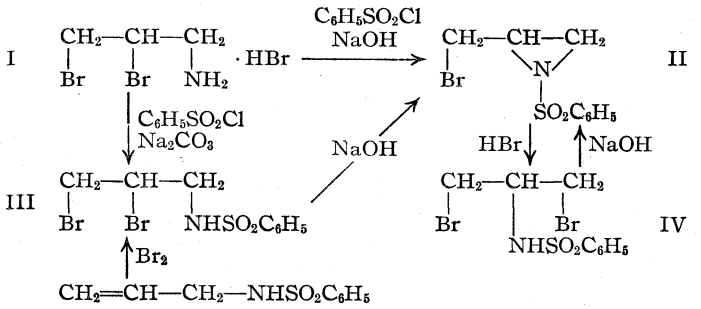
PEORIA, ILLINOIS RECEIVED SEPTEMBER 19, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Benzenesulfonyl Derivatives of 1-Amino-2,3-dibromopropane and 2-Amino-1,3-dibromopropane

BY WALTER J. GENSLER

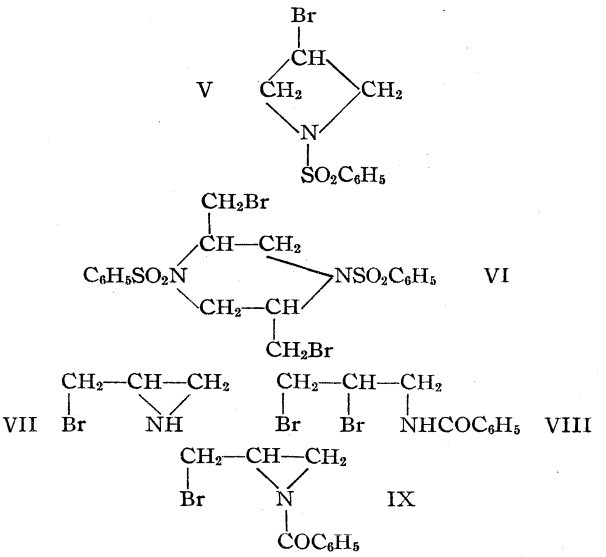
It was reported recently[1] that the action of benzenesulfonyl chloride with 1-amino-2,3-dibromopropane hydrobromide (I) in sodium hydroxide solution resulted in the formation of an alkali insoluble material which furnished analytical figures agreeing not with those calculated for 1-benzenesulfonamido-2,3-dibromopropane (III) but for



III minus a molecule of hydrogen bromide. The structure of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) was proposed for this compound. The present report is concerned with the reactions involved in the formation of II, and the demonstration of its structure.

It was found that III, the normal benzenesulfonyl derivative, could be obtained from the reaction of I and benzenesulfonyl chloride by the use of sodium bicarbonate, or better sodium carbonate, in place of sodium hydroxide. The same compound was formed on the addition of bromine to N-(benzenesulfonyl)-allylamine. Compound III was insoluble in carbonate or bicarbonate solution and could be recovered unchanged after exposure to these reagents. However, when III was treated with dilute sodium hydroxide, a clear solution resulted, which after a few seconds suddenly became milky and deposited a crystalline solid. This solid was identical with the product (II) obtained directly from 1-amino-2,3-dibromopropane.[2]

The facts that 1-benzenesulfonamido-2,3-dibromopropane could be obtained from 1-amino-2,3-dibromopropane under conditions milder than those used in the direct conversion of 1-amino-2,3-dibromopropane to II, and that 1-benzenesulfonamido-2,3-dibromopropane could be converted to II under the same conditions as those in the direct conversion, constituted permissive evidence in favor of the probable course of the reaction, I → [III] → II. It was necessary, however, to consider an alternate course in which 1-amino-2,3-dibromopropane could first cyclize to form 2-bromomethylethyleneimine (VII), which would then react with benzenesulfonyl chloride to yield the product II. To test this possibility 1-amino-2,3-dibromopropane hydrobromide was added to an excess of sodium hydroxide solution. The mixture was allowed to stand for a period equal to the reaction time allowed in the direct formation of II, and under the same conditions. Benzoyl chloride was then added to effect a benzoylation of either the cyclized molecule, VII, or the unchanged starting material. It was found that the product was the derivative of the starting material, 1-benzamido-2,3-dibromopropane, VIII (96% yield, m. p. 125–127°; 66% yield after purification, m. p. 129–129.5°) and not the cyclized form IX. Since no cyclization occurred in the benzoylation experiment, no cyclization to VII was possible in the benzenesulfonation reaction; and therefore in the direct formation of II from 1-amino-2,3-dibromopropane, the reaction path, I → [VII] → II, could be eliminated.



Assignment of the structure of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) for the alkali insoluble compound required proof since at least two other structures, V and VI, could be regarded as reasonably possible. The bimolecular piperazine derivative, VI, was eliminated on the basis of a molecular weight determination, while

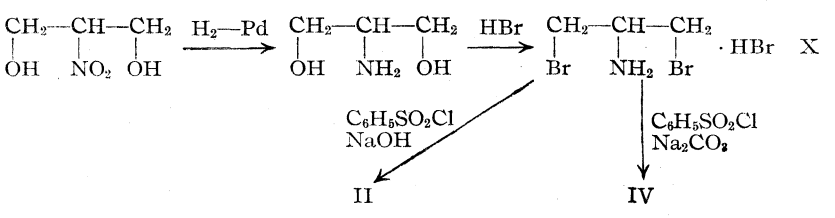
(1) Gensler, THIS JOURNAL, **69**, 1966 (1947).

(2) Similar reactions have been reported before. Adams and Cairns, THIS JOURNAL, **61**, 2464 (1939), converted 1-*p*-bromobenzenesulfonamido-2-methyl-2-chloropropane to 1-*p*-bromobenzenesulfonyl-2,2-dimethylethyleneimine; and Kharasch and Priestley, *ibid.*, p. 3425, obtained N-(*p*-toluenesulfonyl)-styreneimine from 1-*p*-toluenesulfonamido-1-phenyl-2-bromoethane.

the choice of II over V rested on the following two lines of evidence.

Rupture of the ring in the symmetrical trimethyleneimine V with the addition of hydrogen bromide can lead to only one product, 1-benzenesulfonamido-2,3-dibromopropane (III). The unsymmetrical ethyleneimine structure II on the other hand can yield either III or the isomeric compound, 2-benzenesulfonamido-1,3-dibromopropane (IV). On carrying out the experiment using 48% hydrobromic acid there was obtained only one addition product (68% yield) which proved to be not III but IV. The unsymmetrical structure for II was therefore indicated. The structure assigned to IV was supported by its smooth reconversion to II on treatment with alkali.

Conclusive proof was furnished by an unequivocal synthesis of II as well as IV. Hydrogenation of 2-nitro-1,3-dihydroxypropane according to Schmidt and Wilkendorff[3] yielded 2-amino-1,3-dihydroxypropane. Treatment with strong hydrobromic acid at 165–175° converted the aminoglycol to 2-amino-1,3-dibromopropane hydrobromide (X) which was isomeric with compound I. From the reaction of X and benzenesulfonyl chloride in the presence of sodium hydroxide it was possible to obtain a product II identical with the alkali insoluble compound derived from I. The



use of sodium carbonate in place of sodium hydroxide resulted in the formation of 2-benzenesulfonamido-1,3-dibromopropane (IV) identical with the addition product of II and hydrogen bromide. These identities constitute a demonstration of structure, since it is possible to write only the structures of 1-benzenesulfonyl-2-bromomethylethyleneimine (II) and 2-benzenesulfonamido-1,3-dibromopropane (IV) for the compounds derived from 2-amino-1,3-dibromopropane X.

Discussion

The reaction of 1-benzenesulfonamido-2,3-dibromopropane, or 2-benzenesulfonamido-1,3-dibromopropane with alkali to form 1-benzenesulfonyl-2-bromomethylethyleneimine is interpreted on the basis of a nucleophilic attack of the sulfonamide anion on a *beta* carbon atom with the elimination of bromide ion. The dibromo compounds are stable in acidic or weakly alkaline medium since the unshared electron pair on the nitrogen of the undissociated sulfonamide grouping is unavailable for the displacement. At higher *p*H's a proton is removed from the sulfonamide group, and the strongly nucleophilic nitrogen reacts rapidly.

The formation of II rather than V from 1-benzenesulfonamido-2,3-dibromopropane shows that the attack of the sulfonamide anion on the number two carbon is much more rapid than on the number three. Freundlich and Kroepelin[4] have found that the first order rate constants for the cyclization of β-bromoethylamine and γ-bromopropylamine are 0.036 and 0.0005, respectively. If these figures give some measure of the relative tendency of a free unshared electron pair on nitrogen to displace bromide ion from the two- and from the three-positions, then only 1–2% of the four-membered ring compound, V, would be expected in the product from 1-benzenesulfonamido-2,3-dibromopropane. This small amount would be lost in the purification procedure.

In the addition of hydrogen bromide to 1-benzenesulfonyl-2-bromomethylethyleneimine to form 2-benzenesulfonamido-1,3-dibromopropane a solvolysis mechanism is unlikely since it would involve the formation of a primary carbonium ion. On the other hand, by analogy with the behavior of related three-membered ring systems,[5] it is reasonable to regard the reaction as a bimolecular displacement of the sulfonamido group by bromide ion. The electron attracting properties of the sulfonamido group polarize the bond between the nitrogen and carbon of the ring placing the positive end of a dipole at the carbon atom. The resulting low electron density at the carbon together with the normal strain in the three-membered ring would allow a ready attack by bromide ion.

In analogy with related cases the displacement occurs at the methylene rather than at the methine carbon.[6] In this connection it should be pointed out that this mode of ring cleavage is by no means the rule, and that a number of examples

(3) Schmidt and Wilkendorff, *Ber.*, **52**, 389 (1919).

(4) Freundlich and Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).

(5) In the formation of 1-chloro-2-hydroxy-3-halopropane from aqueous hydrogen halide and epichlorohydrin, an oxygen analog, Brönsted, Kilpatrick and Kilpatrick [THIS JOURNAL, **51**, 428 (1929)] have shown that the rate of reaction is dependent on the halide ion–epichlorohydrin concentration product and also on the halide ion–epichlorohydrin–hydronium ion concentration product. Freundlich and Neumann [*Z. physik. Chem.*, **87**, 69 (1914)] have found that in the reaction of ethyleneimine with excess hydrobromic acid to form β-bromoethylamine, the rate depends on the product of the bromide ion and ethyleneimine (ethyleneimmonium ?) concentrations. In these cases a nucleophilic displacement mechanism of halide ion on a carbon atom is in agreement with the observed kinetics. Further, a displacement process by various donor groups on the ring-carbons of an intermediate quaternary ethyleneimmonium salt has been used satisfactorily to interpret the reaction kinetics of the nitrogen mustards (Ph.D. theses, Harvard University, 1944, by C. Gardiner Swain and by Sidney D. Ross).

(6) For example, in the addition of hydrogen bromide [Gabriel and Ohle, *Ber.*, **50**, 815 (1917)] and of hydrogen chloride [Smith and Platon, *ibid.*, **55**, 3143 (1922)] to propyleneimine; and in the addition of the halogen acids to the oxygen analogs, epichlorohydrin and epibromohydrin ["Beilstein," 4th ed., Vol. XVII, pp. 7–8.]

are known in which the process occurs at the more highly, rather than the less highly, substituted carbon atom of the ethyleneimine ring.[7]

Experimental

1-Benzenesulfonamido-2,3-dibromopropane (III) from 1-Amino-2,3-dibromopropane (I).—To a vigorously stirred solution of 1.20 g. of 1-amino-2,3-dibromopropane hydrobromide[8] (0.0040 mole) in 10 ml. of water was added 0.6 ml. of benzenesulfonyl chloride (0.0047 mole) followed immediately by a solution of 1.2 g. of sodium carbonate (0.011 mole) in 10 ml. of water. After the mixture had been stirred for forty-five minutes at room temperature it was filtered, and the solids washed and pressed on the funnel. This material, dried in the air, weighed 1.33 g. (92%) and had m. p. 91–97° (sintering at 85°). It was crystallized from 8 ml. of carbon tetrachloride to yield 1.05 g. (73%) of 1-benzenesulfonamido-2,3-dibromopropane in the form of fine needle-like crystals, m. p. 97–99°.

Two further crystallizations from alcohol brought the melting point to 98–100°.

Anal. Calcd. for $C_9H_{11}NSO_2Br_2$: C, 30.3; H, 3.1. Found: C, 30.6; H, 3.2.

1-Benzenesulfonamido-2,3-dibromopropane (III) from N-(Benzenesulfonyl)-allylamine.—The product of the reaction of benzenesulfonyl chloride and allylamine in aqueous alkali was readily purified by distillation. The fraction which boiled at 156–158° (2 mm.) and solidified to a white solid, m. p. 39.5–41.5°, was taken as N-(benzenesulfonyl)-allylamine.[9]

Twenty-five milliliters of chloroform containing 4.05 g. of bromine (0.025 mole) was added over a period of one and three-quarters hours to a cold (10°) vigorously stirred solution of 5.00 g. of N-(benzenesulfonyl)-allylamine (0.025 mole) in 50 ml. of chloroform. After the addition was complete the reaction mixture, from which crystals of the product had separated, was allowed to stand at 10–15° for one hour. The solvent was then removed, with only slight warming, by distillation under reduced pressure. To the residue was added 15 ml. of alcohol and again all volatile material was removed with suction. Crystallization of the crude product from alcohol yielded 7.48 g. (83%) of white crystals, m. p. 97.5–101.5°, which showed no depression in mixed melting point with the 1-benzenesulfonamido-2,3-dibromopropane from 1-amino-2,3-dibromopropane. Further crystallizations did not improve the melting point.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 1-Amino-2,3-dibromopropane (I).—A solution of 1.20 g. of 1-amino-2,3-dibromopropane hydrobromide (0.0040 mole) in 5 ml. of water was mixed with 0.70 ml. of benzenesulfonyl chloride (0.0054 mole). Five milliliters of sodium hydroxide solution, containing 0.97 g. or 0.024 mole of sodium hydroxide, was added without delay and with vigorous stirring. Immediately after the addition of the alkali the mixture became almost entirely clear, but after a few seconds a heavy turbidity suddenly developed which soon gave way to a precipitate. After the mixture had been stirred at room temperature for thirty-five minutes, the solids were collected, washed with water, and finally air-dried. The crude product, which weighed 0.95 g. (86%) and melted at 86–88.5°, was purified by crystallization from ethyl alcohol, and furnished 0.82 g. (74%) of 1-benzenesulfonyl-2-bromomethylethyleneimine, m. p. 89–90° (faint sintering at 86°). This material gave no depression in mixed melting point with the analytical sample of the material previously prepared,[1] while the mixed melting point with 1-benzenesulfonamido-2,3-dibromopropane was 76–91°.

A Rast molecular weight determination gave values lying between 272 and 281. The calculated molecular weight for II is 276.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 2-Amino-1,3-dibromopropane (X).—The procedure employed was the same as that described above for the reaction with 1-amino-2,3-dibromopropane. The same product was obtained (melting point and mixed melting point, 89–90°) in 76% yield.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 1-Benzenesulfonamido-2,3-dibromopropane (III).—A solution of 1.4064 g. of 1-benzenesulfonamido-2,3-dibromopropane (0.00394 mole) in 10 ml. of alcohol was added in one portion to 50.00 ml. of 0.099 *N* sodium hydroxide (0.00495 equivalent). The addition was made as complete as possible by rinsing the flask with two 5-ml. portions of alcohol. The stirred solution remained perfectly clear for about fifteen seconds and then suddenly became milky. After the addition of 25 ml. of water the mixture was cooled in an ice-bath and filtered. The time which elapsed between the addition and the filtration was no longer than fifteen minutes. The solids, washed thoroughly on the funnel with approximately 50 ml. of water, pressed, and air-dried, weighed 1.02 g. (94%) and showed m. p. 88.5–90° (sintering at 85°). One crystallization from alcohol afforded 0.76 g. (70%) of pure 1-benzenesulfonyl-2-bromomethylethyleneimine, with melting point and mixed melting point, 89–90°.

The aqueous alkaline filtrate, together with the wash water, was titrated with 9.50 ml. of 0.100 *N* hydrochloric acid to the disappearance of the red color of phenolphthalein. This revealed that the amount of sodium hydroxide consumed in the cyclization process was 0.0040 equivalents, in good agreement with the theoretical value of 0.00394.

1-Benzenesulfonyl-2-bromomethylethyleneimine (II) from 2-Benzenesulfonamido-1,3-dibromopropane (IV).—The cyclization of IV followed essentially the directions given for the cyclization of III. However, it was noted in this case that the addition of the alcoholic solution of the 1,3-dibromide to the aqueous alkali did not result in a clear solution, but in an immediate turbidity. The crude air-dried product (m. p. 87–89°; 99% yield) was crystallized from alcohol, and furnished pure 1-benzenesulfonyl-2-bromomethylethyleneimine, m. p. 89–89.5°, in 81% yield. Mixed melting point determinations with II, III, and IV established the identity of the product.

1-Benzamido-2,3-dibromopropane (VIII).—The benzoylation of 1-amino-2,3-dibromopropane was carried out by following essentially the directions for the preparation of 1-benzenesulfonyl-2-bromomethylethyleneimine from 1-amino-2,3-dibromopropane. From the reaction of 1.20 g. of the amino-dibromide hydrobromide (0.0040 mole), 0.62 ml. of benzoyl chloride (0.0054 mole), and a solution of 0.98 g. of sodium hydroxide, there was obtained 1.18 g. (91%) of washed and air-dried product, m. p. 128–129°. One crystallization of this material from alcohol yielded 0.79 g. (61%) of 1-benzamido-2,3-dibromopropane, m. p. 129–129.5°. Two further crystallizations were carried out to obtain the analytical sample, m. p. 129.5–130°.[10]

Anal. Calcd. for $C_{10}H_{11}NOBr_2$: C, 37.4; H, 3.5. Found: C, 37.5; H, 3.4.

Repetition of this experiment with the one difference of stirring the mixture of amino-dibromide hydrobromide in the sodium hydroxide solution for thirty-five minutes at room temperature before the addition of the benzoyl

(7) This is the case in the formation of 1-*p*-toluenesulfonamido-2-phenyl-2-bromoethane from N-(*p*-toluenesulfonyl)-styreneimine and hydrobromic acid [Kharasch and Priestley, THIS JOURNAL, **61**, 3425 (1939)]; in the formation of 1-amino-2-methylpropanol-2 from isobutyleneimine and dilute sulfuric acid [Cairns, *ibid.*, **63**, 871 (1941)]; and in the action of hydrogen chloride with isobutyleneimine and with 2,2-diphenylethyleneimine to form the tertiary chlorides [Campbell and Campbell, reported at the New York Meeting of the American Chemical Society, September, 1947].

(8) Paal and Hermann, *Ber.*, **22**, 3076 (1889).

(9) Ginzberg, *Ber.*, **36**, 2703 (1903), reported m. p. 40.5–41° for N-(benzenesulfonyl)-allylamine.

(10) Bergmann, Dreyer and Radt, *Ber.*, **54**, 2139 (1921), reported m. p. 135° for this compound. Abderhalden and Paquin, *ibid.*, **53**, 1125 (1920), who prepared the compound without recognizing its structure, found m. p. 130°.

chloride gave practically the same results. There was obtained 1.24 g. (96%) of dry unpurified product, m. p. 125–127°, and after crystallization, 0.85 g. (66%) of white crystals, m. p. 129–129.5°. There was no depression in the mixed melting point with 1-benzamido-2,3-dibromopropane.

2-Benzenesulfonamido-1,3-dibromopropane (IV) from 1-Benzenesulfonyl-2-bromomethylethyleneimine (II).—A stirred mixture of 63 ml. of 48% hydrobromic acid and 3.40 g. of 1-benzenesulfonyl-2-bromomethylethyleneimine (0.012 mole) was heated on the steam-bath under a condenser for three and one-half hours. After the addition of 100 ml. of water, the reaction mixture was cooled in an ice-bath and the solids collected, washed with cold water, and finally air-dried. This material (3.38 g. melting at 91–94.5°) was crystallized from carbon tetrachloride (decolorizing carbon used) to yield 3.0 g. (68%) of well-formed pure white crystals of 2-benzenesulfonyl-1,3-dibromopropane, m. p. 93–93.5°. The melting point was not raised by further recrystallization.

Anal. Calcd. for $C_9H_{11}NO_2SBr_2$: C, 30.3; H, 3.1. Found: C, 30.2; H, 3.0.

The mixed melting point with 1-benzenesulfonamido-2,3-dibromopropane was 70–80°; the mixed melting point with the starting material was 66–78°.

2-Benzenesulfonamido-1,3-dibromopropane (IV) from 2-Amino-1,3-dibromopropane (X).—The directions for the preparation of 1-benzenesulfonamido-2,3-dibromopropane from the corresponding amino-dibromide were followed. However, in this case the water-insoluble material formed in the reaction mixture was only semi-solid after forty-five minutes of stirring. The material was taken up in ether, the ethereal solution washed with water and dried over magnesium sulfate. Removal of all solvent left a colorless mobile oil possessing a strong odor of benzenesulfonyl chloride. The oil crystallized partially on standing; it was found that the addition of low-boiling petroleum ether containing a small amount of ether dissolved only the oily portion and allowed the solids to be collected. There was obtained white crystals, m. p. 87–94.5° (sintering at 65°) in 14% yield. Two crystallizations of this material from carbon tetrachloride yielded pure 2-benzenesulfonamido-1,3-dibromopropane (10%), which melted alone or mixed with the material prepared from 1-benzenesulfonyl-2-bromomethylethyleneimine at 93–93.5°. The mixed melting points with 1-benzenesulfonamido-2,3-dibromopropane and with 1-benzenesulfonyl-2-bromomethylethyleneimine were depressed 17° and 23°, respectively.

Attempts at improving the yield by allowing a longer period for reaction resulted in an oily mixture from which only a small amount of 1-benzenesulfonyl-2-bromomethylethyleneimine could be isolated. A longer reaction period, using bicarbonate instead of carbonate to preclude ring closure, yielded an oil from which no solid product could be obtained.

2-Amino-1,3-dibromopropane Hydrobromide (X).—A warm solution of 5.0 g. of barium hydroxide octahydrate (0.016 mole) in 40 ml. of water was added with stirring to a warm solution of 4.0 g. of 2-amino-1,3-dihydroxypropane oxalate[3] (containing 0.0294 mole of the amino-glycol) in 30 ml. of water. The mixture was filtered and the barium oxalate rinsed thoroughly with water. To remove the excess barium the combined filtrate and washings were saturated with carbon dioxide, then boiled for ten minutes to decompose bicarbonate, and filtered. After acidification of the filtrate with 5 ml. of 48% hydrobromic acid, all the solvent was removed by distillation under reduced pressure. More hydrobromic acid was added and again removed. The residual material dissolved in 23 ml. of hydrobromic acid was saturated at 0° with gaseous hydrogen bromide, and heated in a Carius tube for three hours at 165–175°.

The resulting dark-colored mixture, in which some carbonized material was present, was diluted with 200 ml. of water and treated with decolorizing carbon (Nuchar) to obtain a water-white solution. This was taken to dryness under reduced pressures on the steam-bath, absolute alcohol was added to the crystalline residue, and the volatile matter again removed. The crude product was dissolved in absolute alcohol, and after a small amount of insoluble ammonium bromide was removed, the solution was concentrated to the first appearance of solid and diluted with an excess of ethyl acetate. The white crystalline product was removed from the cooled mixture, washed with ethyl acetate and dried on the steam-bath. 2-Amino-1,3-dibromopropane hydrobromide, m. p. 152–157°, was obtained in a yield of 6.55 g. (75%). One crystallization from absolute alcohol–ethyl acetate (1 to 5) furnished 4.57 g. (52%) of crystals melting at 154–158° (preliminary sintering); a second crystallization gave 3.4 g. (39%) with m. p. 158–162° (preliminary sintering). The material in the mother liquors could be recovered and reworked.

A number of further recrystallizations, involving much loss of material, was necessary before constant melting point of 162–162.5° was reached.

Anal. Calcd. for $C_3H_8NBr_3$: C, 12.1; H, 2.7. Found C, 12.4; H, 2.9.

2-Amino-1,3-dibromopropane hydrobromide differed from the isomeric 1-amino-2,3-dibromopropane hydrobromide (m. p. 167–169.5°) in the crystal form and in solubility behavior (the former was very soluble in absolute alcohol, while the latter could be recrystallized from this solvent); the mixed melting point was depressed 30°.

The attempts at forming 2-amino-1,3-dibromopropane by boiling the amino-glycol with 48% hydrobromic acid and concentrated sulfuric acid, or with hydrobromic acid according to the directions for the conversion of ethanolamine to β-bromoethylamine hydrobromide,[11] failed.

Summary

1-Amino-2,3-dibromopropane and 2-amino-1,3-dibromopropane react with benzenesulfonyl chloride in the presence of aqueous sodium carbonate to form the normal derivatives, 1-benzenesulfonamido-2,3-dibromopropane and 2-benzenesulfonamido-1,3-dibromopropane, respectively. With free alkali the product from either amino-dibromide and benzenesulfonyl chloride, or from either normal benzenesulfonyl derivative is 1-benzenesulfonyl-2-bromomethylethyleneimine.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 9, 1947

(11) Cortese, "Org. Syn.," Coll. Vol. II (1943), p. 91.

[CONTRIBUTION FROM THE WILLIAM G. KERCKHOFF LABORATORIES OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Synthesis of a Biologically Active Nicotinic Acid Precursor: 2-Amino-3-hydroxybenzoic Acid

BY JOSEPH F. NYC AND HERSCHEL K. MITCHELL

Recent investigations[1,2] in this Laboratory have provided evidence that the mold *Neurospora* synthesizes nicotinic acid from tryptophan through the intermediates kynurenine and hydroxyanthranilic acid (2-amino-3-hydroxybenzoic acid). Although it has also been established that higher animals have the capacity for converting tryptophan to nicotinic acid[3,4] it is not yet known whether or not the mechanism is similar to that in *Neurospora*. In order to provide material for further investigations along these lines, it has been necessary to develop methods for synthesis of 2-amino-3-hydroxybenzoic acid. Since this compound has evidently not been previously synthesized, two independent methods of preparation have been devised in order to establish the structure of the products.

A purported preparation of 2-amino-3-hydroxybenzoic acid by degradation of the alkaloid damascenine was reported by Keller in 1908.[5] It is quite evident, however, that the product described by Keller is actually 2-amino-3-methoxybenzoic acid. The data in Table I are in accord with this conclusion.

TABLE I

MELTING TEMPERATURES OF 2-AMINO-3-HYDROXYBENZOIC ACID, 2-AMINO-3-METHOXYBENZOIC ACID, THE COMPOUND OF KELLER AND THE CORRESPONDING HYDROCHLORIDES

	Compound	M. p., °C.
1	2-Amino-3-hydroxybenzoic acid[a]	254–255 (cor.)
2	2-Amino-3-methoxybenzoic acid[a]	171 (cor.)
3	Compound of Keller	164
4	Hydrochloride of 1[a]	227 (cor.)
5	Hydrochloride of 2[a]	205–206 (cor.)
6	Hydrochloride of 3	199–200

[a] Synthesized in this Laboratory.

In addition to the data in Table I, Keller stated that he did not report a carbon analysis because it was too high. He did report a halogen analysis on the hydrochloride but miscalculated the theoretical value and his analysis actually checks very well with the theoretical figure for the hydrochloride of 2-amino-3-methoxybenzoic acid.

The first method for synthesis of 2-amino-3-hydroxybenzoic acid that has been utilized in this Laboratory involves reduction of 2-nitro-3-methoxybenzoic acid followed by demethylation. The nitro compound was previously prepared from 3-methoxybenzoic acid by Ewins[6] and its reduction by chemical means has been reported by several workers.[6,7,8]

In the present work, the reduction was carried out by catalytic hydrogenation and the final demethylation step by treatment of 2-amino-3-methoxybenzoic acid with hydriodic acid.

The second method of synthesis that is described in this paper involves oxidation of 8-methoxyquinoline to give 2-(N-methyl-N-formyl)-amino-3-methoxybenzoic acid.[9] By appropriate treatment of this product with hydriodic acid 2-amino-3-hydroxybenzoic acid was obtained. The products from the two methods of synthesis possessed identical physical properties and the same biological activity for *Neurospora*.[2]

Experimental

2-Nitro-3-methoxybenzoic Acid.—This compound was prepared by a modification of the method of Ewins.[6] A mixture of 10 g. of 3-methoxybenzoic acid and 40 ml. of nitric acid (sp. gr. 1.4) was heated gently in a 250 ml. flask. After the beginning of the exothermic reaction the mixture was maintained at 55° by occasional immersions in cold water. A voluminous precipitate of nitration products appeared as the reaction progressed. After standing three hours at room temperature the precipitate was filtered off, washed with water and treated with three times its weight of boiling ethyl alcohol. The esulting suspension was filtered hot and the undissolved material was crystallized from a minimum amount of boiling ethanol; yield, 0.85 g., 2-nitro-3-methoxybenzoic acid, m. p. 260–263° (cor.). An additional 0.15 g. of the desired product was obtained by two recrystallizations of the material precipitated after cooling of the filtrate of the first hot alcohol extraction.

2-Amino-3-methoxybenzoic Acid.—One-half gram of 2-nitro-3-methoxybenzoic acid was dissolved in 50 ml. of absolute ethanol and hydrogenated at 1 atmosphere pressure and at room temperature, in the presence of 100 mg. of 5% palladium-on-charcoal. Following filtration the solution was evaporated to dryness and the product was crystallized from boiling benzene, yield, 0.4 g., m. p. 170–171° (cor.).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.73; H, 5.49; N, 8.54. Absorption spectrum Fig. 1, curve B. The hydrochloride of this compound crystallized from concentrated aqueous hydrochloric acid, m. p. 205–206° (cor.).

2-Amino-3-hydroxybenzoic Acid. Method I.—A mixture of 200 mg. of 2-amino-3-methoxybenzoic acid, 50 mg. of red phosphorus and 4 ml. of hydriodic acid (sp. gr. 1.7) was heated in a sealed tube at 100° for eight hours. The hydriodic acid salt of 2-amino-3-hydroxybenzoic acid crystallized on cooling. After filtration this product, containing phosphorus, was dissolved in 15 ml. of water and again filtered. Solid sodium carbonate was carefully added to the filtrate until the acid reaction to congo red just disappeared. The crude product was obtained as a crystalline powder, m. p. 238–242°. Recrystallization from ethanol yielded 124 mg. of compound, m. p. 254–255° (cor.); absorption spectrum, Fig. 1, curve A.

(1) Beadle, Mitchell and Nyc, *Proc. Nat. Acad. Sci.*, **33**, 155 (1947).
(2) Mitchell and Nyc, *Proc. Nat. Acad. Sci.*, **34**, 1 (1948).
(3) Krehl, Tepley, Sarma and Elvehjem, *Sci.*, **101**, 489 (1945).
(4) Sarett and Goldsmith, *J. Biol. Chem.*, **167**, 293 (1947).
(5) Keller, *Arch. der Pharm.*, **246**, 1 (1908).
(6) Ewins, *J. Chem. Soc.*, **101**, 549 (1912).
(7) Pschorr, *Ann.*, **391**, 27 (1912).
(8) Froelicher and Cohn, *J. Chem. Soc.*, **119**, 1425 (1921).
(9) Kaufmann and Rothlen, *Ber.*, **49**, 578 (1916).

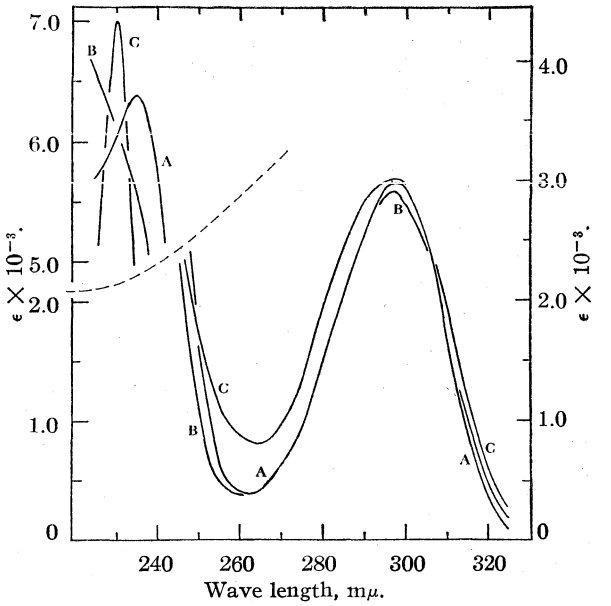


Fig. 1.—Absorption spectra in 0.1 *M* hydrochloric acid: A, 2-amino-3-hydroxybenzoic acid; B, 2-amino-3-methoxybenzoic acid; C, 2-(N-methyl-N-formyl)-amino-3-methoxybenzoic acid.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.00; H, 4.83; N, 9.13.

2-Amino-3-hydroxybenzoic Acid Hydrochloride.—This compound crystallized from a hot solution of 2-amino-3-hydroxybenzoic acid in concentrated aqueous hydrochloric acid, m. p. 227° (cor.). *Anal.* Calcd. for $C_7H_8NO_3Cl$: N, 7.39; Cl, 18.70. Found: N, 7.68; Cl, 18.59.

2-Amino-3-hydroxybenzoic Acid. Method II.—2-(N-Methyl-N-formyl)-amino-3-methoxybenzoic acid was prepared according to the procedure of Kaufmann and Rothlen.[9] A mixture of 200 mg. of this compound, 50 mg. of red phosphorus and 4 ml. of hydriodic acid (sp. gr. 1.7) was heated in a sealed tube at 135° for twelve hours. The product was isolated and purified by the procedure described under Method I, yield 57 mg., m. p. 254–255° (cor.), hydrochloride m. p. 227° (cor.).

The products from both methods I and II possessed identical absorption spectra and biological activity on a nicotinic acid requiring mutant of *Neurospora*.[2]

Discussion

Hydroxyanthranilic acid (2-amino-3-hydroxybenzoic acid) has been synthesized by two independent methods each providing in itself nearly conclusive evidence for the structure of the product. It is evident from a consideration of the properties of these products and from the facts given by Keller that the latter investigator did not prepare hydroxyanthranilic acid as reported. No evidence has been found for a synthesis of the compound prior to the present work.

It is to be noted from Fig. 1 that the absorption spectra of some methyl and formyl substituted 2-amino-3-hydroxybenzoic acids are quite similar to that of the parent compound. This is true also for damascenine and damasceninic acid. In the case of the unsubstituted acid considerable variations in spectrum have been observed at wave lengths below 260 mμ. This is evidently due to traces of impurities derived from oxidation of the compound in mildly acid or alkaline solutions. A pure white product can be obtained only from acidic solutions since oxidation is rapid even at neutrality.

Summary

1. Two independent methods have been described for the synthesis of 2-amino-3-hydroxybenzoic acid.

2. Data have been presented to show that the product previously obtained by Keller and reported to be 2-amino-3-hydroxybenzoic acid was actually 2-amino-3-methoxybenzoic acid.

PASADENA 4, CALIFORNIA RECEIVED DECEMBER 9, 1947

[CONTRIBUTION NO. 638 FROM THE DEPARTMENTS OF CHEMISTRY AND PHYSICS, UNIVERSITY OF PITTSBURGH]

X-Ray Investigation of Glycerides. VII. Diffraction Analyses of Synthetic 1,3-Dielaidin[1]

BY B. F. DAUBERT AND S. S. SIDHU

In a recent publication by Carter and Malkin,[2] X-ray diffraction data were reported for a series of unsaturated symmetrical 1,3-diglycerides, including 1,3-diolein, 1,3-dierucin, and their *trans* isomers, 1,3-dielaidin and 1,3-dibrassidin.

In our study of the physical properties of synthetic glycerides, an X-ray diffraction study of 1,3-dielaidin had been completed but not reported prior to the publication by Carter and Malkin,[2] although X-ray diffraction data for 1,3-diolein, 1,3-dilinolein, and 1,3-dilinolenin were recently reported by Daubert and Lutton.[3]

The purpose, therefore, of the present communication is to report the X-ray data on 1,3-dielaidin prepared both by direct synthesis and elaidinization of 1,3-diolein.

Experimental

Preparation of 1,3-Dielaidin.—1-Monotrityl glycerol (10 g.) (m. p. 109.5–110.0°) was dissolved, with slight warming, in a mixture of quinoline (15 ml.) and dry chloroform (40 ml.). To this mixture elaidyl chloride (18.0 g.) was added slowly. The mixture, after standing

(1) The generous financial assistance of the Buhl Foundation in support of this investigation is gratefully acknowledged.

(2) Carter and Malkin, *J. Chem. Soc.*, 554 (1947).

(3) Daubert and Lutton, THIS JOURNAL, **69**, 1449 (1947).

at room temperature for one hour, was refluxed on a steam-bath for a similar period of time. The mixture, after cooling, was dissolved in ether and the ether solution washed successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution, distilled water, and finally dried over anhydrous sodium sulfate. The ether was removed *in vacuo* and the sirupy liquid remaining was dissolved in a 1:1 mixture of ether and ethyl alcohol. The solution was cooled to −20° for twenty-four hours. The crystalline mass was suction-filtered, recrystallized several times from ethyl ether, and dried over phosphorus pentoxide. The 1-trityl-2,3-dielaidin melted at 36.5–37.0°; mol. wt. 857 (calcd. 863); iodine value 58.5 (calcd. 58.8); yield, 20.2 g., 75.6%.

Anal. Calcd. for $C_{58}H_{86}O_5$: C, 80.69; H, 10.04. Found: C, 80.37, 80.46; H, 10.02, 10.08.

The 1-trityl-2,3-dielaidin (10 g.) was hydrolyzed to 1,3-dielaidin after the method of Verkade, *et al.*[4] The 1,3-dielaidin on slow crystallization from petroleum ether had the following constants: m. p. 54.0–54.5°; mol. wt. 619 (calcd. 621); iodine value 81.6 (calcd. 81.8), yield, 5.3 g., 73.6%. Slow crystallization was accomplished by slowly cooling to room temperature (approximately 25°) a petroleum ether solution of the 1,3-dielaidin saturated at 30–35°. Rapid crystallization, on the other hand, was accomplished by quickly chilling a subsaturated solution of the compound to −20°. Carter and Malkin[2] reported a melting point of 55° for the β form of this diglyceride when prepared by the direct reaction of elaidyl chloride with 1-monoelaidin.

The 1,3-dielaidin was also prepared by the elaidinization of 1,3-diolein[3] (m. p. 21.5°) as follows: 1,3-diolein (2 g.) was floated on 100 ml. of 30% nitric acid at room temperature. Small additions (*ca.* 250 mg.) of sodium nitrite were made, with stirring, until solidification occurred. A total of 1.0 g. of sodium nitrite was required over a period of thirty minutes. The 1,3-dielaidin was suction-filtered and washed with water until free of mineral acid. Slow crystallization from petroleum ether yielded 0.5 g. of a product melting at 55°. Mixed melting point with 1,3-dielaidin obtained by hydrolysis of the trityl derivative showed no depression.

The dielaidins prepared by the two different methods were hydrogenated to 1,3-distearin (m. p. 79.0°) by the method of Daubert, *et al.*[5]

X-Ray Diffraction Analysis.—The X-ray diffraction patterns of the different polymorphic forms were obtained by the same procedure as described by Sidhu and Daubert[6] for symmetrical diacid diglycerides.

In view of the comments of Malkin[2] in a recent publication criticising the X-ray procedure used in the first paper of this series, it is perhaps appropriate to emphasize again that *filtered* radiation has been used exclusively in the diffraction analyses of all of the glycerides thus far reported from this laboratory.

With reference to the mounting of specimens in nylon tubes, the standard procedure in X-ray diffraction work was followed. The diffraction pattern of the tube was taken with and without the specimens, exposing the tube to the same X-ray beam for the same length of time. This procedure has been followed in obtaining all of the data we have published so far on glycerides. The diffraction patterns of the nylon capillary tubes were taken and the lines thus obtained were carefully noted for structure, intensity, and position of the pattern. The effect on the intensities of the diffraction lines originating from the specimen due to superimposition of the nylon tube lines was ascertained by obtaining diffraction patterns of a few of the specimens without the use of nylon capillary tubes. Knowing the number of diffraction lines originating from the nylon tube, their position on the pattern, their intensities, and their effect on the intensities of the lines originating from the specimen, *d* values of the specimen were determined and intensities of the lines estimated. The diffraction data on all glycerides reported by us contain lines obtained from the specimens only.

Discussion

In confirmation of the observations of Carter and Malkin,[2] it was noted that slow crystallization of 1,3-dielaidin from solvent invariably yielded the *beta* form.

The *beta prime* form in the present investigation was obtained by rapid crystallization from solvent. Previous observations in our laboratory on the crystallization of diacid diglycerides[6] demonstrated that under similar crystallization conditions *beta* (*beta-a*) was obtained for some compounds, *beta prime* (*beta-b*) for others. Malkin obtained the *beta prime* form for 1,3-dielaidin from melted layers and rods. It will be seen from the data in Table I that the side spacings for the form obtained by rapid crystallization of dielaidin from solvent are in good agreement with those reported by Malkin for the *beta prime* form. No X-ray evidence could be found for an *alpha* form.

TABLE I

COMPARISON OF X-RAY DIFFRACTION DATA FOR 1,3-DIELAIDIN

	Malkin[2]			This study	
M. p. °C.	β	β′	α	β	β′
Long spacing, Å.	55 52.6	53 49.8	49	54.5–55.0 52.4	52.5 50.0
Side spacing, Å.	4.6 (S) 3.9 (S) 3.7 (S)	4.61 (S) 3.95 (W) 3.75 (S) 3.6 (W)		4.63 (S) 3.88 (S) 3.73 (S)	4.62 (S) 3.91 (W) 3.74 (S) 3.66 (W)

S = strong. W = weak.

In contrast to the data obtained for 1,3-dielaidin, Daubert and Lutton[3] found no X-ray or melting evidence for other than one form of 1,3-diolein. The complexity of the side-spacing data for that diglyceride was not conducive to characterization of the form as *beta prime* or *beta*. Although Carter and Malkin[2] reported a melting point (18°) based on cooling curve data for a supposed *alpha* form of diolein, they were not able to confirm the existence of the form by X-ray evidence.

In agreement with Malkin, it seems that the side-spacing data for the *beta* and *beta prime* forms correspond to those of the saturated diglycerides originally called *beta-a* and *beta-b*, respectively, by Malkin, *et al.*[7]

Summary

The preparation of 1,3-dielaidin by (1) direct synthesis from 1-trityl-2,3-dielaidin, a new compound, and (2) elaidinization of 1,3-diolein is reported.

The X-ray and melting point data confirm the observations of Malkin relative to the existence of two crystalline forms called by him *beta* and *beta prime*.

PITTSBURGH, PENNSYLVANIA

RECEIVED NOVEMBER 10, 1947

(4) Verkade and van der Lee, *Rec. trav. chim.*, **55**, 267 (1936).

(5) Daubert, Fricke, and Longenecker, THIS JOURNAL, **65**, 2142 (1943).

(6) Sidhu and Daubert, *ibid.*, **68**, 2603 (1946).

(7) Malkin, Shurbagy and Meara, *J. Chem. Soc.*, 1409 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Regeneration of Insulin from Insulin Fibrils by the Action of Alkali

BY DAVID F. WAUGH

Insulin may be converted into highly asymmetric fibrils having lengths up to tens of thousands of ångström units and widths averaging about 150 Å.[1] Aggregation of these fibrils into spherites and the further clumping of spherites accounts for the visible heat precipitate of insulin.[2] Several investigations in which fibrils are produced by the unfolding of globular proteins and the aligning of polypeptide chains thus produced have been reported.[3] Evidence from monolayers, which showed that films of native insulin and fibrous insulin had the same properties[4] and the fact that mild treatment with alkali would greatly decrease the high viscosity of a suspension of fibrils indicated the possibility that the insulin particle (molecule) was *not* unfolded to any extent during fibril formation. This implies the linkage of corpuscular or globular units, a circumstance to be demonstrated in this publication. The reversible linkage of corpuscular units, along with the relative stability of the fibril, place insulin in a rather unique position of considerable importance.

Additional indications of reversion came from early studies of the "heat precipitate" of insulin.[5,6,7,8] In these it was claimed that the heat precipitate, inactive in itself, could be treated with alkali to give a product having at least 80% of the original activity. Greenstein, however, indicates that insulin may be opened up to expose disulfide groupings without loss of biological activity[9] and Rothen, *et al.*, report that surface films of insulin are active.[10] Thus reversion to the native state cannot be assumed on the basis of biological activity alone.

The present communication considers the reversion of insulin fibrils by alkali and compares the reversion product with native insulin. During the process of reversion of fibrils (or regeneration of insulin) the system contains fibrils and a reversion product which will be referred to as r-insulin. Native insulin will be referred to as n-insulin, insulin treated with alkali as a-insulin, and fibrous insulin as f-insulin.

(1) D. F. Waugh, THIS JOURNAL, **66**, 663 (1944); *Am. J. Physiol.*, **133**, 484 (1941).

(2) D. F. Waugh, *ibid.*, **68**, 247 (1946).

(3) H. P. Lundgren, *Silk J.*, **23**, No. **269**, 48 and No. **270**, 32 (1946); *Textile Research J.*, **15**, 335 (1945); THIS JOURNAL, **63**, 2854 (1941); G. C. Nutting, M. Halwer, M. J. Copley and F. R. Senti, *Textile Research J.*, **16**, 599 (1946); G. C. Nutting, F. R. Senti and M. J. Copley, *Science*, **99**, 328 (1944); F. R. Senti, C. R. Eddy and G. C. Nutting, THIS JOURNAL, **65**, 2473 (1943); K. J. Palmer and J. A. Galvin, *ibid.*, **65**, 2187 (1943).

(4) I. Langmuir and D. F. Waugh, *ibid.*, **62**, 2771 (1940).

(5) N. R. Blatherwick, F. Bischoff, L. C. Maxwell, J. Berger and M. Sahyun, *J. Biol. Chem.*, **72**, 57 (1927).

(6) V. du Vigneaud, E. M. K. Geiling and C. A. Eddy, *J. Pharmacol.*, **33** 497 (1928).

(7) T. D. Gerlough and R. W. Bates, *ibid.*, **45**, 19 (1932).

(8) V. du Vigneaud, R. H. Sifferd and R. R. Sealock, *J. Biol. Chem.*, **102**, 521 (1933).

(9) H. Neurath, J. P. Greenstein, F. W. Putnam and J. O. Erickson, *Chem. Revs.*, **34**, 157 (1944), p. 185.

(10) A. Rothen, B. F. Chow, R. O. Greep and H. B. Van Dyke, *Cold Spring Harbor Symposia Quant. Biol.*, **9**, 272 (1941).

Preparation of Fibrous Insulin

Quantitative knowledge concerning r-insulin and the process of reversion of f-insulin necessitated finding methods by which insulin could be converted completely into freely suspended insulin fibrils.

The following method is satisfactory. Crystalline zinc insulin 2% by weight in 0.035 to 0.05 *N* hydrochloric acid (*p*H about 1.8) is sealed in acid washed glass ampules, 2 cc. per ampule. The ampules are immersed for about five to twelve minutes in a water-bath at 100°. During this period weak flow double refraction and, in some cases, incipient flocculation appear.[11] At this time the ampule is cooled in tap water, dried, and frozen by immersion in solid carbon dioxide and acetone. After two minutes the tube is withdrawn, thawed, and reimmersed in water at 100° for five to eight minutes.

The initial heating period produces small numbers of relatively long fibrils. The effect of the freezing–thawing is to break such elongated fibrils into short segments. Each of these acts as a new center for elongation. Since fibril elongation is quite rapid at 100°[12] lateral alignment and spherite formation[2] do not take place. The tube gels within a few seconds and may remain clear except for light scattering associated with highly asymmetric particles. After orienting the fibrils (initially oriented at random) the tube shows intense interference colors when viewed between crossed polaroids. Gels prepared in this way will be referred to as standard fibrous gels.

Extent of Fibril Formation in Standard Gel.—The amount of n-insulin and material incapable of forming fibrils present in a standard fibrous gel may be estimated from the following.

1. Filtration through no. 50 Whatman paper removed over 95% of the nitrogen (fibrils) from the original gel. An ultra-fine Buchner funnel removes 99% of the nitrogen even after repeated washings. The great lengths of insulin fibrils may be appreciated from their inability to pass through such a filter paper.

2. It has been shown that insulin fibrils, once formed, will elongate rapidly at room temperature.[12] After mixing 2 ml. of 2% n-insulin and 0.8 ml. 2% fibrous insulin at 25° 86% of the n-insulin was converted into fibrils in forty-six hours. The reaction, which is pseudo monomolecular, has a Q_{10} (temperature coefficient) of about 4.0. If this material had been heated at 100° for six minutes, assuming a temperature coefficient of 4 over the range between 25 and 100°, less than 0.02% would have remained in the n-insulin form.

Under the conditions given for preparing a standard gel it is therefore estimated that conversion to fibrils is better than 99% and that unconverted n-insulin may be neglected. The possibility that n-insulin is adsorbed to fibrils is treated in the discussion.

Crystallization Procedure

A modification of the final crystallization of Romans, Scott and Fisher[13] was used. The preparation to be

(11) Flow double refraction is observed by tilting the vial between crossed polaroids. The flow thus produced aligns only the longer fibrils.

(12) D. F. Waugh, *Proceedings of Federation of Societies for Experimental Biology*, **5**, No. 1, 111 (1946).

(13) R. G. Romans, D. A. Scott and A. M. Fisher, *Ind. Eng. Chem.*, **32**, 908 (1940).

crystallized is brought to *p*H 5.3–5.5 with 0.3 *N* acetic acid and centrifuged for fifteen to twenty minutes with a clinical centrifuge (*ca.* 400 g.). The precipitate is dissolved in sufficient 0.327 *N* acetic acid to give a theoretical insulin concentration of 0.2 to 0.4%. A volume of 0.31 *N* ammonium hydroxide equal to the volume of acetic acid is added and the *p*H adjusted to 8.0. For each 10 ml. solution is then added 0.15 ml. of zinc acetate in 0.3 *N* ammonium acetate buffer at *p*H 6.0–6.3 containing 0.25 mg. of zinc per ml. The *p*H is then adjusted to 5.9–6.1 with 0.31 *N* ammonium hydroxide and crystallization is allowed to proceed for six days, after which the crystals are assayed.

Slight variations, mainly concerned with protein concentration, will be indicated in the text.

Assay of Crystals.—Amounts of crystals were obtained directly by washing in distilled water, drying and weighing. In most instances, however, samples of 10 mg. or less were used. Rapid and effective assays of such crystalline materials were obtained by transferring from the crystallizing vial to an assay tube consisting of a 10 ml. test-tube with a heavy-walled capillary 4 cm. long and 1.3 mm. in internal diameter sealed on the end. The assay tube was centrifuged on a clinical centrifuge for two to three minutes after which the length of capillary tube occupied by the crystals was measured. Insulin crystals, having a density considerably higher than any other materials present, pack first and the upper boundary of the crystalline material may be seen quite easily. The lengths of capillary occupied by the crystals may be converted to mg. of n-insulin in the crystallizing vial or to final mg. crystals with some degree of accuracy as shown in Table I and Table II. In Table I the first column gives the mg. of initial n-insulin crystallized in a final volume of about 10 ml.

TABLE I

THE CAPILLARY ASSAY OF CRYSTALLIZED INSULIN

n-Insulin, mg.	Crystal size	Capillary assay, mm.	Calculated capillary assay, mm./10 mg.
1	Small	1.5	15
2	Medium	3.0	15
3	Large	4.0	13.5
4	Large	5.5	13.7
5	Large	6.5	13.0
10	Large	13.5	13.5
10	Large	13.5	13.5
10	Small	13.5	13.5
10	Medium	13.5	13.5
10	Large	12.8	12.8
10	Large	13.5	13.5
			Av. 13.4 ± 0.1

Crystals from last six determinations weighed 38 mg. after careful washing which reduced the 80.3 mm. recorded above to 79.8 mm.

TABLE II

RELATIONSHIPS BETWEEN WEIGHT AND CAPILLARY ASSAY

Insulin type	Crystal size	Capillary assay mm. crystals	Crystal weight, mg.	M. crystals mm. assay
n-Insulin	Mixed	79.8	38.0	0.48
a-Insulin	Mixed	109.5	53.5	.49
a-Insulin	Small	49.5	25.0	.50
r-Insulin	Large	82.5	47.0	.57
r-Insulin	Mixed	126.5	64.5	.51
a-Insulin	Small	55.5	27.0	.49
			Av.	.51 ± 0.2

Medium crystals are between 30 and 80 μ. Large and small are on either side of this range.

The second column indicates crystal size, the third mm. crystals as measured in the assay capillary and the last column calculated mm. assay column for 10 mg. n-insulin. The first two values in the last column are probably too high due to the fact that small amounts were being assayed in a capillary which had a somewhat rounded end. The remaining figures average 13.4 mm. for each 10 mg. of n-insulin dissolved and crystallized.

Table II shows the relationship between total length in the capillary and the weights of these same crystals. In these, crystals from similar experiments were pooled. The first row of Table II represents the pooling of the last six samples of Table I. In column 1, Table II, a-insulin is insulin which has been first treated with alkali and r-insulin is material obtained after the reversion of fibrils. The second column gives crystal size, the third and fourth mm. in assay tubes and mg. dry weight of the same crystals and the last column the ratio, f, of mg. weight and mm. in assay tubes. The last column averages f = 0.5.

Effects of Alkali on Insulin

Sufficiently strong alkali irreversibly inactivates insulin. At the same time crystallizing potency is lost. These effects, for a given reagent, may be minimized by working at low temperature. Thus, at 36°, 0.033 *N* sodium hydroxide not only inactivates in three hours but, after twenty-five hours, 0.5% hydrogen sulfide appears.[14] At 0–4° the molecule is not appreciably affected after ten hours. According to Jensen and Geiling[15] insulin may be treated with 0.01 *N* alkali at 0° for forty-eight hours without noticeable loss in physiological activity.

The effects of alkali on the crystallizing ability of n-insulin have been examined. Figure 1 and Table III summarize the results. In all cases 10 mg. of n-insulin dissolved in 0.5 ml. of 0.035 *N* hydrochloric acid were added to 5.0 ml. of alkali of appropriate concentration at 0°. After the times indicated, the alkali was neutralized to *p*H 5.35 with 0.3 *N* acetic acid and the precipitate centrifuged and crystallized. The crystals within certain groups shown in Table III were pooled,

TABLE III

THE EFFECT OF 0.03 *N* SODIUM HYDROXIDE ON NATIVE INSULIN AT 0°

Time, min.	Crystal size	Crystal assay, mm.	Group
0	Large	11.25	
60	Small	14.35	
105	Small	14.2	I
180	Small	12.0	
300	Medium	6.0	
1380	Mixed	10.2	
14	Small	14.5	
19	Small	14.4	II
30	Small	14.5	
45	Small	15.5	

Group I, total mm. 49.5; total weight, 25.0 mg.; *f* = 0.50. Group II, total mm. 55.5; total weight, 27.0 mg.; *f* = 0.49.

(14) K. Freudenberg and A. Münch, *Z. physiol. Chem.*, **263**, 1 (1940).

(15) H. Jensen and E. M. K. Geiling, *J. Pharmacol.*, **35**, 511 (1928).

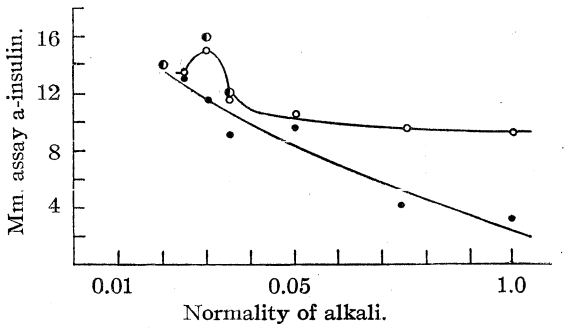


Fig. 1.—The effect of sodium hydroxide treatment on the crystallizing ability of *n*-insulin: ○, 345 min.; ◐, 405 min.; ●, 1380 min.

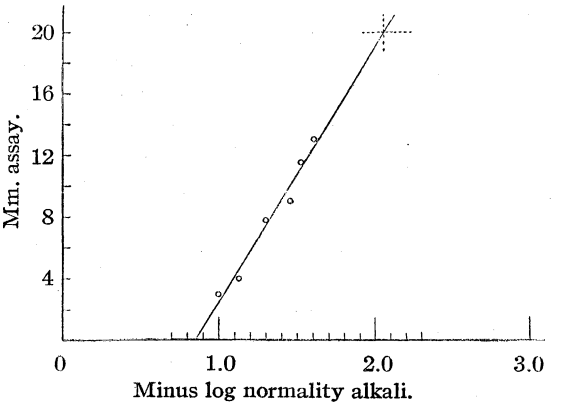


Fig. 2.—Recovery of insulin after 1380 minutes of treatment with sodium hydroxide of different concentrations. The intercept at 0 mm. indicates that 0.141 *N* alkali will abolish crystallization in this time. The abscissa corresponding to 20 mm. recovery indicates that 0.0085 *N* alkali is the maximum concentration which will have no effect in 1380 minutes (twenty-three hours).

washed with distilled water, dried *in vacuo* and weighed. The total mm. crystals and mg. dry weight are given at the base of the table for each group.

The data for 345, 405 and 1380 minutes are represented in Fig. 1. Recovery of crystals in mm. is plotted as ordinate against the normality of the alkali used. It seems that the shorter treatment times with alkali concentrations near 0.03 *N* "condition" the insulin so that a larger yield of crystals is obtained. Thus, although a yield of 13.5 mm. crystals is obtained with no alkaline treatment (see Table I), treatment with 0.03 *N* sodium hydroxide may increase this value to as much as 16 mm. as shown by the double circle of Fig. 1, the maximum for 405 minutes. However, the "conditioning" effect of alkali is not reproducible as seen by comparing the data for 0.03 *N* alkali at 300 and 180 min. in Table III with the values for 0.03 *N* alkali in Fig. 1.[16]

The longest time used, 1380 minutes, indicates a gradual destruction of insulin over the entire alkali range used. Thus one may assume that "conditioning" effects have been maximal at some previous time and that the expected slow destruction of insulin is taking place. Figure 2 represents a plot of the data for 1380 minutes using mm. recovery *versus* minus log normality. A small but undetermined displacement of the curve to higher abscissas and subtraction from 14 would bring these latter values in close correspondence with the *p*H's of the solutions. The alkaline destruction of insulin appears as a linear function of *p*H, thus indicating proton dissociation as being an important step. Extrapolation indicates first, that 0.141 *N* sodium hydroxide would reduce crystallization to 0 mm. in 1380 minutes, and second, that 0.0085 *N* sodium hydroxide is the highest concentration of alkali which will exert no effect on crystallization (recovery of 20 mm.) in the same length of time. Isolated values in the literature are in agreement with those predicted in this way.

The data of Fig. 1 and Table III indicate that 0.03 *N* sodium hydroxide is best for regeneration purposes. Table III, which shows slow destruction with times greater than one to two hours, suggests that regeneration be accomplished within sixty minutes. All recoveries are dependent upon crystallizing procedure.[16] It is felt that improvements in this technique will not appreciably alter these conclusions.

Alkaline Regeneration of Insulin from Fibrils

General Effects of Alkali on Spherites and Fibrils.—As indicated previously: alkali will disperse spherites into their constituent fibrils at *p*H's between 11.0 and 11.5. Above a *p*H of 11.5 the fibrils disappear, more rapidly as the *p*H increases. Thus at *p*H 12 to 14, fibrils disappear within a few hours to a few minutes. To minimize the inactivating effects of alkali experiments were performed at 0°. *p*H values as such were not measured but, as in the case of alkali-treated n-insulin, a standard procedure for treating insulin fibrils was used. Thus 0.5 ml. (containing 10 mg. protein) of the fibril preparation was mixed with 5.0 ml. of carbonate free alkali previously cooled to 0°. After standing the solution was brought to *p*H 5.35 with 0.3 *N* acetic acid, centrifuged, and the precipitate crystallized as described.

Initial Treatments of Standard Fibrous Gel.—As a preliminary, portions of standard gel were treated with 0.02, 0.25 and 0.03 *N* sodium hydroxide for eighteen and sixty-six hours. Even after sixty-six hours flow double refraction was present which decreased in the order 0.02, 0.025, 0.03 *N* alkali. Table IV shows typical results of crystallization. The first column shows

(16) The yield of crystals is a function of the crystallizing procedure as well as the alkaline pretreatment. Thus the "conditioning effect" of alkali might be expected to disappear under those conditions where a quantitative yield of crystallizable protein is obtained. One would expect 20 mm. crystals per 10 mg. insulin. This indicates that the crystallizing technique used recovers about 70 to 80% of the potentially crystallizable protein. It is probable that short alkaline treatments cause a more rapid crystallization, thus increasing relative yields. This is under investigation.

alkali concentration, the second time in hours and the third mm. crystals per 10 mg. of fibrils. With the exception of 0.02 *N* sodium hydroxide the longer treatment times destroy part of the r-insulin for the recovery falls. The low yields of r-insulin with 0.02 *N* sodium hydroxide indicated that longer treatment times would not be particularly effective. Methods were sought by which the rate of liberation of r-insulin could be increased.

TABLE IV

REGENERATION OF r-INSULIN FROM STANDARD FIBROUS GEL WITH ALKALI AT 0°

Alkali normality	Time in alkali hours	Mm. crystals per 10 mg. fibrils mm.
0.02	18	2.2
.02	66	8.2
.025	18	9.9
.025	66	3.7
.03	18	7.7
.03	66	5.5

Further Treatments of Standard Gel.—Among others, it was considered that the reversion of fibrils by alkali might depend upon the number of available fibril ends rather than on the total fibril surface area. Thus, that fibrils disaggregate in a sequence about the reverse of that in which they form. This was tested by freezing standard gel in solid carbon dioxide–acetone and thawing just before subjecting the fibrils to alkaline treatment.

As indicated previously[1] the effect of freezing and thawing is to break the longer fibrils into short segments. Such segments are quite active and will unite again in a matter of minutes at room temperature. Therefore the frozen-thawed material is treated immediately. Standard gels have been subject to multiple freezing-thawing cycles and have been treated with a number of alkali concentrations in the range 0.025 to 0.05 *N*. The results with 0.03 *N* sodium hydroxide are typical. With two freezing-thawing cycles and alkali exposure times of 30, 60, 300 and 1380 minutes assays showed 12.0, 11.0, 10.0 and 8.2 mm. crystals indicating, as found previously, that exposure times of sixty minutes or less are most effective.

Table V shows a typical experiment using forty-five min. exposure times with 0.03 *N* sodium hydroxide at 0°. The samples were frozen-thawed as

TABLE V

FREEZING–THAWING CYCLES AND REGENERATION YIELDS

These data were obtained with a modified crystalline technique

Freezing–thawing cycles	0	1	2	3	4
Calculated recovery, g.	0	5.2	7.2	7.2	7.6

shown in the first row, the row below giving recoveries, in mg., calculated from mm. assay. The sudden rise in regeneration yield with the first cycle and the smaller but significant rise with the second cycle are typical. Little is gained after two freezing–thawing treatments. This agrees with visual observation for, after two cycles, the insulin fibrils are clumped and are not further broken up.

Essentially the same results as those described have been obtained with mechanical methods for breaking fibrils (homogenization) thus eliminating any specific effects of freezing–thawing as increasing regeneration yield and indicating that the numerical increase in fibril ends is the responsible factor.

Table VI shows typical recoveries for 2, 3 and 4 freezing–thawing treatments using 0.3 *N* sodium hydroxide and times, at 0°, of ten, twenty, thirty and forty-five minutes. The averages shown in the last row for thirty and forty-five minutes indicate that about 12.0 mm. crystals may be realized from the reversion of 10 mg. fibrils. This figure may be compared with a figure of 14.5 mm. obtained after a similar alkaline treatment of native insulin (Table III and Fig. 1, 0.03 *N* alkali). If the crystallization properties of a-insulin and r-insulin are the same, 75 to 83% of the insulin in the fibrils may be recovered in crystalline form.

TABLE VI

REGENERATION YIELDS OF r-INSULIN AS AFFECTED BY TIME AND FREEZING–THAWING CYCLES AT 0° USING 0.03 *N* SODIUM HYDROXIDE

Freezing–thawing cycles	Mm. crystals per 10 mg. fibrils after treatment (time, min.) 10	20	30	45	Row
2	6	10.5	12.0	12.0	1
2	9.8	12.2	11.0	12.7	2
3	10.2	12.0	12.0	12.5	3
3	10.2	12.0	12.5	12.7	4
4	8.5	10.5	12.2	10.8	5
4	10.8	12.2	12.1	12.2	6
Average	9.2	11.6	12.0	12.1	7

Total crystals recovered from rows 2 and 3 weighed 47 mg.; from rows 4, 5, and 6, 64.5 mg.

The treatments described do not transform all of the fibrous material. The unreverted fibrils, after the crystallization following the first alkali treatment, may be recovered, washed, and subjected to another reversion treatment. In this way an additional 1–1.5 mm. of crystalline material may be obtained bringing the total recovery to 13 to 13.5 mm. or about 85 to 90% of the original protein. This is in good agreement with determinations of biological activity after alkaline treatment of the heat precipitate[5,6,7,8] in which reactivations of 80 to 100% have been claimed for biological activity and with our more recent regenerations by a variety of reagents.

From the foregoing information it appears that crystalline recoveries of 85 to 90% may be obtained by treating twice frozen–thawed fibrils with 0.03 *N* sodium hydroxide at 0° for forty-five minutes with a ratio of 0.5 ml. of 2% fibrils to 5.0 ml. alkali.

The Effect of Sodium Chloride on Alkaline Reversion of Fibrils.—Reversion has been carried out with the procedure described at the end of the preceding section with the addition of sodium chloride to the alkali. The results are summarized in Fig. 3 which shows mg. of recovery of crystalline r-insulin (calculated from mm. of assay and using 10 mg. of starting fibrils) plotted against the normality of sodium chloride present in the alkali. The resulting curve, an average of several values, shows that inhibition of reversion starts with salt concentrations somewhat in excess of 0.01 *N* and is marked at 1.0 *N*. With 2.0 *N* sodium chloride complete inhibition is obtained. These results will be considered in the discussion.

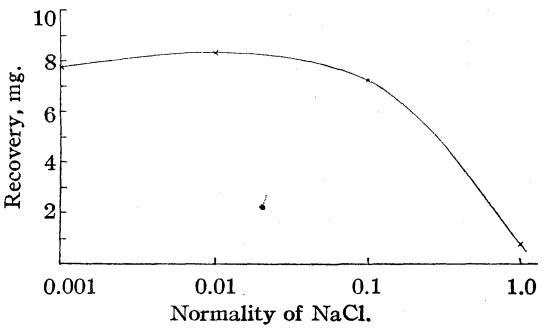


Fig. 3.—Regeneration of insulin from fibrils when various amounts of sodium chloride (abscissa) have been added to the regenerating alkali. Recoveries are calculated from mm. assay using $f = 0.5$.

Properties of r-Insulin Regenerated from Fibrils by Alkali

Crystallizatiom.—In agreement with the properties of n-insulin, crystallization of r-insulin will not proceed in the absence of zinc. Other metal ions which may be substituted for zinc have not been tested. In these experiments relatively zinc free preparations were made by dialyzing an acid solution of r-insulin and by precipitating an acid solution with organic solvents according to Scott.[17] Recrystallization of the same preparations in the presence of zinc produced typical crystals.

r-Insulin and n-insulin have the same crystal form although r-insulin generally gives somewhat larger crystals than n-insulin. A comparison of recrystallized n-insulin and r-insulin with a petrographic microscope reveals the two types of crystals described by Abel, Geiling, Rouiller, Bell and Wintersteiner.[18] The type showing well-defined negative double refraction seemed more numerous in n-insulin samples, r-insulin containing proportionately more crystals having well defined edges with little double refraction.

The recoveries of r-insulin and n-insulin were not significantly different on recrystallization.

Biological Activity.—Crystals of r-insulin and n-insulin were washed with distilled water and dried *in vacuo*. Biological assays arranged by Dr. R. E. Thompson[19] gave

r-insulin, 20.2 units per mg. ± 5.9%
n-insulin, 22.1 units per mg. ± 7.8%

The small difference between regenerated and native insulins is not considered significant and is probably due to inert protein, the drying procedure, or some other uncontrolled factor.

Ultracentrifuge Determinations.—Recrystallized n-insulin was converted to standard fibrous gel and r-insulin was regenerated. The resulting r-insulin crystals were carefully washed and a clear lot isolated. This amounted to 42.4% by weight of the initial insulin. Dr. J. L. Oncley[20] has compared the behavior of n-insulin and r-insulin in the ultracentrifuge.

Dr. Oncley writes, "Solutions of insulin crystals obtained from r-insulin containing 1 and 2% of protein were studied in an air-driven ultracentrifuge[21,22] equipped with a modified Philpot schlieren optical system.[23] The measurements were made in a cell 1.5 cm. high, 1.0 cm. thick, whose center was 6.5 cm. from the axis of rotation. A speed of 54,000 r.p.m., equivalent to centrifugal forces of from 200,000 to 240,000 times gravity, was used and the average temperature was about 24°. Values of sedimentation constant have been reduced to the value in a solvent of the density and viscosity of water at 20°. A phosphate buffer of 0.1 ionic strength, *p*H 7.2, was used as a diluent. The protein solutions were made by dissolving dried insulin crystals in a small volume of dilute hydrochloric acid and neutralizing with a phosphate buffer calculated to yield a final ionic strength of 0.1 and *p*H 7.2. A solution made from ordinary crystalline insulin (from beef)[24] was used for comparison. Sedimentation diagrams of unmodified crystalline insulin and the crystals obtained from r-insulin were compared and found to be practically identical. The sedimentation constant usually assigned to crystalline insulin at this *p*H was obtained, that is, about 3.3 to 3.6.[25,26,27] The diagrams from the r-insulin showed no more evidence of faster moving components than is usually obtained from commercial insulin crystals, and the 'apparent diffusion constant' obtained by analysis of the sedimentation diagrams was only slightly larger than the observed diffusion con-

(17) D. A. Scott, *Biochem. J.*, **28**, 1592 (1934).

(18) J. J. Abel, E. M. K. Geiling, C. A. Rouiller, F. K. Bell and O. Wintersteiner, *J. Pharmacol.*, **31**, 65 (1927).

(19) The author is indebted to the Chemical Research and Development Laboratories of Armour and Company for these assays. Many others confirm the conclusions drawn here.

(20) Great appreciation is expressed to Dr. J. L. Oncley of the Department of Physical Chemistry, Harvard Medical School, for this analysis.

(21) J. H. Bauer and E. G. Pickels, *J. Exp. Med.*, **65**, 565 (1937); also in T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford Press, 1940.

(22) E. G. Pickels, *Rev. Sci. Instruments*, **9**, 358 (1938); **13**, 426 (1942).

(23) J. St. L. Philpot, *Nature*, **141**, 283 (1938).

(24) Obtained from Eli Lilly & Company.

(25) B. Sjögren and T. Svedberg, THIS JOURNAL, **53**, 2657 (1931).

(26) G. L. Miller and K. J. I. Andersson, *J. Biol. Chem.*, **144**, 459 (1942).

(27) H. Gutfreund and A. G. Ogston, *Biochem. J.*, **40**, 432 (1946).

stant, again indicating the homogeneity of the materials."

In addition the ultracentrifuge data suggest that r-insulin is able to go through the same cycle of reversible fragmentation as n-insulin.

Sensitivity to Alkali.—Crystallization of the isoelectric precipitate obtained after treating 0.5 ml. of 2% crystalline r-insulin (10 mg.) with 5.0 ml. of 0.03 *N* sodium hydroxide at 0° for times of 0 to 400 minutes gave consistent yields of about 95% ± 5% up to times of 200 minutes after which the recovery fell to 86% and at 400 minutes 84%. Up to 200 minutes, therefore, r-insulin seems less sensitive to alkali treatment than n-insulin since treatment of n-insulin with 0.03 *N* alkali usually gives yields of about 80% with times up to 200 minutes (Table III). This difference, at present, cannot be interpreted as showing significant differences between the effects of alkali on r- and n-insulins but could be due to the crystallization procedure which may handle r-insulin somewhat better than n-insulin.[16]

Labile Ammonia.—It has been considered generally that liberation of ammonia accompanied the heat precipitation of insulin although du Vigneaud, Sifferd and Sealock[8] found no relationship between amounts of ammonia liberated and heat precipitate formed. Insulin fibrils seeded into solutions of n-insulin will elongate at room temperature and transform the n-insulin into fibrils.[12] One can therefore test for liberation of ammonia at 25°. n-Insulin and n-insulin seeded with short fibrils (80 mg. n-insulin, 20 mg. short fibrils) were dialyzed against 10 ml. 0.01 *N* hydrochloric acid. All dialysis fluids, by Nesslerization, had the same nitrogen contents within the experimental error. The liberation of 0.03% nitrogen could have been detected.

Disulfide and Sulfhydryl.—The nitroprusside reaction[8] was used to test for free sulfhydryl groups. This has been shown to be negative in n-insulin and fibrous insulin.[28] Free disulfides, as shown by the cyanide–nitroprusside reaction, do not increase on fibril formation. This test is not particularly indicative since n-insulin gives a strong cyanide–nitroprusside reaction equivalent to about 25–30% of the total sulfur present.

In agreement with others[8] reduction with cyanide abolishes the heat precipitate and fibril formation. The status of the disulfide linkage will be treated in the discussion.

Fibril Formation with r-Insulin.—When dissolved in 2% concentrated at *p*H 1.6–1.7 (0.05 *N* hydrochloric acid) n-insulin remains quite stable at 20° or below and shows evidence of fibril formation only after many weeks, and, in instances, months.

Unpurified products of alkaline reversion precipitated at *p*H 5.35 and taken up in acid show rapid fibril formation at room temperature or in the ice chest. Treatment with alkali, however, usually does not revert quantitatively since the presence of unreverted fibrils may be demonstrated by double refraction of flow or other methods. These act as active centers,[12] elongate at low temperatures, and under proper conditions give rise to products ranging from the heat precipitate to a clear fibrous gel. In order to compare r-insulin and n-insulin these unreverted fibrils must be removed. Recrystallization has been used with success. The r-insulin after the first recrystallization differs from n-insulin in forming a fibrous gel having brilliant double refraction in two to three minutes at 100° and in showing slow but appreciable fibril formation at room temperature over a period of several days. The insulin was dissolved in 2% conc. in 0.05 *N* hydrochloric acid (*p*H 1.6–1.7). Under the same conditions twice recrystallized r-insulin, washed many times with distilled water, shows rapid fibril formation at 100° but at room temperature very faint flow double refraction only was detected after several weeks. After a third recrystallization the product, representing 46% by weight of the initial fibrous insulin, showed no double refraction or alterations in other properties, such as viscosity and clarity, over a period of fourteen weeks. At 100° the thrice-recrystallized r-insulin seems to show fibril formation slightly faster than commercial, untreated n-insulin. However, fibril formation is sensitive to a number of variables including salt concentration, *p*H, anions, etc. Thus n-insulin will show varying rates of fibril formation, particularly at higher temperatures, after manipulations such as recrystallization. The rates of fibril formation obtained with thrice recrystallized r-insulin at 100° are well within the normal range.

Repeated crystallization, therefore, leads to an r-insulin which approaches n-insulin in the characteristics of fibril formation at low and high temperatures.

Discussion

The physical, chemical and biological tests applied cannot thus far differentiate between r-insulin and n-insulin. These tests include crystallization, ultracentrifuge analysis, biological activity, changes in labile groups such as amino and disulfide, and fibril formation. Before an analysis is undertaken consideration should be given to the extent to which n-insulin enters into the basic fibril forming reaction. Thus, high yields of r-insulin of 80–90% do not rule out the possibility that 10% of the n-insulin irreversibly unfolds and gives rise to a fiber "skeleton" while the remaining 90% is physically adsorbed to this skeleton as n-insulin. Several lines of evidence exclude this possibility. First, the adsorption of n-insulin onto fibrils has been examined in connection with reaction kinetics. Adsorption becomes important only at *p*H's well above 3.0. Second, fibrils form and elongate at *p*H's which render insulin highly soluble and in which strong repulsive forces would be

(28) M. L. Sackler, Chemical Modifications of Insulin and Their Relation to Fibril Formation, Master's Thesis, 1945, Massachusetts Institute of Technology, Cambridge, Mass.

expected to occur between the molecules.[2] Third, washing a fibrous gel with acid does not produce elution. Fourth, the fibril once initiated can elongate at room temperature or below.[12] Insulin shows its maximal stability at *p*H's close to 2.0 at low temperatures and would not be expected to show spontaneous unfolding under these conditions. Fifth, the fibril, in alkali, liberates r-insulin selectively from its ends and not uniformly over the entire surface as one might expect from a skeleton containing 4 to 9 times its weight of adsorbed material. It seems reasonable to conclude that all of the n-insulin enters the basic fibril structure.

Native insulin may be defined on the basis of certain intrinsic properties such as crystallizability, biological activity and fibril forming capacity. Although there is evidence that these characteristics may be dissociated to some extent (*i. e.*, an insulin which will form fibrils but will not crystallize), certain series are recognized (*i.e.*, if an insulin crystallizes it also has biological activity and shows fibril formation). In this way, crystallization emerges as a delicate test for insulin, other properties requiring less precise structure.

A number of modifications of insulin have been reported. Such modifications may be divided into those involving mainly surface groups and those in which internal structure has been obviously altered. Examples of the first type are the acetylation of insulin with ketene[29] reported by Stern and White and the linking of insulin with diazonium salts reported by Reiner and Lang.[30] In instances these "surface" modifications retain their biological activity and form crystals. A number of reagents, used primarily for surface group modification, are suspected of causing internal structural changes. In these cases both biological activity and crystal formation are irreversibly lost. Directed changes in internal structure have been quantitatively studied thus far by reduction of some of the disulfide groups (of which seven or eight are usually available out of a total of 23). Reduction of an average of 1 or 2 groups per molecule leads to a 50% loss in biological activity.[31] On *reoxidation* the activity decreases to about 1% of original. More drastic reduction[8,28,32] causes a complete loss of crystallizability, biological activity and fibril formation. It should be mentioned here that an extensive unfolding of the protein would be expected to involve the breaking of several disulfide linkages. On the basis of evidence mentioned a refolding with the formation of new disulfide linkages should lead to a product having none of the intrinsic characteristics of insulin. Mild alkaline treatment[28] may lead to a simultaneous loss of biological activity and crystallizability while treatment with concentrated solutions of guanidine and urea may produce a complete loss of crystallizing ability with only a slight diminution in fibril forming capacity.

Thus it would appear that demonstrable changes in internal structure lead to irreversible loss of one or more of the characteristic properties. r-Insulin retains these labile characteristics completely. From this and the fact that fibril elongation may proceed below 20° it is concluded that fibril formation involves the endwise linkage of globular (corpuscular) units which are not appreciably unfolded in the process.

A Note on "Denaturation."—According to most definitions the stable fibrous form of insulin would represent a denatured protein, for the fibrils retain few of the properties of n-insulin. Regeneration, however, shows that the insulin molecules have not lost these properties irreversibly. It seems obvious that four general factors determine the over-all reversibility of this system. These are the strength of the intermolecular bond, the ability of a regenerating agent to overcome this bond, and the ability of the fibrils and reversion product to withstand the damaging action of the reverting (regenerating) agent. The rates of the several reactions enter as important variables. A somewhat stronger inter-insulin bond would require more drastic alkaline treatments. These would effect reversion but the r-insulin liberated would be inactivated and irreversibly altered during the process. If the sequence of events were not clearly recognized, one might conclude that the n-insulin had suffered irreversible changes during the process of fibril formation itself. Many coagulations have been considered irreversible. Evidence should be presented which shows that the structure of the protein has been irreversibly altered during the process of coagulation and not subsequently.

Mechanism of Reversion.—Calculations from amino acid analyses and titration data[33,34] show that a molecule of insulin of molecular weight 40,000 contains about 80 free carboxyl groups, 40 free amino groups, and 50 hydroxyl groups, some of which are available.[9]

Fibril formation and fibril aggregation or heat precipitation[2] have been shown to be dependent to a marked degree on mechanisms which change the repulsive forces between the molecules. It seems clear that acid *p*H's are necessary to produce a variety of insulin which can enter the fibril forming reactions. However, once this condition has been fulfilled the addition of neutral salt, such as sodium chloride, greatly increases the rate of fibril formation, presumably by causing a decrease in electrostatic repulsion. In acid solution, *p*H's below 3.0, one would expect the carboxyl groups to be largely un-ionized and thus a quantity of insulin corresponding to mol. wt. 40,000 would have

(29) K. G. Stern and A. White, *J. Biol. Chem.*, **122**, 371 (1938).
(30) L. Reiner and E. H. Lang, *ibid.*, **139**, 641 (1941).
(31) K. G. Stern and A. White, *ibid.*, **117**, 95 (1937).
(32) O. Wintersteiner, *ibid.*, **102**, 473 (1933).
(33) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943.
(34) C. R. Harrington and A. Neuberger, *Biochem. J.*, **30**, 809 (1936).

about 40 positive charges. The effect of salt would be to decrease the repulsive forces due to these charges and allow a greater proportion of the molecular collisions to be effective in bonding.

At the regenerating *p*H of about 12.3 one would expect the amino groups to lose their charge while the carboxyl groups and some hydroxyl groups would now ionize and become charged. Thus the net charge would change from an average of roughly +40 to over −80. It seems clear that the great increase in net charge in going from acid to alkali would set up stronger repulsive forces which would aid in disrupting the inter-insulin bond. Evidence in support of this mechanism as being part of the process comes from the action of salt, which decreases reversion as shown in Fig. 3, and those experiments which indicate that reversion proceeds at the ends of the fibrils where the inter-insulin bonds would be weakest since fewer insulin units would be engaged in their stabilization. Reversion and the inter-insulin bond are receiving further attention.

Acknowledgment.—The author wishes to acknowledge the generous support which Armour and Company has given to this and other research.

Summary

Insulin fibrils may be reverted by treatment with alkali to give a crystalline product similar to native insulin: the alkali has therefore regenerated an insulin termed r-insulin. Limiting conditions for regeneration procedure were determined by studying the effect of alkali on native insulin. Using 0.5 ml. of 2% insulin (10 mg.) and 5.0 ml. of sodium hydroxide experiments indicated 0.03 *N* alkali, 0°, and forty-five minute treatment time would be optimal. This was found to be the case. In addition reversion of fibrils is greatly accelerated by increasing the number of available fibril ends suggesting that disaggregation occurs mainly at these positions. Sodium chloride in the alkali inhibits reversion by 90% in 1.0 *N* concentration. Thus, the repulsive forces between similarly charged groups may play a part in the mechanism of disaggregation.

The crystalline product from reverted fibrils is not significantly different from native insulin in certain intrinsic properties such as: crystallization, in which r-insulin will not crystallize in the absence of zinc, and recrystallization recovery; biological activity (20 I.U. per mg.); ultracentrifuge pattern (sedimentation constant 3.3–3.6); and fibril formation (at 20 and 100°). Tests for changes in labile groups, such as amino and disulfide, have been negative.

The absence of changes in labile groups, the retention by r-insulin of the characteristic properties of insulin, the known sensitivity of these characteristic properties to structural changes, and the fact that fibril elongation may take place at low temperatures in the *p*H region of maximum stability, are interpreted as showing that only small structural changes take place during fibril formation and that the process is therefore one in which globular or corpuscular units are linked endwise.

CAMBRIDGE 39, MASSACHUSETTS
RECEIVED NOVEMBER 18, 1947

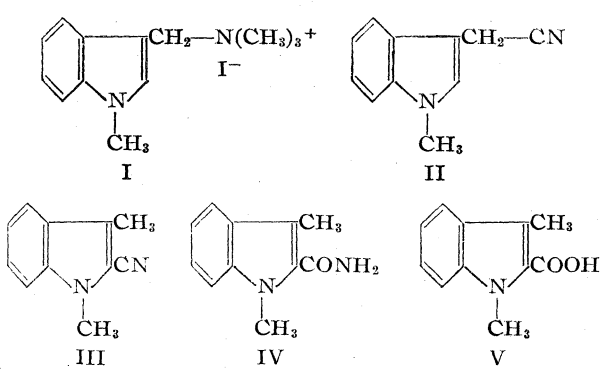
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Allylic Rearrangement in an Alkylation by a Quaternary Ammonium Salt

BY H. R. SNYDER AND ERNEST L. ELIEL

In a previous communication[1] it was stated that the reaction of 1-methylgramine methiodide (I) with aqueous sodium cyanide produced not only 1-methyl-3-indoleacetonitrile (II) but also an isomer of this nitrile. This isomer has now been identified as 1,3-dimethyl-2-cyanoindole (III). The pure isomer (III) was isolated from the reaction mixture in 4.3% yield, but in view of the difficulties encountered in the purification it is believed to have been formed in an appreciably larger amount, perhaps to the extent of 10–15%.

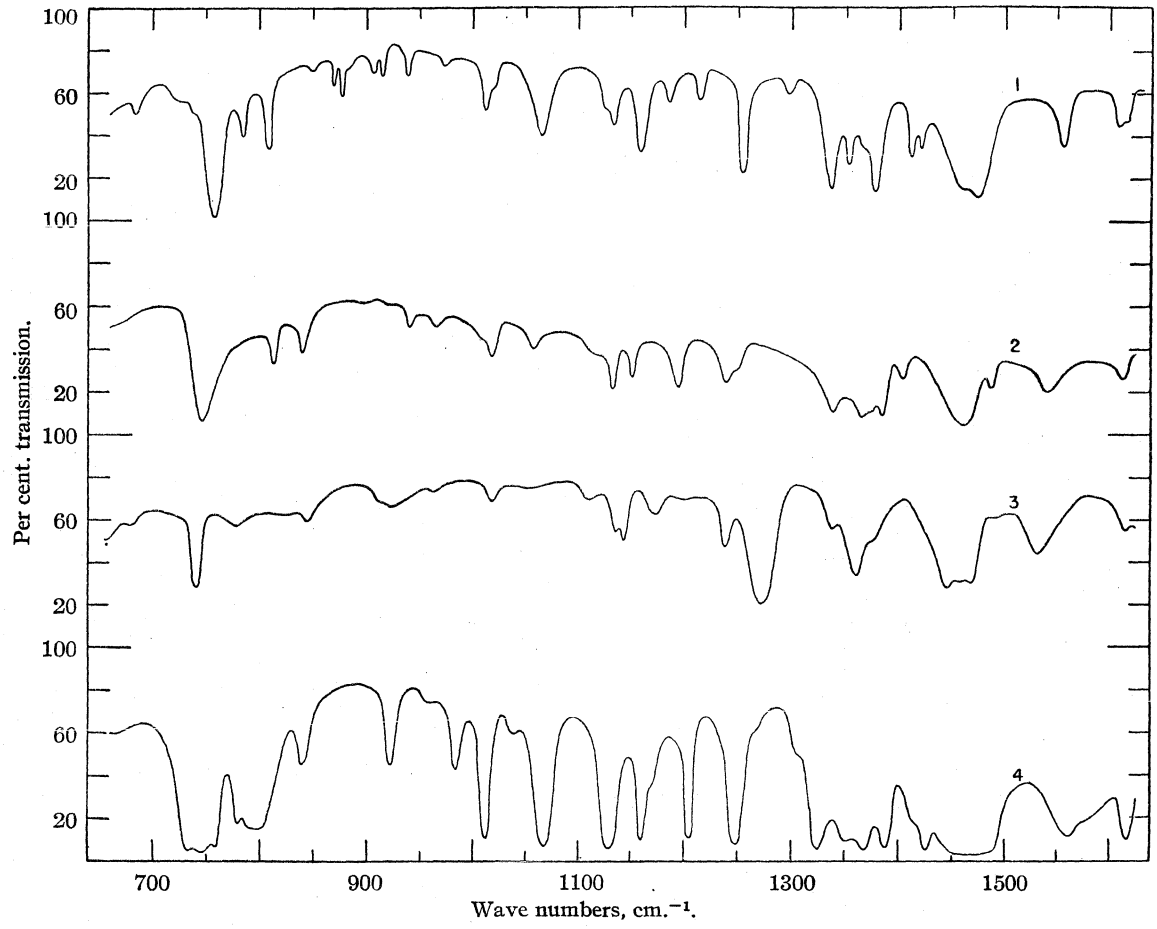
Comparison of the infrared absorption spectra of (II) and its isomer revealed a shift of the CN-absorption band of 36 cm.$^{-1}$ toward smaller wave numbers in the case of the isomer (III) (see the figures), indicating conjugation of the cyano group with one of the double bonds of the rings. Alkaline hydrolysis of the isomeric nitrile (III) yielded mainly the corresponding amide and only very



small amounts of the acid, probably because of steric hindrance of the nitrile function. The acid was finally obtained in poor yield by increasing the concentration of alkali and extending the reaction time in the hydrolysis.

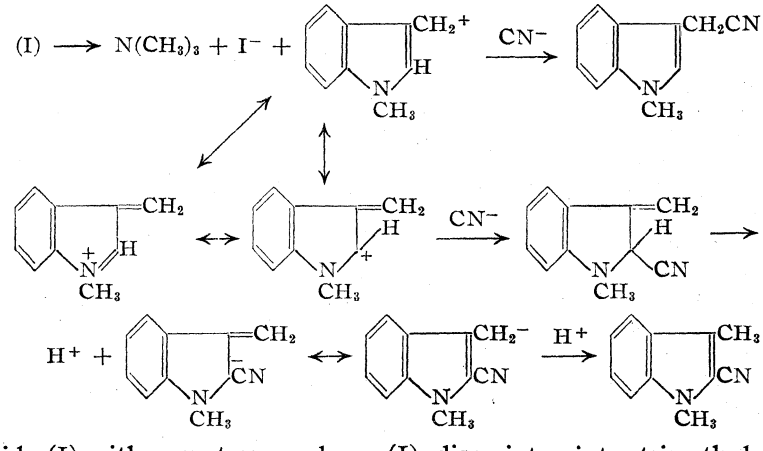
The acid (V) was synthesized by a known

(1) Snyder and Eliel, THIS JOURNAL, **70**, 1703 (1948).



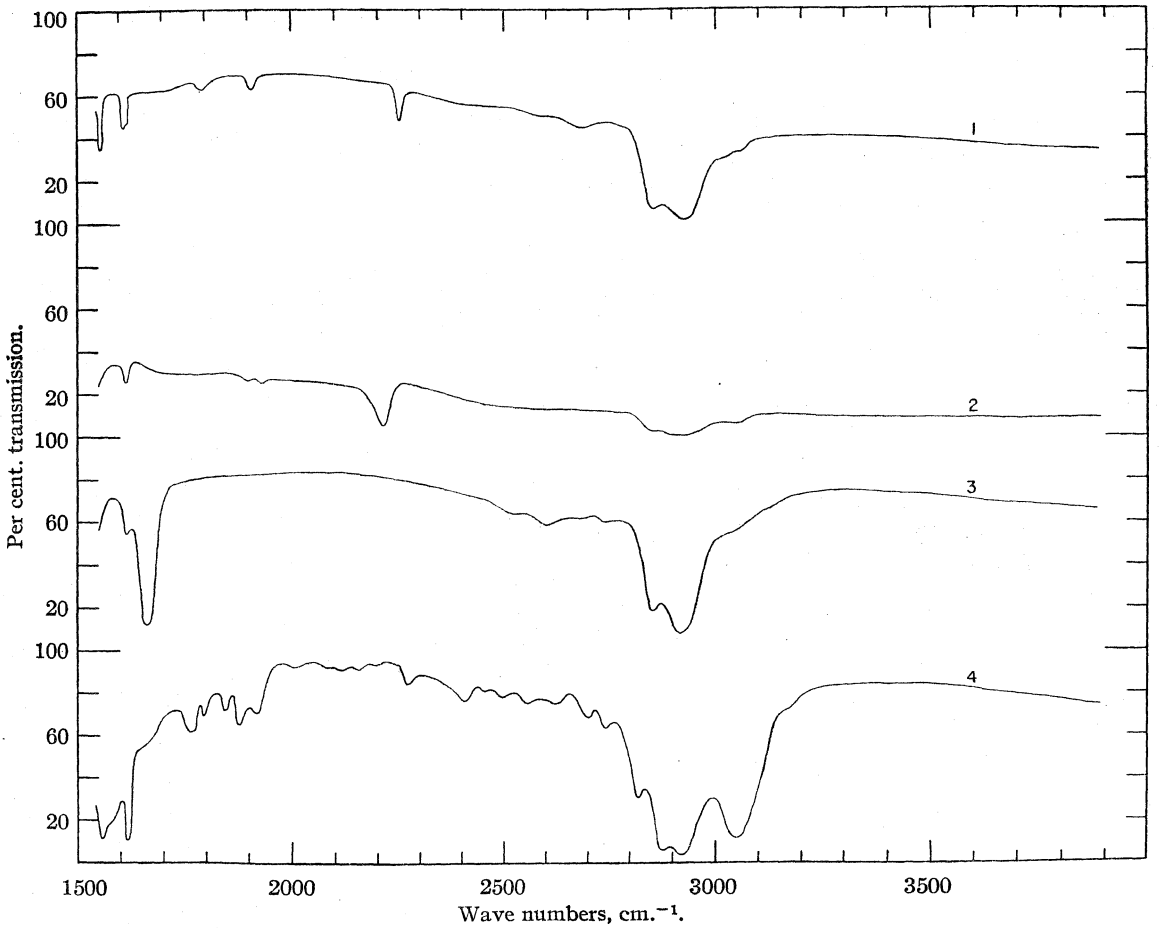
Figs. 1a, b.—Infrared absorption spectra: 1, 1-methyl-3-indoleacetonitrile; 2, 1,3-dimethyl-2-cyanoindole; 3, 1,3-dimethyl-2-indolecarboxylic acid (two identical spectra); 4, 1,3-dimethylindole (two identical spectra). Curves 1, 2 and 3 were obtained from Nujol suspensions. The absorption bands due to Nujol C–H frequencies occur

method[2] from *as*-methylphenylhydrazine and α-ketobutyric acid obtained by hydrolysis of α-benzoylaminocrotonic azlactone.[3,4] 1,3 - Dimethyl - 2 - indolecarboxylic acid (V) thus obtained proved to be identical with the hydrolysis product of the nitrile (III). The acid (V) prepared by nuclear synthesis was converted into its amide by treatment with phosphorus pentachloride in acetyl chloride solution followed by reaction with concentrated aqueous ammonia. This amide was identical with the one from the partial hydrolysis of the nitrile (III). Formulas III and IV must therefore be assigned to this nitrile and the corresponding amide.



It has thus been proved that in the reaction of 1-methylgramine methiodide (I) with sodium cyanide rearrangement occurs along with the normal reaction. The migration may be explained by the provisional assumption that the quaternary base (I) dissociates into trimethylamine and a carbonium ion which may rearrange, as shown in the accompanying diagram. An analogy exists in the reaction of furfuryl chloride with sodium cyanide to give 5-methyl-2-furo-

(2) Kermack, Perkin and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).
(3) Carter, Handler and Melville, *J. Biol. Chem.*, **129**, 359 (1939).
(4) Carter and Stevens, *ibid.*, **133**, 117 (1940).



at 2920, 2855, 1460 and 1375 cm.$^{-1}$. Sample no. 4 was seen in a liquid cell of 0.05 mm. thickness. The low transmission of the two nitriles in the high frequency regions is due to the light scattering of the crystals in the Nujol suspension.

nitrile.[5,6] Simple α,β-unsaturated halides, on the other hand, do not seem to undergo rearrangement in reactions with sodium cyanide,[5] but do so in reactions with sodium carbonate in water and with various metallic acetates in acetic acid solution.[7-10]

Experimental[11,12]

2-Cyano-1,3-dimethylindole (III).—The product of the reaction of 18.1 g. of 1-methylgramine methiodide with sodium cyanide[1] was fractionated *in vacuo* through a short Vigreux column. The fraction collected at 96–109° (0.15 mm.) and twice recrystallized from petroleum ether (b. p. 30–60°) formed large white prisms of m. p. 69.5–70.5°, weight 0.32 g. The next fraction, b. p. 109–120° (0.15 mm.), was twice extracted with hot petroleum ether (b. p. 30–60°). After the waxy residue of this extraction had been freed of insoluble oils by pressing on a porous plate, it dissolved in the hot petroleum ether extract. The crystals which separated from the cooled solution were recrystallized five times from petroleum ether to yield 0.08 g. of material of m. p. 69–70.5° [total yield, 0.40 g. (4.3%)].

1,3-Dimethyl-2-indolecarboxamide (IV). From III.—A solution of 0.39 g. of the above nitrile and 1 g. of potassium hydroxide in 1 ml. of water and 9 ml. of ethanol was refluxed for twenty-two hours. After dilution of the mixture with 4 ml. of water most of the ethanol was distilled. Crystals of the amide (IV) which separated from the cooled solution were collected, washed and dried; yield, 0.30 g. (69.5%). The amide crystallized from benzene in fine white needles, m. p. 213–214°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.89. Found: C, 70.18; H, 6.48; N, 14.70.

From the alkaline mother liquors of the hydrolysis of the nitrile, only 0.01 g. of acid could be isolated.

1,3-Dimethyl-2-indolecarboxylic Acid. From the Amide.—A solution of 0.19 g. of the above amide and 1 g. of potassium hydroxide in 0.5 ml. of water and 4.5 ml. of ethanol was refluxed for fifty-six hours. After dilution of the mixture with 4.5 ml. of water the alcohol was distilled. The cooled solution was filtered to remove unchanged amide. The filtrate was extracted with ether, boiled with charcoal, filtered, and acidified. The acid was collected, washed with water, and dried; yield, 0.04 g. (21%). After recrystallization from benzene–petroleum ether (b. p. 30–60°), from benzene, and again from benzene–petroleum ether, the acid melted at 215–216° (dec.).

(5) Reichstein, *Ber.*, **63**, 749 (1930).
(6) Runde, Scott and Johnson, THIS JOURNAL, **52**, 1284 (1930).
(7) Young and Andrews, *ibid.*, **66**, 421 (1944).
(8) Claisen, *J. prakt. Chem.*, [2] **105**, 65 (1922–1923).
(9) Meisenheimer and Beutter, *Ann.*, **508**, 58 (1933).
(10) Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942).
(11) All melting points are corrected.
(12) Microanalyses by Miss Theta Spoor and Miss Jane Wood.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86. Found: C, 69.97; H, 5.79.

From α-Benzoylaminocrotonic Azlactone.—Five grams of a mixture of the *cis* and *trans* forms of α-benzoylaminocrotonic azlactone[13] of m. p. 118–122° was hydrolyzed by refluxing for three hours with 200 ml. of 1 *N* hydrochloric acid.[3] After the solution had cooled, 3 g. of what was presumably a mixture of α-benzoylaminocrotonic and benzoic acids was removed by filtration. The filtrate was neutralized with 2 *N* sodium hydroxide, and a solution of 3.4 g. of *as*-methylphenylhydrazine in 10 ml. of water and 5 ml. of glacial acetic acid was added to it. After standing overnight the solution was chilled and the solid methylphenylhydrazone that had separated was collected and washed. It was suspended in a solution of 15 ml. of concentrated hydrochloric acid in 30 ml. of water, and the mixture was heated on the steam-bath with swirling for thirty minutes. The suspension was cooled and filtered, and the solid was dissolved in aqueous sodium hydroxide. After removal of oily impurities by ether extraction, the aqueous solution was boiled with charcoal, filtered and acidified. The acid that separated was collected, washed with water and dried at 60°; yield, 1.3 g. (29.4% from the azlactone). After three recrystallizations from benzene, the melting point of the acid (and of mixtures with the acid described in the preceding paragraph) was 215–216° (dec., lit.,[2] 213°). The infrared absorption spectra[14] of the samples obtained by the two different methods were identical (see the figures). Both samples separated from benzene solution as needles which in contact with the mother liquor soon changed into crystals of granular texture.

Decarboxylation of the above acid at 225° followed by distillation at 15 mm. (bath temperature 130–160°) yielded 1,3-dimethylindole, identified by its refractive index ($n^{20}D$ 1.5929), infrared absorption spectrum (see the figure), and the melting point and mixed melting point (142.5–143°) of the picrate. The sample used for comparison had been obtained by hydrolysis and decarboxylation of 1-methyl-3-indoleacetonitrile (II).[1]

1,3-Dimethyl-2-indolecarboxamide. From the Acid.—A suspension of 0.32 g. of the above acid (V) in 3.2 ml. of redistilled acetyl chloride was cooled in an ice-bath and 0.42 g. of phosphorus pentachloride was added. The mixture was swirled until homogeneous and then allowed to stand at room temperature for two and three-fourths hours. The solvent was removed *in vacuo* with the bath temperature not exceeding 45°. The solid residue was chilled and 10 ml. of ice-cold concentrated aqueous ammonia solution was added to it. The temperature was slowly raised to 72° over a period of thirty minutes with constant stirring. The suspension of the amide was then cooled and the solid was collected, washed with concentrated aqueous ammonia followed by water, and dried at 60°; yield, 0.28 g. (87.5%). After two recrystallizations from benzene–absolute alcohol the product melted at 213.5–214°. The mixed melting point with the amide obtained by hydrolysis of 1,3-dimethyl-2-cyanoindole (III) was 213–214°.

(13) The azlactone was kindly put at the authors' disposal by Dr. H. E. Carter.

(14) The authors are indebted to Mrs. Agatha Roberts Johnson for the absorption studies.

Summary

The reaction of the methiodide of 1-methyl-3-dimethylaminomethylindole with aqueous sodium cyanide affords, in addition to the normal alkylation product, a small amount of 1,3-dimethyl-2-cyanoindole. The structure of this product has been proved by conversion to the corresponding amide and acid which were identical with compounds obtained by independent syntheses.

URBANA, ILLINOIS RECEIVED JANUARY 2, 1948

[CONTRIBUTION FROM DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

Studies on Double Refraction of Flow. IV. Human Serum γ-Globulin and Crystallized Bovine Serum Albumin[1]

BY JOHN T. EDSALL AND JOSEPH F. FOSTER[2]

In previous papers of this series, the molecular dimensions of zein[3] and of fibrinogen[4] have been studied by the method of double refraction of flow, the results being interpreted in the light of viscosity, sedimentation and other measurements. In the present study, we report results of similar investigations on human serum γ-globulin[5] and crystallized bovine albumin.[6] The orientation of these molecules, by means of a velocity gradient, to an extent sufficient for accurate double refraction measurements, required the use of solvents of high viscosity, in order to diminish the rotary Brownian movement. Whereas fibrinogen, with a molecular length near 700 Å., could be readily studied in 40% glycerol, γ-globulin required 60–76% glycerol, and serum albumin approximately 90% glycerol.

(1) This paper is Number 68 in the series "Studies on the Plasma Proteins" from Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry, and Number XVII in the series "Preparation and Properties of Serum and Plasma Proteins" from the same laboratory.

The preparations of serum globulin employed were prepared from blood collected by the American Red Cross, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

(2) Present address, Department of Chemistry, Iowa State College, Ames, Iowa.

(3) J. F. Foster and J. T. Edsall, THIS JOURNAL, **67**, 617 (1945).

(4) J. T. Edsall, J. F. Foster and H. Scheinberg, *ibid.*, **69**, 2731 (1947).

(5) J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., in preparation.

(6) E. J. Cohn, W. L. Hughes, Jr., and J. H. Weare, *ibid.*, **69**, 1753 (1947).

Experimental Methods

The apparatus used[7] and the methods of measurement[3,4] have already been described in detail.

The great majority of the measurements on γ-globulin were made on a single preparation (IIG1-L371) prepared from Fraction II + III of human plasma[8] by method 3c as described by Oncley, *et al.*[5] Electrophoretically, this preparation contained 97% γ-globulin, 2% albumin, and 1% β-globulin. Such preparations, however, have been

(7) J. T. Edsall, C. G. Gordon, J. W. Mehl, H. Scheinberg and D. W. Mann, *Rev. Sci. Instruments*, **15**, 243 (1944).

(8) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, THIS JOURNAL, **68**, 459 (1946).

shown by Oncley, Scatchard and Brown[9] to be heterogeneous in the ultracentrifuge. The implications of this heterogeneity are further discussed later in this paper. One run not reported in detail here was made on preparation IIG1-120, with results essentially indistinguishable from others in the series.

The crystallized bovine albumin was from lot 27–315, prepared at the Armour Laboratories according to methods developed by Cohn and Hughes.[6]

The glycerol–water mixtures used as solvents were prepared by the method previously described for the studies on fibrinogen. The γ-globulin preparations contained a small amount of sodium chloride in addition to the glycerol–water used as solvent. No salt was added to the albumin preparations. At the very high glycerol concentrations employed in the studies of albumin (88.5–94.5% by weight) the viscosity varies rapidly with slight changes in the composition of the solvent. Therefore, great care was taken in the control of glycerol concentration. Both γ-globulin and albumin gave clear and stable solutions in the glycerol-water mixtures employed.

Experimental Results

γ-Globulin.—A series of measurements on γ-globulin preparation IIG1-L371 was made at protein concentrations varying from 1.25 to 5 g. per 100 cc., and at glycerol concentrations varying from 60 to 76%. In almost all of these experiments, studies were made at two different temperatures; one set near 6° and the other at 18 to 19°. The results of one experiment are given in detail in Table I, together with the calculated values of the rotary diffusion constants (Θ) derived from the measurements. The values of Θ are not reported as such, but are multiplied by the ratio of the viscosity of the solvent (η) to the absolute temperature (T), since these $\eta\Theta/T$ values should be independent of the particular solvent and temperature employed, as long as the molecules retain their shape. The values of the extinction angle, χ, in two experiments were so close to 45° that the probable error in the calculations is very large, and the resulting values of $\eta\Theta/T$ are given no weight. These values are enclosed in parentheses in the final column of Table I. The other values are all reasonably consistent, and lead to an over-all estimated $\eta\Theta/T$ of 22 poise per sec. per degree (see Table II). The double refraction measurements are reported in the second half of Table I. The measured phase differences are a linear function of the product ($G\eta$) of the velocity gradient and viscosity, at $G\eta$ values up to 4000 or above. The increase of phase difference at higher velocity gradients is slightly less than linear, as would be expected from theoretical considerations.

TABLE I

MEASUREMENTS OF χ AND Δ ON HUMAN γ-GLOBULIN PREPARATION IIG1-L371

Protein concentration 1.25%. Solvent: glycerol 76%, water 24% by weight. Viscosity of solvent (η) 0.93 at 6°, 0.49 at 18.7°.

Temp., °C.	Speed, R. P. M.	$G\eta$	χ	α	$\frac{\eta\Theta}{T}$
6.3	300	2850	44.3 ± 0.78	0.147	(70)
6.0	360	3500	43.0 ± .52	0.42	(30)
6.0	450	4400	41.5 ± .56	0.635	25
6.0	720	7000	38.8 ± .18	1.30	25.5
6.0	900	8800	38.1 ± .24	1.45	22
6.0	1028	10000	37.2 ± .39	1.64	22
18.5	720	3700	42.6 ± .49	0.50	25.3
18.7	900	4100	41.9 ± .45	0.65	21.5
19.0	1200	6100	40.4 ± .23	0.98	21.2

Δ Values at $t = 6.4°$, $\eta = 0.91$

Δ Values for λ = 546 mμ	$G\eta$	$\Delta/G\eta c$
20.6	2900	0.0057
24.8	3450	.0057
30.5	4300	.0057
39.3	5700	.0055
45.4	6900	.0053
53.9	8600	.0050

From the measured value of $\eta\Theta/T$ the length of the molecule may be calculated if it is assumed for simplicity to be an ellipsoid of revolution. An approximate estimate of the axial ratio, derived for instance from viscosity measurements, must be employed in making this calculation, but the value of the derived length is very insensitive to the exact value. The length, l, assuming the molecule to be an elongated ellipsoid of revolution, is given by the equation

$$l^3 = 1.5\frac{kQ}{\pi}\left(\frac{\eta\Theta}{T}\right)^{-1} \qquad (1)$$

where k is Boltzmann's constant and $Q = -1 + 2\ln 2a/b$. For a/b we have taken the value 5.35 given by Oncley, Scatchard and Brown[9] and derived from viscosity and sedimentation data. This gives for γ-globulin a Q value of 3.74, so that the length ($2a$) in Å. becomes $l = 627(\eta\Theta/T)^{-1/3}$. Thus, the calculated length from the experiments in Table I is 224 Å., slightly below the value of 235 reported by Oncley, Scatchard and Brown.[9]

In Table II the results of these and other experiments on γ-globulin are summarized, and some of the data are reported also in Figs. 1, 2 and 3. It is immediately apparent that there is a marked downward trend in $\eta\Theta/T$ as the concen-

TABLE II

SUMMARY OF RESULTS ON γ-GLOBULIN (PREP. IIG1-L371)

Protein concn., C, g./100 cc.	Temp., °C.	Wt. % glycerol in solvent	Viscosity of solvent η	Range of $G\eta$ × 10^{-3}	$\eta\Theta/T$	$(\Delta/G\eta c)_0$
1.25	6.0– 6.3	76.0	0.93	2.85–10.0	22	0.0057
1.25	18.5–19.0	76.0	.49	3.7 – 6.1	22	...
2.5	6.1– 6.5	76.0	.94	2.9 – 9.1	14	.0071
2.5	19.0–19.8	76.0	.48	1.8 – 5.9	18	.0062
2.5[a]	6.2– 6.7	76.0	.90	2.8 – 8.4	19	.0070
2.5[a]	18.0–18.6	76.0	.49	2.3 – 6.2	21	.0055
3.3	6.1– 6.6	68.7	.42	0.6 – 4.0	9	.0100
3.3	19.5–19.9	68.7	.22	0.7 – 3.4	11	.0080
3.4	6.0– 6.5	60.5	.19	0.6 – 3.0	8	.0120
5.0	6.0	76.0	.91	1.1 – 6.9	7	.0100
5.0	18.0–19.2	76.0	.48	1.0 – 4.5	8	.0080

[a] Solution in acetate buffer, pH 3.93 before addition of glycerol. All other solutions studied at pH near 7.

(9) J. L. Oncley, G. Scatchard and A. Brown, *J. Phys. Colloid Chem.*, **51**, 184 (1947).

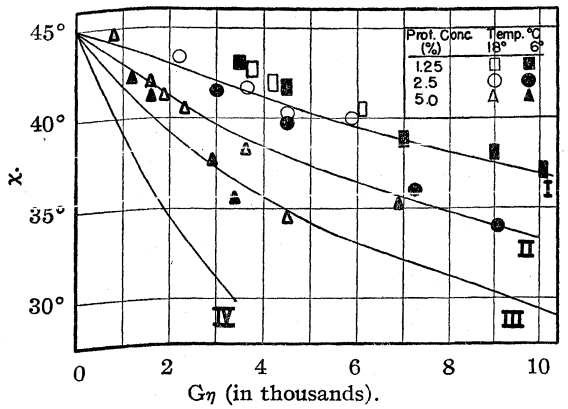


Fig. 1.—Value of χ as a function of $G\eta$ for solutions of human γ-globulin. Curves I, II, III, and IV are calculated as discussed in the text. Curve I is for the pure monomer, 235 × 44 Å. Curve IV is for the pure dimer, 470 × 44 Å. Curve II is for a mixture of 95% monomer and 5% dimer. Curve III is for a mixture of 85% monomer and 15% dimer. Points are experimental values derived under the conditions indicated in the figure.

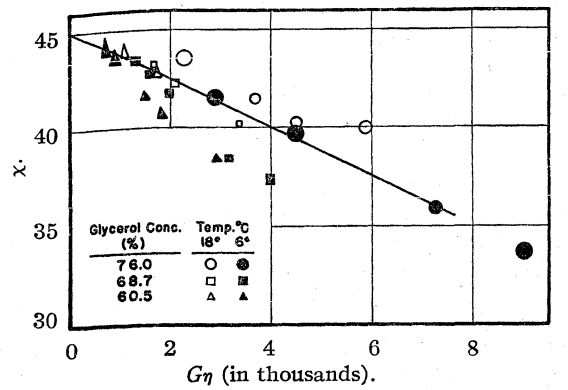


Fig. 2.—χ Values for human γ-globulin solutions as a function of $G\eta$ at various temperatures and glycerol concentrations. Protein concentration in all experiments indicated between 2.5 and 3.3 g./100 cc. Points are experimental values; the curve is calculated for a single molecule, for which $\eta\Theta/T = 13$.

tration of protein increases. This trend is similar to that already observed in the case of zein (concentration range 1 to 3%) and fibrinogen (concentration range 0.12 to 0.5%). Clearly it must be attributed to interactions between the protein molecules. As is to be expected, the influence of increasing concentration becomes apparent at relatively high dilutions in the case of fibrinogen solutions, where the molecules are very long. In the case of zein and γ-globulin, the concentration effects are marked only at concentrations considerably above 1%.

The effect of variation in glycerol concentration (Fig. 2) is rather less striking than that of variation in protein concentration. The observed χ values, at a given value of $G\eta$, deviate somewhat more from 45° in the solvents of low glycerol content and therefore of low viscosity. The effects, however, are relatively small and it is probably premature to attempt to interpret them at this time.

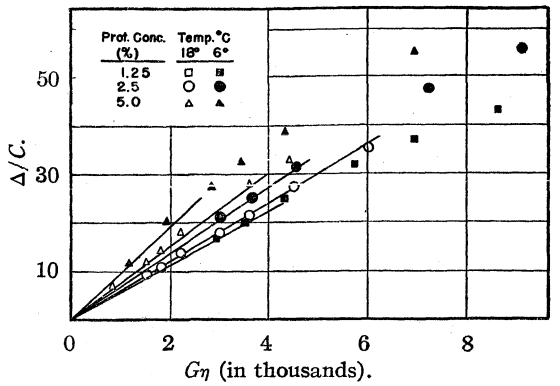


Fig. 3.—Double refraction of γ-globulin as a function of $G\eta$ for three different concentrations and two different temperatures. Ordinates are expressed as measured phase differences divided by concentration; these may be converted to double refraction values ($n_e - n_0$) by the conversion factor given in the footnote to Table IV.

The effects of temperature are indicated in Figs. 1, 2, and 3 by plotting the results at low temperature using shaded symbols, and those at the higher temperature using open symbols. The χ values, plotted as functions of $G\eta$, appear very little affected by temperature. What small effects are discernible are in the direction that would be expected on the basis of decreased Brownian movement and increased protein–protein interaction at the lower temperature.

The specific double refraction values (Δ/c), when plotted as a function of $G\eta$ (see Fig. 3 and Table II) show a definite upward trend with increasing protein concentration and a slight downward trend with increasing temperature at constant concentration. Both these effects are in the direction that would be expected from the effects of concentration and temperature on protein–protein interaction.

In two experiments, indicated by asterisks in the first column of Table II, the *p*H of the γ-globulin solution was adjusted to 3.93 before glycerol was added. The results obtained in these runs were indistinguishable from others in the series, indicating that the size and shape of the γ-globulin molecules were unaltered in the more acid solution.

Calculations for a Two-Component System.—γ-Globulin preparations, of the type studied here, although electrophoretically homogeneous, show at least two major components in the ultracentrifuge. The sedimentation constant, s_{20}, is near 7.2 *S* for the major component (75–85% of the total) and approximately 10 *S* for the chief secondary component. Oncley, Scatchard and Brown,[9] who reported these data, tentatively interpreted them on the assumption that the $s = 10$ component

was a dimer, made up of two molecules of the $s = 7$ component associated end to end. The viscosity data were entirely compatible with this view. We have, therefore, examined the applicability of the same hypothesis to the double refraction of flow measurements.

For simplicity, we have assumed both monomer and dimer to be ellipsoids, the former being 235 Å. long, as assumed by Oncley, Scatchard and Brown,[9] and the latter 470 Å. long. The principal axis of the cross-section of both ellipsoids was taken as 44 Å. Such a model is certainly oversimplified, but the available evidence at this time scarcely warrants a more refined treatment. On calculating rotary diffusion constants for the ellipsoidal molecules, we find for the large molecule (component 1) that $\eta\Theta_1/T = 3.26$ and for the small molecule (component 2) that $\eta\Theta_2/T = 18.2$.

The fundamental equations for double refraction of flow in a polydisperse system have been given by Sadron[10] (see also Peterlin and Stuart[11]). The equations and figures in the papers of Peterlin and Stuart[11,12] give values of χ and of the relative double refraction, f, as a function of $\alpha = G/\Theta$, in a form which may be applied to each individual component with a given Θ value. In evaluating the double refraction given by the system composed of monomer and dimer, we have assumed that both components would give the same amount of double refraction at the same weight fraction in solution, if all the molecules in both solutions could be oriented with their major axes parallel.[13]

Values of χ were calculated for the two component system for two cases, assuming the weight fraction of dimer to be 0.15 in the first case and 0.05 in the second. The resulting curves for χ as a function of $G\eta$, for both these systems, are shown in Fig. 1, together with the corresponding curves for the monomer and dimer alone. Experimental data at several concentrations are indicated by the points in the figure. It is apparent that, at the two lowest concentrations studied, the experimental data approximate very closely to the calculated curve for the small component and show no evidence of the presence of the dimer. At the highest concentration of protein (5%), the data, for the most part, lie in the region between the two calculated curves for the polydispersed system. It is, therefore, possible to interpret the increased molecular interaction which is manifest at the higher protein concentrations, either as being due to an orienting influence exerted by each protein molecule on its neighbors in its field of flow, or to an actual association of some of the molecules into longer units.

(10) C. Sadron, *J. Phys. Radium*, [7] **9**, 381 (1938).

(11) A. Peterlin and H. A. Stuart, "Hand- und Jahrbuch der chemischen Physik," Band 8, Abschnitt IB, 1943, especially pages 88–91, inclusive.

(12) A. Peterlin, *Z. Physik*, **111**, 232 (1938); A. Peterlin and H. A. Stuart, *ibid.*, **112**, 1, 129 (1939).

(13) Details of the method of calculation for polydisperse systems will be given in a separate note by H. A. Scheraga and the present authors.

These results are obviously different from those of Oncley, Scatchard and Brown[9] who observed a considerable amount of the $s = 10$ component even at the lowest concentrations studied, and did not observe any great change in the ultracentrifuge diagram with change in protein concentration. However, their studies were carried out in aqueous solution, whereas ours were made in 60–76% glycerol. It is possible that the addition of glycerol causes a dissociation of the dimer molecules into the smaller units, and that under these conditions it is necessary to go to considerably higher protein concentrations before association occurs. The most striking conclusion from our own observations, however, is the remarkably good agreement at low protein concentrations between the experiments and the calculated values for a molecule approximately 235 Å. long, postulated as the main component by Oncley, Scatchard and Brown.[9]

We have based our calculation of a length of 220–230 Å. on the values obtained at the lowest protein concentration studied, and have not attempted to extrapolate the data to infinite dilution. If such an extrapolation were made on the basis of the data in Table II, using a linear plot of $\eta\Theta/T$ against concentration, we should obtain a still lower value for the length than that reported above, and the agreement with the other data would be less good. However, the basis for such an extrapolation is still uncertain and we have preferred, for the present, to use the experimental values at the lowest concentration studied.

Bovine Serum Albumin.—Only three experiments on serum albumin were carried out, and two of these gave rather fragmentary results, on account of the great technical difficulty of making observations in media of such extremely high viscosity. The results of the most extensive and satisfactory experiment are listed in Table III. In such experiments, the large amount of energy dissipation in the liquid during the maintenance of a velocity gradient leads to heating of the liquid to an extent which is difficult to compensate for by the circulation of water at constant temperature through the jacket of the outer cylinder. The dissipation of energy in the liquid per second is equal to $G^2\eta$ per unit volume.[14] Even more serious than the rise of temperature produced is the fact that thermal gradients are produced in the liquid, which can distort the path of the light beam and falsify the optical measurements. These difficulties have been discussed in detail by Björnståhl,[15] but we have not attempted to apply his quantitative calculations to our data, since the boundary conditions which Björnståhl assumed at the inner and outer cylinders do not correspond to the conditions existing in our apparatus. All these difficulties indicate that the results of the meas-

(14) See for instance, J. R. Robinson, *Proc. Roy. Soc.* (*London*), **A170**, 519 (1939), especially pages 540 ff.

(15) Y. Björnståhl, *Z. Physik*, **119**, 245 (1942).

urements on serum albumin solution are to be regarded with great caution.

TABLE III

DOUBLE REFRACTION OF FLOW OF BOVINE SERUM ALBUMIN (LOT 27-315)

Solvent: 88.45% glycerol; η at 5°, 4.5; at 21°, 1.76. Protein concentration: 4.48 g./100 cc.

t, °C.	Speed, R. P. M.	$G\eta$	x	α	$\eta\Theta/T$	Apparent length, Å.
5.0	132	6250	41.5	0.74	30	190
4.5	212	10200	38.3	1.42	26	200
5.2	300	14000	35.6	1.92	26	200
5.0	360	17000	36.2	1.85	33	184
5.0	450	21300	34.2	2.3	33	184
20.6	450	8500	40.1	1.04	28	195
20.8	600	11300	40.0	1.06	36	179
21.0	720	13300	35.4	2.02	25	202
21.5	900	16100	34.4	2.22	25	202

Δ values at t = 4.5°			Δ values at t = 21.5°		
R. P. M.	Δ	$\Delta/G\eta c$	R. P. M.	Δ	$\Delta/G\eta c$
100	8.9°	0.00040	360	8.5°	0.00029
152	13.0	.00039	450	10.1	.00028
240	18.8	.00035	600	12.9	.00027
300	21.1	.00032	720	14.8	.00025
360	23.3	.00029	900	16.8	.00023
450	25.5	.00026			

Our values for $\eta\Theta/T$ are of the order of magnitude of 30 for serum albumin. For horse serum albumin (carbohydrate free) Oncley[16] has found from dielectric dispersion measurements two critical frequencies (0.44 and 2.1 megacycles, referred to solutions in water at 25°) corresponding to $\eta\Theta/T$ values of 41 and 195, respectively. The higher value would not be detectable in our apparatus, but the lower one is remarkably close to our own measurements, particularly in view of the great difference—200 to 500 fold—in the viscosities of the solvents employed in the two series of measurements. Recent dielectric dispersion studies on human and bovine serum albumin give rotary diffusion constants very close to those of horse serum albumin.[17] On the other hand, the molecular model assumed by Oncley, Scatchard and Brown[9]—namely, an elongated ellipsoid of revolution with a major axis of 150 Å. and a minor axis of 38 Å.—gives a calculated value of $\eta\Theta/T$ of 61. The length calculated from our own data is only about 30% greater than that of the model of Oncley, Scatchard and Brown. On the whole, in view of the difficult conditions under which our measurements were made, it may be concluded that the agreement is remarkably good, and our results may be taken as an approximate confirmation of those deduced[9] from ultracentrifuge, diffusion, viscosity and dielectric dispersion measurements.

(16) J. D. Ferry and J. L. Oncley, THIS JOURNAL, **60**, 1123 (1938); J. L. Oncley, *J. Phys. Chem.*, **44**, 1103 (1940).

(17) J. L. Oncley, personal communication.

Interpretation of Double Refraction Measurements (Phase Differences) for Protein Solutions.—Measurements of the magnitude of the double refraction in solutions of zein, fibrinogen, γ-globulin and serum albumin have been tabulated in this and preceding papers of this series. The data, when expressed as double refraction, $n_e - n_0$, divided by $G\eta c$, show a difference of more than 600-fold between fibrinogen and serum albumin. The values for γ-globulin and zein are roughly twenty times as large as those for albumin, and of the order of one-thirtieth of those for fibrinogen.

These differences, however, are largely a reflection of the very different degrees of orientation obtained, at the same $G\eta$ value, for protein molecules of various lengths. To compare the birefringence of the different proteins in solution, the ideal arrangement would be to obtain completely parallel orientation of the axes of all the protein molecules in each solution, and measure the birefringence under these conditions, which is obviously the maximum attainable for the given system. Such a direct measurement is of course impossible in practice, owing to the Brownian movement of the protein molecules, but the results that would be so obtained can be derived by calculation from the actual experimental data, employing the theoretical treatment of Peterlin and Stuart.[11,12] They have expressed the observed double refraction, $n_e - n_0$, at any given velocity gradient, as the product of an optical factor, $g_1 - g_2$, and an orientation factor $f(\alpha, a/b)$.

$$n_e - n_0 = \frac{2\pi\Phi}{n}(g_1 - g_2)\, f(\alpha, a/b) \qquad (2)$$

Here Φ is the volume fraction of protein in the system, n is the refractive index of the solvent, and a/b is the axial ratio of the ellipsoidal molecule.

The function f is the same orientation function previously mentioned in connection with the calculation for the two component system. At low velocity gradients (low α values) f reduces to the form

$$\lim_{\alpha \to 0} f = \frac{\alpha}{15}\frac{a^2 - b^2}{a^2 + b^2} \qquad (3)$$

When all the molecules of any given species are oriented with their axes parallel, f becomes equal to unity.[18] Hence, from the observed values of the two quantities, $(n_e - n_0)/G\eta c$ and $\eta\Theta/T = G\eta/\alpha T$, it is possible to evaluate the amount of double refraction for any of the proteins studied at the degree of orientation attained when $\alpha = 1$. One may then calculate the maximum double refraction, $n_e - n_0$, for a 1% solution at complete orientation. These values are given in the next to the last column of Table IV. The final column contains the optical anisotropy factor, $g_1 - g_2$, for each protein as calculated from equation 3.

It should be clearly recognized that even the

(18) See the definition of f given by Peterlin and Stuart, ref. 11 page 52, equation 51a.

TABLE IV

DOUBLE REFRACTION OF FIBRINOGEN, ZEIN, γ-GLOBULIN AND SERUM ALBUMIN IN SOLUTION

Protein	c in g./100 cc.	Solvent	$n^{20}D$	t, °C.	$\left(\frac{n_e - n_0}{G\eta c}\right)_0 \times 10^{10}$	$\eta\Theta/T$	$\left(\frac{n_e - n_0}{c}\right)_{\alpha=1} \times 10^8$	$(n_e - n_0)^{1\%}_{max.}$	$g_1 - g_2$
Fibrinogen	0.32	Gl, 38.7%	1.3823	20.5	89	1.2	315	4.7×10^{-5}	0.00143
Fibrinogen	0.12	Gl, 53.6%	1.4035	18.0	72	1.0	210	3.2×10^{-5}	.00100
γ-Globulin	3.3	Gl, 68.7%	1.4259	19.7	3.4	11	110	1.8×10^{-5}	.00055
γ-Globulin	1.25	Gl, 76.0%	1.4368	6.0	2.4	22	150	2.4×10^{-5}	.00074
Zein	1.0	P. G.	1.4331	20.5	3.3	8	75	1.2×10^{-5}	.00036
Serum albumin	4.48	Gl, 88.5%	1.4561	20.5	0.12	30	11	1.9×10^{-6}	.00006

Gl, followed by a percentage figure, denotes a glycerol–water mixture containing the indicated percentage glycerol; P. G. is propylene glycol. The zein preparation was laboratory zein (Foster and Edsall). Values for refractive index ($n^{20}D$), for glycerol–water mixtures, from L. F. Hoyt, *Ind. and Eng. Chem.*, **26**, 329 (1934); for proyplene glycol, from A. G. Pukirev, *Trans. Inst. Pure Chem. Reagents* (Moscow), **15**, 45 (1937), as reported in *Chem. Abstracts*, **32**, 5378 (1938). Other symbols are explained in text, or previous tables. It should be noted that the double refraction values are given for $\lambda = 546$ mμ, although the available data for the refractive indices of the solvents are given for the sodium D line. The differences in refractive index for the two wave lengths, however, represent only second order effects in the phenomena considered here. For our apparatus (length of cylinder 7 cm.) and for light of wave length 546 mμ, $n_e - n_0$ is related to the observed phase difference Δ, by the equation: $n_e - n_0 = 4.24 \times 10^{-8}\ \Delta$.

values of $g_1 - g_2$ so calculated are not inherent characteristics of the protein molecules themselves. Actually $g_1 - g_2$ is a function of two terms, the intrinsic birefringence of the protein itself and the form birefringence which depends upon the differences in refractive index between the protein molecule and the solvent. The refractive index of most protein molecules for light of the wave lengths here considered is in the range 1.57 to 1.61.[19] For serum albumin, Armstrong, Budka, Morrison and Hasson[20] have calculated a value (nD) of 1.598, and for γ-globulin a value of 1.618. These values are for the anhydrous protein, however, and take no account of solvation. We have attempted to calculate the intrinsic birefringence of the proteins studied here, employing the value 1.60 as the mean refractive index of the protein, and using the values for the refractive index for the solvent given in Table IV.[21] Our calculations yielded negative values for the intrinsic birefringence of all the proteins studied; in other words, if these calculations are to be trusted, the axis of maximum polarizability in these proteins is perpendicular to the long axis of the molecules. We are not yet confident, however, that this conclusion is correct, since the effects of solvation may be important, and may vary from one solvent to another. To draw definite conclusions, it would be necessary to study these proteins in a variety of solvents with a much wider range of refractive index than we have yet employed.[22] It would appear, however, that fibrinogen is not only the most geometrically asymmetrical of all the molecules, but optically the most anisotropic, while serum albumin is the least. γ-Globulin, while less geometrically asymmetrical than zein, shows a higher degree of optic anisotropy. Both γ-globulin and zein were studied in solvents of very nearly the same refractive index; hence this conclusion should apply directly to the intrinsic birefringence of these molecules.

Discussion

The only previous study of double refraction of flow in serum albumin and globulin, of which we are aware, is by Sadron, Bonot and Mosimann.[23] The plasma fractions which they studied were obtained by ammonium sulfate fractionation, and the globulin fractions are not directly comparable to ours.[24] Their serum globulin preparations contained considerable lipid which, in glycerol–water mixtures, became detached from the protein and gave rise to birefringence of opposite sign from that produced by the protein. The γ-globulin preparations studied by us, on the other hand, were practically lipid-free, so that this complication did not arise. From the curves for extinction angle given by Sadron, Bonot and Mosimann[23] for their serum globulin, it is apparent that $\eta\Theta/T$ was of the order of unity but somewhat less; and hence only about one-twentieth of the value found for our γ-globulin. Their figure would correspond closely to that to be expected for a very elongated molecule of the order of 900 Å. in length, of the sort observed in sera of high antibody titer in several species of animals.[25]

(19) M. P. Putzeys and Mlle. J. Brosteaux, *Bull. soc. chim. biol.*, **18**, 1681 (1936). Values close to 1.57 are also obtained from measurements of the double refraction of protein fibers determined in media of varying refractive index; see for instance H. H. Weber, *Arch. ges. Physiol.*, **235**, 205 (1934–1935).

(20) S. H. Armstrong, Jr., M. J. E. Budka, K. C. Morrison and M. Hasson, THIS JOURNAL, **69**, 1747 (1947).

(21) The equation for resolving observed birefringence into form and intrinsic birefringences are given by Peterlin and Stuart, ref. 12, pages 13 and 135. There is a misprint in the formulas as given on page 13; the term L_1L_2 should read $L_1 - L_2$.

(22) The streaming birefringence of tobacco mosaic virus in glycerol–aniline–water mixtures was studied by M. A. Lauffer, *J. Phys. Chem.*, **42**, 935 (1938). The observed birefringence fell practically to zero in a solvent of refractive index near 1.57; hence this virus protein appears to possess little or no intrinsic birefringence.

(23) Ch. Sadron, A. Bonot and H. Mosimann, *J. Chim. Phys.*, **36**, 78 (1939).

(24) The species of animal from which their plasma was taken is not explicitly stated, but it would appear from the context that it was horse plasma.

(25) See for instance E. A. Kabat, *J. Immunol.*, **47**, 513 (1943). It is not necessary to assume that the lipoprotein in the globulin preparations of Sadron, *et al.*, was identical with the elongated component giving rise to double refraction of flow. It seems probable that the preparation contained several components and that the lipoprotein was a less elongated protein molecule than some of the others.

Sadron, *et al.*, could obtain no evidence of double refraction of flow in their crystallized serum albumin preparations. This is in qualitative accord with our own results, since the albumin preparation studied by us gave no detectible double refraction in 70% glycerol, and it was only when the concentration of glycerol approached 90% that a measurable degree of orientation was obtained. Some of the other albumin fractions studied in Sadron's work did show appreciable double refraction, with values of $(n_e - n_0) \times 10^{10}/G\eta c$ ranging from 0.2 to 1.1, as compared with 0.12 for our preparation. Corresponding values for Sadron's globulin fractions G_1 and G_2 were 3.1 and 5, respectively, very close to those for human γ-globulin as reported in Table IV. Thus, the double refraction values of Sadron's preparations are quite similar to ours, although the rotary diffusion constants differ considerably.

Oncley[16] has studied the dielectric dispersion of γ-pseudoglobulin from horse plasma. The two frequencies obtained by him correspond to $\eta\Theta/T$ values of 6 and 53, respectively. The former value is not far from that obtained by us for human γ-globulin in the highest concentrations studied; but, as already indicated, our values under these conditions are greatly influenced by association or molecular interactions, or both. It is probable that the horse γ-pseudoglobulin is a more elongated molecule than the main component of the human γ-globulin. The latter preparation contains a considerable amount of euglobulin, which precipitates at *p*H near 7 at very low ionic strength. Dielectric dispersion measurements on this preparation can be made, therefore, only on the pseudoglobulin component, and are not yet available for comparison.

In the previous study of fibrinogen,[4] we have given a detailed analysis of several possible molecular models, in light of all the available experimental evidence. In the case of albumin and γ-globulin, we have little to add to the discussion already given by Oncley, Scatchard and Brown.[9] The γ-globulin preparations certainly contain more than one component, and therefore a detailed analysis based on a model containing only a single component would hardly be profitable to carry out.[26] The results on serum albumin presented in Table III represent measurements made under extremely difficult conditions, on account of the high viscosity of the liquid and the small amount of double refraction observed. Under the circumstances, we consider it remarkable that the agreement between our data and those obtained from the ultracentrifuge, viscosity and diffusion measurements is as good as it is. Oncley, Scatchard and Brown[9] calculated a length for serum albumin of 150 Å., whereas our estimates would lead to a value of 190–200 Å. We believe that our value deserves far less weight than theirs, and present it simply as confirmatory evidence for the general consistency of our results and those obtained by other methods.

Summary

1. Double refraction of flow measurements have been made on purified human serum γ-globulin and crystalline bovine serum albumin, employing as solvents glycerol–water mixtures of high viscosity.

2. The measurements of γ-globulin lead to an estimated molecular length near 230 Å., in excellent agreement with the value deduced from ultracentrifuge, viscosity and diffusion measurements by Oncley, Scatchard and Brown.[9] The γ-globulin preparations, at least in dilute solution, behaved as if the protein molecules were uniform with respect to molecular length.

3. The measurements of serum albumin lead to an estimated length of 190–200 Å., but this value is considered less reliable than the figure of 150 Å. previously reported by Oncley, Scatchard and Brown.[9]

4. Critical comparison has been given of the amount of double refraction given by four different proteins under comparable conditions.

BOSTON, MASS. RECEIVED JANUARY 2, 1948

(26) It should be remembered in this connection, that Oncley, Scatchard and Brown give dimensions for the *hydrated* protein molecule. Since their measurements were carried out in aqueous solution and ours in glycerol–water mixtures, the degree of solvation of the protein cannot be expected to be identical in these different media. Obviously some change in the frictional coefficient must occur when the protein is transferred from one solvent medium to the other. We have no basis at present for calculating what this change is likely to be, although it seems probable that it is small.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Methane Formation in the Photolysis of Acetone at 130°[1]

BY WALLACE DAVIS, JR.[2]

The quantum yield of carbon monoxide formation during the photochemical decomposition of acetone has been found to be unity at temperatures slightly above 100°,[3] thus permitting this reaction to be used as an actinometer. Ethane has been reported as the main hydrocarbon produced under the experimental conditions used by most authors, although small amounts of methane have usually been found. The work of Spence and Wild[4] indicates that under certain experimental conditions the amount of methane formed may be quite large. Hence in using the photochemical decomposition of acetone as an actinometer the fraction of the products uncondensed by liquid nitrogen must be analyzed for both carbon monoxide and methane (as well as for traces of ethane) to ensure accurate results.

This paper presents results of a study of methane formation during the photochemical decomposition of acetone at temperatures ranging from 126 to 138°. While certain statements concerning the reaction mechanism are permissible at the present time, details will be left for later presentation after further information is available.

Experimental

The methods of purifying the acetone and of analyzing the reaction products have already been described.[5] The light source and filter solutions used for isolation of the 3130 Å. line of mercury have also been described.[6] The basic equations used for calculation of light absorbed[7] have been expanded[5] and need not be repeated here.

Some of the experiments (6A–18A in Table I) were made using the AH-6 General Electric Company high pressure arc, the beam diameter being 10 mm. The remaining experiments (19A–21A in Table I) were performed with a UA30A2 Hanovia medium pressure arc with a beam diameter of 15 mm.

The values of I_a (the "absorbed intensity") given in Table I have been obtained by dividing the number of quanta absorbed per second by the acetone by the volume of the light beam. Since the cell was 200 mm. in length the latter has the values 15.7 and 35.4 cm.^{3}, respectively, for the two light beams referred to in the preceding paragraph. The light absorbed per unit path length is not constant and moreover the intensity is undoubtedly not uniform over a given cross section of the beam. Nevertheless the quantity given is the average number of quanta absorbed per cc. per second in the light beam and it is believed that this figure represents most nearly the one which should be used in rate equations for those cases in which any activated molecules and free atoms or radicals do not diffuse appreciably out of the light beam.

TABLE I

THE QUANTUM YIELD OF METHANE FORMATION FROM ACETONE

Wave length = 3130 Å.; quantum yield of carbon monoxide formation = 1 (assumed)

Run	Temp., °C.	Acetone pressure, mm.	$I_a \times 10^{-13}$ quanta/sec./cm.^{3}	Φ_{CH_4}
6A	126	194	1.64	0.40
7A	120	205	0.22	.91
8A	120	233	.23	.97
9A	127	152	.24	.60
10A	122	95	.27	.62
11A	126.5	109	.21	.63
12A	138	148.2	.29	.73
13A	137	111.1	.23	.56
14A	134.5	226.0	.21	.96
15A	137	191	.17	1.04
16A	134.5	145.2	.12	0.93
17A	131.5	199.6	.14	0.99
18A	138	184.4	.14	1.06
19A	133	189.6	.042	1.27
20A	136	137.6	.039	1.14
21A	136	101.3	.027	1.15

Results and Discussion

Table I presents the data on quantum yield of methane formation from the photochemical decomposition of acetone at temperatures ranging from 120 to 138°. Since it has been shown previously that the quantum yield of carbon monoxide formation is very close to unity at these temperatures,[3] the values are based on that assumption and should be taken, in reality, as relative values.

Since the carbon monoxide yield is certainly very close to unity, any acetyl radicals produced in the primary process must decompose almost immediately either thermally or due to energy retained from the primary process. Hence for this case of high temperatures one may write

$$CH_3COCH_3 + h\nu = 2CH_3 + CO \qquad (1)$$

Methane is almost certainly produced by the reaction

$$CH_3 + CH_3COCH_3 = CH_4 + CH_2COCH_3 \qquad (2)$$

Methyl radicals can disappear by reaction (2) as well as by reactions (3) and (4)

$$CH_3 + CH_3 = C_2H_6 \qquad (3)$$

$$CH_3 + CH_2COCH_3 = CH_3CH_2COCH_3[8] \qquad (4)$$

The acetonyl radicals can also form biacetonyl

$$2CH_2COCH_3 = (CH_2COCH_3)_2 \qquad (5)$$

If reactions (1) to (5), inclusive, are all that can occur and it is assumed that they are all homogeneous gas phase reactions, some kinetic expressions could be derived providing analyses could be

(1) This work was supported by Contract N6-onr-241, Task I with the Office of Naval Research, United States Navy.

(2) Present address: Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee.

(3) J. A. Leermakers, THIS JOURNAL, **56**, 1899 (1934); C. A. Winkler, *Trans. Faraday Soc.*, **31**, 761 (1935); D. S. Herr and W. A. Noyes, Jr., THIS JOURNAL, **62**, 2052 (1940).

(4) R. Spence and W. Wild, *J. Chem. Soc.*, 352 (1937).

(5) W. Davis, Jr. and W. A. Noyes, Jr., *ibid.*, **69**, 2153 (1947).

(6) R. E. Hunt and W. Davis, Jr., THIS JOURNAL, **69**, 1415 (1947).

(7) R. E. Hunt and T. L. Hill, *J. Chem. Phys.*, **15**, 111 (1947).

(8) A. O. Allen, THIS JOURNAL, **63**, 708 (1941).

made for all of the products. If C_2H_6, CH_4, and CO were all known certain conclusions would be possible.

The pressures are high enough in the present experiments to ensure that the majority of the bimolecular reactions will occur homogeneously. Consequently the derived expression for the quantum yield becomes so complex that it cannot be applied to the data without making assumptions. It seems best to defer a detailed theoretical treatment until a later date. It may be stated, however, that if the energy of activation for (3) is low,[9] the energy of activation of (2) must also be low.

(9) *Cf.* E. W. R. Steacie, "Atomic and Free Radical Reactions," The Reinhold Publishing Corporation, New York, N. Y., 1946, p. 520.

Summary

1. The quantum yield of methane formation during the photochemical decomposition of acetone in the temperature range 120 to 138° has been determined.

2. In a general way the yield of methane increases with increase in acetone pressure and with decrease in intensity, but a detailed discussion of theory is postponed until a later date.

3. The energy of activation of the reaction $CH_3 + CH_3COCH_3 = CH_4 + CH_3COCH_2$ must be low.

ROCHESTER, NEW YORK RECEIVED[10] FEBRUARY 13, 1948

(10) Original manuscript received September 18, 1947.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Photochemical Decomposition of Diethyl Ketone at 3130 Å.[1]

BY WALLACE DAVIS, JR.[2]

Previous work[3] has indicated some ethylene and ethane to be produced along with carbon monoxide and butane during the photochemical decomposition of diethyl ketone at wave lengths below 2000 Å. These same products in different proportions have been reported at longer wave lengths.[3,4] Bamford and Norrish[4] suggested that the Type III decomposition directly into ethylene and propionaldehyde proposed by Norrish and Appleyard[5] would account for the ethylene formed, although these authors did not identify propionaldehyde positively. Disproportionation of ethyl radicals to ethylene and ethane has also been suggested.[3]

This paper presents determinations of the quantum yield of various products during the photochemical decomposition of diethyl ketone.

Experimental

The diethyl ketone used in this work was purified by Dr. A. B. F. Duncan for spectroscopic experiments. C. P. diethyl ketone, b. p. range 5°, was washed with potassium carbonate and sodium bisulfite to remove acids and peroxides. After drying over anhydrous calcium chloride the ketone was fractionally distilled in a column, a portion with a boiling range of 0.1° being kept. This product was further fractionated several times at low pressure.

The determination of carbon monoxide was accomplished by removing that portion of the products not condensed by liquid nitrogen. For short runs combustion of this fraction over CuO at 200–240° indicated pure carbon monoxide within experimental error. For longer runs leading to a larger amount of product, duplicate oxygen combustion analyses indicated that as much as 5% of this fraction was a C_2 hydrocarbon.

The C_2 hydrocarbons (C_2H_4 and C_2H_6) were separated from other products, after removal of carbon monoxide by being removed at −165° using a Ward apparatus[6] with a Toepler pump. In some experiments only the quantity of C_2 hydrocarbons was determined; in others this fraction was burned with oxygen on a platinum filament at about 600°. The combustions were all carried out with a trap immersed in dry ice between the filament and any source of mercury vapor to minimize oxidation of the latter.

After removal of the C_2 hydrocarbons, another fraction was removed at about −120°. This fraction was shown to be butane either by vapor pressure measurements or by combustion.

Other experimental details have already been published.[7-9]

Results and Discussion

The quantum yields of carbon monoxide and of C_2 hydrocarbons from diethyl ketone at several temperatures and intensities are presented in Table I. It will be noted that the variation in pressure is small. Experiments 1D–12D were made with a A-H6 General Electric Company high pressure mercury arc, while runs 13D–16D were made with the Hanovia UA30 A2 Uviarc.

It is seen that $\Phi_{CO} = 1.0$ within a 13% experimental error in runs 1D–7D and 11D. For the uviarc runs $\Phi_{CO} = 1.03 \pm 0.05$, assuming a calibration error of not to exceed 1.6%. Therefore the quantum yield of the primary process

$$C_2H_5COC_2H_5 + h\nu = 2C_2H_5 + CO \qquad (1)$$

must be close to unity unless some secondary reaction gives rise to carbon monoxide formation. The absence of any real increase of carbon mon-

(1) This work was supported by Contract N6-onr-241, Task I with the Office of Naval Research, United States Navy.

(2) Present address: Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee.

(3) V. R. Ells and W. A. Noyes, Jr., THIS JOURNAL, **61**, 2492 (1939).

(4) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1931 (1938).

(5) R. G. W. Norrish and M. E. S. Appleyard, *ibid.*, 874 (1934).

(6) E. C. Ward, *Ind. Eng. Chem., Anal. Ed.*, **10**, 169 (1938).

(7) R. E. Hunt and W. Davis, Jr., THIS JOURNAL, **69**, 1415 (1947).

(8) R. E. Hunt and T. L. Hill, *J. Chem. Phys.*, **15**, 111 (1947).

(9) W. Davis, Jr., and W. A. Noyes, Jr., THIS JOURNAL, **69**, 2153 (1947).

oxide yield with temperature indicates that probably the latter is not the case.

Values of Φ_{CO} for experiments 8D–10D should not be considered as valid since recalibration of the photo-cell galvanometer system showed a changed sensitivity.

TABLE I

QUANTUM YIELDS OF CO AND OF C_2 HYDROCARBONS DURING PHOTOCHEMICAL DECOMPOSITION OF DIETHYL KETONE

Run	Temp., °C.	Ketone pressure, mm.	$I_a \times 10^{-18}$ quanta/sec./ccm.	Φ_{CO}	Φ_{C_2}	Analysis of C_2 fraction
1D	28	41	0.22	1.03 ± 0.14		
2D	28	40	.19	0.99 ± .13		
3D	27	37	.17	1.05 ± .14		
4D	27	38	.16	0.93 ± .13		
5D	27	38	.17	0.93 ± .13		
6D	25	34.5	.14	0.99 ± .13		
7D	26	22.0	.084	1.05 ± .14		
8D	86	38.2	.20	0.74 ± .10		
9D	86.4	38.0	.21	0.83 ± .10	0.44	V. P.
10D	86.2	37.9	.24	0.83 ± .10	0.41	V. P.
11D	26	38.0	.15	0.97 ± .13	0.28	V. P.
12D	26	38	(.11)	(1.00)	0.68	
13D	136	36.8	.017	1.05 ± .05	1.48	$C_{2.04}H_{5.92}$
14D	137.5	41.0	.019	1.02 ± .05	1.38	$C_{2.09}H_{5.76}$
15D	136	38	.017	(1.035)[a]	1.47	$C_{2.00}H_{6.02}$ $C_{2.01}H_{5.92}$
16D	26.8	39.6	.014	1.03 ± .05	0.86	$C_{2.02}H_{5.40}$

[a] Φ_{CO} for Run 15D taken as the average of Φ_{CO} from Runs 13D and 14D.

In view of the fact that ethane exceeds ethylene considerably under the conditions of these experiments, these two gases cannot be formed mainly by a disproportionation reaction and the ethane can arise from a reaction of the type

$$C_2H_5 + C_2H_5COC_2H_5 = C_2H_6 + C_2H_4COC_2H_5 \quad (2)$$

This reaction would be analogous to that of methane formation in acetone.[10] One of the main competing reactions for ethyl radicals will certainly be that of butane formation

$$C_2H_5 + C_2H_5 = C_4H_{10}$$

Some ethyl radicals may disappear in forming the compound $C_2H_5COC_4H_9$, but a complete analysis of all products would be necessary before a detailed mechanism could be developed.

From equations (2) and (3) the quantum yields of ethane and of butane formation are found to be given by the following expressions

$$\Phi_{C_2H_6} = k_2(C_2H_5)(C_2H_5COC_2H_5)/I_a \quad (4)$$

$$\Phi_{C_4H_{10}} = k_3(C_2H_5)^2/I_a \quad (5)$$

where the subscripts of the k's correspond to the equation numbers. Hence one may write

$$\Phi^2_{C_2H_6}/\Phi_{C_4H_{10}} = k_2^2(C_2H_5COC_2H_5)^2/k_3I_a \quad (6)$$

If it is assumed that butane is formed by all ethyl radicals which do not form ethane, one can apply equation (6) to the data in Table I. Unfortunately the data are not extensive enough to warrant many conclusions, particularly since the fates of all ethyl radicals are undoubtedly not given by equations (2) and (3) alone. However, equation (6) is at least approximately obeyed.

If one writes $k_2 = a_2\ exp\ (-E_2/RT)$ and $k_3 = a_3\ exp\ (-E_3/RT)$ the data at about 136° and at about 26° may be used to calculate $2E_2 - E_3 = 5000$ cal. with an uncertainty of about 1500 cal. While an exact value of E_3 is not known, the figure is considered to be small.[11] Thus E_2 may be as little as 2500 cal. and probably is less than 5000 cal.

It is evident that the amount of ethane depends markedly on light intensity, as well as on temperature, and that at high intensities butane should be formed relatively more than at low intensities. If ethylene is formed solely by a disproportionation reaction its yield also would be expected to increase at high intensities. More work is necessary before details of the mechanism can be stated, but complete analysis for all possible products will be difficult.

Summary

1. The quantum yields of CO and of C_2 hydrocarbons during the photochemical decomposition of diethyl ketone have been determined at several temperatures ranging from 26 to 138°.

2. The C_2 hydrocarbons produced during the reaction consist almost solely of C_2H_6.

3. The energy of activation of the reaction $C_2H_5 + C_2H_5COC_2H_5 = C_2H_6 + C_2H_4COC_2H_5$ may be as low as 2500 cal. and is almost certainly below 5000 cal.

ROCHESTER, NEW YORK RECEIVED[12] FEBRUARY 13, 1948

(10) W. Davis, Jr., *ibid.*, **70**, 1868 (1948).

(11) *Cf.* E. W. R. Steacie, "Atomic and Free Radical Reactions," The Reinhold Publishing Corporation, New York, N. Y., 1946, p. 520.

(12) Original manuscript received September 18 1947.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF WESTERN AUSTRALIA, AND THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

Ionic Hydration and Activity in Electrolyte Solutions

BY R. H. STOKES[1a] AND R. A. ROBINSON[1b]

General Introduction

There are two useful lines of approach to the problem of explaining activity data in electrolyte solutions. The first is to extend the treatment of Debye and Hückel (which was developed for dilute solutions) to moderately high concentrations by applying relevant "corrections." This method has received a great deal of attention in the past twenty years or so. The other is to examine data for very concentrated solutions, where the Debye–Hückel treatment is certainly not applicable, seeking relationships which may throw light on the general problem. In this paper it is shown that the concept of ion–solvent interaction, or ionic hydration, is capable of explaining quantitatively a large body of experimental observations in both cases. Part I discusses a modified form of the Debye–Hückel equation, introducing the effect of ion–solvent interaction in terms of "hydration," which is applicable up to ionic strengths of about 4. In Part II the effect of the solvent at concentrations above about 12 M is approached in another way, similar to that of the Brunauer–Emmett–Teller adsorption isotherm.

I. A One-parameter Equation for Activity Coefficients.—The evaluation by Debye and Hückel[1c] of the free energy change due to the coulomb forces between ions led to a tremendous expansion of our understanding of the behavior of electrolyte solutions. There is now no doubt that the familiar Debye–Hückel expression

$$\log f = -\frac{A\sqrt{c}}{1 + B\mathring{a}\sqrt{c}} \qquad (1)$$

gives an adequate representation of the activity coefficients of normally dissociated salts of 1:1 and 2:1 valence types in sufficiently dilute solutions, in terms of the single arbitrary parameter å (the mean distance of "closest approach" of the ions), and the volume concentration c. Equation (1) however predicts an activity coefficient which is always a decreasing function of the concentration, whereas experimentally a minimum usually occurs, followed by a more or less rapid rise of the activity coefficient at high concentrations. Hückel[2] explained this effect in terms of the change in dielectric constant of the solvent near the ions, which led to a second arbitrary constant D in the equation

$$\log f = -\frac{A\sqrt{c}}{1 + B\mathring{a}\sqrt{c}} + Dc \qquad (2)$$

Equation (2) has been of great practical value, and has been extensively employed for the extrapolation of standard potentials and for the representation of activity coefficient data.[3] Its theoretical foundations have, however, been frequently criticized. Furthermore, it usually fails to give a reasonably accurate representation of observed activity coefficients at ionic strengths much greater than unity. To overcome this, further arbitrary terms in c^2 and even higher powers are sometimes introduced, but such equations are of no theoretical value.

In recent years our knowledge of activity coefficients in concentrated solutions has been greatly extended, mainly through the application of the isopiestic vapor pressure technique. It has become increasingly clear, especially in the case of 2:1 electrolytes, that any treatment of the properties of concentrated solutions must take specific account of the hydration of the ions. There seems to be no adequate alternative explanation of the fantastically high activity coefficients often encountered at high concentrations. For instance, a 5 M solution of magnesium iodide at 25° has a stoichiometric activity coefficient of over 100, while that of 5 M sodium chloride is only 0.874. The first formally correct treatment of the effect of hydration on the activity coefficient appears to have been given by Bjerrum,[4] a few years before the appearance of the Debye–Hückel theory. Apart from recognition by Scatchard[5] in connection with hydrochloric acid, and an important discussion of a "hydration–association" model for electrolytes by Frank,[6] the subject does not appear to have been accorded the attention which its importance warrants in this connection. It will now be shown that by allowing for the ion-solvent interaction in terms of a simple hydration model it is possible to obtain as a first step a two-parameter equation, and by a slight elaboration of the model a one-parameter equation, which will represent the experimental activity coefficients up to remarkably high concentrations. These equations are derived and tested for a large number of salts in aqueous solution at 25°.

The "Hydration Correction" to the Activity Coefficient.[7]—The concentrations, activities, etc., of the hydrated solute will be distinguished by primed symbols, the corresponding "apparent" quantities (computed with neglect of hy-

(1a) Present address: Physical Chemistry Laboratories, Free School Lane, Cambridge, England.

(1b) Present address: Chemistry Department, Raffles College, Singapore.

(1c) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

(2) E. Hückel, *ibid.*, **26**, 93 (1925).

(3) See, *e. g.*, R. A. Robinson and H. S. Harned, *Chem. Rev.*, **28**, 420 (1941).

(4) N. Bjerrum, *Medd. Vetenskapsakad. Nobelinst.*, **5**, 1 (1919).

(5) G. Scatchard, THIS JOURNAL, **47**, 2098 (1925).

(6) H. S. Frank, *ibid.*, **63**, 1789 (1941).

(7) This treatment leads to a result equivalent to that of Bjerrum, though by a somewhat different route.

dration) being denoted by the usual unprimed symbols. Let 1 molecule of solute give rise in solution to ν ions. We shall now assume that the total interaction between these ν ions and the surrounding solvent, *in all cases where this interaction is significantly large compared to kT*, can be allowed for as a "binding" of n molecules of water in their "hydration shells." We need not at this stage discuss the manner in which this "bound" water is shared between anions and cations.

Then in a solution of molality, m, there are nm molecules of "bound" water to $(55.51 - nm)$ molecules of "free" water. The "true" molality m' (moles of hydrated solute per 1000 g. of "free" water) is therefore

$$m' = \frac{55.51\ m}{55.51 - nm} = \frac{m}{1 - 0.018\ nm} \qquad (3)$$

Then if a' be the activity of the hydrated solute, and a that of the water, the Gibbs–Duhem relation becomes

$$\mathrm{d} \ln a' = -(55.51/m')\ \mathrm{d} \ln a_w$$

This is equally as valid as the ordinary form using the stoichiometric molality and activity, computed with disregard of hydration

$$\mathrm{d} \ln a = -(55.51/m)\ \mathrm{d} \ln a_w$$

Hence, introducing the mean molal activity coefficients γ' and γ, we have

$$\mathrm{d} \ln \gamma' = -(55.51/\nu m')\ \mathrm{d} \ln a_w - \mathrm{d} \ln m' \qquad (4)$$

and

$$\mathrm{d} \ln \gamma = -(55.51/\nu m)\ \mathrm{d} \ln a_w - \mathrm{d} \ln m \qquad (5)$$

from which by substituting for m' from (3) we obtain

$$\begin{aligned} \mathrm{d} \ln \gamma' &= -(55.51/\nu m)\ (1 - 0.108nm)\ \mathrm{d} \ln a_w \\ &\quad - \mathrm{d} \ln m + \mathrm{d} \ln (1 - 0.018nm) \\ &= \mathrm{d} \ln \gamma + (n/\nu)\ \mathrm{d} \ln a_w + \mathrm{d} \ln (1 - 0.018nm). \end{aligned}$$

Upon integrating between molalities zero and m we obtain, remembering that both γ and γ' must approach unity at zero concentration

$$\ln \gamma' = \ln \gamma + (n/\nu) \ln a_w + \ln (1 - 0.018nm) \qquad (6)$$

We shall, however, be concerned rather with the mean *rational* activity coefficient of the hydrated solute, f'. This is clearly related to γ' by the equation

$$\ln f' = \ln \gamma' + \ln (1 + 0.018\nu m') \qquad (7)$$

which is the analog of the familiar (unprimed) equation established by Scatchard[5] for the unhydrated case. Combining (7) with (6), and simplifying with the aid of (3) we obtain

$$\ln \gamma = \ln f' - (n/\nu) \ln a_w - \ln [1 - 0.018(n - \nu)m] \qquad (8)$$

This gives a relation between the observed stoichiometric activity coefficient and the rational activity coefficient of the hydrated solute, in terms of the "hydration parameter" n.[8]

(8) If we allow for a possible variation of n with concentration, we must replace $(n/\nu) \ln a_w$ by $\int_0^m \frac{n}{\nu} \mathrm{d} \ln a_w$.

Application of Equation (8) to the Debye–Hückel Theory.—In order to fit equations (1) or (2) to observed activity coefficients, it is in general necessary to use values of the "mean distance of closest approach of the ions," $\mathring{a}$, which are substantially larger than the known crystallographic radius sums of the ions. This is very reasonably attributed to hydration of the ions. Consequently we should surely regard the Debye–Hückel treatment as predicting the activity coefficient of the *hydrated* ions, *i. e.*, the f' of equation (8). If the hydration effect is alone responsible for the observed increase in the activity coefficient, activity coefficients in water at 25° should be capable of representation by the equation

$$\log \gamma = -\frac{0.5092 z_1 z_2 \sqrt{\mu}}{1 + 0.3286 \mathring{a} \sqrt{\mu}} - \frac{n}{\nu} \log a_w - \log [1 - 0.018(n - \nu)m] \qquad (9)$$

where we have replaced the term $\log f'$ by the Debye–Hückel expression (1), using the modern values[9] of the physical constants involved. Here z_1 and z_2 are the valencies, μ is the ionic strength in volume units, and $\mathring{a}$ is to be expressed in ångström units. The three terms on the right of (9) may conveniently be called the "*D–H* term," the "solvent term," and the "scale term," respectively. The *D–H* term is always negative, and the solvent term is always positive since $a_w < 1$. The scale term is positive, zero, or negative according as $n > \nu$, $n = \nu$, or $n < \nu$. The importance of the solvent term has often been overlooked in discussion of hydration effects. In point of fact the scale term and the solvent term are usually of the same order of magnitude.

Equation (9) still contains two adjustable parameters, a and n. In this form it proves to be capable of representing observed activity coefficients with an accuracy about as good as that of equation (2), but over a much wider range of concentration, extending in many cases to an ionic strength of 5. Its superiority to equation (2) is especially evident in the case of 2:1 halides, where equation (2) generally fails at an ionic strength of about 1 (*i. e.*, about 0.3 *M*). In Table I are listed the n and $\mathring{a}$ values giving the best fits to the experimental γ values, with the range of validity and the average and maximum deviations. The concentrations at which the comparisons are made are those listed in Tables II and III in connection with the one-parameter equation. The experimental activity coefficients with which the comparisons are made are mainly values which we have recently recomputed from our isopiestic measurements, using the most recent standard data for the reference solutions.[10,11] These activity coefficients are also listed in Tables II and III. Those of hydrochloric and hydrobromic acids are from the compilation by Harned and

(9) G. G. Manov, *et al.*, THIS JOURNAL, **65**, 1765 (1943).

(10) R. A. Robinson, *Trans. Roy. Soc., New Zealand*, **75** [II], 203 (1945).

(11) R. H. Stokes, *Trans. Faraday Soc.*, **44**, in press (1948).

Owen.[12] These activity coefficients are listed in Tables II and III in connection with the one-parameter equation now to be developed. The solvent term $-n/\nu \log a_w$ can *in principle* be computed from the values of f' for a given n and $\mathring{a}$, but such a procedure would be extremely arduous from the computational point of view. This term has therefore been evaluated from the experimental osmotic coefficients ϕ, since for aqueous solutions, by definition

$$-1/\nu \log a_w = 0.007824 m\phi$$

The One-parameter Equation.—Examination of the n and $\mathring{a}$ values of Table I shows that the $\mathring{a}$ values are much the same as those normally needed in equation (2). The n values, however, are substantially greater than the values we might expect to find on current ideas of hydration, which are largely based on the treatment by Bernal and Fowler[13] of the apparent molal volumes in dilute solutions. Furthermore they do not depend only on the cation as we should at first sight expect if we accept those authors' view that the large anions Cl^-, Br^- and I^- are unhydrated.

We are inclined to accept the idea that it is the cations rather than the anions which are hydrated, especially as it has been shown[13a] by comparing the activity coefficients of the pairs: calcium chloride–sodium sulfate, lanthanum chloride–potassium ferricyanide and thorium nitrate–potassium ferrocyanide, that polyvalent cations lead to high activity coefficients and polyvalent anions to low coefficients. We wish to emphasize, however, that our n is not the same thing as the conventional number of water molecules in the first layer round the ion. It is rather a number introduced to allow for the average effect of all ion–solvent interactions where these are large compared to kT, and may therefore very well contain contributions from solvent molecules outside the first layer. The feature of Table I which does seem difficult to explain is the *increase* of n with increasing anion size, for a given cation. Even this is, however, not necessarily impossible, when we consider that in the concentration range considered the water molecules are not bound simply by the fields of isolated ions, but rather by the resultant field of an ion and its neighbors, which of course depends on their dimensions.

It is clear from Table I that there is some sort of connection between the n and $\mathring{a}$ values, which in general increase together. $\mathring{a}$ is to be interpreted as the closest distance to which the center of the (unhydrated) anion can approach that of the (hydrated) cation. We may estimate the size of the cation from the n value as follows: From the density of pure water, we know that a "normal" water molecule occupies at 25° an effective volume of 30.0 cubic ångström units. Round the smaller cations, however, there is, as Bernal and Fowler[13] have shown, a closer-packing effect which in many cases actually makes the apparent ionic volume of the cation negative. We can allow for this close-packing effect, as well as for the volume occupied by the cation itself, by putting the volume of the n-hydrated cation equal to $(30n + V_+)$, where V_+ is the apparent ionic volume of the cation (in cubic Å. per ion). In most cases V_+ is only a small fraction of $30n$, so that it need not be determined with great accuracy, and any variation of V_+ with concentration can be ignored. To estimate V_+ from the observed apparent molal volumes, we have fol-

TABLE I

CONSTANTS OF THE TWO-PARAMETER EQUATION (9), GIVING BEST FITS TO THE EXPERIMENTAL ACTIVITY COEFFICIENTS

Salt	n	$\mathring{a}$ (ångströms)	Range fitted (molality)	Average difference in γ	Maximum difference in γ
HCl	8.0	4.47	0.01–1.0	0.001	0.0025
HBr	8.6	5.18	.1–1.0	.001	.002
HI	10.6	5.69	.1–0.7	.002	.002
$HClO_4$	7.4	5.09	.1–2.0	.001	.003
LiCl	7.1	4.32	.1–1.0	.001	.002
LiBr	7.6	4.56	.1–1.5	.001	.002
LiI	9.0	5.60	.1–1.0	.003	.008
$LiClO_4$	8.7	5.63	.2–1.0	.003	.007
NaCl	3.5	3.97	.1–5.0	.002	.003
NaBr	4.2	4.24	.1–4.0	.001	.002
NaI	5.5	4.47	.1–1.5	.002	.004
$NaClO_4$	2.1	4.04	.2–4.0	.0015	.003
KCl	1.9	3.63	.1–4.0	.002	.003
KBr	2.1	3.85	.1–4.0	.0025	.004
KI	2.5	4.16	.1–4.0	.001	.002
RbCl	1.2	3.49	.1–1.5	.001	.002
RbBr	0.9	3.48	.1–1.5	.001	.001
RbI	0.6	3.56	.1–1.5	.005	.003
$MgCl_2$	13.7	5.02	.1–1.4	.001	.002
$MgBr_2$	17.0	5.46	.1–1.0	.002	.004
MgI_2	19.0	6.18	.1–0.7	.001	.002
$CaCl_2$	12.0	4.73	.01–1.4	.001	.002
$CaBr_2$	14.6	5.02	.1–1.0	.0005	.001
CaI_2	17.0	5.69	.1–0.7	.0005	.002
$SrCl_2$	10.7	4.61	.1–1.8	.001	.002
$SrBr_2$	12.7	4.89	.1–1.4	.0015	.002
SrI_2	15.5	5.58	.1–1.0	.001	.002
$BaCl_2$	7.7	4.45	.1–1.8	.001	.003
$BaBr_2$	10.7	4.68	.1–1.5	.001	.002
BaI_2	15.0	5.44	.1–1.0	.0025	.005
$MnCl_2$	11.0	4.74	.1–1.4	.001	.004
$FeCl_2$	12.0	4.80	.1–1.4	.002	.003
$CoCl_2$	13.0	4.81	.1–1.0	.001	.001
$NiCl_2$	13.0	4.86	.1–1.4	.0015	.003
$Zn(ClO_4)_2$	20.0	6.18	.1–0.7	.001	.003

The data of J. H. Jones, *J. Phys. Chem.*, **51**, 516 (1947), have been used for lithium and sodium perchlorate.

(12) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943.

(13) J. D. Bernal and R. H. Fowler, *J. Chem. Phys.*, **1**, 515 (1933).

(13a) R. A. Robinson and B. J. Levien, *Trans. Roy. Soc. N. Z.*, **76**, 295 (1947).

lowed the procedure of Bernal and Fowler with slight modifications. The apparent molal volumes at 1*M* were computed from the density data of "International Critical Tables." It turns out that the values for cesium and rubidium chloride, bromide and iodide can be represented within a few per cent. by $V_{app} = 6.47(r_+^3 + r_-^3)$ cu. Å. per molecule, where r_+ and r_- are Pauling's[14] crystallographic radii (in Å.). The molal volumes in the solid state are also fairly close to this. Since these salts have anions and cations of not greatly differing sizes, it is reasonable to attribute to the anions in other salts a contribution of 6.47 r_-^3 cu. Å./ion toward the apparent molal volume. The contribution of the cation, including the closer-packing effect on the water, is then calculated as $V_+ = (V_{app} - 6.47 z_1 r_-^3)$ where z_1 is the cation valence.

We can now calculate a kind of "idealized" radius r_1 for the *n*-hydrated cation, given by $4/3\pi r_1^3 = 30n + V_+$. Upon adding r_1 to the crystallographic radius of the anion, we obtain an "idealized" distance of closest approach. When this calculation is carried out, we find a clear connection between these "idealized" distances and the $\mathring{a}$ values actually needed (Table I) for the best fit. The sum $(r_1 + r_-)$ exceeds $\mathring{a}$ by a matter of 0.7 Å. for the alkali halides and 1.3 Å. for the alkaline-earth halides. The variation in this difference from salt to salt is scarcely more than can be accounted for by the usual elasticity of a two-parameter equation. We can interpret this difference in two ways: as a penetration of the hydration shell of the cation by the anion (following a suggestion of Frank[6]) or as a distortion of the ions by the field. Either explanation will also cover the fact that the difference is nearly twice as great for doubly charged as for singly charged cations. It is to be noted that the three halide anions considered have radii varying only from 1.81 to 2.16 Å. so that we should expect them all to penetrate to much the same extent.

This admittedly empirical relation between *n* and $\mathring{a}$ turns out to be of sufficient accuracy to make possible the evaluation of $\mathring{a}$ from *n*, the densities of the solutions, and the known crystallographic radii of the ions. We therefore have the activity coefficient in terms of the single parameter *n*, as follows

$$\log \gamma = \frac{0.5092 z_1 z_2 \sqrt{\mu}}{1 + 0.3296\sqrt{\mu}\left\{\left[\frac{3}{4\pi}(30n + V_+)\right]^{1/3} + r_- - \Delta\right\}} - (n/\nu)\log a_w - \log[1 - 0.018(n - \nu)m] \ldots \quad (10)$$

where $\Delta = 0.7$ Å. for the univalent halides and 1.3 Å. for the bivalent metal halides.

By choosing the appropriate value of *n* by a trial-and-error process, equation (10) will give a satisfactory representation of the observed activity coefficients (over a usefully wide range of concentrations) as shown in Tables II and III and Fig. 1.

It is noteworthy that in the majority of cases the equation breaks down when the product of *n* and the molality exceeds about 10 or 15. This is to be expected, as there are only 55.51 moles of water altogether for *m* moles of salt, and the effects of "competition" between neighboring ions of the same sign must become noticeable. To proceed to higher concentrations we would have to use an *n* which was a suitably decreasing function of concentration. It is important to note that when equation (10) begins to fail by more than 1% or so, the predicted γ values are *higher* than the experimental values, as a natural consequence of the use of too large an *n* value. The only exceptions to this last statement occur in the case of the rubidium halides, where the predicted γ values become too *low* above 2 *M*. Here of course the relation between *n* and $\mathring{a}$ is being stretched to rather absurd lengths, in treating the ions as spherical with such small *n* values as are needed. The activity coefficients of the cesium halides cannot be reconciled with equation (10); they are equally difficult to fit with the conventional equation (2), requiring $\mathring{a}$ values substantially *less* than the radius sums.

One cannot claim that the accuracy of fit obtainable with the one-parameter equation (10) is quite as good as can be done with equation (9) using two parameters; but it is at least able to predict activity coefficients within about twice the experimental error, and with an accuracy nearly always better than 1% up to remarkably high concentrations.

The simplicity of the physical model makes its success the more striking. Though there are many obvious criticisms which can be made, the empirical value of the one-parameter equation is clear from the figures, and is sufficient to justify the decidedly *ad hoc* arguments used in its development.

II. Water Activities in Very Concentrated Electrolyte Solutions.—In the course of isopiestic measurements on very concentrated calcium nitrate solutions it was found that, while the solution is saturated at 8.4 *M* at 25°[15] it readily supersaturates. These supersaturated solutions, on further concentration (by isothermal evaporation at 25°) pass into semi-solid gels. The transition from a freely flowing solution to a transparent, rigid gel is marked by no visible discontinuity, and the vapor pressure–concentration curve is also continuous. The measurements were extended to 21 *M*, at which concentration the clear homogeneous gel broke down into a striated form. Vapor pressure measurements were not made on these striated gels, because equilibrium was not reached sufficiently rapidly. These phenomena suggested the possibility that at high concentrations the system could be treated as an adsorbent (calcium nitrate)–adsorbate (water) system.

(14) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1944.

(15) H. Bassett and H. S. Taylor, *J. Chem. Soc.*, **101**, 576 (1912).

TABLE II

COMPARISON OF EXPERIMENTAL ACTIVITY COEFFICIENTS OF UNI-UNIVALENT HALIDES AT 25° WITH THOSE CALCULATED BY THE ONE-PARAMETER EQUATION (10)

The value of n is given below the formula of each salt. In all cases the "penetration distance" is taken as 0.7 Å.

	HCl n = 7.3 (4.84)		HBr n = 8.6 (5.18)		HI n = 10.6 (5.69)		LiCl n = 6.5 (4.66)		LiBr n = 7.1 (4.92)		LiI n = 10.0 (5.59)		NaCl n = 3.5 (3.97)		NaBr n = 4.15 (4.30)	
m	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.
0.1	0.796	0.799	0.805	0.807	0.818	0.820	0.790	0.795	0.796	0.800	0.815	0.817	0.778	0.776	0.782	0.783
.2	.767	.770	.782	.784	.807	.806	.757	.762	.766	.770	.802	.800	.735	.731	.741	.742
.3	...	...	.778	.778	.811	.809	.744	.748	.756	.759	.804	.801	.710	.707	.719	.720
.5	.757	.758	.789	.789	.839	.838	.739	.741	.753	.759	.824	.824	.681	.679	.697	.698
.7	...	...	.815	.815	.883	.881	.748	.749	.767	.772	.852	.863	.667	.666	.689	.690
1.0	.809	.807	.871	.870	.963	.976	.774	.773	.803	.805			.657	.657	.687	.689
1.5	.896	.895					.838	.838	.895	.890			.656	.659	.703	.703
2.0	1.009	1.018					.921	.926	1.015	1.009			.668	.671	.731	.730
2.5									1.161	1.164			.688	.691	.768	.769
3.0													.714	.716	.812	.810
4.0													.783	.781	.929	.924
5.0													.874	.870		

	NaI n = 5.05 (4.73)		KCl n = 1.9 (3.63)		KBr n = 2.05 (3.84)		KI n = 2.45 (4.20)		RbCl n = 1.25 (3.47)		RbBr n = 0.9 (3.48)		RbI n = 0.6 (3.56)	
m	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.
0.1	0.787	0.791	0.770	0.767	0.772	.770	0.778	0.777	0.764	0.762	0.763	0.762	0.762	0.762
.2	.751	.755	.718	.716	.722	.721	.733	.731	.709	.708	.706	.707	.705	.708
.3	.735	.738	.688	.686	.693	.692	.707	.708	.675	.676	.673	.674	.671	.674
.5	.723	.725	.649	.649	.657	.658	.676	.675	.634	.635	.632	.632	.629	.632
.7	.724	.725	.626	.626	.636	.638	.660	.659	.608	.609	.605	.606	.602	.605
1.0	.736	.734	.604	.606	.617	.619	.645	.645	.583	.584	.578	.579	.575	.577
1.5	.771	.768	.583	.586	.600	.603	.637	.636	.559	.558	.551	.552	.547	.547
2.0	.820	.819	.573	.576	.593	.596	.637	.636	.546	.542	.536	.531	.533	.526
2.5	.883	.883	.569	.571	.593	.594	.644	.641						
3.0	.963	.962	.569	.571	.595	.596	.652	.650						
4.0			.577	.575	.608	.606	.673	.673						

The $\mathring{a}$ values given in parentheses for comparison with Table I are not parameters but are computed from n and the apparent ionic volumes.

TABLE III

COMPARISON OF EXPERIMENTAL ACTIVITY COEFFICIENTS FOR BI-UNIVALENT HALIDES AT 25° WITH THOSE CALCULATED BY THE ONE-PARAMETER EQUATION (10)

The value of n is given below the formula of each salt. In all cases the "penetration distance" is taken as 1.3 Å.

	$MgCl_2$ (4.99) n = 13.9		$MgBr_2$ (5.48) n = 17.0		MgI_2 (5.96) n = 20.0		$CaCl_2$ (4.75) n = 11.9		$CaBr_2$ (5.17) n = 14.0		CaI_2 (5.68) n = 17.0		$SrCl_2$ (4.60) n = 10.8		$SrBr_2$ (4.99) n = 12.4	
m	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.
0.1	0.529	0.530	0.550	0.552	0.580	0.574	0.518	0.519	0.532	0.536	0.560	0.559	0.511	0.511	0.526	0.528
.2	.489	.489	.518	.523	.558	.555	.472	.472	.492	.497	.531	.531	.462	.461	.483	.485
.3	.477	.477	.517	.519	.567	.562	.455	.454	.482	.486	.531	.530	.442	.441	.468	.469
.5	.481	.481	.545	.546	.614	.613	.448	.448	.491	.494	.561	.560	.430	.430	.467	.469
.7	.506	.506	.599	.599	.698	.703	.460	.460	.522	.521	.614	.614	.434	.436	.484	.486
1.0	.570	.572	.723	.727			.500	.499	.597	.603	.741	.748	.461	.462	.535	.535
1.4	.709	.714					.587	.586					.524	.524	.643	.648
1.8							.712	.720					.614	.619		

	SrI_2 (5.55) n = 15.5		$BaCl_2$ (4.29) n = 8.4		$BaBr_2$ (4.77) n = 10.3		BaI_2 (5.51) n = 14.7		$MnCl_2$ (4.65) n = 11.4		$FeCl_2$ (4.75) n = 12.1		$CoCl_2$ (4.83) n = 13.0		$NiCl_2$ (4.83) n = 13.1	
m	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.	Obs.	Calcd.
0.1	0.553	0.552	0.500	0.496	0.513	0.516	0.542	0.548	0.516	0.514	0.518	0.518	0.522	0.523	0.522	0.523
.2	.520	.519	.444	.440	.465	.468	.509	.515	.469	.466	.473	.472	.479	.479	.479	.479
.3	.517	.514	.419	.415	.446	.448	.502	.508	.450	.446	.454	.454	.463	.464	.463	.464
.5	.536	.534	.397	.393	.435	.437	.523	.524	.440	.438	.450	.449	.462	.463	.464	.463
.7	.578	.577	.391	.388	.442	.443	.562	.561	.448	.447	.463	.462	.479	.481	.482	.482
1.0	.680	.680	.395	.395	.469	.469	.649	.650	.479	.479	.506	.504	.531	.533	.536	.535
1.4			.419	.420	.529	.528			.542	.550	.596	.594	.634	.644	.647	.650
1.8			.449	.458	.609	.615					.719	.731				

As in Table II the $\mathring{a}$ values in parentheses are not parameters but are computed from n and the apparent ionic volumes.

Experimental

Calcium nitrate from British Drug Houses, Limited, was recrystallized twice from water. Solutions, analyzed for calcium as carbonate, were equilibrated against sulfuric acid by the isopiestic method.[16] From the experimental results, given in Table IV, the osmotic and activity coefficients were evaluated (Table V) with the aid of the data

(16) R. A. Robinson and D. A. Sinclair, THIS JOURNAL, **56**, 1830 (1934).

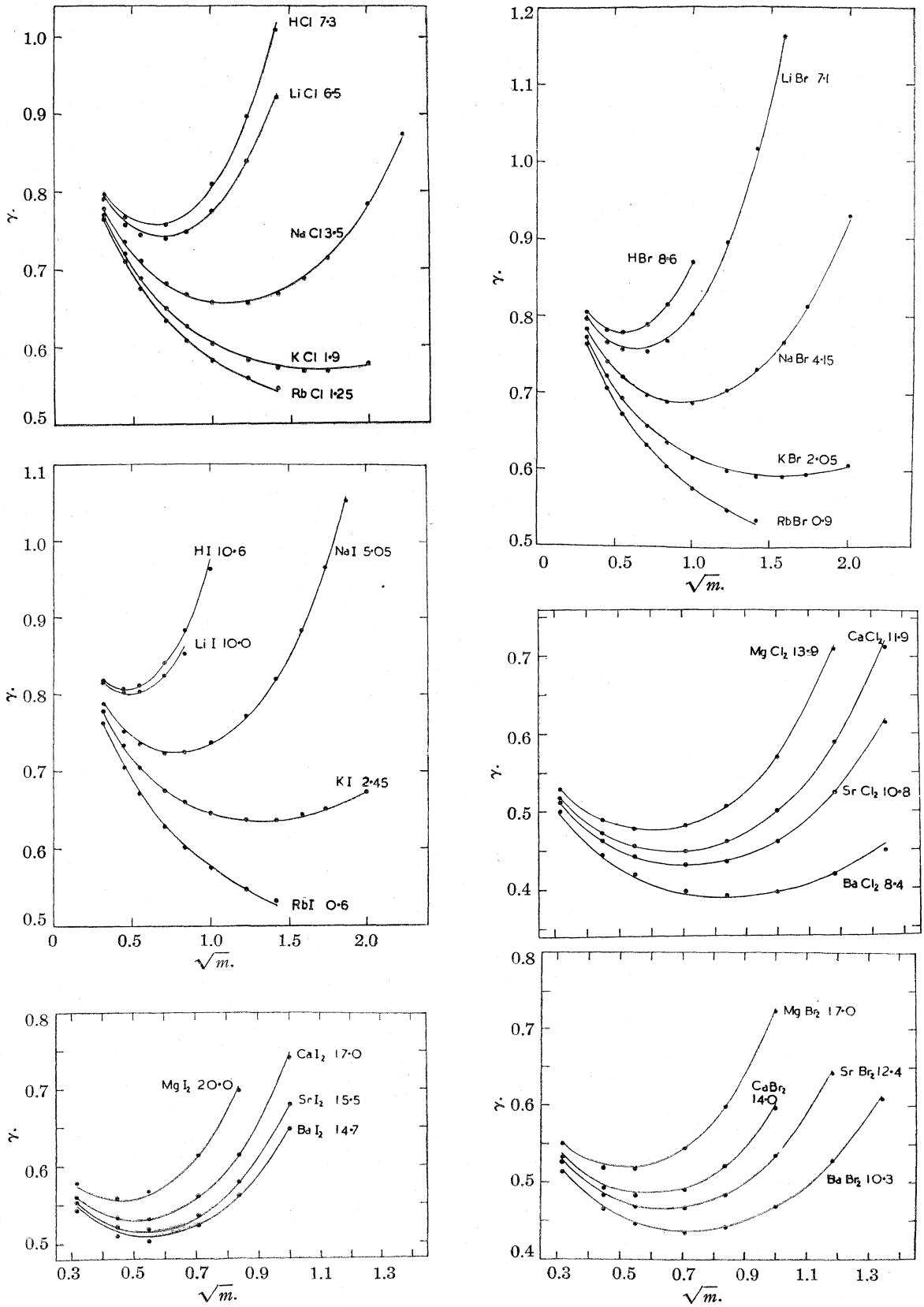


Fig. 1.—Comparison of experimental activity coefficients with those predicted by the one-parameter equation (10). The full curves are calculated from equation (10), using the value for the "hydration parameter" n following the formula of each salt. The circles give the experimental values. Diameter of circles equals 0.004 in γ.

for sulfuric acid.[17,18] Previous values[19] at concentrations up to 3 M have been recalculated to conform to more recent standards. Compared with such salts as calcium chloride low γ values are obtained for calcium nitrate over the whole concentration range. Thus at 6 M we find $\gamma_{Ca(NO_3)_2} = 0.592$, $\gamma_{CaCl_2} = 11.11$. This is consistent with the general behavior of bivalent metal nitrates, and is probably to be explained in terms of Bjerrum's ideas of ion-pair formation. It seems quite likely that at high concentrations the salt would be better formulated as $(CaNO_3)^+ \cdot NO_3^-$.

TABLE IV

ISOPIESTIC SOLUTIONS OF CALCIUM NITRATE AND SULFURIC ACID AT 25°

$M_{Ca(NO_3)_2}$	$M_{H_2SO_4}$	$M_{Ca(NO_3)_2}$	$M_{H_2SO_4}$	$M_{Ca(NO_3)_2}$	$M_{H_2SO_4}$	$M_{Ca(NO_3)_2}$	$M_{H_2SO_4}$
3.070	3.184	3.784	3.823	4.535	4.494	5.505	5.346
7.038	6.675	7.208	6.815	7.426	7.000	7.860	7.386
8.110	7.615	9.148	8.530	10.44	9.610	11.35	10.31
11.88	10.73	12.07	10.87	14.28	12.50	15.67	13.39
16.34	13.89	17.00	14.35	17.94	14.92	18.96	15.45
19.67	15.79	21.58	16.80				

TABLE V

OSMOTIC AND ACTIVITY COEFFICIENTS OF CALCIUM NITRATE AT 25°

M	φ	γ	M	φ	γ
0.1	0.827	0.485	4.0	1.157	0.435
.2	.819	.426	4.5	1.210	.469
.3	.818	.395	5.0	1.263	.507
.4	.821	.376	6.0	1.361	.592
.5	.825	.363	7.0	1.452	.690
.6	.831	.354	8.0	1.535	.801
.7	.837	.347	9.0	1.622	.935
.8	.843	.342	10.0	1.683	1.065
.9	.850	.338	11.0	1.722	1.184
1.0	.859	.336	12.0	1.759	1.311
1.2	.879	.335	13.0	1.780	1.425
1.4	.898	.335	14.0	1.798	1.538
1.6	.917	.337	15.0	1.803	1.633
1.8	.934	.340	16.0	1.805	1.724
2.0	.953	.345	17.0	1.820	1.838
2.5	1.001	.360	18.0	1.815	1.917
3.0	1.051	.380	19.0	1.795	1.961
3.5	1.103	.405	20.0	1.778	2.008

In the case of calcium nitrate and other highly soluble salts it would be futile to attempt any form of extension of the Debye–Hückel treatment, into the very concentrated solutions. We have only to note that in an 18 molal solution there are only about 3 molecules of water per molecule of solute, to realize the hopelessness of such an approach. Another important point is that at these concentrations there can be little left of the normal coordinated structure of water; for in a solution with say 5 moles of a 2:1 electrolyte per liter, there are $(15 \times 6.023 \times 10^{20})$ ions per cc., so that the average distance between an ion and its nearest neighbors can be only about 5 Å. Clearly there can be in such a solution no water molecules which are not subject to quite large electrical forces from the ionic field. It is in fact rather surprising that the Debye–Hückel treatment as extended in Part I of this paper gives such reasonable results as it does in the case of say 5 M sodium chloride. In very dilute solutions the ion–ion forces are dominant, and the simple Debye–Hückel treatment is applicable. In moderate concentrations, the ion–ion and ion–solvent forces become of comparable importance, and the method of Part I provides a satisfactory treatment. We believe that at very high concentrations the ion–solvent forces are the dominant factor, and shall therefore develop as a first approximation a treatment which ignores the ion–ion forces, or rather assumes that they are little affected by concentration in the range to be discussed. There is some justification for this: (a) the Debye–Hückel function $[A\sqrt{c}/(1 + \mathring{a}B\sqrt{c})]$ flattens out with rising concentration, approaching the limit $A/\mathring{a}B$. (b) From an entirely different viewpoint, we might treat the solution as a somewhat irregular ionic lattice with interspersed water molecules, a view supported by the X-ray data of Beck,[20] for example, on concentrated solutions of lithium chloride and bromide and rubidium bromide. The ion–ion energy on this picture might reasonably be expected to be proportional to the inverse cube root of the volume–concentration, so that again it should vary rather slowly with concentration.

The behavior of concentrated calcium nitrate "solutions," described above, raised the question of whether we could obtain a relation between molality and water activity by the application of an adsorption isotherm. Though calcium nitrate is the only electrolyte which we have found to form gels, we have obtained vapor pressure data for a number of other electrolytes at equally high concentrations, and there would seem to be nothing to prevent the application of the same idea to these also. We may picture a concentrated solution as containing ions in various stages of hydration, some with a complete hydration shell forming a monomolecular layer round the ion, others with incomplete shells, and others with more than one layer, the second and higher layers being of course much less strongly bound. All these would be in equilibrium, the relative amounts of each varying with concentration. Now this model bears a strong resemblance to that from which the adsorption isotherm derived by Brunauer, Emmett and Teller[21] was derived. Modifying the notation of these authors to suit the present case, we may write their equation as

$$\frac{ma_w}{55.51(1 - a_w)} = \frac{1}{cr} + \frac{c - 1}{cr} a_w \qquad (11)$$

(17) S. Shankman and A. R. Gordon, THIS JOURNAL, **61**, 2370 (1939).

(18) R. H. Stokes, *ibid.*, **69**, 1291 (1947).

(19) R. A. Robinson, *ibid.*, **62**, 3130 (1940).

(20) Beck, *Physik. Z.*, **40**, 474 (1939).

(21) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938).

where: a_w is the water activity of the solution; m its molality; r is the number of molecules of water in the monomolecular hydration layer *when complete;* and c is a constant related to the heat of adsorption E of the molecules in the layer by the approximate relation $c = \exp(E - E_L)/RT$, E_L being the heat of liquefaction of pure water. Equation (11) may be tested by plotting the left-hand side (determined from the experimental m and a_w) against a_w. We find that good straight lines are obtained from the following electrolytes in the concentration range where $a_w < 0.3$: calcium nitrate, calcium chloride,[11] calcium bromide,[22] lithium chloride,[23] lithium bromide,[22] zinc chloride,[11] zinc bromide,[11] perchloric acid,[24] hydrochloric acid,[25] and sodium hydroxide.[26] Table VI gives the best values of the parameters c and r for these electrolytes, obtained by a least-squaring process. Also recorded are the average deviations of the water activity observed from that required to reproduce the experimental molality with equation (11) rewritten in the form

$$m = \frac{55.51(1 - a_w)}{a_w}\left\{\frac{1}{cr} + \frac{c - 1}{cr}a_w\right\} \qquad (11a)$$

The accuracy of fit is on the whole surprisingly good; it should be remembered that the experimental accuracy of vapor pressure measurements at these high concentrations is in the majority of cases not much better than 0.0010 in a_w. It is immediately noticeable that the r values for the 1:1 electrolytes are between 3 and 4, while those of calcium chloride and calcium bromide are about twice as large. Zinc chloride and bromide have r values similar to those of 1:1 electrolytes, which is to be explained on the grounds that concentrated solutions of these salts should really be formulated as Zn $(ZnCl_4)$ and Zn $(Zn\ Br_4)$[27] so that only half the zinc is in the form of ions free to undergo hydration. The free zinc ions then have r values similar to those of calcium in calcium chloride and bromide. In the case of calcium nitrate if we adopt the formulation $CaNO_3^+ \cdot NO_3^-$ it is reasonable that the r value should be in the range characteristic of 1:1 electrolytes. The values of the parameter c are also reasonable, corresponding to $E - E_L = 1$ to 3 kcal. per mole of water adsorbed. An unsatisfactory feature of equation (11) is that it demands the non-integral r values of Table VI. These can scarcely correspond to any physical reality, and have more likely arisen as a result of approximations in the B–E–T. theory and its application to this case. The most drastic of these approximations is that of treating all water molecules beyond the first layer as held by ordinary liquid forces, with a heat of liquefaction E_L. Anderson[28] has deduced a modification of the B–E–T equation in which the subsequent layers (up to about the tenth) have a heat of adsorption less than that of water by d. This has the effect of multiplying a_w, wherever it occurs in (11), by a factor $K = e^{-d/RT}$ leading to the equation

$$\frac{ma_w}{55.51(1 - Ka_w)} = \frac{1}{cKr} + \frac{c - 1}{cr}a_w \qquad (12)$$

We shall now investigate whether this equation, with r fixed at 4.000 or 8.000 according to the salt considered, will represent the observed relation between m and a_w by an appropriate choice of the two constants c and K. To make the test we rewrite (12) in the form

$$c = \left\{\frac{1}{K} - a_w\right\} \Big/ \left\{\frac{rma_w}{55.51(1 - Ka_w)} - a_w\right\}$$

and find by trial a value of K which lends to a reasonably constant c over the widest possible range of molality. The c and K values found for the nine electrolytes are listed in Table VII. The range of validity of equation (12) is somewhat wider than that of equation (11), extending in most cases up to $a_w = 0.5$. The average deviations are on the whole slightly greater, though there would be little difference if equation (12) were restricted to the same range of water activities as equation (11).

TABLE VI

CONSTANTS OF EQUATION (11)

Electrolyte	r	c	Range fitted	Average deviation in a_w
LiCl	3.64	17.2	$12M$–$29M$	0.0008
LiBr	3.82	43.0	$11M$–$20M$	.0015
HCl	3.50	19.1	$12M$–$16M$	.0009
$HClO_4$	3.93	59.0	$10M$–$16M$	.0017
$Ca(NO_3)_2$	3.86	9.40	$12M$–$20M$	.0007
$ZnCl_2$	3.69	22.6	$12M$–$22M$	.0017
$ZnBr_2$	4.01	19.8	$11M$–$20M$	.0008
$CaCl_2$	6.73	9.50	$7M$–$10.5M$	.0004
$CaBr_2$	7.06	42.6	$6M$–$9M$	.0031
NaOH	3.20	19.3	$14M$–$29M$	.0011

The c parameter of equation (12) ranges from 9.0_4 to 58.2, corresponding to values of $E - E_L$ of 1.3 to 2.4 kilocalories per mole of water. These magnitudes seem reasonable enough. The K parameter range corresponds to $d = 0$ to 150 cal./mole of water in the second and subsequent layers. This relatively small energy might easily correspond to a weak ordering effect on the water molecules concerned. It would however clearly be unwise to go too far in attempting to attach an exact physical meaning to K in terms of the model. It is sufficient to have shown that with an integral r value of 4 or 8, and a c corresponding to a reasonable "energy of adsorption," equation (12) is applicable over the remarkably wide ranges of con-

(22) R. A. Robinson and H. J. McCoach, THIS JOURNAL, **69**, 2244 (1947).

(23) R. A. Robinson, *Trans. Faraday Soc.*, **41**, 756 (1945).

(24) R. A. Robinson and O. J. Baker, *Trans. Roy. Soc. New Zealand*, **76**, 250 (1946).

(25) G. Åkerlöf and J. W. Teare, THIS JOURNAL, **59**, 1855 (1937).

(26) R. H. Stokes, *ibid.*, **67**, 1689 (1945).

(27) R. H. Stokes, *Trans. Faraday Soc.*, **44**, in press (1948).

(28) R. B. Anderson, THIS JOURNAL, **68**, 686 (1946).

centration given in Table VII. The K parameter can then be regarded as a convenient carry-all for such effects as ordering in the second and higher layers and the otherwise neglected variation in the ion–ion energy with concentration. In view of the approximate nature of the treatment, the accuracy with which the molality can be related to the water activity by equations (11) and (12) is more than satisfactory.

TABLE VII

CONSTANTS OF EQUATION (12)

Electrolyte	r	c	K	Range fitted	Average deviation in a_w.
LiCl	4.00	15.84	0.860	$8M$–$20M$	0.0006
LiBr	4.00	42.0	0.890	$8M$–$20M$	.0018
HCl	4.00	14.38	0.850	$7M$–$16M$	.0019
$HClO_4$	4.00	58.2	0.950	$9M$–$16M$	.0024
$Ca(NO_3)_2$	4.00	9.04	0.960	$9M$–$20M$	.0010
$ZnCl_2$	4.00	20.5	0.880	$10M$–$22M$	.0025
$ZnBr_2$	4.00	20.0	1.000	$11M$–$20M$	.0009
$CaCl_2$	8.00	9.24	0.775	$4M$–$10.5M$	.0016
$CaBr_2$	8.00	34.1	0.770	$4.5M$–$9M$	.0007

In the case of hydrochloric acid, the data available[24] cover the temperature range 0–50°, so that an interesting test of these ideas is possible. Table VIII gives the values of the K and C parameters, taking $r = 4$, for hydrochloric acid at various temperatures. The variation in C is considerable, but corresponds to a practically constant value of $E - E_L$ in the equation

$$C = \exp (E - E_L)/RT$$

This is consistent with the idea of strong electrostatic forces causing the "adsorption." The K values on the other hand do not correspond to a constant value of d; but the various effects covered by the introduction of K are not clearly enough defined to justify the expectation that it would be constant.

TABLE VIII

CONSTANTS OF EQUATION (12) FOR HYDROCHLORIC ACID AT VARIOUS TEMPERATURES

$r = 4.00$ in each case. $c = \exp (E - E_L)/RT$. Range fitted 10 M–16 M at each temperature

Temp., °C.	K	c	$(E - E_L)$, kcal.	Average deviation in a_w.
0	0.870	18.28	1.58	0.0010
10	.861	16.52	1.58	.0020
20	.852	14.98	1.58	.0020
25	.850	14.38	1.58	.0019
30	.843	13.68	1.58	.0016
40	.834	12.45	1.57	.0016
50	.825	11.29	1.56	.0013

We consider that the ideas put forward in this section are worth developing further, perhaps by an attempt to evaluate the ion–ion energies in the quasi-lattice of the concentrated solution. If these energies could be included the treatment should find a firmer theoretical basis. The ideas put forward in the two sections of this paper are not self-contradictory. In Part I we have shown that the introduction into the Debye–Hückel equation of the concept of ion–solvent molecule interaction will account for observed activity coefficients up to a total ionic strength of about 4. In part II we have accounted for vapor pressure data at concentrations above about 12 M by assuming that ion–solvent molecule interaction occurs by a mechanism similar to that of the Brunauer–Emmett–Teller theory. Between these concentrations the hydration number, n, is diminishing and the ions are tending to a quasi-crystalline structure with some of the water molecules imbedded in the remnants of the crystal lattice (adsorbed water) and some present as "free" solvent. There is nothing contradictory in these two methods of approach; rather do we regard them as limiting cases of a more general theory which would cover the entire concentration range.

Summary

Part I: By superimposing on the Debye–Hückel treatment an allowance for the ion–solvent interaction in terms of a hydration model, a two parameter equation for activity coefficients is obtained. This has a range of validity greater than that of the usual Hückel equation. When dealing with the class of the chlorides, bromides and iodides of hydrogen and the alkali metals, the two-parameter form can be reduced to a one-parameter equation by the assumption that the anion can penetrate a distance of 0.7 Å. into the hydration sheath of the cation. A closely similar one-parameter equation holds for the alkaline-earth halides and other normally dissociated bivalent metal halides, the "penetration distance" for this class being 1.3 Å. Within each class only the single parameter n, the effective hydration number of the cation, is required to represent the observed activity coefficients, usually up to an ionic strength of about 4.

Part II: An approximate treatment of the water activity of very concentrated electrolyte solutions is based on the application of the adsorption isotherms of Brunauer, Emmett and Teller and of Anderson. The resulting equations apply with surprising accuracy to nine electrolytes which have recently been studied at very high concentrations. The parameters of the equations are listed and their physical significance discussed.

NEDLANDS, WESTERN AUSTRALIA
NEW HAVEN, CONN. RECEIVED JUNE 24, 1947

[A CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Polarographic Behavior of Phenolphthalein

BY I. M. KOLTHOFF AND D. J. LEHMICKE[1,2]

In the course of a polarographic study of the reduction of various acid–base indicators, phenolphthalein was found to exhibit such unusual characteristics that a thorough investigation was made of its polarographic behavior under conditions of varying *p*H, solvent and temperature. A unique current–voltage curve was found in 25% alcohol at a *p*H of about 7, the curve showing a typical diffusion current plateau, the diffusion current then decreasing to a minimum value close to zero at a potential about half a volt more negative than the half-wave potential. The normal diffusion current in 25% ethanol was found to decrease almost to zero when the water in the solvent was being replaced by ethanol. An interpretation of the observed phenomena is given in the discussion section.

In a subsequent paper it will be shown that the polarograph is very suitable, not only to follow the fading of phenolphthalein in alkaline medium, but also to determine the rate of reaction of the colorless carbinol form with hydrogen ions in acid medium, which is not easily followed colorimetrically.

Experimental

Apparatus.—Unless otherwise stated the current–voltage curves were determined using a type VIII Heyrovsky polarograph. Exact data of diffusion currents and sometimes of half wave potentials were obtained with a manual apparatus. The galvanometer had a unit sensitivity of 3.19×10^{-3} microamperes per millimeter.[3] Two capillaries were used with the following characteristics. Capillary 1: droptime, $t = 3.55$ sec., $m = 2.93$ mg./sec., $m^{2/3}t^{1/6} = 2.52$. Capillary 2: $t = 2.96$, $m = 1.427$ and $m^{2/3}t^{1/6} = 1.52$. Unless otherwise noted capillary 2 was used.

The electrolysis cells consisted of 50-ml. Erlenmeyer flasks with side-arms for the admission of nitrogen and for connection with the saturated calomel electrode, which as a rule served as a reference electrode. All the potentials are referred to the saturated calomel electrode (S.C.E.). Several runs were made with a pool of mercury on the bottom of the electrolysis cell as anode. In these instances the anode potential was measured against the S.C.E. All diffusion currents as measured from the polarographic records were corrected for the residual current. In case two diffusion currents were found, their relative values were referred to the same value of $m^{2/3}t^{1/6}$.[4]

The electrolysis experiments were carried out in a thermostat at 25 ± 0.01°.

Materials. Phenolphthalein.—A National Aniline Company product with a melting point of 262–264° (cor.) (Beilstein, XVIII, 143 reports 254° uncor.).

Phenolphthalin.—This substance was prepared by reduction of phenolphthalein with zinc dust in 2 *N* sodium hydroxide according to the directions of Baeyer.[5]

Basic Fuchsine.—A National Aniline product; a 0.1% solution of the dye in water was prepared which served to eliminate maxima.

Nitrogen.—Tank nitrogen, purified by passing through a train consisting of acid chromous chloride solution, sodium hydroxide solution, mercuric chloride solution and water. In all polarographic experiments air was replaced with nitrogen.

Other chemicals were reagent grade. Standard acid and base solutions were prepared and standardized by conventional methods.

Buffer Solutions.—In the range of *p*H between 1 and 10 Clark and Lubs buffer solutions were used. The *p*H was checked with the aid of a glass electrode. The *p*H data refer to water as a solvent and not to solvents containing alcohol. Solutions with a *p*H higher than 10 were prepared using 0.1 *N* sodium carbonate (*p*H 11), 0.01 *N* sodium hydroxide (*p*H 12) and 0.1 *N* sodium hydroxide (*p*H 13).

Medium.—Except where the alcohol content was varied 25% ethanol by volume was present. In other instances the ethanol content is also expressed in per cent. by volume. In general, the concentration of phenolphthalein was 0.001 *M*. In order to work at this concentration it was necessary to have 25% ethanol in the solvent.

The test solutions contained 50% by volume of buffer solution and 0.001% of basic fuchsine. In the absence of the dye pronounced maxima in current–voltage curves were usually found. In addition, the solutions were usually 0.1 *N* in potassium chloride.

Results

Experiments in 25% Ethanol. Effect of *p*H.—Polarograms were run of 0.001 *M* solutions of phenolphthalein in 25% ethanol over the *p*H range between −0.6 and 13. Four different types of curves were obtained as shown in Figs. 1 and 2.

In solutions with a *p*H less than about 3.5 a single wave of the normal type was observed (Fig. 1). In the *p*H range between 4 and 8.5 one step reduction waves were observed, with well defined diffusion currents. The polarogram at a *p*H of 7.4 has quite an abnormal appearance (Fig. 1). The diffusion current remains practically constant in a potential range between about −1 and −1.2 volt, it decreases very slightly between −1.2 and −1.4 volt and then drops suddenly to attain a minimum value at a potential of about −1.6 volt. The minimum value remains constant to a potential of about −1.75 volt, whereupon the wave yielded by the supporting electrolyte appears. At a *p*H of 4.7 the decrease in the diffusion current starts at a potential of about −1.1 volt; however, before a flat minimum as at a *p*H of 7.4 is attained the wave of the supporting electrolyte appears. In still more acid medium (*p*H < 3.5) no decrease of the diffusion current is observed, as the hydrogen wave appears before the decrease of the diffusion current occurs. In the *p*H range corresponding roughly to the color-change inter-

(1) Present address: E. I. du Pont de Nemours & Company, Wilmington, Delaware.

(2) From a thesis submitted by D. J. Lehmicke to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1946.

(3) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 227.

(4) I. M. Kolthoff and E. F. Orlemann, THIS JOURNAL, **63**, 2085 (1941).

(5) A. Baeyer, *Ann.*, **202**, 80 (1880).

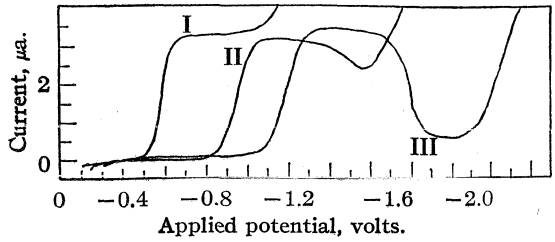


Fig. 1.—Current-voltage curves of millimolar phenolphthalein in 25% ethanol: I, solution is 3.8 N in HCl and 0.001% in basic fuchsine; II, biphthalate buffer, pH 4.73; III, phosphate buffer, pH 7.40. Abscissa scales for curves II and III start 0.1 and 0.2 volts, respectively, to the right of curve I.

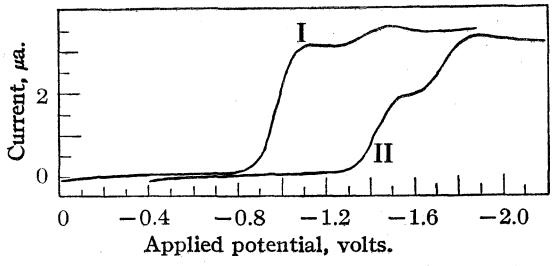


Fig. 2.—Current-voltage curves of millimolar phenolphthalein in 25% ethanol solution: I, in borate buffer, pH 9.55; II, in borate buffer, pH 10.25. Abscissa scale for curve II starts 0.4 volt to the right of curve I.

val of phenolphthalein two waves are observed. At a pH of about 9 the first diffusion current is almost equal to the total diffusion current found at lower pH, the second wave comprising only a few per cent. of the total current. In more alkaline medium the second wave increases at the cost of the first one (Fig. 2), the total current remaining the same. At a pH of 10.25 (Fig. 2) and at higher pH two waves of equal height are found. It is interesting to note that no decrease of the total diffusion current with increasing negative potential is found at a pH greater than 9.

The "apparent" diffusion currents (constant value before the dip) found at a pH of 7 and in more acid medium, and the total diffusion currents in alkaline medium are all of about the same value, indicating that these currents represent true diffusion currents. The polarograms in strongly alkaline medium must be taken immediately after preparation of the solutions, as the diffusion currents decrease slowly as a result of carbinol formation.

In order to provide further evidence that the apparent diffusion currents at a pH of 7 or smaller are true diffusion currents, their variation with concentration was determined. It was found that the diffusion current is proportional to the concentration. A few values of $K = i_d/c$ in a phosphate buffer of pH 7 in the presence of 0.1 N potassium chloride are: 0.50×10^{-3} M phenolphthalein, $K = 3.94$; 0.001 M, $K = 3.90$; 0.0015 M, $K = 3.90$.

In the phosphate buffer of pH 7 the apparent diffusion current is hardly affected by the concentration of electrolyte. However, the decrease in the current and the appearance of the well-defined minimum (Fig. 1) depend on the total electrolyte content of the solution. Experiments were carried out in which the polarograms were determined in a buffer solution of pyridine and pyridinium hydrochloride, the total chloride concentration being 2.4×10^{-4} M, the pyridine concentration 2×10^{-3} M and the phenolphthalein concentration 1×10^{-3} M (pH 6.85). The polarogram had a normal appearance, and the diffusion current did not decrease at more negative potentials. It remained constant until the wave of the supporting electrolyte appeared. When the solution was made 2.8×10^{-4} M in potassium chloride the dip came into evidence, and it became more pronounced as more potassium chloride was added. The non-appearance of the minimum in the pyridine buffer without salt, therefore, cannot be attributed to an increasing pH at the surface of the dropping mercury during the reduction (two hydrogen ions are consumed in the reduction), as the pH would change in a similar way in the presence of the potassium chloride. The effect of the potassium chloride must be a typical "electrolyte effect."

The appearance of the dip at pH values between 4 and 8 is a matter of practical consequence, when dealing with a mixture of phenolphthalein and a substance which is reduced at more negative potentials. This is demonstrated in Fig. 3, giving the polarogram of a 0.0015 M phenolphthalein and 0.001 M cobalt solution in 26% ethanol containing ammonium acetate as a buffer and fuchsine as an eliminator of maxima. First the diffusion current of phenolphthalein is observed; however, just before the diffusion current of cobalt is attained the dip in the phenolphthalein manifests itself and the current decreases to a fairly constant value, this value being equal to the sum of the diffusion current of cobalt and the small minimum current of phenolphthalein.

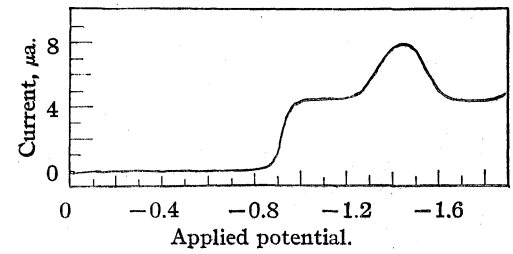


Fig. 3.—Current-voltage curve of millimolar cobalt acetate in the presence of 1.5×10^{-3} molar phenolphthalein in 26% ethanol. Solution is 0.2 M in ammonium acetate and contains 0.001% basic fuchsine.

When the solution contains in addition to phenolphthalein a substance which is reduced at more positive values than phenolphthalein the

polarogram is simply interpreted, the phenolphthalein wave being superimposed upon the previous wave. This was shown to be true in the electrolysis of a mixture of benzoquinone and phenolphthalein.

Two-step Reduction in Alkaline Medium.—Apparently the red form of phenolphthalein (Fig. 2) gives a two-step reduction, whereas the colorless forms give only a single wave. In Table I are given the values of i_{d_1} (i_1) and i_{d_2} (i_2) at varying pH obtained with a 0.001 M phenolphthalein solution in 25% ethanol. In all instances the values of i_{d_1} have been corrected to the same value of $m^{2/3}t^{1/6}$ as prevailed at the potential at which i_t was measured ($i_{d_2} = i_t - i_{d_{1corr.}}$). The pH in the mixture was measured with the glass electrode.

TABLE I

VALUES OF i_{d_1} AND i_{d_2} IN MICROAMPERES OF PHENOLPHTHALEIN IN ALKALINE MEDIUM

i_t = total diffusion current uncorrected for $m^{2/3}t^{1/6}$

pH	i_1 (uncor.)	i_t	i_2	$i_2/^1/_2i_t$
9.18	2.99	3.05	0.13	0.08
9.55	2.91	3.15	.33	.21
9.79	2.59	3.14	.61	.39
9.96	2.28	3.11	.90	.58
10.18	2.09	3.22	1.18	.73
10.25	1.70	3.11	1.45	.93
(13.0	1.33	2.51	1.20	.96)
(13.3	1.34	2.61	1.29	.99)

It is seen that the total diffusion current is found reasonably constant, except in the last two solutions which were 0.1 and 0.2 N in sodium hydroxide, respectively. In these solutions part of the red form was transformed into the carbinol form which does not give a reduction wave under the above conditions. At a pH of 10.3 the two waves become of equal height and remain of equal height with increasing pH.

When the ratio of $i_2/^1/_2i_t$ is plotted against pH, a curve is obtained which has the appearance of a dissociation curve of an acid. The curve is almost identical with the curve obtained on plotting the fraction of phenolphthalein in the red form against pH, as determined by Michaelis and Gyemont.[6] The fact that the two curves practically superimpose indicates that the rate of transformation of the red form into the colorless reducible one is relatively small. If the dissociation equilibrium of the phenolphthalein in buffer solutions with pH between 9 and 10.5 were established very rapidly only one wave corresponding to that of the colorless form would have been observed.

Half-wave Potentials.—The half-wave potentials in 25% ethanol at varying pH are summarized in Table II.

Reduction of Phenolphthalin.—Solutions of phenolphthalin in 25% ethanol were electrolyzed at the dropping electrode in a pH range between 0 and 13. No reduction waves were observed.

(6) L. Michaelis and A. Gyemont, *Biochem. Z.*, **109**, 165 (1920).

TABLE II

HALF-WAVE POTENTIALS AS FUNCTION OF pH

pH	−0.06	0	1	2.5	3.5	4.7	5.8	6.9
$-(\pi^{1/2})_1$	0.49	0.53	0.60	0.67	0.71	0.75	0.80	0.86
$-(\pi^{1/2})_2$								
pH	7.4	8.2	9.6	10.06	12	13	13.3	
$-(\pi^{1/2})_1$	0.89	0.93	0.98	1.01	(.84)	(.82)	(.81)	
$-(\pi^{1/2})_2$			1.35	1.33	1.33	1.23	1.24	

Effect of Ethanol Concentration on Current–Voltage Curves in Neutral Medium.—The experiments were carried out with a 0.001 M phenolphthalein solution, except in 10% ethanol. The concentration in this medium was 0.0005 M, as a 0.001 M solution was supersaturated. All solutions contained a phosphate buffer of pH 7, and were 0.001% in fuchsine and 0.1 M in potassium chloride. Column II of Table III lists the diffusion currents. The value of i_{d_0} in water was found by graphical extrapolation.

Abnormally small values of the diffusion current were found at alcohol concentrations greater than 40%. In order to be quite sure that these small values of the diffusion current were typical for phenolphthalein and not due to a general effect of the solvent, diffusion currents of benzoquinone were determined at the same ethanol concentrations. Column III of Table III lists for phenolphthalein the ratio of the value of i_d in solutions of varying alcohol content to the (extrapolated) value in water (i_{d_0}). Column IV lists the same values for quinone, and Column V the ratio of the values in Columns II and IV.

TABLE III

EFFECT OF ETHANOL CONCENTRATION ON DIFFUSION CURRENT

Ethanol concn., %	$i_{d_{phpht}}$	$(i_d/i_{d_0})_{phpht}$	$(i_d/i_{d_0})_{quinone}$	Column III / Column IV
0	(4.17)	(1.00)	1.00	1.00
10	3.97	0.95	0.90	1.05
20	..	..	.75	..
25	3.29	.79	.69	1.14
30	2.66	.64	.65	0.99
35	1.84	.44	.62	.71
40	0.97	.23	.60	.38
50	0.24	.06	.59	.10
70	0.04	.02	.63	.03

As an illustration Fig. 4 shows the current–voltage curve at an ethanol concentration of 40%.

From the last column in Table III it is seen that up to an alcohol concentration of 30% the diffusion currents of phenolphthalein and quinone are affected in about the same way. At higher alcohol concentrations the diffusion current of phenolphthalein is decreased much more than that of quinone. At an ethanol concentration of 70% the phenolphthalein diffusion current has become vanishingly small.

Assuming that the electroreduction of phenolphthalein involves two electrons it is possible to calculate its diffusion coefficient in water from the

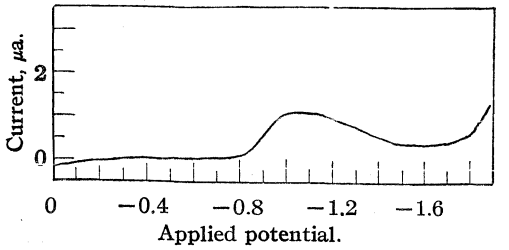


Fig. 4.—Current–voltage curve of millimolar phenolphthalein in 40% ethanol. Solution contains phosphate buffer; *p*H 7.

extrapolated value of the diffusion current with the aid of the Ilkovic equation

$$i_d = 605nD^{1/2}m^{2/3}t^{1/6}$$

The value of $m^{2/3}t^{1/6}$ at −1.0 volt, at which i_d was measured was 1.51 mg.$^{2/3}$ sec.$^{-1/2}$ and i_d in 0.001 *M* solution was 4.17 microamperes. This yields a value of $D = 5.2 \times 10^{-6}$ sq. cm./sec. at 25°. For benzoquinone a diffusion coefficient of $8.6 \pm 0.2 \times 10^{-6}$ was calculated at 25°.[7] The values for phenolphthalein and benzoquinone are of the same order of magnitude, showing conclusively that the reduction of phenolphthalein at the dropping electrode involves two electrons.

Effect of the Temperature on the Current–Voltage Curves in 25% Ethanol in Neutral Medium.—All experiments were carried out with the same solution which was 0.001 *M* in phenolphthalein, 25% in ethanol, 0.1 *M* in potassium chloride, 0.001% in basic fuchsine and which contained 50% of a phosphate buffer of *p*H 7. Experiments at 0° were carried out in an ice-bath, and at temperatures above 25° in a water-bath, the temperature of which was controlled manually. In these experiments the temperature was constant within 2°.

The diffusion current was found to increase with increasing temperature in a predictable fashion, but the current at the minimum of the c.–v. curve showed a relative increase at temperatures above 25°, which was many times greater than that of the diffusion current. This is demonstrated in Table IV in which i_{min} denotes the current at the minimum in the c.–v. curve.

TABLE IV

EFFECT OF TEMPERATURE ON CURRENT–VOLTAGE CURVES OF 0.001 *M* PHENOLPHTHALEIN IN 25% ETHANOL IN PRESENCE OF PHOSPHATE BUFFER

Temp., °C.	i_d, microamperes	i_{min}, microamperes	i_{min}/i_d
0	2.00	0.14	0.06
25	3.29	0.24	.07
50	4.77	1.15	.24
75	6.41	3.49	.56

Figure 5 illustrates the c.–v. curve at 75°.

A run was also made at 85°, within two degrees of the boiling point of the 25% ethanol solution. At this temperature the diffusion current varied somewhat irregularly (about 7.2 microamperes), but the current–voltage curve did not show a dip. Hence the minimum had practically disappeared.

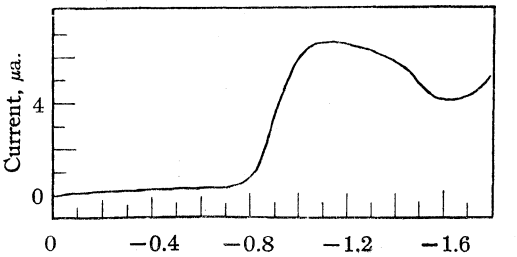
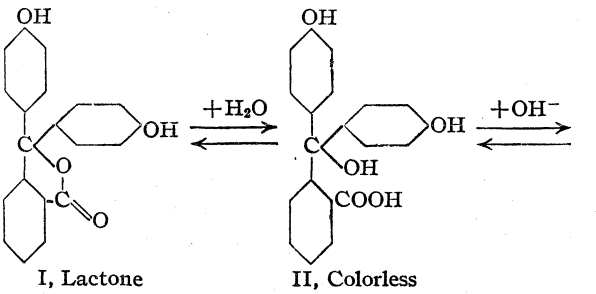
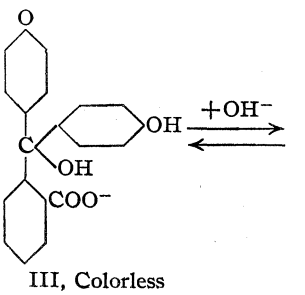


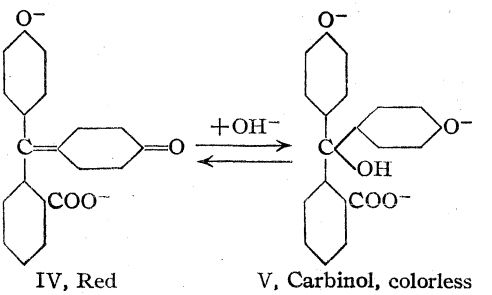
Fig. 5.—Current–voltage curve of millimolar phenolphthalein in 25% ethanol at 75°. Solution contains phosphate buffer; *p*H 7.

Discussion

1. Phenolphthalein in solution can exist in different forms, which are in equilibrium. Representing the various forms by the classical formulas we have







At a *p*H smaller than 8 practically all of the phenolphthalein is present in the lactone form I. It is estimated that the concentration of II is

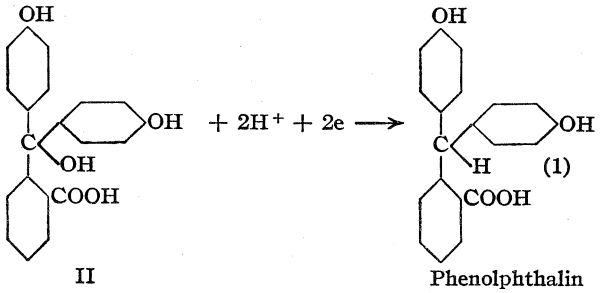
(7) I. M. Kolthoff and E. F. Orlemann, THIS JOURNAL, **63**, 664 (1941).

less than 0.01% of that of I.[8] For reasons mentioned below it is concluded that form II is reducible at the dropping electrode, but form I is not, at least at potentials more positive than that at which the wave of the supporting electrolyte used appears. Both forms II and III give a single reduction wave. The red form IV gives a two step reduction, both waves being of equal height. The colorless carbinol form V formed in strongly alkaline medium does not give a reduction wave, at least not at potentials more positive than that at which the sodium wave appears. When a strongly alkaline solution of phenolphthalein is permitted to stand the color fades and a corresponding reduction of the diffusion current is observed.

In the region of *p*H between 0 and about 10 the half wave potential varies according to

$$\pi^{1}/_{2} = -0.54 - 0.046pH$$

The reduction which is irreversible can be represented by the equation



II Phenolphthalin

This mechanism is supported by the following facts.

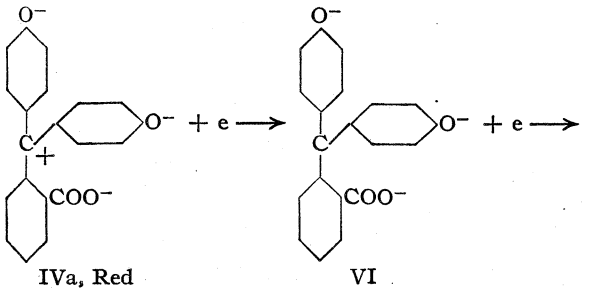
The diffusion current corresponds to a transfer of two electrons as shown in the experimental part. It also has been shown that phenolphthalin does not yield a reduction wave at the dropping electrode.

The reduction of form III can be represented by a similar equation as that of form II. The reduction of the red form IV, however, occurs in two steps. The first wave could correspond to the formation of the trivalent anion of phenolphthalin. As shown in the experimental part, the first wave of the red form is identical with the wave of form III. It does not seem plausible that the quinone form would be reduced at the same potentials as form III. However, it is peculiar that the half wave potential of form III varies with *p*H, whereas the half wave potentials of both waves of form IV appear to be independent of *p*H (Table II). Accepting the dipolar structure[9] of forms III and IV the coincidence of the reduction wave of III and of the first wave of IV becomes more reasonable.

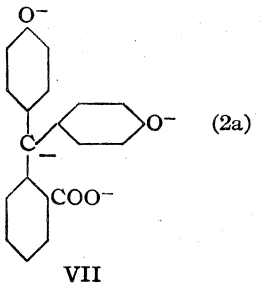
Although the final reduction product is VIIa, form VII is formed intermediately at the surface of the electrode. The reduction of the colorless form III is found at higher hydrogen ion concentrations

(8) I. M. Kolthoff and C. Rosenblum, "Acid-Base Indicators," The Macmillan Company, New York, N. Y., 1937, p. 223.

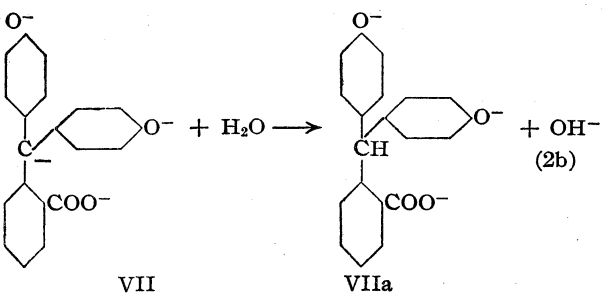
(9) H. Lund, *J. Chem. Soc.*, 1844 (1930).



IVa, Red VI

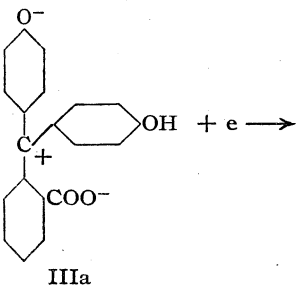


VII

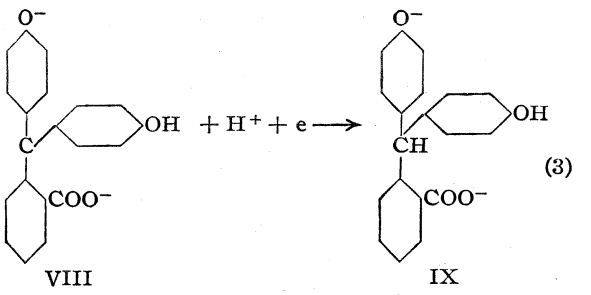


VII VIIa

than that of form IV. The reduction of III can be represented by



IIIa



VIII IX

The first steps in the reductions of IVa and IIIa are comparable, but the form corresponding to VII is not formed in the reduction of VIII or if it would be formed it would react instantaneously with hy-

drogen ions with formation of IX. The potential of reduction of VIII to IX becomes dependent upon the hydrogen ion concentration, and the second wave coincides with the first one.

2. From Table II it is seen that up to 30% ethanol the diffusion currents of phenolphthalein (*p*H 7) and benzoquinone are affected in the same way by the alcohol. This is mainly a viscosity effect. When the ethanol concentration becomes greater than 30% the diffusion current of phenolphthalein decreases much more than that of the quinone and in 70% ethanol the diffusion current of phenolphthalein becomes almost vanishingly small. This can be explained if it is assumed that form II, but not form I, is reducible. In the transformation of I into II the concentration of water becomes rate-determining. The experimental results indicate that at concentrations of less than 25% ethanol the rate of formation of II is so large that it is reformed from I immediately at the surface of the electrode when it is reduced. Therefore, at ethanol concentrations of 25% or less the apparent diffusion current corresponds to the true diffusion current of phenolphthalein. When the alcohol concentration increases the concentration of water decreases and the rate of transformation of I into II decreases. The apparent diffusion current now decreases and becomes partly diffusion and partly rate controlled. At alcohol concentrations greater than 50% the current becomes so small that it is practically entirely rate controlled. Under these circumstances the current should become independent of the height of the mercury in the reservoir.[10]

At the higher alcohol concentrations the polarographic behavior of phenolphthalein becomes comparable to that of some reducing sugars, like glucose and lactose in aqueous medium. As shown by Wiesner[11] the small "apparent" diffusion currents of these sugars are determined entirely by

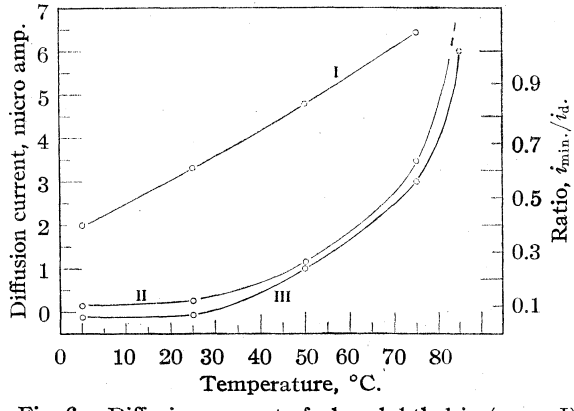


Fig. 6.—Diffusion current of phenolphthalein (curve I), minimum current (curve II) and ratio of minimum current to diffusion current (curve III) *versus* temperature.

(10) Comp. K. Wiesner, *Z. Elektrochem.*, **49**, 164 (1943); R. Brdicka and K. Wiesner, *Coll. Czechoslov. Chem. Commun.*, **12**, 138 (1947).

(11) K. Wiesner, *ibid.*, **12**, 64 (1947).

the rate of transformation of the non-reducible form of the sugars into the reducible form.

3. In 25% ethanol and in the presence of a phosphate buffer (*p*H 7) the diffusion current varies with the temperature in a normal way (see Fig. 6). From the slope of curve I in Fig. 6 it is calculated that the diffusion current increases by about 1.8% per one degree increase of temperature. This value is of the same order of magnitude as that of normal diffusion currents.[12] However, the effect of temperature on the minimum value of the current is quite different. Curve III in Fig. 6 gives the change of the ratio of $i_{min.}/i_d$ with the temperature. At temperatures between 0 and 30° i_d and $i_{min.}$ vary in about the same way, but at temperatures higher than 30° $i_{min.}$ increases much more than i_d.

First, we tried to explain the occurrence of the unprecedented minimum (see Fig. 1) by assuming that phenolphthalein is reduced only in the adsorbed state and that at potentials corresponding to that of the minimum current the phenolphthalein is desorbed. However, several phenomena are contrary to this interpretation. In general, the adsorption at the surface of the mercury decreases with increasing temperature. If phenolphthalein were reduced only in the adsorbed state the minimum current should decrease rather than increase with increasing temperature. The opposite is found. Another fact of significance is that at a *p*H of 9 a normal polarogram is observed. At this *p*H the second wave is negligibly small, and the (first) diffusion current retains its normal value until the wave of the supporting electrolyte occurs. At a *p*H of 9 little of the non-reducible form I is present, most of the phenolphthalein being in form III, and there is no indication that this form is being reduced in the adsorbed state. If it were reduced in the adsorbed state a desorption would be expected at more negative potentials, before the sodium wave (of the supporting electrolyte) appears. This would be accompanied by a decrease of the diffusion current, which has not been observed.

We attribute the occurrence of the minimum to a decreased rate of transformation of I into II *at the surface* of the electrode. The very large effect of the temperature upon $i_{min.}$ strongly suggests that we are dealing with a process which is rate controlled. If our interpretation is correct the rate of tranformation of I into II at the interface mercury–water should decrease with increasing potential. This is not strange, if it is realized that the structure of the double layer at the interface mercury–water varies in a complicated manner with the potential, and the type and concentration of electrolyte in the solution. Quite generally, strongly adsorbable organic compounds are being completely desorbed in the presence of electrolyte at negative potentials of the order of −1.5

(12) Comp. I. M. Kolthoff and J. J. Lingane, *Chem. Rev.*, **24**, 37 (1939).

volt. Similarly the orientation of water molecules at and in the interface changes with the potential of the mercury, thus affecting the rate of hydration of I. When the electrolyte content in the solution is small, as was the case in our experiment with a very dilute pyridine–pyridinium hydrochloride buffer, the structure of the double layer, especially at more negative potentials, is quite different from that in 0.1 *M* potassium chloride solution, which was the normal salt content in our experiments. In the very dilute buffer no dip in the current–voltage curve and no minimum were observed. Although the exact mechanism of the decreasing rate of the reaction I + $H_2O \rightarrow$ II with increasing negative potential needs further study, there is no doubt that the occurrence of the minimum, as in Fig. 1 (curve III), must be attributed to a decreasing rate of the above reaction at the electrode surface with increasing negative potential.

Summary

1. The polarographic behavior of phenolpthalein has been investigated under widely varying conditions. In 25% ethanol phenolphthalein gives a one-step reduction wave in a *p*H range between 0 and 9. In this range the half-wave potential changes according to $\pi^1/_2$ (*vs.* S.C.E.) = 0.54 − 0.046 *p*H. The red form of phenolphthalein yields two waves of equal height, each wave giving a well-defined diffusion current. The sum of the two diffusion currents is equal to that of the single wave observed at lower *p*H. The polarographic reduction of phenolphthalein to phenolphthalin is accompanied by a transfer of two electrons.

2. In the presence of a phosphate buffer of a *p*H of 7 the diffusion current decreases abnormally when the ethanol concentration is increased. In 60% ethanol the "apparent" diffusion current becomes extremely small at 25°. It is concluded that the lactone form of phenolphthalein is not reduced, but its hydrated form is. At alcohol concentrations of 25% or less the rate of hydration at the surface of the electrode is so large that a normal diffusion current is observed. At high alcohol concentrations the "apparent diffusion current" becomes entirely rate- and not diffusion-controlled. Experiments carried out at various temperatures substantiate this interpretation.

3. In 25% ethanol in the presence of a buffer of *p*H 7 the diffusion current remains constant in a potential range between −1.0 and −1.2 volt; it decreases slightly between −1.2 and −1.4 volt and then drops suddenly to attain a small minimum value at a potential of about −1.6 volt. Experimental evidence has been given substantiating the interpretation that the occurrence of the minimum is to be attributed to a decreased rate of transformation of the lactone form into the reducible hydrated form at the surface of the dropping electrode.

MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 10, 1947

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Polarographic Behavior of Nitrosophenylhydroxylamine[1]

BY I. M. KOLTHOFF AND A. LIBERTI[2]

The ammonium salt of nitrosophenylhydroxylamine, called cupferron, is a well-known analytical reagent, which precipitates a great number of metal ions in acid medium. In connection with a study of the use of cupferron as a reagent in amperometric titrations, the polarographic behavior of nitrosophenylhydroxylamine has been investigated over a wide range of *p*H.

Experimental

Materials Used: Cupferron.—Eastman Kodak Co. and G. F. Smith Chemical Co. products were recrystallized from ethanol. The crystals had the appearance of silver-white leaflets (m. p. 163–164°). The solid product was stored in a dark bottle over solid ammonium carbonate to prevent decomposition. A stock solution (0.02 *M*) in water was found to be stable for more than two weeks when kept in the dark in a cool place. The solution is not stable in acid medium, as the phenylnitrosohydroxylamine decomposes. The rate of decomposition increases with decreasing *p*H. When polarograms were determined in acid medium at a *p*H smaller than 3, a measured volume of an air-free stock solution of cupferron was added to a suitable volume of air-free buffer solution in the cell and the current-voltage curve was determined soon after mixing. In some experiments the lithium salt of nitrosophenylhydroxylamine was used, which was prepared from cupferron and lithium hydroxide.

Buffer Solutions.—In the *p*H range between 1 and 5.6 Clark and Lubs buffers served to adjust the *p*H. In the range between *p*H 3 and 10 the universal buffers of Britton and Robinson[3] were used. The buffer mixtures were prepared by addition of lithium hydroxide to a solution which was 0.04 *M* in phosphoric, 0.04 *M* in acetic and 0.04 *M* in boric acids. In addition, Clark and Lubs buffers, prepared from boric acid and lithium hydroxide and lithium chloride, were used in the *p*H range between 8 and 10.

Tetramethylammonium Hydroxide Solution.—An Eastman Kodak Co. product of the bromide of this base was purified by repeated recrystallizations from ethanol–water mixtures. A stock solution of the hydroxide was prepared from the purified bromide with silver hydroxide as described by Peracchio and Meloche.[4] Buffer solutions prepared from tetramethylammonium hydroxide and phos-

(1) From a Master's thesis (1947) of A. Liberti, submitted to the Graduate School of the University of Minnesota.

(2) Present address: Instituto Chimico, Università di Roma, Italy.

(3) H. T. S. Britton and R. A. Robinson, *J. Chem. Soc.*, 1456 (1931).

(4) E. S. Peracchio and V. W. Meloche, THIS JOURNAL, **60**, 1770 (1938).

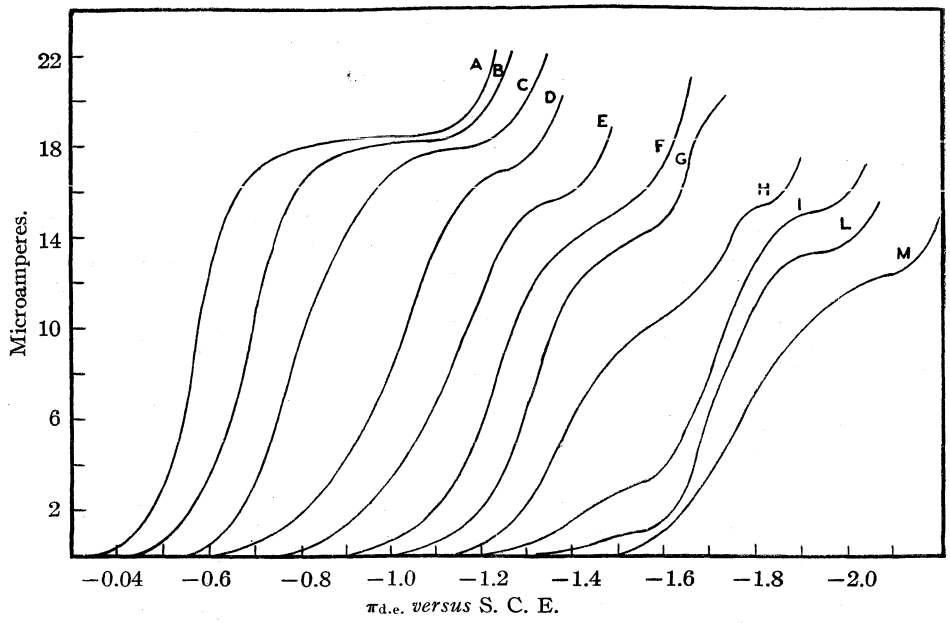


Fig. 1.—Polarograms of cupferron (8×10^{-4} *M*) in buffer solutions at the following *p*H values: A 1.2, B 2.1, C 3.1, D 4.4, E 5.2, F 5.9, G 6.6, H 7.2, I 7.9, L 8.8, M 12.5.

phoric acid or boric acid were prepared. Polarograms obtained with these buffers gave poorly reproducible and irregular currents near the potentials at which the cupferron waves appeared. For this reason these buffers could not be used in the present polarographic work. On the other hand, well defined waves were obtained in tetramethylammonium hydroxide solutions.

Gelatin Solution.—A 0.1% gelatin solution in water was stored under a layer of toluene to prevent decomposition. When used in a concentration of the order of 0.01%, gelatin was found to eliminate maxima in the polarograms at a *p*H smaller than 3. At a *p*H greater than 3 no maxima were observed even in the absence of gelatin.

Determination of Polarograms.—Both the manual polarograph[5] and the automatic Heyrovsky instrument, Model XI, have been used in this work. In all the experiments an outside saturated calomel electrode (S.C.E.) served as the reference electrode. All the potentials refer to the S.C.E.

Under the experimental conditions the capillary had a drop time *t* of 3.00 seconds at zero applied e.m.f. and the mass of mercury *m* flowing out per second was 2.37 mg. The values of *m* and *t* were determined in the potential range between 0 and 2 volts. The values of the diffusion current could thus be referred to the same value of $m^{2/3}t^{1/6}$. The reported values of diffusion or limiting currents are corrected for the residual current and refer to a $m^{2/3}t^{1/6}$ value at a potential of 0.5 volt.

The electrolysis cell was provided at the bottom with an inlet tube for purified nitrogen. Another inlet tube through the stopper of the cell served for the introduction of nitrogen to the gas phase above the solution during the measurements. All the experiments were carried out in a thermostat at 25.0 ± 0.1°.

Experimental Results

As an illustration some representative polarograms in the *p*H range between 1 and 12.5 are given in Fig. 1. Without correction for the residual current many of the limiting currents appear poorly defined. For this reason the polarograms represented in Fig. 1 give the currents found with the manual apparatus, corrected for the residual current and referred to a constant value of $m^{2/3}t^{1/6}$. Since at a *p*H between 1 and 3 the decomposition of phenylnitrosohydroxylamine is rapid, 24 ml. of the supporting buffer solution was made air-free in the cell, 1 ml. of standard air-free cupferron solution was added and the current-voltage curve determined immediately after mixing. The determinations were well reproducible.

Only one wave was found in acid medium, up to a *p*H of 6.6. The apparent diffusion or limiting current decreased with increasing *p*H, the change becoming very pronounced when the *p*H became greater than 6. At *p*H values between 3 and 6 the limiting current was found to be proportional to the concentration of cupferron added to the buffers. This is illustrated in Fig. 2.

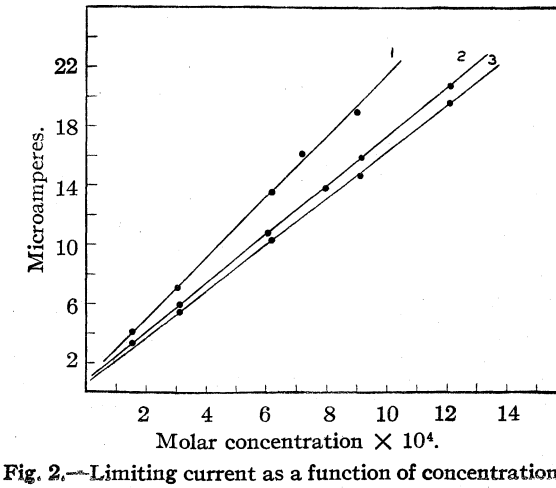


Fig. 2.—Limiting current as a function of concentration at: 1, *p*H 2.9; 2, *p*H 5.2; 3, *p*H, 6.6.

(5) J. J. Lingane and I. M. Kolthoff, THIS JOURNAL, 61, 825 (1939).

A plot of the values of log $i/(i_d - i)$ *versus* the potential at a *p*H of 1 yields a straight line with a slope of 182 mv. This indicates that the reduction is irreversible; as it seems impossible that a reversible reduction would involve three electrons.

In the *p*H range between 7 and 9 two waves were observed. The first wave was poorly defined (see Fig. 1 and 3); its limiting value was estimated by the tangent method (see Fig. 3). The second wave appeared to attain a constant value at a *p*H greater than 8.

Only one wave due to reduction of the cupferronate was observed at a *p*H greater than 9, its height remaining unchanged when the *p*H was raised to 12.5.

Some of the experimental data are summarized in Table I.

TABLE I

WAVE HEIGHTS AND HALF WAVE POTENTIALS IN 8×10^{-4} *M* SOLUTIONS OF CUPFERRON AT VARYING *p*H AT 25°

*p*H	Supporting electrolyte	Height first wave in μA	$-(\pi_{1/2})_1$	Height second wave in μA	$-(\pi_{1/2})_2$
1.1	Clark and Lubs; HCl–KCl	18.5	0.672		
1.4	Clark and Lubs; HCl–KCl	18.4	.71		
2.1	Clark and Lubs; Phthalate	18.3	.785		
3.0	Clark and Lubs; Phthalate	17.8	.89		
4.4	Clark and Lubs; Phthalate	16.6	1.10		
5.2	Clark and Lubs; Phthalate	15.5	1.22		
5.9	Britton and Robinson	14.6	1.32		
6.6	Britton and Robinson	13.2	1.405		
7.2	Britton and Robinson	9.0	1.46	6	1.79
7.9	Britton and Robinson	3.8	1.53	11.2	1.81
8.3	Britton and Robinson	2.8	1.56	12.2	1.81
8.8	Britton and Robinson	1.0	1.57	12.2	1.82
10.0	Boric acid–lithium hydroxide	..	..	12.2	1.85
12.5	Tetramethylammonium hydroxide	..	..	12.2	1.86

The half wave potential of the first wave was found to depend greatly upon the *p*H. The plot of the half wave potential against the *p*H yields a straight line with a slope of 128 mv. per *p*H unit. Thus, the half wave potential $-\pi_{1/2}$ is found to vary with the *p*H according to $-\pi_{1/2} = -\pi^0_{1/2} - 0.128$ *p*H in which $\pi^0_{1/2} = -0.58$ v. (*versus* the S.C.E.) at 25°.

This relation expresses that the half wave potential varies with the square of the hydrogen ion concentration, which is a very unusual relation. The half wave potential of the second wave appears to be practically independent of the *p*H. Its value was found to be −1.80 v.

For reasons given in the discussion section the height of the first and of the second waves at a *p*H of 8.25 were determined as a function of the height, *h*, of the mercury in the reservoir. In these experiments the lithium salt of nitrosophenylhydroxylamine was used instead of cupferron in order to eliminate the ammonium wave. The experiments were carried out in boric acid–lithium hydroxide buffers. The measured values of the limiting currents were corrected again for the residual current and referred to a constant value of $m^{2/3}t^{1/6}$. The results are given in Table II.

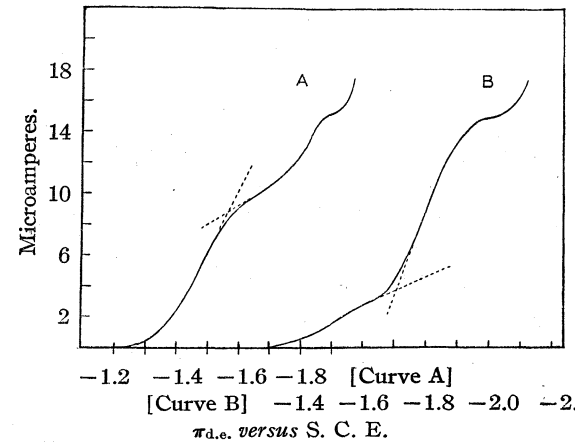


Fig. 3.—Polarograms of 8×10^{-4} *M* cupferron at *p*H 7.2 (curve A) and *p*H 7.9 (curve B).

TABLE II

VALUES OF THE FIRST (i_1) AND THE SECOND (i_2) LIMITING CURRENTS AT *p*H 8.25 AS FUNCTION OF THE HEIGHT OF MERCURY IN THE RESERVOIR

Height *h* of mercury in reservoir in cm.	Drop time *t* in seconds	i_1	i_2	$i_2/h^{1/2}$
94	2.4	2.80	13.55	1.40
75	3.0	2.80	12.20	1.41
56	4.2	2.76	10.64	1.42
39	6.3	2.70	8.60	1.37

It is seen that the height of the first wave is not affected by the height of the mercury in the reservoir, while that of the second wave is proportional to the square root of the height of the mercury. Therefore, the height of the second wave is diffusion controlled, like that of an ordinary diffusion current.

Discussion

(1) From the fact that in the *p*H range between 7 and 9 two reduction waves are observed it is evident that the acid form of nitrosophenylhydroxylamine and its anion are reduced at different potentials. However, in the acid range at a *p*H greater than 3 the height of the wave of the acid form is much greater than corresponds to the concentration of the undissociated acid in the bulk of the solution. Only at a *p*H smaller than 2 does the limiting current correspond to the true diffusion current of the undissociated acid. From the work of Hantzsch[6] and of Pyatnitokii[7] it is estimated that the ionization constant K_a of phenylnitrosohydroxylamine at 25° is equal to 5.3×10^{-5}. Assuming that the limiting value of the current of 18.5 μ in 8×10^{-4} *M* cupferron solution at *p*H 1 is the true diffusion current of the

(6) A. Hantzsch, *Ber.*, **35**, 265 (1902).

(7) V. Pyatnitokii, *Zhur. Anal. Khim.*, **1**, 135 (1946); *Chem. Abs.*, **41**, 725 (1947).

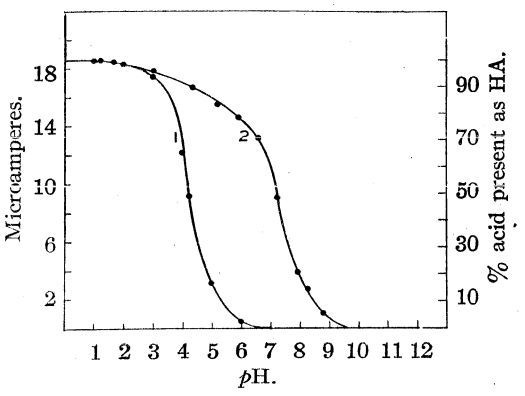


Fig. 4.—Curve 1, dissociation curve of nitrosophenylhydroxylamine; curve 2, change of the limiting current of the acid form of nitrosophenylhydroxylamine.

acid, the values of i_d at higher pH can be calculated. Plotting the calculated values against pH yields curve 1 in Fig. 4. Curve 2 represents the limiting currents due to the acid form observed at varying pH. It is seen that the mid-way point is shifted 3 units to a higher pH. The reason for this shift is that upon reduction of the free acid at the surface of the electrode, more acid is formed as a result of the association of hydrogen ions with the anions A^- of the acid

$$H^+ + A^- \longrightarrow HA \qquad (1)$$

From Fig. 4 it is seen that at a pH greater than 6 the current due to the equilibrium concentration of HA is negligibly small and that the limiting current is determined entirely by the rate of formation of HA at the surface of the electrode. This current may be called the kinetic current. The polarographic behavior of nitrosophenylhydroxylamine in acid medium is very similar to that of pyruvic acid and of phenylglyoxalic acid discussed by Brdička and Wiesner.[8] These authors derived the following expression for the limiting value of the kinetic current $(i_k)_l$

$$(i_k)_l = \frac{\mu k[H^+]acK_a}{(K_a + [H^+])(\mu k[H^+] + a\cdot 10^3/nFyq)} \qquad (2)$$

in which k is the rate constant of reaction (1), μ is the thickness of the layer around the electrode where the association takes place, a is the constant in the Ilkovič equation $i_d = ac$, c is the total concentration (dissociated plus undissociated) of the acid with ionization constant K_a, n is the number of electrons involved in the reduction, Fy the faraday, and q the average surface of mercury per drop.

When the concentration of HA in the bulk of the solution is not negligibly small the total current i_t due to the reduction of the acid form becomes

$$i_t = (i_d)_{HA} + i_k \qquad (3)$$

in which $(i_d)_{HA}$ is the diffusion current of the acid corresponding to the reduction of the undissociated acid present in the bulk of the solution. It can be shown[8] that when i_t is equal to one half of the maximum value of $(i_d)_{HA}$ (in our case found at pH of 1)

$$\mu k = \frac{K_a - [H^+]}{(K_a + [H^+])[H^+]} \times \frac{a\cdot 10^3}{nFyq} \qquad (4)$$

Under our experimental conditions, a had a value of 0.0230 and q of 0.0189. Using these figures in equation (3) a value of μk of 3.34×10^4 is found. Brdička and Wiesner estimate that μ is of the order of 10^{-7} cm. Using this value, a rate constant k (equation 1) of the order of 3.3×10^{11} is found. This value is only an approximation, because equation (2) has been derived on the basis of some simplifying assumptions. A highly mathematical and more exact treatment is given by Koutecky and Brdička.[9]

Using the above value of μk it is possible to calculate the limiting kinetic currents at various pH. The values thus obtained are plotted in Fig. 5 and are compared with the experimental values found by subtracting the calculated values of $(i_d)_{HA}$ from i_t (equation 3). Considering that equation (2) is only approximately valid the agreement between the calculated and experimental values is satisfactory.

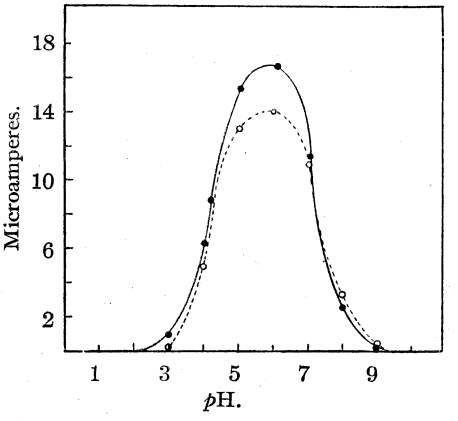


Fig. 5.—Change of the kinetic current at varying pH. The dotted curve shows the experimental values and the drawn curve the calculated values.

The correctness of the interpretation of the polarograms in acid medium is supported by the effect of the height of mercury in the reservoir upon the first and the second waves at a pH of 8.25. At this pH $(i_d)_{HA}$ is equal to zero and the height of the first wave is equal to $(i_k)_l$. Moreover, at this pH, $a\cdot 10^3/nFyq$ is much greater than $\mu k\,[H^+]$. Hence, at this pH

$$i_1 = (i_k)_l = \frac{\mu k[H^+]acnFyq}{(K_a + [H^+])\,a\cdot 10^3} \qquad (5)$$

It is seen that a cancels in equation (5) and that the height of the first wave becomes proportional

(8) R. Brdička and K. Wiesner, *Coll. Czechoslov. Chem. Commun.*, **12**, 138 (1947).

(9) J. Koutecky and R. Brdička, *Coll. Czechoslov. Chem. Commun.*, **12**, 337 (1947).

to q. Since the surface of the mercury is proportional to $m^{2/3}t^{2/3}$ the height of the mercury in the reservoir should not have any effect on i_1 at a pH of 8.25. Indeed, it is seen from Table II that the pressure of the mercury does not affect i_1. On the other hand i_2 is diffusion controlled; therefore, i_2 varies with the square root of the height of the mercury in the reservoir.

(2) It has been mentioned that the limiting current measured at a pH of 1 corresponds to the true diffusion current of the nitrosophenylhydroxylamine. Assuming that the diffusion coefficient of this acid is equal to that of the benzoate ion, it is possible to calculate the number of electrons n involved in the reduction. From the Ilkovič equation it is found that

$$n = \frac{i_d}{0.605\, cD^{1/2}m^{2/3}t^{1/6}}$$

In 8×10^{-4} M cupferron solution at a pH of 1, i_d was found equal to 18.5 microamperes, while $m^{2/3}t^{1/6}$ was 2.14. Taking D equal to 8.81×10^{-6} yields a value of 6.0 for n. Hence six electrons are involved in the reduction of nitrosophenylhydroxylamine.

On the other hand in alkaline medium where we are dealing with the reduction of the anion the diffusion current was found to be equal to two thirds of that at a pH of 1. Hence the reduction of the anion involves four electrons.

Various structures have been suggested for nitrosophenylhydroxylamine. Angeli[10] proposed the structure $C_6H_5-N(=O)-NOH$, while Hantzsch[11] prefers $C_6H_5-N(-OH)-NO$. Diehl[12] suggested that the two forms are in tautomeric equilibrium. Considering the relatively strong acid character of nitrosophenylhydroxylamine G. Fieser and M. Fieser[13] assume that there is an equilibrium between the nitrosohydroxy form, a, and the more strongly acid amine oxide form, b

$$C_6H_5-N(-OH)-N=O \rightleftharpoons C_6H_5-N^+(-O^-)=NOH$$

a b

The reduction of nitro- and nitroso- compounds occurs in steps. In acid medium, in which the reduction at the dropping electrode involves six electrons the final reaction product must be the phenylhydrazine

$$C_6H_5N(NO)-OH + 2H^+ + 2e \longrightarrow C_6H_5N(NHOH)-OH$$

$$+ 2H^+ + 2e \longrightarrow C_6H_5N(NH_2)-OH$$

$$+ 2H^+ + 2e \longrightarrow C_6H_5N(NH_2)-H$$

In alkaline medium the reduction involves four electrons and the anion $C_6H_5N(N=O)-O^-$ (Hantzsch) or $C_6H_5-N^+(O^-)=NO^-$ (Fieser and Fieser) apparently is reduced to $C_6H_5-N(NH_2)-O^-$.

(10) A. Angeli, *Gazz. chim. ital.*, **60**, 352 (1931).
(11) A. Hantzsch, *Ber.*, **64**, 695 (1931).
(12) H. Diehl, *Chem. Rev.*, **21**, 751 (1937).
(13) G. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath Co., Boston, 1944.

Summary

1. Nitrosophenylhydroxylamine solutions at a pH of 1 yield a diffusion current corresponding to a reduction which involves 6 electrons. At a pH greater than 9 the anion of the acid gives a diffusion current corresponding to an electron transfer of 4. The half wave potential of the acid wave varied with the pH: $\pi_{1/2} = -0.58 - 0.128$ pH *vs.* S.C.E.; the half wave potential of the alkaline wave is -1.80 v. and does not vary with the pH.

2. Only one wave is found in acid medium up to a pH of about 6.6, two waves are found in the pH range between 6.6 and 9.0; at higher pH only one wave is found.

3. In the acid range at a pH greater than 3 the height of the wave is much greater than corresponds to the concentration of the undissociated acid in the bulk of the solution. This is explained by the fact that the current is partly controlled by the rate of formation of acid at the surface of the electrode: $H^+ + A^- \rightarrow HA$. Using Brdička and Wiesner's[8] formulation a rate constant of the order of 3.3×10^{11} is calculated. When the kinetic current is very small with regard to the diffusion current the former becomes independent of the height of the mercury in the reservoir. This is found to be true at a pH of 8.25, where the height of the first wave (kinetic current) is independent of the height of mercury in the reservoir, while the second wave is diffusion controlled.

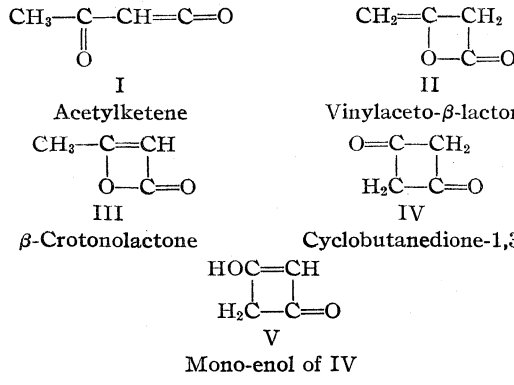
MINNEAPOLIS, MINNESOTA RECEIVED DECEMBER 12, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Diketene: Infrared Spectrum and Structure

BY FOIL A. MILLER* AND STANLEY D. KOCH, JR.†

The structure of the ketene dimer, $(CH_2{=}C{=}O)_2$, has been in question ever since its discovery in 1908. Five possible forms have been seriously considered at various times:



I Acetylketene

II Vinylaceto-β-lactone

III β-Crotonolactone

IV Cyclobutanedione-1,3

V Mono-enol of IV

The present status of the problem has been well summarized by Boese[1] and by Hanford and Sauer.[2] Chemical reactions appear to have been of little help in elucidating the structure, for some indicate one form and some another. It is very difficult to evaluate such evidence critically because of the considerable possibility of rearrangements. Since the problem is to establish the structure of the ground electronic state of diketene, it seems undesirable to argue from evidence that involves also an unknown activated state. One is therefore inclined to discount such evidence and to rely on physical measurements made only on the ground state if possible. These, however, have also led to contradictions. The non-zero dipole moment[3,4] eliminates the possibility that the structure may be symmetrical form IV alone. The Raman spectrum has been obtained for the liquid,[5,6,7] and the infrared spectrum for both liquid and solutions.[8] The absence of any O-H stretching frequency eliminates V, and the many coincidences between the Raman and infrared spectra eliminate again the existence of form IV alone. A further decision between the remaining forms I, II, and III has not yet been made from the data. It is noteworthy that five strong bands are found in the double bond stretching region (1500–2000 cm.$^{-1}$), whereas each of the postulated forms would have only two fundamentals there. (Form I may be an exception, with only one band in this region. The ketene group in this molecule probably would give one band above this range and one below it.) The remaining three (or four) bands must then be explained either as combination tones, or as due to the presence of more than one form. The ultraviolet absorption maximum at 3130 A (ϵ = 2) would seem to favor III.[9] (This too involves an upper electronic state, however.) Electron diffraction studies are said to be compatible with II or III, incompatible with I and IV.[10] Unfortunately none of these data provide unambiguous proof for any one of the possible structures. Because of this it has been suggested several times[2,8] that there may be two (or more) forms in equilibrium.

It occurred to us that the existence of such an equilibrium, Form A $\rightleftarrows$ Form B, might possibly be demonstrated by measuring the infrared spectrum as a function of temperature. The van't Hoff equation, $d \ln K/dT = \Delta H/RT^2$, indicates that if ΔH is sufficiently large the equilibrium constant will change appreciably with temperature. The resulting alteration in the composition of the equilibrium mixture may then be evidenced in the infrared spectrum. Conversely, however, a spectrum which changes with temperature does not indicate the existence of an equilibrium unless other temperature effects are excluded. Two such effects come to mind immediately. (a) An irreversible chemical change. This possibility can be eliminated if the changes in the spectrum are found to be reversed when the sample is brought back to its original temperature. (b) Altered population of the energy levels in accordance with the Boltzmann factor. For a moderate rise in temperature the increased population of the higher vibrational levels will increase the intensity of difference bands, but should not appreciably affect the relative intensities of fundamentals. Hence a very few weak bands may become markedly intensified at higher temperatures, but they should be calculable as difference tones. The effect of increased temperature on the rotational fine structure is one of broadening and flattening the rotational branches. If the width of a vibration–rotation band of an asymmetric rotator is defined as the separation of points on the

* Present address: Mellon Institute of Industrial Research, Pittsburgh 13, Pa.

† Present address: Department of Chemistry, Cornell University, Ithaca, N. Y.

(1) Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).

(2) Hanford and Sauer, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1947, pp. 127 ff.

(3) Oesper and Smyth, THIS JOURNAL, **64**, 768 (1942).

(4) Hurdis and Smyth, *ibid.*, **65**, 89 (1943).

(5) Angus, Leckie, LeFevre, LeFevre and Wassermann, *J. Chem. Soc.*, 1751 (1935).

(6) Kohlrausch and Skrabal, *Proc. Indian Acad. Sci.*, **8A**, 424 (1938).

(7) Taufen and Murray, THIS JOURNAL, **67**, 754 (1945).

(8) Whiffen and Thompson, *J. Chem. Soc.*, 1005 (1946).

(9) Calvin, Magel and Hurd, THIS JOURNAL, **63**, 2174 (1941).

(10) Private communication from Bauer, Bregman and Wrightson to Hanford and Sauer, as reported in reference 2, p. 218, footnote. See also Abstracts of Papers, 109th meeting of American Chemical Society, April, 1946.

band envelope where the intensity has a given value, then the width of the band is proportional to the square root of the absolute temperature.[11] Thus in going from 30 to 180° the band width will increase by a factor of about 1.2. This should not be a confusing effect, as we shall be looking for more marked changes in the spectrum.

Experimental

Diketene was prepared by the dimerization of ketene according to the method of Williams and Krynitsky.[12,13] The spectrum was measured from 3 to 15 μ with a Model 12-B Perkin–Elmer infrared spectrometer equipped with rocksalt optics, a General Motors breaker-type amplifier, and a Brown recorder. A 5-cm. Pyrex cell was used for the vapor. The rocksalt windows were sealed on with glyptal resin, which was found to hold well at temperatures up to 180° if one heats or cools rather slowly to avoid cracking the seal. The cell was heated in a small oven consisting of a sheet metal cylinder closed with endplates of transite that were held together by four tie rods. A window was cut in each piece of transite and closed by clamping over it a polished rocksalt plate. A suitably insulated electrical heating element was wrapped around the metal cylinder. The cell was connected by glass tubing to an external sample reservoir immersed in a water bath. The connecting tube had a small U-type mercury manometer sealed to it so that pressures in the range 0–20 mm. could be read. The primary purpose of the manometer was to indicate any failure in the glyptal seals. The connecting tube and manometer were wrapped with a spiral of resistance wire and heated electrically to a temperature sufficiently high so that no condensation occurred in them. In this manner the reservoir was made the coolest part of the system. The pressure of the vapor was thus determined by the temperature of the liquid reservoir, whereas the temperature of the vapor in the beam was determined by that of the oven.

Spectra were measured at vapor temperatures of approximately 30, 60, 100, 140 and 180°. Experimental conditions for the various determinations were

No.	Temp. of reservoir, °C.	Temp. of cell, °C.
1	28	60
2	29	100 ± 2
3	34	141 ± 2
4	35	182 ± 1
5	< −50	183 ± 2
6	29	102 ± 3
7	28	31 ± 1
8	< −50	30

In runs 5 and 8 the vapor was condensed into the liquid reservoir by cooling with a Dry Ice-bath. These runs thus served as blanks to give the transmission through the empty cell, and to demonstrate that no deposit had formed on the windows. After completion of run 5 vapor was readmitted to the cell at 180°, the cell was slowly cooled to 100°, and the spectrum was remeasured at this temperature. The apparatus was then allowed to stand overnight to reach temperature equilibrium with the room, and run 7 was made with the vapor at 31°. The cell then stood overnight again while the sample reservoir was cooled with a Dry Ice-bath, and blank run 8 was made. It was necessary to wait this long because it was found during blank runs 5 and 8 that about 3 mm. of residual permanent gas was present in the system. This impeded the diffusion of vapor back into the reservoir. We believe that this gas was air which degassed from the system during heating, for it gave no infrared absorption.

Another experiment was performed for the purpose of locating very weak bands. In this case a dish of liquid diketene was placed within the smaller or source housing of the spectrometer. This provided a path length of 40 cm. at a vapor pressure of about 13 mm.

Finally, the spectra of solutions of diketene in carbon tetrachloride and carbon disulfide were obtained to get a comparison between our samples and those used by Whiffen and Thompson.

Results

In brief, the spectrum was found to change markedly with temperature, and these changes were reversed on cooling.

Table I summarizes our results at 30°, and gives for comparison the data reported by Whiffen and Thompson[8] for the pure liquid and for solutions. The agreement is reasonably satisfactory. We observed the same change in the relative intensities of certain bands in the 1700–1900 cm.$^{-1}$ region upon change of solvent that was noted by these authors. Our bands in the 3000 cm.$^{-1}$ region are accurate to only about ±15 cm.$^{-1}$ because of poor dispersion, but the spectrum was scanned to 3600 cm.$^{-1}$ to confirm the absence of hydroxyl groups in the vapor. It is noteworthy that the very intense band of ketene monomer at 2153 cm.$^{-1}$ is not present in any of our spectra at any temperature.

It is necessary to point out at this time that the intensities reported in this paper are only qualitatively correct for the following two reasons. First, our procedure was to record a radiation curve through an empty cell, and then to use this in calculating transmission for all the other determinations. (Run 8 was used for this purpose.) Many of the experimental conditions varied slightly from run to run—amplifier gain, energy output from the globar, atmospheric water vapor in the air path, and so on—so the runs are not strictly comparable. Secondly, the concentration of the vapor molecules in the beam was not quite the same at the various temperatures. Assuming an ideal gas, the concentration is proportional to P/T. We hoped to measure the pressure with the little manometer, and to adjust it by changing the temperature of the reservoir in such a manner as to keep P/T constant for the vapor. However, because of the permanent gas alluded to earlier, there was an error in all the pressure measurements. Since the vapor pressure was of the order of 15 mm., a 3 mm. error was relatively large. Hence the amount of sample in the beam was not the same for the various runs. For these two reasons it is evident that we will not be justified in comparing absolute intensities. Nevertheless a comparison of the relative intensities of two bands in one spectrum with the relative intensities of the same two bands in another spectrum will be meaningful. In this connection it should be remembered that the intensity of a band is to be measured by the area under the band envelope

(11) Badger and Zumwalt, *J. Chem. Phys.*, **6**, 711 (1938); see also Avery and Ellis, *ibid.*, **10**, 10 (1942).

(12) Williams and Krynitsky, "Organic Syntheses," Vol. 21, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 64.

(13) We are indebted to Mr. J. L. Anderson of the Organic Manufactures program of this Department for preparation of one of the two samples used.

TABLE I

THE INFRARED SPECTRUM OF DIKETENE

Whiffen and Thompson[8] (liq., soln.) Cm.$^{-1}$	I^a	This work (solution) Cm.$^{-1}$	I^a	This work (vapor, 30°) Cm.$^{-1}$	I^a
				796	
805	s	804	s	803	m
				811	
846	s	840	s	838	m
				879	
868	s	875	vs	887	vs
				893	
893	?	893	vw		
914	?	914	vw		
946	?				
957	m	958	vw		
986					
				1001	
1009	s	1006	vs	1013	s
1055	w				
1106	m	1095	w		
1130	m	1125	m	1130	w
				1209	[b]
1194	m	1199	w	1220	vw
1239	s	1238	s	1237	m
				1250	w
		1288	w	1292	w
1375	m	1367	m	1371	m
1393	m	1392	m		
1417	m	1411	m		
1685	s	1675	s	1676	s
1705	s	1709	vs	1720	vs
1745	s	1750	s	1776	m
1865	s	1869	s	1875	s
1895	s	1899	vs	1922	vs
		1960	vw	1970	vw
2010	w	2007	w	2012	w
2040	w				
2110	w	2112	vw	2124	w
2230	w				
2420	vw				
2480	vw				
2560	w				
2660	vw				
2710	w				
				2846	[b]
				2923	w
2970	m	2999	vw		
3010	m			3007	[b]
3082	w				
3370	w				
3620	w				

[a] vs = very strong, s = strong, m = medium, w = weak, vw = very weak. [b] Observed only for the 40 cm. absorbing path described in the text.

rather than by the position of maximum absorption, because a band will flatten and broaden as the temperature increases.

Figure 1 compares the two 100° spectra (runs 2 and 6). Although the two curves are not quantitatively identical, the general agreement is good except for the two bands at 1133 and 1838 cm.$^{-1}$. The first of these will be discussed later. The second is apparently due to some extraneous material such as the glyptal lacquer because it is most intense in the first run, weaker in the second, and missing in all the others. The two spectra are sufficiently similar to indicate that reversibility is established.

Figure 2 compares the spectrum at 60° with that at 180° (runs 1 and 4). Examination will reveal several significant differences. Consider first the region 1600–1820 cm.$^{-1}$, which contains the four bands at 1676, 1720, 1776, and 1797 cm.$^{-1}$. At 60°, 1720 is much the strongest, 1776 is very slightly more intense than 1676, and 1797 is completely missing. At 180° the intensity is in the order 1776 $\simeq$ 1720 > 1676, and 1797 has appeared. Figure 3B shows that these changes occur gradually as the temperature is increased. A comparison of 1676 and 1776, for example, shows that the intensity of the 1776 cm.$^{-1}$ band changes from less than that of 1676 at 30° to much more at 180°. The changes are reversible, as indicated by the rerun at 100°, and by the fact that the 30° run (which was made last of all) fits the general trend. This group of four bands thus shows a very definite and reversible change with temperature. The 1797 cm.$^{-1}$ band cannot be explained as any reasonable difference tone.

Similar changes are found in the 1100–1300 cm.$^{-1}$ region, as shown in Fig. 3A. The band at 1133 cm.$^{-1}$ is most intense in the first spectrum measured (60°), and is completely gone at 180°. On cooling back to 100° it reappears, but not as intensely as in the first 100° run. On further cooling to 30° it is still present, but with rather low intensity. Hence this band seems to indicate an irreversible change. Since there is little other evidence for irreversibility in the spectrum, one might attribute the band to some impurity. It is reported by Whiffen and Thompson, but by none of the Raman investigators. On the other hand it does reappear, even though weakly, at the lower temperatures. We have no explanation for the behavior. The band at about 1185 cm.$^{-1}$ comes in as temperature increases and goes out again on cooling. It may be the difference tones 1683 − 504(R) = 1179 and 1722 − 531(R) = 1181 (R = Raman band). On the other hand, the 1237-1250 doublet shows the converse behavior, disappearing as the temperature increases. Another band at 1292 cm.$^{-1}$ is present only at the lower temperatures. This band is not reported in any earlier work, and so it may be due to an impurity. Other characteristic changes in the spectrum are noticeable too. For example, as the temperature increases, the intensity of the 1919 cm.$^{-1}$ band relative to that of the 1676–1720–1776 group becomes markedly less. This change is also reversible with temperature.

There can be no doubt, then, that there are real changes in the spectrum as the temperature is increased. We feel that they cannot be due to

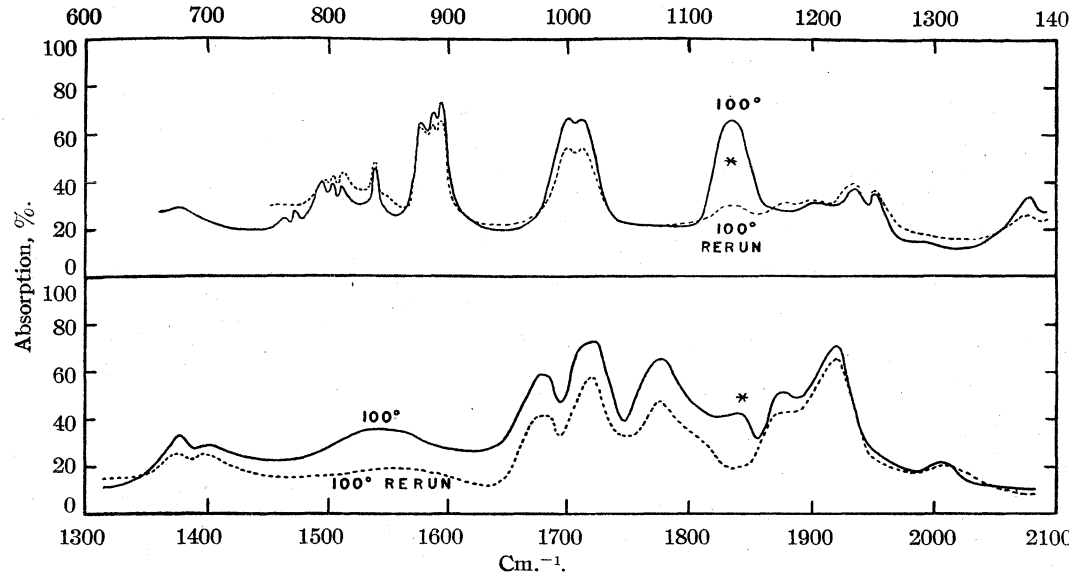


Fig. 1.—Infrared spectrum of diketene vapor at 100° (runs 2 and 6). Bands marked with an asterisk are of questionable origin. See discussion in text.

an irreversible chemical reaction because the original features of the spectrum are recovered on cooling. (The 1133 cm.$^{-1}$ band is an exception to this.) Also the changes are much too marked to be attributed entirely to changes in the population of the vibrational and rotational levels. Hence we feel that the results indicate the existence of an equilibrium between two forms of diketene which co-exist at room temperature.

Discussion

If one accepts the existence of such an equilibrium, it becomes much easier to understand the anomalous behavior of diketene which has been so puzzling heretofore. For example, one chemical reaction may proceed through one form, and another reaction through the other form. It is also now reasonable to find five strong bands in the double bond stretching region. Four (or three) fundamentals are to be expected, leaving only one (or two) to be explained as a combination tone.

The question as to which forms comprise the equilibrium mixture now presents itself. The spectroscopic evidence has been thoroughly discussed by Whiffen and Thompson.[8] We feel that

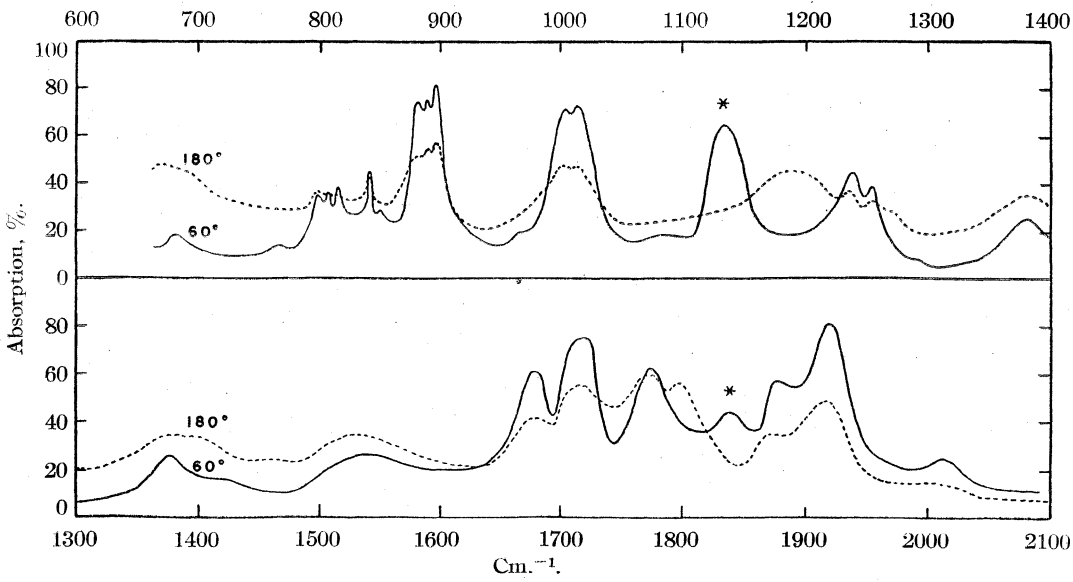


Fig. 2.—Infrared spectrum of diketene vapor at 60° and 180° (runs 1 and 4). Bands marked with an asterisk are of questionable origin. See discussion in text.

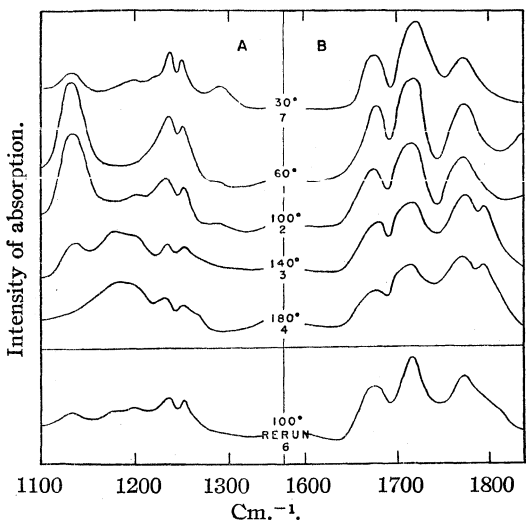


Fig. 3.—Detailed comparison of selected bands at the various temperatures. The curves have been displaced vertically.

their reason for eliminating the acetylketene structure (I)—the lack of a ketene group band near 2150 cm.$^{-1}$—is very compelling. It is our opinion that if as much as 2–4% of the material were in Form I, a band would have been observed in the region 2100–2200 cm.$^{-1}$. This elimination of Form I receives further support from the electron diffraction results cited earlier.[10] Forms II and III seem to be adequate to explain all the observations on diketene—chemical reactions, electron diffraction, ultraviolet absorption, vibrational spectrum, dipole moment. There remains the possibility that Form IV (cyclobutanedione-1,3) may be one of the components of the mixture. It has been amply proved that this structure alone cannot represent diketene, but it is not so easy to prove that it is not present in the equilibrium mixture. However, if there are only two components, it seems probable that they would be II and III rather than either one of these with IV. The conversion between II and III is accomplished by transfer of a proton and the shift of a double bond. Changes of this type are fairly common. On the other hand the conversion of IV into either II or III involves breaking and reforming the four-membered ring, and one would expect the activation energy to be higher for this process than for the former one. Some chemical evidence can also be adduced to support the elimination of IV. It has been shown that diketene does not react with sodium metal, with acetyl chloride, nor with phenyl isocyanate.[14] These reagents are sensitive to the presence of hydroxyl groups, and so it is apparent that diketene contains neither hydroxyl groups nor a potential enolic structure. Judging by analogy with other compounds, Form IV would be expected to enolize sufficiently to show some reaction with these reagents. The fact that no such reaction has been detected indicates that Form IV is not present. This argument is not by itself convincing, because of its speculative nature, but it does add some support to the conclusion reached above.

To summarize, then, it seems that diketene is probably an equilibrium mixture of Forms II and III (vinylaceto-β-lactone and β-crotonolactone).

We have been unable to decide which form is favored by increasing the temperature. One can say, however, that certain of the vibrational bands belong to the high temperature form and certain others to the low temperature form. One thus has an experimental method for following the separation of the two forms.

Summary

1. The infrared spectrum of diketene vapor has been measured at five temperatures ranging from 30 to 180°.

2. The spectrum changes with temperature in such a manner as to indicate an equilibrium mixture of two (or more) kinds of molecules.

3. The equilibrium is probably between two of the three structures: vinylaceto-β-lactone, β-crotonolactone, and cyclobutanedione-1,3. The first two seem most likely; they are capable of accounting for all the experimental observations on diketene.

URBANA, ILLINOIS RECEIVED JANUARY 2, 1948

(14) Chick and Wilsmore, *J. Chem. Soc.*, **97**, 1981 (1910); Hurd and Williams, THIS JOURNAL, **58**, 964 (1936).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

o-Methoxy-, p-Benzyl-, o-Fluoro-, and o-Cyano-styrenes. Further Examples of the Disproportionation of Phenylmethylcarbinols to Ethylbenzenes[1]

BY C. S. MARVEL AND D. W. HEIN

In connection with the study of a variety of substituted styrenes as substitutes for styrene in GR-S, the syntheses of *o*-methoxy-, *p*-benzyl-, *o*-fluoro-, and *o*-cyano-styrenes have been accomplished by routes not previously described.

o-Methoxystyrene

o-Methoxystyrene has been prepared by a number of methods[2] which need not be enumerated. We first applied the hot tube cracking process of Mowry, Renoll and Huber[3] to 1-(*o*-methoxyphenyl)-ethanol which was prepared both from *o*-methoxybenzaldehyde and methylmagnesium iodide and from *o*-methoxyphenylmagnesium bromide and acetaldehyde. In the first of these processes there was obtained along with the carbinol, a considerable amount of bis-[1-(*o*-methoxyphenyl)-ethyl] ether. This ether cleaved readily over hot alumina to give the desired *o*-methoxystyrene in 75% yields.

The *o*-methoxystyrene produced by catalytic dehydration of 1-(*o*-methoxyphenyl)-ethanol or its ether did not copolymerize well in standard GR-S recipes. Examination of the styrene showed that it contained about 10% of *o*-ethylphenol and a lesser proportion of *o*-ethylanisole. Presumably the *o*-ethylanisole was produced by a disproportionation reaction similar to the one observed in the attempted dehydration of *m*-N-methylaminophenylmethylcarbinol.[4] The *o*-ethylphenol was undoubtedly produced by cleavage of the ether group of *o*-ethylanisole. The other fragment of the disproportionation reaction is undoubtedly the substituted acetophenone since Hunter and Groombridge[5] have observed the formation of acetophenone during the dehydration of phenylmethylcarbinol over alumina.

Even after the removal of the phenolic impurities the sample of *o*-methoxystyrene prepared from the α-arylcarbinol was not satisfactory for polymerization studies. A very good sample of *o*-methoxystyrene was obtained by the conversion of *o*-methoxyphenylmagnesium bromide to 2-(*o*-methoxyphenyl)-ethanol by the action of ethylene oxide and the dehydration of this alcohol over hot potassium hydroxide. The styrene was obtained in good yield and the polymerization rates were satisfactory but the starting material was somewhat difficult to obtain.

Finally *o*-methoxystyrene was prepared by the method of Walling and Wolfstirn.[2g] After the *o*-methoxystyrene thus prepared had been washed with alkali it copolymerized satisfactorily. The yields are less satisfactory than in the preceding preparation but *o*-methoxybenzaldehyde is a more readily available starting material than *o*-bromoanisole.

1-(*o*-Methoxyphenyl)-ethanol.—This alcohol was prepared by the reaction of methylmagnesium iodide with *o*-methoxybenzaldehyde by procedures which have been described.[6] We obtained in every run a by-product boiling at 109° at 0.05 mm., m. p. 93.5°, which appears to be the ether formed by dehydration of the carbinol.

Anal.[7] Calcd. for $C_{18}H_{22}O_3$: C, 75.44; H, 7.75. Found: C, 75.37; H, 7.58.

This by-product was not described in the earlier reports. In one experiment a yield of crude carbinol amounting to 82% was obtained, but on distillation it was found to contain about 30% of the ether.

From *o*-methoxyphenylmagnesium bromide (from 187 g. of *o*-bromoanisole) and acetaldehyde, a 70% yield of the above alcohol was obtained. No ether was isolated in this run.

2-(*o*-Methoxyphenyl)-ethanol.—To an ether solution of *o*-methoxyphenylmagnesium bromide (from 100 g. of *o*-bromoanisole) was added an ether solution of 44 g. of ethylene oxide and the reaction was carried out in the usual manner. The product amounted to 54.5 g. (67%) and boiled at 79–80° at 0.26 mm. pressure, $n^{20}D$ 1.5391, d^{20}_4 1.0889.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.61; H, 7.64.

The phenylurethan was prepared in the usual manner and after recrystallization from ethanol melted at 76°.

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.05; H, 6.42; N, 5.11.

***o*-Methoxystyrene.**—Dehydration of 150 g. of 1-(*o*-methoxyphenyl)-ethanol over (Alorco) activated alumina at 310° at 30–40 mm. pressure gave 102 g. of product boiling at 73–75° at 10 mm., $n^{20}D$ 1.5530. This refractive index is lower than most of the values recorded previously for this styrene. In a redistillation it was observed that there was considerable variation in the refractive index at different stages of distillation although the boiling point was unchanged.

By-products in *o*-Methoxystyrene from 1-(*o*-Methoxyphenyl)-ethanol.—A solution of 153 g. of *o*-methoxystyrene made as above in 1 liter of low boiling petroleum ether was repeatedly washed with 500-cc. portions of 2% aqueous sodium hydroxide. The alkaline extracts were combined and acidified with hydrochloric acid and extracted with ether. After evaporation of the ether, the residual oil was distilled under reduced pressure. Redistillation of the main fraction gave about 11 g. of material, b. p. 48° at 0.05 mm., $n^{20}D$ 1.5367, d^{20}_4 1.0283.

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.71; H, 7.91.

This material had a strong creosote-like odor, absorbed bromine in carbon tetrachloride, decolorized 1% aqueous potassium permanganate solution and gave a violet blue color with ferric chloride in alcohol. These properties agree with those of *o*-ethylphenol as reported by Behal and Choay.[8] To confirm the identification the phenol was converted to *o*-ethylphenoxyacetic acid which is reported to melt at 141°.[9] The product we obtained melted at 134° and a sample made from an authentic specimen of *o*-ethylphenol ($n^{20}D$ 1.5335) melted at 137–138°. A mixture of the two materials melted at 136–137°.

Careful distillation of the *o*-methoxystyrene which had

(1) The work described in this manuscript was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) (a) Perkin, *Ber.*, **11**, 515 (1878); (b) Klages and Eppelsheim, *ibid.*, **36**, 3584 (1903); (c) Pschorr and Einbeck, *ibid.*, **38**, 2077 (1905); (d) v. Auwers, *Ann.*, **413**, 297 (1916); (e) Shorygin and Shorygina, *J. Gen. Chem. (USSR)*, **9**, 845 (1939); *C. A.*, **34**, 389 (1940); (f) Quelet and Golse, *Compt. rend.*, **223**, 159 (1946); (g) Walling and Wolfstirn, THIS JOURNAL, **69**, 853 (1947).

(3) Mowry, Renoll and Huber, *ibid.*, **68**, 1105 (1946).

(4) Marvel and Overberger, *ibid.*, **68**, 185 (1946).

(5) Hunter and Groombridge, British Patent 589,015; *C. A.*, **41**, 6897[d] (1947).

(6) Klages and Eppelsheim, *Ber.*, **36**, 3584 (1903); Pschorr and Einbeck, *ibid.*, **38**, 2077 (1905); Stedman and Stedman, *J. Chem. Soc.*, 609 (1929).

(7) All microanalyses reported are by H. S. Clark of the Illinois State Geological Survey.

(8) Behal and Choay, *Bull. soc. chim.*, [3] **11**, 210 (1894).

(9) Steinkopf and Hopner, *J. prakt. Chem.*, [2] **113**, 140, 153 (1926).

been washed with alkali to remove phenol showed that it also was not a homogeneous material. The material was divided into five fractions as follows: (1) 9 g., b. p. 33–35° at 0.6 mm., $n^{20}D$ 1.5282.; (2) 21.6 g., b. p. 32–35° at 0.4–0.55 mm., $n^{20}D$ 1.5390; (3) 26.7 g., b. p. 33–36° at 0.35 mm., $n^{20}D$ 1.5500; (4) 47.6 g., b. p. 34° at 0.3 mm., $n^{20}D$ 1.5582; (5) 20.3 g., b. p. 34° at 0.25 mm., $n^{20}D$ 1.5592.

Fractions 1 and 2 were combined and redistilled at a reflux ratio of 5 to 1. About 1.5 g. of distillate boiling at 72° and 13 mm. was collected, $n^{20}D$ 1.5169. The residue was heated in the distillation apparatus under total reflux for two hours to polymerize any *o*-methoxystyrene and then distillation was continued. Seven grams of product boiling at 73° under 14 mm. pressure, $n^{20}D$ 1.5142 were obtained.

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.58; H, 8.67.

Klages and Eppelsheim[2b] have reported a boiling point of 70–71° at 11 mm., and $n^{20}D$ 1.512 for *o*-ethylanisole.

Further confirmation that this product was *o*-ethylanisole was obtained by conversion to a tribromide by bromination with excess bromine in carbon disulfide with a trace of iodine as a catalyst. The product was recrystallized to a constant melting point from 95% alcohol and melted at 108–109°.

An authentic specimen of *o*-ethylanisole was similarly brominated to give a product which melted at 109°. A mixture of the two tribromo derivatives melted at 108–109°.

Anal. Calcd. for $C_9H_9OBr_3$: C, 28.99; H, 2.43; Br, 64.29. Found: C, 28.81; H, 2.28; Br, 64.24.

The dinitro derivative was prepared from the *o*-ethylanisole isolated from the *o*-methoxystyrene and also from authentic *o*-ethylanisole. After recrystallization from 95% alcohol the sample from the *o*-ethylanisole isolated from the styrene preparation melted at 67°, the authentic specimen at 67.5° and the mixture of the two at 67°.

Anal. Calcd. for $C_9H_{10}O_5N_2$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.98; H, 4.58; N, 12.37.

o-Methoxystyrene from 2-(*o*-Methoxyphenyl)-ethanol.—In a 500-cc. round-bottomed flask fitted with a dropping funnel and a distilling tube with receiver, was placed 150 g. of U.S.P. potassium hydroxide pellets. A very small amount of picric acid was introduced to act as a polymerization inhibitor. The apparatus was pumped out to about 12 mm. pressure, the reaction flask heated to 225° and after the water had distilled out of the potassium hydroxide, 54.5 g. of 2-(*o*-methoxyphenyl)-ethanol was added dropwise at the rate of 15–20 drops per minute. To the distillate was added 100 cc. of low boiling petroleum ether, the water separated and the solvent distilled. The residue was distilled to yield 33.3 g. (69.4%) of quite pure *o*-methoxystyrene boiling at 35° under 0.20 mm. pressure, $n^{20}D$ 1.5595.

o-Methoxystyrene from *trans*-*o*-Methoxycinnamic Acid.—The procedure was that of Walling and Wolfstirn[2g] except that it was found necessary to wash the substituted styrene with sodium hydroxide solution to remove traces of phenolic compounds and unchanged acid. The major portion of this product boiled at 36–37° under 0.2 mm., $n^{20}D$ 1.5600.

p-Benzylstyrene

The synthesis of *p*-benzylstyrene from diphenylmethane was effected by the usual methods of acetylation, reduction and dehydration. The general procedure of Mowry, Renoll and Huber[3] for the preparation of alkylacetophenones was followed for the acetylation of diphenylmethane and as a by-product some bis-(*p*-acetylphenyl)-methane was obtained. This was converted to the new bis-(*p*-vinylphenyl)-methane which was characterized.

The *p*-benzylstyrene which resulted from the dehydration of 1-(*p*-benzylphenyl)-ethanol was found to contain small amounts of *p*-benzylethylbenzene. This is further evidence that the disproportionation of phenylmethylcarbinols over alumina[4,5] is a general reaction.

***p*-Benzylacetophenone.**—When the general procedure of Mowry, Renoll and Huber[3] was followed, 425 g. of diphenylmethane gave 413 g. of *p*-benzylacetophenone, m. p. 39° (lit.[10], 39°), and 60 g. of higher boiling residue.

Bis-(*p*-acetylphenyl)-methane.—Three hundred and five grams of high boiling residues from the above preparation was distilled at 180° and 0.05 mm. and the distillate was recrystallized from 95% alcohol. The yield of diketone was 210 g., m. p. 90–92°. Duval[10] reported a melting point of 93°.

1-(*p*-Benzylphenyl)-ethanol.—A solution of 170 g. of *p*-benzylacetophenone in enough absolute alcohol to make 510 cc. of solution was treated with Raney nickel catalyst at the boiling point for two hours; the nickel was removed by filtration; fresh catalyst was added and reduction with hydrogen was carried out at 75° and 1600 p.s.i. The catalyst was removed by centrifuging, the alcohol was distilled and the product purified by distillation. The yield was 147.5 g., b. p. 125–130° at 0.1 mm., m. p. 43–45°. A small sample was redistilled and it boiled at 114° at 0.06 mm. and melted at 46°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.69; H, 7.88.

***p*-Benzylstyrene.**—Dehydration of 150 g. of 1-(*p*-benzylphenyl)-ethanol over (Alorco) activated alumina at 310° at 30–40 mm. pressure gave 114 g. (83.3%) of *p*-benzylstyrene, b. p. 76–78° at 0.06 mm., $n^{20}D$ 1.5949; d^{20}_4 1.0011.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.88; H, 7.28.

One cubic centimeter of the above styrene was treated with bromine in glacial acetic acid until the color of bromine persisted. It was then warmed on a steam cone a few minutes and diluted with water. The solid which separated on cooling was recrystallized from methanol. The product melted at 92–93°.

Anal. Calcd. for $C_{15}H_{14}Br_2$: C, 50.87; H, 3.99. Found: C, 51.17; H, 3.96.

A sample of 58 g. of the crude *p*-benzylstyrene was heated under total reflux for two hours and distilled to give 30 g. of product b. p. 83–90° at 0.2 mm., $n^{20}D$ 1.5806. This product was treated with bromine in glacial acetic acid until no more bromine was absorbed and then diluted with water. The oil was collected in ether and the solvent evaporated. The residue was crystallized from alcohol to remove most of the *p*-benzylstyrene dibromide. The alcoholic mother liquors were then distilled under reduced pressure to yield 2 g. of a product which boiled at 89–96° at 0.08 mm. pressure, $n^{20}D$ 1.5622. Another distillation gave a purer product, $n^{20}D$ 1.5620.

Anal. Calcd. for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.57; H, 8.19.

Walker[11] reported that *p*-benzylethylbenzene boils at 294–295° at 754 mm. but gave no refractive index. A small sample of *p*-benzylstyrene was reduced over Raney nickel catalyst to give *p*-benzylethylbenzene which boiled at 85° at 0.2 mm., $n^{20}D$ 1.5616.

Bis-[*p*-(1-hydroxyethyl)-phenyl]-methane.—A solution of 210 g. of bis-(*p*-acetylphenyl)-methane in 1500 cc. of alcohol was first treated with Raney nickel catalyst and then reduced with hydrogen over fresh catalyst at 75° and 1600 p.s.i. The catalyst was removed by filtration, the solution evaporated and a crude residue of 200 g. was obtained. Most of this material was used directly for dehydration. Five grams of the crude product was purified by twice recrystallizing from a 1:2 mixture of low boiling petroleum ether and benzene to yield a product, m. p. 85–86°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.85; H, 7.81.

The diphenylurethan prepared by the usual procedure was washed with carbon tetrachloride and low boiling

(10) Duval, *Compt. rend.*, **146**, 341 (1908); *Bull. soc. chim.*, [4] **7**, 796 (1910).

(11) Walker, *Ber.*, **5**, 686 (1872).

petroleum ether and then recrystallized from 95% alcohol. The product melted at 149–150°.

Anal. Calcd. for $C_{31}H_{30}O_4N_2$: C, 75.28; H, 6.11; N, 5.67. Found: C, 75.37; H, 6.27; N, 5.73.

Bis-(*p*-vinylphenyl)-methane.—The crude dicarbinol (134 g.) obtained above, dehydrated as described under *p*-benzylstyrene at 310° and 12 mm., gave 89 g. of crude product. Attempts to distil part of the product produced polymer in the distilling flask even when an inhibitor such as picric acid was added. By dissolving the product in ethyl alcohol at room temperature and cooling in a Dry Ice-bath and filtering at low temperature, pure hydrocarbon melting at 32° was obtained.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.62; H, 7.32. Found: C, 92.80; H, 7.18.

The tetrabromide was made by adding bromine in glacial acetic acid to glacial acetic acid solution of 2 g. of the hydrocarbon. The product was precipitated with water and recrystallized from a mixture of 20 cc. of methanol and 10 cc. of benzene; m. p. 146°.

Anal. Calcd. for $C_{17}H_{16}Br_4$: C, 37.81; H, 2.99. Found: C, 38.09; H, 2.97.

o-Fluorostyrene

o-Fluorostyrene has been prepared by Brooks.[12] We have applied the general styrene synthesis of Walling and Wolfstirn[2g] to *o*-fluorobenzaldehyde and found the method very satisfactory.

o-Fluorotoluene.—When the general procedure described for the preparation of fluorobenzene[13] was used, 574 g. of *o*-toluidine hydrochloride gave 207 g. of *o*-fluorotoluene.

o-Fluorobenzaldehyde.—When the general procedure described for the preparation of *p*-bromobenzaldehyde[14] was followed, 127.6 g. of *o*-fluorotoluene gave 100 g. (71.3%) of *o*-fluorobenzaldehyde. Brooks[12] used chlorination in place of bromination in this preparation and obtained a 48% yield.

o-Fluorocinnamic Acid.—When the general procedure of Walling and Wolfstirn[2g] was used, 100 g. of *o*-fluorobenzaldehyde gave 101 g. of the corresponding cinnamic acid, m. p. 177–178°. Kindler,[15] who prepared this acid by a different route reports it as melting at 175°.

o-Fluorostyrene.—The general procedure of Walling and Wolfstirn[2g] was used for the decarboxylation and from 95 g. of the cinnamic acid 45.6 g. (65.6%) of *o*-fluorostyrene, boiling at 46° at 32 mm., $n^{20}D$ 1.5201, was obtained. Brooks[12] reports $n^{20}D$ 1.5197.

o-Cyanostyrene

o-Cyanostyrene was prepared from *o*-tolunitrile by oxidation to *o*-cyanobenzaldehyde, followed by condensation with malonic acid and subsequent decarboxylation of the substituted cinnamic acid. The polymerization of this substituted styrene has not been studied.

o-Cyanobenzaldehyde Diacetate.—The procedure described for the conversion of *p*-nitrotoluene to *p*-nitrobenzaldehyde diacetate[16] was used. From 84.2 g. of *o*-toluonitrile there was obtained 58.2 g. (34.6%) of the *o*-cyanobenzaldehyde diacetate, m. p. 94–95° after recrystallization from 95% alcohol.

Anal. Calcd. for $C_{12}H_{11}O_4N$: C, 61.79; H, 4.76. Found: C, 61.95; H, 4.69.

o-Cyanobenzaldehyde.—Hydrolysis of the above diacetate was carried out as described for the corresponding *p*-nitro compound.[16] From 58.2 g. of diacetate there was obtained 26.7 g. (81.6%) of *o*-cyanobenzaldehyde which melted at 103–104° after recrystallization from alcohol. Blicke and Pobelski[17] prepared this aldehyde from the corresponding benzal dibromide and reported the melting point at 108–109°.

o-Cyanocinnamic Acid.—The *o*-cyanobenzaldehyde, m. p. 103–104°, was converted to the cinnamic acid by the procedure of Walling and Wolfstirn[2g] except the reaction mixture was heated for five hours. From 48.5 g. of aldehyde there was obtained 39.5 g. (61.7%) of *o*-cyanocinnamic acid, m. p. 253–254°. This agrees with the melting point (255°) reported in the Bayer Company patent.[18]

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.42; H, 3.80; N, 8.07.

o-Cyanostyrene.—The general method of Walling and Wolfstirn[2g] was modified for the decarboxylation of *o*-cyanocinnamic acid by using more quinoline and distilling more slowly than they recommend. Twenty-three grams of the cinnamic acid, 5 g. of copper bronze powder and 275 g. of quinoline were used. About five-sixths of the material distilled in ninety minutes. Redistillation gave 5 g. (28.9%) of product, b. p. 53° at 0.15 mm., $n^{20}D$ 1.5756.

Anal. Calcd. for C_9H_7N: C, 83.69; H, 5.46. Found: C, 84.55; H, 5.61.

o-Cyanostyrene has been described as boiling at 96–100° at 9 mm., $d^{29}{}_{15}$ 1.012.[19]

o-Cyanostyrene Dibromide.—Addition of excess bromine to a glacial acetic acid solution of *o*-cyanostyrene followed by dilution with water gave a solid dibromide. After recrystallization from alcohol it melted at 86–86.5°.

Anal. Calcd. for $C_9H_7NBr_2$: C, 37.40; H, 2.44; Br, 55.31. Found: C, 37.65; H, 2.51; Br, 55.15.

Polymers of the New Styrene Derivatives.—Two cubic centimeters of monomer was placed in a quartz tube and placed under a 500-watt ultraviolet lamp until a solid polymer had formed. The time varied from two to four days for different monomers. The polymer was dissolved in 50 cc. of benzene and precipitated by dropping the solution into 500 cc. of vigorously stirred methanol. The powder thus obtained was dried in a vacuum desiccator at 0.03 mm. pressure.

Poly-*p*-benzylstyrene softened in a melting point tube at 105° and shrunk to a soft mass at 110°. It was slightly soluble in benzene, $[\eta]$ 0.91.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 91.84; H, 7.51.

Poly-bis-(*p*-vinylphenylmethane) did not soften visibly below 250°. It was insoluble in benzene, chloroform, nitromethane, carbon disulfide and other common solvents.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 91.65; H, 7.74.

Poly-*o*-methoxystyrene softened at 125° and turned to a soft mass at 130°. It was very soluble in benzene, $[\eta]$ 0.57.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.45; H, 7.40.

Poly-*o*-fluorostyrene softened at 105° and shrunk to a soft mass at 110°. It was very soluble in benzene, $[\eta]$ 0.36.

Anal. Calcd. for C_8H_7F: C, 78.86; H, 5.78. Found: C, 77.88; H, 6.07.

The copolymerization of these styrenes with butadiene will be described later.

Summary

p-Benzylstyrene and bis-(*p*-vinylphenyl)-methane and their polymers are described for the first

(12) Brooks, THIS JOURNAL, **66**, 1295 (1944).

(13) Flood, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 295.

(14) Coleman and Honeywell, *ibid.*, p. 89.

(15) Kindler, *Ann.*, **464**, 278 (1928).

(16) Lieberman and Connor, "Organic Syntheses" Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943 p. 441.

(17) Blicke and Pobelski, THIS JOURNAL, **58**, 559 (1936).

(18) Bayer and Company, German Patent 116,123; *Chem. Zentr.*, **72**, I, 69 (1901); see also Drory, *Ber.*, **24**, 2574 (1891); Werner and Piquet, *ibid.*, **37**, 4310 (1904).

(19) Wingfoot Corporation, British Patent 571,829 (1945); *C. A.*, **41**, 3323 (1947).

time. New procedures for preparing *o*-fluorostyrene, *o*-methoxystyrene and *o*-cyanostyrene are described.

Two more examples of the disproportionation of phenylmethylcarbinols to ethylbenzenes under the influence of activated alumina have been observed in the dehydration of *p*-benzylphenylmethylcarbinol and *o*-methoxyphenylmethylcarbinol.

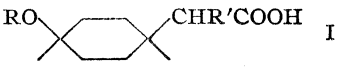
URBANA, ILLINOIS RECEIVED JANUARY 9, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

The Hydrogenation of Phenolic Acids

BY HERBERT E. UNGNADE AND FRANCIS V. MORRISS

The catalytic reduction of phenolic acids has been investigated in the hope of obtaining a reasonably simple method for the preparation of acids of the type (I).



I

Previous attempts to prepare the methoxy acid (I, R = CH_3, R′ = H) by catalytic reduction of the corresponding aromatic acid with platinum catalyst have been unsuccessful.[1] In numerous other investigations the catalytic reduction of phenolic acids has been reported to give low yields of hydroxycyclohexane acids due to side reactions. Low pressure hydrogenation, particularly in acid medium, causes considerable hydrogenolysis of the carbon–oxygen linkage with resultant loss of the hydroxyl group[2,3,4] whereas high pressure hydrogenation with nickel catalyst leads largely to decarboxylation[5] regardless of whether the acids or their sodium salts are reduced.[4] The hydrogenolysis reaction in the low pressure hydrogenation with platinum can be repressed by reducing in the presence of alkali. Good yields of 4-hydroxycyclohexanecarboxylic acid have thus far been reported only for the hydrogenation of *p*-hydroxybenzoic acid in ethyl acetate over palladium-on-strontium carbonate under high pressure.[4]

It has been shown in the present investigation that phenolic acids can be reduced smoothly to the hexahydro compounds by high pressure hydrogenation of their esters in alcoholic solution with W-2 Raney nickel catalyst[6] in the presence of approximately 0.3 mole % of the sodium salts of these compounds. The reduction products are pure substances which consist of mixtures of *cis*- and *trans*-isomers and which are formed in nearly quantitative yield. A direct separation of the isomers is rather difficult. A partial separation can be effected by adsorption of the esters on alumina. The *trans*-isomer is more strongly adsorbed.

The best method for the preparation of the pure *cis*- and *trans*-isomers consists in the reduction of the keto acids by specific reduction methods. Sodium and alcohol or sodium amalgam gives fairly pure *trans*-alcohols while the catalytic reduction with Raney nickel at room temperature yields predominantly *cis*-isomers.[3]

Experimental[7,8]

The phenolic acids used in this investigation were commercial products with the exception of α-(*p*-hydroxyphenyl)-butyric acid which was prepared according to Wilds and Biggerstaff.[9,10]

The ethyl esters of the phenolic acids were prepared by esterification of the acids with ethyl alcohol and sulfuric acid or by the method of Thielepape.[11] They were distilled under reduced pressure prior to reduction.

Hydrogenation of the Phenolic Esters.—The phenolic esters (0.2–1.0 mole) were dissolved in 100 cc. of absolute ethyl alcohol containing 0.3 mole % (on the basis of phenolic ester) of sodium ethoxide. Raney nickel (3–6 g.) was added and the mixture was immediately hydrogenated at between 160–220° (240–270 atm.) until the pressure remained constant. The catalyst was filtered off, the solvent was removed and the residue was distilled under reduced pressure. The constants of the products are given in Table I.

Preparation of the Keto Acids.—The hydroxycyclohexane esters described above were hydrolyzed by refluxing for two hours with four volumes of 10–20% aqueous sodium hydroxide solution and one volume of ethyl alcohol. The resultant solution was acidified with hydrochloric acid and extracted continuously with benzene. Most of the water and benzene were removed by distillation from a water-bath, the last traces under reduced pressure. The residual acids were used for the preparation of the keto acids without further purification. The mixtures of the isomeric acids were oxidized with chromic anhydride in aqueous acetic acid below 15°. Ethyl 4-hydroxycyclohexanecarboxylate was oxidized without previous hydrolysis. The resulting keto ester was purified through its bisulfite addition compound and was hydrolyzed on regeneration. The experimental data are given in Table II.

The keto acids were isolated by dilution of the reaction mixture with water and continuous extraction of the resultant solution with ether. The ether was removed by

(1) Ruggli, Leupin and Businger, *Helv. Chim. Acta*, **24**, 339 (1941).

(2) Balas and Kosik, *Časopis Československ. Lékárnictva*, **7**, 105 (1927); Balas and Srol, *Coll. Czescoslov. Chem. Commun.*, **1**, 658 (1929); Edson, *J. Soc. Chem. Ind.*, **53**, 138T (1934); Long and Burger, *J. Org. Chem.*, **6**, 852 (1941); Price, Enos and Kaplan, THIS JOURNAL, **69**, 2261 (1947).

(3) Hardegger, Plattner and Blank, *Helv. Chim. Acta*, **27**, 793 (1944).

(4) Levin and Pendergrass, THIS JOURNAL, **69**, 2436 (1947).

(5) Ipatiew and Razuvajew, *Ber.*, **58B**, 306 (1926); Mitsuii, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **A18**, 329 (1935); Martin and Robinson, *J. Chem. Soc.*, 491 (1943).

(6) Adkins and Pavlic, THIS JOURNAL, **69**, 3040 (1947).

(7) All temperatures uncorrected.

(8) Analyses by Karl Zilch.

(9) Wilds and Biggerstaff, THIS JOURNAL, **67**, 789 (1945).

(10) The authors are indebted to Dr. V. H. Wallingford of the Mallinckrodt Chemical Works for a generous supply of diethyl ethylphenylmalonate from which this acid was prepared.

(11) Thielepape, *Ber.*, **66**, 1454 (1933).

TABLE I

HYDROGENATION PRODUCTS OF THE PHENOLIC ACIDS

Ethyl ester	B. p. °C.[a]	Mm.	Yield,[b] %	$n^{20}D$	d^{20}_4	M_D Calcd.	M_D Found
2-Hydroxycyclohexanecarboxylate	98.5–100	7	85	1.4625	1.0505	44.74	45.11
3-Hydroxycyclohexanecarboxylate	133–138	9	75[c]	1.4665	1.0564	44.74	45.22
4-Hydroxycyclohexanecarboxylate	136	8	87	1.4698	1.0667	44.74	44.96
4-Hydroxycyclohexaneacetate[d]	138–142	7	89	1.4705	1.0533	49.36	49.38
α-(4-Hydroxycyclohexane)-butyrate[e]	147	6	83	1.4710	1.0083	58.58	59.50

[a] The products boiled without forerun. [b] On the basis of purified products. [c] The low yield in this case was due to mechanical losses. [d] *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.72. Found: C, 64.41; H, 9.91. [e] *Anal.* Calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.29; H, 10.24.

TABLE II

CHROMIC ACID OXIDATION OF THE HYDROXY ACIDS

Hydroxy compound	G.	CrO_3, g.	HOAc, cc.	H_2O, cc.	Yield, %[a]	M. p., °C.
Ethyl 4-hydroxycyclohexanecarboxylate	8.0	4.0	400	10	45.7	66–68
4-Hydroxycyclohexaneacetic acid	17.0	4.0	50	3	34.4	67–68
α-(4-Hydroxycyclohexane)-butyric acid	5.8	2.4	38	2	55	73–75

[a] The yields are based on crystallized products.

distillation, the residual acids were dried by removing the benzene–water azeotrope and were crystallized from Skellysolve B. The purification of the acids proved tedious since several weeks were required for the crystallization of the reaction products. Analyses of the acids and their semicarbazones are given in Table III.

TABLE III

KETO ACIDS

4-Ketocyclohexane acid	Calcd. %C	Calcd. %H	Found %C	Found %H	Semicarbazones M. p., °C.	Calcd. %C	Calcd. %H	Found %C	Found %H
R—COOH					196 (dec.)[12]				
R—CH_2—COOH	61.52	7.76	61.29	8.07	175–176 (dec.)	50.69	7.09	50.33	7.12
R—CH(—C_2H_5)—COOH	65.20	8.76	65.54	9.06	208–210 (dec.)	54.75	7.94	55.00	8.03

***cis*-4-Hydroxycyclohexaneacetic Acid.**—The keto acid (0.45 g.), dissolved in 11 cc. of 1 *N* aqueous sodium hydroxide solution, was reduced with 1.5 g. of Raney nickel under 50 mm. of hydrogen. The calculated amount of hydrogen was taken up in thirty-five minutes. The solution was filtered from the catalyst, acidified with concentrated hydrochloric acid and extracted continuously with ether for fourteen hours. The residue obtained after removing the solvent was dried by distillation with benzene. The remaining solid material (0.46 g.), m. p. 115–123°, was purified by crystallization from ethyl acetate. The pure acid melted at 133.5–134°.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.47; H, 9.09. Found: C, 60.64; H, 9.14.

***trans*-4-Hydroxycyclohexaneacetic Acid.**—Sodium amalgam (75 g., 4%) was added in small pieces over a period of two hours with stirring to a solution of 2.3 g. of 4-ketocyclohexaneacetic acid in 140 cc. of 2 *N* aqueous sodium carbonate solution. The mixture was allowed to stand for fifteen hours. Sodium bicarbonate (10 g.) was then added to the mixture with stirring and stirring was continued for six hours. The mercury was removed by decantation and the aqueous solution was acidified with hydrochloric acid. Continuous extraction of the water solution with ether gave 2.4 g. of crude acid, m. p. 134–136°, which melted at 139.5–140° after repeated crystallization from ethyl acetate. The mixture with the *cis*-acid melted at 110–120°.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 9.09. Found: C, 60.48; H, 9.08.

***cis*-α-(4-Hydroxycyclohexane)-butyric Acid.**—The catalytic reduction of the keto acid (0.4 g.) was carried out as described for *cis*-4-hydroxycyclohexaneacetic acid. The crude product (0.4 g., m. p. 102–107°) was crystallized from ethyl acetate. The pure hydroxy acid melted at 110.5–111°.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.72. Found: C, 64.47; H, 9.95.

***trans*-α-(4-Hydroxycyclohexane)-butyric Acid.**—The mixture of isomeric hydroxy esters (3.73 g.) from the high pressure hydrogenation of ethyl α-(*p*-hydroxyphenyl)-butyrate was adsorbed on alumina from Skellysolve A solution. The less strongly adsorbed *cis*-isomer was eluted with the same solvent, the *trans*-compound was eluted with benzene. A portion of the benzene eluate (0.82 g.) was refluxed for three hours with 25 cc. of 10% aqueous sodium hydroxide solution and 10 cc. of ethyl alcohol. The solution was acidified with hydrochloric acid and extracted with ether in a continuous extractor. The ether was displaced with benzene, the latter removed by distillation, the last traces under reduced pressure. The residue (0.62 g.) solidified on standing and melted at 93–107°. Three crystallizations from benzene–Skellysolve B mixtures raised the melting point to 123.5–124°. The substance depressed the melting point of the *cis*-isomer.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.72. Found: C, 64.35; H, 9.75.

Summary

The ethyl esters of the three hydroxybenzoic acids, *p*-hydroxyphenylacetic acid and α-(*p*-hydroxyphenyl)-butyric acid, have been reduced in good yield to the hexahydro compounds by high pressure hydrogenation over Raney nickel catalyst in alcoholic solution containing 0.3 mole % of sodium ethoxide. A method has been described for the conversion of these reduction products to the corresponding keto acids. The *cis*- and *trans*-isomers of 4-hydroxycyclohexaneacetic acid and α-(4-hydroxycyclohexane)-butyric acid have been prepared.

COLUMBIA, MO. RECEIVED FEBRUARY 2, 1948

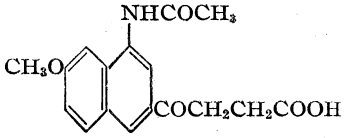
(12) Perkins, *J. Chem. Soc.*, **85**, 427 (1904).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Succinoylation of 1-Acetylamino-7-methoxynaphthalene

BY LEONARD E. MILLER AND EDWIN F. MORELLO[1]

The reaction of 1-acetylamino-7-methoxynaphthalene with succinic anhydride in nitrobenzene in the presence of aluminum chloride has been found to give β-(1-acetylamino-7-methoxy-3-naphthoyl)-propionic acid (I).



I

The structure of (I) was established by hydrochloric acid hydrolysis, diazotization and deamination using hypophosphorous acid to give the known β-(2-methoxy-6-naphthoyl)-propionic acid (II).[2] The melting points of this acid and its methyl ester were in agreement with those reported. In addition, an alkaline hypochlorite oxidation of (II) produced the known 2-methoxy-6-naphthoic acid (III). Demethylation of (III) with hydrobromic acid in acetic acid gave the known 2-hydroxy-6-naphthoic acid.

Since under similar conditions of reaction the 6-position of 2-methoxynaphthalene is the most reactive one,[2] it may be concluded that the directive influence of the methoxyl group plays the predominant role in the succinoylation of 1-acetylamino-7-methoxynaphthalene in nitrobenzene.

Experimental[3]

1-Acetylamino-7-methoxynaphthalene.—Using Cleve's acid-1,7, this material was prepared by the method of Bachmann and Horton.[4] The procedure used was similar to that given in detail by Wilds and Close[5] for the 1,6-isomer. After distillation at 147° (0.05 mm.), the material crystallized from methanol (Norite) as fine colorless needles, m. p. 160–161°.[4]

β-(1-Acetylamino-7-methoxy-3-naphthoyl)-propionic Acid.—A mixture of 37.6 g. (0.175 mole) of 1-acetylamino-7-methoxynaphthalene and 17.0 g. (0.170 mole) of succinic anhydride was added in small portions to a mechanically stirred, ice-cold solution of 80 g. (0.595 mole) of powdered, anhydrous aluminum chloride in 200 ml. of nitrobenzene. This addition required approximately one hour. After stirring for seventeen hours at 0°, the mixture was poured on 200 g. of ice containing 3 ml. of concentrated hydrochloric acid. The nitrobenzene was distilled off with water vapor at 37° (22 mm.). The solid residue was separated on a filter. The filtrate was heated under reduced pressure once more to remove the residual nitrobenzene. The combined solid residues were treated then with aqueous sodium carbonate. The insoluble material, consisting of starting material and aluminum hydroxide, was removed on a filter. It was treated further with a mixture of ether and aqueous sodium carbonate and was separated on a filter. The combined alkaline filtrates were washed with ether. On acidification with dilute hydrochloric acid, the solid which separated was collected on a filter and permitted to dry in air. It was crystallized from 40% acetic acid to give small colorless needles, m. p. 202–203°; the yield was 45.1 g. (84%). From the ether extracts 1.8 g. of pure starting material was isolated. The yield calculated on the basis of 1-acetylamino-7-methoxynaphthalene consumed was 86%.

Anal. Calcd. for $C_{17}H_{17}O_5N$: C, 64.8; H, 5.4; N, 4.4. Found: C, 64.7; H, 5.7; N, 4.6.

β-(2-Methoxy-6-naphthoyl)-propionic Acid.—A mixture of 43.5 g. of β-(1-acetylamino-7-methoxy-3-naphthoyl)-propionic acid, 150 ml. of water and 300 ml. of concentrated hydrochloric acid was heated under reflux for one hour. On cooling in an ice-bath, the hydrochloride crystallized and was collected on a filter. After one recrystallization from dilute hydrochloric acid, it was used without further purification in the following reaction. The yield was 40.4 g. (94.5%).

Anal. Calcd. for $C_{15}H_{16}O_4NCl$: N, 4.5. Found: N, 4.6.

A mechanically stirred mixture of 10.9 g. (0.035 mole) of the hydrochloride, 100 ml. of glacial acetic acid and 75 ml. of concentrated hydrochloric acid was cooled in an ice-water-bath to 0°. To this suspension of the hydrochloride, 2.9 g. of sodium nitrite in 14 ml. of water was added dropwise very slowly (two hours). At this time 0.5 g. of urea in 5 ml. of water was added to destroy the excess nitrous acid; the mixture was stirred for an additional hour. To the stirred solution at 0°, 87 ml. of ice-cold 50% hypophosphorous acid was added over a fifteen minute period. After being stirred for an additional two hours, the mixture was placed in a refrigerator for thirty-eight hours. After heating on a steam cone for ten minutes, the liquids were removed at 32° (22 mm.). The solid residue was dissolved in aqueous sodium carbonate, filtered and then acidified with dilute hydrochloric acid. After collection on a filter, it was treated with an ethereal solution of diazomethane for a short time (five minutes). The ether solution was washed with cold 2% sodium hydroxide and was dried over magnesium sulfate. After removal of the ether, the residue was evaporatively distilled at 190–195° (0.02 mm.). It crystallized from methanol in long needles, m. p. 97–97.5°.[2]

A solution of 1.8 g. of the methyl ester of β-(2-methoxy-6-naphthoyl)-propionic acid and 4.0 ml. of 10% sodium hydroxide in 100 ml. of methanol was heated under reflux for two hours. On evaporation of the methanol, the solid residue was dissolved in 100 ml. of water. Upon acidification with dilute hydrochloric acid, the free acid precipitated. It crystallized from methanol in shiny colorless plates, m. p. 149.5–150.5°.[2] The yield was 1.6 g. (17.7% based on amine hydrochloride).

2-Methoxy-6-naphthoic acid was prepared from (II) according to Short, Stromberg and Wiles.[2] After five recrystallizations from ethyl acetate colorless needles were isolated, m. p. 200–202° (reported, 205°).

2-Hydroxy-6-naphthoic acid was prepared by the method of Knowles, Kuck and Elderfield[6] from 110 mg. of the methoxynaphthoic acid after heating under reflux for two and one-half hours with 1 ml. of acetic acid, 1 ml. of 48% hydrobromic acid and 1 ml. of acetic acid saturated with hydrogen bromide. It was recrystallized from water (Norite) three times; m. p. 240–242° (reported, 240–241°,[7] 242–244°,[8] 245–248[7]).

(1) Present address: University of Minnesota, Minneapolis, Minn.

(2) Short, Stromberg and Wiles, *J. Chem. Soc.*, 319–322 (1936).

(3) All melting points are uncorrected.

(4) Bachmann and Horton, THIS JOURNAL, **69**, 58 (1947).

(5) Wilds and Close, *ibid.*, **69**, 3080 (1947).

(6) Knowles, Kuck and Elderfield, *J. Org. Chem.*, **7**, 380 (1942).

(7) Butler and Royle, *J. Chem. Soc.*, **123**, 1649 (1923).

(8) Cason, THIS JOURNAL, **63**, 828 (1941).

Summary

The reaction of 1-acetylamino-7-methoxynaphthalene with succinic anhydride in the presence of aluminum chloride using nitrobenzene as a solvent proceeds smoothly to give β-(1-acetylamino-7-methoxy-3-naphthoyl)-propionic acid in 86% yield. The structure of the reaction product has been established.

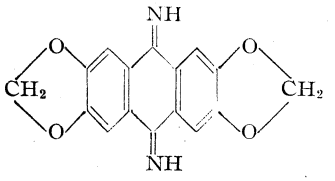
URBANA, ILLINOIS RECEIVED FEBRUARY 4, 1948

[COMMUNICATION NO. 1141 FROM THE KODAK RESEARCH LABORATORIES]

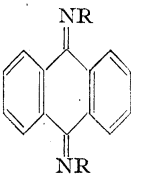
The So-Called "Anthraquinonediimines"; Symmetrical Trisubstituted Triazines

BY C. V. WILSON

Some years ago Brown and Robinson[1] treated 3,4-methylenedioxybenzonitrile with chlorosulfonic acid in chloroform and obtained a substance that was sparingly soluble in the usual solvents, but dissolved in sulfuric acid to give a deep crimson solution. The color of the solution resembled those which are obtained with methoxyanthraquinones and sulfuric acid. On reduction with hydriodic acid followed by zinc dust distillation and subsequent oxidation a product was obtained which gave a positive color test in the oxanthranol reaction. This was interpreted as indicating the presence of anthracene. From these properties and the analysis of the compound, and despite the recorded fact that the substance was unchanged by boiling hydrochloric acid, Brown and Robinson assigned to it the structure I.



I



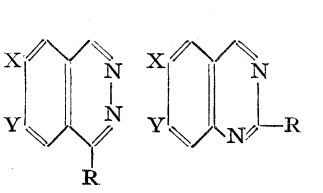
II

Later Keffler[2] attempted a molecular weight determination on the substance but found it so insoluble that he was unable to accomplish his purpose. However, he synthesized two closely related products from veratronitrile and 3-methoxy-4-ethoxybenzonitrile and found them sufficiently soluble in thymol to make possible molecular weight determinations by the cryoscopic method. On the basis of the results he concluded that the products were dimerides of the related nitriles and that the Brown and Robinson formulation was correct.

However, the properties recorded for these substances do not resemble those of 9,10-diiminoanthracene (II, R = H). The latter is prepared from the corresponding diamino compound with silver oxide, is soluble in ether, and is easily changed to anthraquinone with aqueous acids.[3] The latter property is also observed for the substituted diiminoanthracenes (II, R = C_6H_5, $CH_3C_6H_4$, etc.).[4] The great stability of the compounds reported by Keffler[2] toward concentrated hydrochloric acid is not compatible with the properties of the simple, unsubstituted 9,10-diiminoanthracene (II, R = H). It is difficult to believe that the substituents would alter this property of the diimine so markedly.

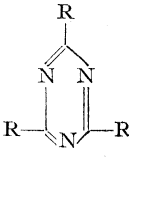
Since substituted anthraquinones that should be obtainable from these diiminoanthracenes were required in connection with another problem in these Laboratories, they were investigated further. A Zerewitinoff determination on the "piperonitrile dimer," prepared as described by Keffler,[2] showed no active hydrogen. This is not in agreement with the proposed structure, which should show two active hydrogens.

It is possible for the nitriles to polymerize in other ways. Thus they may dimerize by the diene synthesis to give phthalazines (III) or quinazolines (IV), or they may trimerize to triazines of structure V. Unlike the diiminoanthracene structure (I) these compounds would have no active hydrogen.

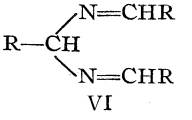


III

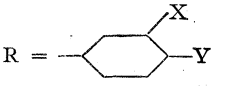
IV

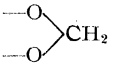


V



VI



where X = Y = OCH_3, or X + Y = 

A literature survey revealed that the triazine (V, X + Y = —OCH_2O—) has been prepared by two different methods, and, surprisingly enough, the melting points recorded were the same as those given by Robinson[1] and Keffler[2] for the so-called dimer. In one of these methods[5] nitro-

(1) Brown and Robinson, *J. Chem. Soc.*, **111**, 957 (1917).
(2) Keffler, *J. Chem. Soc.*, **119**, 1476 (1921).
(3) German Patent 590,366 [*Frdl.*, **19**, 1908 (1934)].
(4) German Patent 529,484 [*Frdl.*, **19**, 1907 (1934)].
(5) Davis, *J. Chem. Soc.*, **87**, 1835 (1905).

gen tetrasulfide (N_4S_4) was digested with piperonal for forty-six hours and the triazine (m. p. 266°) was obtained, along with the sulfate of 3,4-methylenedioxybenzamidine. In the other method[6] "piperhydramide" (VI, X + Y = O—CH_2—O—) was prepared[7] and oxidized with iodine and sodium carbonate to form the triazine (m. p. 265°). In this work the triazine was prepared by the latter method and, after recrystallization from pyridine, melted at 270°, and showed no depression of the melting point when mixed with the compound obtained by Robinson's procedure.

This established the identity of the two compounds. There still remained the question of molecular weight which led Keffler to report the compounds as dimers. As the author pointed out, molecular weight determinations were made difficult because of the insolubility of the substances in most solvents. Since the methoxy derivative is the most soluble of the compounds under consideration, it was used in this work for molecular weight determinations. Use of the cryoscopic method proved unreliable so attention was turned to the ebullioscopic method.

The molecular weight of a closely related product obtained by the action of nitrogen sulfide on *p*-methoxybenzonitrile has been determined by the ebullioscopic method and the results are in agreement with the trimeric formula.[8] This method was applied to the compound in question using pyridine as a solvent. The values obtained for the molecular weight show that the compound is trimeric. There can be little doubt, therefore, that the so-called "anthraquinonediimines" of Keffler and Robinson are in reality trisubstituted triazines.

Since Keffler's molecular weight determinations had indicated that the compounds were dimeric, two possible dimeric substances were synthesized prior to investigating a trimeric form: the phthalazine (III, X + Y = —O—CH_2—O—) and the quinazoline (IV, X + Y = —O—CH_2—O—). The phthalazine was synthesized by condensing piperonoylhydrazine[9] with piperonal followed by ring closure with hydrogen chloride in amyl alcohol.[10] The quinazoline was prepared by treating the product from 6-aminopiperonal[11] and piperonoyl chloride with ammonia under pressure. An attempt to cyclize the Schiff base from piperonal and 6-aminopiperonitrile was abandoned when the quinazoline was obtained by the method described above.

The mechanism of the formation of a triazine is doubtful, but it can be accounted for by an extension of the ideas of Alder[12] and Kilpatrick.[13]

(6) Bougault and Robin, *Compt. rend.*, **169**, 978 (1919); Robin, *Ann. chim.*, [9] **16**, 120 (1921).
(7) Wallach, *Ber.*, **14**, 792 (1881).
(8) Francis and Davis, *J. Chem. Soc.*, **85**, 1537 (1904).
(9) McFadyen and Stevens, *ibid.*, 584 (1936).
(10) Aggarival, Darbari and Ray, *ibid.*, 1941 (1929).
(11) Marr and Bogert, THIS JOURNAL, **57**, 1329 (1935).
(12) Alder, *Die Chemie*, **55**, 55 (1942).
(13) Kilpatrick, THIS JOURNAL, **69**, 42 (1947).

Experimental

1,3,5-Tri-(3′,4′-methylenedioxyphenyl)-*s*-triazine (V, X + Y = —O—CH_2—O—).—The so-called "2,3,6,7-dimethylenetetraoxyanthraquinonediimine" was prepared by the procedure described previously.[1,2] On recrystallization from pyridine it melted at 270°.

The triazine was also prepared by oxidizing "piperhydramide" (VI, X + Y = —O—CH_2—O—),[7] with iodine and potassium carbonate, as described by Robin.[6] The product obtained was recrystallized from pyridine, melted at 270°, and showed no depression of the melting point when mixed with the substance obtained by Robinson's procedure.

1,3,5-Tri-(3′,4′-dimethoxyphenyl)-*s*-triazine was prepared by Keffler's procedure.[2] It melted, when recrystallized from pyridine, at 263°. A molecular weight determination by the cryoscopic method with *p*-bromophenol as a solvent gave the following results: 0.2 g. of the polymeric nitrile in 10 g. of *p*-bromophenol gave a depression of 0.68°, from which the molecular weight is 329 (calcd. for a dimer 326), the constant for *p*-bromophenol being 11.2. However, the substance gave a deep yellow solution in *p*-bromophenol indicating that some change had occurred. As a result other solvents were investigated. Cyclopentadecanone has a fairly high constant (21.3),[14] but the triazine crystallized from it above the setting point at a dilution of 1.4 parts per 100. With 2-aminopyridine the same difficulty was experienced. It is entirely possible that this crystallization above the setting point may be taking place also with the phenolic solvents, thymol and *p*-bromophenol. With camphor as a solvent it was found difficult to obtain consistent results.

When the ebullioscopic method was applied, pyridine was used as the solvent. The constant (K_{1000}) was determined using acetanilide, *p*-amino-N-ethylacetanilide, and *p*-nitrophenylacetonitrile as reference compounds. The average of the values thus obtained, 2.65, 2.68 and 2.63, respectively, was used as the constant. With this value 0.5115 g. of the methoxy derivative in 44.8380 g. of pyridine gave a boiling point elevation of 0.070° from which the molecular weight is 488; similarly, 1.0027 g. of the methoxy derivative in 46.7087 g. of pyridine gave a boiling point elevation of 0.115° from which the molecular weight is 494. Since the calculated value for a trimer is 489 the conclusion that the compounds are triazines is inevitable.

Piperonal-β-(3,4-methylenedioxybenzoyl)-hydrazone was made by condensing piperonal with piperonoylhydrazine,[9] as described for an analogous compound[10]; 5.4 g. of piperonal and 6 g. of the hydrazine were refluxed for two hours in 60 ml. of alcohol containing 1 ml. of 40% sodium hydroxide (later it was found that the alkali was unnecessary). The solid that separated on cooling was collected and washed with alcohol. The yield was 9.7 g.; m. p. at about 210–220°, with preliminary darkening at about 205°. A sample recrystallized from alcohol melted at 193–196°, but if the melting-point tube was inserted in a bath preheated to 150°, there appeared to be decomposition. The substance reacted similarly when recrystallized from propanol, acetic acid, or ethyleneglycolmonomethyl ether. For analysis, the material recrystallized from alcohol was dried in a vacuum oven at 110°.

Anal. Calcd. for $C_{16}H_{12}N_2O_5$: C, 61.5; H, 3.8; N, 8.9. Found: C, 61.3; H, 3.9; N, 8.8.

1-(3′,4′-Methylenedioxyphenyl)-6,7-methylenedioxyphthalazine.—The hydrazone (4 g.) was added to 50 ml. of amyl alcohol which had been saturated at 10–15° with hydrogen chloride. The mixture was heated for one hour on the steam-bath and a further hour with a free flame. The resulting mixture was transferred to a beaker and the solvent allowed to evaporate spontaneously. When almost dry, the residue was digested with benzene and filtered. The remaining solid was shaken with 50 ml. of 10% sodium hydroxide, filtered, washed with water, and dried. One crystallization from alcohol gave 0.5 g.

(14) Giral, *Anales soc. espan. fis. quim.*, **33**, 438 (1935) [*C. A.*, **29**, 6489 (1935)].

of a buff-colored product melting at 203–204°. It was recrystallized from a small volume of ethyl acetate.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4; N, 9.5. Found: C, 64.6, 64.9; H, 3.4, 3.8; N, 9.5.

When the reaction was run in chloroform with phosphoryl chloride as the condensing agent, an imidchloride, which is probably an intermediate, was obtained. It melted at 166–167° after recrystallization from benzene.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_4$: C, 58.2; H, 3.3; N, 8.5. Found: C, 58.0; H, 3.2; N, 8.6.

Veratroylhydrazine.—A mixture of 10 g. of methyl veratrate, 12 ml. of ethyl alcohol, and 10 ml. of 80% hydrazine hydrate was refluxed for two hours. The product was isolated by dilution with water and cooling; it was collected and recrystallized from alcohol. The yield was 6.7 g., m. p. 145°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: N, 14.3. Found: N, 14.5.

Veratral β-(3,4-Dimethoxybenzoyl)-hydrazone.—A solution of 6.7 g. of veratroylhydrazine and 6 g. of veratral in 50 ml. of alcohol was treated with 1 ml. of 40% sodium hydroxide and refluxed for two hours. The clear, colored solution was allowed to cool (overnight) and the solid that formed collected on a filter. The solid was digested with 200 ml. of alcohol and again filtered. The yield was 6.5 g.; m. p. 198–205°. Recrystallization of the material from acetic acid or ethyleneglycolmonomethyl ether gave products that still showed indefinite melting points. The crude material was analyzed.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.7; H, 5.8; N, 8.1. Found: C, 61.5; H, 5.8; N, 8.1.

1-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxyphthalazine.—The hydrazone (5 g.) was placed in 50 ml. of amyl alcohol saturated with hydrogen chloride and heated under reflux for one hour on the steam-bath and for one hour at the boiling point. The cooled mixture was filtered and the solid shaken with 50 ml. of 10% sodium hydroxide. The solid was separated by filtration, washed with water, and recrystallized from alcohol. The yield of yellow crystals was 1.6 g.; m. p. 193–194°.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.3; H, 5.5; N, 8.6. Found: C, 66.2; H, 5.9; N, 8.2.

6-Piperonoylaminopiperonal.—A mixture of 3.3 g. of 6-aminopiperonal,[11] 3.7 g. of piperonoyl chloride, 1.6 g. of pyridine, and 75 ml. of xylene was refluxed for one hour. The solution was filtered from a small amount of gummy material and the required product separated from the filtrate. The yield was 3.2 g.; m. p. 221°.

Anal. Calcd. for $C_{16}H_{12}NO_6$: C, 61.3; H, 3.5; N, 4.5. Found: C, 61.6; H, 4.0; N, 4.6.

This material was also prepared from the aminoaldehyde and the acid chloride in acetic acid containing sodium acetate. The yield was not as good.

2-(3′,4′-Methylenedioxyphenyl)-6,7-methylenedioxyquinazoline.—6-Piperonoylaminopiperonal (3 g.) was placed in a small pressure bottle, 125 ml. of ethanol added, and the mixture saturated with ammonia. The bottle was sealed and shaken for two and one-half hours at 80–85°. The mixture was cooled and filtered to recover the solid that separated. The yield was 2.5 g.; m. p. 248–249°. The solid was dissolved in xylene; the solution was decolorized and filtered. On cooling, yellow crystals of melting point 248–249° were obtained.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4: N, 9.5. Found: C, 65.7; H, 3.8; N, 9.8.

6-Aminopiperonitrile.—6-Nitropiperonitrile[2] (20 g.) was added in portions to a solution of 100 g. of stannous chloride dihydrate in 100 ml. of hydrochloric acid. The temperature was maintained between 40–50° by cooling when necessary. When complete solution had resulted, the mixture was chilled in ice and treated slowly with sodium hydroxide solution until an excess had been added. During the addition, the temperature was maintained below 40°. The solid was collected on a filter, dried, and extracted with boiling methanol. On dilution with water, the methanol filtrate deposited, on cooling, 14 g. of pale yellow crystals; m. p. 142°.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.2; H, 3.6; N, 17.0.

Schiff Base from 6-Aminopiperonitrile and Piperonal.—A solution of 8.7 g. of 6-aminopiperonitrile and 8.5 g. of piperonal in 170 ml. of alcohol was refluxed for one hour. The addition of a drop of sulfuric acid caused immediate formation of a precipitate. The mixture was allowed to reflux for one hour and then cooled. The solid was collected, washed with alcohol, and ether. The yield was 14 g., 88%. A small sample was recrystallized from alcohol; m. p. 184°.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.3; H, 3.4; N, 9.5. Found: C, 65.9; H, 3.5; N, 9.4.

6-Aminoveratronitrile was prepared by a procedure very similar to that just described for 6-aminopiperonitrile. It was obtained in 82% yield and melted at 99–100°. McKee, McKee and Bost[15] record a melting point of 92–93.5° for the compound.

Summary

1. It has been shown that the so-called "anthraquinonediimines" obtained from certain nitriles are in reality triazine derivatives; the reaction is a trimerization rather than a dimerization, as originally reported.

2. The synthesis of certain quinazolines and phthalazines is described.

3. A procedure for the preparation of 6-aminopiperonitrile is given.

ROCHESTER 4, NEW YORK RECEIVED JANUARY 14, 1948

(15) McKee, McKee and Bost, THIS JOURNAL, **68**, 1903 (1946).

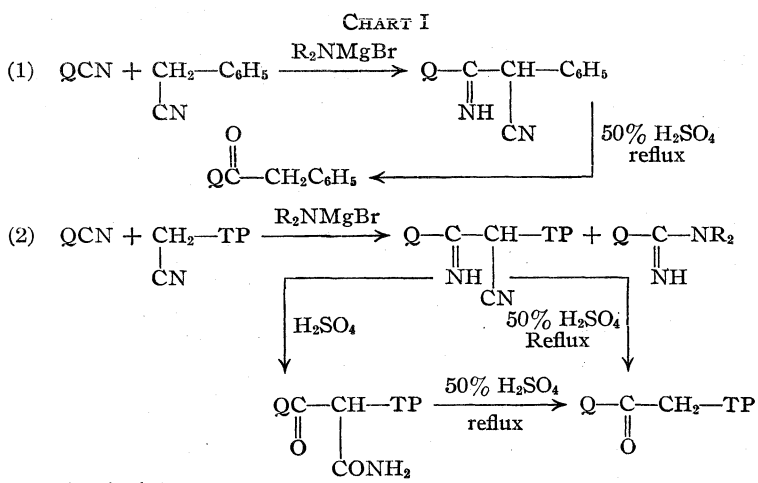
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Reaction of Halogenomagnesium Dialkylamides with Nitriles. The Preparation of N,N-Disubstituted Amidines

BY EMIL LORZ AND RICHARD BALTZLY

The 4-acyl quinolines required for a variety of syntheses are usually prepared by Claisen-type condensations of ethyl cinchoninate or its derivatives with the appropriate aliphatic esters. Since cinchoninic acid is most conveniently obtained by the hydrolysis of 4-cyanoquinoline it seemed likely that a more economical synthesis would be provided by a Ziegler type condensation of 4-cyanoquinoline itself with the desired nitrile using lithium or halomagnesium dialkylamides as the condensing agents. This expectation was realized in a model experiment, phenylacetonitrile and 4-cyanoquinoline reacting in the presence of bromomagnesium dibutylamide to give in 66% yield of α-phenyl-β-(4-quinolyl)-β-imidopropionitrile from which 4-phenacetylquinoline was obtained by refluxing with sulfuric acid (50% by volume). The course of these reactions is shown by equation 1.

CHART I



Q = 4-quinolyl
TP = 4-tetrahydropyranyl

When, however, 4-tetrahydropyranacetonitrile was used in place of phenylacetonitrile the principal product obtained was a basic substance that survived refluxing with 50% sulfuric acid and which was eventually shown to be N,N-di-*n*-butylquinoline-4-carboxamidine. This substance had evidently been produced by an addition of the bromomagnesium dibutylamide to 4-cyanoquinoline, a reaction that was not anticipated since Ziegler and Ohlinger[1] reported that the metal derivatives of secondary amines did not add to nitriles. Ziegler operated exclusively with aliphatic nitriles and it would appear from examination of his procedures and comparison with our own that the addition reaction must proceed much more rapidly with aromatic nitriles than with aliphatic. Addition does take place with aliphatic nitriles, however, since in a later experiment using bromomagnesium di-*n*-amylamide, 4-cyanoquinoline and tetrahydropyranacetonitrile, a small amount of N,N-di-*n*-amyltetrahydropyran-4-acetamidine was obtained. Since the properties of this type of amidine are unfavorable for isolation it is to be presumed that homologous substances were formed in traces in other experiments also. A recent paper by Hullin, Miller and Short[2] on the synthesis of amidines by the addition of magnesium amides to nitriles lends support to this belief as these authors report the formation of N,N-diethylvaleramidine in 26% yield by the reaction of bromomagnesium diethylamide with valeronitrile.

Further investigation showed that under suitable conditions, 40–50% yields of α-tetrahydropyranyl-β-(4-quinolyl)-β-imidopropionitrile could be obtained but that 4-quinoline-N,N-dialkylcarboxamidines were also formed in comparable amounts. This finding and subsequent transformations of the imidonitrile are represented by equation 2. This picture was not significantly altered by the use of lithium dialkylamides and, after this was ascertained, the more convenient magnesium compounds were used exclusively. Since amidines were being obtained in any case, a number of preparations of the imidonitrile were made using available secondary amines in the condensation, the corresponding amidines being isolated as by-products.

The amidines XII, XIV, XVI and XVII were tested for anti-plasmodial action, of which they proved to be devoid. General pharmacological screening, however, showed the presence of local anesthetic activity. When the antimalarial program was suspended it appeared advisable to investigate the addition of halomagnesium dialkyl amides to nitriles as a preparative method and a program was initiated with the object of learning the limitations and utility of the method and also of studying the pharmacology of the amidines produced. This report is concerned primarily with the first part of the program.

During the preparation of this paper the publication of Hullin, Miller and Short[2] appeared. It

(1) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(2) Hullin, Miller and Short, *J. Chem. Soc.*, 394 (1947).

deals largely with the same subject, but while our findings are in general agreement with theirs we are able to augment and extend their experiments in some respects.

Hullin, Miller and Short found this amidine preparation to be most useful when an aromatic nitrile reacted with a magnesium dialkylamide. The yield was somewhat less when the magnesium amide was derived from methylaniline and the reaction failed with bromomagnesium diphenylamide. This is in agreement with our own experiments. It would appear that the metal–nitrogen bond acquires more of a salt-like character as the acidity of the amine increases and that this sets a limit on the ability of the metal amide to behave as a nitrogen–Grignard reagent. The British authors also found the magnesium amides obtained from aniline and benzylamine to add less readily to aromatic nitriles than bromomagnesium diethylamide. This seems inconsistent with the work of Ziegler and Ohlinger in which amidine formation was prominent when bromomagnesium ethylamide reacted with dialkyl acetonitriles but was absent when bromomagnesium diethylamide was used. Each group of workers operated with nitriles of restricted variety, however, and it is probable that further investigation will resolve this inconsistency.

While we are in agreement with Hullin, Miller and Short that the addition of halomagnesium dialkylamides to aliphatic nitriles is of small preparative value, we have had somewhat more favorable experience with aromatic nitriles, the yields in such cases being generally good. In one respect this reaction is considerably superior to the classical Pinner[3] method. As might be predicted from Kadesch's[4] discussion of steric hindrance in aromatic ketones, this addition is little subject to hindrance. Whereas the Pinner method is reported to fail with *o*-tolunitrile and α-naphthonitrile[5] amidines have been prepared from both by the present procedure in satisfactory yield. Furthermore, both 2-methoxyl-1-naphthonitrile and cyanomesitylene react with bromomagnesium di-*n*-butylamide with no apparent difficulty.

If halomagnesium dialkylamides be supposed to act in essentially the same manner as a Grignard reagent, they should add to some at least of the functions characteristically vulnerable to ordinary Grignard reagents. Most of the products to be expected from such reactions, however, would be either unstable or more readily accessible by other methods. It did seem possible that the reaction $R'R^2NMgBr + RX \rightarrow RR'R^2N + MgBrX$ would be of value in the preparation of tertiary amines. This possibility was explored by refluxing *n*-butyl bromide in ethereal solution with bromomagnesium benzyl-*n*-butylamide. After three hours less than 10% of tertiary amine had been formed showing that reaction in the expected fashion was not rapid and that consequently selective alkylation was improbable.

(3) Pinner, "Die Imidoäther und ihre Derivate," Berlin, Germany, 1890.

(4) Kadesch, THIS JOURNAL, **66**, 1207 (1944).

(5) Pinner, *Ber.*, **23**, 161 (1890).

Experimental

Physical and analytical data on the amidines prepared are shown in Table I. All melting points are corrected.

General Procedure for the Addition Reactions.—To a solution of ethylmagnesium bromide containing about 50% excess Grignard reagent (on the basis of the nitrile to be used) was added gradually a slight excess of the secondary amine. Evolution of ethane generally continued for about thirty minutes.[1] The solution was then refluxed fifteen to twenty minutes further and the nitrile was added, usually in ethereal solution, but in some cases dissolved in benzene (for reasons of solubility). After the solutions had been refluxed for two to three hours or occasionally longer (as indicated in Table I), the reaction mixtures were decomposed with ice and ammonium chloride solution and worked up further according to three general procedures.

Method A.—The total material from the hydrolysis of the reaction mixture was made strongly alkaline. The amidine base and remaining secondary amine were taken into ether, dried, and separated by distillation *in vacuo*. This procedure was preferred for the more volatile amidines.

Method B.—The material from the hydrolysis of the reaction mixture was steam distilled, thereby removing unreacted nitrile and secondary amine. It was usually necessary to add some strong alkali in order to ensure volatilization of secondary amine. The residual material was then made strongly alkaline and the remaining bases were taken into ether. When quite involatile secondary amines were employed (di-octylamine) it was advantageous to extract the ethereal layer with successive inadequate amounts of dilute hydrochloric acid, a separation being thus obtained of stronger from weaker bases. The aqueous extracts were made acid to congo paper, evaporated separately *in vacuo* and the residues were crystallized from suitable solvents.

Method C.—In certain cases, the amidine base precipitated during the hydrolysis of the reaction mixture with ammonium chloride solution. The bulk of the product could thus be filtered off at this stage. It was usually necessary to partition it between dilute sodium hydroxide solution and benzene in order to free the base of small amounts of magnesium salts. The bases could then be acidified with ethanolic hydrogen chloride solution and crystallized as the hydrochlorides.

All the amidines here reported crystallized readily as the hydrochlorides though seldom in characteristic form. Most of the crystals appeared to be stubby prisms or rhombs. The acridine derivative (XI) and the dibenzylbenzamidine (XIII) were crystallized from absolute ethanol; the piperazine derivative XXIV, was crystallized from 95% ethanol. All the others were purified by crystallization from ethanol–ether mixtures.

α-Phenyl-β-(4-quinolyl)-β-imidopropionitrile.—Preliminary experiments using benzonitrile and benzyl cyanide had indicated that the best conditions for condensation were obtained when the two nitriles were added simultaneously.

To a solution of ethylmagnesium bromide prepared from 3.7 g. of magnesium and 16.5 g. (0.15 mole) of ethyl bromide in 200 cc. of ether was added 20 g. (0.155 mole) of di-*n*-butylamine. The solution was refluxed fifteen minutes after addition and a solution of 12 g. (0.1 mole) of benzyl cyanide and 15.5 g. (0.1 mole) of 4-cyanoquinoline dissolved in a mixture of benzene and anisole was added gradually. There was considerable heat of reaction and a red color appeared followed by precipitation of an orange solid. The mixture was refluxed for five hours and allowed to stand overnight. The orange precipitate was filtered off and washed with benzene. The filtrate and precipitate were hydrolyzed separately with ammonium chloride solution, the former eventually yielding 1.5 g. of the condensation product. The precipitate on hydrolysis

TABLE I

N,N-DIALKYLAMIDINE HYDROCHLORIDES, $R-C(=NH_2\cdot Cl)-NR'_2$

No.	R	R′	Method of isolation	Yield, %	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	Phenyl	*n*-Butyl	A	82[a]	174[b]	$C_{15}H_{25}ClN_2$	67.02	9.37	67.07	9.29
II	*o*-Tolyl	*n*-Butyl	A	70[a]	192[c]	$C_{16}H_{27}ClN_2$	67.94	9.62	68.19	9.80
III	*o*-Methoxyphenyl	*n*-Butyl	B	45[d,e]	161	$C_{16}H_{27}ClN_2O$	64.30	9.11	64.14	9.13
IV	*o*-Chlorophenyl	*n*-Butyl	B	83[e]	234	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.50	8.15
V	*m*-Chlorophenyl	*n*-Butyl	B	70[e]	170	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.40	7.90
VI	*p*-Chlorophenyl	*n*-Butyl	B	80[e]	149	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.37	8.04
VII	*p*-Dimethylaminophenyl	*n*-Butyl	B	74[e]	197	$C_{17}H_{30}ClN_3$	65.46	9.70	65.70	9.82
VIII	Styryl	*n*-Butyl	C	55[f]	204	$C_{17}H_{27}ClN_2$	69.24	9.23	69.06	9.24
IX	1-Naphthyl	*n*-Butyl	B	72[e]	211	$C_{19}H_{27}ClN_2$	71.53	8.54	71.38	8.48
X	2-Methoxy-1-naphthyl	*n*-Butyl	C	63[d,f]	196	$C_{20}H_{29}ClN_2O$	68.84	8.38	68.83	8.45
XI	9-Acridyl	*n*-Butyl	B	69[d,e]	285 (dec.)	$C_{22}H_{28}ClN_3$	71.42	7.63	71.33	7.49
XII	4-Tetrahydropyranyl-methyl	*n*-Amyl		[g]	128	$C_{17}H_{35}ClN_2O$	64.02	11.06	63.76	11.12
XIII	Phenyl	Benzyl	C	66[f]	228	$C_{21}H_{21}ClN_2$	74.87	6.28	74.55	6.44
XIV	4-Quinolyl	Ethyl		[g]	213.5 (dec.)	$C_{14}H_{18}ClN_3$	63.75	6.88	63.92	7.00
	Base of XIV			[h]	111	$C_{14}H_{17}N_3$	73.97	7.54	74.16	7.20
XV	4-Quinolyl	*n*-Propyl	B	80[e]	266 (dec.)	$C_{16}H_{22}ClN_3$	65.85	7.60	65.87	7.58
XVI	4-Quinolyl	*n*-Butyl		[g,i]	214	$C_{18}H_{26}ClN_3$	67.57	8.20	67.66	8.47
XVII	4-Quinolyl	*n*-Amyl		[g]	151 (dec.)	$C_{20}H_{30}ClN_3$	69.11	8.72	69.00	8.80
XVIII	4-Quinolyl	*n*-Hexyl	B	69[e]	159	$C_{22}H_{34}ClN_3$	70.28	9.12	70.35	9.09
XIX	4-Quinolyl	*n*-Heptyl	B	70[e]	154–155	$C_{24}H_{38}ClN_3$	71.34	9.48	71.42	9.30
XX	4-Quinolyl	*n*-Octyl	B	60[e]	149	$C_{26}H_{42}ClN_3$	72.27	9.80	72.21	9.64
XXI	Mesityl	*n*-Butyl	B	72[e,l]	254–255	$C_{18}H_{31}ClN_2$	69.54	10.05	69.54	10.30
XXII	N-Phenyl-N-*n*-butyl benzamidine hydrochloride		A	50[a,k]	214	$C_{17}H_{21}ClN_2$	70.69	7.33	70.55	7.37
XXIII	1-Phenyl carbimido-1,2,3,4-tetrahydroquinoline hydrochloride		B	45[e]	229 (dec.)	$C_{16}H_{17}ClN_2$	70.45	6.28	70.45	6.27
XXIV	N-Benzyl-N′-phenylcarbimido piperazine dihydrochloride		C	52[f]	267 (dec.)	$C_{18}H_{23}Cl_2N_3$	61.36	6.58	61.22	6.59

[a] Yield calcd. on weight of distilled base. [b] B. p. of base, 120–121° (1 mm.). [c] B. p. of base, 140° (1 mm.). [d] The nitrile was dissolved in benzene for addition to the bromomagnesium dialkylamide. [e] Yield calcd. on weight of purified hydrochloride. [f] Yield calcd. on weight of crude base precipitated during hydrolysis of reaction mixture. [g] Obtained as byproduct in condensation. [h] Crystallized from ethyl acetate–ether mixture. [i] B. p. of base, 180–190° (1 mm.). [k] B. p. of base, 172° (1 mm.). [l] After addition of the nitrile the solution was allowed to stand for sixteen hours at room temperature and refluxed five hours longer. Allowing for recovered cyanomesitylene, the yield was 93%.

changed to a sandy solid which was washed successively with methanol and ether, wt. 16.5 g. This substance after crystallization from alcohol formed cream-colored prisms, m. p. 189–190°.

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.67; H, 4.83, Found: C, 79.80; H, 5.15.

4-Phenacetylquinoline.—On addition of 5.5 g. of the imidonitrile to a solution of 25 cc. of concd. sulfuric acid and 25 cc. of water an orange-red solid (presumably a sulfate) precipitated. The mixture was heated cautiously at first as there was considerable frothing. The red color faded gradually being succeeded by a deep yellow. After four hours of refluxing the solution was cooled and basified with sodium carbonate. A yellow oil separated which solidified and was recrystallized first from dilute methanol, then from ether–hexane mixture. It then formed colorless rectangular plates melting at 89–89.5°.

Anal. Calcd. for $C_{17}H_{13}ON$: C, 82.53; H, 5.30. Found: C, 82.62; H, 5.50.

α-(4′-Tetrahydropyranyl)-β-(4-quinolyl)-β-imidopropionitrile.—To a solution in 200 cc. of ether of ethylmagnesium bromide prepared from 10 g. of magnesium and 43.6 g. (0.4 mole) of ethyl bromide was added 51.6 g. (0.4 mole) of di-*n*-butylamine. The solution was refluxed for one-half hour and a solution in 400 cc. of 50% anisole–benzene of 30.8 g. (0.2 mole) of 4-cyanoquinoline and 25.2 g. (0.203 mole) of tetrahydropyran-4-acetonitrile was added rapidly. The reaction mixture was refluxed one-half hour (longer reaction times affected the yield adversely) and poured into a solution of 40 g. of ammonium chloride in 200 cc. of ice water. At this stage a faint but definite odor of hydrogen cyanide could be noted. A considerable amount of solid (the imidonitrile) separated at this point and was filtered off and washed with water and ether. The combined filtrates and washings were steam-distilled and the residue was extracted with ether. A further portion of imidonitrile separated during this extraction and was added to the earlier crop. The ethereal extract was dried over potassium carbonate and yielded, on acidification with ethanolic hydrogen chloride, 20 g. of crude N,N-di-*n*-butyl cinchoninamidine hydrochloride (XVI).

The imidonitrile obtained from the hydrolysis of the reaction mixture (weight, 28.6 g.) was not free of magnesium, was very high-melting and virtually insoluble in organic solvents. When dissolved in iced 3 *N* hydrochloric acid and cautiously basified it could be obtained substantially pure.

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.07; H, 6.14. Found: C, 72.79; H, 6.43.

α-(4′-Tetrahydropyranyl)-β-(4-quinolyl)-β-oxopropionamide.—Five grams of the imidonitrile was allowed to stand overnight at room temperature with 8 cc. of concd. sulfuric acid and 2 cc. of water. In the morning the resultant solution was poured onto ice. A light yellow pre-

cipitate formed which was collected and crystallized from absolute ethanol, m. p. 211° (dec.).

Anal. Calcd. for $C_{17}H_{19}N_2O_3 \cdot H_2SO_4$: C, 51.36; H, 5.33; N, 7.06. Found: C, 51.30; H, 5.19; N (Dumas), 6.99.

4-Quinolyl-4'-tetrahydropyranylmethyl Ketone.—Twenty-eight grams of the crude imidonitrile was allowed to stand for two days with 100 cc. of concd. sulfuric acid. The solution was then diluted with 100 cc. of water and the whole was refluxed five hours. The mixture was cooled, diluted and basified with sodium carbonate. The precipitated oil was taken into ether, dried over potassium carbonate and acidified with 48% hydrobromic acid. The hydrobromide crystallized from absolute ethanol as yellow plates melting at 214° (dec.).

Anal. Calcd. for $C_{16}H_{18}NO_2 \cdot HBr$: C, 56.97; H, 5.68. Found: C, 56.75; H, 5.73.

In our hands the bromination of both 4-phenacetyl quinoline and the corresponding tetrahydropyranyl ketone proved quite unsatisfactory. A number of products were isolated but their identity was dubious and they proved valueless for synthetic purposes.

Acknowledgment.—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel W. Blackman for the micro-analyses here recorded.

Summary

1. The condensations of 4-cyanoquinoline with benzyl cyanide and tetrahydropyrane-4-acetonitrile using halomagnesium dialkylamides as condensing agents have been studied. While feasible, these condensations appear inferior to the more usual ester condensations, a marked complication being amidine formation between the condensing agent and the aromatic nitrile.

2. The additions of halomagnesium dialkyl or alkyl aryl amides to aromatic nitriles proceed readily and with good yields, thus constituting a useful synthesis of N,N-disubstituted amidines. A particular advantage of the reaction is its relative independence of steric hindrance.

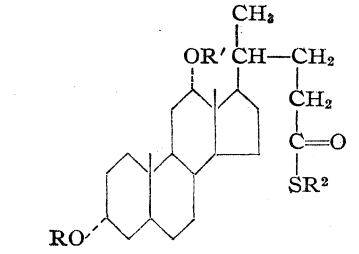
TUCKAHOE 7, NEW YORK RECEIVED AUGUST 27, 1947

[CONTRIBUTION FROM THE RESEARCH DIVISION, THE UPJOHN COMPANY]

Steroid Acids and Their Transformation Products. II. Desulfurization of Thiol Esters of Desoxycholic Acid[1a]

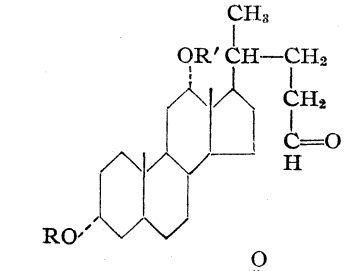
BY GEORGE B. SPERO, A. VERN MCINTOSH, JR., AND ROBERT H. LEVIN

The preparation of a number of thiol esters of steroid acids, including ethyl 3(α),12(α)-diformoxythiolcholanate (Ia),[1b] was reported recently.[2] According to the literature desulfurization of thiol esters with Raney nickel catalyst may yield alcohols[3] or aldehydes.[4] In our laboratory the course of the desulfurization of I was found to be dependent on the character of the Raney nickel catalyst. Using freshly prepared standard Raney nickel[5] the ethyl thiol ester (Ia) was converted to the cholane alcohol (III) and traces of the cholanic aldehyde (II). These results were obtained with 60 to 90% alcohol as a solvent, reflux times of one to five hours, and a ratio of 5 to 20 g. of catalyst per gram of thiol ester. When the more active W-4 Raney catalyst[6] was used, the thiol ester (Ia) was rapidly and quantitatively reduced and desulfurized to the alcohol (III). Karabinos[7] has suggested that if the reaction is interrupted immediately after the thiol ester has disappeared (as tested by odor after acidification) a good yield of



Ia, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = C_2H_5$

b, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = CH_2C_6H_5$



IIa, R = R' = $\overset{O}{\overset{\|}{C}}$H

b, R = H; R' = $\overset{O}{\overset{\|}{C}}$H

c, R = R' = H

(1a) Presented before the Division of Medicinal Chemistry at the 112th A. C. S. Meeting, New York, September, 1947.

(1b) Formulation of desoxycholic acid as 3(α),12(α) is according to the latest stereochemical evidence. For a discussion see the review article by Reichstein and Reich, *Ann. Rev. Biochem.*, **15**, 162 (1946).

(2) Levin, McIntosh, Spero, Rayman and Meinzer, THIS JOURNAL, **70**, 511 (1948).

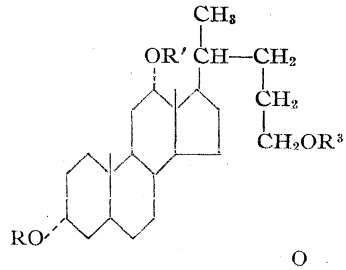
(3) (a) Prelog, Norymberski and Jeger, *Helv. Chim. Acta*, **29**, 360 (1946); (b) Jeger, Norymberski, Szpilfogel and Prelog, *ibid.*, **29**, 684 (1946); (c) Ruzicka, Szilfogel and Jeger, *ibid.*, **29**, 1520 (1946).

(4) Wolfrom and Karabinos, THIS JOURNAL, **68**, 1455 (1946).

(5) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 20.

(6) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(7) Private communication.



IIIa, R = R^3 = H; R′ = $-C(=O)-H$

b, R = R′ = R^3 = H

c, R = R′ = R^3 = $-C(=O)-CH_3$

aldehyde may be obtained. This method was not practical for us, apparently because even our standard Raney Nickel[5] was more active than the catalyst used by Wolfrom and Karabinos,[4,8] and also because of the small quantities of high molecular weight esters with which we were working.

However, we have been able to produce the cholanic aldehyde (II) in good yields by partially deactivating the standard Raney nickel. Two deactivation procedures were tried. Heating the catalyst with an inert solvent while passing a stream of nitrogen through for twenty-four hours did not give sufficient deactivation. Refluxing with acetone for two hours under standardized conditions was found to give reproducible results, and the aldehyde could then be obtained by adding the thiol ester in acetone–water and refluxing for an additional hour. The aldehyde (II) from ethyl 3(α),12(α)-diformoxythiolcholanate (Ia) was isolated in 60–80% yields as the crude semicarbazone, apparently a mixture of the mono- and diformoxy compounds. Separation of the pure diformyl compound as the semicarbazone by recrystallization could only be accomplished in low yield. The 2,4-dinitrophenylhydrazone of the crude aldehyde (II) was also prepared. The hydrochloric acid used in the dinitrophenylhydrazone preparation apparently caused the hydrolysis of both formyl groups. Benzyl 3(α),12(α)-diformoxythiolcholanate, (Ib) prepared by the previously described methods[2] but not crystallized, was similarly desulfurized to give the C-24 aldehyde. The free aldehyde was isolated from the crude reaction mixture via its bisulfite addition complex according to the procedure developed in this laboratory for the 3-substituted bisnor-Δ^5-cholenic aldehyde.[9] Hydrolysis of the formyl groups occurred during the process. Crystallization from dilute acetic acid and chloroform–hexane gave 3(α),12(α)-dihydroxycholan-24-al (IIc). The experimental data indicate that the desulfurization to produce the aldehyde takes place to the extent of 60–80%, but that the choice of a diformyl derivative has made the isolation of pure products difficult in this instance.

As previously noted,[2] the formoxy groups at positions 3 and 12 are not firmly bound. During the refluxing of ethyl 3(α),12(α)-diformoxythiolcholanate with W-4 Raney nickel in 80% ethanol there was complete deformylation at position 3 and partial deformylation at position 12, giving a mixture of 3(α),24-dihydroxy-12(α)-formoxycholane (IIIa), m. p. 185–186.5°, and 3(α),12(α),24-cholanetriol (IIIb), m. p. 90–125°, which could be separated by fractional crystallization. A better method of separation was chromatography over alumina which gave 60% of the triol monoformate (IIIa), and 40% of the triol (IIIb). When the monoformate (IIIa) was rechromatographed it was recovered unchanged, further indicating that deformylation at position 12 was not due to the alumina. Saponification of IIIa gave the triol (IIIb); however, the compound was difficult to purify to constant m. p. because it formed various hydrates. Acetylation with acetic anhydride and pyridine gave 3(α),12(α),24-triacetoxycholane (IIIc), which crystallized beautifully and gave good analyses. Saponification of the triacetate (IIIc) again gave a triol of unsharp m. p. and variously hydrated.

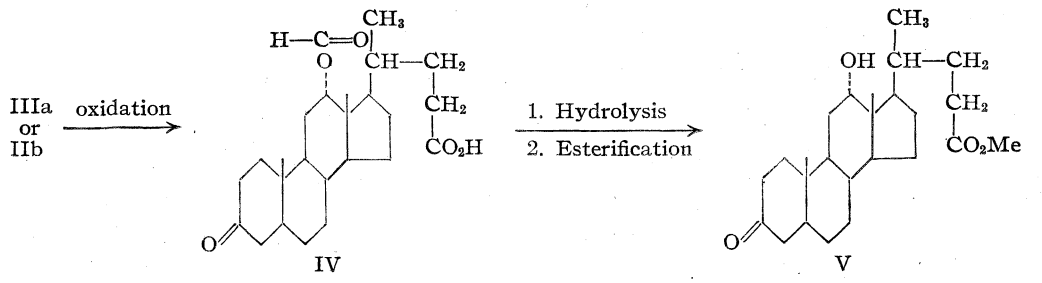
The structure of the monoformoxy triol (IIIa) was postulated as 3(α)-hydroxy,12(α)-formoxy because of the well-known greater ease of hydrolysis of 3-esters as compared to 12-esters in desoxycholic acid. To prove the correctness of this structure, the monoformate (IIIa) was oxidized with chromic acid in acetic acid at room temperature. The resulting 3-keto acid (IV) was not crystallized, but on hydrolysis followed by esterification gave a good yield of the known methyl 3-keto-12-(α)-hydroxycholanate (V).[10]

This series of reactions was repeated on the crude aldehyde (II) to give a 55% yield of methyl 3-keto-12(α)-hydroxycholanate (V). There remained the possibility that our conditions of oxidation might have caused deformylation and then a partial oxidation of the 3,12-dihydroxy compound to the 3-keto-12-hydroxycholanic acid. Accordingly, using the same experimental conditions, the cholantriol (IIIb) was oxidized to dehydrodesoxycholic acid and methyl diformyldesoxycholate (VI) was recovered substantially unchanged. Methyl diformyldesoxycholate, which apparently has not been recorded previously in the literature, was prepared by direct formylation of methyl desoxycholate. The diformyl compound (VI) was selectively deformylated in the 3-position using the chromatographic technique previously developed,[2] and the resulting 3-hydroxy com-

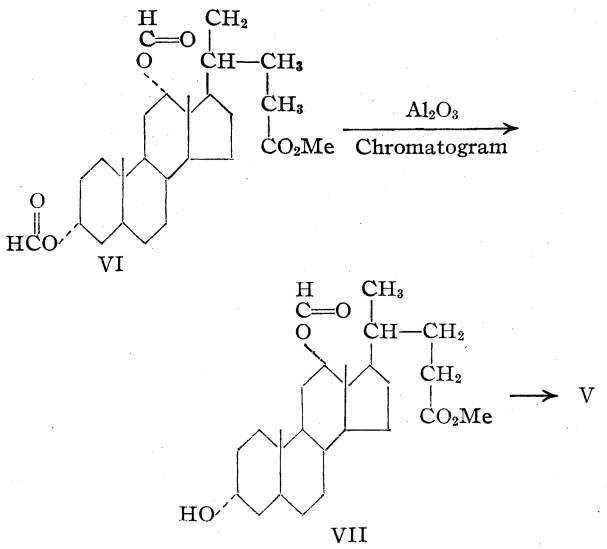
(8) In a check experiment we reduced ethyl thiol benzoate with standard Raney nickel catalyst following the directions of Wolfrom and Karabinos[4] and obtained just a trace of benzaldehyde. It is possible that the aldehyde is not even an intermediate in the formation of the alcohol from the thiol ester. Thus, in desulfurization experiments with ethyl 3(α),12(α)-diacetoxy-*nor*-thiolcholanate (to be reported shortly) we were able to obtain a good yield of alcohol, recovery of most of the remaining material as thiol ester, and just a trace of aldehyde, isolated as the semicarbazone.

(9) Centolella, Heyl and Herr, to be published shortly.

(10) Yamasaki and Kyogoku, *Z. physiol. Chem.*, **233**, 29 (1935).



pound (VII) was converted to methyl 3-keto-12-(α)-hydroxycholanate (V).



Experimental[11,12]

Desulfurization of Ethyl 3(α),12(α)-Diformoxythiolcholanate (Ia) with Deactivated Raney Nickel. Aldehyde Formation.—Standard Raney nickel[5] (20 g.) was added to 60 ml. of acetone and heated under reflux with mechanical stirring for two hours. A solution of 2 g. (0.004 mole) of the thiol ester (Ia) in 40 ml. of acetone and 40 ml. of water was then added and refluxing was continued for an additional hour. The catalyst was separated by filtration and the filtrate concentrated *in vacuo* to a volume of 50 ml., then extracted with 100 ml. of ether. The ether was washed in portions with 100 ml. of cold 1% sodium hydroxide, 100 ml. of 1 *N* hydrochloric acid and 300 ml. of water. After drying over anhydrous sodium sulfate and evaporating to dryness *in vacuo*, 1.8 g. of crude aldehyde was obtained as a colorless oil.

Anal. Calcd. for the diformoxy aldehyde (IIa) $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Calcd. for the monoformoxy aldehyde (IIb) $C_{24}H_{40}O_4$: C, 74.21; H, 9.97. Calcd. for the dihydroxy aldehyde (IIc) $C_{24}H_{40}O_3$: C, 76.54; H, 10.71. Found: C, 72.94, 73.06; H, 9.39, 9.59.

The **semicarbazone** was prepared from the crude aldehyde from the desulfurization of 2 g. of thiol ester. This was dissolved in 80 ml. of 3A alcohol[13] and a solution of 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate in 20 ml. of water was added. The resulting solution was heated under reflux for two hours, cooled, and the product precipitated by the addition of 200 ml. of water; yield 1.8 g., m. p. 170–185°. Several crystallizations from methanol gave a product melting at 217–220°.

Anal. Calcd. for the diformoxy semicarbazone $C_{27}H_{43}O_5N_3$: C, 66.23; H, 8.85; N, 8.58. Calcd. for monoformoxy semicarbazone $C_{26}H_{43}O_4N_3$: C, 67.64; H, 9.39, N, 9.10. Calcd. for diol semicarbazone $C_{25}H_{43}O_3N_3$: C, 69.24; H, 10.00; N, 9.68. Found: C, 66.44, 66.39; H, 8.49, 8.48; N, 8.36, 8.30.

The **2,4-dinitrophenylhydrazone** was prepared by dissolving 860 mg. of the crude aldehyde in 70 ml. of 3A alcohol and adding 560 mg. of 2,4-dinitrophenylhydrazine. The solution was heated to boiling and 1 ml. of hydrochloric acid added. After refluxing for twenty-five minutes the solution was concentrated to half volume and allowed to cool, giving 520 mg. of product, m. p. 105–140°. An additional 120 mg. of product was obtained by concentrating the mother liquor. These fractions were combined and recrystallized from methanol to give pure 2,4-dinitrophenylhydrazone, m. p. 157–158°.

Anal. Calcd. for the diformoxy derivative $C_{32}H_{44}O_8N_4$: C, 62.72; H, 7.24; N, 9.15. Calcd. for the monoformoxy derivative $C_{31}H_{44}O_7N_4$: C, 63.68; H, 7.59; N, 9.58. Calcd. for the dihydroxy derivative $C_{30}H_{44}O_6N_4$: C, 64.72; H, 7.97; N, 10.06. Found: C, 64.32, 64.48; H, 8.22, 8.23; N, 10.22, 10.29.

3(α),12(α)-dihydroxycholan-24-al (IIc) was obtained by treating the crude reaction product from the desulfurization of 3 g. of ethyl thiol ester (Ia) with sodium bisulfite and subsequent decomposition of the aldehyde bisulfite complex with sodium carbonate.[9] The yield of aldehyde material was 1.12 g. (49%). Saponification of the formyl groups occurs during this decomposition. The aldehyde was crystallized from 50 ml. of dilute acetic acid and then repeatedly from chloroform–hexane, giving 0.27 g. (12%), m. p. 155.5–156.6°.

Anal. Calcd. for $C_{24}H_{40}O_3 \cdot H_2O$: C, 73.05; H, 10.73. Found: C, 73.38; H, 10.22.

Benzyl 3(α),12(α)-diformoxythiolcholenate (1b), prepared from 4.5 g. (0.01 mole) of 3,12-diformoxydesoxycholic acid and 2.4 g. of lead benzyl mercaptide, but not crystallized, was similarly desulfurized using 40 g. of deactivated nickel in 160 ml. of acetone and 80 ml. of water to yield 3.72 g. of aldehyde fraction. Portions of this crude aldehyde were converted to the identical semicarbazone and 2,4-dinitrophenylhydrazone derivatives described above.

Treatment of Ethyl 3(α),12(α)-diformoxythiolcholanate (Ia) with W-4 Raney Nickel. Alcohol formation.—To 2.0 g. (0.004 mole) of the thiol ester (Ia) in 40 ml. of 3A alcohol was added 10 g. of W-4 Raney nickel catalyst[6] and 10 ml. of water. The mixture was heated under reflux for one hour and the catalyst was separated by filtration and washed with 20 ml. of 3A alcohol. The filtrate was diluted with 200 ml. of water and extracted with 3 100 ml. portions of ether. The ether phase was washed with 100 ml. of 0.15 *N* sodium hydroxide, 300 ml. of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue, which weighed 1.7 g., was dissolved in warm alcohol and water added to incipient cloudiness. On cooling, 0.7 g. of oil settled out and was separated by decantation. The mother liquor was diluted with water and cooled, giving 0.47 g. of crystalline material, m. p. 143–160°. Three crystallizations from alcohol–water

(11) All analyses and rotations by the Upjohn microanalytical group.

(12) All m. p.'s are corrected unless otherwise indicated.

(13) 3A alcohol is commercial 95% alcohol denatured by the addition of 5% methanol.

gave pure 3(α),24-dihydroxy-12(α)-formoxycholane (IIIa), m. p. 185–186.5°; $[\alpha]^{25}D$ + 86.6° (100.5 mg. in 10 cc. chloroform; 1 dcm. tube; α, +0.87°).

Anal. Calcd. for $C_{25}H_{42}O_4$: C, 73.84; H, 10.41. Found: C, 73.91; H, 10.46.

Further dilution of the mother liquor, after separation of (IIIa), yielded 0.37 g. of 3(α),12(α),24-trihydroxycholane (IIIb), m. p. 90–110°. We were unsuccessful in purifying this compound to a sharp m. p. because of its tendency to solvate. It crystallized nicely from acetone–benzene, m. p. 105–125°, and from alcohol–water, m. p. 106–118°. However, it formed a beautiful triacetoxy compound, m. p. 79.5–80.5°, which will be described below.

Although IIIa and IIIb could be separated by fractional crystallization, chromatography over alumina[14] proved to be a much better method. A portion of the crude reaction product (850 mg.) was dissolved in 150 ml. of benzene and the solution was run through 39 g. of alumina contained in a column 2 cm. in diameter. The column was eluted with three 33-ml. portions each of benzene, benzene and 0.4% methanol, benzene and 1% methanol, benzene and 2% methanol, benzene and 4% methanol, and benzene and 8% methanol. Two separate fractions were obtained. In the benzene and 4% methanol there was 538 mg. of compound IIIa, m. p. 182–186°, and in the benzene and 8% methanol there was 232 mg. of the triol (IIIb), m. p. 90–120°.

The monoformoxy compound (IIIa) (115 mg.) was dissolved in 30 ml. of benzene and chromatographed over 9.7 g. of alumina in a column 1.2 cm. in diameter. The column was eluted with 7 ml. portions of solvent as outlined above. The benzene and 4% methanol fraction contained 107 mg. of unchanged 3(α),24-dihydroxy-12(α)-formoxycholane, m. p. 185–186.5.

Saponification of 3(α),24-Dihydroxy-12(α)-formoxycholane (IIIa). The monoformoxy compound (IIIa) (300 mg.) was dissolved in 10 ml. of 5% methanolic sodium hydroxide solution and heated under reflux for ninety minutes. After cooling the solution was diluted with 30 ml. of water and extracted with ether. The ether extract was washed until neutral, dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization of the residue from 3A alcohol and water gave 290 mg. of 3(α),12(α),24-cholantriol (IIIb), m. p. 90–102°.

3(α),12(α),24-triacetoxycholane (IIIc) was formed by acetylating 1 g. of the triol (IIIb) with 15 ml. of acetic anhydride and 15 ml. of pyridine under reflux for two and one-half hours. After three recrystallizations from 3A alcohol and water 640 mg. of product was obtained, m. p. 79.5–80.5°; $[\alpha]^{25}D$ +93.6° (99.4 mg. in 10 ml. chloroform; 1 dcm. tube; α, +0.93°).

Anal. Calcd. for $C_{30}H_{47}O_6$: C, 71.39; H, 9.59; CH_3CO, 25.59. Found: C, 71.43; H, 9.46; CH_3CO, 26.96.

Saponification of 500 mg. of pure 3(α),12(α),24-triacetoxycholane (IIIc), m. p. 79.5–80.5°, yielded 350 mg. of triol, m. p. 100–110°, after repeated crystallizations.

Conversion of 3(α),24-Dihydroxy-12(α)-formoxycholane (IIIa) to Methyl 3-Keto-12(α)-hydroxycholanate (V).—To 100 mg. of IIIa was added 8 ml. of a solution of 1% chromic acid in 95% acetic acid and the resulting solution was allowed to stand at room temperature for thirty minutes. It was then diluted to 40 ml. with water and extracted with 50-ml. of ether, in portions. The ether phase was washed with water and was extracted with 80 ml. of 1% sodium hydroxide solution. The basic extract was acidified with 10% hydrochloric acid and was extracted with 50 ml. of ether. After washing with water and drying over anhydrous sodium sulfate, the ether was removed by evaporation to yield 103 mg. of 3-keto-12(α)-formoxycholanic acid as an oil which was not crystallized.

The oil was dissolved in 20 ml. of 2% ethanolic sodium hydroxide and the solution was refluxed for thirty minutes, cooled, acidified with 10% hydrochloric acid, diluted to four times its volume with water and extracted with 70 ml. of ether. The ether extract was washed with water, dried and evaporated to dryness. The residue, 84 mg., was dissolved in 10 ml. of methanol and 0.2 ml. of acetyl chloride was added. After standing for sixteen hours at room temperature, the solution was diluted to four times its volume with water and extracted with 50 ml. of ether. The ether phase was washed with 30 ml. of 1% sodium hydroxide solution and with water, dried and evaporated to dryness. The residue crystallized on scratching. The yield of methyl 3-keto-12(α)-hydroxycholanate (V) was 72 mg., m. p. 124–139°. Recrystallization from acetone and water, and from acetone and petroleum ether, gave a pure product, m. p. 142–145°. The mixture melting point with an authentic sample showed no depression.

Using the above series of reactions, the following additional conversions to known compounds were made: 100 mg. of the crude aldehyde (probably a mixture of IIa and IIb) gave 59 mg. of V. 221 mg. of methyl 3(α)-hydroxy-12(α)-formoxycholanate (VII) gave 163 mg. of V. 100 mg. of 3(α),12(α),24-trihydroxycholane (IIIb) was oxidized as above to yield 86 mg. of dehydrodesoxycholic acid, m. p. 170–178°. Recrystallized twice from alcohol and water, m. p. 180–184°. An admixture with an authentic sample showed no m. p. depression.

Methyl 3(α),12(α)-Diformoxycholanate.—A solution of 5.0 g. of methyl desoxycholate was heated with 50 ml. of 87% formic acid at 55° for five hours. After diluting with water and working up as usual, crystallization from 170 ml. of 80% alcohol gave 2.8 g. of product, m. p. 78–81°. Two additional crystallizations from the same solvent yielded 2.0 g. of methyl diformyldesoxycholate, m. p. 81.5–82.5°; $[\alpha]^{25}D$ +99° (100 mg. in 10 ml. chloroform, αD, +0.99).

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.03; H, 9.15.

A 250-mg. sample of methyl diformoxycholanate was dissolved in benzene and passed over alumina. The main fraction, consisting of 221 mg. of material, was eluted with benzene +4% methanol and gave an $[\alpha]^{25}D$ of +74°. It was used directly for the oxidation described above.

Summary

1. The Raney nickel desulfurization of thiol esters of desoxycholic acid can be controlled to produce either the corresponding aldehyde or alcohol in good yield.

2. The structures of the resulting products were confirmed by their conversion into known keto derivatives of desoxycholic acid.

3. 3(α),12(α)-Dihydroxycholan-24-al, 3(α),12(α),24-trihydroxycholane, and various derivatives have been characterized.

KALAMAZOO, MICHIGAN RECEIVED DECEMBER 31, 1947

(14) The alumina used in our chromatographic work was "Fisher Adsorption Alumina" obtained from the Fisher Scientific Company and used without further treatment.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

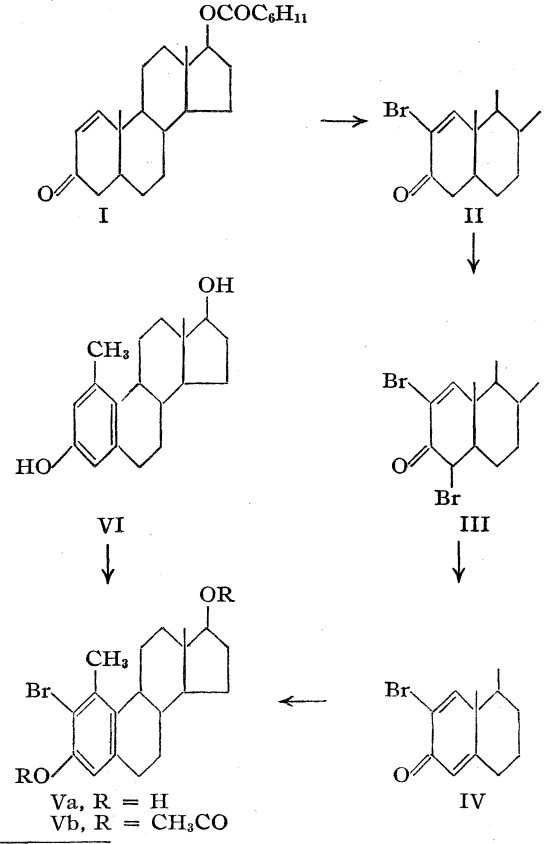
The Preparation and Dienone-Phenol Rearrangement of 2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate

BY CARL DJERASSI AND CAESAR R. SCHOLZ

In 1944, Huang-Minlon and co-workers[1] described the dienone–phenol rearrangement of bromosantonin to bromodesmotroposantonin. In connection with our work on such rearrangements in the steroid series,[2,3] we have studied the preparation and rearrangement of a brominated dienone, 2-bromo-1,4-androstadien-17-ol-3-one-17-hexahydrobenzoate (IV).[4] A recent report of such a rearrangement in the dihydronaphthalene series[5] prompts us to record our results at this time.

The Δ^1-2-bromo derivative II, required as starting material, has been prepared previously by dehydrobromination of the corresponding 2,2-dibromo-3-ketosteroid.[2,3,6] For comparison purposes, and also as an alternate synthesis for compounds of type II, we have studied the bromination of Δ^1-testosterone hexahydrobenzoate (I). With either bromine or pyridine hydrobromide perbromide[7] in glacial acetic acid, the ketone I took up one mole of bromine with the simultaneous evolution of hydrogen bromide. Since the reaction product was the Δ^1-2-bromo ketone II, it is evident that the primary phase was addition of bromine to the double bond, followed by spontaneous loss of hydrogen bromide. By comparison, the bromination of the Δ^1-2-bromo-3-ketone II proceeded at a very much slower rate and resulted in the stable substitution product III. The structure of the Δ^1-2,4-dibromo ketone III was proven by dehydrobromination with collidine, which led in 80% yield to the desired 2-bromo-1,4-androstadien-17-ol-3-one 17-hexahydrobenzoate (IV).[8] In the bromination of II leading to III, the net result is one of substitution rather than addition, but the reaction may also have occurred through primary addition to the double bond to form a 1,2,2-tribromo-3-ketone which rearranged to the unstable 1,2,4-tribromo isomer, followed by spontaneous loss of hydrogen bromide to yield ultimately III.

The dienone–phenol rearrangement of the brominated dienone IV occurred readily in acetic anhydride–sulfuric acid solution with the formation of 1-methyl-2-bromoestradiol (V),[9] which was purified in the form of its diacetate (Vb). 1-Methylestradiol (VI),[2] on monobromination should lead either to Va or the isomeric 1-methyl-4-bromoestradiol. Bromination of VI with pyridine hydrobromide perbromide[7] was found to proceed rapidly, resulting in a good yield of a monobromophenol, which was found to be identical with Va[10] prepared from IV by the dienone–phenol rear-



(1) Huang-Minlon, Lo and Chu, THIS JOURNAL, **66**, 1954 (1944).

(2) Wilds and Djerassi, *ibid.*, **68**, 1712, 1715, 2125 (1946).

(3) Djerassi and Scholz, *ibid.*, **69**, 2404 (1947).

(4) We are refraining at this time from assigning a configuration to the 17-hydroxyl group of the compounds described in this paper, which are all derived from dihydrotestosterone. In our earlier papers (ref. 2 and 3), the (α) configuration was employed, but recent work summarized by Miescher ("Recent Progress in Hormone Research," Vol. III, in press) seems to indicate that the 17-hydroxyl group possesses the (β) configuration (*cis* to the C-13 methyl group).

(5) Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947).

(6) Inhoffen and Zuehlsdorff, *Ber.*, **76**, 233 (1943).

(7) Djerassi and Scholz, THIS JOURNAL, **70**, 417 (1948).

(8) An examination of the ultraviolet absorption spectra of the three unsaturated ketones II, III and IV (Fig. 1) shows that introduction of a bromine atom in II shifts the maximum from 255 to 261 mμ (III), but that this bathochromic shift is nullified in converting III to the dienone IV, which again shows a maximum around 255 mμ.

(9) On the basis of the reaction conditions and considering the reaction mechanism (ref. 5), it is unlikely that rearrangement of the 2-bromo substituent to the 4-position should have occurred during the migration of the angular methyl group. Our rearrangement product, therefore, very probably has the assigned structure V. It should be noted, however, that in the two examples of the rearrangement of an α-bromo dienone recorded in the literature (refs. 1 and 5), the alternate position corresponding to C-4 in IV was blocked.

(10) The ultraviolet absorption spectra (Fig. 2) of Va and Vb showed the characteristic differences established previously (see ref. 3) for phenols and their acetates, but the presence of the bromine atom resulted in a bathochromic shift of 5 mμ for the acetate and 7 mμ for the phenol. For comparison the spectra of 1-methylestradiol (VI) and its diacetate are also reproduced.

rangement, thus establishing a connecting link between the two series.

Experimental[11]

Bromination of Δ^1-Androsten-17-ol-3-one 17-Hexahydrobenzoate (I) (Δ^1-Testosterone Hexahydrobenzoate).—A solution of 100 mg. of the ketone I[3,6] in 2 cc. of C. P. glacial acetic acid was treated with 80 mg. of pyridine hydrobromide perbromide and the reaction mixture was warmed slightly until all the reagent dissolved. Decolorization was almost instantaneous and was accompanied by evolution of hydrogen bromide. After standing at room temperature overnight, the crude product was precipitated with water. Although it showed a single maximum at 254.5 mμ, characteristic for the Δ^1-2-bromo ketone II, the compound was seemingly contaminated by some dibromo derivative (Found: Br, 21.30). The crude product was purified readily by chromatographing over alumina, yielding 50 mg. (42%) of **Δ^1-2-bromoandrosten-17-ol-3-one 17-hexahydrobenzoate (II)**, which was shown to be identical with authentic material[2,3] by comparison of the melting points, rotations, absorption spectra and analysis (Calcd.: Br, 16.76, Found: Br, 16.37).

Δ^1-2,4-Dibromoandrosten-17-ol-3-one 17-Hexahydrobenzoate (III).—To a solution of 1.2 g. of the Δ^1-2-bromo ketone II[2,3,6] in 50 cc. of pure, fractionated glacial acetic acid (containing 13 mg. of water/10 cc. of acid; see ref. 3) was added 3 drops of 4 *N* hydrogen bromide in acetic acid followed by 6.25 cc. of a standard solution of bromine in acetic acid (1.6 g. of bromine in 25 cc. of pure acetic acid) and the reaction mixture was allowed to stand overnight. Decolorization was nearly complete after six hours. The solution was poured into cold water, the crude product was collected, washed well with water, dried and recrystallized from ethanol to yield 1.08 g. (77%) of Δ^1-2,4-dibromo ketone III of m. p. 143.5–146°, $[\alpha]^{24}D$ + 16.5°. The analytical sample crystallized from ethanol as colorless, prismatic needles with m. p. 147–148°, $[\alpha]^{24}D$ + 11.3°, maximum at 261 mμ, log E = 3.81, minimum at 230.5 mμ, log E = 3.27 (Fig. 1).

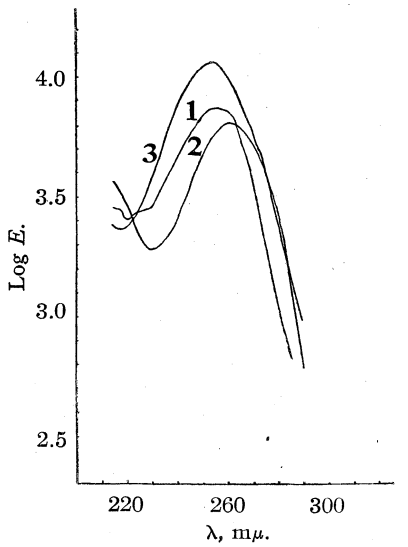


Fig. 1.—Ultraviolet absorption spectra (in 95% ethanol): curve 1, compound II; curve 2, compound III; curve 3, compound IV.

Anal.[12] Calcd. for $C_{26}H_{36}O_3Br_2$: C, 56.12; H, 6.52; Br, 28.73. Found: C, 56.14; H, 6.69; Br, 29.24.

Pyridine hydrobromide perbromide[7] could be substituted for bromine to effect bromination in the 4-position.

2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate (IV).—Dehydrobromination of the dibromo ketone III was effected by refluxing 0.5 g. of the ketone with 2.5 cc. of collidine[13] for one-half hour. The amount of collidine hydrobromide (0.17 g.), isolated by dilution with ether, filtering and washing with the same solvent, corresponded to 93% of the calculated quantity. The ether solution was washed several times with 5% hydrochloric acid solution, water, 5% sodium hydroxide solution, and again water, dried over sodium sulfate and the solvent was removed in a current of air. Trituration of the residue with hexane gave 0.35 g. (82%) of nearly colorless dienone of m. p. ranging from 132–137° to 139–142° which was satisfactory for the next step (Found: Br, 16.76). The compound crystallized from hexane as rosets of colorless, prismatic needles which retained solvent very tenaciously. When dried at 55° and 30 mm., the material melted at *ca.* 105–111° (turbid), resolidified and melted at 142–144°. The solvent was removed completely on drying at 130° and 0.1 mm. for five hours (m. p. 144°). The rotations of three different, dry samples were: $[\alpha]^{25}D$ +7.4°, 8.1°, 12.9°. The absorption spectrum is shown in Fig. 1, and exhibited a maximum at 254.5 mμ, log E = 4.06, and a minimum at 218 mμ, log E = 3.36.

Anal. Calcd. for $C_{26}H_{35}O_3Br$: C, 65.68; H, 7.42; Br, 16.81. Found: C, 65.76, 65.85; H, 7.73, 7.60; Br, 16.49.

1-Methyl-2-bromoestradiol-3,17-diacetate (Vb). (a) By Dienone–Phenol Rearrangement of 2-Bromo-1,4-androstadien-17-ol-3-one 17-Hexahydrobenzoate (IV).—The

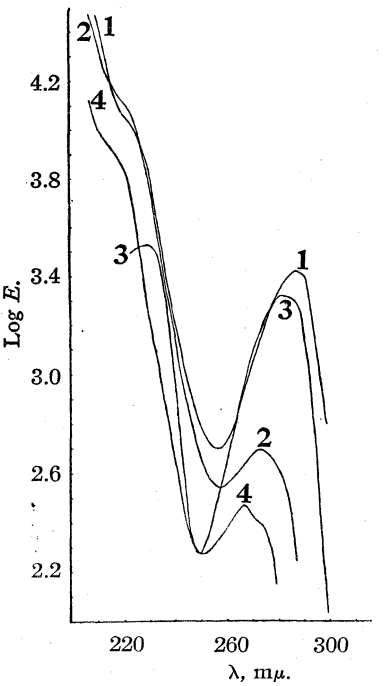


Fig. 2.—Ultraviolet absorption spectra (in 95% ethanol): curve 1, 1-methyl-2-bromoestradiol (Va); curve 2, 1-methyl-2-bromoestradiol diacetate (Vb); curve 3, 1-methylestradiol (VI); curve 4, 1-methylestradiol diacetate.

(11) All melting points are corrected. The optical rotations were determined on 5–10 mg. of sample in 1.2 cc. of chloroform using a 1-dcm. tube of 1-cc. capacity. The ultraviolet absorption spectra measurements were carried out in 95% ethanol solution using a Beckman Quartz Photoelectric Spectrophotometer; $E = 1/c \log I_0/I$ for a 1 cm. cell, where c is the concentration in moles per liter.

(12) All microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J., and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

(13) The γ-collidine used for the dehydrobromination was Eastman Kodak Co. white label product, which was fractionated before use.

dienone–phenol rearrangement was carried out by treating 0.26 g. of the 2-bromodienone IV in 5 cc. of acetic anhydride with 0.09 g. of concentrated sulfuric acid and allowing the solution to stand at room temperature for five hours. The mixture was poured into water, swirled to hydrolyze most of the acetic anhydride and the product was extracted with ether. After saponification by refluxing with 5% methanolic potassium hydroxide for seventy-five minutes, the crude 1-methyl-2-bromoestradiol was acetylated by means of acetic anhydride and pyridine, and the diacetate was precipitated by dilution with 5% hydrochloric acid. After recrystallization from ethanol, the colorless crystals (0.13 g., 53%) melted at 185–191°, $[\alpha]^{25}D$ + 126°. The analytical sample crystallized as colorless rosets of shiny needles and had the following constants: m. p. 192.5–194°, $[\alpha]^{25}D$ + 128°, maximum at 273 mμ, log E = 2.67, minimum at 256.5 mμ, log E = 2.44 (Fig. 2).

Anal. Calcd. for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.51; Br, 17.78. Found: C, 61.66; H, 6.58; Br, 18.10.

(b) By Bromination of 1-Methylestradiol (VI).—When a solution of 55 mg. of 1-methylestradiol (VI)[2] in 1.4 cc. of glacial acetic acid was warmed with 63 mg. of pyridine hydrobromide perbromide for *ca.* thirty seconds, decolorization resulted with evolution of hydrogen bromide. After standing for a few minutes, the product was precipitated by the addition of water, filtered, and acetylated as in (a) to give 60 mg. (70% over-all yield) of the diacetate of m. p. 188–192°. Further recrystallization led to crystals melting at 193–194.5°, $[\alpha]^{25}D$ + 125°, which gave no depression in m. p. when mixed with a sample prepared according to (a). The ultraviolet absorption spectrum was also practically identical with that shown for the above sample (method a), maximum at 272.5 mμ, log E = 2.70, minimum at 257.5 mμ, log E = 2.54.

1-Methyl-2-bromoestradiol (Va).—Sixty milligrams of the diacetate Vb on saponification with methanolic potassium hydroxide gave 40 mg. of 1-methyl-2-bromoestradiol (Va) of m. p. 166–167.5°. Recrystallization from hexane or dilute ethanol raised the m. p. to 167.5–169°, $[\alpha]^{24}D$ + 189°, 185°, maximum at 288.5 mμ, log E = 3.42, minimum at 257 mμ, log E = 2.70 (Fig. 2). The same material was obtained from samples of the diacetate prepared according to (a) and (b) above.

Anal. Calcd. for $C_{19}H_{25}O_2Br$: C, 62.47; H, 6.90; Br, 21.88. Found: C, 62.81; H, 7.05; Br, 21.63.

The authors are greatly indebted to Jean Rogers and Helen Dudek for assistance in the experimental work.

Summary

It has been shown that while the bromination of Δ^1-androsten-17-ol-3-one 17-hexahydrobenzoate (I) proceeded rapidly with the formation of the corresponding Δ^1-2-bromo-3-ketone II, the latter reacted only slowly with bromine to form Δ^1-2,4-dibromoandrosten-17-ol-3-one 17-hexahydrobenzoate (III). The dibromo compound was dehydrobrominated with collidine yielding a 2-bromo-1,4-dienone IV, which underwent the dienone–phenol rearrangement to 1-methyl-2-bromoestradiol (V). The latter was also obtained on direct bromination of 1-methylestradiol (VI), thus establishing a link between the two series.

SUMMIT, NEW JERSEY RECEIVED NOVEMBER 24, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Optical Activity of the 4,5-Phenanthrene Type: 4-(1-Methylbenzo[c]phenanthryl)-acetic Acid and 1-Methylbenzo[c]phenanthrene[1]

BY MELVIN S. NEWMAN AND WILLIAM B. WHEATLEY[2]

The theoretical considerations leading to the prediction of optical activity in compounds of the 4,5-dimethylphenanthrene type have been presented.[3] The structural feature necessary for this type of optical isomerism (called optical activity of the 4,5-phenanthrene type) involves the substitution in the 4 and 5 positions of phenanthrene of groups large enough to prevent their existence in the same plane as that of the aromatic rings. The preparation and resolution of one compound of this type, 4,5,8-trimethyl-1-phenanthrylacetic acid, have been described.[3b,c] In order to obtain an additional example of compounds exhibiting this type of optical activity we undertook the synthesis and resolution of 4-(1-methylbenzo[c]phenanthryl)-acetic acid, I. This has been successfully accomplished and is herein reported. We have also synthesized 1-methylbenzo[c]phenanthrene, II, the last monomethyl derivative of the parent hydrocarbon which remained to be prepared.[4] This compound is to be tested for carcinogenic activity.

The optical activity in I is undoubtedly due to the fact that the methyl group is forced out of the plane of the aromatic rings.[3c] The hydrocarbon, II, should also be capable of resolution but no suitable resolving agent for hydrocarbons is known. We hope to prepare such a resolving agent in the future. We are also planning to synthesize compounds with larger interfering groups so that more accurate studies on the rates of racemization can be made.

The synthetic methods used are outlined in the chart.

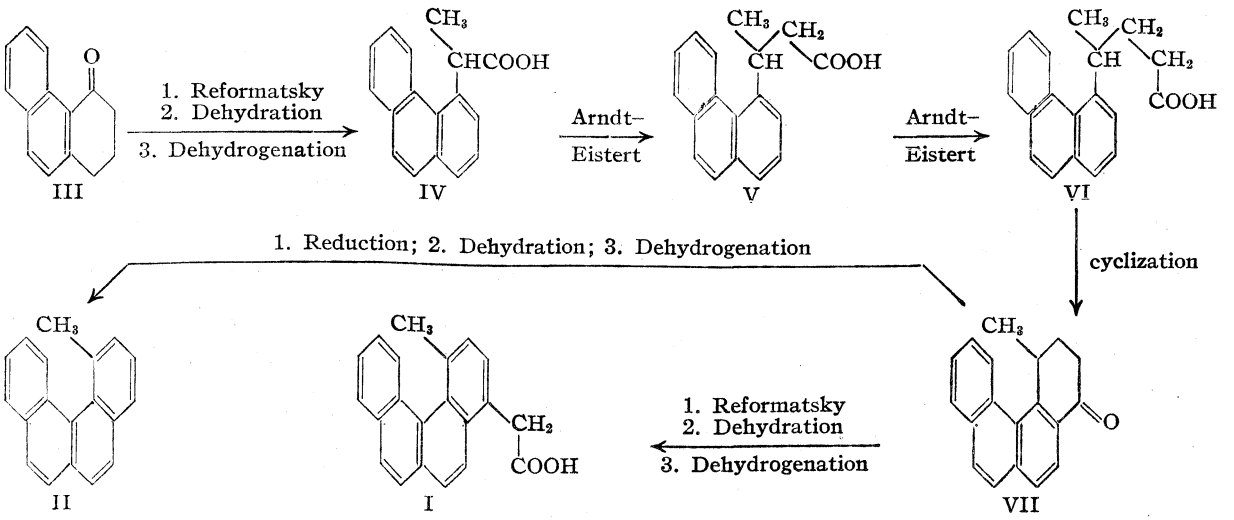
The mixture of unsaturated esters resulting from the Reformatsky reaction of ketone III and ethyl α-bromopropionate was dehydrogenated

(1) The material herein presented was taken from the Ph.D. Thesis of W. B. W., The Ohio State University, June, 1947, and was presented before the Division of Organic Chemistry of the ACS, New York, September, 1947.

(2) Present address, Bristol Laboratories, Inc., Syracuse, New York.

(3) (a) Newman, THIS JOURNAL, **62**, 2295 (1940); (b) Newman and Hussey, *ibid.*, **69**, 978 (1947); (c) Newman and Hussey, **69**, 3023 (1947).

(4) 2-, 3- and 4-isomers, Hewett, *J. Chem. Soc.*, 1286 (1938); 5-isomer, Hewett, *ibid.*, 596 (1936); 6-isomer, Hewett, *ibid.*, 293 (1940).



over palladized charcoal to yield the acid, IV. As in the similar stage of the synthesis of 1,4,5-trimethylphenanthrene[3c] considerable cleavage to phenanthrene occurred during this step. The remaining steps occasioned no particular difficulty.

Two properties of the hydrocarbon, II, are of interest: its high melting point of 141.4–141.9° and its failure to yield a picrate. Since the melting point is higher than that of the parent benzo[c]phenanthrene or the other five monomethyl derivatives, which range from 54 to 81°, it was suspected that I might have been further cyclodehydrogenated into 1,12-methylenebenzo[c]phenanthrene, m. p. 134–135°, a compound previously synthesized from pyrene.[5] However, a comparison of physical and chemical properties indicated that our compound was decidedly different from that reported by Vollmann.[5] The failure to yield a picrate was surprizing in view of the fact that benzo[c]phenanthrene and the 2-, 3-, 4-, 5-, and 6-methylbenzo[c]phenanthrenes all give picrates. We were able to prepare a trinitrofluorenone[6] derivative.

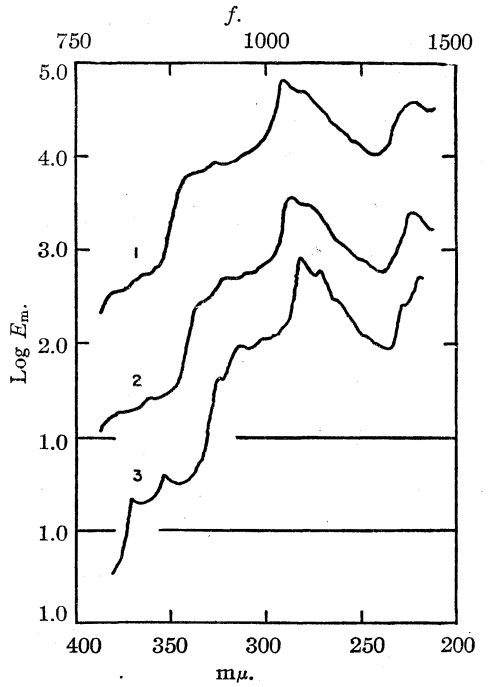


Fig. 1.—Ultraviolet absorption spectra: 1, 4-(1-methylbenzo[c]phenanthryl)-acetic acid; 2, 1-methylbenzo[c]phenanthrene; 3, benzo[c]phenanthrene. Curves 2 and 3 are dropped one and two log E_m units, respectively, to avoid undue overlapping with Curve 1.

The ultraviolet absorption spectra of I and II are given in Fig. 1 where they are compared to that of benzo[c]phenanthrene.[7] It is easily seen that they resemble the parent hydrocarbon but that there is some loss of fine structure.

The resolution of the acid I was not accomplished without much trouble. We were not able to find a suitable salt of I with an alkaloid. By treating the acid chloride of I with *l*-menthol we were able to obtain a quantity of *d*-acid which had evidently not been esterified.[8] On recrystallization this acid gave specific rotations which varied from +1.0 to +2.1°. On standing the rotation gradually disappeared. In this respect, this acid behaved quite the same as that previously reported, 4,5,8-trimethyl-1-phenanthrylacetic acid.[3c]

We would like to take this opportunity to acknowledge a grant-in-aid from a special fund donated by the Ohio State University Research Foundation and administered by the Graduate School.

(5) Vollman, *et al.*, *Ann.*, **531**, 135 (1937).

(6) Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

(7) The curve for benzo[c]phenanthrene is reproduced from an article by Mayneord and Roe, *Proc. Roy. Soc. London*, **A152**, 299 (1935). The curve for benzo[c]phenanthrene as given by Clar in "Aromatische Kohlerwasserstoffe," Springer Verlag, 1941, p. 112, is incorrect. The curve is apparently that of 1′,2′-naphtha-2,3-fluorene which is also given by Mayneord and Roe.

(8) Compare partial esterifications of Marckwald and McKenzie, *Ber.*, **32**, 2130 (1899).

Experimental[9]

α-4-Phenanthrylpropionic Acid, IV.—A solution of 70 g. (0.357 mole) of ketone III[10] and 75 g. (0.415 mole) of ethyl α-bromopropionate in 400 cc. of dry benzene was added dropwise with stirring to 27 g. (0.415 mole) of hydrochloric acid-washed granular zinc. The reaction started easily upon the addition of a few crystals of iodine, and portions of iodine were added three times during the course of the reaction. Refluxing was maintained by external heating during the addition of the ketone–ester solution, which required about an hour, and for an additional two hours. After cooling, the reaction mixture was hydrolyzed with ice and hydrochloric acid and the organic matter taken into benzene and washed with saturated sodium bicarbonate solution. On removal of the last of the benzene, spontaneous dehydration of the crude hydroxy-ester occurred. Distillation *in vacuo* yielded 86 g. of an orange-red oil, which was saponified by refluxing one hour with dilute methanolic potassium hydroxide and the resulting mixture worked up into neutral and acidic fractions. The neutral fraction yielded 22.4 g. (32%) of recovered ketone, III; the acidic fraction was esterified in the usual manner with methanol and dry hydrogen chloride. Distillation gave 55.7 g. (59%, or 86% based on ketone consumed) of ester, a yellow oil boiling at 163–165 (1 mm.). The ester crystallized in part and on crystallization from low boiling petroleum ether, colorless stout needles, m. p. 67–72°, were obtained.

Anal. (d) Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 80.7; H, 6.9.

The acid obtained from this ester was crystallized from benzene until it melted at 176.6–177.2° dec.

Anal. (c) Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 81.0, 81.1; H, 6.0, 6.2.

In the best of many experiments 160 g. (0.6 mole) of the above crude ester in four equal batches was dehydrogenated by heating with 20% palladium-on-charcoal catalyst for forty-five minutes at 280–320°; 40% of the theoretical quantity of hydrogen was collected during this time. The reaction product was worked up into neutral and acidic fractions. The neutral fraction, which amounted to 11.3 g., (10.5%) was identified as phenanthrene. Recrystallization of the crude acid from benzene gave 63.9 g. (43%) of acid melting above 215.8° and almost as much non-crystalline acid. By esterifying and further dehydrogenation more crystalline acid could be obtained from these non-crystalline fractions. A sample of acid recrystallized several times melted at 218.1–218.6°. *Anal.* (c) Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 81.1; H, 5.8. Longer heating of the dihydroester with the catalyst caused more hydrogen to be evolved, but lower yields of crystalline acid were obtained, along with greater amounts of neutral material. Dehydrogenation with sulfur gave similar but inferior results.

β-4-Phenanthrylbutyric Acid, V.—A solution of 52.5 g. (0.21 mole) of acid IV, 30 cc. of purified thionyl chloride and 5 drops of pyridine in 750 cc. of dry ether was stirred for three hours at room temperature. Removal of solvent and excess thionyl chloride under reduced pressure left a solid residue which on recrystallization from benzene gave 41.1 g. (73%) of acid chloride. A solution of 32.5 g. (0.12 mole) of the above acid chloride in 400 cc. of dry ether was added dropwise over a period of three hours to a dry ethereal solution of diazomethane, prepared from 63 g. of N-nitrosomethylurea,[11] stirred vigorously and maintained at below 5° by an ice-bath.

After stirring overnight, during which time the solution came to room temperature, the ether was removed under reduced pressure. The solid yellow residue was suspended in 250 cc. of methanol and 75 cc. of dioxane and the suspension heated to 55°. Portions of freshly prepared silver oxide were added at ten-minute intervals to this diazoketone suspension and, after two hours of heating at 55°, the theoretical amount of nitrogen had been collected. After refluxing for an hour, the reaction mixture was filtered; the filtrate stripped and distilled *in vacuo*, yielding 27.3 g. of reddish oil which was saponified and worked up into neutral and acidic fractions. The neutral fraction, a dark red viscous oil, was discarded. The acidic fraction was recrystallized from benzene to give 16.3 g. (51%) of acid V, m. p. 143–145°. An analytical sample crystallized in colorless prisms, m. p. 145.8–146.5°.

Anal. (a) Calcd. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1; neut. equiv., 264. Found: C, 82.1, 81.9; H, 6.4, 6.5; neut. equiv., 263, 266.

γ-4-Phenanthrylvaleric Acid, VI.—An Arndt–Eistert synthesis was carried out on acid V in a manner similar to that described above. In this case, the rearrangement of the diazoketone proceeded more rapidly so that the theoretical amount of nitrogen was evolved in forty-five minutes. There was obtained by crystallization of the acid fraction from benzene a first crop of crystalline acid VI, m. p. 136.0–137.8° (57%) and a second crop melting at 135.6–137.2° (6%). An analytical sample melted at 138.4–139.0°.

Anal. (a) Calcd. for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5; neut. equiv., 278. Found: C, 82.5, 82.1; H, 6.8, 6.4; neut. equiv., 280, 278.

4-Keto-1-methyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene, VII.—To a well-stirred, ice-cold solution of the acid chloride of VI, prepared from 9.0 g. (0.00524 mole) of acid VI by treatment with thionyl chloride and pyridine as described above, in 100 cc. of anhydrous *sym*-tetrachloroethane was added rapidly 10 cc. of fuming stannic chloride. A yellow complex separated almost immediately. After thirty minutes the mixture was hydrolyzed with dilute hydrochloric acid and the solvent removed by steam distillation.

After vacuum distillation there was obtained 7.9 g. (95%) of ketone VII as a viscous yellow oil which solidified on standing a few weeks. An analytical sample, recrystallized from Skellysolve B, melted at 80.2–81.2°.

Anal. (b) Calcd. for $C_{19}H_{16}O$: C, 87.7; H, 6.2. Found: C, 87.6, 87.9; H, 6.3, 6.4.

The 2,4-dinitrophenylhydrazone of VII melted at 300–302° uncor. dec.

Anal. (b) Calcd. for $C_{25}H_{20}O_4N_4$: C, 68.2; H, 4.6; N, 12.7. Found: C, 68.2, 68.1; H, 4.6, 4.7; N, 12.5, 12.6.

1-Methylbenzo[c]phenanthrene, I.—After aluminum isopropoxide–isopropyl alcohol reduction of 4.87 g. (0.019 mole) of VII, dehydration of the resulting carbinol by heating to 215°, and vacuum distillation there was obtained 4.22 g. (92%) of a light yellow oil. A mixture of 4.10 g. (0.017 mole) of this oil and 0.525 g. (0.016 mole) of sulfur was heated for one hour at 205–225°, then immediately vacuum distilled, yielding 3.39 g. of light green oil. This oil was dissolved in petroleum ether b. p. 35–40° (Skellysolve F) and absorbed on a column of −80 mesh alumina. Elution with petroleum ether, b. p. 95–100° (Skellysolve C), followed by several recrystallizations of the crystalline material so obtained, gave 0.81 g. (20%) of colorless 1-methylbenzo[c]phenanthrene (I), m. p. 141.4–141.9°.

Anal. (b) Calcd. for $C_{19}H_{14}$: C, 94.2; H, 5.8. Found: C, 94.2, 94.2; H, 6.0, 6.1.

In contrast to the yellow hydrocarbon, m. p. 134–135° of Vollman,[5] I is colorless and gives a violet color in concentrated sulfuric acid rather than a yellow color with green fluorescence.[5] Furthermore, on chromic acid oxidation, no trace of the quinone mentioned by Vollman was obtained.

While several attempts to prepare the picrate I were unsuccessful, a derivative with 2,4,7-trinitrofluorenone was obtained in the following manner; equivalent amounts of

(9) Analyses marked (a) by Arlington Laboratories, (b) by W. J. Polglase, (c) by S. Olsen, and (d) by D. Mowry. All melting points corrected unless otherwise noted.

(10) Bachmann and Edgerton, THIS JOURNAL, **62**, 2970 (1940).

(11) Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 50.

the hydrocarbon and trinitrofluorenone were dissolved in hot benzene. On standing in an ice box overnight, the solution deposited light yellow crystals, apparently the hydrocarbon. After several weeks in the ice box, a number of bright red clusters were present. These were picked out, washed in turn with benzene, acetone, and Skellysolve C, then dried *in vacuo;* m. p. 130.6–131.4°.

Anal. (b) Calcd. for $C_{32}H_{19}O_7N_3$: C, 68.9; H, 3.4; N, 7.5. Found: C, 68.7, 68.7; H, 3.5, 3.6; N, 7.6, 7.6.

4-(1-Methylbenzo[c]phenanthryl)-acetic acid, II.—To a solution of 11.12 g. (0.043 mole) of ketone VII in 150 cc. of dry benzene was added 6.0 g. (0.036 mole) of ethyl bromoacetate, 2.4 g. (0.036 mole) of granular zinc and a pinch of iodine. After fifteen minutes of refluxing, the reaction began. Five more like quantities of ester, zinc and iodine were added at half-hour intervals, during which time refluxing was maintained by external heating. Following hydrolysis with dilute hydrochloric acid, the benzene layer was separated and the aqueous layer washed twice with benzene. The combined benzene extracts were evaporated, the residual oil heated ten minutes at 190–200° to effect dehydration, and then distilled *in vacuo*. The distillate was saponified and the resulting product worked up to give a neutral fraction of 1.60 g. (14%) of recovered ketone and an acid fraction which was esterified with methanol–hydrogen chloride, yielding 8.57 g. (63%) of distilled ester.

A mixture of 7.08 g. (0.022 mole) of the above ester and 0.71 g. (0.022 mole) of sulfur was heated for one and one-half hours at 220°, then distilled *in vacuo*. The distillate was saponified, the acid fraction dissolved in acetone and passed through a column of charcoal (Norite A). There was obtained 3.86 g. (57%) of acid II melting above 208°. An analytical sample, colorless prisms from benzene–acetone, melted at 210.1–210.6°.

Anal. (b) Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.4; neut. equiv., 300. Found: C, 83.7, 83.8; H, 5.3, 5.5; neut. equiv., 297, 300.

The amide of II, recrystallized from benzene–acetone, melted at 234.5–235.5° uncor.

Anal. (b) Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7; N, 4.7. Found: C, 84.4, 84.4; H, 6.1, 5.9; N, 4.7, 4.7.

Resolution of II.—A solution of the chloride of acid II, prepared by treatment of 1.54 g. (0.0041 mole) of II with thionyl chloride and pyridine, in 50 cc. of dry benzene was added dropwise to a well-stirred ice-cold solution of 0.80 g. (0.0051 mole) of *l*-menthol ($[\alpha]_D$ −49.8°, *c*, 2 in absolute ethanol) in 25 cc. of dry benzene. After being stirred for an hour, during which time it came to room temperature, the reaction mixture was hydrolyzed. The benzene layer was separated, washed in turn with dilute hydrochloric acid, water, saturated sodium bicarbonate solution and then dried. Evaporation of the benzene under reduced pressure left an orange oil, which gave 0.39 g. of crystalline material on trituration with Skellysolve F. This material, after five recrystallizations from chloroform–Skellysolve F, melted at 185.5–187.0° and showed a specific rotation of +1.4 ± 0.2° (*c*, 1 in chloroform). Although it was at first believed that this material was the *l*-menthyl ester of II, the analysis indicated that it was impure.

Anal. (b) Calcd. for $C_{31}H_{34}O_2$ (ester): C, 84.9; H, 7.8. Calcd. for $C_{21}H_{16}O_2$ (acid): C, 84.0; H, 5.4. Found: C, 84.9, 84.9; H, 5.4, 5.4.

The five-times recrystallized material was shaken with alcoholic potassium hydroxide for ten minutes, the mixture then diluted with a large quantity of water and extracted repeatedly with ether. Acidification of the aqueous layer precipitated the acid, which was extracted with ether. Evaporation of the ether from the combined extracts left light tan crystals of acid II, m. p. 208.8–209.6°, alone and when mixed with an authentic sample of II. A solution of 0.1053 g. of this acid in 5 cc. of acetone gave an observed rotation of +0.09 ± 0.02°; $[\alpha]^{25}_D$ +2.1 ± 0.4°. No rotation could be observed the following day. Two other resolutions were carried out in the manner described above, giving samples of acid with specific rotations of +1.6 and +1.0°. The acetone solutions of both of these samples displayed no optical activity after standing for twelve hours at room temperature.

Summary

The synthesis of 1-methylbenzo[c]phenanthrene is described. This synthesis completes the series of methylbenzo[c]phenanthrenes, as the other five isomers have been previously described.

The synthesis of 4-(1-methylbenzo[c]phenanthryl)-acetic acid is described, and the dextrorotatory form of this acid has been isolated. The isolation of this optically active acid provides another instance of optical activity of the 4,5-phenanthrene type.

COLUMBUS 10, OHIO RECEIVED FEBRUARY 12, 1948

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, MONSANTO CHEMICAL COMPANY]

Vinyl Aromatic Compounds. V. Ortho-, Meta- and Para-Isopropenylbiphenyls[1]

BY DAVID T. MOWRY, JOACHIM DAZZI, MARY RENOLL[2] AND ROBERT W. SHORTRIDGE[3]

In a preceding paper[4] the synthesis of ortho-, meta- and para-vinylbiphenyls from the corresponding xenylmethylcarbinols has been described. The present work deals with the preparation of the corresponding isopropenyl derivatives of biphenyl.

In general, the methods employed resembled those used in the earlier work. *o*-Aminobiphenyl was converted to *o*-iodobiphenyl, which by means of its Grignard reagent with acetone gave dimethyl-*o*-xenylcarbinol. This was dehydrated catalytically in the vapor phase over alumina to give *o*-isopropenylbiphenyl in 83% yield. It is interesting to note that under these conditions the reaction takes a different course from that reported by Anchel and Blatt[5] who dehydrated the same carbinol in the liquid phase with sulfuric acid or a mixture of acetic acid and hydrogen chloride to give nearly quantitative yields of 9,9-

(1) Preceding paper in this series, THIS JOURNAL, **69**, 851 (1947).

(2) Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

(3) Present address: Midwest Research Institute, Kansas City, Missouri.

(4) Huber, Renoll, Rossow and Mowry, THIS JOURNAL, **68**, 1109 (1946).

(5) Anchel and Blatt, *ibid.*, **63**, 1948–1952 (1941).

dimethylfluorene. No dimethylfluorene was detected in the product from the vapor phase dehydration, although it is possible that minor amounts may have been formed.

p-Acetylbiphenyl was treated with methylmagnesium bromide to give a 78–85% yield of dimethyl-*p*-xenylcarbinol. This was dehydrated in a similar fashion to *p*-isopropenylbiphenyl.

m-Bromobiphenyl was prepared in four steps from *o*-aminobiphenyl as previously described.[4] The Grignard reagent from the bromide was treated with acetone to give crude dimethyl-*m*-xenylcarbinol which could not be distilled without decomposition and could not be induced to crystallize. This behavior was to be expected since several previously described meta derivatives of biphenyl are reported to freeze to non-crystalline glasses on cooling.[4] Consequently the crude material was dehydrated by refluxing with acetic anhydride to give *m*-isopropenylbiphenyl in 57% yield based on the *m*-bromobiphenyl.

Experimental

Dimethyl-*o*-xenylcarbinol.—*o*-Iodobiphenyl was prepared in 83% yield from *o*-aminobiphenyl by the Sandmeyer method according to the procedure of Gilman, Kirby and Kenney.[6] Four hundred sixty-seven grams of this product, b. p. 145–147° (6 mm.), was converted to the Grignard reagent, using 44 g. of magnesium in 750 cc. of anhydrous ether. The solution was cooled to 5° and 97 g. of dry acetone in 100 cc. of ether was added with stirring during ninety minutes, keeping the temperature below 20°. After standing overnight, a solution of 250 g. of ammonium chloride in 1200 cc. of water was added and the ether layer separated and evaporated. The crystalline residue was recrystallized twice from hexane to give 122 g. (34%) of fluffy needles, m. p. 69.5–70.5°; mixed melting point with biphenyl, 46–48°. Anchel and Blatt[5] report m. p. 73° for a sample prepared from the methyl Grignard reagent and methyl *o*-phenylbenzoate.

o-Isopropenylbiphenyl.—A solution of 231 g. of dimethyl-*o*-xenylcarbinol in 275 cc. of dioxane was passed over activated alumina at 275° and 90–100 mm. pressure using the technique and apparatus that has been described previously.[7] Two distillations gave 176.5 g. (83%) of *o*-isopropenylbiphenyl, b. p. 107–109° (2 mm.), $n^{25}D$ 1.5925 which freezes to a glass at about −40°. A bromide–bromate analysis[8] indicated that the material was 98.5% pure.

(6) Gilman, Kirby and Kenney, THIS JOURNAL, **52**, 2252 (1929).

(7) Mowry, Renoll and Huber, *ibid.*, **68**, 1105 (1946).

(8) Mulliken and Wakeman, *Ind. Eng. Chem., Anal. Ed.*, **7**, 59 (1935).

Anal.[9] Calcd. for $C_{15}H_{14}$: C, 92.73; H, 7.26. Found: C, 92.59; H, 7.29.

Dimethyl-*p*-xenylcarbinol.—An ethereal solution of the Grignard reagent prepared in the usual manner from 48.6 g. of magnesium (2.0 moles) and methyl bromide was treated with 371 g. (1.84 moles) of *p*-acetylbiphenyl dissolved in 1.5 l. of benzene during the course of one hour. After standing overnight the material was hydrolyzed with dilute sulfuric acid. The organic layer was separated, washed with water and evaporated to give 330 g. (85%) of crude dimethyl-*p*-xenylcarbinol. Another similar run gave a 78% yield. The material after recrystallization from a mixture of benzene and hexane melted at 92–93°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 85.22; H, 7.62.

***p*-Isopropenylbiphenyl.**—A 30% solution of dimethyl-*p*-xenylcarbinol in dioxane was dehydrated in a manner similar to that described for the ortho isomer. A 79–84% yield of the hydrocarbon, b. p. 122–124° (1 mm.) was obtained. After recrystallization from dilute ethanol, the material melted at 119.0–119.5°. When mixed with a sample of *p*-vinylbiphenyl[4] (m. p. 120°) the melting point was markedly depressed. The material showed 100.1% unsaturation by the bromide–bromate titration.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.72; H, 7.26. Found: C, 92.60; H, 7.25.

***m*-Isopropenylbiphenyl.**—*m*-Bromobiphenyl was prepared from *o*-aminobiphenyl in 62% over-all yield by the four-step synthesis previously described.[1] The improvement in yield (51% was formerly reported) was due to a modification in the deamination step where the crude *m*-bromobiphenyl resulting from decomposition of the diazonium solution was extracted with benzene and washed free of sulfuric acid before distillation. The Grignard reagent was prepared from 150 g. of the bromide (0.64 mole) in the usual fashion and treated with a 20% excess of dry acetone in ether. After standing overnight, the material was hydrolyzed with dilute hydrochloric acid, separated, washed with water and evaporated to give 124 g. (92%) of crude oily dimethyl-*m*-xenylcarbinol which could not be purified by crystallization or distillation.

Two hundred forty-three grams of this crude product was refluxed with an excess (280 g.) of acetic anhydride for three hours. The acetic acid and excess anhydride were removed under vacuum and the product fractionated to give 29 g. of biphenyl and 141 g. of *m*-isopropenylbiphenyl, b. p. 160–161° (12 mm.); $n^{25}D$ 1.6128. A bromide–bromate titration indicated a purity of 99.6%.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.72; H, 7.26. Found: C, 92.23; H, 7.50.

Summary

Ortho-, meta- and para-isopropenylbiphenyl have been synthesized by dehydration of the appropriate dimethylxenylcarbinols.

DAYTON, OHIO RECEIVED JANUARY 23, 1948

(9) Ultimate analyses by the Oakwold Laboratories, Alexandria, Virginia.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF DEPAUW UNIVERSITY]

1,4-Dimethyl-3-alkylcarbostyrils

BY D. J. COOK AND WILLIAM C. LAWALL[1]

Recently the preparation of various 3-alkyl-4-methylcarbostyrils has been reported.[2] Since the preparation of several N-alkyl-4-methylcarbostyrils has been described,[3] it was of interest to prepare a series of 1,4-dimethylcarbostyrils with alkyl substituents in the 3 position. As intermediate products the corresponding N-methyl-α-alkylacetoacetanilides have also been prepared. Ring closure of these compounds with concentrated sulfuric acid gave the corresponding 1,4-dimethyl-3-alkylcarbostyril. The properties of the substituted acetoacetanilides are given in Table I and the data for the 1,4-dimethyl-3-alkylcarbostyrils are recorded in Table II.

TABLE I

N-METHYL-α-ALKYLACETOACETANILIDES OF THE TYPE $CH_3COCH(R)CON(CH_3)C_6H_5$

R—	B. p. °C. at 1 mm.	Yield, %	Formula	N Analyses, % Calcd.	N Analyses, % Found	2,4-Dinitrophenylhydrazone, m. p., °C.
Methyl	136–137	41	$C_{12}H_{15}NO_2$	6.83	7.14	134–135
Ethyl	144–145	42	$C_{13}H_{17}NO_2$	6.39	6.48	104–105
Propyl	160–163[a]	40	$C_{14}H_{19}NO_2$	6.00	6.33	73–74
Butyl	152–154	37	$C_{15}H_{21}NO_2$	5.67	6.01	
Allyl	142–144	37	$C_{14}H_{17}NO_2$	6.03	6.38	
Benzyl	184–187	47	$C_{18}H_{19}NO_2$	4.98	5.18	165–167

[a] Pressure was 3 mm.

TABLE II

1,4-DIMETHYL-3-ALKYLCARBOSTYRIL $(C_{11}H_{10}NO)R$

R—	M. p., °C.	Yield, %	Formula	N Analyses, % Calcd.	N Analyses, % Found
Methyl	106.5–107.5	96.5	$C_{12}H_{13}NO$	7.48	7.26
Ethyl	99 –100	75	$C_{13}H_{15}NO$	6.96	6.63
Propyl	79 – 80	85.5	$C_{14}H_{17}NO$	6.51	6.29
Butyl	62.5– 63	70.6	$C_{15}H_{19}NO$	6.11	5.81
Propanol-2	140 –140.5	60.0	$C_{14}H_{17}NO_2$	6.06	6.01

In treating N-methyl-α-allylacetoacetanilide with concentrated sulfuric acid not only did the condensation take place to give the carbostyril, but also the sulfuric acid treatment hydrated the unsaturated bond in the allyl side chain to give the secondary alcohol 1,4-dimethyl-3-(propanol-2)-carbostyril.

This alcohol was characterized by the preparation of the phenylurethan.

It is to be noted that even though the N-methyl-α-benzylacetoacetanilide could be prepared, ring closure of this compound to the corresponding carbostyril could not be accomplished.

(1) Present address: Department of Chemical Engineering, Purdue University, Lafayette, Indiana.

(2) Searles and Lindwall, THIS JOURNAL, **68**, 988 (1946).

(3) Kaslow and Cook, *ibid.*, **67**, 1969 (1945).

Experimental[4,5]

N-Methylacetoacetanilide.—This starting material was prepared as described by Kaslow and Cook.[3]

The preparations of N-methyl-α-methylacetoacetanilide and 1,3,4-trimethylcarbostyril can be used as general methods to describe the preparation of the series of N-methyl-α-alkylacetoacetanilides and 1,4-dimethyl-3-alkylcarbostyrils.

N-Methyl-α-methylacetoacetanilide.—To 300 ml. of absolute alcohol in a 3-necked, round-bottomed flask equipped with a reflux condenser, stirrer and dropping funnel was added slowly 4.6 g. (0.20 mole) of sodium metal. When the sodium had reacted completely, 38.2 g. (0.20 mole) of N-methylacetoacetanilide was added to the mixture and the solution then heated on the steam-bath with constant stirring. To the refluxing solution 28.4 g. (0.20 mole) of methyl iodide was added dropwise and the refluxing continued for twelve hours. The alcohol was then removed under vacuum and the residue extracted with 300–400 ml. of ethyl ether. The ether was removed and the product then recovered by distillation under vacuum. After a small forerun, the product distilled at 136–137° (1 mm.); yield 16.8 g. (41%).

The other N-methyl-α-alkylacetoacetanilides were prepared in an analogous manner using ethyl, *n*-propyl, *n*-butyl and allyl bromides and benzyl chloride.

N-Methyl-α-alkylacetoacetanilide 2,4-Dinitrophenylhydrazone.—The 2,4-dinitrophenylhydrazones of the N-methyl-α-alkylacetoacetanilides were prepared according to the directions given by Shriner and Fuson.[6] These derivatives were purified by recrystallization from alcohol.

1,3,4-Trimethylcarbostyril.—To 50 ml. of concentrated sulfuric acid was added 12.8 g. (0.062 mole) of N-methyl-α-methylacetoacetanilide at such a rate as to maintain the temperature at 75°. During the addition the mixture was stirred continuously. After the addition was complete, the mixture was heated on a steam-bath for ten to fifteen minutes. The mixture was then cooled and poured with vigorous stirring into 500 ml. of a 50:50 mixture of ice and water. The solution was then neutralized with a solution of sodium hydroxide. After standing overnight, the white precipitate was recovered by filtration and dried at 70–75°. The crude product weighed 11.3 g. (96.5%) and melted at 100–101°. One gram of the product was recrystallized by dissolving it in 6–8 ml. of hot alcohol, filtering and adding water to faint turbidity. Upon cooling and scratching the inside of the flask, white needles formed, m. p. 106.5–107.5°.

The other 1,4-dimethyl-3-alkylcarbostyrils were prepared in an analogous manner by ring closure of the corresponding N-methyl-α-alkylacetoacetanilide.

1,4-Dimethyl-3-(propanol-2)-carbostyril.—This compound was prepared in a manner analogous to the preparation of 1,3,4-trimethylcarbostyril by treating 12.0 g. (0.052 mole) of N-methyl-α-allylacetoacetanilide with 50 ml. of concentrated sulfuric acid. White needles were obtained upon dilution with water and subsequent neutralization with sodium hydroxide. The yield was 6.7 g. (60%). The product when recrystallized from alcohol–water gave a m. p. of 140–140.5°. This compound did not change upon drying at 90° in a vacuum oven. It would not add bromine and gave no iodine number. The analysis as given in Table II corresponds to the alcohol and not the allyl substituted carbostyril. The prepara-

(4) All melting points were taken on a Fisher–Johns melting block.

(5) Microanalyses were carried out by Mr. Lorne MacBeth.

(6) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 143.

tion of the phenylurethan is proof of the secondary alcohol being the compound.

The Phenylurethan of 1,4-Dimethyl-3-(propanol-2)-carbostyril.—This derivative was prepared as described by Shriner and Fuson.[7] The compound was recrystallized from carbon tetrachloride. The m. p. was 178–179°.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: N, 8.00. Found: N, 8.28, 7.93.

Summary

1. Several N-methyl-α-alkylacetoacetanilides have been prepared by condensation of N-methylacetoacetanilide with the corresponding alkyl halide.

2. Ring closure of the N-methyl-α-alkylacetoacetanilides with concentrated sulfuric acid resulted in the formation of the 1,4-dimethyl-3-alkylcarbostyrils.

3. N-Methyl-α-allylacetoacetanilide when subjected to the sulfuric acid treatment gave the hydrated product, 1,4-dimethyl-3-(propanol-2)-carbostyril.

(7) Ref. 6, p. 136.

GREENCASTLE, INDIANA RECEIVED JANUARY 23, 1948

[CONTRIBUTION FROM SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Trimethylsilylcellulose

BY H. A. SCHUYTEN, J. W. WEAVER, J. DAVID REID AND J. F. JURGENS

Silicon tetrachloride and aryl- and alkylhalosilanes react easily and rapidly with organic hydroxyl groups,[2,3,4] to yield hydrogen chloride and silicic esters. A number of patents have been issued dealing with the treatment of cellulose with organosilicon halides to impart water repellency.[5,6,7] In one case[5] a surface reaction either with adsorbed moisture or with hydroxyl groups of the cellulose was postulated. However, the amount of product formed was too small to be measured or analyzed. Jullander[8] has studied the reaction of silicon tetrachloride with nitrocellulose and reports the formation of gels due to cross linkage. The present investigation concerns the reaction of some organo-silanes with cellulose, particularly to obtain trimethylsilylcellulose.

It was found that halosilanes will react with cellulose in the presence of pyridine to form relatively stable compounds. The reaction will take place slowly at room temperature and rapidly at reflux temperatures. A group substitution as high as 2.75 trimethylsilyl groups per glucose unit was attained with cotton linters (Fig. 1). With partially substituted cellulose acetate, the total substitution approached 3.0 (Table I).

TABLE I

REACTIONS OF ALKYLCHLOROSILANES WITH CELLULOSE ACETATE

Reagent	Acetyl groups per glucose Before	After	Mole ratio Silane: Cell-OAc	Silyl groups per glucose by Weight	%Si	Total groups
$(CH_3)_3SiCl$	2.30	2.24	2.79	0.69	0.65	2.89–2.93
$(C_2H_5)_3SiCl$	2.30	2.24[a]	4.08	.66	.58	2.82–2.90
$(CH_3)_3SiCl$	2.90	2.87	4.86	.16	.14	3.01–3.03

[b] Assumed.

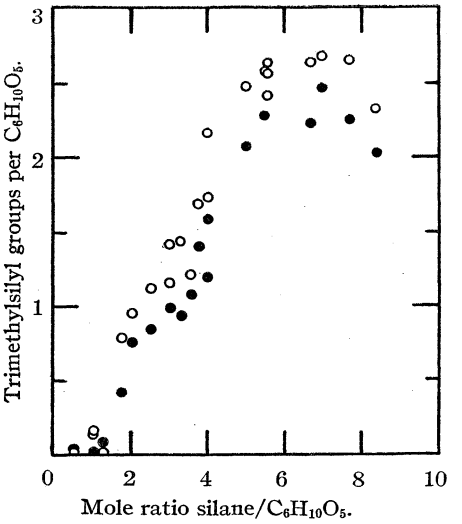


Fig. 1.—Change in trimethylsilyl substitution of cellulose with change in mole ratio of reactants: O, calculated from gain in weight; ●, calculated from silicon content.

Trimethylsilylcellulose is stable in dry air at room temperature but at elevated temperatures or in the presence of atmospheric moisture will decompose slowly. The compound is insoluble in the usual organic solvents and in mixtures of solvents such as are used in dissolving cellulose acetate and other cellulose derivatives.

Materials.—The trimethylchlorosilane used was commercial grade and the acetoxysilanes were prepared according to the method of

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. Presented at the Southwestern Regional Meeting, Houston, Texas, September, 1947.

(2) J. J. Ebelman, *Compt. rend.*, **18**, 1202; **19**, 398 (1844).

(3) M. N. Kalinin, *Compt. rend. acad. sci. URSS*, **26**, 365 (1940).

(4) G. Martin, *J. Chem. Soc.*, **105**, 2860 (1914).

(5) W. I. Patnode, U. S. Patent 2,306,222 (Dec. 22, 1942).

(6) British Thomson-Houston Co., British Patent 575,696 (Feb. 28, 1946).

(7) J. F. Hyde, U. S. Patent 2,413,050 (Dec. 24, 1946).

(8) I. Jullander, "Studies of Nitrocellulose," Almqvist and Wiksells Boktryckeri-A.-B., Stockholm, 1945, or H. K. Lewis and Co., Ltd., London, pp. 109–117.

Schuyten, Weaver and Reid.[9] Other silanes were prepared by the usual methods.

Analyses.—All silicon analyses were carried out by fusion of the silylcellulose in a Parr bomb followed by the usual gravimetric procedure. Ashing before fusion was impractical because of loss of silicon as trimethylsilanol or similar compounds.

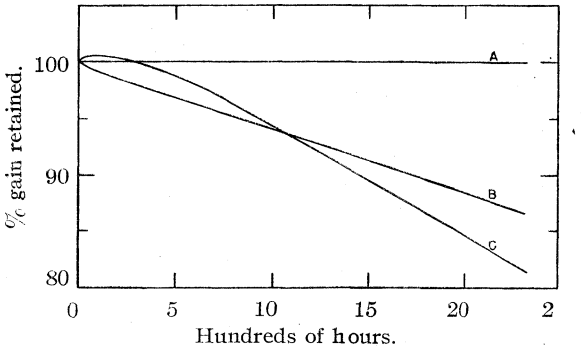


Fig. 2.—Deterioration of trimethylsilylcellulose: A, desiccated (P_2O_5); B, heated (105°); C, conditioned (see text).

Experimental

Trimethylsilylcellulose.—Two grams of oven-dried, low-viscosity cotton linters was suspended in a small amount of anhydrous pyridine in a 500-ml., round-bottom flask provided with a reflux condenser and mercury-sealed stirrer. Trimethylchlorosilane was added from a stock solution in anhydrous pyridine containing 0.05 g. of silane per ml. of solution. The mole ratio of silane per glucose unit of cellulose was varied as indicated in Fig. 1 and the total volume of pyridine was adjusted to 250 ml. The mixture was refluxed and after about one hour the cellulose assumed a dispersed and almost invisible condition. This was undoubtedly due to the nearly identical refractive indices of the compound and pyridine.

After three hours the mixture was cooled and filtered. Washing was done on different runs with both organic solvents and with water; no apparent difference in results were obtained. The samples were vacuum-dried and weighed. Trimethylsilyl group substitution was calculated from gain in weight by

$$\text{Groups} = \frac{\text{Gain in wt.} \times 162.1}{\text{Sample wt.} \times 72.16}$$

and from silicon content by

$$\text{Groups} = \frac{\%\ \text{Si} \times 162.1}{2806 - (72.16 \times \%\ \text{Si})}$$

Other monofunctional group substitutions may be calculated by inserting (group weight—1.008) in place of 72.16.

The correlation of results obtained by these two methods is reasonably good. The difference between results may be due to retention of solvent; it is difficult to remove the last traces of material of this type from cotton.

Other Silanes.—Various other silanes were employed with similar results as recorded in Table II.

Trimethylsilylcellulose Acetate.—Samples of cellulose acetate were dissolved in pyridine and treated as above. The products were soluble in the solvent and were precipitated by pouring into cold water. They were then filtered and washed with water, vacuum-dried, weighed and analyzed. The number of acetyl groups per glucose unit showed little change. The results are given in Table I.

Formation of Trimethylsilylcellulose at Room Temperature.—A sample of cotton linters was treated with trimethylchlorosilane in a mole ratio of 5.58 for four-hundred hours at room temperature. The gain in weight of the cellulose was equivalent to 1.73 groups substitution as compared to 2.53 groups with a similar mole ratio when refluxed for three hours in the pyridine mixture.

(9) H. A. Schuyten, J. W. Weaver and J. David Reid, THIS JOURNAL, **69**, 2110 (1947).

TABLE II

REACTIONS OF VARIOUS SUBSTITUTED SILANES WITH CELLULOSE

Reagent	Weight cellulose, g.	Mole ratio[a]	Gain in weight, g.	Si, %	Silyl groups per glucose by weight	by %, Si
$(C_2H_5)_3SiCl$	2.154	6.06	2.007	11.55	1.32	1.27
$(CH_3)_2SiCl_2$	1.786	5.84	0.202	2.47	[b]	[b]
n-$C_8H_{17}SiCl_3$	1.960	4.01	0.030	1.33	[b]	[b]
$CH_3Si(OAc)_3$	1.904	3.95	0.080	1.16	[b]	[b]

[a] Ratio of moles of silane to glucose unit. [b] Not calculated because of the possibility of cross linkage.

Decomposition of Trimethylsilylcellulose.—Trimethylsilylcellulose may be decomposed by boiling with water or with dilute acid or base. No quantitative results were obtained but boiling with dilute acid yielded a volatile liquid product which burned and deposited silica and was assumed to be trimethylsilanol. Accordingly samples of trimethylsilylcellulose containing 2.6 trimethylsilyl groups per glucose unit were placed in open containers under three sets of conditions: (1) Desiccated over phosphorus pentoxide; (2) dried in an oven at 105°; and (3) conditioned at 70°F. (21.1°) and 65% relative humidity. The samples were weighed at intervals and the per cent. retention of added weight was plotted against time. The results are shown in Fig. 2. The inflection at the beginning of the curve for the conditioned sample is due to increase in moisture content at 65% relative humidity.

Solubility of Trimethylsilylcellulose.—A 0.1-g. sample of trimethylsilylcellulose (2.42 groups per glucose unit) was placed in 5 ml. of solvent in a small tube and tumbled on a wheel for twenty-four hours at room temperature. When the major portion of the material remained undissolved as determined by visual inspection, it was considered insoluble. In some cases (designated below by "sw") the sample particles showed a tendency to swell. No noticeable amount dissolved in the following solvents: acetone, benzene, carbon tetrachloride, chloroform, diethylformamide, ethyl acetate, ethyl alcohol, ethylene dichloride, ether (sw), methylene chloride, methyl ethyl ketone (sw), nitromethane, nitropropane, pyridine (sw), *s*-tetrachloroethane and xylene. The material was not soluble in the following mixtures: acetone (80%), ethanol (15%), ethyl acetate (5%) (sw); toluene (80%), ethanol (20%) (sw); ethylene dichloride (90%), methyl alcohol (10%); and benzene (66%), ethylene dichloride (34%) (sw).

Summary

Trimethylchlorosilane and other chloro- and acetoxysilanes react with cellulose to yield products which by gain in weight and silicon content show a group substitution as high as 2.75 groups per glucose unit. Determination of change in weight of samples of trimethylsilylcellulose over a period of time indicates that it is stable in dry air at room temperature but decomposes at elevated temperatures or in the presence of atmospheric moisture. It may be readily hydrolyzed with boiling water or with dilute acids or alkalies.

The halosilanes react only with the unreacted hydroxyl groups in partially substituted cellulose acetate.

These data indicate the formation of definite compounds of cellulose with substituted silanes.

NEW ORLEANS, LA. RECEIVED FEBRUARY 2, 1947

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY]

Wall Effects in the Oxidation of Boron Triethyl Vapor. Ignition of *n*-Butane[1]

BY RICHARD S. BROKAW, ELMER J. BADIN AND ROBERT N. PEASE

In a recent paper on the oxidation of zinc dimethyl vapor at room temperature,[2] it was shown that the reaction is autocatalytic, becoming explosive if the pressure of zinc dimethyl exceeds 12–15 mm.; and that it will induce the ignition of *n*-butane. Somewhat similar data on boron triethyl vapor are presented here. Particular attention has been given to the effect of solid products and surface treatment on the oxidation.

Experimental

The apparatus was similar to that used for the oxidation studies of zinc dimethyl.[2] Spherical reaction bulbs with inside diameters of 4.6, 6.6, 7.4, 9.8 and 12.7 cm. were used. Both the reaction bulb and the oxygen storage bulb were maintained at 0°. The tubing between them was 6 mm. i.d. rather than capillary to permit rapid mixing of reacting gases. Pressures were measured on a direct reading manometer and small McLeod gage designed to read pressures over a range of 0.01–15.0 mm.

Reaction bulbs were cleaned by treatment with boiling concentrated nitric acid followed by rinsing with distilled water. Drying was carried out in an oven at 135°. Coatings were applied after this standard cleaning procedure. Boron triethyl vapor was first admitted to the reaction bulb at the desired pressure. The reaction bulb was then closed off by its stopcock. Oxygen was admitted to the reservoir in an amount sufficient to give the desired final pressure when the connecting stopcock was opened and the gases allowed to mix. Experiments were carried out in a darkened room in order to make observation of faint flashes. Flashes occurred immediately on opening the stopcock, without measurable induction period.

Boron triethyl was prepared from the Grignard reagent and boron trichloride etherate. As a final purification step, 125 g. was fractionated in a helium atmosphere through a 20-plate column. A third fraction of 20 g. (b. p. 95.0°) was used for all experiments. Oxygen and *n*-butane (C. P.) were high purity tank gases.

Results and Discussion

Boron triethyl vapor ignites instantly on admission of oxygen at substantially lower pressures than does zinc dimethyl. A series of runs in clean dry bulbs of diameters between 4.6 and 12.7 cm. diameter gave values as low as 0.10 mm. of boron triethyl in a 5 volume % mixture with oxygen (stoichiometric mixture for combustion to boron trioxide, carbon dioxide and water: 8.70 vol. %). Data are presented in Table I and Fig. 1.

The product of pressure and bulb diameter was found to be approximately constant, as would be expected if reaction chains start in the gas phase and end on the wall.[3]

TABLE I

MINIMUM IGNITION LIMITS FOR 5 VOLUME % BORON TRIETHYL IN OXYGEN, TEMPERATURE, 0°.

Bulb diameter, *d*, cm.	Limit pressure, *p*, mm.	Partial pressure $B(C_2H_5)_3$, mm.	$p \times d$
Clean dry bulbs			
4.6	7.5	0.38	34
6.6	4.3	.22	28
7.4	4.1	.21	30
9.8	3.1	.16	30
12.7	2.1	.11	27
Bulbs self-coated with products			
4.6	10.7	0.54	49
6.6	9.0	.45	59
7.4	7.3	.37	54
9.8	4.7	.24	46
12.7	3.6	.18	46

A coating of reaction products demands a higher limiting pressure (Table I and Fig. 1), indicating that the solid products are somewhat more effective than the clean Pyrex surface in breaking chains before branching (and ignition)

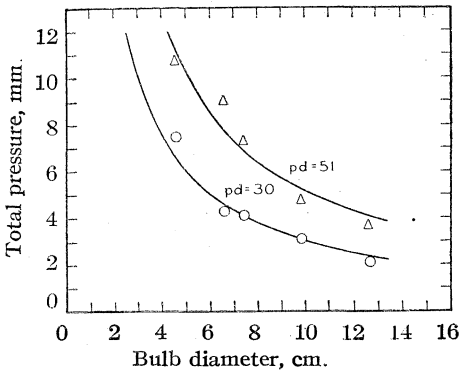


Fig. 1.—Variation of explosion limit with bulb diameter for the oxidation of boron triethyl: △, surface self-coated with reaction products: O, clean "dry" Pyrex surface.

occurs. This would seem to suggest that other surface coatings might likewise be better chain-breakers than Pyrex. It was therefore somewhat puzzling to find that washing out the clean reaction bulb with solutions of boric acid, potassium hydroxide, potassium chloride, hydrochloric acid or paraffin (1% in pentane) gave substantially the same lower limit as clean Pyrex (4.1–5.1 mm. in 6.5 cm. bulb).

No real evidence was obtained of an upper pressure limit such as might be expected of a branched-chain explosion. However, it was observed that the bright green flash due to ignition was somewhat less intense at higher pressures

(1) The work described in this paper was done in connection with Contract NOrd 7920 with the United States Naval Bureau of Ordnance, as coördinated by the Applied Physics Laboratory, The Johns Hopkins University. Acknowledgment is also due Dean H. S. Taylor, who has general supervision of this project.

(2) E. J. Badin, D. R. Walters and R. N. Pease, THIS JOURNAL, **69**, 2586 (1947).

(3) *Cf.* C. N. Hinshelwood, "Kinetics of Chemical Change," Oxford University Press, 1940, p. 15. Similar results have been obtained for, *e. g.*, the phosphine–oxygen reaction, Dalton and Hinshelwood, *Proc. Roy. Soc.* (*London*), **125A**, 294 (1929).

(~100 mm.), especially with rich mixtures, though this probably only represents more effective quenching of chemi-luminescence. It was also noted that the radiation emitted by mixtures just above the lower limit was more bluish and much less intense. This recalls Frankland's observation[4] that a slow current of boron triethyl (or trimethyl) vapor issuing into air burned with a faint blue flame—"the temperature of which is so low that a finger may be held in it for some time without much inconvenience." Evidently, cool flame phenomena are involved near the limit. It was interesting to find that with the coated reaction bulb this cool flame was no longer observed. The bright green flash was observed right down to the limit which, as already stated, was correspondingly higher.

We have no evidence to present regarding the reaction below the low pressure limit, except that there was no pressure-change or detectable deposit in 1,000 seconds. Experiments of Bamford and Newitt[5] on the oxidation of boron trimethyl and tri-*n*-propyl, by slowly admitting oxygen to the vapor at about 1 mm., indicate a very rapid absorption up to the equivalent of $R_3B:O_2$, with no separation of a condensed product. According to Frankland,[4,6] the slow admission of oxygen or air to liquid boron triethyl produces ethane-boronic diethyl ester, $C_2H_5B(OC_2H_5)$. In any event, there is no evidence of the separation of a solid at these low pressures until the ignition limit is passed.

(4) E. Frankland, *J. Chem. Soc.*, **15**, 363 (1862).

(5) C. H. Bamford and D. M. Newitt, *ibid.*, 695 (1946).

(6) See also Krause, *et al.*, *Ber.*, **61**, 271 (1928); **63**, 934 (1930); a similar observation on boron tri-*n*-butyl by Johnson and Van Campen, THIS JOURNAL, **60**, 121 (1938).

This is in contrast to the oxidation of zinc dimethyl vapor where a white mist begins to form immediately on mixing with oxygen.

Finally, a few experiments on the induced ignition of *n*-butane by means of boron tri-ethyl have been carried out, by admitting a stoichiometric mixture of oxygen and *n*-butane (13.3 vol. %) to a bulb containing boron triethyl vapor, the total pressure being 100 mm. With 1 mm. of boron triethyl there was no reaction, but with 3 mm. of boron triethyl there was a violent explosion which travelled back through 6 mm. i. d. tubing to the reservoir flask. However, with 5 or 10 mm. of boron triethyl there was only a faint flash, which was much weaker than that in absence of *n*-butane, and a negligible pressure change.[7] There thus appear to be sharp pressure limits to this induced oxidation.

Summary

1. Boron triethyl vapor ignites spontaneously in oxygen at partial pressures below 1 mm. in a Pyrex bulb held at 0°.

2. The product of minimum pressure and bulb diameter is constant, indicating that chains start in the gas phase and end on the wall. When the glass surface is coated with reaction products, the minimum pressure is greater.

3. There is evidence of a cool flame phenomenon.

4. Boron triethyl will ignite a *n*-butane–oxygen mixture within narrow pressure limits.

(7) The 3 mm. mixture produced a large pressure decrease, presumably due to condensation of water vapor formed by the combustion.

PRINCETON, NEW JERSEY RECEIVED OCTOBER 18, 1947

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Analogs of Pteroylglutamic Acid. I. N^{10}-Alkylpteroic Acid and Derivatives

BY DONNA B. COSULICH AND JAMES M. SMITH, JR.

The structure of pteroylglutamic acid[1] has been demonstrated and several methods of synthesis have been described.[1,2]

This factor of the vitamin B complex is identical with the liver *L. casei* factor[3] and apparently is related to a number of other substances[4] isolated from natural sources. All are necessary for the normal growth and development of certain animals and microörganisms. The question immediately arises as to what the biological effect will be when variations are introduced into the structure of the vitamin by chemical methods of synthesis. There is always the possibility of enhancing the desirable effects of the vitamin, and also of producing new compounds which can be used in treating other syndromes. The use of pteroylglutamic acid antagonists in the treatment of blood dyscrasias, leukemia for example, has been suggested by Franklin, Stokstad, Belt and Jukes.[5a]

Variations of the structure and study of the relationship between structure and biological activity have already received the attention of workers in the field. Dibromobutyraldehyde has

(1) (a) Angier, *et al.*, *Science*, **103**, 667 (1946); (b) Mowat, *et al.*, THIS JOURNAL, **70**, 14 (1948).

(2) (a) Waller, *et al.*, *ibid.*, **70**, 19 (1948); (b) Hultquist, *et al.*, *ibid.*, **70**, 23 (1948); (c) Angier, *et al.*, *ibid.*, **70**, 25 (1948); (d) Boothe, *et al.*, *ibid.*, **70**, 27 (1948).

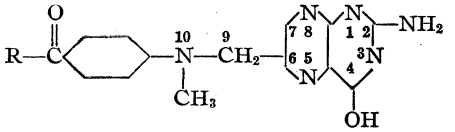
(3) Stokstad, Hutchings and SubbaRow, *ibid.*, **70**, 3 (1948).

(4) (a) Hutchings, Stokstad, Bohonos, Sloane and SubbaRow, *ibid.*, **70**, 1 (1948); (b) Snell and Peterson, *J. Bact.*, **39**, 273 (1940); (c) Hutchings, Bohonos and Peterson, *J. Biol. Chem.*, **141**, 521 (1941); (d) Mitchell, Snell and Williams, THIS JOURNAL, **63**, 2284 (1941); (e) Pfiffner, *et al.*, *Science*, **97**, 404 (1943).

(5) (a) Franklin, Stokstad, Belt and Jukes, *J. Biol. Chem.*, **169**, 427 (1947); (b) Martin, Tolman and Moss, *Archives of Biochemistry*, **12**, 318 (1947); *Science*, **106**, 168 (1947); (c) Franklin, Stokstad and Jukes, *Proc. Soc. Exptl. Biol. Med.*, **65**, 368 (1947); (d) Welch, Heinle, Sharpe, George and Epstein, *ibid.*, **65**, 364 (1947).

been substituted for dibromopropionaldehyde in the synthesis of pteroylglutamic acid[2a] to give a product which is an antagonist for pteroylglutamic acid.[5] The proof of structure of the active material has not been reported, but the crude has been designated as "7-methylfolic acid."[5b] Pteroylaspartic acid has been synthesized in pure form and shows pteroylglutamic acid antagonist activity on a number of species.[6] The derivative of pteroylglutamic acid in which the 4-hydroxyl group is replaced by an amino group has been reported by Seeger, Smith and Hultquist.[7a] It is a powerful antagonist for pteroylglutamic acid. 2,4-Diaminopteridines having antagonist action have been investigated by other workers.[7b]

The present paper describes the synthesis of a series of N[10]-substituted derivatives of pteroylglutamic acid which are antagonists, as for example N-[4-{N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-N-methylamino}-benzoyl]-glutamic acid, (I) hereafter designated as N[10]-methylpteroylglutamic acid.



I, R is $HOOCCH_2CH_2CH(COOH)NH-$
II, R is HO—

N[10]-Methylpteroic acid (II) is the simplest member of the series, and also one of the most active antagonists. It was prepared from dibromopropionaldehyde, 2,4,5-triamino-6-hydroxypyrimidine, and *p*-methylaminobenzoic acid, and purified by the methods described for the synthesis and purification of pteroylglutamic acid.[2a] The other compounds reported in this series were all prepared in a similar manner, only those showing significant activity in the crude being purified.

Alkaline permanganate oxidation of N[10]-methylpteroic acid yielded 2-amino-4-hydroxypteridine-6-carboxylic acid, which was identical with that obtained by the alkaline aerobic oxidation of pteroylglutamic and pteroic acids.[1a] This shows that the point of attachment of the side chain is the 6-position. However, alkaline aerobic oxidation of N[10]-methylpteroic acid under conditions which cleaved pteroylglutamic and pteroic acids yielded only the unchanged material.

It was necessary to obtain pure secondary amines to preclude the presence of pteroic and pteroylglutamic acids which would mask the growth inhibiting properties of the N[10]-alkylated derivatives. As a consequence, useful methods for the preparation of pure monoalkylated *p*-aminobenzoic and *p*-aminobenzoylglutamic acids were devised. These included the treatment of the corresponding iodo compounds with alkyl amines, methylation of aminobenzoic acid by the zinc–alkali reduction of the amino acid and formaldehyde, and the reaction of alkyl iodides with sodium ethyl *p*-formamidobenzoate followed by hydrolysis of the formyl group.

The biological properties of the N[10]-alkylpteroic acid derivatives have been examined by Dr. E. L. R. Stokstad and Dr. B. L. Hutchings of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. For N[10]-methylpteroylglutamic acid the inhibition ratio for half-maximum inhibition of the growth of *Streptococcus faecalis R* was 2.0 at a concentration of pteroylglutamic acid of 0.1 microgram per 10 ml. See also Table I.

The details of the biological work will be published elsewhere.

Experimental[8,9]

p-**Methylaminobenzoic Acid.**[10]—Sixty grams of *p*-aminobenzoic acid was dissolved in 90 ml. of water and 17.5 g. of sodium hydroxide. The resulting solution, and 66 g. of 40% formaldehyde solution, were added simultaneously over a two to three-hour period to a slurry of 90 g. of zinc dust in 205 g. of 50% sodium hydroxide solution and 100 ml. of water. The temperature was maintained at 90–95°. Heating at this temperature was continued while 40 g. more of 40% formaldehyde was added. The total heating time was five to seven hours. Excess zinc was removed by filtration, and the filtrate was allowed to stand several days. The sodium salt of *p*-methylaminobenzoic acid crystallized out. It was filtered off, dissolved in water, and the acid precipitated by adjusting the solution to *p*H 3. This was essentially pure *p*-methylaminobenzoic acid; m. p. 158–161.5°. A mixture melting point with a sample prepared by the method of Houben and Schottmüller[10] gave no depression.

N-Methylanthranilic acid[11] was prepared in a similar experiment.

N[10]-**Methylpteroic Acid.**—This compound was synthesized by the method of Waller, *et al.*,[2a] except that *p*-methylaminobenzoic acid was substituted for *p*-aminobenzoylglutamic acid. A mixture of 12.6 g. of crude N[10]-methylpteroic acid, 9 g. of lime, and 1750 ml. of water, was heated at 60° for forty minutes. After the addition of 25 g. of Hyflo-Supercel the mixture was filtered and the cake washed with 750 ml. of water at 60°. The filtrate and washing were adjusted to *p*H 3 with hydrochloric acid and cooled to 20°. After the addition of 25 g. of Hyflo-Supercel, the mixture was filtered. The cake was washed with water and then slurried in 1 liter of water and sodium hydroxide was added to obtain *p*H 11–12. After heating at 80° for ten minutes, the *p*H of the solution was adjusted to 7, and the mixture then cooled to 20° and filtered. The filtrate was treated with hydrochloric acid to *p*H 3–4. The precipitated material was separated by filtration with Hyflo, slurried in water to give 0.75 g./liter concentration and enough magnesium oxide to obtain about *p*H 9 at 80°, and filtered hot with 0.5 g. of charcoal. The filtrate at 80° was adjusted to *p*H 3–4 with hydrochloric acid and cooled to 20°. Yellow rosets of N[10]-methylpteroic acid crystallized out and were purified for analysis by dissolving (at 0.25 g./l.) in hot dilute sodium hydroxide (*p*H 8–9), clarifying with Hyflo filter-aid, and adjusting the filtrate to *p*H 3–4 while at 90°. On cooling analytically pure yellow microcrystalline material was isolated which had an ultraviolet absorption curve quite similar to that predicted from consideration of data on the ultraviolet curves of pteroic acid, *p*-methylaminobenzoic acid, and *p*-dimethylaminobenzoic acid. See Table I and Fig. 1 for

(6) Hutchings, *et al.*, *J. Biol. Chem.*, **170**, 323 (1947).

(7) (a) Seeger, Smith and Hultquist, THIS JOURNAL, **69**, 2567 (1947); (b) Mallette, Taylor and Cain, *ibid.*, **69**, 1814 (1947).

(8) All melting points are corrected.

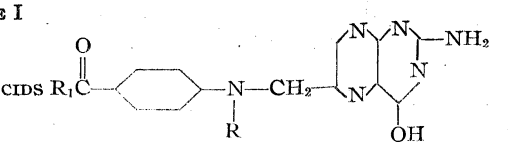
(9) Microanalyses were done by Mr. O. Sundberg and assistants.

(10) Houben and Schottmüller, *Ber.*, **42**, 3739 (1909).

(11) Houben and Brassert, *ibid.*, **39**, 3234 (1906).

TABLE I

N^{10}-SUBSTITUTED PTEROIC AND PTEROYLGLUTAMIC ACIDS



R	R_1	Purity	Ultraviolet absorption spectra maxima, λ mμ.[a] in 0.1 N NaOH			in 0.1 N HCl	Antagonist activity[b]
$-CH_3$	—OH	Analytical	255	290	366	313	15.00
$-CH_3$	—OH	Crude	...	...	...	...	2.00
$-C_2H_5$	—OH	91.2%[c]	254	297	366	314	1.076
$-C_2H_5$	—OH	Crude	...	...	...	...	0.075
$-C_4H_9$	—OH	85%[c]	255	298	367	315	0.135
$-C_4H_9$	—OH	Crude	...	...	...	...	.....
$-CH_2COOH$	—OH	Crude	...	...	...	...	0.022
$-CH_2C_6H_5$	—OH	Crude	...	...	...	...	.....
$-CH_2COC_6H_5$	—OH	Crude	...	...	...	...	0.01
$-CH_3$	—1(+)glutamic acid	Analytical	255	302	368	307	100.00
		Crude	...	...	...	...	22.50
$-CH_2COC_6H_5$	—1(+)glutamic acid	Crude	...	...	...	...	0.01

[a] See footnote to Fig. 1. [b] An arbitrary value of 100 is assigned for the antagonist activity of N^{10}-methylpteroylglutamic acid, for half-maximum inhibition of the growth of *Streptococcus faecalis R.* Values for other compounds are reported in terms of the standard. [c] Estimated by ultraviolet absorption.

biological and ultraviolet absorption data. The analytical sample was dried at 100° and 1 mm. for seven to eight hours.

Anal. Calcd. for $C_{15}H_{14}N_6O_3$: C, 55.2; H, 4.29; N, 25.75. Found (corrected for 2.71% ash): C, 55.3; H, 4.56; N, 25.4.

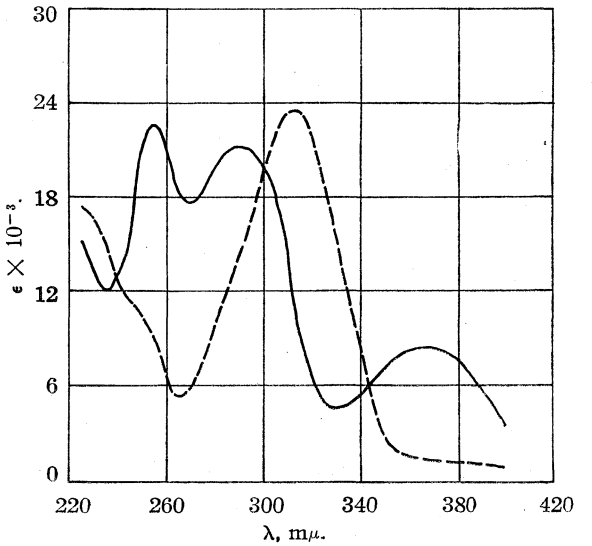


Fig. 1.—Ultraviolet absorption spectra[a] of N^{10}-methylpteroic acid: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Permanganate Oxidation of N^{10}-Methylpteroic Acid.—A hot solution of 730 mg. of N^{10}-methylpteroic acid in 250 ml. of 1 *N* sodium hydroxide was treated with 2% potassium permanganate solution until the solution maintained a dark green color. After adding sodium sulfite to destroy this color, manganese dioxide was filtered off and the filtrate adjusted to *p*H 3–4 with dilute hydrochloric acid. The mixture was cooled, and centrifuged. The crude moist product was purified by adding a few drops of 5 *N* sodium hydroxide to dissolve, and then 4.4 g. of sodium hydroxide pellets to the 22 ml. of solution to give a 5 *N* caustic solution. On cooling, the disodium salt separated out, was filtered off, and precipitated as the free acid by dissolving in water and adjusting to *p*H 3–4. The disodium salt was isolated a second time to give material which was shown to be 2-amino-4-hydroxypteridine-6-carboxylic acid by comparison of the ultraviolet absorption curve with that of an authentic sample.

Attempted Alkaline Aerobic Oxidation of N^{10}-Methylpteroic Acid.—A solution of 500 mg. of N^{10}-methylpteroic acid in 25 ml. of *N* sodium hydroxide was heated at 100°

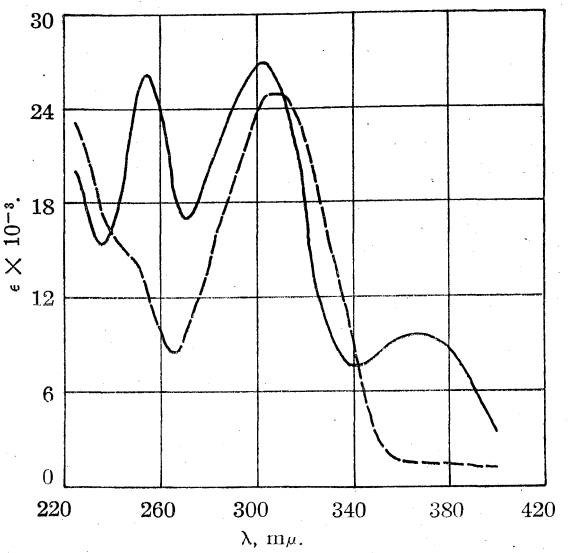


Fig. 2.—Ultraviolet absorption spectra[a] of N^{10}-methylpteroylglutamic acid monohydrate: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

[a] *E* is the molecular extinction coefficient as defined by $I = I_0 10^{-Ecl}$ where *c* is the concentration in moles/liter and *l* is the cell length in centimeters. Transmittancy (I/I_0) measurements of 10 mg./l. solutions were made in 1-cm. cells at 5mμ intervals on a Model DU Beckman spectrophotometer using a solvent filled cell in the reference position. Additional data were obtained at 2 mμ intervals at maxima, minima and points of inflection.

for six hours with a rapid stream of oxygen bubbling through. After cooling and clarifying with 0.5 g. of charcoal, the filtrate was adjusted to 5 *N* by adding 4 g. of sodium hydroxide pellets. When cooled in the icebox overnight, yellow crystals separated, which were filtered and dissolved in water. The yellow solution, after clarifying with 0.2 g. of charcoal, was adjusted to *p*H 3–4 with hydrochloric acid, whereupon an orange substance precipitated. This was isolated by centrifugation and shown to be unchanged N^{10}-methylpteroic acid by comparison of its ultraviolet absorption curve with an authentic sample.

Sodium Ethyl *p*-Formamidobenzoate.—A solution of 82.54 g. of ethyl *p*-aminobenzoate in 578 ml. of ether was treated with 12.5 g. of sodium, added in small pieces. To this was added slowly 37 g. of ethyl formate and the mixture was allowed to stand overnight. The product, isolated as a fine yellow powder, had a neutralization equivalent of 235.4 (theoretical for $C_{10}H_{10}NO_3Na$, 215). A sample was converted to ethyl *p*-formamidobenzoate by neutralization of an aqueous solution with acetic acid; the melting point, 146–149°, agreed with the literature value.[12]

***p*-Ethylaminobenzoic Acid.**[13]—A mixture of 21.5 g. of sodium ethyl *p*-formamidobenzoate, 15.6 g. of ethyl iodide, 125 ml. of ethyl alcohol and 13.4 g. of potassium hydroxide (86%), was refluxed for one hour. Then 25 ml. of water was added and the solution was poured into cold water and neutralized with acetic acid. The crude material was easily purified by two reprecipitations from sodium hydroxide solution to give *p*-ethylaminobenzoic acid. The melting point, 177.9–178.9°, agreed with that obtained by the method of Houben and Freund.[13]

p-Ethylaminobenzoic acid was also prepared from *p*-iodobenzoic acid[14] and ethylamine in a sealed tube in a manner analogous to that described below for the preparation of *p*-methylaminobenzoylglutamic acid.

N^{10}-Ethylpteroic Acid.—This compound was prepared according to the procedure described by Waller, *et al.*,[2a] except that *p*-ethylaminobenzoic acid was substituted for *p*-aminobenzoylglutamic acid. It was purified by a process similar to that described above for N^{10}-methylpteroic acid (see Table I).

N^{10}-Butylpteroic Acid.—This was prepared from *p*-butylaminobenzoic acid[15] and purified as indicated for the N^{10}-ethyl compound above (see Table I).

Ethyl N-(4-Carbethoxyphenyl)-glycinate.—A mixture of 12.25 g. of ethyl chloroacetate and 33 g. of ethyl *p*-aminobenzoate was heated at 130–140° for five to six hours. It was cooled, slurried in ether and filtered. The filtrate was freed of ether by evaporation and the residue was distilled at 215° at 8–11 mm. pressure. The distillate was dissolved in ether and extracted with a small amount of 0.5 *N* hydrochloric acid. Evaporation of the washed and dried ether layer gave the ester which was purified further by recrystallization from aqueous alcohol; m. p. 62.5–62.9°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.77; N, 5.8. Found: C, 62.1; H, 6.87; N, 5.73.

This compound is soluble in acetone, ether, alcohol, isopropyl acetate, carbon tetrachloride and petroleum ether; insoluble in water and carbon disulfide.

N-(4-Carboxyphenyl)-glycine.—The ester above (8.8 g.) was boiled three to four hours in 5 *N* sodium hydroxide solution. On diluting, cooling and acidifying, the pure acid separated out; m. p. 245.7–247.1°, neut. equiv. 98.8 (the theoretical value is 97.5 for $C_9H_9O_4N$).

N^{10}-Carboxymethylpteroic Acid.—This was prepared as a crude as described for other N^{10}-pteroic acids, from N-(4-carboxyphenyl)-glycine.

Other N^{10} Derivatives of Pteroic Acid.—In similar experiments N^{10}-phenacylpteroic acid and N^{10}-benzylpteroic acid were prepared as crudes from *p*-phenacylaminobenzoic acid[16] and *p*-benzylaminobenzoic acid.[1b]

***p*-Iodobenzoylglutamic Acid.**—A solution of 26.5 g. of *p*-aminobenzoylglutamic acid in 50 g. of 35% hydrochloric acid and 150 ml. of water was cooled to 5–10° and 8.5 g. of sodium nitrite in 40 ml. of water was added, until the solution gave a blue spot on starch–iodide test paper. Then 25 g. of potassium iodide in 50 ml. of water was added and the mixture was allowed to stand overnight. It was warmed to 50°, cooled, washed by decantation, and filtered. The crude product was purified by recrystallization from dilute alcohol; m. p. 173.7–176.1°; $[\alpha]^{26}D$ + 16.32 (1 *N* sodium hydroxide).

Anal. Calcd. for $C_{12}H_{13}NO_5I$: C, 38.1; H, 3.44; N, 3.7; I, 33.6. Found: C, 37.7; H, 3.21; N, 3.93; I, 33.6.

***p*-Methylaminobenzoylglutamic Acid.**—A solution of 7.6 g. of *p*-iodobenzoylglutamic acid in 8 ml. of water and sodium hydroxide to give *p*H 8–9 was treated with 8 ml. of aqueous methylamine (24.15 g./100 ml.) and 0.02 g. of fine copper powder in a sealed tube at 125° for three hours. The insolubles were removed by filtration and the excess methylamine was removed by evaporation under vacuum. The sirupy residue was diluted with alcohol to give the disodium *p*-methylaminobenzoylglutamate. The free acid was obtained as an oil by acidification of an aqueous solution of the sodium salt.

Diethyl *p*-Methylaminobenzoylglutamate.—The diethyl ester was obtained by dissolving 3.5 g. of the disodium salt above in 60 ml. of alcoholic hydrogen chloride (20 g./100 ml.) and allowing it to stand three days. After diluting with water and clarifying, the ester was precipitated by the addition of ammonium hydroxide to *p*H 7–8. The crude ester was purified by recrystallization from dilute alcohol; m. p. 89.8–91.0°; $[\alpha]^{25}D$ −21° (1 *N* HCl).

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.14; N, 8.33. Found: C, 60.3; H, 7.09; N, 8.48.

N^{10}-Methylpteroylglutamic Acid.—Synthesis was by the method of Waller, *et al.*[2a] The purification was accomplished as indicated above. The pure material was obtained as yellow spherulites (see Table I). The material, dried at 100° and 1 mm. for eight hours, was a monohydrate.

Anal. Calcd. for $C_{20}H_{21}N_7O_6 \cdot H_2O$: C, 50.8; H, 4.86; N, 20.55. Found: C, 50.8; H, 5.06; N, 20.6.

***p*-Phenacylaminobenzoylglutamic Acid.**—*p*-Aminobenzoylglutamic acid (133 g.) was dissolved in water (500 ml.) by the addition of sodium carbonate (60 g.). The solution was heated to 85° and 75 g. of phenacyl chloride was added in three portions of 25 g. of each fifteen minutes apart. Sodium carbonate was added as necessary to keep the solution slightly alkaline. Heating was continued at 90–95° for three hours. On acidification of the cooled solution the product precipitated out. It was purified by recrystallization from alcohol. The yield was 32 g. of material; m.p. 100–104°.

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: C, 62.5; H, 5.21; N, 7.3. Found (corrected for 4.2% ash): C, 63.5; H, 5.85; N, 7.35.

N^{10}-Phenacylpteroylglutamic Acid.—This compound was prepared in crude form by the method of Waller, *et al.*[2b] See Table I.

Acknowledgment.—We are indebted to Mr. Richard L. Shepard for technical assistance in the preparation of certain of these compounds, and to Miss Ruth Abbott for the ultraviolet absorption data.

Summary

1. N-[4-{N-[(2-Amino-4-hydroxy-6-pteridyl)-methyl]-N-methylamino}-benzoyl]-glutamic acid and 4-{N-[(2-amino-4-hydroxy-6-pteridyl)-methyl]-N-methylamino}-benzoic acid, called herein

(12) Cairncross and Bogert, *Coll. Czechoslov. Chem. Communications*, **8**, 63 (1936).

(13) Houben and Freund, *Ber.*, **42**, 4822 (1909).

(14) Willgerodt, *ibid.*, **27**, 2331 (1894).

(15) Fel'dman and Kopeliovich, *J. Applied Chem.* (*U.S.S.R.*), **17**, 588 (1944).

(16) Scholtz, *Ber.*, **51**, 1653 (1918).

N^{10}-methylpteroylglutamic acid and N^{10}-methylpteroic acid, have been synthesized in pure crystalline form, and found to be antagonists for pteroylglutamic acid.

2. The purified N^{10}-ethyl- and butyl-, and crude N^{10}-carboxymethyl-, benzyl-, and phenacylpteroic acids and N^{10}-phenacylpteroylglutamic acid have also been prepared. These have a lower order of antagonist activity.

3. Convenient methods of obtaining pure N-monosubstituted aminobenzoic and aminobenzoylglutamic acids have been devised.

BOUND BROOK, NEW JERSEY
RECEIVED DECEMBER 5, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

The Synthesis of Thymine Nucleosides[1,2]

BY DONALD W. VISSER,[3] IRVING GOODMAN AND KARL DITTMER

A method for the synthesis of pyrimidine nucleosides was described by Hilbert and Johnson[4] who prepared 1-glucosyluracil by the reaction of 2,4-diethoxypyrimidine with acetobromoglucose followed by hydrolysis. By this method these and other investigators prepared the uracil nucleosides of D-ribose,[5] L-arabinose,[6] D-xylose,[6] D-glucose[4] and D-galactose.[6] However, the literature contains no conclusive report of the synthesis of thymine nucleosides. The syntheses of the D-ribose, D- and L-arabinose, D-glucose and D-galactose nucleosides of thymine by a modification of this procedure are reported in this paper.

When Schmidt–Nickles and Johnson[7] treated 2,4-diethoxy-5-methylpyrimidine with D-acetobromoglucose at 50° for seven days, they obtained a small amount of a crystalline substance which melted at 316°. We repeated this reaction under similar conditions and isolated a small amount of material which, when crystallized from water, melted at 326° and proved to be thymine. Since no other product was isolated from this reaction mixture, various modifications of the original procedure were studied.

It seemed desirable to provide conditions which would enhance the removal of ethyl bromide, a by-product, which might enter into undesirable side reactions.[7] For this reason the reaction between the acetobromoglucose and 2,4-diethoxy-5-methylpyrimidine was carried out at a pressure of 2 mm. for four days at 50°. Since ethyl bromide was collected in a Dry Ice trap, it was assumed that the desired product was formed, even though it could not be isolated. The complete reaction mixture was then hydrolyzed with dry hydrogen chloride in absolute methanol. After the solvents were removed *in vacuo*, glucosylthymine was crystallized from absolute ethyl alcohol.

In a similar manner the other thymine nucleosides were formed, although each behaved differently. The acetoarabinosylethoxythymine crystallized directly in the reaction mixture. Ribosylthymine did not crystallize upon hydrolysis of the reaction mixture. Therefore, an impure intermediate was isolated by fractional precipitation at low temperatures before hydrolysis. Hydrolysis of this intermediate yielded ribosylthymine.

Experimental

2,4-Diethoxy-5-methylpyrimidine.—The 2,4-diethoxy-5-methylpyrimidine was prepared from thymine (commercial source) according to the directions given by Schmidt–Nickles and Johnson.[7]

D-Acetobromoribose.—The directions of Levene and Tipson[8] were followed for the preparation of D-acetobromoribose except that petroleum ether was not used to facilitate crystallization of the product. The ether solution of the acetobromoribose, after treatment with Norite, was slowly concentrated *in vacuo* to about one-third of its original volume. The large colorless crystals were washed with a small amount of cold, dry ether, and dried over phosphorus pentoxide in a vacuum desiccator. Contact with moisture was avoided throughout the procedure. If the proper precautions were not taken, the acetobromcribose began to decompose within ten to fifteen minutes. Unless it was redissolved in dry ether, treated with Norite and recrystallized, complete decomposition took place within a few hours.

D-Acetobromoarabinose.—This compound was prepared according to the directions of Anderson and Snell.[9]

D-Acetobromoglucose.—D-Acetobromoglucose was prepared by a method similar to that described by Karjala and Link.[10]

D-Acetobromogalactose.—A modification of the method of Levene and Raymond[11] was used for the synthesis of D-acetobromogalactose. One hundred grams of glacial acetic acid was saturated with dry hydrogen bromide and cooled to 0°. To this solution 25 g. of dry, finely-powdered D-galactosepentaacetate was added and anhydrous hydrogen bromide was passed through the suspension at 0–10° with stirring until all the galactosepentaacetate had dissolved. The flask was loosely stoppered and allowed to stand for one hour at room temperature. The hydrogen bromide was removed under vacuum, and the product isolated as described for the preparation of acetobromoribose.

(1) Presented in part to the American Society of Biological Chemists in May, 1947, at the thirty-first annual meeting of the Federation of American Societies for Experimental Biology.

(2) This work was supported in part by a contract with the Office of Naval Research.

(3) Present address: Department of Biochemistry and Nutrition, University of Southern California School of Medicine, Los Angeles, California.

(4) Hilbert and Johnson, THIS JOURNAL, **52**, 4489 (1930).

(5) Hilbert and Rist, *J. Biol. Chem.*, **117**, 371 (1937).

(6) Hilbert, THIS JOURNAL, **59**, 330 (1937).

(7) Schmidt–Nickles and Johnson, *ibid.*, **52**, 4511 (1930).

(8) Levene and Tipson, *J. Biol. Chem.*, **92**, 109 (1931).

(9) Anderson and Snell, "Organic Syntheses," Vol. VIII, John Wiley and Sons, New York, N. Y., 1926, p. 18.

(10) Karjala and Link, THIS JOURNAL, **62**, 917 (1940).

(11) Levene and Raymond, *J. Biol. Chem.*, **90**, 247 (1931).

1-D-**Ribosylthymine.**—Eight grams (0.044 mole) of 2,4-diethoxy-5-methylpyrimidine was heated with 8.1 g. (0.024 mole) of D-acetobromoribose in an oven at 50° for four days at 3–4 mm. pressure. To the cloudy, viscous sirup was added 50 ml. of anhydrous ether, and the solution was kept at −10° for three days. A white crystalline material (1.7 g.) was filtered and recrystallized from 50% aqueous ethanol, m. p. 126°. Hydrolysis of this compound in anhydrous methanol and hydrogen chloride yielded thymine. This compound was believed to be 2-D-acetoribosido-4-ethoxy-5-methylpyrimidine. The isolation, purification and properties of this compound will be reported elsewhere. The filtrate was cooled in a Dry Ice–acetone-bath, and the material (3.0 g.) which separated was filtered in a funnel cooled with Dry Ice and acetone. The white amorphous material was hydrolyzed for three days with hydrogen chloride in methanol, and the solvent completely removed *in vacuo*. The residue was dissolved in 10 ml. of absolute ethanol and cooled overnight. The 1-D-ribosylthymine, 0.5 g. (yield 8.1%), was filtered and recrystallized from absolute alcohol, m. p. 252°. The specific rotation was $[\alpha]^{25}D$ −110° (*C*, 2 in water).

Anal. Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.52; H, 5.46; N, 10.82. Found: C, 47.10; H, 5.78; N, 11.02.

1-D-**Arabinosylthymine.**—Ten grams (0.055 mole) of 2,4-diethoxy-5-methylpyrimidine was heated with 10.5 g. (0.031 mole) of D-acetobromoarabinose at 50° for four days at 3–4 mm. pressure. Crystals separated at the end of the first day and a solid cake was formed in the bottom of the reaction flask after the fourth day. Twenty milliliters of anhydrous ether was added and the mixture stirred thoroughly and cooled to 0°. The white needles were filtered and recrystallized from 50% aqueous ethanol. The yield of 1-D-acetoarabinosyl-4-ethoxy-5-methylpyrimidine was 4.5 g. (43%), m. p. 181°. The specific rotation was $[\alpha]^{29}D$ −93.6° (*C*, 3 in 95% ethanol).

The 1-D-acetoarabinosyl-4-ethoxythymine was hydrolyzed with anhydrous hydrogen chloride in methanol. From 3.50 g. of the intermediate, 1.42 g. of 1-D-arabinosylthymine was obtained, m. p. 250–251°. The specific rotation was $[\alpha]^{25}D$ −69° (*C*, 3 in water).

Anal. Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.52; H, 5.46; N, 10.82. Found: C, 45.72; H, 5.93; N, 10.92.

1-L-**Arabinosylthymine.**—According to the procedure just described the 1-L-arabinosylthymine was prepared in yields identical with those obtained in the preparation of the 1-D-arabinosylthymine. The 1-L-acetoarabinosylthymine, m. p. 181°, had a specific rotation, $[\alpha]^{29}D$ + 93.5° (*C*, 3 in 95% ethanol). When this intermediate was hydrolyzed, the 1-L-arabinosylthymine was obtained, m. p. 250–251°; $[\alpha]^{25}D$ + 69° (*C*, 3 in water).

Anal. Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.52; H, 5.46; N, 10.82. Found: C, 46.75; H, 5.52; N, 10.80.

When equal amounts of 1-L-arabinosylthymine and 1-D-arabinosylthymine were mixed and crystallized from water, 1-DL-**arabinosylthymine** was obtained, m. p. 238–239°; it did not rotate polarized light and was considerably less soluble in water than the optical isomers.

1-D-**Glucosylthymine.**—Fifteen grams (0.082 mole) of 2,4-diethoxy-5-methylpyrimidine was heated with 15 g. (0.037 mole) of recrystallized acetobromoglucose at 50° for seven days at 2–3 mm. pressure. The sirup was dissolved in 375 ml. of absolute methanol containing 13 g. of dry hydrogen chloride. The flask was stoppered and allowed to stand at room temperature. After three days the solvents were completely removed *in vacuo*, and the residue was dissolved in 50 ml. of hot absolute alcohol and placed in the cold overnight. The product was filtered and a second crop obtained from the filtrate. The combined yield was recrystallized from an alcohol and water mixture giving 4.6 g. (43%) of 1-D-glucosylthymine, m. p. 271°. The specific rotation was $[\alpha]^{25}D$ + 14.6° (*C*, 2 in water).

Anal. Calcd. for $C_{11}H_{16}O_7N_2$: C, 45.83; H, 5.60; N, 9.72. Found: C, 45.90; H, 5.69; N, 9.53.

1-D-**Galactosylthymine.**—Seventeen grams (0.041 mole) of D-acetobromogalactose was heated with 17 g. (0.093 mole) of 2,4-diethoxy-5-methylpyrimidine as described for the synthesis of glucosylthymine. The light yellow reaction mixture was hydrolyzed and the solvents removed as previously described. The sirupy residue was taken up with an equal weight of hot absolute alcohol and 3 volumes of hot chloroform were added. Upon cooling the solution, a white material was deposited which was collected by filtration and washed several times with chloroform before it was allowed to dry. The material collected on the funnel was dissolved in absolute alcohol and treated with Norite. To the hot filtrate was added 3 volumes of chloroform. The material separating from the solution was filtered and washed first with chloroform and then with ether. The product, 5.7 g. (yield 48%) was a white powder having an indefinite melting point.

Anal. Calcd. for $C_{11}H_{16}O_7N_2$: N, 9.72. Found: N, 8.74.

Ultraviolet Absorption Spectra of Thymine Nucleosides.—The ultraviolet absorption spectra of the D-ribose, D-arabinose and D-glucose thymine nucleosides were determined with a Beckman spectrophotometer with a hydrogen discharge tube as the source of light. The concentration used for all the measurements was 25 mg. in a liter of distilled water. The maximum and minimum absorption values of the thymine nucleosides are recorded in Table I. The absorption spectrum of glucosylthymine is shown in Fig. 1.

TABLE I

THE MAXIMUM AND MINIMUM ULTRAVIOLET ABSORPTION OF THYMINE NUCLEOSIDES

	Maximum, Å.	Minimum, Å.
1-D-Ribosylthymine	2660	2340
1-D-Arabinosylthymine	2640	2320
1-D-Glucosylthymine	2640	2340

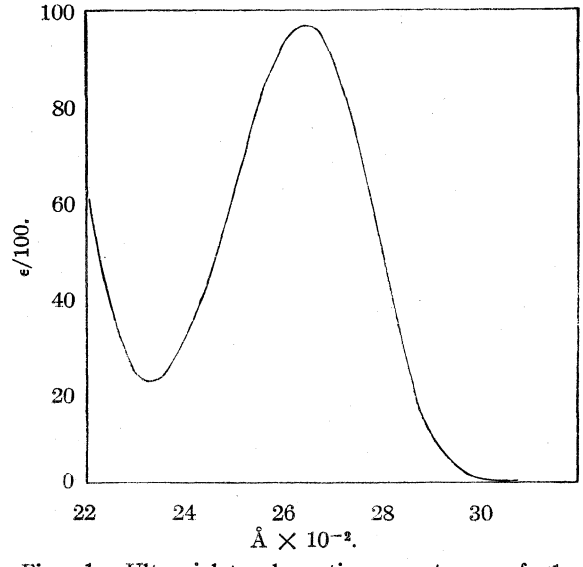


Fig. 1.—Ultraviolet absorption spectrum of 1-D-glucosylthymine. The wave length is plotted against the molecular extinction, ε (ε = $E \times$ mol. wt./cd) where E = extinction, mol. wt. = molecular weight of compound, c = concentration in g. per liter, and d = cell thickness in cm.

Acknowledgment.—The authors are greatly indebted to Dr. J. A. Aeschlimann of the Hoffmann–La Roche Company and to the Chemical

Foundation for generous gifts of thymine and D-ribose. The authors also wish to express their appreciation to Mr. Jack Fox for technical assistance.

Summary

The synthesis of 1-D-ribosyl-, 1-D-arabinosyl-, 1-L-arabinosyl-, 1-D-glucosyl- and 1-D-galactosyl-thymine nucleosides are described. These nucleosides were prepared by reactions between 2,4-diethoxy-5-methylpyrimidine and the proper acetobromo sugar.

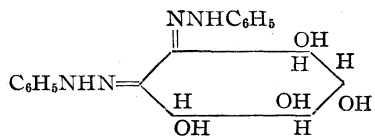
BOULDER, COLORADO RECEIVED DECEMBER 12, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

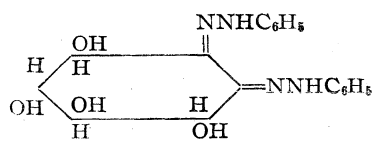
The Action of Periodic Acid on a Cyclohexose Osazone[1]

BY BORIS MAGASANIK[2] AND ERWIN CHARGAFF

It has been shown in a preceding communication[3] that the cyclohexose osazones isolated following the oxidation of *l*- and *d*-inositol by *Acetobacter suboxydans* each consumed three moles of periodic acid per mole of substance. Structure Ia represents the osazone derived from *l*-inositol, Ib that from *d*-inositol.[4]



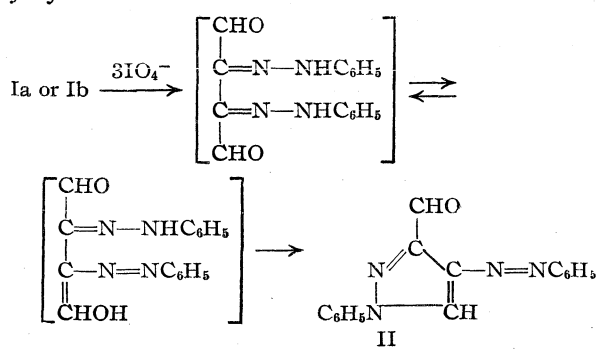
Ia



Ib

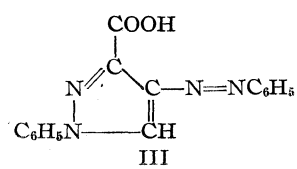
When the oxidation with periodic acid was carried out in a slightly alkaline alcoholic solution, a compound (II) was isolated in a yield of almost 80% whose analytical composition deviated from that of the 2,3-bis-phenylhydrazone of diketosuccinaldehyde, expected by analogy to the behavior of glucose phenylosazone,[5] by the lack of the elements of one molecule of water. The same substance was obtained, though in a lower yield, when the oxidation took place in acidic alcohol. The compound gave the Schiff test and could be oxidized by silver oxide under alkaline conditions to a monocarboxylic acid (III). With semicarbazide it yielded the corresponding semicarbazone.

Compound II appears, therefore, to be derived from the 2,3-bis-phenylhydrazone of diketosuccinaldehyde by the removal of one molecule of water and the concomitant suppression of one aldehyde function. The cyclodehydration of an enolic intermediate would account for the formation of 1-phenyl-4-phenylazo-3-pyrazolecarboxaldehyde (II) from the cyclohexose osazones. This reaction is analogous to the well known formation of 1-phenylpyrazoles from β-diketones and phenylhydrazine.[6]



II

The oxidation of II results in the formation of 1-phenyl-4-phenylazo-3-pyrazolecarboxylic acid (III).



III

The investigation of the absorption spectra of compounds II and III and of IIIa, the sodium salt of compound III, gave results favoring the structures discussed here (see Figure 1). The spectra of II and of the sodium salt IIIa were very similar, showing the low intensity "R band" (molecular extinction ϵ1060 and 940, at wave lengths of 425 and 435 mμ, respectively, obtained by graphical interpolation), and the high intensity "K band" in the ultraviolet, as found characteristic of phenylazo compounds.[7] The free acid III exhibited a slightly different spectrum, probably

(1) This work was supported in part by a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

(2) This report is from a dissertation to be submitted by Boris Magasanik in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(3) E. Chargaff and B. Magasanik, *J. Biol. Chem.*, **165**, 379 (1946); B. Magasanik and E. Chargaff, *ibid.*, **174**, 173 (1948).

(4) The enantiomorphic osazones originating from *l*- and from *d*-inositol, *i. e.* compounds Ia and Ib, yielded, of course, the same oxidation product with periodic acid.

(5) E. Chargaff and B. Magasanik, THIS JOURNAL, **69**, 1459 (1947).

(6) H. Meyer, "Synthese der Kohlenstoffverbindungen", Wien, Vol. II, 1940, p. 891.

(7) A. Burawoy, *J. Chem. Soc.*, 1865 (1937); 1177 (1939).

reflecting contributions by the various tautomeric forms.

The reasons for the readiness with which the pyrazole was formed in the course of the oxidation of the cyclic osazone are not certain. A previous study from this Laboratory[5] has shown the action of periodic acid on the open-chain glucose phenylosazone to result in the production of the 1,2-bis-phenylhydrazone of mesoxalaldehyde; there, an aldehyde group vicinal to an osazone structure was stable. It is possible that the farther-reaching transformation encountered in the present work had its origin in the cyclic nature of the osazone cleaved by periodic acid.

Experimental

1-Phenyl-4-phenylazo-3-pyrazolecarboxaldehyde (II).—A solution of 1.08 g. (3 millimoles) of compound I in 400 cc. of absolute ethyl alcohol was cooled to room temperature and treated with 2.06 g. (9 millimoles) of paraperiodic acid in 300 cc. of 1% aqueous sodium bicarbonate. After one hour the mixture, diluted with one liter of water, was three times extracted with ether. The crystalline evaporation residue of the combined ethereal extracts was recrystallized from aqueous alcohol when *compound II* was obtained as 650 mg. of long orange needles (78% of the theoretical yield). The substance melted[8] at 131°; it gave the Schiff test, was insoluble in water, alkali, and acid, soluble in organic solvents.

Anal. Calcd. for $C_{16}H_{12}ON_4$ (276.3): C, 69.5; H, 4.4; N, 20.3. Found: C, 69.2; H, 4.2; N (Dumas), 20.1.

When the oxidation with periodic acid was carried out in the absence of sodium bicarbonate, the pyrazole II was obtained in a yield of only 18%.

The semicarbazone of II, after several recrystallizations from ethanol–benzene and from ethanol, formed yellow needles, melting at 188–189° (dec.).

Anal. Calculated for $C_{17}H_{15}ON_7$ (333.4): C, 61.2; H, 4.5; N, 29.4. Found: C, 61.5; H, 4.2; N, 29.5.

1-Phenyl-4-phenylazo-3-pyrazolecarboxylic Acid (III).—To a mixture of 555 mg. of silver nitrate in 40 cc. of water and 415 mg. of compound II (1.5 millimoles) in 30 cc. of ethanol, 5 cc. of *N* potassium hydroxide was added dropwise with constant stirring in the course of ninety minutes.[9] The acidification of the filtrate brought about the separation of 280 mg. of the crude acid (64% yield). *Compound III,* following recrystallization from absolute ethanol, formed orange needles, melting at 196–197° (dec.), insoluble in water, soluble in warm aqueous sodium bicarbonate.

Anal. Calculated for $C_{16}H_{12}O_2N_4$ (292.3): C, 65.7; H, 4.1; N, 19.2; neut. equiv., 292. Found: C, 65.6; H, 3.8; N, 19.2; neut. equiv., 288.

(8) The melting points, reported without correction, were determined with an electrically heated stage (Fisher–Johns).

(9) M. Délépine and P. Bonnet, *Compt. rend. Acad. Sci.*, **149**, 39 (1909).

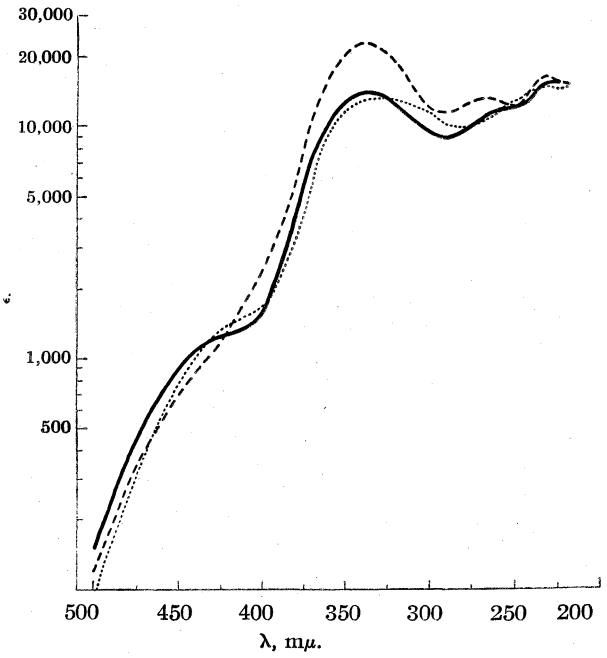


Fig. 1.—Absorption spectra (in absolute ethanol) of compounds II, III and the sodium salt IIIa: ———, IIIa Na salt; — — — — —, III; ..... II.

Absorption Spectra (Fig. 1).—The spectra of compounds II and III and of the sodium salt IIIa (prepared by the exact neutralization of III) were measured by means of a Beckman photoelectric quartz spectrophotometer. About 0.5 and 0.05 millimolar solutions in absolute alcohol were used for visual and ultraviolet spectroscopy, respectively.

The authors are grateful to Mr. W. Saschek and Miss R. Rother for the microanalyses.

Summary

The action of periodic acid on the cyclohexose osazones derived from *l*- and *d*-inositol leads to the formation of 1-phenyl-4-phenylazo-3-pyrazolecarboxaldehyde. Derivatives of this substance (semicarbazone and carboxylic acid) are described. The results of a study of the absorption spectra of these compounds bear out the structures assigned to them.

NEW YORK, N. Y. RECEIVED DECEMBER 17, 1947

[CONTRIBUTION FROM THE FOOD AND DRUG ADMINISTRATION, FEDERAL SECURITY AGENCY]

The Preparation of *o*-Hydroxyphenylacetic Acid

BY JOSEPH LEVINE, T. E. EBLE AND HENRY FISCHBACH

A number of methods have been described for the preparation of *o*-hydroxyphenylacetic acid.[1] In general, the procedures require expensive reagents and usually produce low yields.

The procedure of Czaplicki, *et al.*,[2] entails simultaneous hydrolysis, reduction, and demethylation of *o*-methoxybenzaldehyde cyanohydrin with hydriodic acid. Modification of this procedure for the preparation of the cyanohydrin has now increased the yield from 44 to 95%. Conversion of the cyanohydrin to *o*-methoxyphenylacetic acid was effected in 90% yield with stannous chloride–hydrochloric acid[3] in the presence of a small amount of hydriodic acid. A 75% yield of the pure hydroxy acid was obtained by demethylation with acetic acid–hydrobromic acid mixture containing a small amount of hydriodic acid. In each of the two final steps the use of hydriodic acid resulted in a significant decrease in tar formation.

Methyl *o*-hydroxyphenylacetate, prepared by esterification of the acid with methanol and sulfuric acid, melted at 71°–72°. This compound was reported by Nozu, *et al.*,[4] as melting at 122–124°. From their method of preparation it is evident that their compound is actually the methyl ether, rather than the ester.

Experimental

***o*-Methoxybenzaldehyde** was prepared in 92% yield from salicylaldehyde according to the procedure given in "Organic Syntheses" for the preparation of veratraldehyde.[5] Recrystallized from petroleum ether, it melted sharply at 37°,[6a] as reported by Voswinckel.[6]

***o*-Methoxybenzaldehyde Cyanohydrin.**—To 99 g. of melted *o*-methoxybenzaldehyde was added a saturated solution of 104 g. (1.5 equivalents) of sodium metabisulfite. Upon stirring heat was evolved and the entire mixture solidified. Water was added to obtain a thick suspension, which was covered with ether and cooled. An ice-cold saturated solution of 99 g. of sodium cyanide was added with stirring, and a further 10 g. of sodium bisulfite added, stirring until most of the product was dissolved in the ether. The aqueous layer was diluted with water, extracted with ether, and the combined ether solutions washed with bisulfite solution and then with water. The ether was distilled off and the residue dissolved in benzene and dried azeotropically by refluxing with a water trap. Upon cooling, crystals of the cyanohydrin separated. Petroleum ether was added to effect complete separation. A yield of 113 g. (95%) of granular crystals, m. p. 71–72°, was obtained. Recrystallization from benzene gave a m. p. of 73–74° (Buck[7] reported 73°).

***o*-Methoxyphenylacetic Acid.**—A hot solution of 50 g. of crystalline stannous chloride in 50 ml. of acetic acid, 50 ml. of concentrated hydrochloric acid, and 5 ml. of hydriodic acid (sp. gr. 1.7) was added to 25 g. of *o*-methoxybenzaldehyde cyanohydrin, and the resultant solution heated three hours on a steam-bath. After cooling the solution was filtered to remove stannic chloride which separated during the reaction, diluted with water, and extracted to exhaustion with carbon tetrachloride. The combined extracts were washed with water and evaporated to dryness. A yield of 23 g. (90%) of *o*-methoxyphenylacetic acid was obtained. A portion recrystallized from benzene melted at 124°, the value reported by Pschorr, *et al.*[8]

***o*-Hydroxyphenylacetic Acid.**—Twenty-three grams of *o*-methoxyphenylacetic acid (used directly as obtained above), 70 ml. of glacial acetic acid, 70 ml. of 48% hydrobromic acid, and 7 ml. of hydriodic acid (sp. gr. 1.7) were refluxed sixteen hours. The cooled solution, after dilution with water and addition of a small amount of sodium bisulfite, was extracted first with chloroform and then with ether. The ether extract was washed with water and evaporated; acetic acid in the residue was removed by evaporation with toluene on a steam-bath in a stream of air. The residue was dissolved in ether and sufficient petroleum ether (Skellysolve C) added to form a cloudy solution, from which a small amount of colored gummy material was deposited. The colorless supernatant liquid was decanted and additional petroleum ether added; 15.8 g. (75%) of large snow-white crystals of *o*-hydroxyphenylacetic acid, m. p. 146°–147°, separated; upon recrystallization in the same manner, the m. p. was raised to 149–150° (Czaplicki, *et al.*,[2] reported 147°).

Methyl *o*-Hydroxyphenylacetate.—A solution of 2.0 g. of *o*-hydroxyphenylacetic acid in 20 ml. of methanol and 2 ml. of concentrated sulfuric acid was refluxed for two hours. The cooled solution was diluted with water and extracted with ether. The ether solution, after extraction with sodium bicarbonate solution to remove unreacted acid, was evaporated to dryness. The ester crystallized from petroleum ether as plates (yield, 1.6 g.); upon recrystallization, m. p. 71–72°.

Anal. Calcd. for $C_7H_7OCOOCH_3$: OCH_3, 18.65; sapon. equiv., 166.2. Found: OCH_3, 18.55; sapon. equiv., 163.8.

Summary

o-Hydroxyphenylacetic acid was prepared from *o*-methoxybenzaldehyde (64% over-all yield), *via* the cyanohydrin and *o*-methoxyphenylacetic acid. The methyl ester was prepared.

WASHINGTON, D. C. RECEIVED JANUARY 7, 1948

(1) "Beilstein," **10**, 187; 1 Erg., **10**, 81; Barnes and McElvain, THIS JOURNAL, **59**, 2350 (1937); Niederl and Roth, *ibid.*, **60**, 2140 (1938); King and McMillan, *ibid.*, **68**, 2335 (1946); Ott, Mattano and Coleman, *ibid.*, **68**, 2633 (1946).

(2) Czaplicki, von Kostanecki and Lampe, *Ber.*, **42**, 827 (1909).

(3) Heller, *ibid.*, **46**, 288 (1913).

(4) Nozu, Hamada, Hosino and Kinosita, *J. Chem. Soc. Japan*, **60**, 1189 (1939); *C. A.*, **36**, 6513 (1942).

(5) "Organic Syntheses," Coll. Vol. II, 1943, p. 619.

(6) Voswinckel, *Ber.*, **15**, 2025 (1882).

(6a) All m. p.'s determined on a Fisher–Johns apparatus.

(7) Buck, THIS JOURNAL, **55**, 2593 (1933).

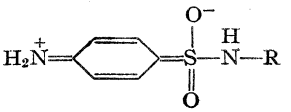
(8) Pschorr, Wolfes and Buckow, *Ber.*, **33**, 167 (1900).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

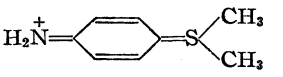
p-Aminophenyldimethylsulfonium β-Naphthalenesulfonate and Antibacterial Activity[1]

BY PHILIP E. WILCOX,[2] JOHN H. OWEN[3] AND MARK A. STAHMANN

Kumler and Daniels[4] have proposed that the anti-*p*-aminobenzoic acid activity of sulfonamides is essentially due to the contribution of the resonant form



to the structure of these compounds. Accordingly it might be expected that a compound such as a *p*-aminophenyldimethylsulfonium salt would exhibit activity of the sulfonamide type since the positive sulfur should readily accept an electron pair from the ring. This would result in the resonant form



which would make a large contribution to the structure of the molecule. Furthermore, from the steric point of view, the *p*-aminophenyldimethylsulfonium cation resembles *p*-aminobenzoic acid and might possess anti-*p*-aminobenzoic acid activity in accordance with the general theory of metabolic antagonists.

Another theory of sulfonamide activity, which has been proposed by Bell and Roblin,[5] and Klotz,[6] correlates the activity of these compounds with their respective acid dissociation constants. From this point of view, it would not be expected that *p*-aminophenyldimethylsulfonium salts would show activity of the sulfonamide type.

In any case, sulfonium compounds are of interest entirely apart from their possible relation to sulfonamides since certain sulfonium compounds do have remarkable physiological activities.[7,8]

Although a great many variations of the sulfonamide structure have been studied, derivatives in which the sulfur appears in the form of a sulfonium group have not been reported. This communication describes the preparation and preliminary microbiological assay of such a compound, *p*-aminophenyldimethylsulfonium β-naphthalenesulfonate. The results furnish supplementary data on the question of the chemical structures which are essential for antibacterial activity of the sulfonamide type.

Many sulfonium compounds are unstable because of the ease with which they undergo dismutation and dealkylation or dearylation. Therefore, it was decided that the synthesis would have the greatest chance for success if the final step was the catalytic reduction under mild conditions of a stable *p*-nitrophenyldimethylsulfonium salt. Preliminary experiments on the hydrogenation of *p*-nitrophenyldimethylsulfonium methyl sulfate with palladium on activated carbon showed that the compound must be reduced in acid solution in order to prevent excessive reduction with the absorption of more than three molar equivalents of hydrogen. On the other hand, in acid solution never more than 80% of the theoretical amount of hydrogen was absorbed even though the catalyst was still active. This reduced solution proved to be quite unstable. The rather insoluble picrate could be isolated if picric acid was added immediately, but attempts to isolate other salts more suitable for antibacterial testing gave only mixtures or oils.

It was found, however, that a more stable solution could be obtained if the reduction was carried out in methanol–water in the presence of an excess of β-naphthalenesulfonic acid. When ether was added to this solution, the desired *p*-aminophenyldimethylsulfonium β-naphthalenesulfonate separated as long needles. Since the β-naphthalenesulfonate anion proved to have no activity in the microbiological tests, this salt was satisfactory for testing.

The structure assigned to the product, namely, *p*-aminophenyldimethylsulfonium β-naphthalenesulfonate, is based on the elementary analysis, the method of synthesis, the fact that the compound is quite soluble in polar solvents, but insoluble in non-polar solvents, and the fact that it gives a strong positive test for a free, primary amino group with glutaconic aldehyde. The instability of some of the sulfonium salts and the greater stability of the same cation in other salts is in conformity with the observations of other investigators, particularly those of Ray and Levine.[9]

p-Aminophenyldimethylsulfonium β-naphthalenesulfonate was tested for anti-*p*-aminobenzoic acid activity against *Staphylococcus aureus* H in a medium which has been described by McIlwain.[10] The compounds involved in the tests were dissolved in sterile water and added aseptically to the sterile medium just before inoculation. Each

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station and supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation, and by a grant from the Schenley Research Institute.

(2) National Research Council Predoctoral Fellow.

(3) Research Assistant in Plant Pathology.

(4) Kumler and Daniels, THIS JOURNAL, **65**, 2190 (1943).

(5) Bell and Roblin, *ibid.*, **64**, 2905 (1942).

(6) Klotz, *ibid.*, **66**, 459 (1944).

(7) Kuhn, Bielig and Dann, *Ber.*, **73B**, 1080 (1940).

(8) Gilman and Philips, *Science*, **103**, 409 (1946).

(9) Ray and Levine, *J. Org. Chem.*, **2**, 267 (1937).

(10) McIlwain, *Brit. J. Exptl. Path.*, **23**, 95 (1942).

tube was inoculated with one drop of a 24-hour culture which had been diluted thirty times. The *p*H of the medium was 6.9 and, after twenty-four hours of incubation at 37°, the growth was determined by measuring the turbidity with an Evelyn colorimeter. For comparison, sulfanilamide was tested in parallel with the sulfonium salt. The activity of each compound was also tested in the presence of *p*-aminobenzoic acid at concentrations of 10 micrograms and 200 micrograms per milliliter.

TABLE I

THE ANTIBACTERIAL ACTIVITY OF *p*-AMINOPHENYLDIMETHYLSULFONIUM β-NAPHTHALENESULFONATE (I), SULFANILAMIDE (II), AND THE EFFECT OF *p*-AMINOBENZOIC ACID

Compound I or II	*p*-Aminobenzoic acid micrograms/ml.	Bacterial growth, expresesd in Evelyn units in the presence of I or II at the following concentrations, and *p*-aminobenzoic acid Micrograms per ml. 1000	500	250	125	62.5	31.7	0
I	0	0	0	5	11	25	28	30
I	10	0	4	13	15	22	24	32
I	200	0	13	18	25	25	26	29
II	0	0	0	0	1	1	12	30
II	10	8	12	19	23	26	28	29
II	200	8	15	22	25	26	28	30

The results of representative tests are presented in Table I. This table shows that sulfanilamide produced almost complete inhibition of growth at a concentration of 62.5 micrograms per ml., and that the addition of either 10 or 200 micrograms of *p*-aminobenzoic acid per ml. allowed almost full growth at 250 micrograms and only partial growth at 1000 micrograms of sulfanilamide per ml. *p*-Aminophenyldimethylsulfonium β-naphthalenesulfonate produced complete inhibition of growth at 500 micrograms per ml. and partial growth at 125 micrograms per ml. The addition of *p*-aminobenzoic acid allowed almost full growth at 125 and partial growth at 500 micrograms per ml. Sodium β-naphthalenesulfonate showed no antibacterial action at a concentration of 2000 micrograms per ml.

These results show that the *p*-aminophenyldimethylsulfonium ion has a low order of antibacterial activity and that this activity is slightly reduced by *p*-aminobenzoic acid. Since it is probable that this ion possesses a resonant form with a quinoidal structure and a positive nitrogen, its low activity indicates that such a resonant form is not sufficient for high action of the sulfonamide type. Apparently, for high anti-*p*-aminobenzoic acid activity, it is necessary to have a negative group comparable to the carboxylate group in the position para to the amino group. However, it must be recognized that the cationic nature of the sulfonium ion may prevent the compound from reaching the points where it could act against a bacterium.

Although sulfonium compounds with a long alkyl chain have high antibacterial activity, the aryl sulfonium group in itself has but a low order of antibacterial activity.[7] In this connection, Freedlander and French[11] have recently shown that methyldiphenylsulfonium nitrate shows no antibacterial activity against *E. coli*, *Staph. aureus*, *B. proteus*, or the tubercle bacillus. Our results would suggest that the introduction of a para amino group into an aromatic sulfonium salt increases the antibacterial activity.

Experimental

Di-*p*-nitrophenyl Disulfide.—This compound was prepared according to the method described for the ortho analog by Bogert and Stull.[12]

***p*-Nitrophenylmethyl Sulfide.**—The disulfide was converted into *p*-nitrophenylmethyl sulfide, according to Brand,[13] in a yield of 61% by the reduction of di-*p*-nitrophenyl disulfide with alkaline sodium sulfide and subsequent direct methylation with methyl sulfate. The product melted sharply at 72.0 to 72.5° in agreement with the literature.

***p*-Nitrophenyldimethylsulfonium Methyl Sulfate and Picrate.**—*p*-Nitrophenylmethyl sulfide was methylated with methyl sulfate according to the method of Brand and Stallmann.[14] The product was recrystallized once from hot methanol and again by the addition of ethyl ether to a methanol solution to give a yield of 84%, m. p. 157.0 to 158.5° (dec.). The picrate was produced in a yield of 95% by the addition of a saturated solution of sodium picrate to an aqueous solution, m. p. 135° to 136° as compared to 137° as reported by Baker and Moffett.[15]

***p*-Aminophenyldimethylsulfonium Picrate.**—Palladium catalyst on activated carbon, prepared according to Hartung,[16] was used for the hydrogenation of *p*-nitrophenyldimethylsulfonium methyl sulfate (3.0 g., 10 millimoles) dissolved in 100 ml. of 90% methanol which contained 20 millimoles of sulfuric acid. The hydrogenation stopped abruptly after 24 millimoles of hydrogen had been absorbed (80% of theory). When this solution is allowed to stand, it became yellow and no crystalline sulfonium salt could be isolated. However, when 3.0 g. (13 millimoles) of picric acid in 100 ml. of water was added immediately to the filtered solution, 3.2 g. (79% yield) of orange prisms separated, m. p. 152 to 153°.

Anal. Calcd. for $C_8H_{12}NS \cdot C_6H_2N_3O_7 \cdot H_2O$: C, 42.0; H, 4.0; N, 14.0; S, 8.0. Found: C, 42.3, 42.3; H, 3.8, 3.7; N, 14.1, 14.1; S, 7.9.

When a methanol solution of this picrate was refluxed for a few hours, long needles of some different, much less soluble picrate separated. This derived compound melted at 165.0 to 165.5° and had an elementary analysis (C, 43.6; H, 3.1; N, 14.5) which indicated that the conversion may have been a reduction.

***p*-Aminophenyldimethylsulfonium β-Naphthalenesulfonate.**—*p*-Nitrophenyldimethylsulfonium methyl sulfate (4.25 g., 14 millimoles) and β-naphthalenesulfonic acid (3.60 g., 17 millimoles) were dissolved in 75 ml. of methanol containing 5% water, and the solution was hydrogenated with palladium catalyst on activated carbon. A total of 30 millimoles of hydrogen was absorbed or 72% of theory. The slightly yellow solution was filtered and 100 ml. of ethyl ether was added immediately. After cooling at 0° for two hours, 3.9 g. (68% yield) of nearly colorless needles of the monohydrate were collected. The product was recrystallized by dissolving it in 120 ml. of absolute methanol, removing the insoluble material by filtration, adding 250 ml. of 30–60° ligroin, and cooling at 0°. The final yield of material was 3.1 g. or 54%, m. p.

(11) Freedlander and French, *Proc. Soc. Expll. Biol. Med.*, **63**, 319 (1946).

(12) Bogert and Stull, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, Inc,. New York, N. Y., 1941, p. 220.

(13) Brand, *Ber.*, **42**, 3463 (1909).

(14) Brand and Stallmann, *ibid.*, **54**, 1578 (1921).

(15) Baker and Moffett, *J. Chem. Soc.*, 1722 (1930).

(16) Hartung, THIS JOURNAL, **50**, 3370 (1928).

130° (dec.). The product was dried at 80° for four hours for analysis.

Anal. Calcd. for $C_8H_{12}NS \cdot C_{10}H_7O_3S \cdot H_2O$: C, 56.9; H, 5.5; N, 3.7; S, 16.9. Found: C, 56.9, 56.7; H, 5.6, 5.8; N, 3.6, 3.7; S, 16.7.

Further recrystallization did not raise the melting point, but seemed to cause deterioration. The salt was soluble in water, methanol, ethanol, and acetic acid, but was insoluble in ether, chloroform, and benzene. Aqueous base causes the salt to decompose with the formation of an orange color and water insoluble material.

Test for Free Primary Aromatic Amino Group.—Both the *p*-aminophenyldimethylsulfonium picrate and β-naphthalenesulfonate yielded a color characteristic of substances containing a primary aromatic amino group when treated with 4-pyridylpyridinium chloride hydrochloride.[17] On the other hand, the second picrate derived from the initial picrate by heating in methanol gave a completely negative test, indicating that the primary amino group had been destroyed.

(17) Feigl, "Qualitative Analysis by Means of Spot Tests," Nordemann Publishing Company, New York, N. Y., 1937, p. 283.

Summary

A new compound, *p*-aminophenyldimethylsulfonium β-naphthalenesulfonate, has been synthesized. The picrate of the sulfonium cation has also been prepared.

Microbiological tests showed that the sulfonium sulfonate has a low order of antibacterial activity which is slightly reversed by *p*-aminobenzoic acid.

The activity of the sulfonium salts has been related to the problem of the mode of action of sulfonamides.

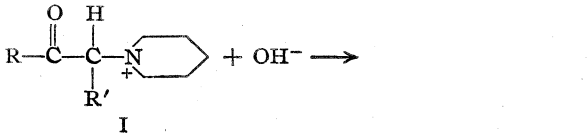
MADISON, WISCONSIN RECEIVED NOVEMBER 3, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

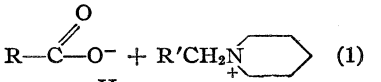
Mechanism of the Alkaline Cleavage of β-Ketoalkylpyridinium Salts[1]

BY RALPH G. PEARSON AND ROBERT L. DILLON

The alkaline hydrolysis of β-ketoalkylpyridinium salts to give the corresponding acid and a simpler alkylpyridinium salt[2] according to equation (1) was studied in some detail by Kröhnke.[3]

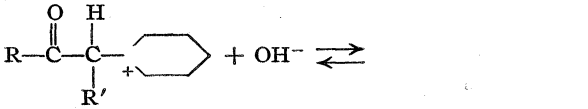


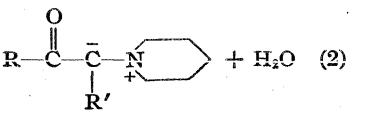
I



II (1)

He showed by kinetic methods that in the presence of excess alkali the reaction was first order and that the stronger the acid, II, formed by the reaction, the greater the rate of hydrolysis. Furthermore, he showed[4] that the initial reaction of the cation, I, with alkali is a typical acid–base equilibrium in which the cation acts as an acid

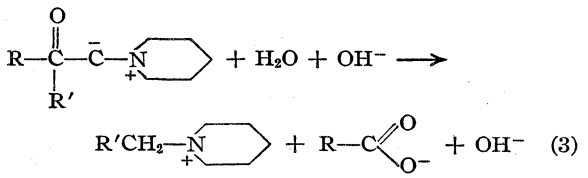




III (2)

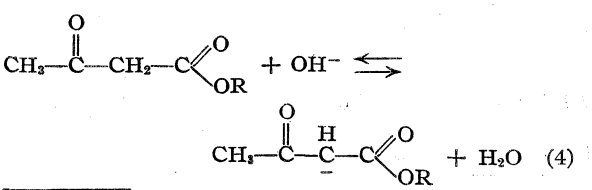
He proposed the name "enol-betaine" for the isolable compound III, writing its structure with the double bond between the two carbon atoms. The enol-betaines in general are highly colored, soluble in organic solvents and not stable in air.

The mechanism that he assumed for the cleavage included the rapid establishment of equilibrium (2) and the subsequent rate-determining reaction of the enol-betaine with excess hydroxide ion and water. If reaction (2) goes well to the right then pseudo first order kinetics will be obtained since hydroxide ion is not used up in (3). However, Kröhnke worked with only one set of concentrations for all of the compounds which he investigated and it can readily be shown that there are several other mechanisms which will turn out to be first order in excess alkali.



(3)

For example in the formally similar hydrolysis of acetoacetic ester by dilute alkali, Goldschmidt and Oslan[5] showed that the reaction was first order under a variety of conditions and the mechanism included an acid-base equilibrium and a rate-determining reaction between hydroxide ion and the unneutralized acetoacetic ester



(4)

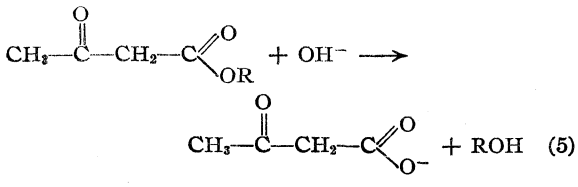
(1) Based on the M.S. thesis of Robert L. Dillon.

(2) (a) Bamberger, *Ber.*, **20**, 3344 (1887); (b) Babcock, Nakamura and Fuson, THIS JOURNAL, **54**, 4407 (1932); (c) Babcock, and Fuson, *ibid.*, **55**, 2946 (1933).

(3) Kröhnke, *Ber.*, **70B**, 864 (1937).

(4) Kröhnke, *ibid.*, **66B**, 604 (1933); **68B**, 1177 (1935).

(5) Goldschmidt and Oslan, *ibid.*, **32**, 3390 (1899); **33**, 1140 (1900).



(5)

Accordingly it seemed advisable to repeat part of Kröhnke's work and to vary the ratios of reactants in such a way as to establish a unique mechanism for the hydrolysis. At the same time the effect of temperature on the rates was investigated and the effect of substituents on the rate constants and the energies of activation determined. The salts selected for this work were phenacylpyridinium iodide and *p*-bromo- and *m*-nitrophenacylpyridinium iodides, all three of which Kröhnke had previously studied as the bromides. The solvent used was distilled water whereas Kröhnke used a mixture of alcohol and water to keep some of the enol-betaines in solution.

Methods and Materials.—The salts used were of high purity[6] and were recrystallized from water–alcohol just before use. The melting points were determined as follows: phenacylpyridinium iodide, 218–219°; *p*-bromophenacylpyridinium iodide, 233–235°; *m*-nitrophenacylpyridinium iodide, 202–203°. Stock solutions made up in distilled water were used within two or three days of preparation.

The extent of reaction was followed by titration of the excess alkali and unreacted enol-betaine. (The enol-betaine is strongly basic.) Selected volumes of solutions of the above salts and carbonate-free standard sodium hydroxide were mixed at the reaction temperature and the zero time recorded. Temperature was controlled to ±0.02° over a range from 13 to 35°. From time to time samples were withdrawn, added to excess acid to stop the hydrolysis and back-titrated. Phenolphthalein indicator was used. A sample was titrated after the reaction was completed also and it was verified that one mole of alkali was used up as in (1). The completion of the reaction could be seen by the disappearance of the intense green-yellow color of the enol-betaine.

As a check on the above method of analysis the kinetics were followed in a few cases with a Beckman photoelectric spectrophotometer. At a wave length of 4400 A. the enol-betaines absorb strongly while the salts themselves and the products do not absorb at all. In this procedure samples were withdrawn from the thermostat into an absorption cell and the transmission measured within a few seconds after withdrawal. The amount of reaction occurring during measurement was negligible.

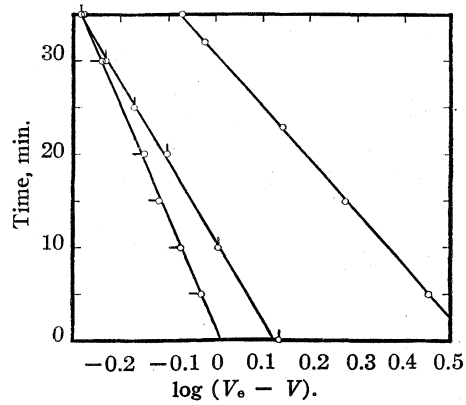


Fig. 1.—O, plot of 0.00714 *M* *p*-bromophenacyl- and 0.01013 *M* NaOH 25.2°; Ọ, 0.00380 *M* *m*-nitrophenacyl- and 0.00482 *M* NaOH 20.0°; O-, 0.00714 *M* phenacyl- and 0.01015 *M* NaOH 25.2°.

(6) Kindly supplied by Dr. L. C. King and prepared by the methods described by him, THIS JOURNAL, 66, 894 (1944), *et seq.*

Calculations and Results

It will be convenient to introduce a list of abbreviations at this point.

- PP^+ = the phenacylpyridinium (substituted or unsubstituted) cation
- $PP^{\pm}$ = the corresponding enol-betaine
- a = concentration of limiting reactant
- $a + b$ = concentration of reactant in excess
- x = concentration of products
- k' = experimental rate constant
- k = corrected rate constant
- K_h = hydrolysis constant for reaction (2)
- V_0 = volume of base needed to back-titrate a sample at time $t = 0$
- V = volume of base needed to back-titrate a sample at time $t = t$
- V_e = volume of base needed to back-titrate a sample at time $t = \infty$

If the acid strength of PP^+ is great enough then (2) goes to completion and $[PP^{\pm}] = (a - x)$ and in solutions where alkali is in excess $[OH^-] = b$ and is constant. When PP^+ is in excess we must solve for $[OH^-]$ from the equilibrium $K_h = [PP^+][OH^-]/[PP^{\pm}]$ so that $[OH^-] = K_h (a - x)/b$, putting in the values of $[PP^{\pm}] = (a - x)$ and $[PP^+] = b$.

In terms of experimental quantities, the volumes of base needed to back-titrate given samples, a is proportional to $(V_e - V_0)$ and $(a - x)$ is proportional to $(V_e - V)$. Accordingly plots of log $(V_e - V)$ against the time were made and straight lines were obtained as shown in Fig. 1 with slopes equal to $k'/2.303$. As Table I brings out the experimental rate constant k' varies with the excess hydroxyl ion concentration so that k'/b is essentially constant.

TABLE I

PHENACYLPYRIDINIUM IODIDE + EXCESS NaOH AT 31.5°

Excess $[OH^-]$ mole/liter	Slope	(Slope) (2.3/$[OH^-]$)	k liters/mole-min.
0.00384	0.01790	10.70	12.2
.00258	.01130	10.00	12.0
.00201	.00840	9.60	12.1
.00062[a]	.00201	7.46	13.8

[a] Spectrophotometric.

In solutions where the salt was in excess $1/(V_e - V)$ was plotted against the time and the results showed a change to second order kinetics in these solutions. Figure 2 presents the type of curves

TABLE II

NaOH + EXCESS PHENACYLPYRIDINIUM SALT

Salt	Temp., °C.	(Slope) $(V_e - V_0)(b/a)$	K_h
Phenacyl-	31.5	5.40×10^{-3}	5.40×10^{-4}
m-Nitrophenacyl-	25.5	1.68×10^{-3}	2.83×10^{-5}
p-Bromophenacyl-	25.2	2.46×10^{-3}	1.87×10^{-4}

that were obtained. Furthermore, the slopes multiplied by $(V_e - V_0)(b/a)$ were constant for a given salt at constant temperature. Table II summarizes the results for solutions where PP^+ was in excess.

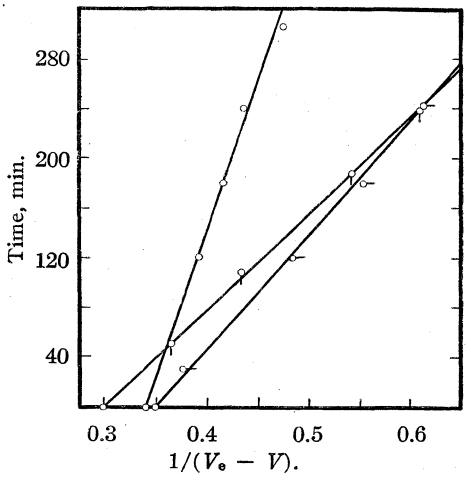


Fig. 2.—O, 0.00882 *M* *m*-nitrophenacyl- and 0.00373 *M* NaOH 25.5°; ○, 0.00833 *M* *p*-bromophenacyl- and 0.00529 *M* NaOH 25.2°; O-, 0.00882 *M* phenacyl- and 0.00373 *M* NaOH 31.5°.

The use of the spectrophotometer has been referred to as a means of following the rate. Here the optical density, *D*, is proportional to $(a - x)$, the concentration of unreacted enol-betaine. So a plot of log *D* *versus* the time should be linear with a slope of $k'/2.3$. Figure 3 shows the results obtained.

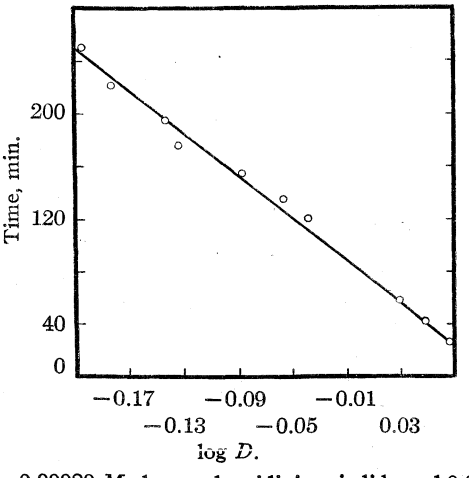


Fig. 3.—0.00080 *M* phenacylpyridinium iodide and 0.00142 *M* NaOH at 25.2°.

Runs were made at least in duplicate at three different temperatures for all three salts. The plot of log *k* against the reciprocal of the absolute temperature gave good straight lines from which the Arrhenius activation energy was computed. Table III gives this information for the three salts.

TABLE III

Salt[a]	Temp., °C.	k,[b] liters/mole-min.	$E_{Arr.}$ kcal.
Phenacyl-	31.5	12.0	13.2
	25.2	7.22	
	20.0	5.00	
m-Nitrophenacyl-	34.0	155	19.7
	25.5	61.2	
	20.0	26.7	
p-Bromophenacyl	34.0	30.1	15.8
	25.2	14.7	
	20.0	8.28	

[a] The salt concentrations were 0.005 to 0.008 *M*; the excess alkali 0.001 to 0.003 *M*. Similar concentrations were used for the same salt at different temperatures. [b] A single value of the hydrolysis constant was used to correct *k* at all three temperatures. While the hydrolysis constant probably changes with temperature, it is used to make only a minor correction and the error introduced is not large.

Discussion

There are two mechanisms consistent with the experimental results. The first is Kröhnke's as shown in (2) and (3) which gives as a rate expression

$$dx/dt = k_1[OH^-][PP^+] \quad (6)$$
$$= k_1 b(a - x) \text{ excess alkali}$$
$$= \frac{k_1 K_h}{b}(a - x)^2 \text{ excess salt} \quad (7)$$

The second is a reaction of the phenacylpyridinium ion with two hydroxyl ions[7] so that

$$dx/dt = k_2[OH^-]^2[PP^+] \quad (8)$$
$$= k_2 K_h b(a - x) \text{ excess alkali}$$
$$= \frac{k_2(K_h)^2}{b}(a - x)^2 \text{ excess salt} \quad (9)$$

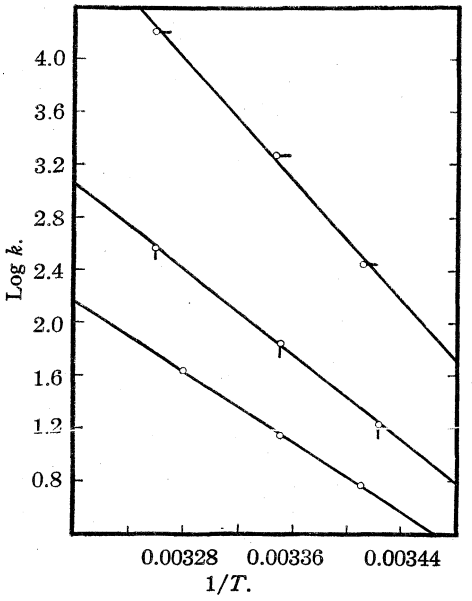


Fig. 4.—O, Phenacyl-; ○, *p*-bromophenacyl-; O-, *m*-nitrophenacyl-.

(7) The authors are indebted to one of the referees for pointing out this possibility of explaining the kinetic data.

Both of these predict correctly pseudo-first order kinetics in excess alkali with a slope varying with the excess alkali and a change to second order kinetics in solutions containing excess salt.

Since for both mechanisms the rate constants in excess alkali and in excess salt differ by a factor of K_h it is possible to evaluate the hydrolysis constant of reaction (2) by dividing (Slope)$(V_s - V_0)(b/a)$ in Table II by k'/b obtained from alkaline solutions at the same temperature. These values are listed in Table II also and it is possible to check the original assumption that $[PP^{\pm}] = (a - x)$. Actually it can be shown that $[PP^{\pm}] = (a - x)[OH^-]/(K_h + [OH^-])$ which reduces to the assumed form when $[OH^-] >> K_h$. The rate constants can be corrected for the small amount of hydrolysis by multiplying them by $(K_h + [OH^-])/[OH^-]$. This has been done for all of the rate constants finally recorded. The magnitude of the effect is seen in Table I where the column (slope)(2.3)/$[OH^-]$ gives the uncorrected rate constant and the last column gives the corrected value. This rate constant k is equal to either k_1 or k_2K_h depending upon which mechanism is correct.

It is interesting to compute the values of K_a, the acid ionization constant of the quaternary ammonium cation, from the values of K_h, the hydrolysis constant. Dividing into the ionization product of water at the temperatures indicated we obtain K_a equal to 3.08×10^{-11}, 5.94×10^{-11}, and 39.6×10^{-11} for the phenacylpyridinium, *p*-bromophenacylpyridinium and *m*-nitrophenacylpyridinium cations, respectively. These values are in the same relative order as the corresponding acidities of the substituted benzoic acids.

Summary

1. The alkaline cleavage of enolizable β-ketoalkylpyridinium salts is shown to be pseudo-first order in excess alkali and second order in the presence of excess salt.

2. The mechanism involves either the reaction of a hydroxyl ion with the enol-betaine or the reaction of two hydroxyl ions with the quaternary cation.

3. The rate constants have been determined for the *m*-nitro-, *p*-bromo- and unsubstituted phenacylpyridinium iodides at several temperatures and the activation energies computed.

EVANSTON, ILLINOIS RECEIVED DECEMBER 22, 1947

[CONTRIBUTION NO. 646 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Reaction of Metallic Copper with Titanium(IV) Chloride

BY DONALD E. KOONTZ AND DOUGLAS G. NICHOLSON

During the course of an investigation of the nature of the reaction(s) taking place in the decolorization of commercial titanium(IV) chloride by metallic copper,[1] it was observed that clean dry metallic copper would react with chemically pure titanium(IV) chloride at room temperature. Accordingly, a detailed study was conducted on the interaction of these substances.

Loose rolls of copper foil made from sheets approximately $4 \times 6 \times 0.0127$ cm. were heated to remove carbonaceous matter, cooled, rinsed in dilute hydrochloric acid, then water, and dried. They were then inserted in Pyrex test-tubes containing 5–8 ml. of titanium(IV) chloride, which were tightly closed with lead foil-covered corks.

The purplish-black scale which became evident after two or three hours could be shaken or jarred off, but on continued exposure the bright copper surface again became coated with the scale. After three to five weeks of exposure, the titanium(IV) chloride had entire disappeared, and an appreciable residue of dry, purplish-black material and flakes of unreacted copper remained. Using dry powdered (150 mesh) copper, the process was complete in twenty to thirty hours, but the residue tended to form a hard cake which, because of its expansion, sometimes cracked the tubes.

The rate of scale formation was not appreciably increased by heating the reaction tubes to approximately 100°, unless the metal surface was re-exposed. It appeared that the scale tended to protect the metal surface from further action.

Small samples of the dry scale, with adhering flakes of metallic copper, were subjected to the tests and analyses described below.

(a) Exposure to atmospheric oxygen showed a gradual color change, becoming progressively gray, tan, and greenish-blue. The material was hygroscopic.

(b) Treatment with distilled water produced an immediate white turbidity which gradually (five to ten minutes) became reddish-brown in color. The interior surface of the retaining vessel became coated with a very thin mirror-like copper-colored deposit. This coating was insoluble in dilute hydrochloric acid, but was readily soluble in nitric acid or ammonia water–hydrogen peroxide mixture, yielding solutions which gave positive tests for copper(II) ion but negative tests for titanium(IV). The initial water solution gave a positive test for titanium(III) ions.

(c) Treatment with 6 *N* hydrochloric acid produced a clear purplish-pink solution containing

(1) From a thesis submitted to the Graduate School of the University of Pittsburgh by Donald E. Koontz in partial fulfillment of the requirements for the Master of Science degree, January, 1948.

suspended flakes of copper. This solution gave a positive test for titanium(III) ions. After filtering to remove the suspended copper, samples of this solution were analyzed to determine the copper:titanium ratio present. This was done as follows: (1) atmospheric oxidation for twenty-four hours; (2) titanium was determined by double precipitation by ammonia water followed by ignition of the precipitate to the dioxide; (3) after removal of ammonia from the combined titanium filtrates, copper present was precipitated by the addition of sodium hydroxide, followed by ignition to the oxide. Analyses of solutions of five different scale samples gave an average weight ratio of the elements copper:titanium of 1.39:1.00. Theoretical weight ratio of these elements (based on one atom of each) is 1.33:1.00. It thus appeared that the black residue was composed of compounds of copper and titanium whose metallic ratio contained one atom of each.

(d) Samples of the metal-free, 6 *N* hydrochloric acid solution of the scale become a pale bluish-green color after exposure to atmospheric oxygen for approximately twenty hours.

A sample of freshly prepared copper(I) chloride was added to a solution of titanium(III) chloride, prepared by electrolytic reduction of aqueous titanium(IV) chloride. A water-clear purplish-pink solution resulted. On standing several minutes after dilution with a 4–5 fold excess of distilled water, the initial color of the solution faded and an adherent copper-like deposit coated the interior surfaces of the vessel. This deposit exhibited the same characteristics as that produced when a sample of purplish-black residue was added to distilled water (b, above).

Discussion

Based on the above-described tests and observations, it appears that the purplish-black scale is a mixture and/or a compound containing a ratio of one atom each of titanium(III) and copper(I) chlorides. Either or both of the following reactions are postulated as the means by which the scale is produced.

$$(1)\quad TiCl_4 + Cu \longrightarrow \underset{\text{black scale}}{CuCl} + TiCl_3$$

$$(2)\quad TiCl_4 + Cu \longrightarrow CuTiCl_4$$

The white precipitate produced immediately on addition of the scale to distilled water was probably copper(I) chloride (a product in reaction (1), or produced by aqueous decomposition of $CuTiCl_4$ formed in reaction (2)) in a solution of titanium(III) chloride hexahydrate.

The gradual color change which took place (with passage of time) in the aqueous mixture of titanium(III) and copper(I) chlorides was probably due to either or both of the two reactions

$$(3)\quad TiCl_3 + CuCl \longrightarrow \underset{\text{copper deposit}}{Cu} + TiCl_4$$

$$(4)\quad 2CuCl \longrightarrow Cu + CuCl_2$$

Of these two equations, (3) and (4), reaction (3) appears to be more probable since reaction (4) indicates that one-half of the total copper initially present would be in solution after the reaction was complete. Tests conducted on the residue and filtrate indicated that only a very small fraction of the total copper initially present was soluble in 6 *N* hydrochloric acid.

It is interesting to note that reaction (3), in aqueous solution, is the reverse of reaction (1) in non-aqueous medium.

The solubility of the purplish-black scale in 6 *N* hydrochloric acid producing a clear purplish-pink solution can be explained by either or both of the following equations

$$(5)\quad \underset{\text{black scale}}{CuCl} + TiCl_3 + HCl \longrightarrow HCuCl_2 + TiCl_3$$

$$(6)\quad CuTiCl_4 + HCl \longrightarrow HCuCl_2 + TiCl_3$$

Conclusions

A detailed study of the reaction of metallic copper with titanium (IV) chloride has been undertaken. This reaction produces a purplish-black scale which contains copper (I) and titanium(III) ions.

PITTSBURGH, PENNSYLVANIA
RECEIVED SEPTEMBER 25, 1947

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1170]

A Comparative Study of the Three Stereoisomeric 1,4-Diphenylbutadienes

BY J. H. PINCKARD, B. WILLE AND L. ZECHMEISTER

It was recently shown, in collaboration with A. Sandoval,[1] that the maximum extinction in the spectrum of ordinary *trans-trans*-1,4-diphenylbutadiene, $C_6H_5CH{=}CHCH{=}CHC_6H_5$, decreased to about half of the original value upon illumination under certain conditions. However, almost entire restoration of the original extinction curve by iodine catalysis proved that no irreversible destruction had taken place. Further experiments for the identification of the chromatographically homogeneous product were announced.

As is known, Straus[2] prepared two stereoisomers of diphenylbutadiene by reduction methods; one was crystalline (m. p. 70.5°, compared to 152–153°, cor., of the *trans–trans* form) and the other was oily. We were able to confirm Straus' data concerning the crystalline compound but have observed by chromatography that the oily sample contains a number of impurities. After their elimination on the Tswett column, this isomer was found to be identical with that obtained photochemically.[1] Of course, illumination is a simpler method of preparing this oily isomer than the reduction of *trans*-diphenylbutenine.[2]

It was observed in the field of the carotenoids[3] that a single *trans* → *cis* rotation shifts the position of $\lambda_{max.}$ by about 7.5 mμ toward shorter wave lengths (*e. g.*, lycopene, in hexane, measured in the Beckman spectrophotometer). We noticed a similar shift when the extinction curves of the three diphenylbutadienes were compared in hexane solution; however, in this case one *trans* → *cis* step causes a wave length difference of 14–15 mμ:

trans–trans form (m. p. 152–153°), $\lambda_{max.}$ at 328 mμ
cis–trans form (oily), $\lambda_{max.}$ at 313 mμ
cis–cis form (m. p. 70.5°), $\lambda_{max.}$ at 299 mμ

These data compare well with those referring to *trans*- and *cis*-stilbene (difference in $\lambda_{max.}$, 15 mμ)[4] and they also agree with the assignment of configurations to stereoisomeric diphenylbutadienes as given by Straus. An absolute structure determination of *cis–cis*-diphenylbutadiene is not yet available.[2a]

The extinction curve of *trans-trans*-diphenylbutadiene shows definite fine structure while the two other isomers are characterized by smooth curves which are rather similar in this respect (Figs. 1–2).

When petroleum ether is used as a developer, the chromatographic sequence on alumina from top to bottom is: *trans-trans*-, *cis-trans*-, and *cis-cis*-diphenylbutadiene. The zone of the *trans-trans* form can be located by its intense bluish fluorescence in ultraviolet light. The presence of one or two *cis* double bonds, however, destroys this power to fluoresce, in adsorbate as well as in solution. On the other hand, zones of the *cis-trans* and *cis-cis* forms, when either is present in appreciable quantity, may be located on the column by the moderate quenching of the weak fluorescence of the alumina itself. Like *cis*- and *trans*-stilbene zones,[5] those of the three diphenylbutadienes are also detected by brushing with permanganate.

A sharp separation of the *cis-trans* and *cis-cis* forms can be accomplished by means of the liquid chromatogram procedure. The detection of either isomer in the successive fractions of the filtrate is carried out by treating small samples of each fraction with catalytic amounts of iodine followed by a brief illumination. Thus, either of these two stereoisomers is converted into the *trans-trans* form, whereupon fluorescence appears in the solution when inspected in ultraviolet light. The limit of detection is 0.5–1.0 milligram per liter or a few micrograms in a 2-ml. test sample. The recovery of each of the three stereoisomers from artificial mixtures was practically quantitative in such resolutions.

Having chromatographically pure samples of all stereoisomeric diphenylbutadienes, a comparison of their behavior under various conditions was made; the result may be summarized as follows.

In petroleum ether, at 4°, and in the absence of light any of the three configurations can be preserved for several months. When hexane solutions are refluxed in all-glass apparatus, in darkness, for forty-five minutes, the three stereoisomers behave identically: their extinction curves were practically unchanged. The isomers showed only a limited difference when kept in the molten state at 205° for ten minutes, with the exclusion of air and light. The *trans-trans* and *cis-trans* configurations were practically unaffected; *cis-cis*-diphenylbutadiene underwent moderate isomerization whereby the amount of the *trans-trans* compound formed did not exceed 5%.

In order to test the relative photo-stabilities, we conducted two series of experiments under very different conditions: (*a*) illumination of the hexane solution (20 mg. per liter) in Pyrex flasks with a 250-watt light bulb for several hours, and

(1) A. Sandoval and L. Zechmeister, THIS JOURNAL, **69**, 553 (1947).

(2) F. Straus, *Ann.*, **342**, 190 (1905), *cf.* C. Kelber and A. Schwarz, *Ber.*, **45**, 1946 (1912); E. Ott and R. Schröter, *ibid.*, **60**, 624 (1927).

(2a) Dr. E. W. Hughes is carrying out a preliminary X-ray examination in these laboratories.

(3) Summary: L. Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

(4) A. Smakula and A. Wassermann, *Z. physik. Chem.*, **A155**, 353 (1931).

(5) L. Zechmeister and W. H. McNeely, THIS JOURNAL, **64**, 1919 (1942).

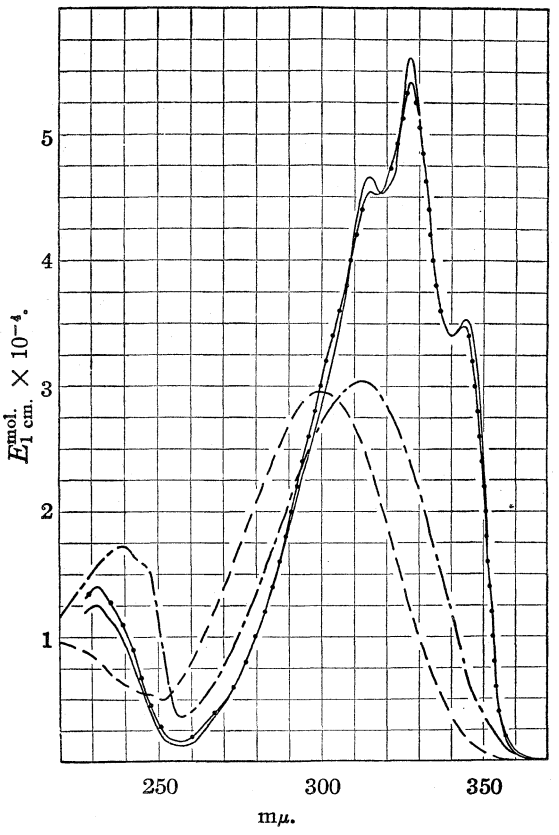


Fig. 1.—Molecular extinction curves of the three stereoisomeric diphenylbutadienes in hexane: —, *trans–trans* compound; – – – –, *cis–trans* compound; – – – –, *cis–cis* compound; —●—●—, after iodine catalysis of any of the foregoing solutions.

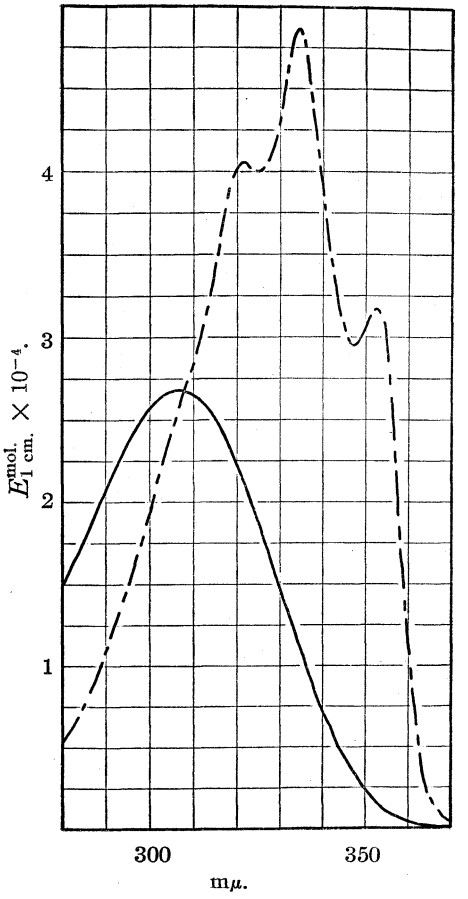


Fig. 2.—Molecular extinction curve of *cis–cis*-diphenylbutadiene in benzene: —, fresh solution; – – – –, after iodine catalysis.

(*b*) insolation, *i. e.*, exposure of more dilute solutions (3–4 mg. per liter) to intense sunshine, in transparent quartz tubes, for one to ten minutes.

In the (*a*) series it was found that the extinction curve of *cis-trans*-diphenylbutadiene was practically unchanged, even after seventeen hours of illumination; the two other isomers underwent almost quantitative rearrangement, and at the end of the irradiation period also showed very nearly the spectral curve of the *cis-trans* form (Figs. 3–4). The *trans-trans* isomer required only one to two hours to reach this state but the *cis-cis* compound as long as thirteen to fourteen hours.

During the insolation as shown by Fig. 5, the fine structure of the *trans-trans* curve had almost entirely disappeared after one minute and the extinction curve approached closely that of the *cis-trans* isomer after ten minutes. The *cis-cis* configuration underwent a similar rearrangement essentially to the *cis-trans* form (Fig. 6), while no appreciable change in the extinction curve was noticed after *cis-trans*-diphenylbutadiene had been insolated for ten minutes.

Whether or not irreversible processes also take place besides photo-isomerization, is revealed by subsequent iodine catalysis and brief illumination with a daylight lamp. If the molecular extinction coefficient at $\lambda_{max.}$ is then found to be smaller than the value established earlier by a similar catalytic treatment of the *trans-trans* form, then the deficit is a fair measure of photochemical destruction. In the experiments with artificial light such losses were smaller than 1–2% of the starting material; however, they amounted to about 8–10% after ten minutes of insolation.

Special experiments showed that upon iodine catalysis in light (like the carotenoids) the stereoisomeric diphenylbutadienes yield practically identical mixtures which in this case contain about 97% all-*trans* form. However, if iodine is added in darkness to the solution, none of the diphenylbutadienes shows a detectable spectral change within half an hour. A subsequent exposure of the *cis-cis* compound even for as little as twenty seconds to the daylight lamp caused noticeable rearrangement. Figure 7 shows, both in the fundamental band and in the secondary maximum near 230 mμ, that the main process in the first stages is a stepwise conversion, *cis-cis* → *cis-trans* → *trans-trans*. If a direct *cis-cis* → *trans-*

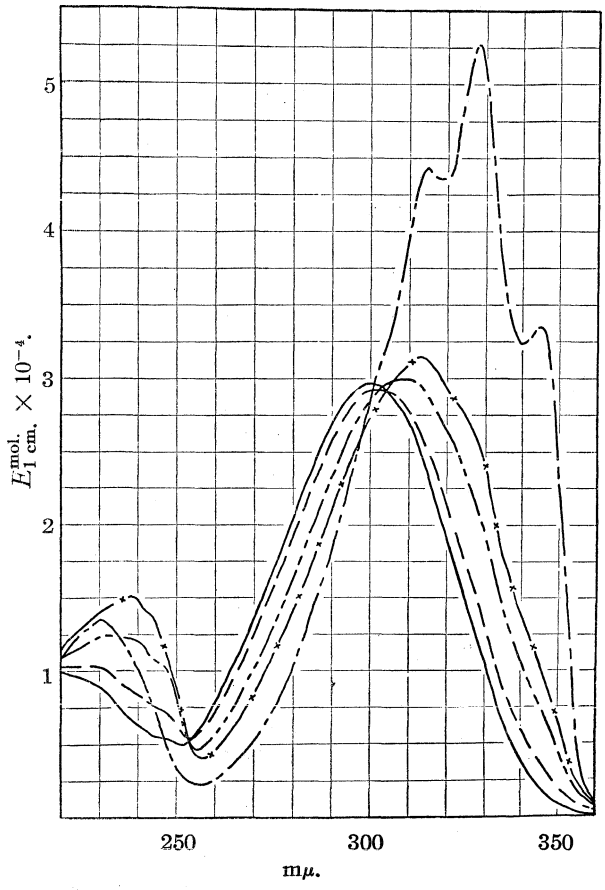


Fig. 3.—Molecular extinction curve of *cis–cis*-diphenylbutadiene in hexane, and its gradual shift toward the curve of the *cis–trans* form during illumination with a 250-watt bulb: —, fresh solution of the *cis–cis* compound; — — —, after forty-five minutes; — — — —, three hours and forty-five minutes; and — x — x —, seventeen hours of illumination; — — — —, after iodine catalysis at the end of seventeen hours of illumination.

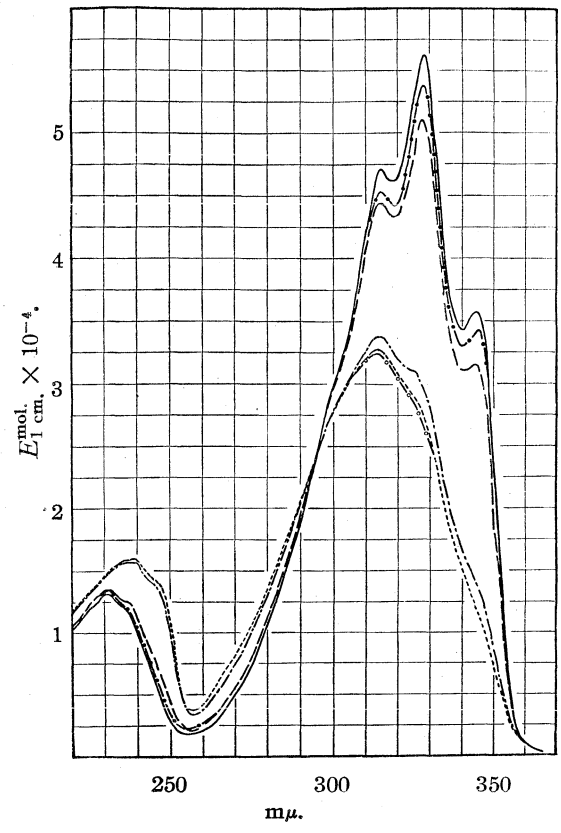


Fig. 4.—Molecular extinction curve of *trans–trans*-diphenylbutadiene in hexane, and its gradual shift toward the curve of the *cis–trans* form during illumination with a 250-watt bulb (strictly parallel experiment to that represented in Fig. 3): —, fresh solution of the *trans–trans* compound; — — — —, after fifteen minutes; — · — ·, forty-five minutes; — — — —, one hour and forty-five minutes; — O — O —, eight hours illumination; —●—●—, after iodine catalysis at the end of seventeen hours of illumination.

trans rearrangement took place, one would expect the appearance of some fine structure in early stages of the illumination; even the presence of 5% *trans-trans* form gives rise to recognizable bulges in the extinction curve, especially around 328 mμ and 344 mμ (in hexane). On the other hand, after illumination for twenty-five minutes the curve in Fig. 7 is essentially that of *trans-trans*-diphenylbutadiene.

The height of $E_{max.}$ also indicates that only a spatial change and no destruction took place. In contrast, when the addition of iodine is followed by excessive illumination, irreversible processes also occur, for example to the extent of 30% during a six-hour exposure to the 250-watt bulb. In the absence of iodine there is no destruction under the same conditions.

Finally, the stability of the three isomers in the absence of solvents was investigated. The oily *cis-trans* compound has the tendency, even in almost complete darkness, to rearrange and deposit crystals of the *trans-trans* isomer; in strong light such crystals appear within a minute.[6,2] Although the oil was handled cautiously, its crystallization tendency was always found to be inferior to its inclination for the spatial change. So far we have failed to obtain *cis-trans*-diphenylbutadiene in crystalline form.

The present study should show that, from the viewpoint of the practical chemist, no one of the three configurations of diphenylbutadiene is the most stable under all conditions. While photochemically the *trans-trans* and the *cis-cis* forms proved to be labile and changed their configuration to *cis-trans*, the latter is much less stable than the others in the absence of solvents. Under none of the conditions tested was the *cis-cis* form the most stable. However, at room temperature the stability of its crystals compared well with the crystalline *trans-trans* compound, and these two forms show no great difference even at 205°.

(6) Reference 1, Fig. 8.

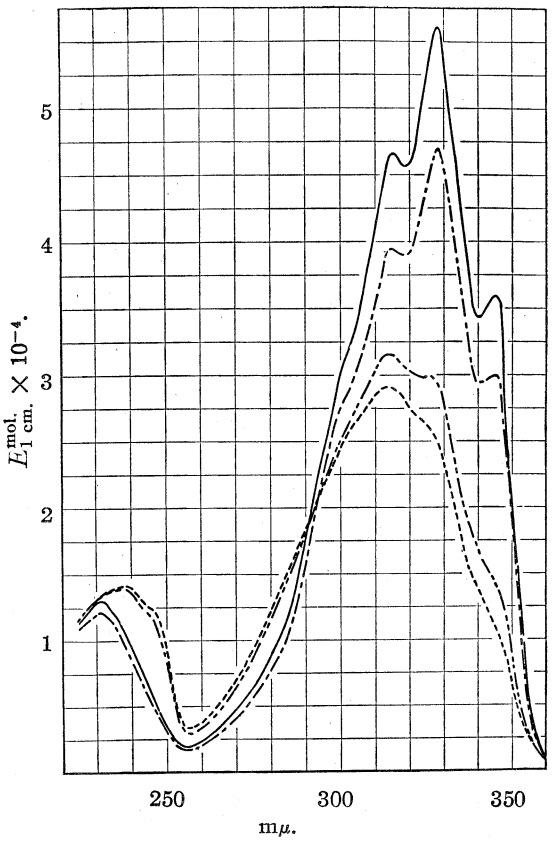


Fig. 5.—Molecular extinction curve of *trans–trans*-diphenylbutadiene in hexane, and its shift toward the curve of the *cis–trans* form during exposure to sunshine: —, fresh solution; — — — —, after one minute; – – – –, ten minutes of insolation; — · — ·, after iodine catalysis at the end of ten minutes of insolation.

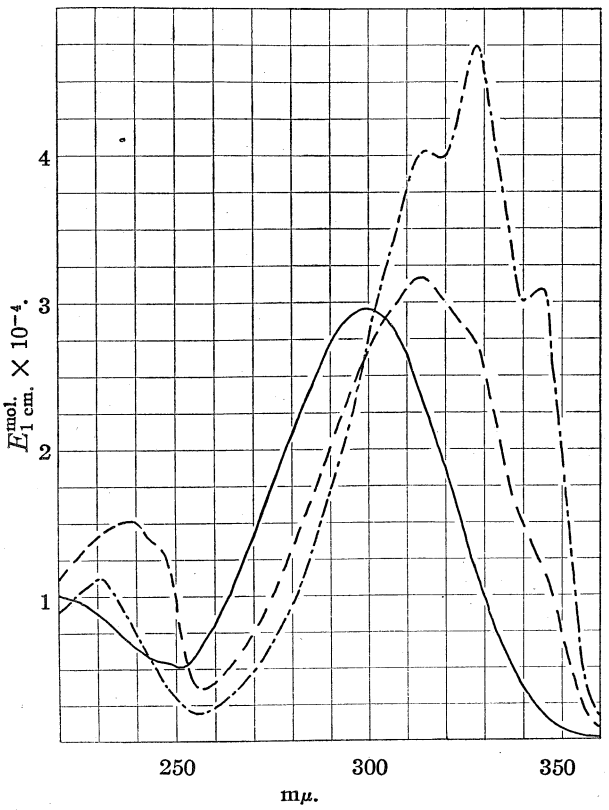


Fig. 6.—Molecular extinction curve of *cis–cis*-diphenylbutadiene in hexane, and its shift toward the curve of the *cis–trans* form during exposure to sunshine: —, fresh solution; – – – –, after ten minutes of insolation; — · — ·, after iodine catalysis at the end of ten minutes of insolation.

Some distinctly individual features of *cis-trans*-diphenylbutadiene as compared to its stereoisomers are also revealed by an inspection of the three models. The dotted lines in Fig. 8 which connect the ends of each resonating system, demonstrate the essentially linear shape of the *trans-trans* and *cis-cis* molecules while the *cis-trans* form shows the pattern of a widely open V. Comparable forms of carotenoids would be[7]: lycopene, neolycopene A, and poly-*cis*-lycopene "IV" (or another poly-*cis*-lycopene).[8] Neolycopene A is characterized by lability of its configuration in the absence of solvents, lack of crystallization tendency (without rearrangement), and by its high *cis*-peak. Although no clearly differentiated *cis*-peak appears in the relatively compressed spectral curve of *cis-trans*-diphenylbutadiene, its extinction at 230 to 240 mμ is the highest of all three stereoisomers. Furthermore, its maximum is located at a 9 mμ longer wave length than the corresponding maximum of the *trans-trans* compound. On the other hand, *cis-cis*-diphenylbutadiene can be compared with a poly-*cis*-lycopene: both show a flat section of the extinction curve in the (potential) *cis*-peak region.

Although extinction areas are more characteristic than the height of maxima, the following data show the very great decrease in $E_{\text{max.}}$ when several *cis* double bonds are formed by rearrangement; and they also indicate that the first *trans* → *cis* step is responsible for the major part of this effect: Relative heights of $E_{\text{max.}}$ in hexane (per cent.): all-*trans*-lycopene, 100; neolycopene A (a central mono*cis* lycopene), 66; poly-*cis*-lycopene "IV," 56; *trans-trans*-diphenylbutadiene, 100; *cis-trans*, 54; and *cis-cis*, 53.

The lack of fine structure in the extinction curve of *cis-trans* or *cis-cis*-diphenylbutadiene parallels to a certain extent the recent observation that all poly-*cis*-lycopenes known at the present time show a very limited fine structure when compared to that of the all-*trans* form.[8]

Acknowledgment.—The authors wish to thank Professor A. J. Haagen-Smit as well as Dr. G. Oppenheimer and Mr. G. Swinehart for microanalyses.

(7) L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, THIS JOURNAL, **65**, 1940 (1943).

(8) L. Zechmeister and J. H. Pinckard, *ibid.*, **69**, 1930 (1947).

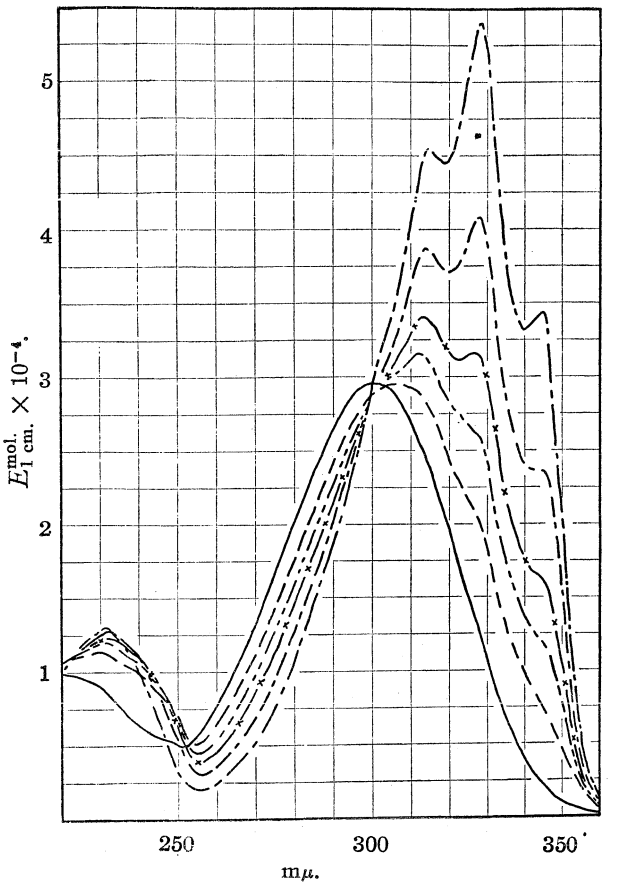


Fig. 7.—Molecular extinction curves in hexane; influence of illumination on the stereoisomerization of *cis–cis*-diphenylbutadiene caused by iodine catalysis: —, fresh solution with iodine, kept in darkness for thirty minutes; – – – –, after eighty seconds; — — — —, one hundred and forty seconds; — x — x —, 200 seconds; — — — — —, 320 seconds; and — — — —, 25 minutes illumination.

Experimental

Adsorbents and Solvents.—"Silicic acid" means Merck reagent silicic acid plus 20% celite. Commercial alumina (Alorco, Grade F, ground to −200 mesh) was used mixed with 25% celite. On such columns 0.5% permanganate is a suitable color reagent for the location of diphenylbutadiene zones by brushing.[5] The petroleum ether was Skellysolve B, b. p. 60–70°. The hexane was prepared from Phillips commercial brand by repeated treatment with fuming sulfuric acid.

Light Sources and Conditions of Illumination.—Chromatograms were inspected in the light of a General Electric Purple X bulb using a moulded Corning light filter No. 5840, 0.25 inch thick; "Mineralight Q31" was less satisfactory due to its different light filter. The conditions for the illumination of iodine catalyzed solutions with a Mazda daylight lamp were described in detail recently.[1] Under the same conditions benzene solutions should be illuminated for an hour. For artificial illumination of iodine-free solutions a 250-watt Mazda clear projection lamp bulb (Code −250 T 14/3 −120V) encased in a water jacket was used (distance from filament to center of Pyrex volumetric flask, 10 cm.). Transparent quartz test-tubes were found satisfactory for insolation experiments (end temperature, 20–25°). The values for each extinction curve, taken in the Beckman photoelectric spectrophotometer, are based on the average of at least two independent determinations.

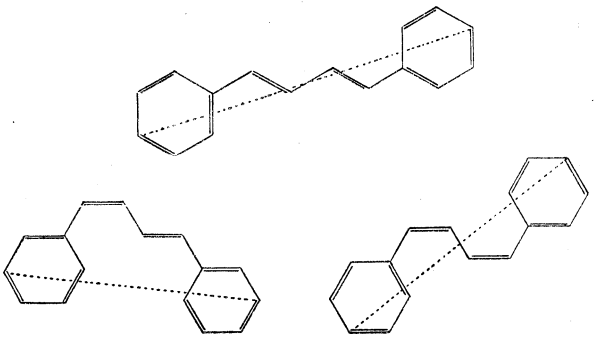


Fig. 8.—Models of *trans–trans*- (top), *cis–trans*- (bottom, left), and *cis–cis*-diphenylbutadiene (bottom, right). (Values: C=C, 1.33 Å.; C—C, 1.46 Å.; and C=C—C angle, 124° 20′. The dotted lines connect the ends of each resonating system.)

Thermal Treatment.—Refluxing of hexane solutions (5–20 mg. per liter) was carried out in darkness, in a slow stream of carbon dioxide. In the melt experiments, 4–12 mg. weighed samples, in evacuated and sealed capillary tubes, were submerged in a dibutyl phthalate bath (205–210°), in darkness. After ten minutes the tubes were rapidly cooled in water and their contents examined without delay.

trans-**Diphenylbutenine,** $C_6H_5CH{=}CHC{\equiv}CC_6H_5$, was prepared (in a crude state) from phenylacetylene–copper according to Straus.[2] Purification: a solution of 8.5 g. of brownish, crude crystals in 100 ml. of petroleum ether was developed with the same solvent on a silicic acid column, 22 × 4.8 cm. (The figures on the left designate thickness of the zones in mm.; fl. means fluorescence or fluorescent in ultraviolet light):

30 several brown zones (in daylight)
30 white fl. (1 g. oil)
7 brown (in daylight)
8 interzone, no fl.
50 white fl. (1 g. oil)
80 column-fl. quenched: main product
Filtrate: no fl.

The main zone was cut out, eluted with ethanol, transferred into petroleum ether, dried with sodium sulfate and completely evaporated *in vacuo*. A solution of the slightly colored crystals (5.5 g.) in 50 ml. of hot methanol deposited 3 g. of white needles in the cold room; m. p. 96°, cor. An additional 1 g. can be obtained by chromatographing the mother liquor as above.

cis–trans-**Diphenylbutadiene from** *trans*-**Diphenylbutenine.**—In an all-glass apparatus (with mercury-sealed stirrer) the solution of 3 g. of the butenine in 250 ml. of alcohol was refluxed in darkness with 2 g. of zinc–copper dust (from copper sulfate and zinc, washed with ethanol) and another 2 g.-portion of the metals was introduced after thirty hours. The sharp extinction maximum (originally at 306 mμ., in petroleum ether) gradually disappeared and, after one hundred and ten hours of refluxing, the smooth maximum of *cis–trans*-diphenylbutadiene was observed in a small sample. Then 250 ml. of petroleum ether and 1 liter of water were added to the filtered liquid; the aqueous layer was re-extracted and the total petroleum ether solution was repeatedly washed and dried. The following chromatogram, obtained with the same solvent, on a 28 × 8 cm. alumina column, refers to one third of the crude solution:

30 several, partly fl. zones
25 blue fl.: *trans-trans*-diphenylbutadiene
140 fl. of alumina quenched: crude *cis-trans*

When the bottom of the lowest zone was 7 cm. from the end of the column, the quenched section was cut out in two halves of which the upper one contained unchanged butenine (its extinction curve was not influenced by iodine). The bottom half of the quenched zone showed the spectroscopic character of *cis-trans*-diphenylbutadiene, and a sample yielded (after iodine catalysis in light) the fine structure of the *trans-trans* form. This fraction was rechromatographed as above.

In order to eliminate the last impurities, especially for optical observations, 3 mg. of the *cis-trans* compound (in 3 ml. of petroleum ether) was adsorbed on a 20 × 1.9 cm.-column and washed with the same solvent. Each 10-ml. portion of the (non-fluorescing) filtrate was tested as follows: A few drops were catalyzed with one drop of iodine solution (0.3 mg./ml.) and the test-tube exposed to the 250-watt lamp from a 10 cm. distance for one to two minutes. If the sample showed fluorescence in ultraviolet light, the fraction was kept, otherwise rejected. This test was positive between the fractions 17–29. Fractions 18–28 were found spectroscopically to contain pure *cis-trans* compound; 3 g. of the butenine yielded 0.75 g. of the purest product.

The molecular extinction coefficients were given earlier.[9]

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 92.73, 92.89; H, 6.84, 6.88.

***cis-cis*-Diphenylbutadiene** was prepared by catalytic reduction of diphenyldiacetylene, $C_6H_5C{\equiv}CC{\equiv}CC_6H_5$, by Kelber and Schwarz as well as by Ott and Schröter[2] in yields of 8–32%, depending on the catalyst. Although our yields remained between these limits (for example, 24%), we recommend the following isolation which is based on spectroscopic control of the reduction process and chromatographic purification of the product. During the reaction the triple bonds are reduced not only to double, but in part also to single bonds. These competing processes can be followed by the changing extinction curve. The sharp and high peaks of diphenyldiacetylene at 306 and 326 mμ. (in hexane) gradually disappear and the much lower, smooth maximum of *cis-cis*-diphenylbutadiene at 300 mμ. then makes the main contribution to the curve. A satisfactory amount of the latter compound is clearly indicated if a small sample (diluted with hexane) is examined in the spectrophotometer before and after iodine catalysis (in light). The new maximum (now at 328 mμ.) should be at least 1.5 times higher than $E_{max.}$ was before this catalytic treatment.

Fig. 9.—Crystals of *cis–cis*-diphenylbutadiene (from methanol).

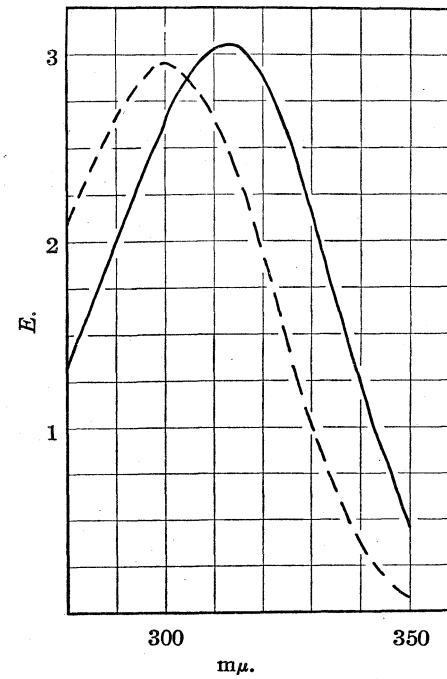


Fig. 10.—Extinction curves (main maxima only) of *cis–cis*- and *cis–trans*-diphenylbutadiene in petroleum ether as obtained by the resolution of their mixture in a liquid chromatogram experiment: ———, *cis–cis*- and ——, *cis–trans*-diphenylbutadiene.

The following operations should be carried out in dim light. A solution of 1 g. of diphenyldiacetylene in 100 ml. of 95% ethanol was shaken with 0.25 g. of palladium–barium sulfate[10] until roughly 350 ml. of hydrogen was taken up within one quarter to one half hour. After filtration, the material was transferred with water into petroleum ether and the aqueous phase re-extracted. The combined petroleum ether solution, after washing, drying and concentrating to 50 ml., was developed on an alumina column (30 × 7.5 cm.) with about 2 liters of the same solvent:

6	dark (in uviol. light)
8	greenish fl.
20	blue fl.: *trans-trans*-diphenylbutadiene
16	non-fl. interzone
60	column-fl. quenched: *cis-trans*-diphenylbutadiene
26	interzone (borders blurred)
50	column-fl. quenched: *cis-cis*- diphenylbutadiene
110	empty section

The location of the *cis-cis* compound possibly could be improved by using a strongly fluorescent column as proposed by Sease.[11]

The *cis-cis* zone was cut out, eluted with ethanol, transferred into petroleum ether, washed, dried and completely evaporated *in vacuo*. The oily residue was then transferred into a small centrifuge tube and dissolved in a minimum amount of warm 95% ethanol. Crystallization was observed at room temperature, whereupon the tube was kept at 4° overnight. Yield, after recrystallization, was 243 mg. of *cis-cis*-diphenylbutadiene which showed distinctly different crystal forms (Fig. 9) from those of the *trans-trans* isomer.[12] The extinction coefficients are given in Table I.

(9) Reference 1, p. 555, Table I; the term "chromatographically homogeneous *cis* form" should now be replaced by "*cis-trans*-diphenylbutadiene." The "All-*trans* form" in the same table refers to *trans-trans*-diphenylbutadiene.

(10) "Organic Syntheses," **26**, 77 (1946).

(11) J. H. Sease, THIS JOURNAL, **69**, 2242 (1947); H. Brockmann and F. Volpers, *Ber.*, **80**, 77 (1947).

(12) Reference 1, Fig. 8.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.13; H, 7.17.

TABLE I

MOLECULAR EXTINCTION COEFFICIENTS OF *cis-cis*-DIPHENYLBUTADIENE AT THE MAXIMA (*italicized*) AND MINIMA

	cis-cis form		Mixture of stereoisomers upon iodine catalysis	
Solvent	mμ	$E^{mol.}_{1 cm.} \times 10^{-4}$	mμ	$E^{mol.}_{1 cm.} \times 10^{-4}$
Hexane	*299–300*	2.96	*344–345*	3.40
	251	0.51	340	3.35
			328	5.36
			318–319	4.50
			315–316	4.56
			255	0.20
			230–231	1.36
Benzene	*306*	2.67	*352–353*	3.17
			347	2.95
			334–335	4.85
			325–326	4.00
			321–322	4.05

Small-Scale Separation of the Three Stereoisomeric Diphenylbutadienes.—A solution which contained 1 mg. of each isomer in 10 ml. of petroleum ether was developed with the same solvent on alumina (20 × 2 cm.); the developer was forced through the column by nitrogen pressure in order to avoid partial evaporation of the filtrate. The fluorescent *trans-trans* compound remained near the top. Small samples of each fraction collected from the filtrate were submitted to the iodine-catalysis and fluorescence test as described. The first 120 ml. of the flow were found to be free of substance; subsequent 5-ml. fractions were tested with the following result ("*cis-cis*" or "*cis-trans*" refer to the configuration before iodine catalysis):

No. 1–7, strong fl.: *cis-cis*
8–9, weak fl.: *cis-cis*
10–12, almost no fl.: traces
13–21, very strong fl.: *cis-trans*
22–26, strong fl.: *cis-trans*
27–30, weak fl.: *cis-trans*
31, no fl.

The fractions were also tested spectroscopically; the extinction curves of fractions 3 and 16 are given in Fig. 10.

Summary

A comparative study of the *trans-trans-*, *cis-trans-*, and *cis-cis-* forms of 1,4-diphenylbutadiene is presented. The relative stability of the respective configurations depends on the nature of the photochemical or thermal treatment. Data characterizing the spectroscopic and chromatographic behavior are given, and the stereoisomeric diphenylbutadienes are compared with some spatial types of the carotenoids.

PASADENA, CALIFORNIA RECEIVED DECEMBER 20, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF WESTERN AUSTRALIA]

Isopiestic Measurements on the Primary Sodium and Potassium Salts of Malonic, Succinic and Adipic Acids at 25°

BY JEAN M. STOKES[1]

The order of the activity coefficient curves for the alkali formates, acetates, and hydroxides is Li < Na < K, a reversal of the usual order K < Na < Li which holds for the halides and many other salts. To account for this, Robinson and Harned[1a] have advanced an hypothesis of "localized hydrolysis," according to which anion and cation are "associated" through interaction with a polarized water molecule, an effect which may be expected to depend on the proton-accepting power of the anion. In order to study this effect for salts of acids of different strengths, the primary sodium and potassium phosphates have been investigated.[2] It was found, however, that these two salts had very low activity coefficients and ionic association probably occurred to a marked extent. Indeed, the primary phosphate ion seems to belong to what Scatchard[3] has termed the second class of anions, in which he included the nitrate, chlorate and perchlorate ions and to which recent measurements[4] indicate the bromate ion should be added.

Measurements are now reported on the salts of three acids of dissociation constant ranging from 10^{-3} to 10^{-5}.

Experimental

Solutions of the sodium and potassium salts of malonic, succinic and adipic acid were prepared by (a) half neutralization of the purified acid with hydroxide in aqueous solution and (b) precipitation of solid salt from alcoholic solutions of acid and base, digestion with alcohol and subsequent solution in water. The two methods gave similar results but the experimental points did not lie on a smooth isopiestic curve as well as other salts that have been investigated. This may be due to sensitivity to the exact composition of the alkali hydrogen salt or to the *p*H of the solution; high accuracy is not claimed for these results, but they are probably accurate to 1% and the order and position of the activity coefficient curves is therefore significant. The molalities of isopiestic solutions are given in Table I and the osmotic and activity coefficients calculated with the aid of the data for the reference salt, sodium chloride,[5] are given in Table II.

Discussion

The activity coefficient curve of sodium hydrogen adipate is close to that of potassium iodide while the potassium salt resembles potassium bromide; sodium and potassium hydrogen succinate are comparable with rubidium chloride and cesium bromide, respectively; sodium hydrogen malo-

(1) Present address: c/o R. H. Stokes, Physical Chemistry Laboratories, Free School Lane, Cambridge, England.

(1a) R. A. Robinson and H. S. Harned, *Chem. Rev.*, **28**, 419 (1941).

(2) J. M. Stokes, *Trans. Faraday Soc.*, **41**, 685 (1945).

(3) G. Scatchard and S. S. Prentiss, THIS JOURNAL, **56**, 807 (1934).

(4) J. H. Jones, *ibid.*, **65**, 1353 (1943); **66**, 1672 (1944).

(5) R. H. Stokes and B. J. Levien, *ibid.*, **68**, 333 (1946).

nate also resembles cesium bromide but the potassium salt exhibits very low activity coefficients comparable with those of sodium bromate.

TABLE I

ISOPIESTIC SOLUTIONS OF SODIUM CHLORIDE AND SODIUM AND POTASSIUM HYDROGEN MALONATE, SUCCINATE AND ADIPATE

M_{NaCl} = molality of sodium chloride. M_X = molality of other salt

M_X	M_{NaCl}	M_X	M_{NaCl}	M_X	M_{NaCl}
Sodium hydrogen malonate					
0.3995	0.3850	0.4305	0.4141	0.9282	0.8676
1.407	1.277	1.799	1.605	2.131	1.863
2.247	1.960	2.850	2.422	3.080	2.573
3.451	2.855	3.849	3.125	4.765	3.727
Potassium hydrogen malonate					
0.2577	0.2498	0.2623	0.2534	0.3910	0.3734
0.6906	0.6322	1.643	1.388	1.697	1.432
1.996	1.655	2.747	2.183	3.741	2.812
4.156	3.044	4.206	3.080	4.996	3.506
5.035	3.530				
Sodium hydrogen succinate					
0.2345	0.2296	0.2831	0.2771	1.193	1.116
1.248	1.167	1.650	1.516	1.931	1.764
2.300	2.081	2.449	2.206	2.897	2.573
3.717	3.232	4.010	3.467	4.935	4.176
Potassium hydrogen succinate					
0.2592	0.2512	0.3183	0.3062	0.5440	0.5168
0.6900	0.6480	0.8451	0.7848	1.123	1.021
1.823	1.601	2.334	2.010	2.530	2.163
2.775	2.353	3.663	3.035	3.848	3.165
4.398	3.553				
Sodium hydrogen adipate					
0.3132	0.3116	0.3441	0.3424	0.4253	0.4224
0.6600	0.6510	0.6863	0.6767		
Potassium hydrogen adipate					
0.2730	0.2690	0.3677	0.3622	0.4576	0.4490
.5700	.5546	.7173	.6950	.7875	.7645
.8451	.8173	.9310	.8970	.9380	.9050
				.9730	.9355

If the reversal of order of the activity coefficient curves of the acetates, etc., is associated in any way with the strength of the acid from which the salt is derived, since the dissociation constants of malonic, succinic and adipic acid are 1.6×10^{-3}, 6.7×10^{-5} and 3.6×10^{-5}, respectively, a reversal of order might be expected with the succinates and adipates but not with the malonates. Figure 1, in which the activity coefficients are plotted, along with those for the acetates, shows that there is no reversal of order with these salts, although the difference between the curves for sodium and potassium hydrogen succinate and adipate is small compared with that found for the halides. This plot, however, does show that there is a difference

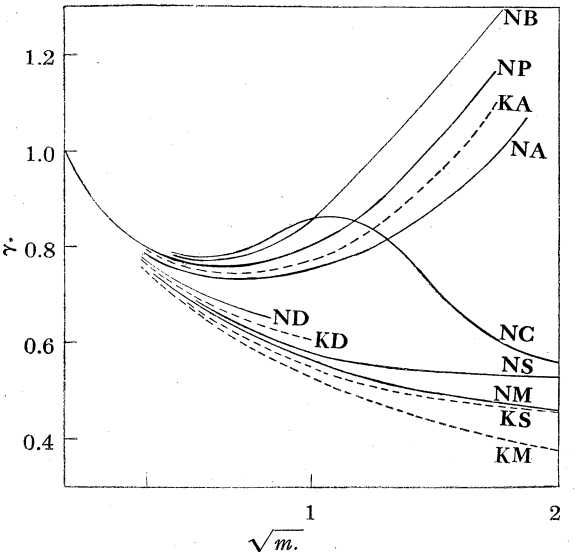


Fig. 1.—Comparison of activity coefficients of the sodium and potassium salts of some simple organic acids: NB, sodium butyrate; NP, sodium propionate; KA, potassium acetate; NA, sodium acetate; ND, sodium adipate; KD, potassium adipate; NC, sodium caproate; NS, sodium succinate; NM, sodium malonate; KS, potassium succinate; KM, potassium malonate.

TABLE II

OSMOTIC AND ACTIVITY COEFFICIENTS AT 25°

	Malonates				Succinates				Adipates			
	K salt		Na salt		K salt		Na salt		K salt		Na salt	
m	ϕ	γ	ϕ	γ	ϕ	γ	ϕ	γ	ϕ	γ	ϕ	γ
0.1	0.920	0.759	0.923	0.764	0.922	0.762	0.924	0.765	0.928	0.772	0.931	0.776
.2	.903	.702	.907	.709	.904	.705	.910	.712	.917	.724	.921	.730
.3	.891	.665	.896	.674	.892	.668	.898	.677	.909	.693	.917	.703
.5	.866	.610	.880	.626	.875	.619	.888	.635	.900	.654	.912	.670
.7	.847	.570	.872	.595	.867	.588	.882	.607	.898	.631	.911	.650
1.0	.829	.528	.863	.563	.856	.553	.878	.579	.899	.609		
1.5	.807	.480	.857	.528	.846	.516	.879	.552				
2.0	.799	.450	.856	.507	.845	.493	.887	.538				
2.5	.792	.427	.855	.490	.848	.478	.895	.529				
3.0	.785	.408	.855	.477	.854	.468	.907	.526				
3.5	.778	.392	.855	.467	.865	.463	.917	.524				
4.0	.771	.377	.856	.458	.870	.457	.929	.525				
4.5	.764	.365	.857	.451	.876	.453	.942	.528				
5.0	.757	.353	.858	.445			.958	.534				

between salts of the type $COOH(CH_2)_nCOONa$ and $CH_3(CH_2)_nCOONa$, a difference which is marked in spite of the anomalous behavior of sodium caproate[6] at high concentration (probably due to micelle formation). Along with this difference between the two types of salts are to be noted the very low values of the activity coefficients of the salts now under investigation, suggesting that the hydrogen malonate, succinate and adipate ions belong to the same category as the nitrate, chlorate and primary phosphate ions. Thus, although "localized hydrolysis" may be a factor resulting in decreasing dispersion of the curves of the sodium and potassium salts as we proceed from the malonate to the adipate, there must be another factor of larger magnitude which lowers the curves of both the sodium and the potassium salts. It is difficult to explain this effect for the nitrate ion and it is equally difficult to understand why it should occur with ions of the hydrogen malonate type; furthermore, it is difficult to find a common factor between nitrates and malonates apart from their low activity coefficients.

I wish to thank Professor N. S. Bayliss for his kind permission to use the facilities of his department.

Summary

Isopiestic measurements have been made on solutions of the primary sodium and potassium salts of malonic, succinic and adipic acid and the osmotic and activity coefficients calculated.

Although these salts are derived from weak acids, their activity coefficient curves are in the order Na > K; in this respect they differ from the sodium salts of monobasic fatty acids. Moreover, their activity coefficients are very low and have an unexpected resemblance in this respect to sodium and potassium nitrate and the primary phosphates.

NEDLANDS, WESTERN AUSTRALIA

RECEIVED FEBRUARY 4, 1948

(6) E. R. B. Smith and R. A. Robinson, *Trans. Faraday Soc.*, **38**, 70 (1942).

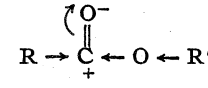
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Effect of Structure on Reactivity.[1] I. Ammonolysis of Esters with Special Reference to the Electron Release Effects of Alkyl and Aryl Groups

BY MAXWELL GORDON,[2] JOHN G. MILLER AND ALLAN R. DAY

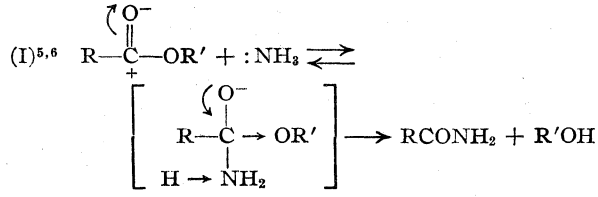
In the interest of augmenting present knowledge of the effect of structure on reactivity, it was decided to measure the rates of ammonolysis of several homologous series of esters. Although several reports have appeared in the literature on the effect of structural variations on the rate of ammonolysis of esters, they have embraced only limited numbers of esters, the possibility of ester interchange in working in alcoholic solution was often overlooked, no calculations of rate constants or activation energies were made in many cases, and the conclusions derived from these studies were, in some instances, conflicting. Most of the references in the literature on this subject have been discussed by Gorvin.[3] Additionally it has been shown by Komatsu and Nakayama[4] that ethyl phenylacetate reacts with ammonia fifteen times as rapidly as does ethyl benzoate.

The present study of the ammonolysis of esters was undertaken in an effort to show the effect of various R and R′ groups in the ester RCOOR′, with special emphasis on tracing the electron release effects in various homologous series. Most of the mechanisms which have been postulated for ammonolysis or hydrolysis of esters[5] indicate that the reactivity of the ester depends on the polarization of the carbonyl group in the ester which then provides the center for nucleophilic attack at the carbon of the carboxyl group. From this representation it may be seen that the greater



the electron release of the R or R′ group, the slower should be the rate of ammonolysis of the ester since the positive charge on the carbonyl carbon would be reduced in magnitude.

One may consider two possible mechanisms for the ammonolysis of esters



Betts and Hammett[7] suggested that both the am-

(1) From a thesis submitted by M. Gordon to the Department of Chemistry and Chemical Engineering of the University of Pennsylvania, Dec. 1947, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) National Institute of Health Predoctoral Research Fellow, 1946–1948.

(3) Gorvin, *J. Chem. Soc.*, 732 (1945).

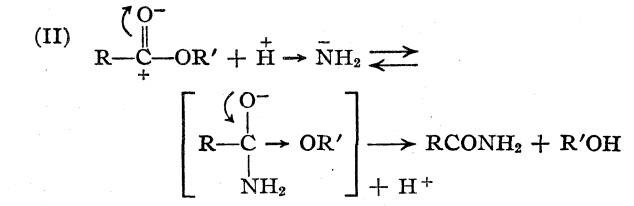
(4) Komatsu and Nakayama, *J. Chem. Soc.* (*Japan*), **54**, 558–569 (1933).

(5) H. Meyer, *Monatsh.*, **27**, 31 (1906); Holmberg, *Ber.*, **45**, 2997 (1912); Ingold and Ingold, *J. Chem. Soc.*, 758 (1932); Polanyi and Szabo, *Trans. Farad. Soc.*, **30**, 508 (1934); Day and Ingold, *ibid.*, **37**, 689 (1941); Watson, *ibid.*, **37**, 712 (1941).

(6) Chattaway, *J. Chem. Soc.*, 355 (1936).

(7) Betts and Hammett, THIS JOURNAL, **59**, 1568 (1937).

monia amide ion and molecular ammonia are the attacking reagents in ammonolysis.



Both mechanisms involve the addition of a nucleophilic agent to the carbonyl carbon atom. The fact that the presence of a polar (ionizing) solvent is necessary for ammonolysis to occur readily suggests that (II) is more probable than I. It is not necessary to postulate free amide ions $(NH_2)^-$ although they may exist to some extent. It is possible that through hydrogen bonding the polarization of the H—NH_2 bond may be increased to the point that it simulates ionization.

Experimental

It was originally hoped to carry out the ammonolysis of esters in anhydrous media, but preliminary experiments showed that ammonolysis of most esters will not proceed at a useful rate in anhydrous dioxane or methanol. This result confirms the work of Grant and Hinshelwood[8] and others.[9]

As Gorvin[3] has noted, aqueous ammonia is not suitable for accurate kinetic studies owing to the complicating factors introduced by the low solubility of the ester. This difficulty may be overcome by the use of suitable organic diluents in the reaction mixtures. The principal solvent employed in this study was 1,4-dioxane. This compound was used for all series of esters except where all of the esters of a series contained the same alcohol component, in which case that alcohol was used as the diluent. Alcohol was used as a diluent where possible because ammonolysis proceeds roughly twice as rapidly in primary alcohols as in dioxane, provided water is present in each case. Dioxane was selected for use as a result of a process of elimination. Alcohols, generally speaking, were unsatisfactory due to the possibility of ester interchange. There was no method immediately evident for ascertaining the extent of this side reaction. Other solvents react with either the esters or ammonia, or interfere with the subsequent titrations of the reaction mixtures, or are not soluble in water.

In the establishment of conditions for this study three major experimental factors had to be considered: (1) the kinetics of the reaction, which involves making the rate of reaction great enough to minimize the experimental errors involved in the measurements; (2) miscibility of the components, which means adjusting concentrations so that the entire series of reaction mixtures is kept homogeneous; (3) stability of ammonia solutions, which involves addition of sufficient water to avoid loss of ammonia in the course of the manipulations of the study. Since the above three factors are more or less mutually exclusive, it was only on the basis of a great deal of trial and error that a satisfactory set of conditions was arrived at that would hold for substantially all of the esters employed.

The dioxane used, a product of Carbide and Carbon Chemicals Corp., was purified by distillation from sodium metal. Alcohols used were freed from water by the method of Lund and Bjerrum.[10] Most of the esters used[11] were available commercially with the exception of methyl isobutyrate, methyl trimethylacetate, *n*-propyl benzoate, *t*-butyl benzoate, *t*-butyl acetate, β-naphthyl acetate, and *t*-butyl lactate. These esters were synthesized by a variety of methods, all of which have been described in the literature. Of special interest is the method of Richard[12] for esterifying sterically hindered acids. This procedure is seldom encountered in contemporary chemical literature.

An azeotrope of methanol and methyl trimethylacetate was encountered which is believed not to have been hitherto described. Its composition was 12.8% of ester by weight; b. p. 65.0° at 760 mm.

The esters, whether synthesized or obtained commercially, were dried over magnesium sulfate and fractionated in all-glass apparatus using an efficient column. The high boiling esters were distilled under reduced pressure. Refractive indices were used to ascertain final purity of esters employed.

Boiling points or melting points and refractive indices (D line) of the esters used were as follows: methyl acetate, b. p. 57.1° at 755 mm., $n^{20}D$ 1.3610; ethyl acetate, 77° at 760 mm., 1.3728 at 20°; *n*-propyl acetate, 101–101.5° at 750 mm., 1.3844, 20°; isopropyl acetate, 88.5–89.0° at 750 mm., 1.3771, 20°; *n*-butyl acetate, 126.5° at 750 mm., 1.3938 at 20°; isobutyl acetate, 116.5–117.0° at 750 mm., 1.3900 at 20°; *s*-butyl acetate, 112.0–112.5° at 755 mm., 1.3885 at 20°; *t*-butyl acetate, 97.5–98.0° at 755 mm., 1.3860 at 20°; *n*-amyl acetate, 148.0–148.5° at 755 mm., 1.4025 at 20°; benzyl acetate, 93° at 7 mm., 1.5020 at 20°; phenyl acetate, 78° at 10 mm., 1.5033 at 20°; vinyl acetate, 69–70° at 755 mm., 1.3941 at 20°; α-naphthyl acetate, m. p. 44–45°; β-naphthyl acetate, m. p. 68°; methyl benzoate, 85° at 10 mm., 1.5170 at 20°; ethyl benzoate, 90° at 10 mm., 1.5058 at 20°; *n*-propyl benzoate, 101.0–101.5° at 9 mm., 1.5000 at 20°; isopropyl benzoate, 94° at 10 mm., 1.4947 at 20°; *t*-butyl benzoate, 105° at 16 mm., 1.4896 at 25°; phenyl benzoate, m. p. 70°; benzyl benzoate, 110° at 0.5 mm., 1.5685 at 20°; methyl formate, 31.5° at 760 mm., 1.3438 at 20°; methyl propionate, 79° at 750 mm., 1.3770 at 20°; methyl isobutyrate, 92.0–92.5° at 755 mm., 1.3840 at 20°; methyl trimethylacetate, 99.5–100.5° at 760 mm., 1.3908 at 20°; methyl crotonate, 119–120° at 755 mm., 1.4250 at 20°; methyl phenylacetate, 79° at 5 mm., 1.5090 at 16°; methyl lactate, 50° at 17 mm., 1.4140 at 20°; ethyl lactate, 54° at 12 mm., 1.4131 at 20°; *n*-propyl lactate, 71° at 20 mm., 1.4170 at 20°; isopropyl lactate, 51° at 8 mm., 1.4102 at 20°; *n*-butyl lactate, 77° at 13 mm., 1.4215 at 20°; isobutyl lactate, 58° at 3.5 mm., 1.4184 at 20°; *s*-butyl lactate, 42° at 1 mm., 1.4168 at 20°; *t*-butyl lactate, 40° at 6 mm., 1.4085 at 30°; *n*-amyl lactate, 66° at 1 mm., 1.4261 at 20°; allyl lactate, 55° at 3 mm., 1.4369 at 20°; *n*-butyl hydracrylate, 69° at 0.5 mm., 1.4288 at 20°.

(8) Grant and Hinshelwood, *J. Chem. Soc.*, 1351 (1933).

(9) Very recent work in this laboratory indicates that by working in ethylene glycol and related compounds, amides can be obtained in good yield under anhydrous conditions. This material is part of the next paper of this series which will be ready for publication in the near future.

(10) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(11) We are indebted to Dr. C. H. Fisher of the Eastern Regional Laboratory, U. S. Department of Agriculture, for generous samples of lactic acid esters.

(12) Richard, *Ann. chim. phys.*, **21**, 323–406 (1910).

TABLE I

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF ACETIC ACID ESTERS AT 25°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Acetate →	Methyl		Ethyl		*n*-Propyl		Isopropyl		*n*-Butyl		Isobutyl	
100	33.0	0.00148	13.4	0.000530	12.1	0.000504	5.2	0.000231	7.2	0.000273	5.1	0.000201
200	50.0	.00142	22.0	.000450	19.2	.000436	7.5	.000202	11.3	.000240	7.0	.000166
300	62.0	.00140	28.1	.000420	24.6	.000370	11.5	.000180	13.6	.000209	9.5	.000153
400	72.0	.00138	32.6	.000390	28.5	.000302	14.5	.000156	16.0	.000178	11.1	.000136
500	80.6	.00140	36.0	.000380	31.6	.000240	16.0	.000135	17.3	.000146	14.0	.000128
Acetate →	*s*-Butyl		*t*-Butyl		*n*-Amyl		Benzyl		α-Naphthyl		β-Naphthyl	
100	5.0	0.000146	4.0	0.000111	7.0	0.000258	21.9	0.000960	1.6	0.000070	1.9	0.000082
200	5.5	.000122	4.0	.000100	11.0	.000230	36.3	.000950	2.5	.000065	2.8	.000070
300	5.9	.000101	4.5	.000090	13.0	.000205	48.0	.000950	3.2	.000060	3.2	.000060
400	6.0	.000090	5.3	.000080	16.3	.000179	58.0	.000950	3.8	.000054	3.7	.000050
500	6.2	.000080	5.3	.000068	18.1	.000154	67.4	.000950	4.2	.000049	4.1	.000046

Phenyl acetate,[a] 0.5 hr., ammonalysis 86.6%, const. 2.02

Vinyl acetate,[a] 0.5 hr., ammonalysis 75.3%, const. 1.34

[a] Ammonolysis was too rapid for a satisfactory rate study, time, 0.5 hour.

In carrying out the ammonolyses, equivalent molar quantities of the various esters were measured into 10-ml. glass ampoules by means of a 1-ml. glass syringe graduated in 0.01 ml. subdivisions and fitted with a #16 gage 3-inch stainless steel needle. The use of the above device made possible the introduction of the esters into the ampoules without wetting the necks of the containers. It was found by a series of control experiments that the quantities of ester delivered by this method were reproducible with an error of less than one-tenth of one per cent. In the case of the volatile esters the opening of the ampoule was tightly closed by means of half a gelatin capsule of appropriate size, then the needle was pushed through the top of the capsule into the ampoule. In all cases the ampoules were closed off by means of intact capsules after the introduction of the esters and were then chilled in ice.

Reproducible results were obtained in the manipulation of the aqueous dioxane–ammonia solutions only by filling eight ampoules from each 100-ml. buretful of solution, using the first and last 10 ml. of each buretful as controls. These control portions of ammonia solution were run into 4% boric acid solution and titrated directly with half-normal hydrochloric acid using methyl red as the indicator. Following the introduction of both ester and ammonia the ampoules were again cooled in ice and then rapidly sealed off in a hot flame, first removing the gelatin closure. This chilling procedure cut down the loss of ammonia during the sealing operation and reduced the likelihood of leaks developing in the sealed ampoules. The ampoules were then shaken thoroughly and placed in a constant temperature bath.

A series of duplicate reaction mixtures was started for each ester. At intervals the ampoules were removed from the thermostat and again chilled. The ampoules were then opened, rinsed into 4% boric acid solution, and titrated directly with standard acid as in the case of the blank runs. The accuracy of the method was ascertained by setting up a series of reaction mixtures and titrating them at intervals as before, but omitting the ester. These blank runs showed that the error in the rest of the method was less than that involved in titrating the solutions.

The amount of competing hydrolysis occurring in the ammonolysis of the acetates was determined by the method of Pucher[13] as modified by French.[14] Results of this direct analytical method corroborated the results obtained in estimating ammonia consumed by difference.

(13) Pucher, Vickery and Leavenworth, *Ind. Eng. Chem., Anal. Ed.*, **7**, 152 (1935).

(14) French, Johnson and Ratekin, THIS JOURNAL, **58**, 1346 (1936).

Determination of activation energies for methyl acetate and the lactates was carried out by setting up parallel reaction mixtures of the various esters and running half of them at 25° and the rest at 30 or 35°. Determination of the activation energies for the benzoates, for the methyl esters other than acetate and formate, and for the acetates above methyl, was omitted because their low reaction velocity made the accurate measurement of temperature coefficients impossible. The ammonolysis of methyl formate proceeded too rapidly for the determination of activation energies with any accuracy.

Sources of Error

A major consideration in working with aqueous ammonia solutions is the possibility of simultaneous hydrolysis and ammonolysis of the ester. This matter will be discussed after presentation of the data.

The possibility of reversibility of the reaction was eliminated when it was found that acetamide will not react with alcohols in aqueous dioxane-ammonia solutions at the temperatures of the experiments. Other side reactions such as the formation of amines or double amides have been ruled out by various investigators. This aspect of the problem has been fully discussed by Betts and Hammett.[7] The possibilities for manipulative error were discussed in the description of the experimental method employed, and it is believed that the maximum error for any single determination is about 2%. The over-all errors persisting in any of the rate constants obtained graphically probably amount to less than 5%.

Results

The values found for the second order rate constants in the ammonolysis of esters of acetic acid at 25° are listed in Table I. Also tabulated are the percentages of total reaction for the times indicated. The amount of ester employed in all of the reaction mixtures of this investigation was 0.007 mole per 10 ml. reaction vessel, or 0.7 mole per liter. The ammonia concentration in every

TABLE II

RELATIVE REACTION RATES FOR AMMONOLYSIS OF ACETIC ACID ESTERS AT 25°

Ester	100 hr.	200 hr.	300 hr.
Phenyl acetate[a]	1365	1422	1443
Vinyl acetate[a]	909	944	957
Methyl acetate	1.00	1.00	1.00
Benzyl acetate	0.649	0.662	0.678
Ethyl acetate	.358	.317	.300
n-Propyl acetate	.341	.307	.264
n-Butyl acetate	.185	.169	.149
n-Amyl acetate	.174	.163	.148
Isopropyl acetate	.156	.142	.128
Isobutyl acetate	.136	.117	.109
s-Butyl acetate	.0986	.0859	.0721
t-Butyl acetate	.0750	.0655	.0643
β-Naphthyl acetate	.0554	.0493	.0429
α-Naphthyl acetate	.0473	.0458	.0429

[a] Reaction has gone to completion by the time 100 hours is reached, but this ester is included for purposes of comparison.

TABLE III

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF BENZOATES AT 25°

Ester	Rate constant	Comparative rate
Phenyl benzoate[a]	0.0620	376
Methyl benzoate	.000165	1.00
Benzyl benzoate[b]	.000087	0.527
Ethyl benzoate	.000084	.509
n-Propyl benzoate	.000065	.391
Isopropyl benzoate	.000056	.341
t-Butyl benzoate	.000019	.116

[a] Owing to the high molecular weight of this ester only 0.467 mole/l. was used. Any greater amount led to separation of layers. Reaction time in this case was twenty-four hours. [b] 0.467 mole/l. of this ester was used.

case was between 2.5 and 2.8 moles/liter. All of the reaction mixtures contained ten moles of water/liter. The diluent used for this series was 1,4-dioxane. The rate constants are bimolecular and are expressed in liters/mole/hour.

Table II lists the relative rate constants for the acetates. All of the rate constants have been divided through by the corresponding rate for methyl acetate so that the latter always has the value unity in the tabulation, and the comparative rates of the other esters may be seen accordingly.

The ammonolysis of benzoic acid esters proceeded so slowly that, in most cases, a satisfactory kinetic study was impractical. The differences in ammonia content found on successive titrations over a period of several days were often so small as to be within the limits of experimental error of the method. Accordingly, only one titration was carried out on each ester after reacting with aqueous dioxane–ammonia for 618.5 hours. Dioxane was used as the diluent. Bimolecular rate constants and comparative rates of ammonolysis of the benzoates are given in Table III.

Second order rate constants and percentages of total reaction in the ammonolysis of lactic acid esters at 30° are listed in Table IV. The diluent for this series was dioxane.

The values found for the second order rate constants and the percentages of total reaction in the ammonolysis of the methyl esters of various acids at 25° are listed in Table VI. The diluent used for this series was absolute methanol.

The compilation in Table VIII is taken from Tables II, III and V in an effort to determine what correlation may be found between structure and reactivity.

The extent of ammonolysis and hydrolysis of acetic acid esters is shown in Table IX.

From the temperature coefficients of ammonolysis an approximate evaluation of the activation energies was possible using the integrated form of the Arrhenius equation. Calculations of PZ factors from the equation $k = PZe^{-A/RT}$ showed that errors in the values of activation energies were too great to permit the use of entropy changes to show the validity of structure–reactivity correlations.

TABLE IV

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF LACTIC ACID ESTERS AT 30°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Lactate →	Methyl		Allyl		Ethyl		*n*-Propyl		*n*-Butyl			
10	55.0	0.0397	54.0	0.0370	25.9	0.0155	16.6	0.00780				
20	78.0	.0372	77.5	.0370	37.0	.0135	26.1	.00760				
30	88.0	.0363	88.0	.0362	45.2	.00950	33.6	.00740	34.0	.00740		
50	94.0	.0361			57.8	.00800	45.0	.00710	46.0	.00710		
100					78.5	.00780	66.2	.00610	66.1	.00608		
150									75.1	.00470		
Lactate →	*n*-Amyl		Isobutyl		Isopropyl		*s*-Butyl		*t*-Butyl		*n*-Butyl hydracrylate[a]	
30	32.5	0.00504	28.2	0.00493	11.1	0.00242	11.0	0.00200	1.10	0.00042	8.5	0.00167
50	42.0	.00500	38.3	.00483	16.0	.00188	16.1	.00184	1.79	.00040	12.0	.00140
100	60.9	.00497	57.5	.00460	25.2	.00137	21.0	.00132			18.4	.00100
150	76.0	.00482	71.0	.00440	31.3	.00108	24.9	.00087			24.0	.00080

[a] Inserted for comparison with *n*-butyl lactate.

TABLE V

RELATIVE REACTION RATES FOR AMMONOLYSIS OF LACTIC ACID ESTERS AT 30°

Ester	30 hr.	50 hr.
Methyl lactate	1.00	1.00
Allyl lactate	0.997	
Ethyl lactate	.262	0.221
n-Propyl lactate	.204	.197
n-Butyl lactate	.204	.197
n-Amyl lactate	.139	.139
Isobutyl lactate	.136	.134
Isopropyl lactate	.0667	.0521
s-Butyl lactate	.0551	.0509
n-Butyl hydracrylate[a]	.0460	.0398
t-Butyl lactate	.0116	.0111

[a] Tabulated for comparison with *n*-butyl lactate.

methyl acetate and the lactates are listed in Table X.

Discussion

While the comparative rates for similar esters of different acids (Table VIII) show that the correlation of structure and reactivity is still far from quantitative, they do show that the relative magnitude of effects may be determined. The variations in reaction rates of most of the esters studied are at least qualitatively predictable from the known electronegativity of the groups attached. While it is true that probably both steric and polarization effects contribute to the variations in rate constants among the reactions of this study, the fact that, except for the case of the naphthyl esters to be discussed later, an explanation based on polarization effects has been found to be adequate has led to the emphasis on the latter. The relative rates for the ammonolysis of the different esters agree in the main with published values obtained in alkaline and acid hydrolysis of esters.[15]

In all of the ester series where the acid component was held constant, we noted that the reactivity of the ester toward ammonia decreased with increase of the molecular weight of the alcohol

TABLE VI

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF METHYL ESTERS AT 25°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Methyl →.	Formate		Lactate		Acetate		Phenylacetate		Crotonate	
50	79.3[a]	1.54	94.0[b]	0.0361	45.0	0.00500	40.0	0.00469	29.0	0.00290
100					63.5	.00480	59.3	.00435	52.8	.00332
150					74.9	.00453	71.0	.00408	71.3	.00370
200					81.3	.00420	77.0	.00375	82.6	.00403
300							84.2	.00315		
Methyl →			Propionate		Benzoate		Isobutyrate		Trimethylacetate[c]	
50			25.0	0.00282	16.0	0.00188	10.0	0.000880	0	0
100			36.8	.00233	18.3	.00110	13.3	.000725	0	0
150			46.0	.00196	20.8	.00075	16.6	.000600	0	0
200			54.0	.00173	23.1	.00058	20.0	.000500	0	0
300			67.4	.00160	27.7	.00043	25.0	.000390	1.43[d]	.0000147

[a] Ammonolysis is too rapid for a satisfactory rate study; time, 0.5 hour. [b] This rate is for dioxane diluent. In methanol the rate is approximately twice this value. [c] Ammonolysis is too slow for a satisfactory rate study. [d] Time, 388 hours.

TABLE VII

RELATIVE REACTION RATES FOR AMMONOLYSIS OF METHYL ESTERS AT 25°

Ester	50 hr.	100 hr.	200 hr.
Methyl formate	308[a]	321[a]	367[a]
Methyl lactate	7.2	7.5[b]	7.9[b]
Methyl acetate	1.00	1.00	1.00
Methyl phenylacetate	0.938	0.906	0.893
Methyl crotonate[c]	.580	.692	.881
Methyl propionate	.564	.485	.412
Methyl benzoate	.376	.239	.138
Methyl isobutyrate	.176	.151	.119
Methyl-trimethylacetate	.00294[d]	.00306[d]	.00350[d]

[a] This ratio is obtained from the rate constant after one-half hour and is used here for purposes of comparison. [b] Taken from data for 50 hours. [c] The reaction of this ester results primarily in 1,4-addition of ammonia. [d] Taken from data for 388 hours.

TABLE VIII

COMPARATIVE RATES OF SIMILAR ESTERS OF DIFFERENT ACIDS

Alcohol component	Acetic acid[a]	Benzoic acid[b]	Lactic acid[c]
Methyl	1.00	1.00	1.00
Ethyl	0.358	0.509	0.221
n-Propyl	.341	.391	.197
Isopropyl	.156	.341	.0521
t-Butyl	.0750	.116	.0111

[a] This comparison is for a reaction time of 100 hours. [b] Reaction time is 618.5 hours. [c] Reaction time is 50 hours.

Possible errors in activation energy calculations were estimated by substituting probable maximum and minimum values of the various rate constants in the integral form of the Arrhenius equation.

Activation energies for the ammonolysis of

(15) Skrabal, *Monatsh.*, **45**, 148 (1924), *et seq.*; Palomaa, *Ber.*, **71B**, 480 (1938); Kindler, *Ber.*, **69B**, 2792 (1936); Sudborough, *J. Chem. Soc.*, **75**, 467 (1899).

TABLE IX

EXTENT OF AMMONOLYSIS AND HYDROLYSIS OF ACETATES

Ester	% Hydrolysis	% Ammonolysis	Time, hr.
Methyl acetate	1.1	75.9	579.5
Methyl acetate	1.1	78.6	699.5
Methyl acetate	0.7	83.9	792.5
Ethyl acetate	1.1	35.4	698.5
n-Propyl acetate	4.3	26.0	862.5
Isopropyl acetate	3.3	7.6	1127
n-Butyl acetate	3.6	23.9	1127
Isobutyl acetate	4.4	17.1	1127
s-Butyl acetate	2.9	3.6	1127
t-Butyl acetate	2.9	2.9	1127
n-Amyl acetate	4.3	20.3	1127

TABLE X

ACTIVATION ENERGIES FOR AMMONOLYSIS

Ester	Activation energy, cal./mole
Methyl acetate	12,700 ± 2000
Methyl lactate	11,800 ± 1000
Ethyl lactate	10,500 ± 1000
n-Propyl lactate	10,700 ± 1000
Isopropyl lactate	9,900 ± 1000
n-Butyl lactate	9,400 ± 1000
Isobutyl lactate	11,800 ± 1000
s-Butyl lactate	11,800 ± 1000
n-Amyl lactate	10,200 ± 1000
Allyl lactate	11,100 ± 1000

component, and, to an even greater extent, with increased branching of the alcohol. Generally speaking, esters of primary alcohols ammonolyze more readily than those of secondary alcohols, and the latter in turn react with ammonia more rapidly than the esters of tertiary alcohols: $CH_3 > C_2H_5 > CH_3CH_2CH_2 > (CH_3)_2CH > (CH_3)_3C$. These results are in accord with accepted electron release effects of alkyl groups.

In the acetate series we found that vinyl acetate had several hundred times the reactivity of ethyl acetate. Writing the resonance forms for vinyl acetate, we see that the positive charge on the oxygen tends to make the carbonyl carbon more

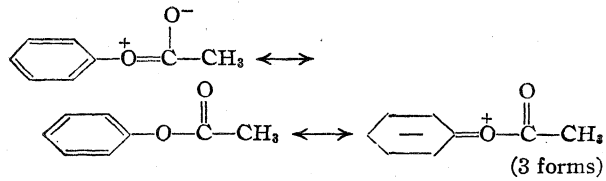
$$CH_2{=}CH{-}O{-} \longleftrightarrow {}^{-}CH_2{-}CH{=}O^{+}{-}$$

electrophilic, which in turn greatly enhances the reactivity of this carbon toward a nucleophilic

$$^{-}CH_2{-}CH{=}O^{+} \leftarrow \overset{+}{C}(=O){-}CH_3$$

attacking species. The latter, in this case, is probably either the ammonia amide ion or a hydrogen bonded water–ammonia complex.

The very great reactivity of phenyl acetate toward ammonia, compared to the other acetates, is likewise attributable to resonance, in this case mainly between the benzene ring and the oxygen bound to it. Writing the various resonance forms we see that all of the charged structures have a positively charged center adjoining the carbonyl carbon. The effect of this charge concentration



(3 forms)

on the reactivity of phenyl acetate is the same as that discussed above for vinyl acetate.

On the basis of resonance it might further be anticipated that the naphthyl acetates would have similarly enhanced reactivities. However, these esters react very slowly with ammonia. This phenomenon can be partly attributed to the large size of the naphthyl groups. Atomic models indicate the reduced susceptibility of the carbonyl carbon to attack due to steric hindrance. In the forms of phenyl acetate in which there is resonance with the benzene ring, there is the spatial requirement that the carbonyl carbon be coplanar with the ring. The decreased likelihood of this restriction being complied with in the naphthyl acetates may further account for their low reactivity toward ammonia.

It was noted that benzyl acetate ammonolyzed twice as rapidly as ethyl acetate and allyl lactate reacted with ammonia five times as rapidly as did *n*-propyl lactate. From these results it must be concluded that the benzyl group is less electron releasing than the ethyl, and the allyl less than the *n*-propyl. These relationships would seem to be at odds with the well-known behavior of the halides of these compounds. For example, benzyl chloride is known to be more reactive than ethyl chloride and this phenomenon is popularly attributed to the greater polarization of the carbon–halogen bond in the benzyl chloride, from which one would have to conclude that the benzyl group is more electron releasing than the ethyl. Similarly the greater reactivity of allyl chloride over *n*-propyl chloride would lead one to believe that the allyl group is more electron releasing than the *n*-propyl.

However, reference to dipole moments shows that precisely the reverse is true. The relative dipole moments of ethyl bromide[16] and benzyl bromide[17] are 2.12 (in benzene) and 1.85 (in benzene), respectively, indicating that the carbon–halogen bond is less polarized in the latter, and that the electron release effect of the benzyl group must be less than that of the ethyl group. Similarly the relative dipole moments of *n*-propyl bromide[16] and allyl bromide[18] are 2.00 (in benzene) and 1.79 (in benzene), respectively, again leading to a conclusion supporting the results of this investigation, namely, that the allyl group is relatively less electron releasing than the *n*-propyl.

The usual high reactivity attributed to allyl halides, alcohols, etc., in unimolecular displacements, when compared to the corresponding saturated

(16) Daily, *Phys. Rev.*, [ii] **34**, 548 (1929).
(17) Smyth and Walls, THIS JOURNAL, **54**, 1854 (1932).
(18) Parts, *Z. physik. Chem.*, **B12**, 312 (1931).

alkyl compounds, is due to stabilization of the carbonium ion through resonance. However, only after ionization does this stabilizing influence

$$CH_2{=}CH{-}CH_2{-}X \longrightarrow CH_2{=}CH{-}CH_2^+ + X^- \quad \updownarrow \quad {}^+CH_2{-}CH{=}CH_2$$

operate, so that while the allyl compound is in the un-ionized form it is perfectly consistent to say that the polarization of the carbon–halogen bond in allyl halides is lower than in *n*-propyl halides.

There is abundant evidence in the literature, well summarized by Branch and Calvin,[19] to show the great effect of resonance stabilization by cations such as allyl and benzyl groups in bimolecular (S_N2) displacements.

The fact that the reactivity of benzyl halides is greater than that of ethyl halides is due to the presence of the allylic system in the former. So we see that the influence on reactivity attributed to the allyl and benzyl groups in this investigation is not incompatible with the normal behavior of these compounds in displacement reactions, since in ammonolysis there is no cleavage of the alkyl–oxygen bond.

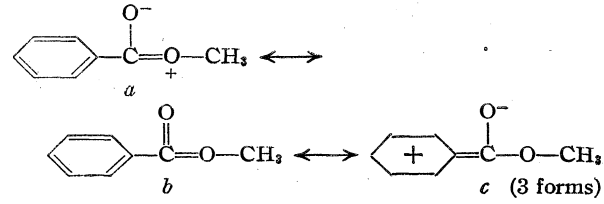
In the case of the saturated aliphatic esters of benzoic and lactic acids the same generalizations apply as in the case of the acetates. The high reactivity of allyl lactate, as compared to *n*-propyl lactate, was noted above. The rate for vinyl esters is much greater than that of allyl esters due to the absence of resonance in the un-ionized form of the latter. *n*-Butyl hydracylate is less than one-fourth as reactive as *n*-butyl lactate because the electron attracting hydroxyl group is farther removed, in *n*-butyl hydracrylate, from the reactive center of the molecule. In general, all of the lactates have from ten to twenty times the reactivity toward ammonia that is exhibited by the corresponding acetates. Here again the difference is due, in part, to the presence of an electron attracting group in the lactic acid esters. Furthermore, to the extent that it occurs, hydrogen bonding in the lactates and hydracrylates could contribute to the electrophilic activity of the carbonyl carbon atom since it assists in the polarization of the carbonyl carbon–oxygen bond. However, hydrogen bonding of the hydroxyl hydrogen to the carbonyl oxygen probably reduces the inductive effect of the hydroxyl group, so that the over-all contribution of hydrogen bonding to the

$$CH_3{-}CH \leftarrow {}^+C{-}O{-}R \quad \downarrow \quad O{-}H\cdots O$$

rate of ammonolysis of the lactates is open to question.

The methyl esters of the various acids show that the variation of R groups in the ester RCOOR′ results in a change in reactivity analogous to that obtained by varying the R′ groups as discussed earlier. However, methyl trimethylacetate has a much lower rate, compared to methyl acetate, than *t*-butyl acetate has compared to methyl acetate. The greater retardation effect of the R_3C grouping in methyl trimethylacetate can be attributed to the closer proximity of that group to the carbonyl carbon than is the case in *t*-butyl acetate. The oxygen, due to its unshared electrons, is probably an efficient conductor of inductive forces, but since the inductive effect falls off rapidly with distance, replacing a given R group in the ester RCOOR′ by any given radical will have greater effect on the rate of ammonolysis of the ester than replacing the corresponding R′ group by the same radical.

In methyl benzoate, unlike phenyl acetate, the conjugation of the carbonyl group with the benzene ring decreases the reactivity toward ammonia. It should be noted that the oxygen attached to the methyl group of methyl benzoate is less positive than that of methyl acetate due to resonance with the ring in the former ester. Writing the resonance structures of methyl benzoate we can see the reasons for the reduced electrophilic nature of the carbonyl carbon atom. Methyl acetate has only the forms corresponding to *a* and *b* above and would therefore be expected to ammonolyze more rapidly than methyl benzoate.



a *b* *c* (3 forms)

In the reaction of methyl crotonate Morsch[20] reported predominantly 1,4-addition of ammonia to give methyl 3-aminobutyrate, which he isolated. In this laboratory these results were confirmed by titrating starting mixtures and reaction products by the bromate–bromide method, whereby about 96% of the product was found to be saturated. These results probably account for the rise in reaction rate constants observed with this ester, as compared with the downward drift in the purely ammonolytic reactions.

In the ammonolysis of methyl formate it was found that the competing hydrolytic reaction may account for as much as 40% of the ester consumed, but nevertheless the ammonia reaction was still several hundred times as rapid as in the case of methyl acetate. Work which had been planned with other formic acid esters was dropped due to the great amount of competing hydrolysis. Another objection to the use of formates was the fact that reaction with ammonia was so rapid as to make accurate kinetic studies exceedingly difficult.

(19) Branch and Calvin, "Theory of Organic Chemistry," 1941, p. 436.

(20) Morsch, *Monatsh.*, 60, 50 (1932).

The amount of hydrolysis found in the case of esters of acetic acid has been given in Table IX. It should be appreciated that hydrolysis figures presented represent extreme upper limits in view of the length of reaction time. These extreme periods of time were specifically employed because the amounts of hydrolysis obtained over periods of time comparable to those used in the ammonolytic studies were of the same order of magnitude as the experimental error of the method and hence meaningless. Since the extent of hydrolysis in all cases tabulated could not be evaluated for periods comparable to those used in the ammonolytic determinations, we were unable to apply any correction to the calculations for the rates of ammonolysis in order to account for the side reaction. In view of the original objectives of this study, an additional expenditure of time on the further study of the hydrolysis of esters was considered unwarranted.[21]

The relative extent of hydrolysis in these experiments, even for extreme periods of reaction time, is well below that encountered by other investigators[14,22] owing to the lower concentrations of water (18%) employed in this Laboratory.

From the foregoing remarks it should be clear that, for the periods of time used in ammonolysis in this study, the amount of hydrolysis is within the limits of experimental error and hence not significant in its effect on the structure–reactivity correlations.

The second order rate constants for the ammonolysis of esters have been found to drift downward with time. The only exception was the case of methyl crotonate, in which, as discussed earlier, the principal reaction was not ammonolysis. The downward drift of rate constants is attributable to two causes; first, to the accumulation of ammonium ions from the competing hydrolytic reaction, the ammonium ions acting to retard the principal reaction and, second, to the fact that reactions were carried out in concentrated solutions in which we would expect to find considerable deviation from ideality.

(21) Results of unpublished work show that the same qualitative structure-reactivity correlations are obtained by working in anhydrous ethylene glycol–ammonia, in which hydrolysis is improbable, as are reported in this paper for aqeuous solutions.

(22) French and Wrightsman, THIS JOURNAL, **60**, 50 (1938).

Summary

The rates of ammonolysis of several series of esters have been determined and have been found to be regulated by the electron release effects of both the R and R′ groups in the ester RCOOR′, with variations of R having the greater effect due to the rapid falling off of the inductive effect with distance.

A kinetic study has revealed the following order of reactivity of acetates with aqueous ammonia: phenyl > vinyl > methyl > benzyl > ethyl > *n*-propyl > *n*-butyl > *n*-amyl > isopropyl > isobutyl > *s*-butyl > *t*-butyl > β-naphthyl > α-naphthyl.

A study of the reactivity of benzoates indicated the following order: phenyl > methyl > benzyl > ethyl > *n*-propyl > isopropyl > *t*-butyl.

The following order of reactivity in the ammonolysis of lactates was observed: methyl > allyl > ethyl > *n*-propyl > *n*-butyl > *n*-amyl > isobutyl > isopropyl > *s*-butyl > *t*-butyl.

By utilizing a series of methyl esters of different acids the effects of structural variations on the acid side of the ester molecule were observed. The following order of ammonolysis of methyl esters was obtained: formate > lactate > acetate > phenylacetate > propionate > benzoate > isobutyrate > trimethylacetate.

In general the relative rates of ammonolysis obtained by varying the alcohol and acid components of the ester follow the anticipated electron release effects and confirm the results obtained by other investigators in the acid and alkaline hydrolysis of esters.

An azeotrope of methanol and methyl trimethylacetate has been described.

PHILADELPHIA, PENNSYLVANIA
RECEIVED NOVEMBER 14, 1947

[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

9,9-Difluorofluorene

BY FRANCIS EARL RAY AND CLARENCE E. ALBERTSON

Only the following fluorine derivatives of fluorene have been prepared: 4-fluoro-5-nitro-1-methylfluorene,[1] 2-fluorofluorenone and its oxime,[2,3] 2-fluoro-9,9-dichlorofluorene and several 9,9- condensation products, and perfluorofluorane ($C_{13}F_{22}$).[4]

Since the 9-position in fluorene has aliphatic properties and has never been fluorinated independently of the rest of the molecule, it seemed of interest to attempt the preparation of 9,9-difluorofluorene. The difluoro compound was selected because it seemed doubtful if the allylic character of the 9-carbon[5] would permit the preparation of 9-monofluorofluorene.

Little difficulty was expected in the preparation of 9,9-difluorofluorene because Henne and Leicester[6] had reported the preparation of diphenyldifluoromethane in yields of 60%.

We treated 9,9-dichlorofluorene with hydrogen fluoride in the presence of mercuric oxide. To reduce the violence of the reaction, toluene or chlorobenzene was used as a diluent. The products that were obtained from the reaction were fluorenone, tolylmercuric chloride and mercuric chloride.

It is not clear whether the formation of fluorenone is the primary reaction. It is possible that hydrogen fluoride reacted with mercuric oxide to produce water and that 9,9-dichlorofluorene was subsequently hydrolyzed to fluorenone.

$$2HF + HgO \longrightarrow H_2O + HgF_2$$

$$\begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CCl_2 + H_2O \longrightarrow \begin{matrix} C_6H_4 \\ | \\ C_6H_4 \end{matrix}\!\!>\!CO + 2HCl$$

Other catalysts such as antimony tri- and pentafluoride and zinc fluoride also gave fluorenone or intractable tars as did the use of uncatalyzed hydrogen fluoride.

Impure 9,9-fluorochlorofluorene may have been present in some of these products. The monofluorochloro derivatives are generally less stable than the difluoro compounds.[7]

Despite the fact that hydrous mercuric fluoride was entirely unsuitable as a catalyst, Henne[8] later found that it was not necessary to isolate mercuric fluoride but simply passed a stream of hydrogen fluoride into the mixture of mercuric oxide and the substance. This was the first method tried and it led to the formation of fluorenone.

The inconvenient preparation of mercuric fluoride from mercuric chloride and fluorine and the bad effects of mercuric oxide in the second method might both be avoided by passing hydrogen fluoride into a mixture of mercuric chloride and the substance to be fluorinated. Daudt and Youker, U. S. Patent 2,005,707, disclose the use of mercuric chloride in vapor phase hydrofluorination at elevated temperatures but give no experimental details.

On carrying out this experiment at 70°, we obtained the desired 9,9-difluorofluorene in addition to some of the unstable material obtained previously and thought to be 9,9-fluorochlorofluorene.

An attempt to increase the yield by operating at 100 pounds pressure produced a sponge-like rubbery hydrocarbon mass of approximately 2800 molecular weight.

9,9-Difluorofluorene formed white crystals that melted at 47–48° and analyzed correctly for fluorine and had the required molecular weight. After standing for two weeks in a desiccator evidence of decomposition was apparent.

It is thus seen that mercuric chloride and hydrogen fluoride form a fluorinating agent that is especially useful in the conversion of the less stable halides to fluorides or in the preparation of the less stable fluorides.

Experimental

9,9-Dichlorofluorene.—Fluorenone was prepared by the method of Huntress, Hershberger and Cliff[9] except that the acetic acid was reduced from 20 moles to 13 moles. This makes the preparation of large amounts more convenient and slightly improves the yields. From 200 g. of fluorene there was obtained some 148 g., 68%, melting at 82.8 to 83.1°. Fluorenone was converted to 9,9-dichlorofluorene by the following modification of Smedley's[10] method.

To 15 g. (0.1 mole) of phosphorus oxychloride in 60 cc. of toluene are added 90 g. (0.5 mole) of fluorenone and 114 g. (0.55 mole) of phosphorus pentachloride. The mixture was heated for three hours on the water-bath and agitated intermittently. The phosphorus pentachloride had disappeared at the end of the first hour and the mixture became dark brown in color. The reaction mass was subjected to vacuum distillation (25 mm.) to remove most of the phosphorus compounds. The residue was dissolved in benzene, washed twice with ice water and dried over calcium chloride. The benzene was removed under reduced pressure and the residue recrystallized from glacial acetic acid. A 66% yield of almost colorless crystals melting at 102.9 to 103.1° was obtained. Smedley[10] gives m. p. 103°. The pure product is quite stable if protected from moisture. Samples of impure material decomposed within a week to give a sticky green-yellow mass with the sharp odor of hydrogen chloride.

9,9-Difluorofluorene.—Most of the experiments were carried out in a stirred copper reactor with a thermometer well and a copper inlet tube. In general runs using about 0.5 mole of 9,9-dichlorofluorene were made. An excess

(1) Stoughton and Adams, THIS JOURNAL, **54**, 4426 (1932).
(2) Bergman, Hoffman and Winter, *Ber.*, **66**, 48 (1933).
(3) Balz and Schiemann, *ibid.*, **60**, 1186 (1927).
(4) McBee and Bechtol, *Ind. Eng. Chem.*, **39**, 380 (1947).
(5) Weissgerber, *Ber.*, **34**, 1659 (1901); Sampey and Reid, THIS JOURNAL, **69**, 234 (1947); Jaeger, U. S. Patent 1,764,023 (1930).
(6) Henne and Leicester, *ibid.*, **60**, 864 (1938).
(7) Henne and Midgley, Jr., *ibid.*, **58**, 884 (1936).
(8) Henne, *ibid.*, **60**, 1569 (1938).
(9) Huntress, Hershberger and Cliff, *ibid.*, **53**, 2720 (1931).
(10) Smedley, *J. Chem. Soc.*, **87**, 1249 (1905).

of 10–28% of mercury salt and 50–60% of hydrofluoric acid was used. Some runs employed 0.25 mole of the chloride and as much as 200% excess hydrofluoric acid. The successful preparation of 9,9-difluorofluorene is described in detail below.

Five-tenths mole (117 g.) of 9,9-dichlorofluorene was dissolved in 200 cc. of chlorobenzene and 0.37 mole (100 g.) of mercuric chloride was now added. Hydrogen fluoride next was bubbled into the stirred solution at a temperature of 30°. After thirty minutes no apparent reaction had occurred so the temperature was raised. At 70° the solution turned a very dark green but in contrast to the large amount of heat liberated when mercuric oxide and hydrofluoric acid are used this reaction showed little evidence of heat evolution. The temperature did not exceed 81° and the time of reaction was one and one-half hours.

The solution was washed with water and sodium carbonate solution, treated with Darco and distilled at 1–5 mm. The first fraction 55–115° (5 mm.), weighed 6 g. and was chlorobenzene. The second fraction, 115–130° (3 mm.), weighed 20 g. It was a light yellow, viscous oil. The third fraction, 125–135° (3 mm.), weighed 13 g. and came over as a yellow oil that solidified in the receiver. On standing overnight fraction 2 had changed to a thick tarry mass with gas bubbles and yellow crystals held in suspension. Some pressure was evidenced and fumes of hydrogen chloride and hydrogen fluoride were evolved when the container was unstoppered. A somewhat similar but much less pronounced effect was observed in fraction 3.

The yellow crystals were separated and recrystallized from ligroin, m. p. 47–48°. They contained fluorine but no chlorine.

Anal. Calcd. for $C_{13}H_8F_2$: F, 18.8; mol. wt., 202.2. Found: F, 17.9; mol. wt., 195.

From the decomposed material, fluorenone was isolated. Probably unstable 9,9-fluorochlorofluorene was the principal product in fraction 2.

Summary

9,9-Difluorofluorene has been prepared by treating 9,9-dichlorofluorene with hydrogen fluoride in the presence of mercuric chloride. It is somewhat unstable. Evidence has been found for the transitory existence of 9-chloro-9-fluorofluorene.

Mercuric chloride and hydrogen fluoride form a fluorinating agent that is especially useful in the preparation of the less stable fluorides.

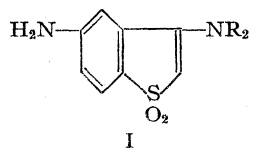
CINCINNATI 21, OHIO RECEIVED DECEMBER 6, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Studies in the Thianaphthene Series.[1] II. Aminothianaphthene-1-dioxides[2]

BY F. G. BORDWELL AND C. J. ALBISETTI, JR.[3]

In a previous paper[4] the synthesis of a sulfanilamide vinylog in which the sulfamyl group was separated from the aromatic ring by a vinyl group was described. As an extension in our synthesis of molecules with chemical characteristics similar to sulfanilamide, but with different stereochemical relationships of the functional groups, the synthesis of 3,5-diaminothianaphthene-1-dioxide (I, R = H) was undertaken. This molecule is a vinylog of sulfanilamide in which the sulfonyl and amino portions of the sulfamyl group have been separated by a vinyl group. It is also noteworthy because of its relationship to bis-(4-aminophenyl) sulfone, a compound which has aroused considerable interest because of its high bacteriostatic activity. Recently 2,8-diaminodibenzothiophene-5-dioxide and 2,8-diaminothiaxanthene-5-dioxide, which are closely related to I, have been synthesized for pharmacological testing.[5]



I

The simplest approach to I appeared to be nitration of 5-nitrothianaphthene, oxidation of the sulfur atom and reduction of the nitro groups.

The preparation of 5-nitrothianaphthene by decarboxylation of 5-nitro-2-thianaphthenecarboxylic acid[6] has been described by Fieser and Kennelly.[7] Our yields of 5-nitro-2-thianaphthenecarboxylic acid from crude 2-chloro-5-nitrobenzaldehyde were about 25%; which compares well with the 28% yield reported by Fieser and Kennelly[7] using pure 2-chloro-5-nitrobenzaldehyde, but is considerably lower than the maximum yield of 45% reported by Fries and his co-workers.[6] The decarboxylation was carried out by a slight modification of the method of Fieser and Kennelly,[7] which was found to be more convenient.

Nitration of 5-nitrothianaphthene to give a pure dinitrothianaphthene was not easy, since it was found that a third nitro group entered the molecule almost as readily as did the second nitro group. By carrying out the nitration with an equivalent amount of potassium nitrate in sulfuric acid at 0–5° for one hour a dinitrothianaphthene, m. p. 171°, was isolated in 46% yield. This compound is very probably 3,5-dinitrothianaphthene since the 3-position is known to be the most active

(1) For the first paper in this series see Bordwell and Albisetti, THIS JOURNAL, **70**, 1558 (1948).

(2) A preliminary account of this work was given at the One Day Technical Meeting of the Chicago Section of the American Chemical Society, January 24, 1947.

(3) Du Pont Predoctoral Fellow, 1946–1947. Present address: du Pont Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Abstracted from the Ph.D. dissertation of C. J. Albisetti, Jr., August, 1947.

(4) Bordwell, Colbert and Alan, THIS JOURNAL, **68**, 1778 (1946).

(5) Neumoyer and Amstutz, *ibid.*, **69**, 1920, 1925 (1947).

(6) Hemmecke, Dissertation, Braunschweig, 1929; Fries, Heering, Hemmecke and Siebert, *Ann.*, **527**, 83 (1936).

(7) Fieser and Kennelly, THIS JOURNAL, **57**, 1611 (1935).

position in the thianaphthene nucleus toward ordinary substitution.[8]

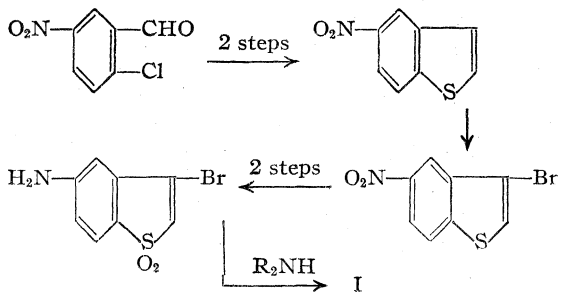
The sulfur atom in 3,5-dinitrothianaphthene was not oxidized by either 30% hydrogen peroxide in acetic acid–acetic anhydride or by sodium dichromate and sulfuric acid. The electron withdrawing effect of the 3-nitro group is responsible for the resistance of the sulfur atom to oxidation, since 5-nitrothianaphthene was readily oxidized to 5-nitrothianaphthene-1-dioxide by 30% hydrogen peroxide in acetic acid–acetic anhydride, but 3-nitrothianaphthene and 3,5,7-trinitrothianaphthene[9] were not oxidized under similar conditions.

No difficulty should be experienced in oxidizing the sulfur atom in 3,5-diacetamidothianaphthene, but attempts to obtain this compound were unsuccessful. In reductions of 3,5-dinitrothianaphthene using palladium on charcoal in the presence of acid the requisite hydrogen was absorbed but no pure products could be isolated. Similar results were obtained in attempted reductive acetylations using hydrogen and palladium catalyst and acetic anhydride in benzene solution. Reduction with tin and hydrochloric acid gave a crystalline tin salt, but attempts to liberate the amine from this salt or to acetylate it according to the method of Hemmecke[6] gave impure materials. Hemmecke[6] was unable to prepare 3-aminothianaphthene in a pure state. Apparently the 3-aminothianaphthenes, like the aminothiophenes, exist to a considerable extent in the imino form, and are very susceptible to oxidation and hydrolysis.

No difficulty is encountered in isolating and purifying aminothianaphthenes in which the amino group is in the benzenoid ring.[6] The nitro group in 5-nitrothianaphthene was reduced by the method of Fieser and Kennelly[7] and the 5-aminothianaphthene produced was converted to 5-(2-diethylaminoethylamino)-thianaphthene for pharmacological testing.[10] In a similar manner 5-aminothianaphthene-1-dioxide was prepared from 5-nitrothianaphthene-1-dioxide.

Synthesis of molecules of type I was finally accomplished by an alternate route. The bromine atom in 3-bromothianaphthene-1-dioxide has been found to be readily replaced by alkylamino groups[1]; therefore, 5-nitrothianaphthene was brominated to 3-bromo-5-nitrothianaphthene and the latter oxidized to 3-bromo-5-nitrothianaphthene-1-dioxide. The bromination of 5-nitrothianaphthene required considerably more vigorous conditions than are necessary for bromination of thianaphthene itself; a 64% yield of 3-bromo-5-nitrothianaphthene was obtained by treating 5-nitrothianaphthene with excess bromine in a refluxing carbon tetrachloride solution for seventy-two hours. The structure of the bromination product was proved by removal of the nitro group by reduction and deamination. The resulting bromothianaphthene was shown to be the 3-derivative by oxidation to 3-bromothianaphthene-1-dioxide.

Refluxing 3-bromo-5-nitrothianaphthene-1-dioxide in alcoholic solution with excess piperidine for thirty minutes gave a 94% yield of 3-(1-piperidino)-5-nitrothianaphthene-1-dioxide. A 94% yield of 3-diethylamino-5-nitrothianaphthene-1-dioxide was obtained in a similar reaction using diethylamine instead of piperidine. Reduction of the nitro group in these compounds could not be accomplished in acid solution without hydrolysis of the 3-alkylamino group.[1] It was, therefore, found to be more convenient to prepare compounds of type I by reduction of 3-bromo-5-nitrothianaphthene-1-dioxide to 3-bromo-5-aminothianaphthene-1-dioxide, which was then coupled with the desired amine. By this procedure 3-diethylamino-5-aminothianaphthene-1-dioxide (I, R = Et) was obtained in good yield. The preparation of 3,5-diaminothianaphthene-1-dioxide I(R = H) could no doubt be accomplished by the reaction of 3-bromo-5-aminothianaphthene-1-dioxide with ammonia according to the procedure used for 3-aminothianaphthene-1-dioxide,[1] but it was felt that 3-diethylamino-5-aminothianaphthene-1-dioxide would serve as well for pharmaceutical testing.



Acknowledgment.—We wish to express our appreciation to the du Pont Company for the fellowship which supported this work. A generous supply of *o*-chlorobenzaldehyde was furnished by the Heyden Chemical Corporation; the 60% sodium sulfide was furnished by the Hooker Electrochemical Company; and the thianaphthene was donated by the Texas Company.

Experimental[11,12]

5-Nitrothianaphthene-2-carboxylic Acid.—This compound was prepared from 2-chloro-5-nitrobenzaldehyde

(8) Fries and co-workers (ref. 6) reported the isolation of a dinitrothianaphthene, m. p. 171°, and a trinitrothianaphthene, m. p. 196°, by nitration of 3-nitrothianaphthene. At present we have under way an investigation of the nitration of thianaphthene, and we hope to be able to isolate the compounds reported by Fries, *et al.*, for comparison with those melting at the same temperature which were obtained by nitration of 5-nitrothianaphthene.

(9) The structure of this compound was not established, but its preparation by nitration of 5-nitrothianaphthene leaves little doubt as to the orientation of the nitro groups.

(10) Block, Lehr and Erlenmeyer, *Helv. Chim. Acta.*, **28**, 1406 (1945), have recently reported 5-aminothianaphthene to be one of the most active of the thirty-seven compounds tested *in vitro* against the tubercle bacillus.

(11) Microanalyses were by Mrs. Margaret Ledyard, Mrs. Nelda Mold and Miss Patricia Craig.

(12) All melting points were taken on a Fisher melting point block and are uncorrected.

essentially by the procedure described by Hemmecke[6] and by Fries, *et al.*,[6] except that the sodium disulfide was prepared and added in a 50% alcoholic solution.

5-Nitrothianaphthene.—A well-stirred mixture of 80 g. (0.36 mole) of 5-nitrothianaphthene-2-carboxylic acid, 400 ml. of quinoline and 20 g. of copper powder was gradually heated to the reflux temperature and the solution was stirred and allowed to reflux for thirty minutes. The mixture was cooled, poured onto 2 kg. of crushed ice and acidified with 18% hydrochloric acid. The suspension was cooled overnight and filtered. The air-dried solids were extracted with one 1.5-liter portion and three 500-ml. portions of boiling acetone (in one experiment a soxhlet extraction apparatus was used). The acetone was clarified with 5 g. of carbon (Norit A) and concentrated to 300 ml. by distillation. On cooling 43 g. (66.7%) of 5-nitrothianaphthene separated from the solution as a light tan powder, m. p. 149–150°.

5-(2-Diethylaminoethylamino)-thianaphthene.—This compound was prepared from 5-aminothianaphthene[7] by a procedure similar to that used by Gilman and Avakian[13] for the attachment of the γ-diethylaminopropylamino side chain on 2-aminodibenzothiophene. The product, obtained in 57% yield, was a yellow oil, b. p. 168–171° at 0.5 mm., which darkened on exposure to air.

Anal. Calcd. for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12. Found: C, 67.87; H, 7.90.

5-Nitrothianaphthene-1-dioxide.—To a warm mixture of 18.0 g. (0.1 mole) of 5-nitrothianaphthene in 100 ml. of acetic acid, 70 ml. of 30% hydrogen peroxide was added at such a rate as to keep the reaction from becoming too vigorous. A further 20 ml. of 30% hydrogen peroxide in 100 ml. of acetic acid was then added and the reaction mixture heated on the steam-bath for three hours. The hot solution was diluted to the point of turbidity and allowed to cool. The product was separated by filtration and purified by crystallization from 300 ml. of alcohol. There was obtained 13.8 g. (65.5%) of material melting at 164°. Further crystallization from alcohol raised the m. p. to 166°.

Anal. Calcd. for $C_8H_5NO_4S$: C, 45.48; H, 2.39. Found: C, 45.71; H, 2.62.

5-Aminothianaphthene-1-dioxide.—This compound was prepared in 44% yield from 5-nitrothianaphthene-1-dioxide by the procedure described by Fieser and Kennelly for reducing 5-nitrothianaphthene. After several crystallizations from 60% alcohol the material melted at 178°.

Anal. Calcd. for $C_8H_7NO_2S$: C, 53.02; H, 3.90. Found: C, 52.96; H, 4.12.

3,5-Dinitrothianaphthene.—To 120 ml. of concd. sulfuric acid stirred at 0–5° was slowly added 10.8 g. (0.06 mole) of carefully purified 5-nitrothianaphthene. To this was added, dropwise, a solution of 6.06 g. (0.06 mole) of potassium nitrate in 120 ml. of sulfuric acid. After being stirred for one hour at 0–5°, the mixture was poured onto ice. Crystallization of the product from 1 l. of a 1:1 benzene–Skellysolve C mixture gave 6.2 g. (46%) of 3,5-dinitrothianaphthene, m. p. 163–166°. Several crystallizations from alcohol gave pale yellow needles, m. p. 171°.

Anal. Calcd. for $C_8H_4N_2O_4S$: C, 42.87; H, 1.80. Found: C, 42.95; H, 1.89.

Unless carefully purified 5-nitrothianaphthene was used in the above method the conversion to 3,5-dinitrothianaphthene was low. 5-Nitrothianaphthene was essentially unchanged when 9.0 g. in 60 ml. of acetic acid was treated with a mixture of 5 ml. of water and 5 ml. of fuming nitric acid (d. 1.49) and the solution boiled for twenty minutes and diluted. This method has been used by Fries and Hemmecke[14] for the preparation of 3-nitrothianaphthene from thianaphthene. Similarly, treatment of a solution of 4.5 g. of 5-nitrothianaphthene in 40 ml. of acetic acid (d. 1.47), stirring the mixture at 40° for two hours and allowing to stand at room temperature for eighteen hours, did not bring about nitration. Except for the longer length of time and the more dilute reaction mixture used in the present experiment, these are the conditions used by Cullinane, Davies and Davies[15] for the successful nitration of dibenzothiophene.

3,5,7-Trinitrothianaphthene.—In another attempt to prepare 3,5-dinitrothianaphthene 1.8 g. (0.01 mole) of 5-nitrothianaphthene was added slowly to 36 ml. of fuming nitric acid at 0–5° over a period of thirty minutes. The mixture was held at this temperature and stirred for two hours and was then diluted. There was obtained 0.9 g. (33%) of material, m. p. 195–196°. After crystallization from 1-butanol the material melted at 196°.

Anal. Calcd. for $C_8H_3N_3O_6S$: C, 35.70; H, 1.12. Found: C, 35.73; H, 1.29.

Dinitration of 5-nitrothianaphthene also occurred by reaction at about 0° when 10 g. of material was added to a cold mixture of 100 ml. of concd. sulfuric acid and 100 ml. of fuming nitric acid (d. 1.49) and the mixture stirred while cold for two hours and diluted.

Attempted Oxidation of 3-Nitrothianaphthenes.—An attempt to oxidize 3,5-dinitrothianaphthene with sodium dichromate in the presence of sulfuric acid in acetic acid solution, according to the method described for dibenzothiophene[16] was unsuccessful. Hydrogen peroxide (30%) in acetic acid had no effect on 3,5-dinitrothianaphthene, and a refluxing solution of 30% hydrogen peroxide, acetic acid and acetic anhydride was likewise ineffective in attempts to convert 3-nitro-[14] and 3,5,7-trinitrothianaphthenes to the corresponding 1-dioxides.

3-Bromo-5-nitrothianaphthene.—A mixture of 7.2 g. (0.04 mole) of carefully purified 5-nitrothianaphthene, 19.2 g. (0.12 mole) of bromine and 800 ml. of chloroform was refluxed for seventy-two hours. The cooled solution was washed with aqueous sodium carbonate, dried over anhydrous sodium carbonate and concentrated. A total of 7.8 g. of material was obtained in three crops. On purification from ethanol 6.6 g. (64%) of material melting at 170–171° was obtained. A sample purified for analysis separated from ethanol in short, pale-yellow needles, m. p. 170.5–171°.

Anal. Calcd. for $C_8H_4NO_2SBr$: C, 37.22; H, 1.56. Found: C, 37.41; H, 1.87.

5-Amino-3-bromothianaphthene.—Reduction of 5-nitro-3-bromothianaphthene with stannous chloride and concd. hydrochloric acid was effected in 75% yield. The product was purified by crystallization from Skellysolve B, the last trace of pink color being removed with the aid of activated alumina. The compound was obtained as fine colorless needles, m. p. 84°.

Anal. Calcd. for C_8H_6NSBr: N, 6.14. Found: N, 6.18.

Proof of Structure of 5-Amino-3-bromothianaphthene.—Deamination was accomplished by diazotization and treatment with ethanol in the presence of copper powder.[17] Steam distillation of the product from an alkaline solution gave a yellow oil, which was oxidized with 30% hydrogen peroxide in acetic acid–acetic anhydride solution to a yellow solid. The purified compound melted at 181–182°, and a mixed melting point with 3-bromothianaphthene-1-dioxide[1] showed no depression.

3-Bromo-5-nitrothianaphthene-1-dioxide.—Oxidation of 3-bromo-5-nitrothianaphthene was accomplished in 74% yield by the method used for the preparation of 3-bromothianaphthene-1-dioxide.[1] The product was a cream-colored solid, m. p. 185–187°. Crystallization from ethanol gave material melting at 190–191°.

Anal. Calcd. for $C_8H_4NO_4SBr$: C, 33.12; H, 1.39. Found: C, 33.09; H, 1.53.

(13) Gilman and Avakian, THIS JOURNAL, **68**, 1514 (1946).

(14) Fries and Hemmecke, *Ann.*, **470**, 1 (1929).

(15) Cullinane, Davies and Davies, *J. Chem. Soc.*, 1435 (1936).

(16) Gilman, Jacoby and Pacevitz, *J. Org. Chem.*, **3**, 120 (1938).

(17) Baker, Albisetti, Dodson, Lappin and Riegel, THIS JOURNAL, **68**, 1534 (1946).

3-(1-Piperidino)-5-nitrothianaphthene-1-dioxide.—A 94% yield of this compound was obtained within thirty minutes by the reaction of 3-bromo-5-nitrothianaphthene-1-dioxide with a two molar excess of piperidine in refluxing ethanol solution. After crystallization from ethanol it melted at 197–198° (with dec.).

Anal. Calcd. for $C_{13}H_{14}O_4N_2S$: N, 9.53. Found: N, 9.29.

In a similar manner a 94% yield of **3-diethylamino-5-nitrothianaphthene-1-dioxide**, m. p. 210°, was obtained.

Anal. Calcd. for $C_{12}H_{14}O_4N_2S$: N, 9.92. Found: N, 9.74.

3-Bromo-5-aminothianaphthene-1-dioxide.—Reduction of 3-bromo-5-nitrothianaphthene-1-dioxide in ethanol solution was brought about in 81% yield using stannous chloride and concd. hydrochloric acid, according to the method of Fries, *et al.*[6] The product, m. p. 233°, was obtained as yellow needles by crystallization from ethanol.

Anal. Calcd. for $C_8H_6O_2NSBr$: N, 5.38. Found: N, 5.46.

3-Diethylamino-5-aminothianaphthene-1-dioxide.—By refluxing a mixture of 0.65 g. (0.0025 mole) of 3-bromo-5-aminothianaphthene-1-dioxide, 0.55 g. (0.0075 mole) of diethylamine and 10 ml. of ethanol for one hour, there was obtained 0.44 g. (70%) of a cream-colored solid, m. p. 180–184°. Purified four times by crystallization from ethanol, the material melted at 194°.

Anal. Calcd. for $C_{12}H_{16}O_2N_2S$: C, 57.11; H, 6.39. Found: C, 56.65; H, 6.43.

Summary

1. 3-Bromo-5-nitrothianaphthene was obtained in the bromination of 5-nitrothianaphthene. From the nitration of 5-nitrothianaphthene a dinitro- and trinitrothianaphthene were isolated, which are believed to be 3,5-dinitro- and 3,5,7-trinitrothianaphthene.

2. The electron attracting power of a nitro group in the 3-position of several thianaphthenes was found to be strong enough to prevent oxidation of the sulfur atom under the usual conditions.

3. 3-Diethylamino-5-aminothianaphthene-1-dioxide, which is a vinylog of N,N-diethyl sulfanilamide, and is closely related to bis-(4-aminophenyl)-sulfone has been prepared.

EVANSTON, ILLINOIS RECEIVED JANUARY 17, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

The Decomposition of Dibutylchloramine

BY GEORGE F WRIGHT

It has recently been found that aliphatic secondary amines can be nitrated in organic acid anhydrides when a chloride catalyst is present[1]; further, that the formation of the nitramine proceeds *via* the chloramine. Unsatisfactory yields of certain nitramines have been attributed to the instability of this intermediate.[2] It thus seemed worthwhile to re-investigate the stability of chloramines. Dibutylchloramine, which was chosen for this study, has been found to decompose to complex mixtures. Partial identification of these mixtures indicates that extensive intramolecular chlorination has taken place.

Chlorine, which has been reported as a product when chloramines are treated with excess hydrogen chloride,[3] was obtained in 68% yield from dibutylchloramine, I, in methanol. The expected dibutylammonium chloride, IV, was produced in 55% yield. It is not unreasonable to assume that this decomposition proceeds by formation from I of dibutylchloramine hydrochloride, II, which decomposes spontaneously in excess of hydrogen chloride to dibutylammonium chloride, IV.

The spontaneous decomposition of dibutylchloramine yielded dibutylammonium chloride released by reaction I → V. No chlorine was evolved. A liquid could be distilled out of the tar left when electropositive chlorine had disappeared, but this liquid showed a peculiar instability. Immediately after distillation a hydrochloride began to precipitate, but ceased after a certain amount had appeared. After redistillation the precipitation was resumed approximately to the same extent as before.

This distillate is considered to be a mixture of VI, VIII, X and XI which is formed by the action of chlorine released by initial decomposition of I. It is thought that the mixture loses hydrogen chloride until the basicity is reduced by hydrochloride formation, and that this loss is resumed after removal from the hydrochloride by distillation. The aldimine structure of the mixture has been confirmed by alkaline decomposition in presence of *p*-bromobenzenesulfonyl chloride to give the bromosulfonyl derivatives of monobutylamine.

Monobutylamine as its hydrochloride also was formed when the hydrochloride of the mixture was treated with methanol. The aldehydic fraction remaining after precipitation of the salt with ether was unstable, so it was treated with phenylhydrazine hydrochloride in ethanol. A distinctive blood-red color appeared which faded when the hydrochloride of ethylglyoxal precipitated. The color change is remindful of that which occurs when dichloroacetaldehyde is converted to glyoxal osazone.[4] Since the color change does not occur when ethylglyoxal is treated with phenylhydrazine, this hydrochloride, which is convertible to the known osazone,[5] is probably formed from

(1) Wright, *et al.*, *Can. J. Res.*, **26B**, 89, 257 (1948).

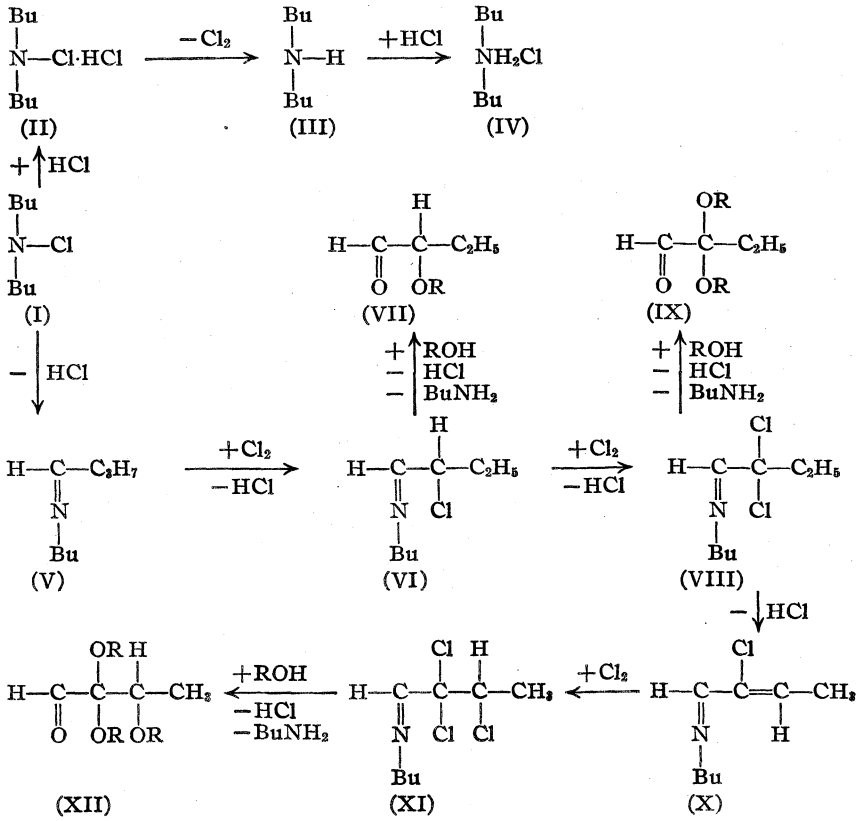
(2) K. K. Carroll and G. F Wright, *ibid.*, **26B**, 271 (1948).

(3) Houben, "Die Methoden der organischen Chemie," 3rd ed., Vol. 4, Georg Thieme, Leipzig, 1941, p. 569.

(4) G. Oddo and G. Cusmano, *Gazz. chim. ital.*, **41**, [II], 246 (1911).

(5) L. Wolff, *Ann.*, **288**, 20 (1895); E. Kolshorn, *Ber.*, **37**, 2476 (1904).

2,2-dichlorobutanal. On this basis the mixture must consist largely of VIII, and its analysis approximated that expected for VIII.



This analysis must, however, have been fortuitous, because in hot ethanol–hydrochloric acid a complex mixture of dinitrophenylhydrazones precipitated after a reproducible and characteristic induction period, presumed to involve alcoholysis. The least soluble compound in the complex mixture from dinitrophenylhydrazine treatment was, according to its analysis, the dinitrophenylosazone of ethoxyethylglyoxal, XII (R = Et, shown as its diethyl ketal). Substantiation for the constitution of XII was obtained when methanolic dinitrophenylhydrazine produced the homologous methyl ether (R = Me). Out of the remaining mixture only the most soluble compound could be identified by analysis; it was the 2,4-dinitrophenylhydrazone of 2-ethoxybutanal, VII. Thus evidence is at hand for three compounds in the postulated mixture, VI, VIII, X and XI.

The reactions I → IX seem to occur in one operation when dibutylchloramine is decomposed during fourteen hours in boiling ethanol. From the solution could be isolated (on the mole for mole basis) a 23% yield of monobutylamine, a 48% yield of dibutylamine, a 9% yield tentatively identified as *n*-butyl-N-butyramide; and finally ethylglyoxal was identified as its osazone. The ethylglyoxal must have been present as such or as its diethylketal, IX, since the red color was not observed during osazone formation.

The decomposition of dibutylchloramine in acetic acid was very slow at 25° but could be accelerated to completion (negative test for electropositive chlorine) in one hour by reaction at 90°. A 39% yield of dibutylammonium chloride was formed, as well as two distillable fractions. Neither of these was N-*n*-butylpyrrolidine.[6] The lower boiling of the two fractions was undoubtedly dibutylacetamide. The other fraction does not undergo the characteristic delayed precipitation with ethanolic dinitrophenylhydrazine.

The decomposition of dibutylchloramine in acetic anhydride was even more extensive than in the solvents recorded above. Reaction in this anhydrous medium was much more rapid than in acetic acid or ethanol, and was violent at 65°. A low yield of dibutylammonium chloride was produced when one or two equivalents of the anhydride were employed, but none was found when three equivalents were used.

The distillate from the residue was unstable. Partial separation provided a 21% yield of butyl butyramide,[2] at least 20% of dibutylacetamide, and two aldehydic fractions from which phenylhydrazine derivatives of ethylglyoxal were obtained.

Aid from the Canadian National Research Council is gratefully acknowledged.

Experimental[7a]

Dibutylchloramine with Hydrogen Chloride.—Five grams (0.0316 mole) of dibutylchloramine in 12 cc. of methanol was cooled to 0° while hydrogen chloride was passed through until saturation. The chlorine which was evolved amounted to 0.023 mole (68%). The residual salts remaining after evaporation of the solvent weighed 3.8 g. and after neutralization with alkali were identified by distillation as 0.02 g. of butylamine, 2.30 g. (55%) of dibutylamine and 0.04 g. of an oil which contained combined chlorine. Aldehydic material was lost during the evaporations, but a remaining trace gave a derivative with dinitrophenylhydrazine melting at 234°. According to its mixed melting point this was identical with the ethoxyethylglyoxal dinitrophenylosazone which is discussed later.

(6) G. H. Coleman and G. E. Goheen, THIS JOURNAL, **60**, 730 (1938).

(7a) All melting points have been corrected against known standards.

Dibutylchloramine with Sulfuric Acid–Water.—When 42.3 g. (0.26 mole) of dibutylchloramine was added to a mixture of 80 cc. (1.5 mole) *concd.* sulfuric acid and 30 cc. (1.67 mole) of water it was necessary to cool the mixture slightly. It was heated one day at 90° with strong evolution of chlorine, but at the end of this time, the electropositive chlorine test was negative. The whole was poured into ice and extracted with ether to remove a little oil which was discarded. The cooled aqueous layer was made basic with 135 g. of sodium hydroxide and was then extracted with ether and this solution dried with sodium hydroxide. Distillation yielded 20.3 g., b. p. 42–51° (11 mm.), $n^{25}D$ 1.4327, of N-butylpyrrolidine in 61% of the theoretical yield. This was redistilled at 155–157° (754 mm.) to free it from contamination with an impurity which contained chlorine. The distillate, which had the same refractive index, was identified by precipitation of N-butylpyrrolidine picrate from hydrochloric acid solution with saturated picric acid, m. p. 123–124.5°, after crystallization from 95% ethanol.[7]

Dibutylchloramine in Ethanol.—A solution of 16.3 g. (0.1 mole) of dibutylchloramine in 50 cc. of absolute ethanol became very dark after boiling for fourteen hours until a negative electropositive chlorine test was obtained. The ethanol was removed under 150 mm. pressure, the residue taken up in 2% hydrochloric acid and extracted three times with ether. This ether solution, dried with magnesium sulfate, was distilled to yield 1.79 g. boiling at 35–42° (0.25 mm.); $n^{25}D$ 1.4484. This was redistilled to remove a small first fraction, then a second fraction at 74–76° (10 mm.). When this main distillate was treated with phenylhydrazine and a little acetic acid in ethanol and then diluted with water, a precipitate (m. p. *ca.* 110°) appeared. This melted at 115° after crystallization from petroleum ether (b. p. 60–70°) and was the osazone of ethylglyoxal.[5]

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.2; H, 6.84; N, 21.0. Found: C, 71.8; H, 7.04; N, 20.7.

The aqueous liquor from which were obtained the acid insoluble fractions described above, was made basic to release an amine fraction. Upon distillation, this yielded 1.7 g. of monobutylamine $n^{25}D$ 1.3643, b. p. 78–80° (754 mm.), (23% of theoretical), and then 6.3 g. of authentic dibutylamine, b. p. 32° (0.25 mm.), $n^{25}D$ 1.4156 (48% of theoretical) and 1.3 g. of material, b. p. 70–78° (0.01 mm.), $n^{25}D$ 1.4413, m. p. −10°. According to boiling point and refractive index this fraction may be N-butylbutyramide. It would not react with dinitrophenylhydrazine in dilute ethanolic hydrochloric acid but on treatment of 0.2 g. overnight with 1 g. of *p*-bromobenzenesulfonyl chloride in 7 cc. of 10% alkali, it yielded 0.1 g. of *n*-butyl bis-*p*-bromobenzenesulfonimide, m. p. 107–114°. After crystallization from ethanol, this melted without depression at 115° when mixed with the authentic material.[8]

Thermal Decomposition of Dibutylchloramine.—It required six weeks at 38° before 4.5 g. (0.028 mole) of dibutylchloramine no longer gave an electropositive chlorine test. The brown residue was suspended in ether and filtered to remove 2.25 g. of dibutylammonium chloride (49% of theoretical) which was identified as its styphnate, m. p. 91.4–91.9°. The ether filtrate was distilled, finally at 0.01 mm. to yield 0.93 g., b. p. 40–47°, $n^{25}D$ 1.4534. This distillate precipitated a small amount of salt. It was redistilled *in toto* at 50° (0.006 mm.) $n^{25}D$ 1.4539.

Anal. Calcd. for $C_8H_{15}NCl_2$: C, 49.2; H, 7.75; N, 7.19. Found: C, 49.8; H, 8.05; N, 7.76.

When 0.489 g. (0.0025 mole) of this material was treated with 1.53 g. (0.006 mole) of *p*-bromobenzenesulfonyl chloride and 19.2 cc. (0.012 mole) of 5% aqueous sodium hydroxide at 0° and then shaken two hours at 25° a solid formed which was filtered off after neutralization of the alkali. It weighed 0.16 g. and melted at about 60°. Several crystallizations from hot ethanol raised this to 115.3°. The identical material could be prepared from the salt remaining after the N-butyldichlorobutaldimine was distilled under reduced pressure. This is evidently identical with the *n*-butyl-*bis*-bromobenzenesulfonimide reported with melting point of 116°.[8]

Anal. Calcd. for $C_{16}H_{17}NO_4S_2Br_2$: C, 37.6; H, 3.36; N, 2.74. Found: C, 37.9; H, 3.64; N, 3.26.

The compound designated above as N-butyldichlorobutanaldimine (5.72 g. 0.029 mole) was dissolved in 25 cc. of dry ether and treated with hydrogen chloride. No chlorine was evolved. After evaporation of the ether, the residue weighed 6.8 g. (quantitative yield). No satisfactory melting point of this material could be obtained. When it was dissolved in 17 cc. of methanol to which 250 cc. of dry ether was added a new precipitate appeared in smaller quantity (2.98 g.). It melted at 213–213.5° and according to analysis was butylammonium chloride in 97% yield.

Anal. Calcd. for $C_4H_{12}NCl$: C, 43.8; H, 11.03. Found: C, 43.4; H, 10.80.

This was identified by treatment of 1 g. (0.0092 mole) of salt with 3 g. (0.012 mole) of bromobenzenesulfonyl chloride and 40 cc. (0.05 mole) of 5% aqueous sodium hydroxide in the cold. This yielded 2.56 g. (97%) of N-butyl-*p*-bromobenzenesulfonamide, m. p. 56–57°, and was contaminated with the 116° compound described above. This was washed with carbon tetrachloride and crystallized twice from 1:4 benzene–petroleum ether (b. p. 60–70°) to melt at 54–54.5°. Since this is lower than that previously reported[7] (58°), the compound was identified by analysis.

Anal. Calcd. for $C_{10}H_{14}NSO_2Br$: C, 41.2; H, 4.84. Found: C, 41.5; H, 4.89.

When the methanol–ether solution, from which the butylammonium chloride was isolated, was evaporated to a small volume and diluted with water, a water-insoluble phase separated. Its ether solution, dried and distilled, yielded 0.37 g., b. p. 43–45° (12 mm.), $n^{25}D$ 1.4515. When this substance was treated with phenylhydrazine hydrochloride in ethanol, the suspension first turned yellow, then after five minutes was blood-red. This color disappeared by the next day to leave yellow crystals melting at 162°. This crop was crystallized from ethanol and then ground in dioxane to melt at 169–170.6°. It was slightly soluble in dilute hydrochloric acid. The compound was evidently a hydrochloride.

Anal. Calcd. for $C_{16}H_{19}N_4Cl$: C, 63.6; H, 6.36; N, 18.5. Found: C, 63.7; H, 6.57; N, 18.5.

When this compound was dissolved in ethanol and treated with aqueous sodium hydroxide and water, the precipitate melted at 110°. Crystallization from petroleum–ether (b. p. 60–70°) raised this to 114–115°. A mixed melting point with the osazone of ethylglyoxal was not lowered.

Crude "N-Butyl Dichlorobutaldimine" with Dinitrophenylhydrazine.—A suspension of 1.45 g. (0.0073 mole) of 2,4-dinitrophenylhydrazine in 150 cc. of ethanol and 3 cc. of concentrated hydrochloric acid was boiled with 1.18 g. (0.006 mole) of crude N-butyldichlorobutanaldimine. After one minute the clear solution became cloudy and a yellow precipitate began to appear. After fifteen minutes, this had become red. The suspension was filtered hot to remove 0.88 g. of orange-red precipitate, m. p. 232–234°. This was crystallized from dioxane (80 cc. per g.) as dark red prisms which melted at 241.1–241.6°. It contained no chlorine and is thought to be the osazone of 3-ethoxyethylglyoxal.

Anal. Calcd. for $C_{18}H_{20}N_8O_9$: C, 44.3: H, 3.69; N, 22.8. Found: C, 44.4; H, 3.67; N, 22.4.

When the ethanol solution (from which this osazone was filtered) was cooled, an orange precipitate weighing 0.25 g., m. p. *ca.* 200°, was obtained. This obvious mixture was crystallized thrice from dioxane (20 cc. per g.) to melt at 227.5–228°. The precipitate contained

(7) L. C. Craig and R. M. Hixon, THIS JOURNAL, **53**, 187 (1931).

(8) Ssolonina, *J. Russ. Phys.-Chem. Soc.*, **31**, 640 (1899).

chlorine. The analysis conformed most closely with that expected for 3-chlorobutanal 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{10}H_{11}N_4O_4Cl$: C, 42.0; H, 3.85; N, 19.5. Found: C, 42.7; H, 3.70; N, 18.9.

The ethanolic filtrate from which this compound was isolated when diluted with water, precipitated 0.17 g. of yellow material, m. p. *ca.* 85°, which was dissolved in hot ethanol to give a first crop, m. p. 185–187°, not further investigated. Further cooling yielded 0.05 g., m. p. 92.8°. This melting point was not raised by further crystallization from ethanol. The compound contained no chlorine.

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.6; H, 5.45; N, 18.9. Found: C, 48.1; H, 5.46; N, 19.1.

When this process with dinitrophenylhydrazine was carried out in methanol instead of ethanol, the hot methanol-insoluble precipitate melted at 234°. It was crystallized from boiling nitromethane (40 cc./g.), then extracted with boiling chloroform and finally recrystallized from nitromethane to melt at 242–244°. A mixed melting point of this dinitrophenyl osazone of 3-methoxyethylglyoxal with the ethoxy analog melted at 227°.

Anal. Calcd. for $C_{17}H_{16}N_8O_9$: C, 42.8; H, 3.28. Found: C, 43.1; H, 3.41.

When the thermal decomposition of dibutylchloramine was effected at higher temperatures the reaction was complete in ten days at 58° and in one day at 95°. The yield of dibutylammonium chloride was lower (40–37%) but the products were essentially the same.

Dibutylchloramine in Acetic Acid.—A solution of 70.6 g. (0.434 mole) of dibutylchloramine $n^{25}D$ 1.4348 in 86 cc. of acetic acid showed no tendency toward salt formation in one day, but when heated to 90°, the electropositive chlorine was consumed in one hour. The solvent was removed under 15 mm. pressure and the residue made alkaline with cold 15% aqueous sodium hydroxide. The oil which separated was taken up in ether, dried with magnesium sulfate and distilled to yield 22 g. (39% of theoretical) of dibutylamine, b. p. 30–36° (0.35 mm.), $n^{25}D$ 1.4162 (identified as the styphnate, m. p. 93°) and then 17 g., b. p. 88–92° (0.05 mm.), $n^{25}D$ 1.4500.

This fraction contained no N-butylpyrrolidine, since its dilute hydrochloric acid extract gave no picrate. When it was shaken with saturated sodium bisulfite, dried under vacuum, and redistilled, it first yielded 4.58 g., b. p. 120–5° (12 mm.), $n^{25}D$ 1.4480, which was evidently impure dibutylacetamide. The characterization of this compound was effected by one-day reflux with an equal weight of sodium methoxide in 5 volumes of methanol which yielded, on distillation, dibutylamine in 20% yield, b. p. 45–50° (12 mm.), $n^{25}D$ 1.4150. This was converted to dibutyl *p*-bromobenzenesulfonamide, m. p. 58–59°, for complete identification by mixed melting point.[9] In addition to this amine, purified dibutylacetamide, $n^{25}D$ 1.4436, b. p. 119–121° (12 mm.), was recovered.

The second and main fraction from this redistillation of the 17-g. portion boiled at 127–130° (12 mm.), $n^{25}D$ 1.4513. The compound contains chlorine. The analysis could not be correlated with any reasonable structure.

Anal. Calcd. for $C_9H_{18}NCl$: C, 61.6; H, 10.3; N, 7.97. Found: C, 61.1; H, 10.1; N, 7.88.

This product did not react with 2,4-dinitrophenylhydrazine in boiling dilute ethanolic hydrochloric acid. Some early fractions after removal of the dibutylamine in the initial distillation did, however, give ethoxyethylglyoxal dinitrophenylosazone, m. p. 238–240°, when treated under the same conditions.

Dibutylchloramine with Acetic Anhydride.—When a mixture of 48.9 g. (0.3 mole) of dibutylchloramine and 91.8 g. (0.9 mole) of acetic anhydride had reacted together for four hours a solid began to appear. After seven days, no more electropositive chlorine could be detected. The whole was poured into 500 g. of ice and neutralized with 140 cc. of 50% aqueous potassium hydroxide and extracted with ether. This ether solution was extracted with 35 cc. of 12% hydrochloric acid, then with aqueous sodium chloride solution, and was dried with magnesium sulfate for distillation. The acid washing liquor was made basic to yield 2.50 g. of oil, b. p. 109° (7 mm.), $n^{25}D$ 1.4439, but no dibutylamine.

The dried ether solution was distilled first at 7 mm. to yield 4 g. of chlorinated material, not identified, $n^{25}D$ 1.1456, and then at 0.5 mm. The principal distillate boiled at 78–95° and weighed 40 g. Although it was contaminated with material which contained halogen, its density at 20° (0.9) and its refractive index, $n^{25}D$ 1.4445, showed that it was essentially halogen-free. By contrast, final fractions of 4.4 g. (b. p. 95–98°) and 7.1 g. (b. p. 128°) were rich in halogen according to their refractive indices, $n^{25}D$ 1.4564 and $n^{25}D$ 1.4729, respectively.

The principal yield of 40 g. was refractionated with difficulty because of continual decomposition. From it was obtained 8.27 g., b. p. 73° (0.02 mm.), $n^{25}D$ 1.4407 melting at −8 to −10°. A mixed melting point with N-butylbutyramide, m. p. −7 to −6° was not lowered. This yield, 21% of theoretical, represents a minimum of the compound which actually was present. The remainder of the 40 g. of product was not positively identified but its refractive index, $n^{25}D$ 1.4437, indicated that it was dibutylacetamide.

Decomposition occurred during all of these distillations and these decomposition products, caught in a trap chilled to −75°, weighed 8.8 g. Fractionation of the material was very unsatisfactory owing to a tendency toward separation into two phases when the liquid was warmed above 60°. The second phase disappeared when the distillation temperature reached 94°. The distillation yielded two main fractions boiling at 90–92° (750 mm.), wt. 2.2 g. and 1.13 g., b. p. 115–125° (750 mm.). The first of these fractions, $n^{25}D$ 1.4580, could not be recognized by its analysis (32.1% carbon, 5.82% hydrogen) but it must have been largely ethylglyoxal since it gave a 60% yield of the monophenylhydrazone when it was treated with 1.1 equivalent of phenylhydrazine in ethanol. This compound, m. p. 133–136°, was purified by crystallization from ethanol and isopropyl ether to melt at 134.5–135.5°. It was then halogen-free.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.3; H, 6.88; N, 15.9. Found: C, 68.6; H, 7.10; N, 15.9.

When 0.3 g. of this ethylglyoxal phenylhydrazone was treated in boiling ethanol solution with 0.3 g. of phenylhydrazine and then filtered, after treatment with Darco decolorizing charcoal, an oil appeared after dilution with water and acetic acid. When hydrochloric acid was added, this solidified to a crystal mass melting at 158–159°. Crystallization from hot ethanol–chloroform mixture yielded the phenylosazone hydrochloride of ethylglyoxal, m. p. 168°. This was identified by mixed melting point.

The aldehydic fraction boiling at 115–125° contained chlorine but no nitrogen, $n^{25}D$ 1.3773, m. p. −8 to 0°. According to its analysis it might be 1-acetoxy-2-chloro-1,2-dihydroxybutane.

Anal. Calcd. for $C_6H_{11}O_4Cl$: C, 39.6; H, 6.1. Found: C, 39.4; H, 6.5.

When this material was treated with excess phenylhydrazine in ethanol plus a trace of acetic acid, it yielded the osazone of ethyglyoxal, m. p. 112–114°, authenticated by mixed melting point.

When 0.18 g. of this aldehydic distillate was treated with 0.18 g. of 2,4-dinitrophenylhydrazine in boiling ethanolic hydrochloric acid only a slight precipitate of ethoxyethylglyoxal 2,4-dinitrophenylosazone appeared. The main product, *ca.* 0.1 g., was precipitated by addition of water to melt at 155–175°. Repeated crystallization from boiling ethanol (30 cc./g.) raised this melting point to 194.5°. The compound contained chlorine, and is believed to be the hydrochloride of ethylglyoxal 2,4-dinitrophenylosazone.

(9) J. W. Suggitt and G. F Wright, THIS JOURNAL, **69**, 2073 (1947).

Anal. Calcd. for $C_{16}H_{15}N_3O_3Cl$: C, 40.0; H, 3.14; N, 23.3. Found: C, 39.9; H, 3.16; N, 23.3.

Summary

1. The spontaneous decomposition of dibutylchloramine yields dibutylammonium chloride and a distillable fraction believed to be a mixture of N-*n*-butyl mono-, di- and trichlorobutanaldimines with the second of these compounds predominating. Other compounds seem to be present, but phenyl and dinitrophenylhydrazones and osazones of these three have been isolated.

2. Decomposition of dibutylchloramine in alcohols follows the same course, but hydrolysis of the aldimines occurs to give monobutylammonium chloride and ethylglyoxal.

3. Decomposition of dibutylchloramine in acetic acid or its anhydride gives also dibutylacetamide and, in the latter reagent, N-*n*-butylbutyramide.

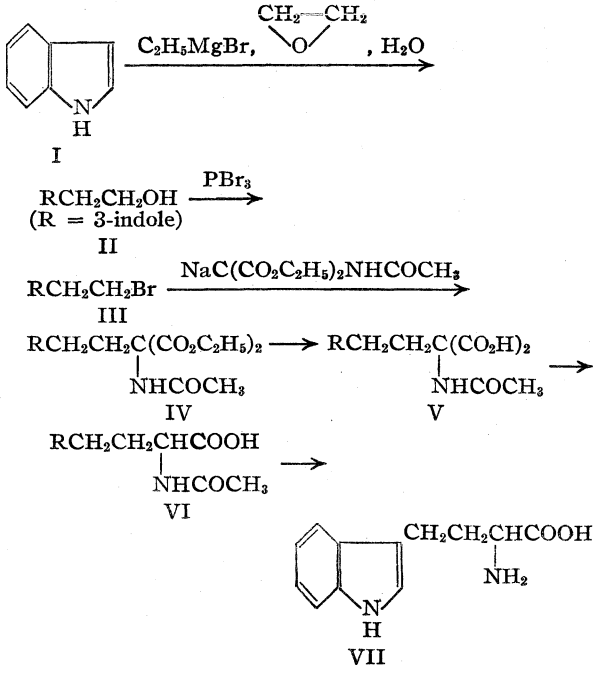
TORONTO, ONTARIO RECEIVED NOVEMBER 26, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Synthesis of *dl*-Homotryptophan

BY H. R. SNYDER AND FREDERICK J. PILGRIM

Homotryptophan [α-amino-γ-(3-indole)-butyric acid, VII] has been synthesized to permit physiological studies of the substance, particularly with reference to its possible action as an antimetabolite. The reactions employed in the synthesis are shown in the accompanying diagram.



Tryptophol (II) was prepared from indole (I) by the method of Oddo and Cambieri[1] which consists in the treatment of indole-magnesium bromide with ethylene oxide. Phosphorus tribromide was employed to convert tryptophol to the corresponding bromide (III) as described previously.[2] Alkylation of ethyl sodioacetylaminomalonate[3] by III was found to take place readily and in good yield (about 60%). The alkylation product, ethyl α-acetamino-α-carbethoxy-γ-(3-indole)-butyrate (IV), as obtained directly from the reaction mixture was of sufficient purity for conversion to V. Saponification of IV to the corresponding malonic acid, V, was effected by refluxing a mixture of IV with dilute sodium hydroxide solution; an almost quantitative yield of V was obtained.

Decarboxylation of the substituted malonic acid was brought about by refluxing an aqueous suspension of the material for several hours. *dl*-N-Acetylhomotryptophan (VI) was isolated from the mixture as the monohydrate. It was found convenient to purify the substance as the monohydrate; deacetylation of the pure monohydrate by hot dilute sodium hydroxide produced *dl*-homotryptophan (VII) in a state of high purity and in almost quantitative yield.

Experimental[4,5]

Ethyl α-Acetamino-α-carbethoxy-γ-(3-indole)-butyrate (IV).—To a solution prepared from 75 ml. of absolute ethanol and 0.58 g. of sodium were added 5.44 g. of ethyl acetaminomalonate and 5.50 g. of β-(3-indole)-ethyl bromide[2] (III). The reaction mixture was refluxed for fifteen hours with mechanical stirring. The hot mixture was filtered, the insoluble material on the filter was washed with 50 ml. of hot absolute ethanol, and the combined filtrate and washings were concentrated under reduced pressure to a small volume (about 20 ml.). The residue was cooled to 5° and filtered. The light yellow crystals on the filter were washed with 50 ml. of cold absolute ethanol to give a white product (IV), m. p. 161–163°; yield, 4.8 g. Concentration of the mother liquor to a few milliliters and addition of 30 ml. of anhydrous ether to the residue yielded a precipitate, mainly sodium bromide. Extraction of this precipitate with small portions of warm water left a residue of crude IV (0.3 g.), m. p. 153–156°. A dark oily residue was obtained when the mother liquor from the second crop of crude product was evaporated to dryness under reduced pressure. No additional product was isolated from the oily residue. The over-all yield of IV, sufficiently pure for conversion to V, was 5.1 g. (57.6%). A sample of pure IV, prepared for analysis by recrystallization from 95% ethanol, melted at 163–164°.

Anal. Calcd. for $C_{19}H_{24}O_5N_2$: N, 7.77. Found: N, 7.74.

(1) Oddo and Cambieri, *Gazz. chim. ital.*, **69**, 19 (1939).

(2) Hoshino and Shimodaira, *Ann.*, **520**, 19 (1935).

(3) (a) Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945); (b) Albertson and Archer, *ibid.*, **67**, 308 (1945).

(4) All melting points are corrected.

(5) Microanalyses by Miss Theta Spoor and Mr. Howard Clark.

α-Acetamino-α-carboxy-γ-(3-indole)-butyric Acid (V).—A reaction mixture consisting of 4 g. of IV, 2.2 g. of sodium hydroxide and 25 ml. of water was refluxed for four hours. The hot mixture was treated with Darco, filtered hot and the filtrate was then cooled to 5°. The addition of 5.7 ml. of cold concentrated hydrochloric acid to the filtrate caused precipitation of slightly pink crystals of V. The mixture, after standing fifteen hours at 5°, was filtered. The solid was washed with 50 ml. of ice-water and dried for two hours at 60°; m. p. 140–141°; yield 3.3 g. (97.5%) of material suitable for conversion to VI.

A sample of pure V, recrystallized from 30% ethanol, melted at 153–154°.

Anal. Calcd. for $C_{15}H_{16}O_5N_2$: N, 9.21. Found: N, 8.94.

α-Acetamino-γ-(3-indole)-butyric Acid (*dl*-N-Acetylhomotryptophan) (VI).—Decarboxylation of the substituted malonic acid V was readily effected by refluxing a suspension of 3.0 g. of V in 25 ml. of water for three hours. The homogeneous reaction mixture was cooled to 5° and made acidic (congo red paper) by the careful addition of 18% hydrochloric acid. The acetyl derivative (VI) separated from the acidic solution as an oil which slowly crystallized. The mixture was filtered and the crude product (2.0 g.) was recrystallized from 40% ethanol. The product isolated from this recrystallization was the monohydrate of VI, m. p. 112–113°; yield, 1.60 g. (58.3%).

Anal. Calcd. for $C_{14}H_{16}O_3N_2 \cdot H_2O$: N, 10.05. Found: N, 10.12.

For the above analysis the crystals were dried for two hours at 25° under 2 mm. pressure. When the crystals were finely pulverized and dried for an additional two hours at the same temperature and pressure the hydrate apparently decomposed to anhydrous VI.

Anal. Calcd. for $C_{14}H_{16}O_3N_2$: N, 10.77. Found: N, 10.53.

α-Amino-γ-(3-indole)-butyric Acid (*dl*-Homotryptophan) (VII).—Recrystallized *dl*-N-acetylhomotryptophan monohydrate (VI, 1.60 g.), sodium hydroxide (1.00 g.) and water (10 ml.) were combined and the solution was refluxed for twenty hours. The hot reaction mixture was treated with Darco, filtered and the filtrate was cooled to 5°. Glacial acetic acid (1.50 g.) was added to the filtrate which was then allowed to stand at 5° for twelve hours to ensure complete precipitation of the amino acid VII. The reaction mixture was filtered and the white solid was found to be almost pure *dl*-homotryptophan, m. p. 306–310°; yield 1.21 g. (96.5%). It was recrystallized from a large volume of 50% ethanol. The glistening platelets of pure VII melted sharply at 308° with decomposition.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.0; H, 6.47; N, 12.84. Found: C, 66.15; H, 6.51; N, 13.16.

Summary

dl-Homotryptophan [α-amino-γ-(3-indole)-butyric acid] has been synthesized *via* the sequence: indole, tryptophol, β-(3-indole)-ethyl bromide, ethyl α-acetamino-α-carbethoxy-γ-(3-indole)-butyrate, α-acetamino-α-carboxy-γ-(3-indole)-butyric acid, α-acetamino-γ-(3-indole)-butyric acid, *dl*-homotryptophan.

URBANA, ILLINOIS RECEIVED JANUARY 2, 1948

NOTES

Correlation of Rates of Halogenation of Methylbenzenes

BY FRANCIS E. CONDON

The rate of chlorination of toluene relative to that of benzene is 345[1]; relative to that at only one position in benzene, it is 345 × 6 = 2070. The product has been reported to be 42% *p*- and 58% *o*-chlorotoluene.[2] Hence the partial relative rate of chlorination of toluene at the para position is 0.42 × 2070 = 870; similarly, the ortho partial relative rate is (0.58/2) × 2070 = 600. The meta partial relative rate may be approximated as 5, which seems reasonable in view of the value of 3 found for meta nitration.[3]

If each of the methyls in a polymethylbenzene exerts the same activating influence as the one in toluene, a partial relative rate of chlorination at each available nuclear position may be calculated as a product of two or more partial relative rates, each corresponding to a methyl and its position. The rate for the polymethylbenzene relative to that for benzene is then one-sixth the sum of the partial relative rates for all available positions.

TABLE I

RELATIVE RATES OF HALOGENATION OF POLYMETHYLBENZENES (BENZENE = 1)

	p-Xylene	*o*-Xylene	*m*-Xylene	Mesitylene	Pentamethylbenzene
Calculated	2.0×10^3	2.5×10^3	2.4×10^5	1.6×10^8	13×10^8
Experimental[1]	2.2×10^3	4.6×10^3	4.3×10^5	1.8×10^8	7.8×10^8
	Pseudocumene	Hemimellitine	Durene	Prehnitene	Isodurene
Calculated	7.4×10^5	8.7×10^5	3.0×10^6	4.4×10^7	5.2×10^8

In *p*-xylene, for example, each of the four available positions is influenced by two methyls, one ortho and one meta. The calculated partial rela-

(1) De la Mare and Robertson, *J. Chem. Soc.*, 270 (1943).

(2) Wertyporoch, *Ann.*, **493**, 153–165 (1932); *C. A.*, **26**, 2177 (1932).

(3) Ingold, Lapworth, Rothstein and Ward, *J. Chem. Soc.*, 1959 (1931).

tive rate at each position is therefore 600 × 5 = 3000; and the rate for *p*-xylene relative to that for benzene is 4 × 3000/6 = 2000. Similarly, inasmuch as the single available position in pentamethylbenzene is influenced by one para, two meta, and two ortho methyls, the rate of chlorination of pentamethylbenzene relative to that of benzene is 870 × 5 × 5 × 600 × 600/6 = 1.3 × 10^9. Such calculated relative rates are compiled in Table I, together with available experimental values[1] for chlorination or bromination. The agreement between the calculated and the experimental values, which is good in view of the 350,000-fold range, inspires considerable confidence in the five values for which experimental confirmation is at present unavailable.

A product of relative rates as calculated above is mathematically related to a sum of activation energy differences calculated from Arrhenius-type equations for the individual rate constants

$$k = Ae^{-E/RT}$$

For

$$k_i/k = (A_i/A)e^{(E-E_i)/RT}$$

and

$$\Sigma(E - E_i) = \Sigma RT \ln (k_i/k) - \Sigma RT \ln (A_i/A) = RT \ln \Pi(k_i/k) - RT \ln \Pi(A_i/A)$$

If the several A terms are equal,[4] the relationship simplifies to

$$\Sigma(E - E_i) = RT \ln \Pi(k_i/k)$$

According to the theory of absolute reaction rates[5]

$$k = (KT/h)e^{-F/RT}$$

where K = Boltzmann constant, h = Planck constant, and F = difference in free energy between initial and activated states, or "activation free energy." Consequently, without any assumption of constancy for an A term, or "frequency factor"[5]

$$k_i/k = e^{(F-F_i)/RT}$$

and

$$\Sigma(F - F_i) = RT \ln \Pi(k_i/k)$$

so that a product of relative rates is simply related to a sum of activation free energy differences.

(4) *Cf.* Bradfield and Jones, *J. Chem. Soc.*, 1006, 3073 (1928); *Trans. Faraday Soc.*, **37**, 737 (1941).

(5) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

BARTLESVILLE, OKLAHOMA RECEIVED NOVEMBER 28, 1947

Liquid Nitrosyl Chloride as an Ionizing Solvent

BY ANTON B. BURG AND GEORGE W. CAMPBELL, JR.[1]

Liquid nitrosyl chloride is expected to be a fairly effective ionizing solvent, for its dielectric constant (18.2 at 12°)[1a] is comparable to that of liquid ammonia. The acid–base system would be defined by the neutralization equation $NO^+ + Cl^- \rightarrow NOCl$. As in the analogous case of carbonyl chloride,[2] the chloride ion should not be appreciably solvated, for the electronic structure of NOCl (resonance between $:\ddot{O}{=}\ddot{N}^+Cl^-$ and $:\ddot{O}{=}\ddot{N}{-}\ddot{Cl}:$)[1,3] will not be affected by an electron-donor so weak as chloride. In agreement with this prediction, potassium chloride is insoluble in liquid nitrosyl chloride, contributing no conductance effect.

The nitrosyl ion, on the other hand, should be solvated very strongly, on account of the resonance structures $\left[:\ddot{O}{=}\ddot{N}{-}\ddot{Cl}{-}\ddot{N}{=}\ddot{O}:\right]^+$, $\left[:\ddot{O}{=}\ddot{N}{-}\ddot{Cl}:\right]\ :\overset{+}{N}{\equiv}O:$, and $:O{\equiv}\overset{+}{N}:\left[:\ddot{Cl}{-}\ddot{N}{=}\ddot{O}:\right]$. Hence it is expected that nitrosyl salts, many of which have been recognized,[4] should be soluble in liquid nitrosyl chloride, with high electrical conductance.

Experimental Results.—These ideas have been tested in a preliminary investigation of the electrical conductance of solutions of typical nitrosyl salts in liquid nitrosyl chloride. The mononitrosyl salts $NOAlCl_4$, $NOFeCl_4$ and $NOSbCl_6$ are readily soluble strong electrolytes, as demanded by the theory (see Table I). The solvation is indicated by the reaction $NOAlCl_4(s) + NOCl(g) \leftrightarrows NOAlCl_4 \cdot NOCl(s)$, recently discovered in our laboratories by Donald E. McKenzie. The dissociation pressure of the product is approximately 240 mm. at 0°.

Less favorable results were obtained with $(NO)_2SnCl_6$, $(NO)_2TiCl_6$, and $(NOSO_4H)$, all of which appeared quite insoluble and non-conducting. Dinitrosyl pyrosulfate, $(NO)_2S_2O_7$,[5] showed a slight conductance which very slowly passed through a maximum (see Table II). Sulfuric acid was inert.

The inert character of potassium chloride was not changed by an "acid" solution of nitrosyl chloroantimonate, which, by analogy with carbonyl "acids" in carbonyl chloride, should have dissolved it. The reason might be a protective coating of $KSbCl_6$.

In an attempt to establish chloride ions in liquid NOCl, the base-action of water was tried. However, the water only dissolved without conductance and was recovered by evaporating the nitrosyl chloride. The usual hydrolysis reaction $H_2O + 2NOCl \rightarrow NO + NO_2 + 2HCl$ is slow at room temperature and the products are nonconducting in nitrosyl chloride.

(1) This note is based upon a thesis submitted by George W. Campbell, Jr., to the Graduate Faculty of the University of Southern California, in partial fulfillment of the requirements for the degree of Master of Science, June, 1947.

(1a) Ketelaar, *Rec. trav. chim.*, **62**, 289 (1943).

(2) (a) Germann and Gagos, *J. Phys. Chem.*, **28**, 965 (1924); (b) Germann and Timpany, *ibid.*, **29**, 1423 (1925); (c) Germann and Birosel, *ibid.*, **29**, 1469 (1925); (d) Germann, THIS JOURNAL, **47**, 2465 (1925); (e) Germann and Timpany, *ibid.*, **47**, 2275 (1925).

(3) Ketelaar and Palmer, *ibid.*, **59**, 2629 (1937).

(4) (a) Willke-Dörfurt and Balz, *Z. anorg. allgem. Chem.*, **159**, 219 (1927); (b) Gall and Mengdehl, *Ber.*, **60B**, 86 (1927); (c) Rheinboldt and Wasserfuhr, *ibid.*, **60B**, 732 (1927); (d) Angus and Leckie, *Proc. Roy. Soc.* (*London*), **A150**, 615 (1935); (e) Klingenberg, *Rec. trav. chim.*, **56**, 749 (1937).

(5) Jones, Price and Webb, *J. Chem. Soc.*, **135**, 312 (1929).

Methods and Numerical Results.—All reagents were prepared and handled with complete exclusion of moisture. The nitrosyl chloride was prepared by the usual reaction $NOSO_4H + HCl \rightarrow H_2SO_4 + NOCl$, and purified by means of a helix-packed column. With electrodes of bright platinum wire 1 mm. thick, having 12 mm. exposed length, and 6 mm. apart, polarization effects caused a 15% uncertainty in the evaluation of the cell constant (0.78) by reference to aqueous KCl, but the various NOCl solutions gave results consistent to 1%. These results accordingly are presented in Tables I and II for purposes of comparison.

TABLE I

CONDUCTANCES IN LIQUID NITROSYL CHLORIDE

Solute	Molarity	Temp., °C.	Spec. cond., mhos.	Molar cond.
$NOAlCl_4$	0.098	−20	1.17×10^{-2}	119
$NOFeCl_4$	.0099	−20	1.34×10^{-3}	136
$NOFeCl_4$	.0094	−21	1.26×10^{-3}	134
$NOFeCl_4$	.0094	−44	1.00×10^{-3}	106
$NOSbCl_6$	.140	−20	2.35×10^{-2}	168
$NOSbCl_6$	.140	−44	2.20×10^{-2}	157
NOCl	Pure	−20	2.88×10^{-6}	...

TABLE II

CONDUCTANCES OF $(NO)_2S_2O_7$ (SATD. IN NOCl) AT −20°

Time, hr.	0	0.75	2	15	46
Spec. cond. $\times 10^6$	4.95	25.0	48.8	23.8	14.7

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES 7, CALIFORNIA

RECEIVED DECEMBER 11, 1947

The Effect of Sulfur Fluorides on the Viscosity of Sulfur

BY R. FANELLI

Recently, it was shown,[1,3] that the halogens, chlorine, bromine, iodine and also hydrogen sulfide and hydrogen persulfides, even when present in minute amounts, reduce the viscosity of sulfur above 160°. The degree of effectiveness decreased, with respect to the halogens, in the order shown. It was also indicated that the increasing viscosity of pure sulfur with rise in temperature might be due to polymerization of sulfur into long straight chains and that reduction of the viscosity was due to the rupture of these chains by the halogens which take up terminal positions of the segments. For example, in the case of chlorine added in the form of sulfur chloride we have

$$S_n(\text{chain}) + S_2Cl_2 \longrightarrow Cl\text{–}S\text{–}S\text{–}S \cdots S\text{–}S\text{–}SCl \text{ and/or } Cl\text{–}S\text{–}S\text{–}S \cdots S\text{–}S\text{–}S.$$

Sulfur mixtures containing 2% chlorine give viscosities under 15 centipoises throughout the entire liquid range, 115–445°. This is in sharp contrast with the maximum viscosity of pure sulfur, 93,200 centipoises, at 186–188°.

Fluorine was not tried in the earlier experiments because of the difficulty in obtaining this element. It was assumed, however, that because of its position in the halogen group it would be much more effective than chlorine. Recently, sulfur hexafluoride became available commercially and it was used in the same manner as sulfur chloride. Because of its high thermal stability, sulfur hexafluoride, if effective, would be an attractive reagent for reducing the viscosity of sulfur.

Experimental

Quantitative data were not obtained as the nature of the work was exploratory. The effect of the sulfur fluorides was determined by visual comparison of the fluidity of the treated sulfur with that of pure sulfur[2] which at 180–195° shows very little or no flow in the space of a few minutes.

Sulfur hexafluoride was bubbled for five and one-half hours through pure sulfur heated to 310° during which period little, if any, decrease in viscosity was noted. On cooling from 310 to 194° with the gas still bubbling through, the sulfur gelled indicating that the sulfur hexafluoride was comparatively ineffective in reducing the viscosity of sulfur. Apparently the stability and inertness of the hexafluoride is such that its reaction with the long sulfur chains is negligible under the conditions of the experiment.

The direct fluorination of sulfur gives in addition to the hexafluoride much smaller and variable concentrations of SF_4, S_2F_2, and (about 1%) S_2F_{10}. As revealed by Schumb,[4] these lower fluorides are removed before the purified hexafluoride is compressed into the cylinders. These lower fluorides are less stable and more reactive than the hexafluoride and might react with the long sulfur chains to appreciably reduce the viscosity.

The effect of the gases SF_4 and S_2F_2 was determined by heating in an electric furnace mixtures of pure sulfur with metallic fluorides in rotating, sealed, heavy-walled Pyrex tubes (free volume about 15 cc.). For the preparation of SF_4 the following reaction, reported to yield this compound,[4–7] was employed

$$4CoF_3 + S \longrightarrow 4CoF_2 + SF_4$$

Under the conditions of this experiment, probably some of the cobaltous fluoride was converted to sulfide. For the formation of S_2F_2 two reactions reported to yield this halide[6,7] were tried

$$2HgF + 3S \longrightarrow Hg_2S + S_2F_2$$
$$2AgF + 3S \longrightarrow Ag_2S + S_2F_2$$

(1) R. F. Bacon and R. Fanelli, THIS JOURNAL, **65**, 639 (1943).
(2) R. F. Bacon and R. Fanelli, *Ind. Eng. Chem.*, **34**, 1043 (1942).
(3) R. Fanelli, *ibid.*, **38**, 39 (1946).
(4) W. C. Schumb, *ibid.*, **39**, 421 (1947).
(5) J. Fischer and J. Werner, *Z. angew. Chem.*, **42**, 810 (1929).
(6) J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. X, Longmans, Green & Company, London, England, 1930, p. 631.
(7) Don M. Yost and Horace Russell, Jr., "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1944, pp. 295 and 299.

Each tube contained 7 g. of pure sulfur mixed separately with 0.3 g. and 1.0 g. of CoF_3; 0.3 g. and 1.0 g. of HgF; 0.5 g. and 1.0 g. of AgF. At the end of the experiments, all tubes were under fairly high pressure indicating formation of the gases had taken place. Only after prolonged heating (about forty-eight hours at 180–440°) was a slight reduction of the viscosity noted.

These experiments lead to the opinion that the observed failure of the sulfur fluorides to greatly affect the viscosity of sulfur is just one more instance of the abnormal behavior of fluorine and its compounds when viewed in comparison with the other halogens.

TEXAS GULF SULFUR CO., INC.
NEW YORK 17, N. Y. RECEIVED DECEMBER 30, 1947

The Melting Point of Mustard Gas

BY W. A. FELSING, C. A. HUNTING AND S. D. FELL

Recently du Vigneaud and Stevens[1] reported a study of the preparation and purification of mustard gas (*bis*-(β-chloroethyl) sulfide) and its action on yeast. They purified the mustard by three recrystallizations from absolute ethanol and once from petroleum ether; the product had a melting point of 14.5°. The authors also cite references to other reliable melting point determinations found in relatively recent literature (*i. e.*, 14.4° and 14.5°).

In Chemical Laboratory Report No. 369, Edgewood Arsenal, Edgewood, Md., dated November 29, 1918, the authors of this note reported the purification and the melting point of mustard gas. Crude Levinstein mustard gas, melting at 8–9°, was distilled at 10 mm. pressure, yielding a distillate melting at 13.6°. This material was thrice distilled at pressures below 10 mm. and subjected to partial freezing. It was collected on a Buchner filter and the adhering liquid was removed rapidly by suction. The collected crystals were melted and again the resulting liquid was partially re-frozen and the crystals collected as before. In all, the crystals were partially frozen, drained and remelted seven times. The final product weighed about 750 g. (original volume of distilled mustard gas was about 1 gallon).

The melting point of the purified mustard gas was determined by the usual procedure of taking temperature readings every thirty seconds until every trace of the crystals had disappeared. The melting point was determined graphically from a time–temperature plot. The melting point apparatus and the thermometer were kindly loaned by the Physical Chemistry Division of Johns Hopkins University. The short-range thermometer, whose ice-point was carefully checked and which was calibrated by the Physikalische Technische Reichsanstalt (P.R.T. No. 26260) was calibrated in 0.1° and temperatures could be estimated to 0.02° by the aid of a magnifier. Two series of determinations yielded a melting point of 14.45° and one of 14.44°.

Both of these values agree markedly well with the values given and cited by du Vigneaud and Stevens.

This note was suggested as a historical record by Chemical Corps Technical Command, Army Chemical Center, Md.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TEXAS
AUSTIN 12, TEXAS RECEIVED JANUARY 9, 1948

(1) du Vigneaud and Stevens, THIS JOURNAL, 69, 1808 (1947).

The Preparation of *p*-Dimethylaminobenzoic Anhydride

BY WILLIAM S. FONES

In connection with other work under way in this Laboratory it was necessary to prepare *p*-dimethylaminobenzoic anhydride. By heating *p*-dimethylaminobenzoic acid in acetic anhydride V. Meyer and Askenasy[1] isolated a substance (m. p. 109°) that analyzed correctly for an addition complex consisting of one molecule of *p*-dimethylaminobenzoic anhydride and one of acetic anhydride. This work was repeated by Van Der Haar,[2] who reported the complex (m. p. 109°) lost acetic anhydride when heated above its melting point to yield a substance sintering at less than 200° and melting at 218°. He assumed the latter material to be the free anhydride.

This assumption is shown to be in error by the present work. The anhydride was prepared by the action of phosphorus pentoxide on *p*-dimethylaminobenzoic acid in boiling xylene (method A) or by adding phosphorus oxychloride to a solution of *p*-dimethylaminobenzoic acid and triethylamine in chloroform (method B). The product from either reaction upon recrystallization from benzene had a m. p. of 157–159° (cor.); a mixed melting point determination showed no depression. By method A the anhydride was obtained in a yield of 30% based on acid used with a 36% recovery of unreacted acid whereas a 50% yield was obtained by method B but no starting material was recovered.

The pure compound gave the expected analysis and was further characterized by conversion to the known methyl *p*-dimethylaminobenzoate,[3] and *p*-dimethylaminobenzamide[4] through the action of methanol and ammonia, respectively.

Experimental

***p*-Dimethylaminobenzoic Anhydride (Method A).**—To a stirred suspension of 9.1 g. of *p*-dimethylaminobenzoic acid in 450 ml. of refluxing *m*-xylene there was added 8 g. of phosphoric anhydride. Stirring and refluxing were continued for seven hours with an additional 8-g. portion of phosphoric anhydride being added at the end of the first,

(1) V. Meyer and P. Askenasy, *Ber.*, **26**, 1365 (1893).
(2) A. W. Van Der Haar, *Rec. trav. chim.*, **47**, 324 (1928).
(3) John Johnston, *Proc. Roy. Soc.* (*London*), **A78**, 82 (1906).
(4) German Patent 77,329 (1892); *Frdl.*, **4**, 173 (1899).

third and fifth hours. After standing overnight the reaction mixture was heated to boiling and filtered. The filter cake was dissolved in water, made slightly alkaline with dilute sodium hydroxide and acidified with acetic acid to precipitate 3.3 g. (36%) unreacted *p*-dimethylaminobenzoic acid. The xylene filtrate was concentrated and cooled to yield 4.1 g. of crystals, m. p. 147–160°. This material was taken up in chloroform, extracted with sodium bicarbonate solution and dried. Stripping of the solvent followed by recrystallization of the residue from benzene gave 2.6 g. (30%) of *p*-dimethylaminobenzoic anhydride, m. p. 157–159° (cor.).

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.3; H, 6.4; N, 9.0. Found: C, 69.6; H, 6.4; N, 8.8.

Method B.—To a solution of 16.0 g. of *p*-dimethylaminobenzoic acid and 60 ml. of triethylamine in 150 ml. of chloroform there was added dropwise 11.7 g. (7.0 ml.) of phosphorus oxychloride. After the initial reaction subsided the solution was heated to reflux for ten minutes and allowed to stand one hour at room temperature. The chloroform solution was extracted with ice-cold dilute sodium hydroxide solution and filtered through anhydrous sodium sulfate. Upon concentration and cooling the chloroform solution deposited 9.6 g. of crystals, m. p. 148–157°. Two recrystallizations of this material from benzene gave 7.5 g. (50%) of *p*-dimethylaminobenzoic anhydride, m. p. 157–159° (cor.), identical with that obtained by method A as evidenced by mixed melting point determination.

Acidification of the alkali extract with acetic acid did not yield any recovery of *p*-dimethylaminobenzoic acid.

Methyl *p*-Dimethylaminobenzoate.—In a sealed tube there was heated for three hours at 100° 0.5 g. of *p*-dimethylaminobenzoic anhydride and 25 ml. of methanol. The reaction mixture was poured into cold dilute sodium hydroxide to dissolve the *p*-dimethylaminobenzoic acid and to precipitate the ester which was collected by filtration. There was thus obtained 0.23 g. (80%) of methyl *p*-dimethylaminobenzoate, m. p. 99–102° (lit. 102°).[3] Acidification of the alkali extract gave 0.18 g. of *p*-dimethylaminobenzoic acid.

***p*-Dimethylaminobenzamide.**—A solution of 0.53 g. of *p*-dimethylaminobenzoic anhydride in 25 ml. of chloroform was saturated with ammonia and then heated in a sealed tube for two hours at 70° and two additional hours at 100°. The chloroform was stripped and the residue recrystallized from water to give 0.21 g. (76%) amide, m. p. 203–206° (lit. 206°).[4]

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF HEALTH
BETHESDA 14, MARYLAND RECEIVED FEBRUARY 4, 1948

Preparation of 2-Phenylbenzoxazole

BY LUCAS C. GALATIS

The preparation of 2-substituted benzoxazoles by heating appropriately *o*-substituted anilines with an organic acid is a well-known reaction. In the case of benzoxazole, apparently the reaction has been used only for the preparation of the parent compound from *o*-aminophenol and formic acid.[1] It has now been found that 2-phenylbenzoxazole (I) may be prepared by the general method by heating *o*-aminophenol with benzoic acid. Purification of crude I presents difficulty especially because of the persistence of a highly fluorescent by-product which has been commonly encountered when I was prepared by heating aminophenol with various benzoyl derivatives.[2] By choosing ligroin as a solvent, I could be extracted from the reaction product free from other by-products, except traces of the above mentioned fluorescent substance, which were in their turn eliminated by taking advantage of a difference in basicity between I and the latter. The fluorescent matter accumulated in the residue of the ligroin extraction was then easily separated and identified as triphen-dioxazine, an oxidation product of *o*-aminophenol.[3]

Experimental

In a large test-tube an intimate mixture of 10.9 g. of *o*-aminophenol and 15 g. of benzoic acid is melted in an oil-bath at 160°. The tube is then fitted with a stopper carrying a gas inlet tube and an exit tube bent downward. The temperature is raised to 195° while passing carbon dioxide through the tube, at which temperature rapid evolution of water occurs. After two hours the temperature is raised to 200–205° and held at that point for ten hours. Every two or three hours the sublimate is melted down from the walls of the tube. After cooling to 130° the melt is poured with stirring into cold water. The insoluble material is ground in a mortar with 2 *N* sodium hydroxide. The dark colored residue is warmed with 300 ml. of ligroin (b. p. 80–120°) until extraction of 2-phenylbenzoxazole from contaminating black material is complete. After filtering, the solution which is strongly fluorescent, although it does not contain but traces of the fluorescent matter, is shaken with two drops of concd. hydrochloric acid which removes the fluorescent impurity as a violet-blue solution. The ligroin solution is filtered through a dry gravity filter and shaken with 80 ml. of concd. hydrochloric acid which removes the benzoxazole. The acid extract is diluted with stirring with four or five volumes of cold water yielding 14 g. (72%) of 2-phenylbenzoxazole as a white or slightly green powder melting at 101°. A perfectly white product may be obtained by distillation of the material after the sodium hydroxide treatment with superheated steam (180°) followed by the treatment with hydrochloric acid in ligroin.

In order to isolate the main quantity of the fluorescent substance, the black residue from the ligroin extraction is repeatedly extracted with boiling alcohol for removal of a red contaminant, and then with boiling xylene. On cooling, the intensively fluorescent xylene solution deposits small red brown needles with a metallic cast. This shows all the properties of triphen-dioxazine including the characteristic production of green vapor on heating at 300°.

Acknowledgement.—The author is indebted to Mr. Nicholas G. Dovletis for his assistance during this work.

(1) Ladenburg, *Ber.*, **10**, 1124 (1877).
(2) Skraup, *Ann.*, **419**, 76 and 82 (1919).
(3) Seidel, *Ber.*, **23**, 182 (1890).

CHEMICAL LABORATORY
OF THE ADMIRALTY
ATHENS, GREECE RECEIVED SEPTEMBER 3, 1947

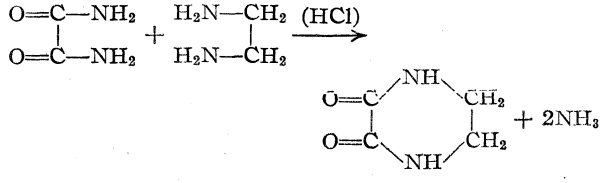
Synthesis of 2,3-Diketopiperazine

BY C. E. GOULDING, JR.,[1] AND C. B. POLLARD

Two prior methods for the preparation of 2,3-diketopiperazine by the reaction between diethyl oxalate and 1,2-ethanediamine[2,3] have been reinvestigated in this Laboratory and found to afford yields of only about 1 and 10%, respectively. A new method involving the reaction of oxamide and 1,2-ethanediamine in 1,4-dioxane was therefore

(1) Present address: Caracas, Venezuela.
(2) Hofmann, *Ber.*, **5**, 247 (1872).
(3) Van Alphen, *Rec. trav. chim.*, **54**, 937 (1935).

undertaken which, using anhydrous reagents and vigorous stirring, has afforded yields of approximately 50%. The reaction is presumably



Procedure.—To 63 g. of finely powdered oxamide in a three-necked flask, 60 g. of anhydrous 1,2-ethanediamine in 250 ml. of anhydrous 1,4-dioxane, and thereafter as a catalyst, 2 ml. of concentrated hydrochloric acid was added. The mixture was heated to reflux and stirred with a collapsible, stainless steel stirrer which swept the sides of the flask for twenty-four hours until ammonia was no longer evolved.

The 1,4-dioxane was removed by evaporation *in vacuo*, the solid material macerated in 3 liters of boiling water and filtered. The filtrate was evaporated on a steam-bath to 300 ml. and the solid 2,3-diketopiperazine removed by filtration. The yield was 41.1 g. (or 50.3%) melting with decomposition at 285°. The product was identified by means of the 1,4-dinitrate-2,3-diketo derivative, m. p. 150°, which, mixed with an authentic sample of the 1,4-dinitrate derivative, melted at 149–150°.

UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA RECEIVED SEPTEMBER 12, 1947

Trifluoroethanol

BY ALBERT L. HENNE, ROBERT M. ALM AND MALCOLM SMOOK

CF_3CH_2OH has been prepared by Swarts[1] by reduction of trifluoroacetic anhydride under pressure, on a platinum catalyst. Although no one has ever voiced any doubt, this reduction has never been successfully repeated, due apparently to Swarts' failure appropriately to describe his catalyst. The reduction of CF_3CONH_2 is also mentioned by Swarts, and has been successfully developed by Gilman[2]; we duplicated Gilman's 77% yield, but had to consume 5 g. of platinum per mole of amide. Scherer[3] has made trifluoroalcohol by treating CF_3CH_2Cl with fused potassium acetate at 225°, and saponifying the resulting acetate. We have repeated this work and found the yields exceedingly sensitive to the reaction temperature, an experience duplicated by other laboratories.

We are now recommending the reduction of a derivative of trifluoroacetic acid (the ester or the acyl halide) with lithium aluminum hydride as the most convenient and efficient way to make the alcohol. Our preferred procedure is given.

Preparation of CF_3COCl.—A two-liter, three-necked flask was fitted with a dropping funnel, a mercury-sealed stirrer and a coiled reflux condenser with outlet leading to a 500-cc. receiver cooled in Dry Ice. The apparatus was thoroughly dried by flaming while sweeping with dry nitrogen; the inlet and outlet were protected by drying tubes. Benzoyl chloride (679 g. or 4.83 moles) was delivered into the flask; then over a one-hour period, trifluoroacetic acid (417 g. or 3.66 moles) was dropped in, with constant stirring. After completing the addition, the dropping funnel was replaced by a thermometer and the mixture heated overnight, up to 150°. The crude trifluoroacetyl chloride distilled through the reflux condenser; its rectification gave 380 g. (2.87 moles = 79%) of pure product, b. p. −27°, and 47 g. (0.41 mole = 11%) of unreacted acid.

Preparation of CF_3CH_2OH.—A five-liter, three-necked flask was fitted with a Dry Ice reflux condenser, a sealed stirrer and a gas inlet tube. The equipment was dried by flaming and sweeping with dry nitrogen. Solid lithium aluminum hydride (54 g. or 1.42 moles) was placed in the flask and covered with three liters of rigorously dried ether; while continuously stirring, CF_3COCl was led into the liquid as fast as the return from the reflux condenser would permit; the addition of 350 g. (2.64 moles) took about three and one-half hours. After this the mixture was refluxed for one more hour on an electric heating mantle. The inlet tube was replaced by a dropping funnel, then 200 cc. of water was slowly added to hydrolyze the excess of hydride. This made a clear solution and a precipitate of white curds. The solution was decanted into 1500 cc. of 6 *N* sulfuric acid containing ice. The ether layer was separated, then used in three portions for extractions of the aqueous layer; the latter was poured back onto the solid residue in the flask, then ether extracted. From the ether extracts, distillation isolated 285 g. of material boiling at 74–75°, which is a mixture of the trifluoroalcohol with 5–10% of water. Distilling from concentrated sulfuric acid gives the desired anhydrous alcohol, CF_3CH_2OH, b. p. 74°. The net yield is 85%.

In later experiments an excess of trifluoroacetyl chloride was used instead of an excess of hydride, because the latter was not readily available; a utilization of about 95% of the hydride was thus obtained, but this procedure is not recommended.

DEPARTMENT OF UNIVERSITY
OHIO STATE UNIVERSITY
COLUMBUS, OHIO RECEIVED FEBRUARY 16, 1948

(1) Swarts, *Bull. soc. chim. Belg.*, **43**, 471 (1934).
(2) Gilman, THIS JOURNAL **70**, 1281 (1948).
(3) Scherer, Scientific Zetko Exchange, P. B. Report No. 765.

Production of Radioactive Carbon Monoxide and Phosgene from Barium Carbonate

BY J. L. HUSTON[1] AND T. H. NORRIS[1]

Recently Kummer[2] has recommended the preparation of radioactive carbon monoxide by exchanging over a hot tungsten filament the C^{14} in a small amount of carbon dioxide with the inactive carbon in a large quantity of ordinary carbon monoxide. Some time ago we had occasion to prepare radioactive carbon monoxide ($C^{14}O$) as the first step in the preparation of radioactive phosgene which was to be used in biological experiments. Since our procedure involves no dilution of the radioactive carbon, and can be accomplished in less time than Kummer's procedure, we are presenting it at this time.

Our method involved the reduction of carbon dioxide to carbon monoxide by hot zinc, which was discovered by Noack.[3] Although this method was considered the most suitable for our purposes it should be pointed out that carbon monoxide can be prepared in good yield by heating alkaline earth

(1) Present address: Chemistry Department, Oregon State College, Corvallis, Oregon.
(2) Kummer, THIS JOURNAL, **69**, 2239 (1947).
(3) E. Noack, *Ber.*, **16**, 75 (1883).

carbonates directly with zinc,[4] and without intermediate conversion to carbon dioxide. The phosgene was then prepared photochemically by the reaction of this carbon monoxide with chlorine. Our preparations were made in the apparatus diagramed in Fig. 1.

Experimental Part

Preparation of Carbon Monoxide.—About 50 g. of reagent zinc was cleaned with dilute acetic acid, washed, dried and placed in tube E. This cleaning was necessary since otherwise the hot zinc would evolve slowly a small quantity of permanent gas (presumably carbon monoxide from decomposition, with reduction, of zinc carbonate). Radioactive barium carbonate (~20 mg. was convenient for our apparatus) was placed in I, and the entire system evacuated. Tube E was surrounded by a small electric furnace and baked out overnight at about 370° (necessary for each fresh batch of zinc only). Temperature was adjusted manually by means of a Variac and read with a thermocouple connected to a millivoltmeter.

With the system open to the high vacuum, radioactive carbon dioxide was next generated by dropping 85% phosphoric acid into I and, after passing through phosphorus pentoxide in H, was trapped in F with liquid air. Stopcock G was now closed and the small quantity of air introduced by the phosphoric acid was pumped off. The temperature of E was raised to 385° and thereafter held within 5° of this temperature: the reaction is too slow at 370° and above 400° there is considerable tendency for the tube E to become plugged, due probably to sublimation and recrystallization of the zinc.

The stopcocks leading to the pumping system were closed; next the liquid air was removed from F and the pressure of carbon dioxide in the system (F and the capillary line extending to, and including, the capillary monometer C) was measured. Carbon monoxide subsequently was stored in the same portion of the apparatus, as it was generated, its pressure thus serving as a measure of the yield.

The two-liter Töpler pump D was now used to pump the carbon dioxide several times, alternately clockwise and counterclockwise, through the hot zinc in E. After each traverse through the zinc, unreacted carbon dioxide was trapped with liquid air in the appropriate spiral S_1 or S_2 while carbon monoxide was pumped into F and its pressure measured with manometer C. The first traverse through the zinc would produce about a 50% yield of carbon monoxide and 5 or 6 more passes made the conversion quantitative within the limit of error in reading the manometer (0.4%). The process, from generation of carbon dioxide to complete conversion to monoxide, required three to four hours.

Preparation of Phosgene.—Bulb B (~500 cc.) contained chlorine (introduced on another gas-handling system) equal in amount to about 2.5 times the stoichiometric quantity required for union with the carbon monoxide. This chlorine was frozen down into the bottom of the bulb with liquid air and the carbon monoxide in F was introduced with the Töpler pump, a small fraction (<2%) remaining in the capillary line. B was then isolated from the line and after removal of the liquid air the gas mixture was irradiated with an ultraviolet mercury vapor lamp. Spiral S_4 was then cooled with liquid air and B was opened to high vacuum *via* this spiral S_4, a small amount of residual carbon monoxide thus being removed from the condensable gases (phosgene and chlorine) which were trapped in the spiral.

The system was again isolated and the mixture of phosgene and chlorine distilled with liquid air to A which contained antimony. Bulb A and spiral S_3 were then closed off from the rest of the system, removed from the line as a unit, warmed to room temperature, and shaken to remove excess chlorine. The antimony appears to react with phosgene to a slight extent to produce a little

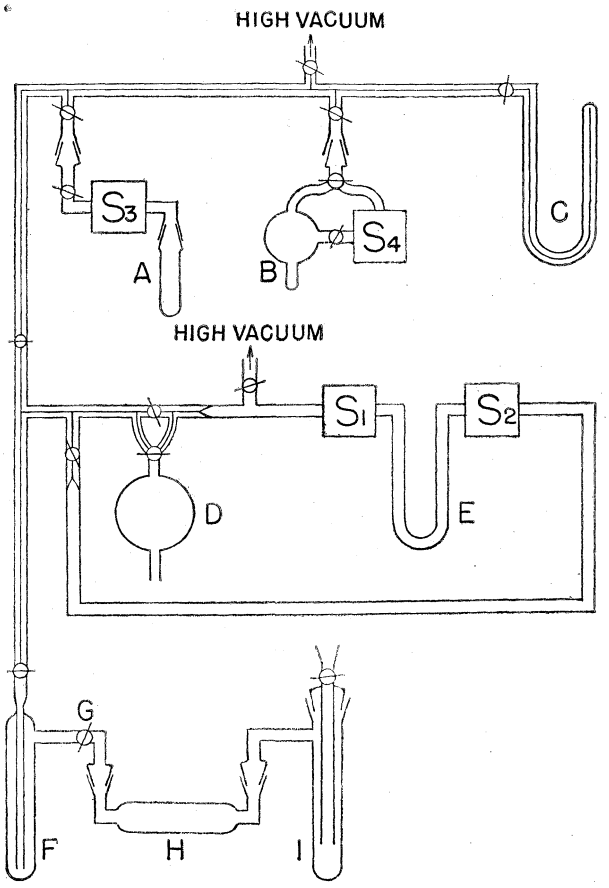


Fig. 1.

carbon monoxide; after A and spiral S_3 were re-attached to the line permanent gas was pumped off while the phosgene was trapped with liquid air in spiral S_3. After distillation to F the pressure of phosgene was read and the yield thus measured. In five runs the yields ranged from 80.0% to 84.5%, based on the original barium carbonate.

It should be noted that since the equilibrium $2CO = C + CO_2$ lies well to the right at these temperatures, reduction to carbon is thermodynamically possible. That our yields of carbon monoxide were quantitative, within the limits of error of our measurements, is in accord with an observation made by Maier and Ralston[5] in their quantitative measurements on the equilibrium $ZnO(s) + CO(g) = Zn(g)$ in the temperature range 500 to 850°. They observed a slight deposition of carbon on molten zinc but estimated that carbon monoxide was thus consumed at about $^1/_{100}$ its rate of formation from carbon dioxide. It should be noted that our procedure was designed to minimize the contact time of carbon monoxide and zinc.

The time required for our procedure could be shortened by substitution of a Dry Ice trap for the drying tube H and the use of molten zinc instead of the solid granular material. Alternatively, if granular zinc is used an automatic Töpler pump could be used to decrease the time required to pump the gases through the zinc. Some of the phosgene was probably absorbed by stopcock grease and its yield could be improved by irradiation in an all-glass container. However, it is doubtful that the labor involved in using this procedure would sufficiently improve the yield to be worth while.

CHEMISTRY DEPARTMENT
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIF.

RECEIVED OCTOBER 30, 1947

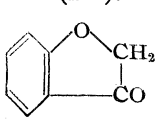
(4) Kenicutt, *Am. Chem. J.*, **5**, 43 (1883); Schwartz, *Ber.*, **19**, 1141 (1886).

(5) Maier and Ralston, THIS JOURNAL, **48**, 364 (1926).

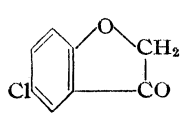
Cyclization of Phenoxyacetic Acid and Some Chlorophenoxyacetic Acids

BY M. L. KALINOWSKI AND L. W. KALINOWSKI*

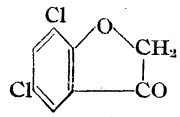
In the course of our studies on the relationship between the chemical structure and the herbicidal activity of organic compounds, such as 2,4-dichlorophenoxyacetic acid, it appeared of interest to prepare coumaran-3-one (I), 5-chlorocoumaran-3-one (II), and 5,7-dichlorocoumaran-3-one (III).



I

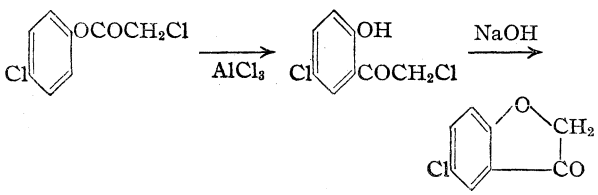


II



III

Three methods of preparation were considered, (1) the cyclization of the corresponding phenoxyacetyl chloride by means of aluminum chloride,[1] (2) the cyclization, by means of dilute alkali, of the corresponding 2-hydroxy-ω-chloroacetophenone,[2] and (3) the cyclodehydration of the corresponding phenoxyacetic acid in benzene solution with phosphorus pentoxide.[3]



Compound (I) was prepared by all three methods; (II) was obtained in traces by methods (1) and (3), and in fair yield by method (2). The disubstituted coumaranone (III) could not be prepared by any of these methods. It appears that the cyclization of phenoxyacetic acid is partially suppressed by chlorine substitution in the 4-position, and apparently completely suppressed by chlorine substitution in the 2,4-positions.

An attempt to effect the Fries rearrangement of 2,4-dichlorophenyl chloroacetate to 3,5-dichloro-2-hydroxy-ω-chloroacetophenone was unsuccessful. This failure of the Fries reaction to take place is not entirely unexpected in view of the work of Tarbell and Fanta.[4] These investigators point out the unreactive character of the phenolic nucleus with two chlorine atoms meta to the position where substitution is to take place, and the further decrease in reactivity by α-substitution in the acetate portion of the molecule.

When 2,4-dichlorophenoxyacetic acid was treated with phosphorus pentoxide the expected 5,7-dichlorocoumaran-3-one was not obtained. However, a good yield of material, m. p. 111.5–112.5°, was isolated which was identified as 2,4-dichlorophenyl-2′,4′-dichlorophenoxyacetate. It appears that cleavage at the ether linkage is effected by phosphorus pentoxide followed by esterification of unreacted 2,4-dichlorophenoxyacetic acid by the phenol fragment. During the reaction, the phosphorus pentoxide acquired a black color, probably due to decomposition products of glycolic acid, and a strong phenolic odor was noted in the crude reaction mixture.

In view of this unexpected reaction of 2,4-dichlorophenoxyacetic acid, the reaction products from the reaction of phenoxyacetic acid and phosphorus pentoxide, and 4-chlorophenoxyacetic acid and phosphorus pentoxide were examined carefully for ester formation. However, in neither case could any ester be found.

In order to have authentic samples of the esters for purposes of identification, phenyl phenoxyacetate, 4-chlorophenyl-4′-chlorophenoxyacetate, and 2,4-dichlorophenyl-2′,4′-dichlorophenoxyacetate were prepared from the phenoxyacetyl chlorides and the appropriate phenols.

Experimental

Cyclization of Acid Chlorides with Aluminum Chloride.—The phenoxyacetyl chlorides were prepared with thionyl chloride. Except that *s*-tetrachloroethane was employed as the solvent in the cyclization reaction, coumaran-3-one, m. p. 99–100°, and 5-chlorocoumaran-3-one, m. p. 114–116°, were prepared according to the procedure given by Stoermer and Atenstadt.[1]

The reaction with 2,4-dichlorophenoxyacetyl chloride in the common Friedel–Crafts solvents under a variety of conditions of temperature and reaction time yielded a resinous product from which no 5,7-dichlorocoumaran-3-one could be isolated.

Cyclization of 2-Hydroxy-ω-chloroacetophenones.—Although this method is indirect, it was found to be the most satisfactory one for the preparation of coumaran-3-one,[5] and 5-chlorocoumaran-3-one.[2]

However, 5,7-dichlorocoumaran-3-one could not be prepared by this procedure. The desired 3,5-dichloro-2-hydroxy-ω-chloroacetophenone was not obtained by heating 2,4-dichlorophenyl chloroacetate with aluminum chloride. Instead a light tan, non-lachrymatory compound, m. p. 135–135.5°, was obtained in 53% yield. This compound was not identified.

Anal. Calcd. for $C_8H_5Cl_3O_2$: Cl, 44.3. Found: Cl, 29.0, 29.7.

The compound 2,4-dichlorophenyl chloroacetate, b. p. 125–130° (1 mm.), has not been reported. The compound was prepared by heating 2,4-dichlorophenol with an excess of chloroacetyl chloride.

Anal. Calcd. for $C_8H_5Cl_3O_2$: Cl, 44.3. Found: Cl, 44.4.

Reaction of the Phenoxyacetic Acids with Phosphorus Pentoxide.—Coumaran-3-one and 5-chlorocoumaran-3-one were prepared by this method according to the procedure given by Stoermer and Bartsch.[3] A reaction time of eight to ten minutes seems to give a maximum yield of coumaranone. For both phenoxyacetic acid and 4-chlorophenoxyacetic acid a longer reaction time of forty-five minutes gave a heavy oil from which no coumaranone or ester could be isolated.

To a solution of 15 g. of 2,4-dichlorophenoxyacetic acid in 125 cc. of anhydrous benzene, 20 g. of phosphorus pentoxide was added. The reaction mixture was stirred and refluxed for forty-five minutes. The phosphorus pentoxide was removed by filtration, the filtrate was washed several times with water, dried over sodium sulfate, and the benzene removed by distillation. A residue of 12 g. of pasty,

* Present address: Sinclair Refining Co., East Chicago, Ind.

(1) Stoermer and Atenstadt, *Ber.*, **35**, 3562 (1902).

(2) Fries, Hasselbach and Schroder, *Ann.*, **405**, 370 (1914).

(3) Stoermer and Bartsch, *Ber.*, **33**, 3177 (1900).

(4) Tarbell and Fanta, THIS JOURNAL, **65**, 2170 (1943).

(5) Fries and Pfaffendorf, *Ber.*, **43**, 215 (1910).

brown solid was obtained which had a strong phenolic odor, and from which no 5,7-dichlorocoumaran-3-one could be isolated by steam distillation. The residue was triturated with a small amount of cold methanol, and the solid was recrystallized from Skelly C, m. p. 111.5–112.5° (yield 8.0 g.) A mixed m. p. with an authentic sample of 2,4-dichlorophenyl-2′,4′-dichlorophenoxyacetate showed no depression.

Anal. Calcd. for $C_{14}H_8Cl_4O_3$: C, 45.9; H, 2.18; Cl, 38.8. Found: C, 46.0; H, 2.18; Cl, 40.1.

A shorter reaction time of ten minutes afforded a lower yield of ester, and none of the 5,7-dichlorocoumaran-3-one.

Preparation of the Phenyl Esters of the Phenoxyacetic Acids.—The ester 2,4-dichlorophenyl 2′,4′-dichlorophenoxyacetate was prepared by heating equivalent amounts of 2,4-dichlorophenol and 2,4-dichlorophenoxyacetyl chloride at 130–140° for three hours. The reaction product was recrystallized from Skelly C, m. p. 112–113°.

Anal. Calcd. for $C_{14}H_8Cl_4O_3$: Cl, 38.8. Found: Cl, 38.0.

In a similar manner, 4-chlorophenyl 4′-chlorophenoxyacetate was prepared, m. p. 118–119°.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_3$: Cl, 23.9. Found: Cl, 24.0.

Phenyl phenoxyacetate was prepared in a similar manner, m. p. 54–57° (reported[6] m.p. 58°).

Herbicidal Activity Tests

The various phenoxyacetic acids, cyclized derivatives, and phenyl esters were tested for plant growth regulating activity. Snap beans, grown under field conditions, were used as the test plant. Approximately 40 mg. of a solution of 1% of the compound in lanolin was applied to the pulvinus of the primary leaves when the first trifoliate leaves were expanding. Each of the compounds was applied to two plants, and the treated plants were observed over a period of eight weeks.

Phenoxyacetic acid, coumaran-3-one, and phenyl phenoxyacetate were without action.

The 4-chlorophenoxyacetic acid was very active, as was the 4-chlorophenyl ester. A slight effect was noted within two days after application, and within ten days the stems were badly swollen and the trifoliate leaves were dwarfed. After eight weeks the plants were alive but were very stunted. When 4-chlorophenoxyacetic acid was cyclicized to 5-chlorocoumaran-3-one all herbicidal activity was lost.

As was expected, 2,4-dichlorophenoxyacetic acid was very active. The 2,4-dichlorophenyl ester possessed the same order of activity, but seemed to act somewhat more slowly.

(6) Morel, *Bull. soc. chim.*, [3] **21**, 967 (1899).

CHICAGO 29, ILLINOIS RECEIVED DECEMBER 31, 1947

Difluoroboron-acetoacetanilide

BY JOSEPH R. KILLELEA

A recent application of the Knorr reaction in this laboratory[1] prompted a study of the use of boron fluoride as the acid catalyst for the cyclization. Small quantities of the expected 4-methylcarbostyril (I) were obtained in some cases. In every case the principal product was difluoroboron-acetoacetanilide (II).[2]

Experimental

Difluoroboron-acetoacetanilide.—To 20 ml. of a 40% solution of boron fluoride in absolute ethanol[3] is added 5.0 g. of acetoacetanilide. The solution is allowed to stand for fifteen minutes and then poured cautiously into an excess of dilute sodium carbonate. The filtered solid is stirred with normal hydrochloric acid to remove inorganic matter and dried over sodium hydroxide. It is dissolved in the minimum volume of dry dioxane, the solution filtered, and the product precipitated by the addition of petroleum ether. The product (5.0 g., 79%) forms fine needles and melts at 154–155°.

Anal. Calcd. for $C_{10}H_{10}O_2NBF_2$: B, 4.8; F, 16.9; N, 6.23. Found: B, 5.2; F, 16.7; N, 6.22.

Properties.—**(a) Hydrolysis.**—One gram of (II) is stirred with 50 ml. of a very dilute ferric chloride solution at room temperature. No color is observed until considerable time (one-half to one hour) has elapsed. The color gradually deepens as hydrolysis proceeds and reaches its maximum after six to eight hours. The solution gives positive qualitative tests for boric acid and fluorides. Nearly the theoretical quantity of acetoacetanilide may be recovered by extraction.

(b) Cyclization.—One gram of (II) is stirred with 3 ml. of concentrated sulfuric acid and the solution warmed to 80–90°. Reaction sets in with the evolution of acidic gases (wet litmus) containing boron (green flame). Nearly the theoretical quantity of (I) may be isolated by the usual method.[1]

(2) Similar compounds from β-diketones have been reported by Morgan, *J. Chem. Soc.*, **125**, 1963 (1924).

(3) The Knorr cyclization was attempted in other solvents and under various conditions. These directions represent a convenient method of preparation of (II).

WILLIAM H. NICHOLS LABORATORY
NEW YORK UNIVERSITY
UNIVERSITY HEIGHTS
NEW YORK 53, N. Y. RECEIVED NOVEMBER 20, 1947

Isomerization of Alkyl Phosphites. VII. Some Derivatives of 2-Bromoethane Phosphonic Acid

BY GENNADY M. KOSOLAPOFF

The reaction of triethyl phosphite with ethylene bromide readily leads to a very reactive diethyl 2-bromoethane phosphonate. It was felt to be of interest to prepare a number of derivatives of this substance through the reactive halogen atom.

The action of alcoholic potassium hydroxide on this ester was found to give good yields of diethyl vinyl phosphonate, which had been earlier reported by Kabachnik,[1] who used a rather involved reaction sequence for his synthesis.

Dialkylamines react with the bromo compound in aqueous solution to give good yields of the corresponding diethyl 2-dialkylaminoethane phosphonates. As might be expected, the use of a nonpolar solvent leads to dehydrohalogenation and the formation of the above-mentioned vinyl derivative.

Experimental Part

Triethyl phosphite (33.2 g., 0.2 m.) and ethylene bromide (150 g., 0.8 m.) were heated for three hours to 160°

(1) Searles and Lindwall, THIS JOURNAL, **68**, 988 (1946).

(1) Kabachnik, *Izvest. Akad. Nauk. S. S. S. R.*, No. 2, 233 (1947).

in the previously described apparatus.[2] Ethyl bromide evolution amounted to 20 g. (theory, 21.8 g.). The product was distilled with a minimum of superheating by the use of a still equipped with a sealed stirrer. The yield of diethyl 2-bromoethanephosphonate, b. p. 86–87° at 2 mm., $n^{25}D$ 1.4555, was 33 g., 67.5%.

Diethyl Vinyl Phosphonate.—Diethyl 2-bromoethanephosphonate (33 g.) was added in the course of thirty minutes to a stirred solution of 7.5 g. of potassium hydroxide in 250 cc. of absolute ethanol with ice cooling. The mixture was warmed to a gentle reflux for fifteen minutes, cooled and filtered. The precipitated potassium bromide was washed with 50 cc. of absolute ethanol and the combined filtrates were distilled to give 21 g. (95%) diethyl vinyl phosphonate as a colorless mobile liquid, b. p. 50° at 1 mm., $n^{25}D$ 1.4260. It decolorized permanganate instantly in the cold and possessed mildly expressed polymerizability.

Diethyl 2-Diethylaminoethanephosphonate.—Diethyl 2-bromoethanephosphonate (24.5 g., 0.1 m.) was added to 25 g. of diethylamine in 50 cc. of water and the mixture was refluxed for two hours. After cooling, 50 cc. of 20% sodium hydroxide was added and the mixture was extracted with 200 cc. of benzene. Distillation of the organic layer gave 17 g. (72%) diethyl 2-diethylaminoethane phosphonate, as a pale yellow oil, b. p. 106–7° at 3 mm., $n^{25}D$ 1.4380, which forms a methiodide, m. p. 104–106°.

Anal. Calcd.: N, 5.9. Found: N, 5.87, 6.01.

Repetition of the above experiment in dry toluene gave only the above described vinyl compound.

Diethyl 2-Di-*n*-butyl-aminoethane Phosphonate.—Diethyl 2-bromoethane phosphonate (24.5 g., 0.1 m.) was refluxed for four hours with 40 g. of di-*n*-butylamine and 50 cc. of water. Isolation, as given above, gave 21 g. (72%) diethyl 2-di-*n*-butyl-aminoethane phosphonate as a pale yellow oil, b. p. 140–142° at 3 mm., $n^{25}D$ 1.4421.

Anal.: Calcd.: C, 57.5; H, 10.9. Found: C, 57.7, 57.64; H, 10.6, 10.9.

(2) Kosolapoff, THIS JOURNAL, **66**, 109 (1944).

CENTRAL RESEARCH DEPARTMENT
MONSANTO CHEMICAL COMPANY
DAYTON 7, OHIO RECEIVED JANUARY 14, 1948

The Preparation of Carboxymethoxylamine Hemihydrochloride

BY MARY HARRIET LOTT

Carboxymethoxylamine has been used frequently as a ketone reagent, for instance in the isolation of α-estradiol from human pregnancy urine.[1] It can be synthesized by the simple procedure of Borek and Clarke[2] whereby acetoxime is condensed with sodium chloroacetate and the resulting acetone carboxymethoxime hydrolyzed with 6 *N* hydrochloric acid. In this Laboratory no difficulty has been encountered in the condensation; however, hydrolysis with 6 *N* hydrochloric acid has not uniformly yielded the desired carboxymethoxylamine hemihydrochloride. Often merely ammonium chloride is obtained. It has furthermore been noted that in the crystallization of the hemihydrochloride from ethanol–ether a fragrant oil often results in the mother liquor. The procedure of Borek and Clarke for hydrolyzing acetone carboxymethoxime has therefore been modified as described below. In this modification the concentration of hydrochloric acid, even after partial evaporation of solvent, is never permitted to become greater than 3.6 normal; isopropyl alcohol is substituted for ethanol under the assumption that esterification with ethanol takes place during crystallization. By the adoption of these modifications it has been possible consistently to obtain carboxymethoxylamine hemihydrochloride in satisfactory yield.

Procedure.—Crude acetone carboxymethoxime is distilled prior to hydrolysis. To a solution of 10.0 g. of acetone carboxymethoxime in 100 cc. of water contained in a 500-ml. wide-mouthed Erlenmeyer flask, 6.0 cc. of concentrated hydrochloric acid is added. The homogeneous solution is then heated on the steam-bath (hood) until the volume of solution is reduced to 20 cc. (approximately three hours time). After having been cooled, this solution is treated with 100 cc. of isopropyl alcohol and 200 cc. of dry, alcohol-free ethyl ether. After a day in the ice-box, the deposited crystals are filtered (Büchner) and washed with cold isopropyl alcohol–ether (1:3). The yield of carboxymethoxylamine hemihydrochloride, after drying, is about 4 g. melting at 150–151° uncor. (with evolution of gas). This material is of sufficient purity for use as a ketone reagent.

Anal.[3] Calcd. for $(C_2H_5O_3N)_2 \cdot HCl$: Cl, 16.22. Found: Cl, 16.08, 16.06.

(1) Huffman, MacCorquodale, Thayer, Doisy, Smith and Smith, *J. Biol. Chem.*, **134**, 591 (1940).

(2) Borek and Clarke, THIS JOURNAL, **58**, 2020 (1936).

(3) Analysis by James E. Ashmore.

DEPARTMENT OF BIOCHEMISTRY
SOUTHWESTERN MEDICAL COLLEGE
DALLAS, TEXAS RECEIVED FEBRUARY 17, 1948

The Synthesis of 3,4,9-Trimethoxyphenanthrene

BY S. F. MACDONALD AND A. J. CHECHAK

The significance, in morphine chemistry, of the function of the 9- or 10-hydroxy group in 9-hydroxycodeine and of the structure of Knorr's 9- or 10-acetoxyacetylmethylmorphol, has been indicated by Knorr[1] (in part) and by Holmes.[2] Evidence on these points would definitely locate the position of the nitrogen in morphine, unless the hydroxy group of 9-hydroxycodeine were on 9 and the nitrogen on 10 or 14. The latter publication has led us to report work which we had done to the same purpose, though it is as yet incomplete.

It was pointed out[2] that the 9-hydroxycodeine structure was not consistent with its failure to react as a carbinolamine with malonic acid, etc.; more conclusive evidence to this effect had already been obtained by Knorr,[1] who found that it did not react with hydroxylamine or with semicarbazide, but who failed to interpret the result thus. As codeine N-oxide is known,[3] there would appear to be little justification for the suggestion, made and disposed of by Holmes,[2] that 9-hydroxycodeine is an N-oxide.

The synthesis of 3,4,9-trimethoxyphenanthrene should permit the determination of the structure of Knorr's acetoxyacetylmethylmorphol. Attempts had therefore been made to convert 3,4-

(1) Knorr and Hörlein, *Ber.*, **39**, 3252 (1906); **40**, 2040, 2042 (1907).

(2) Holmes, *et al.*, THIS JOURNAL, **69**, 1996, 1998 (1947).

(3) Freund and Speyer, *Ber.*, **43**, 3310 (1910).

dimethoxy-9-phenanthrylamine into 3,4-dimethoxy-9-phenanthrol.[1,2] This conversion was carried out quantitatively by a modification of the Bucherer reaction wherein sulfur dioxide replaced the usual bisulfite,[4] and the presence of much aqueous dioxane prevented the formation of the diphenanthrylamine derivative. Analogous deaminations have been carried out by other methods in low or in unstated yields.[5] 3,4-Dimethoxy-9-phenanthrol gave the required 3,4,9-trimethoxyphenanthrene on methylation.

Experimental

α-Phenyl-2-nitro-3,4-dimethoxycinnamic Acid.—This was obtained in 75% yield by Pschorr's method[6] or in 90% yield by the following modification. 2-Nitroveratraldehyde, 2.1 g., phenylacetic acid, 1.4 g., triethylamine, 1.0 g., and acetic anhydride, 5 ml., were heated together at 60° for two days. Isolation and purification according to Pschorr gave the product, 3.0 g., m. p. 222.5–223.5° (uncor.).

3,4-Dimethoxy-9-aminophenanthrene.—Prepared according to Knorr,[1] the base was obtained from its hydrochloride with alcoholic potassium hydroxide.

3,4-Dimethoxy-9-phenanthrol.—3,4-Dimethoxy-9-aminophenanthrene, 4.7 g., was dissolved in 50 ml. of dioxane, 50 ml. of water added, the mixture saturated with SO_2 at 0°, and heated in a sealed tube at 100° for one day. Removal of the solvent *in vacuo*, grinding the residue with water, filtering and drying, gave 3,4-dimethoxy-9-phenanthrol, 4.7 g., m. p. 147–152°. The crude product was distilled (1×10^{-4} mm., bath temp. 130°) and crystallized from toluene, giving pale yellow prisms, m. p. 156°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; OCH_3, 24.4. Found: C, 75.53; H, 5.43; OCH_3, 21.9, 22.4.

3,4,9-Trimethoxyphenanthrene.—3,4-Dimethoxy-9-phenanthrol, 390 mg., was refluxed under nitrogen with water, 10 ml., and *N* sodium hydroxide, 2 ml. Methyl sulfate, 0.5 ml. then 0.4 ml., and *N* sodium hydroxide, 5 ml. then 4 ml., were added alternately. The cooled mixture was extracted with chloroform, the chloroform washed with dilute hydrochloric acid, with dilute sodium hydroxide with water, and dried with sodium sulfate. 3,4,9-Trimethoxyphenanthrene, 330 mg., m. p. 85–95°, was obtained by distilling (1×10^{-4} mm., bath temp. 110°) the residue left on evaporating the chloroform. It was purified by crystallizing from petrol ether (b. p. 60–80°, 20 parts) giving colorless prisms, m. p. 96.5–97.5° after drying.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; OCH_3, 34.70. Found: C, 76.21; H, 6.32; OCH_3, 31.76.

(4) Franzen and Kempf, *Ber.*, **50**, 101 (1917).

(5) Pschorr and Schröter, *Ber.*, **35**, 2726 (1902); Schmidt and Strobel, *Ber.*, **36**, 2508 (1903).

(6) Pschorr and Sumuleanu, *Ber.*, **33**, 1810 (1900).

BANTING & BEST DEPARTMENT OF MEDICAL RESEARCH
UNIVERSITY OF TORONTO
TORONTO, CANADA

RECEIVED JANUARY 28, 1948

X-Ray Diffraction in Aqueous Systems of Dodecyl Sulfonic Acid

BY SULLIVAN S. MARSDEN, JR., AND JAMES W. MCBAIN

Aqueous systems of lauryl sulfonic acid are especially interesting because their X-ray diffraction shows different kinds of patterns for ordinary isotropic solution, concentrated anisotropic liquid crystalline region, and the highly concentrated anisotropic liquid crystalline, and the pure crystalline acid.

1. The ordinary isotropic liquid solution existing at room temperature exhibits only a very diffuse indication of a long spacing even near the highest concentration (23%) at which it can exist. The phase diagram giving the boundaries of this[1] and the two anisotropic phases was published by M. J. Vold. X-Ray diffraction therefore indicates the absence of any strongly repeating structure such as that found in solutions of potassium laurate, except high angle scattering due to neighboring molecules in the colloidal particles of the sulfonic acid.

However, when 3.6% of benzene is added to 19.0% solution of the dodecyl sulfonic acid the solution is still isotropic but gives a diffraction line corresponding to a single order of Bragg spacing of 63.4 Å. But when the amount of benzene is increased to 6.9% the system becomes anisotropic and gives two long Bragg spacings of 67.0 Å. and 48.4 Å. It is assumed that this structure is lamellar in analogy with the system Triton X-100: water: benzene.[2]

2. Most interesting is the aqueous liquid-crystalline phase existing between 23 and 70% of lauryl sulfonic acid. The colloidal particles apparently consist of *fibers* or long rods or elongated ellipsoids. These lie parallel at a distance from each other in hexagonal arrangement. Such a structure was found for certain aqueous systems of tobacco mosaic virus by Bernal and Fankuchen.[3]

The evidence for this interpretation of the X-ray diffraction patterns follows from: (a) The ratios of the successive Bragg spacings to each other are in the proportions $1:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{7}$. These correspond to hexagonal indices $10\bar{1}0$, $11\bar{2}0$, $20\bar{2}0$, $21\bar{3}0$, respectively.

(b) Most important, the relative intensities of the various diffractions, which in the order given above are: very strong, strong, weak and very weak, respectively; in a few cases the second and third lines are strong and strong, respectively.

(c) The variation of the inter-particle distance with concentration, which is approximately as the reciprocal of the square root of the concentration.

The thickness or diameter of the fibers seems to be in the neighborhood of the double length of the soap molecule. The short spacings consist of halos at 7–8 Å. and 4.5–4.6 Å., which indicates a liquid arrangement of neighboring molecules within the fibers.

It should be mentioned that this structure is quite different from that of the anisotropic phases of aqueous potassium laurate as is shown by studies in this laboratory by Oscar A. Hoffman being reported elsewhere. He shows that the potassium laurate systems contain a repeating *lamellar* structure such as was first suggested by Hess and his collaborators.

(1) Vold, THIS JOURNAL, **63**, 1427 (1941).

(2) Marsden and McBain, *J. Phys. & Coll. Chem.*, **52**, 110 (1948).

(3) Bernal and Fankuchen, *J. Gen. Physiol.*, **25**, 111 (1941).

3. Up to the present, only two papers have appeared on X-ray diffraction of aqueous anisotropic phases of soaps or detergents. Ross and McBain reported that a *lamellar* structure *expanding continuously with dilution* exists both in the isotropic and anisotropic phases of the system hexanolamine oleate:water.[4] Marsden and McBain[2] found lamellar structures in the isotropic and anisotropic phases in aqueous systems of nonionic detergents, but the variation of long spacing with concentration is different for the two phases.

The aqueous liquid crystalline phase of dodecylsulfonic acid existing in the very high concentrations in the neighborhood of 85% has a *lamellar* structure, but the long spacing does *not* change with concentration. This long spacing appears to be due to the double length of the detergent molecule tilted at an angle β of about 63°. The various orders of this long spacing are in the ratio of 1:2:3 (that is, Bragg spacings in the proportion of $1:1/\sqrt{4}:1/\sqrt{9}$), with no diffraction lines in between; while the side spacings consist again of halos at 7–8 Å. and 4.5–4.6 Å.

4. For comparison with the various aqueous systems just described it may be mentioned that solid dodecyl sulfonic acid exhibits long spacings corresponding to even orders of pairs of molecules of the acid placed end to end but tilted at an angle β of 55°. No diffraction corresponding to that expected for the odd orders has yet been found.

It is clear that quite different colloidal particles exist in the different concentrations and phases of aqueous dodecyl sulfonic acid. It is evident that thorough study of aqueous systems of association colloids, wherein the fundamental chemical unit is definitely known, must throw light upon the study of closely related but less well characterized systems, such as those of proteins and virus.

(4) Ross and McBain, THIS JOURNAL, **68**, 296 (1946).

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIF. RECEIVED DECEMBER 19, 1947

A New Method of Preparation of Diazomethane

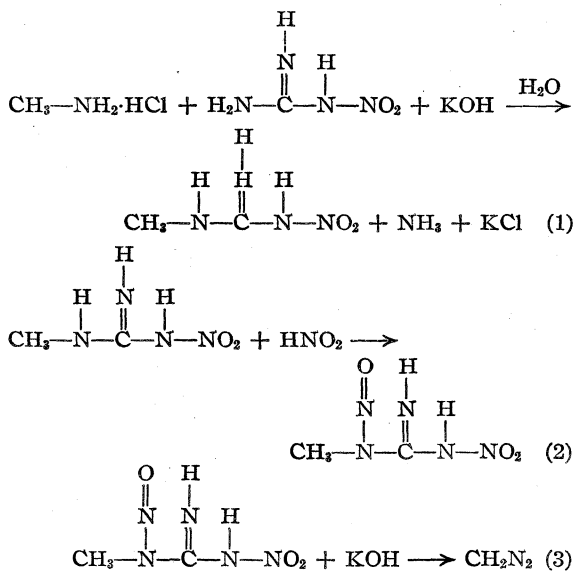
BY A. F. MCKAY

N-Methyl-N-nitroso-N′-nitroguanidine described by McKay and Wright[1] has been found to give diazomethane in 72.6% yield on reaction with aqueous potassium hydroxide.

The available methods[2] of production of diazomethane have disadvantages not encountered in the present method. The chief drawback in the method of Arndt[3] is the instability of methylnitrosourea which limits the production of this compound to 25–50 g. lots. On the other hand N-methyl-N-nitroso-N′-nitroguanidine has been prepared in pound lots and stored in the dark at room temperature for periods of time up to two months without showing signs of decomposition. N-Methyl-N-nitroso-N′-nitroguanidine changes slowly from orange to green in color on exposure to sunlight and loses nitrogen oxides. Moreover, in the purification of this compound it is best to employ an anhydrous solvent, preferably absolute methanol. Prolonged refluxing with 95% ethanol is sufficient to cause partial denitrosation with the production of N-methyl-N′-nitroguanidine.

The only disadvantage noted in handling N-methyl-N-nitroso-N′-nitroguanidine has been a skin irritation. The dermatitis is accompanied by pruritus and a burning sensation. In more severe cases a vesicant action has been noted. These skin reactions were obtained during the nitrosation of N-methyl-N′-nitroguanidine and when using the nitroso compound in other reactions. The simple expedient of performing the reactions in a fume hood eliminated these undesirable effects.

The series of reactions involved in the formation of diazomethane are



The first two reactions have been previously reported,[1] while reaction 3 is described in the experimental section. The diazomethane was characterized by methylating stearic acid. The methyl stearate obtained in quantitative yield melted at 39.0–39.5° alone and on admixture with an authentic sample.

This method is not limited to the production of diazomethane but it has been found to be of general use in the preparation of diazo compounds. The results on the broader application of this method will be published at a later date.

Experimental

Diazomethane.—The procedure used in the preparation of diazomethane from 20 g. (0.13 mole) of N-methyl-N-nitroso-N′-nitroguanidine was the same as the distillation technique described by Arndt[3] in the preparation of diazo-

(1) A. F. McKay and G. F Wright, THIS JOURNAL, **69**, 3028 (1946).

(2) L. I. Smith, *Chem. Revs.*, **23**, 193 (1938).

(3) F. Arndt, *Org. Syntheses*, **15**, 3 (1935).

methane from methylnitrosourea. The solutions in the receivers were combined and diluted to a volume of 250 cc. with anhydrous ether. A 10-cc. aliquot was used in the determination of the yield of diazomethane by the use of benzoic acid as described by Marshall and Acree.[4] The total yield was 4.15 g. or 72.6%.

Characterization of Diazomethane.—To 498 mg. (0.0017 mole) of stearic acid (m. p. 69 ± 0.1°) dissolved in 30 cc. of ether was added 331 mg. (0.0078 mole) of diazomethane in 20 cc. of ether. The ethereal solution was allowed to stand at room temperature for twenty minutes after the evolution of nitrogen had ceased. The excess diazomethane was decomposed with dilute hydrochloric acid solution and the ether fraction separated. After washing the ether solution with water (3 × 40 cc.), it was dried over anhydrous sodium sulfate and evaporated. The colorless residue crystallized on cooling. These crystals melted at 39–39.5° (capillary method) alone and on admixture with an authentic sample of methyl stearate. The yield was 514 mg. or 98.4% by theory.

Acknowledgment.—The author wishes to acknowledge the technical assistance of Mr. W. J. McIntyre.

(4) E. K. Marshall and S. F. Acree, *Ber.*, **43**, 2323 (1910).

DEPARTMENT OF CHEMISTRY
QUEENS UNIVERSITY
KINGSTON, ONTARIO

RECEIVED FEBRUARY 12, 1948

Volatile Decomposition Products of Sugars in Aqueous Solution

BY LOUIS SATTLER AND F. W. ZERBAN

Enders and his co-workers[1] have published a series of papers purporting to show that methylglyoxal is found in the distillate not only when alkaline solutions of glucose and xylose are distilled at constant volume, but that methylglyoxal is found in distillates of neutral and acid solutions of these sugars as well. They also report the finding of methylglyoxal in the distillates from acid solutions of sucrose, maltose, dextrin and soluble starch.

Their conclusion that methylglyoxal is indeed the volatile material in the distillate, is based upon the following observations: the iodoform reaction, the color reaction with pyrrole, the color test of Denigès,[2] as for example with codeine phosphate, the Ariyama reaction[3] with arsenophosphotungstic acid and the characterization of methylglyoxal as its phenyl and 2,4-dinitrophenylosazones.

These color reactions for methylglyoxal are not specific and the reaction with sodium nitroprusside[4] has its limitations. The isolation of the osazones is not conclusive because acetol also yields the same derivatives. Acetol makes the Ariyama test ambiguous because, as with methylglyoxal, there is a great intensification of the blue color upon the addition of sodium cyanide (1 g.). Unfortunately, the conversion of acetol into 4(5)-methylimidazole[5] does not lend itself to micro quantities.

Baudisch and Deuel[6] have shown that sugars when distilled from a 5% sodium bicarbonate solution, yield acetol. The acetol can be specifically identified[7] by its reaction with *o*-aminobenzaldehyde to form 3-hydroxyquinaldine which can be isolated. This compound crystallizes from acetone and water in the form of colorless needles melting at 260°,[8] and possesses a beautiful blue fluorescence when it is illuminated in very dilute aqueous solution with invisible ultraviolet light.

In view of Enders' claim that methylglyoxal is obtained in the distillates when maltose solutions are distilled ranging over a wide *p*H, from strongly acid to strongly alkaline,[1b] it was deemed desirable to test for acetol because of the obvious conflict of these findings with the observations of Baudisch and Deuel. Pure 20% aqueous solutions of glucose and of maltose were distilled at constant volume. The distillates gave a positive test with Ariyama's reagent, and they yielded the reported osazones. However, with *o*-aminobenzaldehyde, under the conditions described by Baudisch and Deuel,[6] the distillates gave strong positive tests for acetol as observed by fluorescence. Baudisch and Deuel found that 1 g. of methylglyoxal gives only a faint acetol test, as observed by the intensity of the fluorescence, whereas 5 mg. of glucose when distilled with a sodium bicarbonate solution, yields a relatively large amount of acetol.

Pinkus[9] obtained the osazone of methylglyoxal when glucose was treated with strong alkali in the presence of phenylhydrazine. While Nef,[10] Wohl,[11] and Neuberg[12] have expressed beliefs that in alkaline solution methylglyoxal is the initial product formed in the rupture of the sugar molecule, Baudisch and Deuel are of the opinion that acetol is the primary compound which is produced because under their experimental conditions the Cannizzaro reaction is apparently negligible. Thymine, which on treatment with ferrous sulfate and sodium bicarbonate in the presence of air, is oxidized to urea, pyruvic acid and acetol, can be detected in the presence of sugar.[6]

Our finding of acetol in the distillates of aqueous sugar solutions does not rule out the simultaneous presence of methylglyoxal. It does point up the conclusion that Enders' quantitative method for the estimation of methylglyoxal is erroneous and that his opinions regarding the formation of methylglyoxal are open to modification. Of further interest to us is the darkening of these triose solutions when they are distilled from a 5% so-

(1) (a) Enders and Marquardt, *Naturwissenschaften*, **29**, 46 (1941); (b) Enders, *Biochem. Z.*, **312**, 349 (1942); (c) Enders and Sigurdsson, *Biochem. Z.*, **317**, 26 (1944).

(2) Denigès, *Bull. soc. chim.*, **5**, 649 (1910).

(3) Ariyama, *J. Biol. Chem.*, **77**, 395 (1928).

(4) Neuberg, *Biochem. Z.*, **71**, 150 (1915).

(5) Weidenhagen and Wegener, *Z. Wirtschaftsgruppe Zuckerind.*, **88**, 927 (1938).

(6) Baudisch and Deuel, THIS JOURNAL, **44**, 1585 (1922).

(7) Baudisch, *Biochem. Z.*, **89**, 279 (1918).

(8) Königs and Stockhausen, *Ber.*, **35**, 2556 (1902).

(9) Pinkus, *ibid.*, **31**, 31 (1898).

(10) Nef, *ibid.*, **335**, 247 (1904).

(11) Wohl, *Biochem. Z.*, **5**, 57 (1907).

(12) Neuberg and Oertel, *ibid.*, **55**, 494 (1913); Neuberg and Rewald, *ibid.*, **71**, 144 (1915).

dium bicarbonate solution because there seems to be a connection with the "browning reaction" observed in food products which contain both sugars and amino derivatives.

Work is in progress on the formation of acetol in sugar solutions, and the quantitative determinations of acetol and methylglyoxal in mixtures of both.

BROOKLYN COLLEGE
BROOKLYN, N. Y.
NEW YORK TRADE LABORATORY
NEW YORK, N. Y. RECEIVED DECEMBER 29, 1947

2-Aryl- and 2-Alkoxycyclohexanols[1]

BY B. C. MCKUSICK[2]

As part of a program to find improved insect-repellents, a number of 2-aryl- and 2-alkoxycyclohexanols were prepared from cyclohexene oxide.

The 2-arylcyclohexanols were obtained by condensing cyclohexene oxide with appropriate aryllithiums[3]; Grignard reagents were not used because the products would have been the isomeric arylcyclopentylcarbinols.[3] The postulated cyclohexanol structure was confirmed for one product, 2-(*p*-tolyl)-cyclohexanol, by oxidizing it to the known δ-*p*-toluylvaleric acid. Yields of cyclohexanols were good except in the case of 2-(*p*-methoxyphenyl)-cyclohexanol, where the low yield is understandable in view of the ease with which the side-reaction of *p*-methoxyphenyllithium with *p*-bromoanisole to give anisole and 5-bromo-2-methoxyphenyllithium is known to occur.[4] Since 2-phenylcyclohexanol prepared from cyclohexene oxide and phenyllithium[3] has been shown to have a *trans*-configuration,[5] it is probable that the present 2-arylcyclohexanols are also *trans*.

The 2-alkoxycyclohexanols were obtained by heating cyclohexene oxide with an excess of the appropriate alcohol in which a trace of sodium had been dissolved.[6] *trans*-1,2-Cyclohexanediol was a by-product of the preparation of 2-(β-phenethoxy)-cyclohexanol and may have been a by-product in other cases.

Experimental

2-Arylcyclohexanols.—The preparation of 2-(*m*-tolyl)-cyclohexanol can be used to illustrate the general procedure. In a 12-liter three-necked flask, 69 g. (20% excess) of lithium in the form of small strips[7] was stirred vigorously in 3 liters of anhydrous ether under nitrogen while 711 g. of *m*-bromotoluene was added at a rate to maintain gentle refluxing of ether. Once reaction set in, the flask was kept immersed in an ice-bath in order to shorten the time necessary for the addition (about one hour). The mixture was heated under reflux for an hour and 408 g. of cyclohexene oxide[8] was added in the same manner. The mixture was cooled in ice and decomposed by the gradual addition of 3 liters of water with stirring. The ether layer was separated, washed with water, dried over magnesium sulfate, and distilled; 655 g. (71% yield) of 2-(*m*-tolyl)-cyclohexanol was collected at 113–114° (1.0 mm.).

The acetate and propionate were obtained by heating 2-(*m*-tolyl)-cyclohexanol at 100° for two hours with 1.5 molar equivalents of acid anhydride and 2 molar equivalents of pyridine and distilling the reaction mixtures under reduced pressure.

TABLE I

2-SUBSTITUTED CYCLOHEXANOLS 

R	Boiling point[a] °C.	Mm.	M. p. or $n^{25}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
m-Tolyl	113–114	1.0	1.5396	71	$C_{13}H_{18}O$	82.1	9.5	82.0	9.9
m-Tolyl[b]	85– 86	0.2	1.5113	93	$C_{15}H_{20}O_2$	77.6	8.7	77.4	8.4
m-Tolyl[c]	96–100	0.3	1.5067	97	$C_{16}H_{22}O_2$	78.0	9.0	78.6	9.2
p-Tolyl	109–113	1	72–73°[d]	84	$C_{13}H_{18}O$	82.1	9.5	82.5	9.9
2,5-Xylyl	114–115	2	1.5377	69	$C_{14}H_{20}O$	82.3	9.9	82.7	10.1
p-Methoxyphenyl	135–140	1.5	71–72°[d]	15	$C_{13}H_{18}O_2$	75.7	8.8	75.8	9.0
n-Propoxy[e]	82– 83	9	1.4538	67	$C_9H_{18}O_2$	..	..	..	..
n-Amyloxy	110–113	11	1.4559	77	$C_{11}H_{22}O_2$	70.9	11.9	70.3	11.6
2-Ethylhexyloxy	134–136	8	1.4576	49	$C_{14}H_{22}O_2$	73.6	12.4	73.1	12.5
Benzyloxy	110–112	0.3	1.5290	55	$C_{13}H_{18}O_2$	75.7	8.8	75.6	9.0
β-Phenethoxy	159–162	9	1.5221	48	$C_{14}H_{20}O_2$	76.3	9.2	75.5	9.1
β-Hydroxyethoxy[f,6]	108–110	0.4	1.4797	54	$C_8H_{16}O_3$	..	..	..	..

[a] Fractionations were through a five-inch indented Claisen distillation head. [b] Acetate. [c] Propionate. [d] Recrystallized from hexane. [e] Mousseron and Granger, *Compt. rend.*, **205**, 327 (1937). [f] Miscible with water.

Oxidation of 2-(*p*-Tolyl)-cyclohexanol.—A solution of 23 g. of chromic anhydride in 80 ml. of 80% acetic acid was added to 55 g. of 2-(*p*-tolyl)-cyclohexanol in 80 ml. of acetic acid, the temperature not being allowed to exceed 50°. After twenty-four hours at 25°, the mixture was poured into water and the products were taken up in ether. The ether solution was extracted with a 10%

(1) This work was performed under Contract NDCrc 136 between Harvard University and the Office of Scientific Research and Development, with Paul D. Bartlett as official investigator.

(2) Present address: Chemical Department, Experimental Station, E. I. du Pont de Nemours & Company, Wilmington, Delaware.

(3) Cook, Hewitt and Lawrence, *J. Chem. Soc.*, 71 (1936).

(4) Wittig, Pockels and Droge, *Ber.*, **71**, 1903 (1938).

(5) Price and Karabinos, THIS JOURNAL, **62**, 1159 (1940).

(6) Holt (assigned to E. I. du Pont de Nemours & Co.), U. S. Patent 2,197,105 (1940).

(7) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940).

(8) The cyclohexene oxide was kindly furnished by Dr. A. P. Tanberg of the Chemical Department, Experimental Station, E. I. du Pont de Nemours & Company, Wilmington, Delaware.

sodium hydroxide solution and distilled; 37 g. of a mixture of starting material and the corresponding ketone was obtained. Acidification of the sodium hydroxide extract caused the precipitation of 7.6 g. of *p*-toluylvaleric acid, m. p. 152.5–154°[9] after recrystallization from a benzene–ethanol mixture; neutralization equivalent, 223 (calcd., 220). δ-Benzoylvaleric acid has been obtained from 2-phenylcyclohexanol under similar conditions.[3]

2-Alkoxycyclohexanols.—In a typical experiment, 2-amyloxycyclohexanol was prepared by refluxing for twenty-two hours a solution of 49 g. of cyclohexene oxide[8] in 200 ml. of *n*-amyl alcohol containing 0.5 g. of dissolved sodium. The reaction mixture was distilled and 72 g. (77%) of 2-amyloxycyclohexanol was collected at 100–113° (11 mm.). When alcohols boiling above 200° were used, the solutions were heated at 180–200°.

In the reaction between 35 g. of cyclohexene oxide and 140 ml. of phenethyl alcohol, the first portion of 2-(β-phenethoxy)-cyclohexanol collected on distillation contained *trans*-1,2-cyclohexanediol, 4 g. of which crystallized out on cooling the mixture. It was recrystallized from hexane and identified by its melting point (102–103°),[10a] dibenzoate melting point (91.5–92°),[10b] and composition.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 62.1; H, 10.4.

(9) Brosche, *Ber.*, **52**, 2080 (1919), reports a melting point of 153–154°.

(10) (a) Verkade, Coops, Maan and Verkade-Sandbergen, *Ann.*, **467**, 217 (1928); (b) **477**, 289 (1930).

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS RECEIVED JANUARY 22, 1948

The Solubility of Aminoguanidonium Bisulfate in Water and in Sulfuric Acid Solutions[1]

BY JOHN J. PITHA[2] AND G. B. L. SMITH[3]

In the reduction of nitroguanidine in a sulfuric acid solution, the end-product of the reaction is aminoguanidonium bisulfate. In order better to control the recovery of this salt, some investigations were made into the solubility of aminoguanidonium bisulfate in water and in solutions of various sulfuric acid concentrations.

Experimental

The solubility of aminoguanidonium bisulfate was determined by preparing a saturated solution of the salt in the appropriate solvent at a definite temperature. After equilibrium had been established, a sample of the solution was withdrawn and transferred to a tared volumetric flask and weighed. This solution was then diluted to volume and analyzed for aminoguanidine by the method of Smith and Wheat.[4]

These studies were carried out in a specially constructed three-necked flask of 100 ml. capacity. One neck was used to insert a thermometer into the solution, one neck allowed the entry of an all-glass stirrer, and the third neck was used as an addition port. Ground glass joints were used throughout. Solution temperatures from 5 to 40° were measured with an unjacketed thermometer, but higher temperatures were measured with a thermometer suspended within a glass jacket. The bulb of the flask and the lower third of the necks were immersed in a 7.5-gal. water-bath. This thermostat was equipped with both heating and cooling coils and the temperature of the solution in the reaction flask was controlled to ±0.03°.

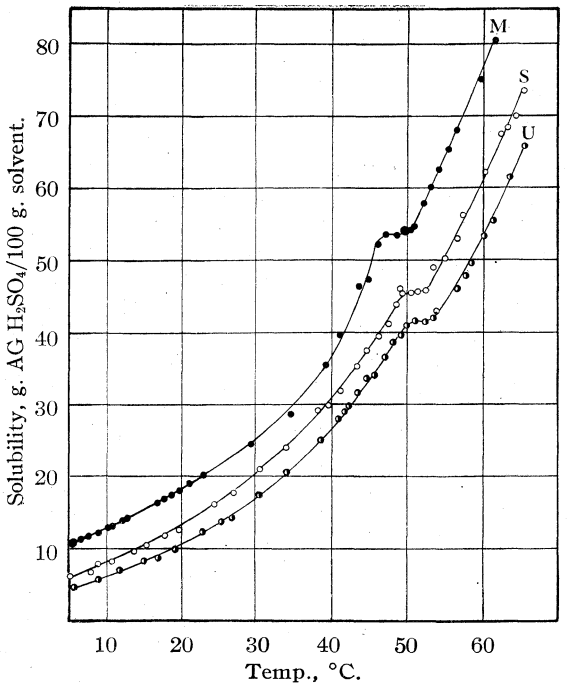


Fig. 1.—M, ●, H_2O; S, ○, 0.7419 *N* H_2SO_4; U, ◑, 1.4088 *N* H_2SO_4.

Saturated solutions of the salt at a particular temperature were prepared by adding an excess of the solute to the solvent and stirring the solution until equilibrium had been established. The attainment of equilibrium was proven by successive sampling and analysis at regular intervals of time until three successive values were in agreement. A half-hour lapse of time after the solution had come to temperature was usually sufficient for equilibrium to be reached. In certain portions of these studies, the equilibrium was approached from both directions in order to establish definitely the values reported.

In order to avoid errors that might occur in the removal and transfer of samples due to crystallization of the salt from the saturated solution while in the sampling tube, pipets used for this purpose were kept in an oven and were used warm. The operation was performed with sufficient speed that no difficulty with crystallization was encountered.

At least three determinations of solubility were made at each temperature, and in the cases where abnormalities were observed sufficient determinations were made to establish the points reported. The accuracy of the analytical procedure was such that an error of 0.1% was average. Precision of results on duplicate sets of samples was of the order of 1 part in 1000 parts. The solubility of aminoguanidonium bisulfate in water, 0.7419 *N* sulfuric acid and 1:4088 *N* sulfuric acid was determined. The results of the solubility determinations are summarized in Fig. 1. Crystals obtained by evaporation at temperatures above and below the inflection temperatures in all cases analyzed 99.5% or better for aminoguanidonium bisulfate, and macro observations of these crystals showed no differences in crystalline form. The nature of the inflection observed in each of the curves is not completely understood, but additional information is being sought and will be reported in a subsequent paper.

(1) This paper is abstracted from the thesis submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn by Mr. Pitha in June, 1942, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(2) Present address: Kedzie Chemical Laboratories, Michigan State College, East Lansing, Mich.

(3) Present address: Inorganic Chemistry Section, Science Department, U. S. Naval Ordnance Test Station, Inyokern, Calif.

(4) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, N. Y. RECEIVED FEBRUARY 7, 1948

Critical Temperature and Pressure of Diborane[1]

BY ARTHUR E. NEWKIRK

In connection with studies of the boron hydrides the critical temperature and pressure of diborane have been measured experimentally by observing the temperature and pressure at which the meniscus between liquid and vapor disappeared on warming. The apparatus was patterned after that of Kay.[2] The temperature was estimated to 0.01° and the pressure to one p.s.i. The sample of diborane was taken from a cylinder and analyzed by low temperature fractional distillation yielding 0.2% of non-condensable gas and 99.8% diborane. The gas used for measurement was therefore vaporized from the cylinder, frozen in a thin layer on the walls of a glass bulb, pumped to remove non-condensable gas and distilled to the capillary. The remainder of the capillary was filled with mercury, attached to the apparatus, and the capillary, its holder and the mercury reservoir placed in a bath at 14°. The bath warmed at the rate of 2° per hour. Several cycles of warming and cooling were made with each run to avoid accidental errors. The results are given in Table I.

TABLE I

	Crit. temp., °C.	Crit. pressure, p. s. i. a.
Run 1	16.94	582
Run 2	16.69	582
Run 2 after 20 hr. at *ca.* 21.5°	17.1	586
Run 2 extrapolated to zero time	16.63	581
Average corrected value	16.7 ± 0.2	581 ± 5

(1) This work was performed under U. S. Army Ordnance Contract TUI-2000.

(2) W. B. Kay, *Ind. Eng. Chem.*, **28**, 1014 (1936).

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, N. Y. RECEIVED FEBRUARY 18, 1948

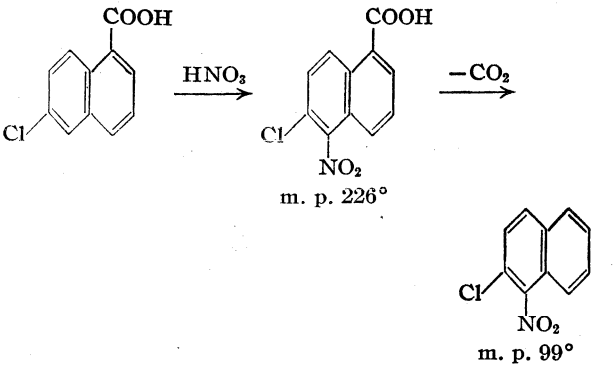
The Nitration of 6-Chloro-1-naphthoic Acid

BY CHARLES C. PRICE, THOMAS J. BARDOS AND HERMAN I. ENOS[1]

In an exploration of possible routes to a heterocyclic ring system analogous to that in morphine[2] but based on the naphthalene rather than the phenanthrene nucleus, we have investigated the nitration of 6-chloro-1-naphthoic acid with the hope that it might produce the 3-nitro derivative. Nitration of the acid, or preferably of its ester, proceeded satisfactorily to give only one product which could be isolated in pure crystalline condition. This material was shown to be the 5-nitro derivative by decarboxylation to 1-nitro-2-chloronaphthalene, identified by mixing melting point with an authentic sample.

(1) Present address: Department of Chemistry, Swarthmore College, Swarthmore, Pa.

(2) Barltrop, *J. Chem. Soc.*, 399 (1947).



Experimental

Preparation of 6-Chloro-1-naphthoic Acid.—The method of Price and Huber[3] was followed in its original form. The ester fraction obtained was hydrolyzed with 15% aqueous sodium hydroxide solution until it dissolved and the acid was precipitated with dilute hydrochloric acid. The total yield of *crude* 6-chloro- and 7-chloro-1-naphthoic acid mixture was 66% (40% from the straight acid fraction and 26% from the ester fraction; the melting points were 183–185° and 171°, respectively). The 6- and 7-chloro isomers were separated through their acid chlorides, following the procedure of Jacobs, Winstein, Seymour and Linden.[4] Methyl 6-chloro-1-naphthoate was obtained (35%, m. p. 66°) and only 8% of the 7-chloro-1-naphthoyl chloride (m. p. 100–104°). The methyl 6-chloro-1-naphthoate was saponified with 20% aqueous sodium hydroxide, and the acid (m. p. 215.5–216°) precipitated.

Nitration of 6-Chloro-1-naphthoic Acid.—An 11-g. sample (0.053 mole) of the pure 6-chloro-1-naphthoic acid was treated with 18 cc. of fuming nitric acid (d. 1.49–1.50). The substance dissolved partly under vigorous evolution of nitrous oxides and of heat. The reaction mixture was warmed for five to ten minutes on the water-bath. After cooling, fine crystals deposited which were collected on a glass filter, washed with some cold nitromethane, and recrystallized from nitromethane. After this first recrystallization, 8.2 g. (62%) of the greenish yellow nitration product was obtained melting in the range of 198–215°. Five more recrystallizations from nitromethane raised the melting point to 224.8–225.5°. The yield of this pure mono-nitro derivative was 3.7 g. (27.5%) obtained as white needles with a greenish tint; neutralization equivalent, 246 (calcd., 251).

Anal. Calcd. for $C_{11}H_6O_4NCl$: C, 52.48; H, 2.41; N, 5.56; Cl, 14.05. Found: C, 52.70; H, 2.21; N, 5.48; Cl, 14.48.

Decarboxylation of the Nitro Acid.—A sample of 0.48 g. of the 6-chloro-nitro-1-naphthoic acid in 1 cc. of redistilled quinoline was heated in an oil-bath to 220–230° until a homogeneous solution was obtained. Then 0.1 g. of hydrogen-reduced copper powder was added. Immediately vigorous carbon dioxide evolution was observed. The temperature was raised to 240° for five minutes and then the mixture was cooled. It was extracted with ether, the ether extract filtered, washed with dilute hydrochloric acid, with 10% aqueous sodium bicarbonate solution and with water. Finally it was treated with some charcoal, filtered and the ether evaporated: large, pale yellow crystals were obtained. This substance was again recrystallized from aqueous ethanol, with charcoal, to yield pale yellow crystals, m. p. 96.5°. After a further recrystallization almost colorless crystals were obtained, m. p. 98.5–99°.

This corresponds closely to the melting point reported for 1-nitro-2-chloronaphthalene. Since the data in the

(3) Price and Huber, THIS JOURNAL, **64**, 2136 (1942).

(4) Jacobs, Winstein, Seymour and Linden, *J. Org. Chem.*, **11**, 292 (1946).

literature are somewhat divergent (Vesely,[5] Colerdi and Moe,[6] Hodgson and Leigh[7]) we synthesized this compound from β-naphthylamine following for the Sandmeyer step the directions of Hodgson and Walker.[8] The 2-chloro-1-nitronaphthalene so obtained had a melting point of 99–99.5°. The mixed melting point with the sample obtained by the decarboxylation of the 6-chloro-nitro-1-naphthoic acid was 98.5–99°. Accordingly our nitro product must be 6-chloro-5-nitro-1-naphthoic acid.

Nitration of Methyl 6-Chloro-1-naphthoate.—A 9.0-g. sample (0.041 mole) of pure methyl 6-chloro-1-naphthoate (m. p. 66°) was treated with 15 cc. of fuming nitric acid (d. 1.49–1.50) and warmed for five minutes on a water-bath. After cooling, a crystalline mass deposited which was collected on a glass filter and washed with a small portion of cold nitromethane. The crystal mass was already almost white, and after one recrystallization from aqueous methanol, pure methyl 6-chloro-5-nitro-1-naphthoate was obtained: yield, 3.3 g. (30%), m. p. 143.5–144°.

Anal. Calcd. for $C_{12}H_8O_4NCl$: C, 54.23; H, 3.03; N, 5.27; Cl, 13.36. Found: C, 54.52; H, 3.23; N, 5.07; Cl, 13.34.

Hydrolysis of the Nitro Ester.—A solution of 0.5 g. of the ester was refluxed in 30 cc. of 20% aqueous potassium hydroxide, to which 4 g. of salt was added. The substance dissolved after one-half hour of vigorous boiling. In acidification, a dark brown precipitate was obtained. This was filtered and twice recrystallized from nitromethane. Greenish-yellow crystals were obtained which melted at 226.5°. A mixed melting point with 6-chloro-5-nitro-1-naphthoic acid above gave 226–226.5°, showing the identity of the two compounds.

Anilide from the Nitro Acid.—A mixture of 0.2 g. of 6-chloro-5-nitro-1-naphthoic acid and 0.5 cc. of thionyl chloride was refluxed for one-half hour. The reaction mixture was treated with 1 cc. of redistilled aniline and dissolved in 15 cc. of benzene. The yellow suspension was washed with water, with dilute hydrochloric acid, with water and with sodium carbonate solution. After evaporation of the benzene, the residue was recrystallized from aqueous ethanol, using charcoal. The slightly greenish crystalline substance had a melting point of 193–193.5°.

Anal. Calcd. for $C_{17}H_{11}O_3N_2Cl$: C, 62.46; H, 3.40; N, 8.57; Cl, 10.85. Found: C, 62.71; H, 3.30; N, 8.68; Cl, 11.10.

Anilide from the Nitro Ester.—(a) A 0.28-g. sample of the ester was treated with three to four-fold excess of anilinomagnesium bromide for ten minutes on the water-bath. (The anilinomagnesium bromide was prepared by addition of 8 g. of aniline to ethylmagnesium bromide, prepared from 2 g. of magnesium and 10 g. of ethyl bromide in 60 cc. of ether, until the very vigorous evolution of ethane ceased.) Ten cc. of dilute hydrochloric acid was added to the mixture and the ether evaporated at room temperature. The dark brown solid residue from the ether layer was separated from the acidic solution by filtration, and it was recrystallized from aqueous ethanol, yielding 0.12 g. of anilide (34%), m. p. 190–191°. This was recrystallized twice (first with charcoal) to give almost colorless crystals, m. p. 193.5–194°, identical with the anilide obtained from the acid.

(b) When 0.3 g. of the ester was heated with 0.2 g. of aniline at 160–170° for twenty minutes, the ester was recovered unchanged, m. p. 143.5–144°.

Amide from the Nitro Acid.—A 0.22-g. sample of 6-chloro-5-nitro-1-naphthoic acid was heated with 1 cc. of thionyl chloride for twenty minutes. The mixture was poured into 10 cc. of ice-cooled 33% ammonium hydroxide. It was cautiously heated on the water-bath for five minutes, then cooled, filtered and recrystallized from aqueous ethanol, m. p. 207–208°.

(5) Vesely, *Ber.*, **38**, 137 (1905).

(6) Colerdi and Moe, *Rend. Int. Lomb.*, **57**, 646 (1924).

(7) Hodgson and Leigh, *J. Chem. Soc.*, 1352 (1937).

(8) Hodgson and Walker, *ibid.*, 1621 (1933).

Anal. Calcd. for $C_{11}H_7O_3N_2Cl$: N, 11.17. Found: N, 10.70.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, INDIANA
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED JANUARY 5, 1948

9,9-Dibromofluorene and Formation of a Dangerous Skin Irritant

BY JOHN R. SAMPEY AND SCOTT J. CHILDRESS

The preparation of 9-bromofluorene by direct photobromination[1] suggested the preparation of 9,9-dibromofluorene by the addition of a second mole of bromine under strong irradiation.

A solution of 16 g. of fluorene in 150 ml. of carbon tetrachloride was placed in a 250 ml. Vitreosil Erlenmeyer flask equipped with reflux condenser. By the use of a six-inch mercury arc close to the flask, the contents were heated to reflux while a solution of 2 moles of bromine in 50 ml. more solvent was added dropwise through the condenser in thirty minutes. Anhydrous conditions were assumed by a calcium chloride tube and irradiation continued thirty minutes after the addition. Evaporation of the solvent yielded a light gray crystalline product recrystallized from acetic acid, *n*-heptane or absolute alcohol. The yield was 45% of material melting at 115° (uncor.). The literature value for 9,9-dibromofluorene is 114°.[2]

Experiments to further identify the 9,9-dibromofluorene were discontinued when two additional workers to those reported previously,[3] were stricken with a severe dermatitis which has spread over large areas of the body, and which is responding slowly to medical treatment. Intense itching, pus formation, and considerable swelling of the hands, arms and face accompany the irritation.

The authors acknowledge with pleasure the interest of Dr. E. Emmet Reid.

(1) J. R. Sampey and E. E. Reid, THIS JOURNAL, **69**, 234–235 (1947).

(2) H. Staudinger and A. Gaule, *Ber.*, **49**, 1951 (1916).

(3) J. R. Sampey, A. B. King, T. A. Roe, Jr., and S. J. Childress, *Science*, **105**, 621 (1947).

DEPARTMENT OF CHEMISTRY
FURMAN UNIVERSITY
GREENVILLE, S. C.

RECEIVED JULY 21, 1947

Nuclear Substituted 9-(4′-Diethylamino-1′-methylbutylamino)-acridines[1]

BY E. R. SHEPARD AND H. A. SHONLE[2]

At the suggestion of the Committee on Medical Research of the OSRD several years ago, the preparation of a series of nuclear substituted acridines was undertaken. They were prepared in order to study clinically the absorption, excretion and metabolic changes which these materials undergo. In addition, it was of interest to inquire further

(1) Presented before the Division of Medicinal Chemistry at the 109th meeting of the American Chemical Society, Atlantic City, New Jersey, April, 1946.

(2) Deceased, February 24, 1947.

into the relationship of structure and antimalarial activity of the acridines.[3]

The following conclusions can be drawn on the basis of duckling tests[4] on the compounds reported here: (a) A substituent in the 1 position (Fig. 1) appears to be mildly dystherapeutic:

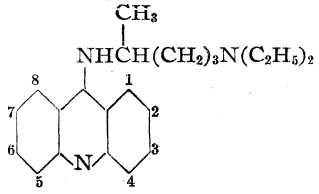


Fig. 1.

(b) One substituent in the 4 or 5 position gives a regular dystherapeutic effect. Since completion of this work, these findings have been supported by Hall and Turner[5] with the amendment that upon substitution in both the 4 and 5 positions, increased activity may be expected.

Experimental

The *o*-chloro-, *o*-bromo and 2,4-dichlorobenzoic acids were obtained commercially. The *o*-chlorobenzoic acid was purified[6] before use.

The anilines with the exception of 2-chloro-4-methoxy and 3,5-dichloroaniline were commercial samples which were distilled or crystallized.

3,5-Dichloroaniline was prepared from 2,6-dichloro-4-nitroaniline by deamination and reduction of the resulting 3,5-dichloronitrobenzene.[7]

2-Chloro-4-methoxyaniline was prepared quite readily in large quantities from technical *p*-anisidine.[8] Phosgene passed into an aqueous solution of pyridine and technical *p*-anisidine gave an 82% yield of N,N'-di-(*p*-methoxy)-phenylurea which was dried and chlorinated in *sym*-tetrachloroethane to give a quantitative yield of the dichlorinated urea. Treatment with 28% ammonium hydroxide at 150–160° for five hours gave a 90–95% yield of 2-chloro-4-methoxyaniline, b. p. 141–144° (25 mm.); N-acetyl derivative, m. p. 113–114.5° (lit.,[8] m. p. 114°).

Diphenylamine-2-carboxylic Acids.—The diphenylaminecarboxylic acids were prepared according to the method of Ullmann.[9] The following more detailed description is typical of the method used for the preparation.

5-Chlorodiphenylamine-2-carboxylic Acid.[10]—One hundred grams (0.52 mole) of 2,4-dichlorobenzoic acid, 60 g. (0.64 mole) of aniline, 82 g. (0.59 mole) of potassium carbonate, 3–5 g. of copper oxide (precipitated powder), and 250 ml. of isoamyl alcohol were refluxed three hours. The hot solution was steam distilled until all of the alcohol and some basic oil came over. The hot residual solution was diluted to 3–4 liters with hot water and decolorized with carbon. The filtrate was acidified with dilute hydrochloric acid, and filtered. The yield was 103–115 g. of crude 5-chlorodiphenylamine-2-carboxylic acid. Since purification was not necessary at this step and would diminish over-all yields, no attempt was made to isolate the pure amino acids.

The crude amino acids were ring closed to the corresponding 9-chloroacridines[11] and these then reacted with excess 5-diethylamino-2-aminopentane in phenol at 100–110° for one to two hours. The reaction mixtures were decomposed with excess sodium hydroxide solution and extracted with ether. The ether layers were washed and extracted with 5% acetic acid. The bases were liberated from the acetate solutions with sodium hydroxide, taken up in ether and heated eventually at 100° at 15 mm. to remove excess 5-diethylamino-2-aminopentane. Dry hydrogen chloride passed into the solutions of the bases in dry ether gave the anhydrous hydrochlorides which were extremely hygroscopic. The melting points of the anhydrous salts varied widely with slight changes in hydrogen chloride content and were therefore meaningless. Table I lists the acridines prepared in this manner.

TABLE I

9-(4'-DIETHYLAMINO-1'-METHYBUTYLAMINO)-ACRIDINES

Substituents (Fig. 1)	Yield, %[a]	Formula	Nitrogen, % Calcd.	Found[b]
None	71[c]	$C_{22}H_{29}N_3 \cdot 2HCl$	10.29	9.60
2-Cl[d]	34	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.68
3-Cl[e]	29	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.23
4-Cl	24	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.69
4-CH_3	37	$C_{23}H_{31}N_3 \cdot 2HCl$	9.95	9.85
4-OCH_3	15	$C_{23}H_{31}N_3O \cdot HCl$	10.48	10.44
1,3-diCl[g]	7[f]	$C_{22}H_{27}Cl_2N_3 \cdot 2HCl \cdot H_2O$	8.48	8.50
2-OCH_3-4-Cl	30[f]	$C_{23}H_{30}ClN_3O \cdot 2HCl$	8.88	8.81
4-OCH_3-6-Cl	59	$C_{23}H_{30}ClN_3O \cdot 2HCl$	8.88	8.43
4-OCH_3-1-CH_3	38	$C_{24}H_{33}N_3O \cdot HCl$	10.10	9.95
2-Cl-4-CH_3	17[f]	$C_{23}H_{30}ClN_3 \cdot 2HCl$	9.20	8.42
3-Cl-4-CH_3	23[f]	$C_{23}H_{30}ClN_3 \cdot 2HCl$	9.20	8.43
2-Br-4-CH_3	11	$C_{23}H_{30}BrN_3 \cdot 2HCl$	8.38	8.16
2-CH_3O-4,6-diCl	29	$C_{23}H_{29}Cl_2N_3O \cdot 2HCl$	8.28	8.21
4-CH_3-3,6-diCl	15	$C_{23}H_{29}Cl_2N_3 \cdot 2HCl$	8.56	8.59
2,4,6-triCl[h]	2	$C_{22}H_{26}Cl_3N \cdot 2HCl \cdot H_2O$	7.94	7.95

[a] Based on 2-chloro or 2,4-dichlorobenzoic acid unless otherwise noted. [b] The samples were dried *in vacuo* for two weeks over potassium hydroxide before analysis. [c] Based on 9-chloroacridine. [d] Previously reported, U. S. Patent 2,077,249. [e] Previously reported, German Patent 571,449. [f] Based on 2-bromobenzoic acid. [g] Recrystallized from ethanol–water–ether, m. p. 138–142°. [h] Recrystallized from ethanol–water–ether, m. p. 158–161°.

LILLY RESEARCH LABORATORIES
INDIANAPOLIS 6, INDIANA RECEIVED FEBRUARY 6, 1948

Ethyl Acetoacetate 4-Nitrophenylhydrazone and 1-(4'-Nitrophenyl)-3-methylpyrazolone-5

BY WARD C. SUMPTER AND PHIL H. WILKEN

The interaction of equimolecular proportions of ethyl acetoacetate and 4-nitrophenylhydrazine at steam-bath temperature in either the presence or absence of ethanol as a solvent yields ethyl acetoacetate 4-nitrophenylhydrazone (I), m. p. 118°, and not 1-(4'-nitrophenyl)-3-methylpyrazolone-5 (II), m. p. 218°, as stated in the literature.[1]

The nitrophenylhydrazone (I) was converted into the pyrazolone (II) by refluxing a solution of I in glacial acetic acid for five hours at steam-bath temperature. Heating I at steam-bath temperature for fifteen minutes with concentrated hydrochloric acid accomplished the same transformation. Similarly II was obtained when ethyl ace-

(1) Altschul, *Ber.*, **25**, 1853 (1892), via Huntress-Mulliken, "Identification of Pure Organic Compounds, Order 1," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 255.

(3) Corse, Shonle and Bryant, THIS JOURNAL, **68**, 1905, 1911 (1946), reported previous series in which the nucleus was held constant and the side chain was varied.

(4) Performed by K. K. Chen, C. L. Rose and R. C. Anderson of these laboratories, using *Plasmodium Lophurae*.

(5) Hall and Turner, *J. Chem. Soc.*, 694 (1945).

(6) "Organic Syntheses," Coll. Vol. II, p. 16, (1943).

(7) Kremer and Bendich, THIS JOURNAL, **61**, 2659 (1939).

(8) French Patent 738,157.

(9) Ullmann, *Ann.*, **355**, 312 (1907).

(10) Ullmann and Wagner, *ibid.*, **355**, 359 (1907).

(11) "Organic Syntheses," **22**, 5 (1942).

toacetate and 4-nitrophenylhydrazine were refluxed together in equimolecular quantities in glacial acetic acid as solvent. The pyrazolone (II) was also obtained when the condensation of ethyl acetoacetate and 4-nitrophenylhydrazine was carried out in the presence of concentrated hydrochloric acid with or without the addition of ethanol.

The samples of II obtained in these several procedures were identified by comparison with an authentic sample prepared by the nitration of 1-phenyl-3-methylpyrazolone-5 as described in German Patent 61794.[2]

Experimental

Ethyl Acetoacetate 4-Nitrophenylhydrazone (I).—A mixture of 15.3 g. (0.1 mole) of 4-nitrophenylhydrazine and 13.0 g. (0.1 mole) of ethyl acetoacetate with or without the addition of a small quantity of ethanol as solvent was heated under reflux on the steam-bath for several hours. The orange colored crystalline product which separated on cooling was purified by crystallization from 95% ethanol; m. p. 118°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: N, 15.84. Found: N, 15.85, 15.76.

1-(4′-Nitrophenyl)-3-methylpyrazolone-5 (II). A.—A sample of ethyl acetoacetate 4-nitrophenylhydrazone (5 g.) was treated with sufficient glacial acetic acid to dissolve it and the resulting solution heated under reflux at steam-bath temperature for five hours. The yellow crystalline product which separated on cooling was purified by crystallization from 95% ethanol from which it separated as light yellow crystals; m. p. 218°. Heating the hydrazone (I) for fifteen minutes at steam-bath temperature with concentrated hydrochloric acid brought about the same transformation.

B.—A mixture of 7.65 g. (0.05 mole) of 4-nitrophenylhydrazine, 6.5 g. (0.05 mole) of ethyl acetoacetate and 25 g. of glacial acetic acid was heated under reflux at steam-bath temperature for five hours. The product which separated on cooling was crystallized from 95% ethanol from which it separated as light yellow crystals; m. p. 218°. The pyrazolone (II) was also obtained when a mixture of ethyl acetoacetate (0.05 mole) and 4-nitrophenylhydrazine (0.05 mole) was heated in the presence of 2 ml. of concentrated hydrochloric acid either with or without the addition of ethanol.

C.—The compound was prepared from 1-phenyl-3-methylpyrazolone-5 by nitration according to the procedure given in German Patent 61794[2]; light yellow crystals; m. p. 218°.

The identity of the samples prepared by procedures A, B and C was established by melting point methods. The melting points reported herein are uncorrected.

Anal. Calcd. for $C_{10}H_9N_3O_3$: N, 19.17. Found: N, 18.74, 18.80.

(2) *Friedländer*, **3**, 926.

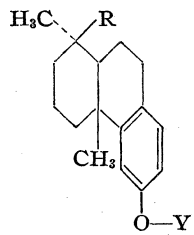
DEPARTMENT OF CHEMISTRY
WESTERN KENTUCKY STATE COLLEGE
BOWLING GREEN, KENTUCKY

RECEIVED JANUARY 10, 1948

Studies on Resin Acids. III. A Direct Reduction of Podocarpic Acid[1]

BY HAROLD H. ZEISS, CHESTER E. SLIMOWICZ AND VARSENIG Z. PASTERNAK

The constitution of the naturally occurring podocarpic acid (I) has suggested this resin acid as an unusually attractive starting material for the preparation of compounds having structural and perhaps physiological similarity to estradiol. One such compound is the hitherto unknown podocarpinol (II), the preparation of which is described in one step from podocarpic acid in this paper.



I, R = COOH; Y = H
II, R = CH_2OH; Y = H
III, R = COOCH; Y = CH_3
IV, R = COCl; Y = CH_3
V, R = CH_2OH; Y = CH_3

The direct reduction of the carboxylic acid group of the resin acids is usually attended by more or less difficulty, depending upon the configuration of these groups at the C_1 position. The *trans* acids,[2] represented by abietic acid, are less hindered and therefore more easily reduced than the *cis* acids,[2] represented by agathic and podocarpic acids, which are quite resistant to reaction owing to the extremely large effect of steric hindrance. While methyl abietate responds readily to a forced Bouveault-Blanc reduction, the methyl ester of isonoragathic acid is converted to isonoragathenol in very poor yield.[3] Alternately Campbell and Todd[4] have used an indirect method for reducing the O-methyl derivative of podocarpic acid to O-methylpodocarpinol *via* the acid chloride and the aldehyde.

It has been found that lithium aluminum hydride,[5] a compound recently discovered by Schlesinger and co-workers[6] and developed by Nystrom and Brown,[7] converts podocarpic acid directly to podocarpinol in satisfactory yield (56%). Under the same experimental conditions the methyl ester (III) and the acid chloride (IV) of O-methylpodocarpic acid also react with lithium aluminum hydride to give, after hydrolysis of the metal complex, O-methylpodocarpinol (V). The identity of podocarpinol is established by methylation to the known O-methylpodocarpinol.

Although the rate of reaction of lithium aluminum hydride with podocarpic acid is slow, it appears that the reduction of hindered acids with this reagent is not unreasonably limited by steric effects.

Experimental

Podocarpinol (II).—A solution of 8 g. of lithium aluminum hydride in 300 ml. of dry ether was placed in a one-liter flask equipped with dropping funnel, reflux condenser and mercury seal stirrer. All outlets were provided with calcium chloride tubes to exclude moisture during the reaction. To this solution was added dropwise with stirring 7 g. of podocarpic acid (m. p. 194–196°) dissolved in 150 ml. of ether. The mixture was then

(1) Paper II: Zeiss, THIS JOURNAL, **70**, 858 (1948).

(2) Zeiss, *Chem. Rev.*, **42**, 163 (1948).

(3) Ruzicka and Jacobs, *Rev. trav. chim.*, **57**, 509 (1938).

(4) Campbell and Todd, THIS JOURNAL, **64**, 928 (1942).

(5) Metal Hydrides, Inc., Beverly, Mass.

(6) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

(7) Nystrom and Brown, *ibid.*, **69**, 1197; **69**, 2548 (1947).

allowed to stand for four days with occasional warming. Ice was next introduced to decompose excess hydride reagent and the reaction complex then hydrolyzed with dilute sulfuric acid. The ether layer was removed and the aqueous layer extracted with fresh ether. The combined ether extracts were then washed with water and extracted with dilute sodium carbonate solution to remove unreacted podocarpic acid. After drying over anhydrous potassium carbonate the ether solution was concentrated and hexane added. On cooling transparent cubes of podocarpinol crystallized out of solution; m. p. 177–178.5°. Recrystallization from ether gave 3.7 g. (56%) of pure material; m. p. 178–179°.

Anal.[8] Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.09; H, 9.08.

In an earlier run in which the total reaction time was two hours a yield of 4.6% of podocarpinol was obtained.

Methylation of podocarpinol with dimethyl sulfate in the usual manner gave O-methylpodocarpinol (m. p. 90–91°), first prepared by Campbell and Todd.[4] A mixed m. p. with the O-methylpodocarpinol prepared as described below showed no depression.

O-Methylpodocarpinol (V). (*a*) **From O-Methylpodocarpoyl Chloride (IV).**—Reaction between 33 g. of O-methylpodocarpoyl chloride (m. p. 61°) in 1 liter of ether and 10 g. of lithium aluminum hydride in 800 ml. of ether was carried out over a period of four days. The mixture was worked up in the same manner as described above (m. p. 91°) from which 28 g. (92%) of pure O-methylpodocarpinol was obtained after one crystallization from ether–hexane.

(*b*) **From Methyl O-Methylpodocarpate (III).**—Lithium aluminum hydride (8 g.) in 400 ml. of ether was treated with 15 g. of methyl O-methylpodocarpate m. p. 158–159° in 300 ml. of ether as above. From this experiment there was obtained 12.7 g. (93%) of O-methylpodocarpinol; m. p. 91°.

(8) Analysis by Dr. Carl Tiedcke Microlaboratories, New York.

RIDBO LABORATORIES, INC.
PATERSON 3, NEW JERSEY RECEIVED JANUARY 12, 1948

NEW COMPOUNDS

α-Nitrostilbene Analogs

The *alpha*-nitrostilbenes are physiologically active. Also compounds of the *alpha*, *beta*-diphenylethylamine type obtained by further reduction have been reported to have a selective effect in damaging sarcoma cells.[3]

Accordingly we have prepared nitro compounds of this type and submitted them to the National Cancer Institute for testing.

1-α-Thienyl-2-phenyl-2-nitroethylene was prepared by mixing 9.0 g. phenylnitromethane, 8.1 g. 2-thiophenealdehyde[4] and 3 ml. of a 10% solution of methylamine in methanol, warming gently, then shaking for three hours at room temperature. The bright yellow crystals which separated weighed 4.9 g. After triple recrystallization from absolute ethanol the product melted at 123° cor.

Anal. Calcd. for $C_{12}H_9O_2SN$: C, 62.34; H, 3.90; N, 6.06. Found: C, 62.45; H, 3.76; N, 6.06.

(1) Present address: Medical School, University of Tennessee, Memphis, Tennessee.

(2) Present address: Plough, Inc., Memphis, Tennessee.

(3) Shear, *et al.*, *Approaches to Tumor Chemotherapy*, American Association for the Advancement of Science, Washington, D. C. (1947), page 236 ff.; also Hartwell and Kornberg, THIS JOURNAL, **67**, 1607 (1946).

(4) Purchased from Aragohes Chemicals, Inc., Boulder, Colo.

1-α-Furyl-2-*o*-chlorophenyl-2-nitroethylene was prepared by mixing 7.82 g. of *o*-chlorophenylnitromethane, 4.36 g. of freshly distilled furfural, and 5.16 cc. of a 16% solution of methylamine in methanol. The crystals which separated on standing three days weighed 3.96 g. The product was dissolved in absolute ethanol and the solution decolorized with activated carbon. After recrystallization from absolute ethanol the melting point was 101.1° cor.

Anal. Calcd. for $C_{12}H_8NO_3Cl$: C, 57.72; H, 3.21; N, 5.61. Found: C, 57.92; H, 3.12; N, 5.53.

1-*m*-Nitrophenyl-2-phenyl-2-nitroethylene was prepared by mixing 3 ml. of phenylnitromethane, 3.0 g. of *m*-nitrobenzaldehyde,[5] 0.5 ml. of 10% methylamine and 6 ml. of methanol. After standing four days the solution was diluted with 25 ml. of petroleum ether and chilled in Dry Ice. The yield of crystals was only 0.4 g. (7.5%). After recrystallization from absolute ethanol the melting point was 112.0° cor.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 62.22; H, 3.70; N, 10.37. Found: C, 62.60; H, 3.75; N, 10.12.

1-*p*-Nitrophenyl-2-phenyl-2-nitroethylene, reported by Baker and Wilson[6] as melting at 155°, was prepared by us and found to melt at 157.5° cor., after repeated recrystallization.

Acknowledgment.—We wish to acknowledge our indebtedness to Dr. M. J. Shear and Dr. Jonathan L. Hartwell of the National Cancer Institute for suggestions and encouragement, to Mr. Charles A. Kinser and Mrs. Margaret M. Ledyard of the National Institute of Health for carrying out the microanalyses recorded above, and to the National Cancer Institute for financial assistance.

(5) Purchased from Eastman Kodak Company, Rochester, N. Y.

(6) Baker and Wilson, *J. Chem. Soc.*, 842–848 (1927).

CHEMISTRY DEPARTMENT
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENNESSEE
CARL T. BAHNER,
HARRY E. DICKSON[1]
LYDIA MOORE[2]

RECEIVED FEBRUARY 24, 1948

3-Chloro-6-methoxy-8-nitroquinoline

To a stirred mixture of 300 ml. of concentrated hydrochloric acid, 50.4 g. of 3-nitro-4-aminoanisole and 85.2 g. of arsenic acid, at 100°, there was added 30.0 g. of α-chloroacrolein during one hour. After an additional hour at 100°, the mixture was poured on ice. A solid which separated was filtered off and recrystallized from acetone; yield 16 g., m. p. 151–153°. Recrystallization from methanol raised the m. p. to 159.5–160°.

Anal. Calcd. for $C_{10}H_7ClN_2O_3$: C, 50.31; H, 2.94; Cl, 14.88; N, 11.74. Found: C, 50.68; H, 2.84; Cl, 15.06; N, 11.75.

The original aqueous filtrate gave no product on neutralization.

THE DIVISION OF MEDICINAL CHEMISTRY
THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH
NEW BRUNSWICK, N. J.
HARRY L. YALE

RECEIVED JANUARY 23, 1948

New Compounds as Insect Repellents

The compounds listed in Table I were prepared as part of a project to discover new insect repellents.[1]

2,2-Diethyl-1,3-Propanediol.—A solution of 43 g. of potassium hydroxide in 400 ml. of 95% ethanol was added to an ice-cooled, well-stirred mixture of 167 g. of 38% formaldehyde solution and 100 g. of 2-ethylbutyraldehyde (Eastman Kodak Co.) at such a rate that the tem-

(1) This work was performed under Contract NDCrc 136 between Harvard University and the Office of Scientific Research and Development, with Paul D. Bartlett as official investigator.

TABLE I

Compound	Boiling point[a] °C.	Mm.	M. p., °C.	$n^{25}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2,2-Diethyl-1,3-propanediol	130–133	16	53–55	1.4574[b]	76	$C_7H_{16}O_2$	63.6	12.2	63.9	12.5
2,2-Diethyl-1,3-propanediol diacetate	73– 76	0.5	...	1.4332	65	$C_{11}H_{20}O_4$	61.1	9.3	61.0	9.4
2-(*p*-Methoxyphenyl)-5,5-diethyl-*m*-dioxane	167	2.5	30–32	1.5122[b]	49	$C_{15}H_{22}O_3$	72.0	8.9	72.1	9.0
1-Phenyl-1,3-propanediol dipropionate	114–117	0.3	...	1.4880	83	$C_{15}H_{20}O_4$	68.2	7.6	68.7	7.8
n-Propyl piperonylate	101–103	0.3	...	1.5295	72[c]	$C_{11}H_{12}O_4$	63.5	5.8	63.0	5.9
n-Butyl piperonylate	101–104	0.1	...	1.5238	60[c]	$C_{12}H_{14}O_4$	64.9	6.4	64.5	6.3
n-Amyl piperonylate	117–120	0.1	52–53	....	50[c]	$C_{13}H_{16}O_4$	66.1	6.8	66.6	7.1
n-Propyl *p*-methoxycinnamate	110–120	0.1	13–14	1.5706	73	$C_{13}H_{16}O_3$	70.9	7.3	70.9	7.4
Isoamyl *p*-methoxycinnamate	156–158	0.7	...	1.5549	72	$C_{15}H_{20}O_3$	72.6	8.1	72.7	7.8
Diisopropyl hexahydrophthalate	136–138	10	...	1.4421	48	$C_{14}H_{24}O_4$	65.6	9.4	65.7	9.5
Di-*n*-butyl hexahydrophthalate	135–136	0.7	...	1.4511	77	$C_{16}H_{28}O_4$	67.6	9.9	67.1	10.1
Benzaldehyde di-*n*-butyrate	128–130	1	...	1.4791	77	$C_{15}H_{20}O_4$	68.2	7.6	68.7	7.9
p-*n*-Propylphenethyl alcohol	97– 98	1	...	1.5155	36	$C_{11}H_{16}O$	80.4	9.8	79.9	10.0
N-Cyclohexyl-N-phenylpropionamide	122	0.2	86–87	....	81	$C_{15}H_{21}NO$	77.9	9.2	78.3	8.9

[a] Fractionations were through a five-inch indented Claisen distillation head. [b] For super-cooled liquid. [c] Based on piperonylic acid.

perature did not exceed 16°. The resultant solution stood at room temperature for three days, was neutralized with carbon dioxide, and the alcohol was removed by distillation. The oily layer was taken up in ether and the extract was washed once with a small amount of water, dried with magnesium sulfate and distilled.

2,2-Diethyl-1,3-Propanediol Diacetate.—A solution of 23.5 g. of 2,2-diethyl-1,3-propanediol and 75 ml. of acetic anhydride was heated on a steam-bath for twelve hours with 10 g. of sodium acetate.

2-(*p*-Methoxyphenyl)-5,5-diethyl-*m*-dioxane.—A solution of 21 g. of 2,2-diethyl-1,3-propanediol, 23.8 g. of anisaldehyde, 0.2 g. of *p*-toluenesulfonic acid and 50 ml. of benzene was refluxed overnight in an apparatus which trapped water as formed.

1-Phenyl-1,3-propanediol Dipropionate.—A solution of 30 g. of 1-phenyl-1,3-propanediol,[2] 76 ml. of propionic anhydride and 63 ml. of pyridine was heated at 100° for two hours and distilled.

Piperonylates.—The acid chloride[3] of piperonylic acid[4] was heated at 100° with pyridine and a several-fold excess of suitable alcohol.

***p*-Methoxycinnamates.**—These esters were obtained by transesterification. A solution of ethyl *p*-methoxycinnamate[5] in 3 parts by weight of the appropriate alcohol containing 0.2% of dissolved sodium was slowly distilled through a short Vigreux column.

Hexahydrophthalates.—Dimethyl hexahydrophthalate, b. p. 91–93° (1.3 mm.), $n^{25}D$ 1.4567, was obtained in 92% yield by hydrogenation of dimethyl phthalate over Raney nickel at 175°. It was converted to higher esters by transesterification as described for the *p*-methoxycinnamates.

Benzaldehyde Di-*n*-butyrate.—A drop of 95% sulfuric acid was added to a solution of 25 g. of benzaldehyde in 41 g. of butyric anhydride. Heat was evolved. After the solution had cooled back to room temperature, it was taken up in ether and the ether solution was washed with water, dried, and distilled.

***p*-*n*-Propylphenethyl Alcohol.**—To an ether solution of the Grignard reagent prepared from 50 g. of *p*-bromo-*n*-propylbenzene (Eastman Kodak Co.) there was added with stirring 12 g. (10% excess) of ethylene oxide. A gum precipitated. While stirring continued, the ether was removed by distillation, toluene being gradually added to take its place. The mixture was stirred for an hour at 95° and poured while still hot into aqueous ammonium chloride solution. The oil which separated was taken up in ether and the ether extract was dried over magnesium sulfate and distilled.

N-Cyclohexyl-N-phenylpropionamide.—A solution of 28 g. of cyclohexylaniline (Monsanto Co.) and 47 g. of propionic anhydride was refluxed for eight hours and distilled. The product was recrystallized from hexane.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS
B. C. McKUSICK[6]

RECEIVED FEBRUARY 3, 1948

(2) Prins, *Chem. Weekblad*, **16**, 1510 (1919); Fourneau, Benoit and Firmenich, *Bull. soc. chim.*, **47**, 858, 894 (1930).

(3) Barger, *J. Chem. Soc.*, **93**, 563 (1908).

(4) Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley, New York, N. Y., 1943, p. 538.

(5) Reychler, *Bull. soc. chim.*, [3] **17**, 510 (1897).

(6) Present address: Chemical Department, Experimental Station, E. I. du Pont de Nemours & Company, Wilmington, Delaware.

COMMUNICATIONS TO THE EDITOR

ADSORPTION AT THE DROPPING MERCURY ELECTRODE

Sir:

Despite the large quantity of work which has been carried out with capillary-active substances as maximum suppressors in polarographic analysis, a detailed consideration of their effect on the diffusion current itself has apparently not been made. One may find references in the literature[1,2,3] to interference with the diffusion current, brought about by the use of capillary-active materials, but no satisfactory explanation has been offered.

Polarograms prepared from solutions which contained various concentrations of purified horse albumin at *p*H 8 and which were 1×10^{-4} *M* in the dye *p*-hydroxyphenylazophenylarsonic acid, 0.15 *M* in sodium chloride, and 0.02 *M* in veronal indicated that the diffusion current was suppressed to approximately 90% of its true value at a protein concentration of 1×10^{-6} *M* and to an asymptotic value of about 25% at 1×10^{-5} *M*.

It seems likely that the albumin, a capillary-active substance, is adsorbed on the growing mercury drops, decreasing the surface available for reaction with the reducible molecules or ions and so decreasing the diffusion current. If so, the fractional change of free surface and the consequent fractional change in instantaneous diffusion current should at any stage in the life of the drop be a function of the change in the concentration of protein. At moderately high concentrations of protein, however, a monomolecular layer would be formed and an asymptotic diffusion current would be attained corresponding to the remaining free surface between the adsorbed protein molecules. (Even in closest packing these large molecules might well leave holes large enough to permit the smaller molecules of reducible material to reach the electrode.) These considerations are in qualitative agreement with the experimental results; furthermore, for protein concentrations C_p giving diffusion currents i_d not too close to the asymptotic current for a given constant dye concentration, they lead to a theoretical relation similar to the equation $\log i_d = -k_1 C_p + k_2$ which was found empirically.

As the concentration of a reducible substance is increased beyond a critical value, the "diffusion current constant" decreases and the current approaches a saturation value. It might be expected that an electrode covered over to a given extent, say with a monomolecular layer of adsorbed large molecules, would reach saturation at the same concentration of reducible substance as a normal electrode, but that the saturation current would be reduced; *i. e.*, with a given protein concentration, the diffusion current should be reduced by a constant fraction, which is independent of the dye concentration. A series of polarograms of the same system, this time with the protein absent or held constant at a comparatively high concentration, showed a 70% reduction of the saturation current, in the presence of protein, but no change in the concentration of dye required to reach saturation.

The probable relation of these results to the phenomenon of maximum suppression is being explored. A more detailed account of the work will be published later.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA BERTRAM KEILIN

RECEIVED MARCH 8, 1948

(1) Salac, *Kvas*, **64**, 383 (1936).
(2) Brdicka, *Z. Elektrochem.* **48**, 278, 686 (1942).
(3) Kolthoff and Barnum, THIS JOURNAL, **63**, 520 (1941).

THE INFRARED SPECTRUM OF SPRUCE NATIVE LIGNIN

Sir:

Initial work on an extensive study of the applications of infrared spectroscopy to the problem of lignin structure has resulted in the establishment of the spectrum of Brauns' spruce native lignin by several independent methods of sample preparation. Typical curves (obtained with a Perkin–Elmer Model 12-B recording spectrometer using a sodium chloride prism) are shown in Fig. 1.

The film method of sample preparation warrants a brief description. By filling a shallow cup comprised of a metal ring and salt plate base with ethyl alcohol, adding a small proportion of dioxane solution, and allowing evaporation to take place slowly, the lignin was deposited as a strongly adherent clear film. The films thus obtained were dried for sixteen hours in a vacuum desiccator before use. Of particular value is the fact that dioxane is sufficiently transparent to permit its use as a solvent in the important carbonyl (1650–1850 cm.$^{-1}$) and hydroxyl (3000–3700 cm.$^{-1}$) regions, as shown in Curve A.

Two important points have been established: (1) The infrared spectrum of native lignin in film form is essentially unchanged by as much as ten hours of heating at 100°. (2) The broad band centered at 3350 cm.$^{-1}$ for film and Nujol dispersion and the shift of this band to higher frequency in dioxane solution is indicative of strong hydrogen bonding in lignin. Experiments on dilution and heating effects are planned which should yield valuable evidence as to the nature of this bond.

An investigation of the spectra of related com-

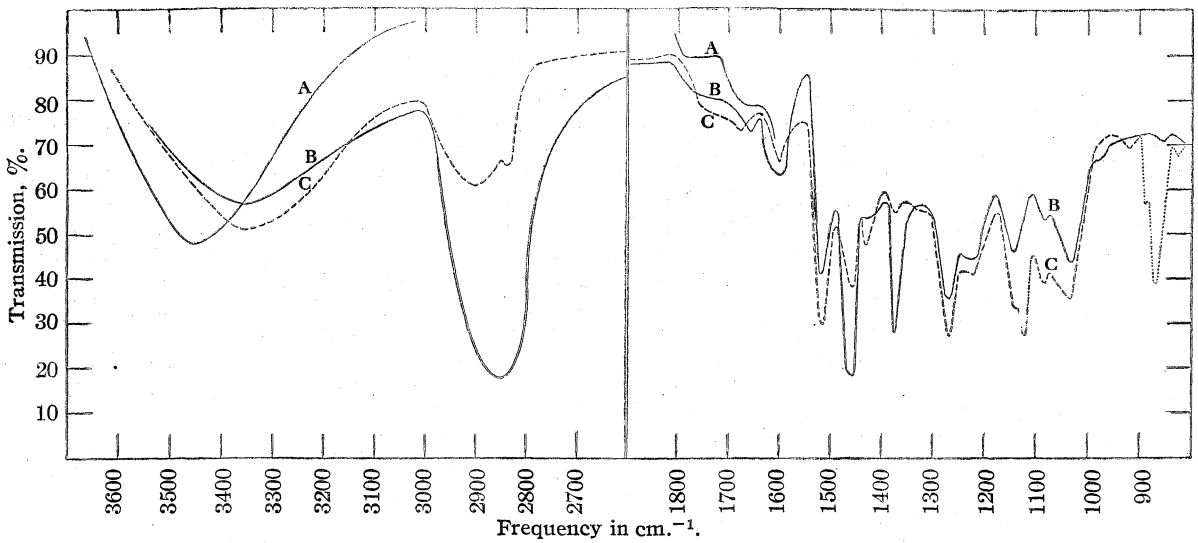


Fig. 1.—Spruce native lignin: curve A, 3% solution in dioxane, 0.127 mm. cell; curve B, 10–15% dispersion in Nujol, smear on salt plate; curve C, film from dioxane–EtOH on salt plate (1900 cm.$^{-1}$–2600 cm.$^{-1}$ section essentially transparent).

pounds, of lignin derivatives, and of lignin from other sources and as the result of industrial processing is in progress.

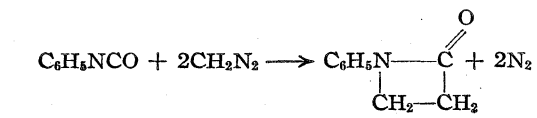
THE INSTITUTE OF PAPER CHEMISTRY
APPLETON, WISCONSIN EDWARD J. JONES

RECEIVED APRIL 3, 1948

A NOVEL SYNTHESIS OF A β-LACTAM

Sir:

In the course of an investigation of amino acid derivatives, a unique synthesis of the β-lactam of N-phenyl-β-alanine was discovered. The reaction between an isocyanate and diazomethane does not seem to have been studied previously. We have found that in the case of phenyl isocyanate two methylene units are added in a reaction analogous to the formation of cyclobutanone from ketene and diazomethane.[1]



To a solution of 2.38 g. (0.02 mole) of freshly distilled phenyl isocyanate in 25 ml. of anhydrous ether was added 109 ml. of a 0.46 *M* cold ethereal solution of diazomethane (0.05 mole) dried over sodium. Within about two minutes a vigorous reaction commenced with evolution of nitrogen and the simultaneous deposition of an amorphous orange precipitate. After twenty hours at 0–5° the solution was separated from insoluble material (0.9 g.), and concentrated under reduced pressure to a brown, viscous oil (1.8 g.). Evaporative distillation at 80–120° and 1 mm. gave 0.59 g. (20%) of the colorless crystalline β-lactam of N-phenyl-β-alanine, m. p. 74–76°. An analytical sample, recrystallized twice from acetone–isooctane, was obtained as colorless glistening platelets, m. p. 78–79°.

Anal. Calcd. for C_9H_9ON: C, 73.43; H, 6.16; N, 9.52; mol. wt., 147.2. Found: C, 73.20; H, 6.23; N, 9.58; mol. wt., 139 (Rast).

A suspension of the lactam (0.5 g.) in 5 ml. of *N* sodium hydroxide was warmed with shaking to 70–80°. After ten to twelve minutes the solution became completely clear. From the cooled acidified solution crystalline N-phenyl-β-alanine (0.25 g., m. p. 59–60°) was recovered by ether extraction, evaporative distillation, and crystallization from carbon disulfide–ligroin. No depression in melting point was observed for a mixture with authentic N-phenyl-β-alanine (m. p. 58–59°), prepared from aniline and β-iodopropionic acid by the method of Bischoff and Mintz.[2]

This appears to be the simplest β-lactam reported; other known representatives of this class of compounds have at least two substituents on the ring.[3] It is of interest to note the ease of hydrolysis in the present case as compared to more highly substituted β-lactams or normal amides. The reaction between diazomethane and other isocyanates and isothiocyanates has been investigated and will be reported shortly.

We are indebted to Dr. John D. Roberts for valuable suggestions and to Swift and Company for support of a fellowship for one of us (P.T.I.).

DEPARTMENT OF CHEMISTRY JOHN C. SHEEHAN
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS PATRICK T. IZZO

RECEIVED APRIL 15, 1948

(1) P. Lipp and R. Köster, *Ber.*, **64**, 2823 (1931).

(2) C. A. Bischoff and N. Mintz, *Ber.*, **25**, 2351 (1892).

(3) H. Staudinger and S. Jelagin, *ibid.*, **44**, 373 (1911); Staudinger, *ibid.*, **50**, 1038 (1917); H. Breckpot, *Bull. soc. chim. Belg.*, **32**, 424 (1923); H. Gilman and M. Speeter, THIS JOURNAL, **65**, 2255 (1943).

ION-EXCHANGE SEPARATION OF THE ALKALI METALS

Sir:

We wish to report preliminary results on the separation of alkali-metal ions by an ion-exchange procedure, using the identical column and resin bed used by Mayer and Tompkins[1] in their 61-Eu separation (1.0 sq. cm. × 10.4 cm. colloidal agglomerates of Dowex-50; 2.83 g. oven-dried resin weight; 8.84 ml. bed solution volume = one V-unit[1]) and a recording counter to assay the relative activity in the effluent solution.

was then begun with 0.15 *N* HCl at a flow rate (*ca.* 0.3 ml./min.) slow enough to permit an approach to equilibrium conditions.[1] The effluent from the column was collected in a number of fractions, each of which was radiometrically analyzed for Na^{24}, K^{42}, Rb^{86}, and Cs^{134}.

The results are shown in Fig. 1. The automatically-recorded curve (normalized) is superimposed upon the block diagram and serves to locate the valley between Na and K and the peak of K, both of which occurred while the column was unattended. The table at the top of the figure shows

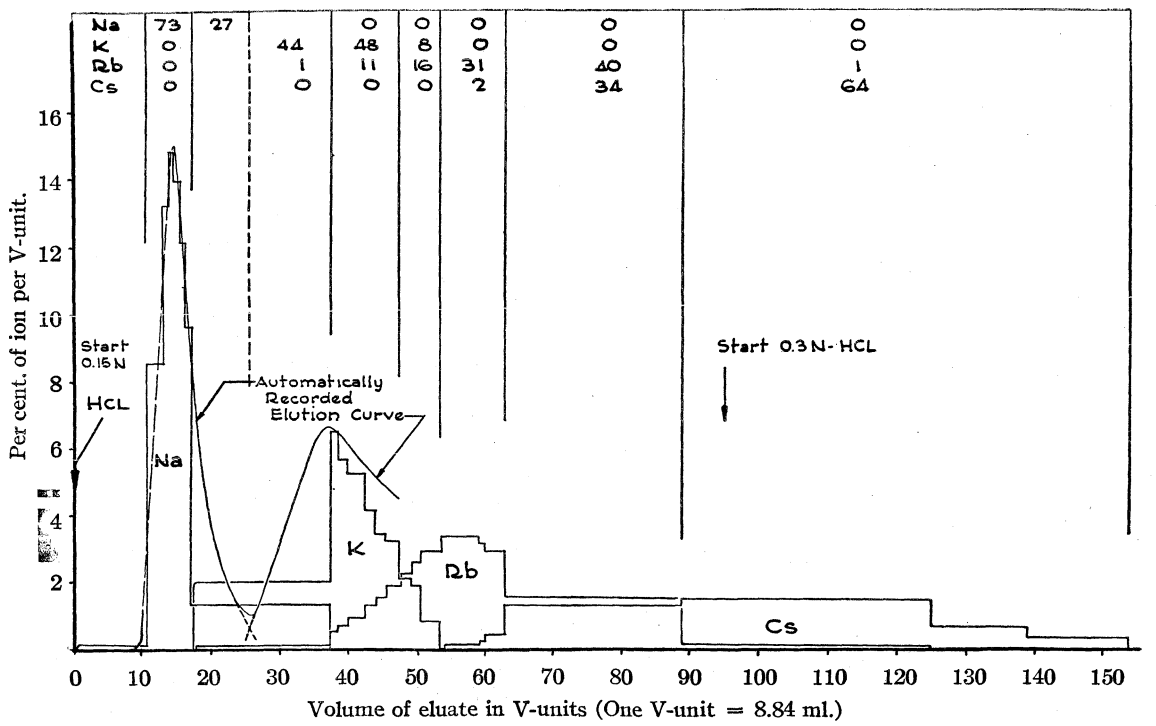


Fig. 1.—The separation of the alkali metal ions by elution from an ion exchanger.

A neutron-activated mixture of 1.0 mg. Na, 10 mg. K, 8 mg. Rb and 13 mg. Cs, in the form of their chlorides, was dissolved in water and absorbed on the hydrogen-form column.[2] Elution

(1) S. W. Mayer and E. R. Tompkins, THIS JOURNAL, **69**, 2866 (1947).

(2) B. D. Polis and J. G. Reinhold, *J. Biol. Chem.*, **156**, 231 (1944).

the relative purities and recoveries in the various fractions.

DIVISIONS OF BIOLOGY AND CHEMISTRY
OAK RIDGE NATIONAL LABORATORY WALDO E. COHN
OAK RIDGE, TENNESSEE HAROLD W. KOHN

RECEIVED APRIL 8, 1948

NEW BOOKS

Modern Colloids. An Introduction to the Physical Chemistry of Large Molecules and Small Particles. By ROBERT B. DEAN, Ph.D., Assistant Professor of Chemistry, University of Oregon. D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y., 1948. xi + 303 pp. 16 × 23.5 cm. Price, $3.75.

As stated in the Preface, this book is designed to serve as an introduction to the behavior of colloidal material. According to the author, colloid chemistry had fallen into bad repute, but much of the dead wood is being cleared away. The reviewer doubts that this book will assist in this process of rejuvenation.

The author's definition of colloids is not up to date and will give the reader an entirely wrong impression of what colloid chemistry stands for. The statement that nearly all of the properties of lyophobic colloids are due to the presence of impurities makes one wonder if the author realizes that this statement is not only incorrect but is a serious affront to the memory of men like Wo. Ostwald, H. Freundlich, and to all those who still are devoting their lives to the study of lyophobic colloids.

Ultramicroscopy by incident light and its applications in research pertaining to lyogels are not mentioned. A more adequate discussion of ultramicroscopes, their construction and application would be far more appropriate than the eulogy of the electron microscope, which also has its limitations, particularly in the study of lyophilic colloids. That solutions of proteins and other high polymers show no Faraday–Tyndall effect is contrary to fact. In the chapter on liquid surfaces, the drop weight, drop number and pendant drop methods are not mentioned. The statement that a thixotropic gel sets only when the particles associate is contrary to experimental evidence. Ebonite, or hard rubber, is not a thermosett, but a thermoplastic resin. The discussion of rubber latex is incomplete because it disregards the most basic colloidal phenomena. The structural diagram of montmorillonite (Fig. 11–7) does not explain cation exchange because it lacks the ion substitutions in the Gibbsite layer necessary for this phenomenon. The explanation as offered is not in line with known facts. When using illustrations copied from other publications, reference should be made to the one in which it originally appeared. The references to scientific and technical books and periodicals are incomplete.

Based on these statements, the reviewer's opinion may now be summarized:

The author deserves credit for his enthusiasm and for his desire to stimulate the interest of others in the multifarious colloidal phenomena in such diverse fields as chemistry, biology, medicine and agriculture. It would be risky, however, to depend upon this book for an introduction to the behavior of colloidal materials, because it disregards many basic phenomena characteristic of this state of matter or offers inadequate explanations; and its organization will confuse the reader more than it will enlighten him.

ERNST A. HAUSER

Autoxidation of Diethyl Ether and its Inhibition by Diphenylamine. A Chemical, Biological and Clinical Study of Some Practically Important Problems Concerning the Protection of Anesthetic Ether against Disintegration. By GUNNAR LINDGREN. P. A. Norstedt and Son, Stockholm, Sweden 1946. 190 pp.

The subtitle of this monograph is rather misleading. Ether does not *disintegrate* or lose its potency, like other delicate *materia medica*. However, as is well known, if ether stands for some time in bottles with access of air from frequent pourings, it forms through oxidation small amounts (seldom greater than 1%) of undesirable impurities, chiefly peroxides, acetaldehyde and acid. Of course, such treatment of ether intended for anesthesia is wisely interdicted by the pharmacopoeias of all nations. It is this familiar but complicated oxidation reaction and its prevention which forms the central theme of this investigation.

It also seems misleading to say (*vide* p. 10) apropos of the experiments of Mendenhall, Knoefel, *et al.* (*vide* p. 83) that "it therefore seems clear that *the existence of autoxidation products in anesthetic ether involves considerable practical inconvenience* . . . . . on account of autoxidated ether containing biologically extremely active substances, which may possibly disturb the course of the anesthesia and also involve an increased risk for the patient," because only through gross carelessness could ether containing 0.05% peroxide and 0.13% of aldehyde find its way into the operating room.

The standards of acceptability for the *freshly* prepared product are now so rigorous that no such amounts of auto-oxidation products could exist in it and one may say without fear of contradiction that anesthetic ether almost the world over is one of the purest substances used in medicine. Furthermore, anesthetic ether of the composition prescribed by the U. S. Pharmacopoeia in the manufacturer's original packages will keep its original purity for long periods of time—amply sufficient for all practical purposes.

The situation is somewhat different in Sweden, however, as the Swedish Pharmacopoeia prescribes for anesthetic purposes and designates as "Aether ad Narcosin" an ether free from alcohol and water (presumably treated with metallic sodium to remove the last traces of water) and put up in bottles of 100 grams capacity. Apparently one of the principal objects of this investigation was to ascertain whether any of the cheaper grades of Swedish ether could be substituted for this expensive product and still retain satisfactory keeping qualities. The author shows how this end may be accomplished by the addition of 0.02% of diphenylamine (one of the many substances known to inhibit the formation of peroxides in ether) to a grade of Swedish ether designated simply as "Aether Ph.S.," which is bottled in dark glass to exclude the actinic rays. The use of inhibitors, however, has not met with favor in America. Here the problem has been solved by the use of a pure ether of a slightly different composition[1] than that made in Sweden, and packaged in specially treated tin containers. The author states that in his stability tests this cheaper grade of Swedish ether, if no diphenylamine was added, acquired peroxides more rapidly than did the specially prepared "Aether ad Narcosin," but points out that one should not conclude that "Aether ad Narcosin" possesses more stability, since the bottles and light exposure were not identical in the two stability tests. It is to be regretted that this interesting grade, namely, "Aether ad Narcosin," was not included for direct comparison.

The author also tested the stability of ether in drums, and on page 48 we find the statement that ether in drums seems less stable than in bottles. The basis for this statement was the fact that the special grade, "Aether ad Narcosin," in bottles had kept almost perfectly for a year, whereas the grade known simply as "Aether Ph.S." in the manufacturer's drums had shown a marked decomposition. Since the grades of ether were entirely different, and the drums were galvanized (zinc being a very undesirable metal in contact with ether), the conclusion seems hardly rigorous; indeed, it is partially retracted on the next page.

(1) "Ether contains from 96 per cent. to 98 per cent. of $C_4H_{10}O$, the remainder consisting of alcohol and water" (U. S. P. XIII).

An excellent summary and criticism of the various methods for the determination of peroxide, acetaldehyde and acid is given in the section on chemistry. In passing we would like to remark that with a little experience an approximation of the amounts of peroxide and aldehyde, sufficient for evaluating the quality of anesthetic ether, can be made instantaneously by simple visible comparisons of the colors obtained with the well known sulfocyanate test for peroxides and Nessler's reagent for aldehyde as against sets of standards.

Under the heading, "Purification of Autoxidated Ether by Potassium Hydroxide," and also in other sections, Lindgren discusses the results obtained in his experiments and, taking cognizance of some similar results of Reimers, he concludes that "with the help of potassium hydroxide it is possible to obtain an ether almost free from peroxide, aldehyde and acid which is rather stable when kept in the dark." Twenty years ago this reviewer, E. Mallinckrodt, THIS JOURNAL, 49, 2655 (1927), in studying the then widely used German Pharmacopoeia (Ph.G.VI) test for aldehyde, which is based upon this reaction, showed that with anhydrous ether to which as much as 0.1% pure acetaldehyde has been added, the formation of brown aldehyde resin on the surfaces of the lumps of potassium hydroxide does not occur unless a small amount of moisture is present in the outer layer of the lumps of solid caustic. Thus, the efficacy of Lindgren's purification procedure when applied to Swedish anesthetic ether which is anhydrous cannot be taken for granted unless the above precautions are taken into account. It should also be noted that he used only about one-third of the proportions of caustic to ether that the German Pharmacopoeia prescribes for the aldehyde test.

In Part II, under the heading, "Experiments on Animals," a considerable point is made of the fact published by Knoefel and Murrell in 1935, and confirmed and continued by Lindgren, that the time required to induce anesthesia in mice is longer if ether containing peroxides and acetaldehyde from long exposure to air and light is used, than if pure ether is administered under otherwise identical conditions. How important this observation of Lindgren and others may be one cannot say, unless one knows why this slowing is present. It would seem that in a work as extensive as this one, a direct attack upon this interesting problem would have been made other than by speculation. If, as seems probable, delay in induction is to be explained by the action of irritant substances reducing the respiratory minute volume, this might have been studied directly and in conjunction with the rate at which the anesthetic blood level of ether was achieved. Larger animals than mice would be required.

In this paper conclusions based upon deductions are sometimes resorted to, where direct examination would have been better and not difficult, as for example, in ascertaining whether an important accumulation of carbon dioxide in the bottles where mice were confined had occurred. It should also be pointed out that the untoward biological effects of ether containing peroxide and aldehyde, cited by the author, were obtained with specimens of ether containing much larger amounts than the various pharmacopoeias allow. It is thus hardly proper to refer to the ether used in Mendenhall and Connolly's investigation on the cilia of oysters, which contained 0.02% peroxides and 0.02% of aldehydes, as a "low percentage of autoxidation products"; this is at least ten and probably twenty times as much as the standard American anesthetic ether is allowed to contain.

In Part III under the heading, "Clinical Study," a tremendous amount of work has been done, but the study is too broad in that too many variables are considered for the number of cases studied. Moreover, important differences appear to have been overlooked and much unimportant data dilute the observations pertinent to the subject. Largely for these reasons, the clinical studies fail to carry conviction.

This study, as the author points out, was concerned wholly with Swedish absolute ether and so has no direct bearing on the anesthetic ether used in this country. Even with this restriction, however, little contribution has been made to an understanding of the auto-oxidation of ether in general.

Based upon its effect on mice, the author concludes that peroxidized ether treated with potassium hydroxide to remove peroxides and aldehyde contains an unknown biologically active principle not revealed by the usual chemical tests for the purity of ether. One must await with interest further evidence substantiating this possibility.

It is gratifying to have this study published in the English language and thus made accessible to a wide circle of readers. There are occasional lapses in clarity and in good usage, and often the results are presented in a curiously circuitous way, which a more careful editing could have eliminated, but the language is indeed commendable for authors whose native language is not English.

E. MALLINCKRODT

BOOKS RECEIVED

March 10, 1948–April 10, 1948

A. E. BAILEY. "Cottonseed and Cottonseed Products. Their Chemistry and Chemical Technology." Interscience Publishers, Inc., 215 Fourth Ave., New York 3, N. Y., 1948. 936 pp. $17.50.

HARVEY DIEHL. "Electrochemical Analysis with Graded Cathode Potential Control." The G. Frederick Smith Chemical Co., 867 McKinley Ave., Columbus, Ohio. 56 pp. $1.00 (bound). Paper back copies available free of charge.

GORTON R. FONDA AND FREDERICK SEITZ. "Preparation and Characteristics of Solid Luminescent Materials." John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y., 1948. 459 pp. $5.00.

ROBERT S. HARRIS AND KENNETH V. THIMANN, Editors. "Vitamins and Hormones. Vol. V. Advances in Research and Applications." Academic Press, Inc., Publishers, 125 E. 23rd St., New York, N. Y., 1947. 478 pp. $7.50.

GREGORY PINCUS, Editor. "Recent Progress in Hormone Research. The Proceedings of the Laurentian Hormone Conference." Academic Press, Inc., Publishers, 125 E. 23rd St., New York, N. Y., 1948. 427 pp. $8.00.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 70 JUNE 30, 1948 NUMBER 6

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF WASHINGTON]

Studies of Sulfonates. IX. Transference Numbers and Activity of 1-Dodecanesulfonic Acid in Aqueous Solutions at 40°[1,2]

BY L. L. NEFF,[3] O. L. WHEELER,[4] H. V. TARTAR AND E. C. LINGAFELTER

One of the most important properties for the interpretation of the behavior of solutions is the thermodynamic activity. While many studies have been made of solutions of paraffin-chain salts as colloidal electrolytes, the only activity data are the freezing point measurements of McBain and co-workers[5] and of Ralston and associates,[6] the vapor pressure measurements of McBain and co-workers,[7] and, appearing since the completion of the present study, the electromotive force measurements of Walton.[8]

It was felt that an independent determination of these activities would be desirable. We have therefore determined the activity of 1-dodecanesulfonic acid in aqueous solutions at 40° up to 0.4 *m* by electromotive force measurements. Two types of cells were used. In the concentration range 0–0.02 *m* we have used cells of the type

$$\mathrm{Pt,\ H_2|C_{12}H_{25}SO_3H}(m_1)|\mathrm{C_{12}H_{25}SO_3H}(m_2)|\mathrm{H_2,\ Pt} \quad (1)$$

(concentration cells with liquid junction). In the concentration range 0.01–0.4 *m* we have used cells of the type

$$\mathrm{Pt,\ H_2|C_{12}H_{25}SO_3H}(m)|\mathrm{Hg_2(C_{12}H_{25}SO_3)_2{\cdot}2H_2O(s),\ Hg} \quad (2)$$

(concentration cells without liquid junction).

The transference numbers necessary for the calculation of activities from the measured electromotive force of cells of type (1) were determined by the Hittorf method over the concentration range 0–0.6 *m*.

Experimental

Materials.—The 1-dodecanesulfonic acid was prepared from its sodium salt by the method of Zuffanti.[9] The sodium 1-dodecanesulfonate had been prepared by the action of aqueous sodium sulfite on *n*-dodecyl bromide in a bomb at 160°.

The mercurous 1-dodecanesulfonate for use in the mercury–mercurous electrodes was prepared by precipitation from a solution of either the 1-dodecanesulfonic acid or its sodium salt with an excess of mercurous nitrate. The precipitated salt was washed thoroughly with distilled water and stored until used under 0.1 *m* 1-dodecanesulfonic acid in contact with mercury. Microscopic examination showed the solid to consist of very small, well-formed crystals. Analysis of the solid for mercury by the method of Hager and Hulett[10] gave results in agreement with the composition $Hg_2(C_{12}H_{25}SO_3)_2{\cdot}2H_2O$ (% Hg found: 42.77, 42.99, 43.00; calcd. 42.86).

The solubility of mercurous 1-dodecanesulfonate in water at several temperatures was determined by evaporating to dryness 50-ml. samples of the saturated solutions. At 40° the result obtained was 5.7×10^{-5} *M*.

The mercury used in the preparation of the mercury–mercurous sulfonate electrodes had been washed with nitric acid and distilled twice *in vacuo*.

Commercial tank hydrogen was used for the hydrogen electrodes, the oxygen being removed by passing the gas through a quartz tube filled with granular copper filings heated electrically to about 700°.

Conductivity water from a Barnstead still was used for the preparation of all solutions. The solutions were made up by weight from a stock solution of 1-dodecanesulfonic acid. This stock solution was standardized by weight titration against a sodium hydroxide solution which had been standardized against twice-recrystallized Baker C. P. grade potassium acid phthalate.

Apparatus and Procedure.—The transference numbers were determined in a modified Washburn[11] apparatus con-

(1) Presented at the New York Meeting of the American Chemical Society, New York, September, 1944.

(2) Taken in part from theses submitted by L. L. Neff and by O. L. Wheeler in partial fulfillment of the requirements for the Ph.D. degree.

(3) Present address: Union Oil Company of California, Wilmington, California.

(4) Present address: Plastics Division, Monsanto Chemical Company, Springfield, Massachusetts.

(5) (a) J. W. McBain and Betz, THIS JOURNAL, **57**, 1909 (1935); (b) E. L. McBain, Dye and Johnston, *ibid.*, **61**, 3210 (1939).

(6) Ralston, Hoerr and Hoffman, *ibid.*, **63**, 2576 (1941).

(7) (a) J. W. McBain and Williams, *ibid.*, **55**, 2250 (1933); (b) Randall, J. W. McBain and White, *ibid.*, **48**, 2517 (1926); (c) J. W. McBain and Barker, *Trans. Faraday Soc.*, **31**, 149 (1935).

(8) Walton, THIS JOURNAL, **68**, 1180 (1946).

(9) Zuffanti, *ibid.*, **62**, 1044 (1940).

(10) Hager and Hulett, *J. Phys. Chem.*, **36**, 2095 (1932).

(11) Washburn, THIS JOURNAL, **31**, 322 (1909).

structed of 2-cm. Pyrex glass tubing according to the specifications of MacInnes and Dole.[12]

Two silver coulometers, constructed according to the specifications of the U. S. Bureau of Standards,[13] were placed in series with the transference cell, one on either side.

The temperature was held to 40 ±0.03° in a Freas water thermostat. The cathode of the transference cell was a coiled silver wire coated with silver chloride. The anode was of lead (anode reaction, $Pb + 2C_{12}H_{25}SO_3^- = Pb(C_{12}H_{25}SO_3)_2 + 2e^-$) for concentrations of sulfonic acid below 0.05 *m*, and of platinum (anode reaction, $2H_2O = 4H^+ + O_2 + 4e^-$) for concentrations above 0.05 *m*.

In all runs, the transference numbers were calculated from data on both anolyte and catholyte and the two values were averaged. In solutions below 0.05 *m* these two values agreed within 1% in all cases. Above 0.05 *m* the agreement was somewhat less satisfactory, but always within 3%.

The electromotive forces were measured by means of a Leeds and Northrup Type K potentiometer with a Type R galvanometer. The standard cell was checked by means of a White potentiometer against a pair of cells recently standardized by the United States Bureau of Standards.

The temperature was controlled at 40±0.05° by means of an air thermostat.

The cells used were very similar to those described by Tartar, Newschwander and Ness.[14]

Results and Discussion

The transference numbers are given in Table I. The data are quite similar to those obtained by McBain[15] at 20°, although our data indicate no change in transference number below the critical concentration.

TABLE I

TRANSFERENCE NUMBERS OF THE HYDROGEN ION IN AQUEOUS SOLUTIONS OF DODECANE SULFONIC ACID AT 40°

Molality	Transference number	Molality	Transference number
0.0000	0.930	0.1124	0.680
.00526	.924	.1632	.721
.00795	.929	.1971	.733
.01743	.816	.2300	.762
.03134	.740	.3134	.738
.04038	.715	.3490	.730
.0554	.680	.4651	.738
.0671	.718	.6067	.753
.0801	.694		

The expression of e.m.f. in terms of activities for a cell containing a colloidal electrolyte such as 1-dodecanesulfonic acid is complicated by the transference of micelles, as well as single ions, across the liquid junction. It can be shown, however, that the expression assumes a form identical with that for an ordinary electrolyte.

In calculating and discussing the results, we may make use of an activity coefficient defined as the ratio of the mean ionic activity to the total stoichiometric molality, $\gamma = a_\pm/m$.

The activity coefficients in the concentration range 0–0.02 *m* were calculated from the measured e. m. f. of the cells of type (1) by the method outlined by MacInnes.[16]

Table II gives measured e. m. f. and molality of solution 2, solution 1 being constant at 0.00526 *m*. Table III includes the values of the mean ionic activity of 1-dodecane sulfonic acid at rounded concentrations. The data are plotted in Fig 1.

TABLE II

ELECTROMOTIVE FORCES OF CELLS WITH TRANSFERENCE

Molality (m_2)	E. m. f., mv.	Molality (m_2)	E. m. f., mv.
0.00301	−2.13	0.00898	1.66
.00372	−1.19	.01008	1.91
.00416	−1.11	.01031	2.01
.00526	0.00	.01039	1.81
.00590	0.56	.01094	2.00
.00638	0.52	.01147	2.38
.00657	0.98	.01321	2.13
.00697	1.28	.01408	2.31
.00781	1.41	.01532	2.40
.00794	1.97	.01567	2.40
.00878	1.79	.02287	2.91
.00885	2.12		

TABLE III

ACTIVITY OF 1-DODECANESULFONIC ACID IN AQUEOUS SOLUTION FROM E. M. F. OF CELLS WITH TRANSFERENCE

Molality	Activity	Molality	Activity
0.00300	0.00293	0.01200	0.00846
.00400	.00384	.01300	.00856
.00500	.00481	.01400	.00848
.00600	.00587	.01500	.00860
.00700	.00691	.01600	.00878
.00800	.00780	.01700	.00888
.00900	.00808	.01800	.00898
.01000	.00814	.01900	.00906
.01100	.00835	.02000	.00915

It was found that the mercury–mercurous 1-dodecanesulfonate electrode was not constant or reproducible in very dilute solutions and measurements in solutions below 0.01 *m* were made with hydrogen electrodes in concentration cells with liquid junction (type 1). In solutions of concentration 0.01 *m* and greater, the mercurous sulfonate electrode functioned satisfactorily and cells without liquid junction (type 2) were used. Their reversibility was proven by the calculation of E^0 in a series of concentrations where the activity coefficients had been determined from the electromo-

TABLE IV

E^0 OF THE MERCURY–MERCUROUS 1-DODECANESULFONATE ELECTRODE

$2Hg + 2C_{12}H_{25}SO_3^- + 2H_2O = Hg_2(C_{12}H_{25}SO_3)_2 \cdot 2H_2O + 2e^-$

Concentration (*m*)	E^0, volts
0.00992	−0.3856, −0.3828
.01030	− .3870, −0.3863
.01532	− .3844
.02100	− .3870
	− .386 (mean)

(12) MacInnes and Dole, THIS JOURNAL, **53**, 1357 (1931).

(13) U. S. Bur. Stand. Bull. No. 285 (1916).

(14) Tartar, Newschwander and Ness, THIS JOURNAL, **63**, 28 (1941).

(15) M. E. L. McBain, *J. Phys. Chem.*, **47**, 196 (1943).

(16) MacInnes, "The Principles of Electrochemistry," Reinhold Pub. Corp., New York, N. Y., 1939.

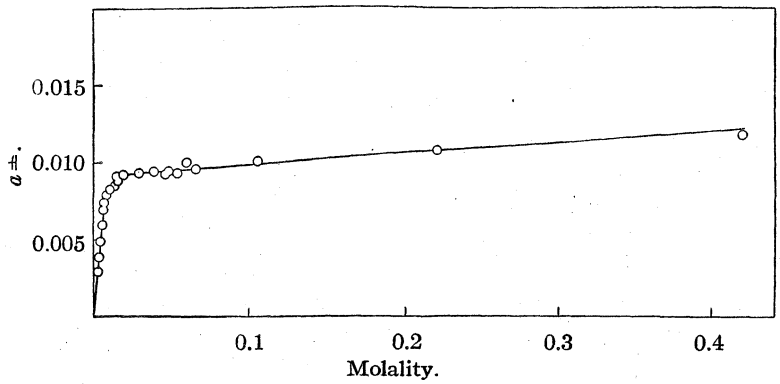


Fig. 1.—Mean ionic activity of 1-dodecanesulfonic acid in aqueous solution at 40°.

tive force of cells with liquid junction; these values of E^0 are shown in Table IV. The average value, 0.386 volt, is identical with the value obtained by Walton[8] at 25°.

The average value of E^0 was used to calculate the solubility of mercurous 1-dodecanesulfonate to check the result obtained analytically; the result obtained was 2.5×10^{-5} mole per liter. This agrees quite well with the analytical value of 5.7×10^{-5} mole per liter. Part of the difference may be due to the value of the standard potential of the mercury–mercurous ion electrode. Since its value was not known experimentally at 40°, an approximation was made from its value and temperature coefficient at 25° assuming that the temperature coefficient was constant from 25 to 40°. This temperature coefficient was calculated from the standard entropy change of the reaction $2Hg + 2H^+ = Hg_2^{++} + H_2$ reported by Latimer, Pitzer and Smith.[17] The analytical value is undoubtedly high because of the nature of the salt; minute crystals were present in the filtrate as shown by a carbon arc and because of the limited solubility these caused a rather large error in the result.

Data from cells of type 2 were used to calculate activities in solutions of 1-dodecanesulfonic acid where the sulfonate electrodes would function. The activity in a reference solution (near 0.01 *m*) was obtained from those determined by means of cells with liquid junction, and the activity in the other solutions calculated from the electromotive force of the above cell. The mean ionic activities are listed in Table V and are plotted in Fig. 1.

It may be seen from Fig. 1 that the behavior to be expected on the basis of the mass law is shown by these solutions. Below the critical concentration the activity of the 1-dodecanesulfonic acid increases with concentration as expected for an ordinary univalent strong electrolyte. Above the critical concentration, the activity is almost constant, rising only very slowly with increasing concentration.

Our results agree very well with those of Walton.[8] The extent of the agreement is indicated by the fact that our data, if plotted on Fig. 2 of his paper, fall almost exactly on the dashed line. Thus the three sets of data, at 0, 25 and 40°, form a consistent body, both with respect to the values of the activities and the position of the critical concentration.

TABLE V

ACTIVITY OF 1-DODECANESULFONIC ACID IN AQUEOUS SOLUTION FROM E. M. F. OF CELLS WITHOUT TRANSFERENCE

Molality	Activity	Molality	Activity
0.01030	0.00819	0.05485	0.00932
.01532	.00917	.05554	.00944
.02100	.00925	.05995	.01001
.03030	.00933	.06594	.00956
.04009	.00931	.10630	.01012
.04678	.00922	.22105	.01070
.04860	.00933	.39871	.01184

McBain and Bolduan[18] in discussing osmotic coefficients of colloidal electrolytes seem to attach considerable importance to the fact that the coefficient, after dropping markedly above the criti-

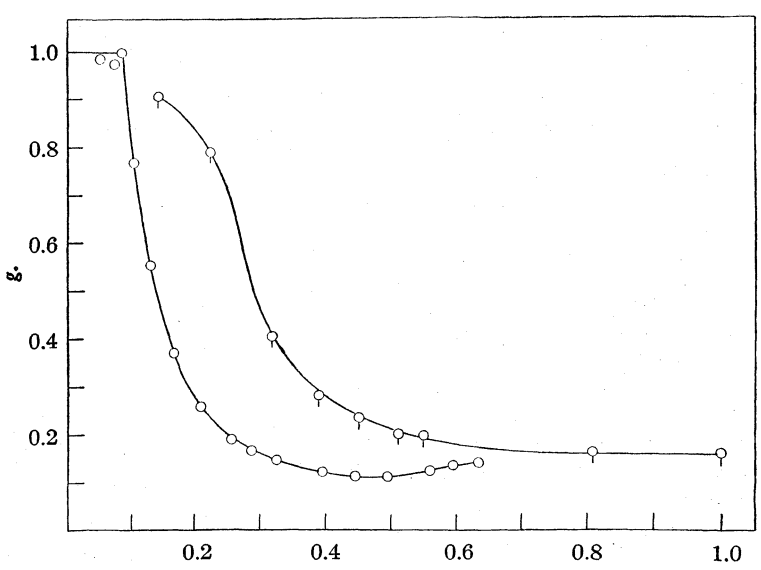


Fig. 2.—Osmotic coefficients: O, 1-dodecanesulfonic acid (this research); ♀, potassium laurate (McBain and Bolduan).

(17) Latimer, Pitzer and Smith, THIS JOURNAL, **60**, 1829 (1938).

(18) McBain and Bolduan, *J. Phys. Chem.*, **47**, 94 (1943).

cal concentration, ceases to fall in moderate dilution and may even increase. In order to investigate this phenomenon further, we have calculated the osmotic coefficients from our activity data. These results are plotted in Fig. 2 along with the values for potassium laurate from McBain and Bolduan. Although the curve of activity against concentration above the critical shows no discontinuity, or even deviation from a straight line, the osmotic coefficient curve calculated therefrom ceases to fall and even rises more abruptly than that of potassium laurate. Thus this "outstanding property of colloidal electrolytes (*g* ceasing to fall in moderate dilution)" would appear to be due entirely to the nature of the osmotic coefficient, and not to any changes occurring in the solution.

Similarly, the interpretation of the minimum as a "critical concentration for completion of the formation of micelles"[19] is unwarranted.

We do not wish to imply from the above that these data prove that no change does occur, but merely wish to point out that one must be extremely careful in attaching significance to a change in direction of a curve.

Summary

1. Thermodynamic activity of 1-dodecanesulfonic acid in aqueous solution at 40° in the concentration range 0–0.4 *m* has been determined by e.m.f. measurements.

2. The activity of 1-dodecanesulfonic acid in aqueous solution agrees with that expected on the basis of the mass law.

(19) Johnston and McBain, *Proc. Roy. Soc.* (*London*), **A181**, 127 (1942).

SEATTLE 5, WASHINGTON RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

The Electrical Conductance and Density of Solutions of Potassium 9,10-Dihydroxystearate and Potassium Stearate at 60°

BY N. W. GREGORY AND H. V. TARTAR

To determine the effect of substitution of hydroxyl groups in the middle of the carbon chain of a fatty acid soap on electrical conductance and micelle formation, studies have been made on solutions of the potassium salts of stearic and 9,10-dihydroxystearic acids.

A comparison of this type has not been made previously. Data concerning the electrical conductance of solutions of potassium 9,10-dihydroxystearate are not on record. The conductance of solutions of potassium stearate and related compounds has been reported by Bunbury and Martin[1] and by McBain and co-workers.[2,3,4] In these studies, however, any break in the conductance curves, indicating a critical concentration at which micelles are formed, would likely be masked by hydrolysis with the concomitant formation of slightly soluble acid soaps. This difficulty has been obviated in the investigation reported herein by using as a solvent an alkaline solution of sufficient concentration to repress hydrolysis. Measurements were made at 60° because of the slight solubility of potassium stearate at room temperature.

Experimental Part

Preparation of Materials.—The 9,10-dihydroxystearic acid (high melting form) was prepared by the oxidation of oleic acid with alkaline permanganate in dilute solution. Oleic acid (U.S.P. quality) was purified by a treatment modified from the methods described by Brown and Shimarowa[5] and Smith,[6] and conversion of oleic acid to dihydroxystearic acid effected by oxidation in a manner similar to that reported by Smith.[6]

The impure 9,10-dihydroxystearic acid resulting from the oxidation was extracted twice with boiling wate to remove any hexa- or tetra-hydroxy acids, and recrystallized from 95% alcohol. After drying, the acid was extracted with both petroleum and ethyl ethers to remove any stearic acid and the residue recrystallized four times from 95% alcohol. The resulting compound was crystalline and melted at 131.6°. This is in excellent agreement with the melting point reported by Le Sueur–Freundler,[7] and others.[8]

Four hundred grams of oleic acid (U.S.P.) yielded 150 g. of the purified dihydroxystearic acid. The yield from the oxidation was very good and the principal losses incurred were in the purification procedures.

The potassium salt of dihydroxystearic acid was prepared in a manner adapted from the method of preparation of sodium stearate reported by McBain, Vold and Frick.[9] A hot alcoholic solution of dihydroxystearic acid was neutralized with an alcoholic solution of potassium ethoxide using phenolphthalein as an indicator. Upon cooling the resulting solution, the potassium salt separated as a silky crystalline precipitate. The crystals were washed thoroughly with alcohol, dried at 110°, and recrystallized from alcohol. The purity of the salt was checked by regenerating the acid from a small aliquot and determining the melting point.

Potassium stearate was prepared in an analogous manner from stearic acid (U.S.P. stearic acid recrystallized

(1) Bunbury and Martin, *J. Chem. Soc.*, **105**, 424 (1914).

(2) McBain and Taylor, *Z. physik. Chem.*, **76**, 179 (1911).

(3) McBain, Cornish and Bowden, *J. Chem. Soc.*, **101**, 2042 (1912).

(4) McBain and Salmon, THIS JOURNAL, **42**, 426 (1920).

(5) Brown and Shimarowa, *ibid.*, **59**, 16 (1937).

(6) Smith, *J. Chem. Soc.*, 974 (1939).

(7) Melting point of 9,10-dihydroxystearic acid reported to be 131–132° by Le Sueur–Freundler, *J. Chem. Soc.*, 1316 (1901).

(8) K. S. Markley, "Fatty Acids," Chapter XV, Interscience Publishers, Inc., New York, N. Y., 1947.

(9) McBain, Vold and Frick, *J. Phys. Chem.*, **44**, 1013 (1940).

from alcohol) and was purified as directed by Scheringa.[10] The salt was recrystallized eight times from 66% alcohol. Upon regeneration of stearic acid from an aliquot of the final material, it was found to have a melting point of 69.0°.[11]

The potassium hydroxide solution used as a solvent in the conductivity measurements was prepared in the following manner: a 50% aqueous (conductivity water) solution of potassium hydroxide (analyzed reagent grade) was prepared and the small amount of carbonate present precipitated with dilute barium hydroxide solution. The barium ion concentration of the solution was reduced to a minimum by careful titration against dilute potassium carbonate solution until the two were balanced. The total volume of the solution was 100 ml. and contained 50 g. of potassium hydroxide. Five-tenths ml. of this solution was diluted with conductivity water to a normality of approximately 0.001. Standardization of the dilute solution was effected with potassium acid phthalate, using a weight buret and neutral phenolphthalein. The titrations were carried out in an atmosphere of nitrogen.

Equipment and Procedure.—Conductance measurements were made using a Jones and Josephs-Dike conductivity bridge[12,13] calibrated to an accuracy of 0.02%, with current supplied by an a.c. vacuum-tube oscillator. A two-stage amplifier with telephone formed the detecting circuit. Measurements were made at a frequency of 1000 cycles, occasionally checking at 2000 cycles.

Measurements were made at 60° using an oil-bath with temperature controlled to ±0.001°. The temperature of the bath was determined by means of a platinum resistance thermometer (calibrated by the National Bureau of Standards).

Cells of the Jones and Bollinger type[14] were used for the conductivity measurements. It was found necessary to modify the cells slightly, to permit passage of nitrogen over the liquid in the filling tubes during the measurements, in order to eliminate drifts caused by absorption of carbon dioxide from the air by the alkaline solvent. By the use of nitrogen, drifts in the measured resistance were reduced to less than 0.005% per minute. The lowest resistance measured over a period of ten minutes after thermal equilibrium had been attained was the value used in calculating the conductance of the solution. The two cells used were found to have constants at 60° of 2.6841 and 25.904, respectively.[15]

All solutions were made up by weight. The samples were weighed on an analytical balance with an accuracy of 0.1 milligram, and the solvent on a larger balance (accuracy ± one milligram). The conductance of the stock potassium hydroxide was checked from time to time during the period in which measurements were made and was found not to vary beyond the limits of experimental error. Transfer of solutions was effected in glass systems by applying a pressure of nitrogen and solutions were maintained under nitrogen at all times. The bottles in which the solutions were stored had been carefully aged and paraffined before use.

In the case of the stearate, which is rather insoluble at room temperatures, it was found necessary to fill the conductance cell at 60°. This requirement renders the probable error in the stearate measurements somewhat greater than those for the dihydroxystearate. The latter is sufficiently soluble at room temperature to enable the cells to be filled without difficulty.

The density of the solutions was measured at 60° in a modified Sprengel type pycnometer,[16] which consisted of a 25 ml. pipet with the ends drawn down to capillary dimensions and fitted with ground glass caps. The pycnometer was calibrated with water at 60°. The accuracy of the density measurements is estimated to be ±0.00003.

The authors estimate that values for the conductance of the solutions, except those at very low concentrations, have a maximum probable error of the order of 0.1%.

Results and Discussion

The results of the density and conductance measurements are tabulated in Tables I and II and are illustrated graphically in Figs. 1 and 2. The solvent for all but the values designated *a* for the dihydroxystearate was 0.001317 N_w po-

TABLE I

DENSITY OF SOLUTIONS

Potassium 9,10-dihydroxystearate in 1.317 × 10^{-3} *N* KOH		Potassium stearate in 1.038 × 10^{-3} *N* KOH	
Molality × 10^2	Density	Molality × 10^2	Density
0.09062	0.98324	0.1713	0.98324
2.145	.98396	1.460	.98337
7.020	.98597	4.428	.98339
15.97	.98916	8.908	.98343
		14.93	.98345

TABLE II

CONDUCTANCE OF SOLUTIONS

Normality, N_V × 10^3	Specific conductance of solution, K × 10^3 mho	Specific[b] conductance of solvent, K × 10^4 mho	Equivalent[b] conductance of soap, mho
Potassium 9,10-Dihydroxystearate			
0.5083	0.69110	6.070	165.4
1.503	.84376	6.038	159.7
2.982[a]	.91625[a]	4.513[a]	155.9[a]
5.634[a]	1.2985[a]	4.470[a]	151.1[a]
6.690[a]	1.4516[a]	4.454[a]	150.4[a]
7.323	1.6901	5.933	149.8
9.810	1.9993	5.933	143.3
9.819	1.9939	5.933	142.6
19.587	3.2059	5.933	133.4
27.330	4.1096	5.933	128.7
37.816	5.2306	5.933	122.6
67.526	8.4126	5.933	115.8
84.764	10.210	5.933	113.5
149.71	17.162	5.933	110.7
202.64	22.724	5.933	109.2
Potassium Stearate			
0.4551	0.53291	4.594	161.5
.9091	.57937	4.594	132.0
2.712	.72495	4.594	97.92
3.231	.75566	4.594	91.71
4.415	.82286	4.594	82.33
9.831	1.1739	4.594	72.68
14.290	1.4046	4.594	66.14
24.931	1.9578	4.594	60.14
29.666	2.2926	4.594	61.80
42.931	2.9068	4.594	57.01
64.794	4.2152	4.594	57.97
70.028	4.5791	4.594	58.83
91.946	5.8111	4.594	58.21
140.06	9.1259	4.594	61.88

[a] Different solvent (see text).
[b] Approximated as indicated in text.

(10) Scheringa, *Chem. Weekblad*, **29**, 605 (1932).

(11) "I. C. T.," Vol. IV, McGraw-Hill Book Co., Inc., New York, N. Y., 1930, p. 10. Melting point of stearic acid reported as 69.3°.

(12) Dike, *Rev. Sci. Inst.*, **2**, 379 (1931).

(13) Jones and Josephs, THIS JOURNAL, **50**, 1049 (1928).

(14) Jones and Bollinger, *ibid.*, **53**, 411 (1931).

(15) The authors are indebted to A. B. Scott for the determination of these cell constants.

(16) This pycnometer was designed by Scott: doctorate thesis, University of Washington, 1941.

tassium hydroxide; that for the a values was 0.001038 N_w potassium hydroxide. The latter solvent was used entirely for the potassium stearate measurements. All data were obtained at 60°.

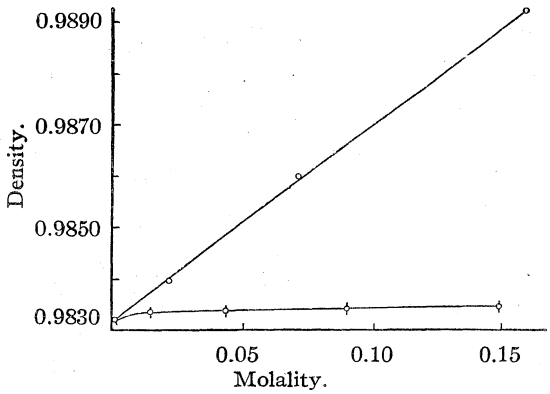


Fig. 1.—Change of density with concentration at 60°: O, potassium 9,10-dihydroxystearate; -O-, potassium stearate.

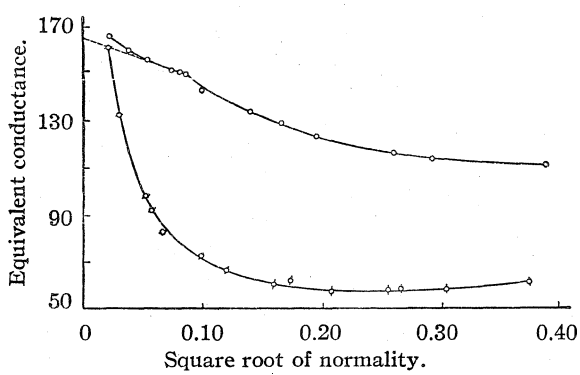


Fig. 2.—Equivalent conductance curves for solutions of potassium 9,10-dihydroxystearate and potassium stearate: O, potassium 9,10-dihydroxystearate; -O-, potassium stearate.

The concentration of potassium hydroxide necessary to repress hydrolysis of the soaps was computed on the basis of an assumed ionization constant for stearic acid. The constant for dihydroxystearic acid was assumed not to be appreciably different from that of stearic acid. Since ionization data for these acids are not available, a constant of 1.5×10^{-5} at 60° was taken, based on the known values of other members of the stearic acid homologous series up to caprylic acid. Using K_w for water as 9×10^{-14} at 60°, a concentration of hydroxyl ion of 0.001 mole/liter was calculated as sufficient to repress the concentration of the acid soap below 10^{-5} mole/liter. That this concentration was sufficient was confirmed by the observation that the more dilute solutions were either clear or only faintly colloidal, indicating negligible formation of acid soaps due to hydrolysis.

The use of the potassium hydroxide solution as the solvent requires a correction to be applied to the measured resistance of the solution, if the true conductance of the soap is to be determined. According to the Onsager theory, the conductance is determined by the total ionic strength of the solution. The concentration of the potassium hydroxide in the solvent remains constant and is sufficiently dilute to be treated by the Onsager equation. The soap has been assumed to be completely ionized at concentrations below that at which formation of micelles is indicated.

On this basis, the Onsager correction for the conductance of the potassium hydroxide, due to changing ionic strength of the solution, has been made up to the concentration at which micelles begin to form. The Onsager correction was computed from the general relation

$$\Lambda = \Lambda_0 - (\alpha\Lambda_0 + \beta)\sqrt{\mu}$$

where

Λ = equivalent conductance
Λ_0 = equivalent conductance at infinite dilution
α = 0.2627, β = 119.6 } Onsager constants at 60°
μ = total ionic strength

Since Λ_0 may be obtained from the measured conductivity of the standard potassium hydroxide by assuming an Onsager slope, the actual specific conductance due to the solvent may be found by calculating the total ionic strength of the solution, and substituting this value in the expression above. This involves the assumptions that the potassium hydroxide and the soap are completely dissociated up to the concentration at which micelles are formed. The difference between the total measured conductance and the value calculated for the solvent yields the value for the conductance of the soap.

In solutions of soaps in micellar form, determination of the ionic strength is not straightforward. Consequently, for lack of a precise method of treatment, a constant correction (the value calculated at the critical concentration) was applied to correct the measured conductance data for the contribution of the solvent. While it is realized that the equivalent conductance values determined on this basis are only approximate, it is doubtful that appreciable errors are involved, and certainly would not be of such a nature to change materially the over-all form of the curve.

Comparison of the two equivalent conductance curves illustrated in Fig. 2 reveals a striking difference. The dihydroxystearate is more soluble than the stearate, as would be expected from the influence of the hydroxyl groups. Its equivalent conductance is considerably greater than that of the stearate over most of the concentration range investigated.

There is a small break in the equivalent conductance curve for the dihydroxy compound occurring at a concentration of approximately 0.0075 N, at which point micelles may be formed. Below this concentration the curve follows an Onsager slope (indicated by the dotted line). The apparent up-

ward trend of the conductance curve in the region of very low concentration is not felt to be real. The conductance of the solution in this region is almost entirely due to the solvent and the value for the soap is obtained only by taking the difference of two relatively large numbers. Neglecting the two values at high dilution, the soap exhibits a behavior characteristic of a strong electrolyte until the critical concentration is reached.

The change in slope in the equivalent conductance curve for potassium 9,10-dihydroxystearate at the critical concentration is not nearly as great as has been observed in the studies of sulfonates and other soaps in which the carbon chain does not contain substituted hydrophilic groups. This would indicate that the micelle formed is possibly somewhat smaller and of a different type as the result of the influence of the hydroxyl groups in the middle of the chain, and hence does not change the ionic characteristics of the soap as markedly.

In studying the conductance curve of potassium stearate, the critical concentration for micelle formation was not established. The soap behaved as a colloidal electrolyte throughout the concentration range investigated. It may be seen from Fig. 2 that the critical concentration must lie very close to 0.0005 N (the lower limit of the concentration range studied), in order that the curve for the stearate intersect the ordinate at a reasonable value of Λ_0. Since measurements were not made below the critical concentration, as an approximation, a constant correction for the conductance of the solvent (the value of the conductance of the pure solvent) was applied in reducing the data.

Qualitative observations of the stearate solutions confirm the colloidal nature of the soap as indicated in the conductance measurements. All solutions were observed to be faintly opalescent whereas those of the dihydroxy compound were clear in dilute solution. The conductance curve obtained for potassium stearate is similar to that given by Bunbury and Martin,[1] if the fact that their measurements were made at 90° without repression of hydrolysis is considered.

While the critical concentration for the formation of micelles may be somewhat different in solutions not alkaline in character, the value indicated by these data is, without question, characteristic of the soap in the solvent used, and serves to evaluate the effect of the hydroxyl groups.

The change in density of solutions of the dihydroxystearate with concentration in the potassium hydroxide solvent presents an interesting contrast with that observed for potassium stearate. The density curves are illustrated in Fig. 1 and re-emphasize the pronounced effect of the hydroxyl groups in the molecule. It seems quite likely that the higher density observed for the potassium dihydroxystearate indicates association of water molecules by the hydroxyl groups.

Summary

1. The electrical conductance and density of solutions of potassium 9,10-dihydroxystearate and potassium stearate in 0.001 N potassium hydroxide have been determined at 60°. A comparison of data for the two compounds reveals that the hydroxyl groups have considerable influence.

2. The critical concentration for the formation of micelles in 0.001 N potassium hydroxide is indicated at 0.0075 N for potassium 9,10-dihydroxystearate. The value for potassium stearate was not established but is probably in the vicinity of 0.0005 N.

SEATTLE, WASHINGTON RECEIVED SEPTEMBER 16, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Solubility of Cesium and Rubidium Dichloroiodides in Hydrochloric Acid Solutions

BY PAUL BENDER AND ROGER A. STREHLOW

Introduction

In the usual procedure for the purification of cesium or rubidium salts the repeated recrystallization of the dichloroiodide from hydrochloric acid solution is employed for the elimination of the other alkali metals. The quantity of material to be processed is ordinarily limited and the solubility of the complex salt appreciable, so that the attainment of efficiency in the purification process can be accomplished only through a quantitative knowledge of the solubility relationships involved. The present study was carried out to supply the required data which have not previously been available in the literature.

Experimental

Preparation of Materials.—Cesium chloride of spectroscopic purity was prepared from Pollucite by the method of Wells.[1] Rubidium chloride was prepared from Lepidolite (from Pala, Calif.) essentially as described by Kennard and Rambo.[2] The five-fold recrystallization as rubidium acid tartrate recommended by Archibald[3] was carried out to ensure the removal of cesium. Other reagents employed were of analytical grade.

In the preparation of the dichloroiodides a slight excess of iodine was added to a hot hydrochloric acid solution of the alkali chloride and chlorine gas bubbled through the

(1) H. L. Wells, *Am. Chem. J.*, **26**, 265 (1901).

(2) T. G. Kennard and A. I. Rambo, *Am. J. Sci.*, **28**, 102 (1934).

(3) E. H. Archibald, "The Preparation of Pure Inorganic Substances," John Wiley and Sons, New York, N. Y., 1932.

solution until the last of the iodine had dissolved. The salt which separated on cooling was recrystallized four times before use. Analysis of the air dried products gave the following result in terms of % ICl: $CsCl_2I$, calcd. 49.11, found 49.19; $RbCl_2I$, calcd. 57.28, found 57.32.

Solubility Measurements.—Standard procedures were followed in the solubility determinations. The thermostat temperature was maintained at 25.00 ± 0.02° and 0.00 ± 0.02° for the two series of measurements; the thermometers employed were calibrated before use. Duplicate determinations were run at each hydrochloric acid concentration to provide a check on the attainment of equilibrium.

Analytical Methods.—Samples of the saturated solutions were transferred to the weighing flasks by air pressure. Glass wool plugs were used as filters in the delivery tubes. Approximately 50-cc. samples of the cesium dichloroiodide solutions were taken, and 25-cc. samples of the rubidium dichloroiodide solutions. The analysis was made by evaporating the weighed sample to dryness, igniting lightly to drive off the ICl, and weighing the residual cesium or rubidium chloride. Due precautions were taken to ensure complete removal of the iodine chloride. Hydrochloric acid solutions used were standardized by means of silver chloride. Calibrated weights were used in all determinations. Weld specific gravity bottles were used in the density measurements required for the conversion of the results to the volume concentration basis.

TABLE I

THE SOLUBILITY OF CESIUM DICHLOROIODIDE IN HYDROCHLORIC ACID SOLUTIONS

A. at 25° *m* HCl	G. salt/100 g. solution	G. salt/100 cc. solution
0.8805	9.059	9.805
1.998	8.274	9.052
2.989	7.470	8.236
4.909	6.097	6.824
6.987	5.057	5.746
8.989	4.455	5.142
10.75	4.139	4.841
12.48	3.964	4.697
15.29	3.894	4.700
B. at 0° *m* HCl	**G. salt/100 g. solution**	**G. salt/100 cc. solution**
0.8805	3.623	3.783
1.998	3.524	3.745
2.989	3.321	3.577
4.909	2.890	3.187
6.987	2.553	2.877
8.989	2.343	2.691
10.75	2.231	2.604
12.48	2.189	2.591
15.29	2.195	2.652

TABLE II

THE SOLUBILITY OF RUBIDIUM DICHLOROIODIDE IN HYDROCHLORIC ACID SOLUTIONS

A. at 25° *m* HCl	G. salt/100 g. solution	G. salt/100 cc. solution
1.998	44.02	64.92
4.909	28.73	38.20
8.989	17.51	22.17
12.48	13.58	17.16
B. at 0° *m* HCl	**G. salt/100 g. solution**	**G. salt/100 cc. solution**
1.998	25.20	31.68
4.909	17.51	21.50
8.989	10.66	12.98
12.48	8.75	10.83

Results

In Tables I and II are summarized the results of the solubility determinations. The accuracy of the data is estimated at 0.2% for the cesium dichloroiodide, and 0.3% for the rubidium dichloroiodide.

Discussion

Solubility measurements were not carried out at higher temperatures because the high temperature coefficient of solubility permits the volume of solvent employed to be adjusted simply on the basis of convenience in the filtration following crystallization. Precautions must of course be taken to avoid loss of iodine chloride from the hot solutions. The use of approximately nine molal hydrochloric acid as solvent is recommended as giving minimum inconvenience from hydrogen chloride in the vapor while retaining nearly the maximum advantage of the cosolute effect.

Summary

The solubility of cesium and rubidium dichloroiodides in hydrochloric acid solutions has been measured at 0 and 25°.

MADISON, WISCONSIN RECEIVED FEBRUARY 27 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Potentiometric Titration of +4 and +6 Selenium and Tellurium with Chromous Ion

BY JAMES J. LINGANE AND LEONARD NIEDRACH*

This paper presents the results of a potentiometric investigation of the reduction of selenium and tellurium from the +6 and +4 oxidation states by chromous ion. Tomicek,[1] and Willard and Fenwick,[2] studied the reduction of selenium and tellurium compounds with titanous ion, but titrimetric reduction with chromous ion has not previously been investigated.

This study has led to the development of new methods for the accurate determination of Se(IV) and Te(IV), both separately and in mixtures of these two elements.

Preparation of Materials

Tellurium Dioxide.—This was prepared from U. S. P. elementary tellurium by the method of Schuhmann.[3,4] Finely granulated tellurium was added slowly to excess concentrated nitric acid at 70°. When the metal had all dissolved the solution was allowed to evaporate at 80° until crystallization of the basic tellurium (IV) nitrate, $2TeO_2 \cdot HNO_3$, began. The crystals obtained by cooling were air dried and then ignited strongly in a platinum crucible to convert to TeO_2. The latter was dissolved in concentrated hydrochloric acid, the acidity was adjusted to approximately 10 *M*, and the solution was saturated with sulfur dioxide to precipitate any selenium. Tellurium is not easily reduced at this acid concentration. The solution was then filtered, diluted until the hydrochloric acid concentration was about 2 *M*, and treated again with sulfur dioxide to precipitate elementary tellurium. This was converted to the basic nitrate, and the latter was ignited for four hours in a muffle furnace at 400° to obtain pure TeO_2 which was stored in a desiccator.

When assayed by oxidation to the +6 state with excess potassium dichromate and potentiometric titration of the excess dichromate with ferrous ion, as recommended by Shrenk and Browning,[5] a purity factor of 99.87 ± 0.06% was obtained. Gravimetric assay by precipitation as the element from a boiling hydrochloric acid solution with sulfur dioxide and hydrazine hydrochloride[6] gave a purity factor of 99.90 ± 0.06%.

Since tellurium dioxide is only very slightly soluble in water, standard solutions were prepared in dilute hydrochloric acid.

Telluric Acid.—The method of Meyer and Franke,[7] involving oxidation of elemental tellurium with chloric acid solution, was used. The crystals of orthotelluric acid, H_6TeO_6, obtained by evaporating the solution were purified by two further recrystallizations from water.

A stock solution in water was prepared and standardized by the method of Gooch and Howland[8] which employs the reaction $H_6TeO_6 + 2Br^- + 2H^+ = H_2TeO_3 + Br_2 + 3H_2O$ in dilute sulfuric acid. The bromine produced was distilled with the aid of pure carbon dioxide or nitrogen into an excess of potassium iodide solution, and the liberated iodine was titrated with thiosulfate.

Selenium Dioxide.—This was prepared from U. S. P. elementary selenium by the method described by Biltz, Hall and Blanchard.[9] The finely pulverized selenium was dissolved by treatment with excess concentrated nitric acid, the solution was evaporated to dryness, and the resulting selenium dioxide was sublimed. The sublimate was dissolved in 10 *M* hydrochloric acid and reduced to elementary selenium with sulfur dioxide in the cold. To prevent the formation of Se_2Cl_2 it was necessary to partially neutralize the solution with sodium hydroxide near the end of the reduction. The precipitated selenium was washed free of chloride ion, converted to the dioxide with nitric acid, and the selenium dioxide was finally sublimed.

A stock solution was prepared in water. Acidimetric titration with carbonate-free sodium hydroxide using the glass electrode[5] showed a molarity of 0.05093. A molarity of 0.05097 was found by precipitation as elemental selenium from a tartaric acid solution with hydroxylamine hydrochloride.[10]

Selenic Acid.—Following the procedure outlined by Gilbertson and King[11] selenic acid solution was prepared by oxidizing a solution of the previously purified selenium dioxide with 30% hydrogen peroxide. The solution was standardized by titration with sodium hydroxide, which yielded a molarity of 0.02024, and also by the method of Gooch and Howland[8] which led to a molarity of 0.02026.

Titration Technique

Titrations were performed with standard 0.1000 *M* solutions of chromous sulfate, prepared in either 0.1 or 1 *N* sulfuric acid by the method described by Lingane and Pecsok.[12]

A 250-cc., three-necked balloon flask served as titration vessel.[12] A bright platinum indicator electrode was used, in conjunction with the saturated calomel electrode. The salt bridge contained dilute sulfuric acid. Carbon dioxide or nitrogen, purified by passage through a wash bottle containing chromous sulfate solution, was bubbled rapidly through the solution to remove air for at least ten minutes before a titration was started, and at a slower rate during the titration. Magnetic stirring was employed. The solutions were adjusted to an initial volume of 150 cc.

Potentials were read on a Leeds and Northrup potentiometer in the usual manner.

Results and Discussion

+4 Selenium.—In solutions acidified with hydrochloric or sulfuric acid +4 selenium is reduced to the elemental state by chromous ion, according to

$$H_2SeO_3 + 4Cr^{++} + 4H^+ = Se + 4Cr^{+++} + 3H_2O$$

Typical titration curves for titrations in various concentrations of hydrochloric acid are shown in Fig. 1.

Steady potentials are reached in two or three minutes at room temperature, and somewhat more rapidly at 70°. It was necessary to clean the platinum indicator electrode with concentrated nitric acid before each titration to obtain repro-

* Allied Chemical and Dye Corporation Fellow, 1947–48.

(1) O. Tomicek, *Bull. soc. chim.*, **41**, 1389 (1927); *Rec. trav. chim.*, **43**, 793 (1924).

(2) H. H. Willard and F. Fenwick, THIS JOURNAL, **45**, 933 (1933).

(3) R. Schuhmann, *ibid.*, **47**, 356 (1925).

(4) D. M. Yost and H. Russell, "Systematic Inorganic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1944, p. 312.

(5) W. T. Shrenk and B. L. Browning, THIS JOURNAL, **48**, 139 (1926).

(6) V. Lenher and A. W. Homberger, *ibid.*, **30**, 387 (1908).

(7) J. Meyer and W. Franke, *Z. anorg. Chem.*, **193**, 191 (1930).

(8) F. A. Gooch and J. Howland, *Am. J. Sci.*, [3] **48**, 375 (1894).

(9) H. and W. Biltz, W. T. Hall and A. A. Blanchard, "Laboratory Methods of Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1928.

(10) V. Lenher and C. H. Kao, THIS JOURNAL, **47**, 2454 (1925).

(11) L. I. Gilbertson and G. B. King, *ibid.*, **58**, 180 (1936).

(12) J. J. Lingane and R. L. Pecsok, *Anal. Chem.*, **20**, 425 (1948).

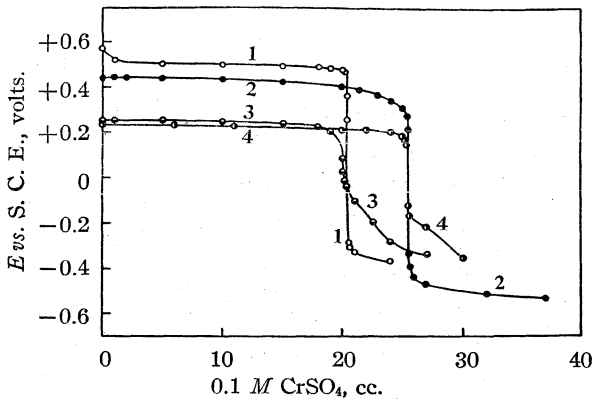


Fig. 1.—Titration of +4 selenium in hydrochloric acid media: (1) 9 *N* acid at 70°; (2) 6 *N* acid at 25°; (3) 0.1 *N* acid at 25°; (4) 1 *N* acid at 25°.

ducible potentials; when this was omitted the potential values before the equivalence point were abnormally low, although the e. p. could be determined without difficulty.

In 0.1 and 1 *N* hydrochloric acid the shape of the curves immediately after the e. p. suggests the partial reduction of Se to hydrogen selenide, and the characteristic odor of this gas could be detected. The formation of H_2Se was most pronounced in titrations in 9 *N* hydrochloric acid at 70°. The standard potential of the half reaction $Se + 2H^+ + 2e = H_2Se$ is −0.36 v. *vs.* N. H. E., which is only slightly more oxidizing than that of the chromic–chromous couple (−0.40 v.) and consequently complete reduction to hydrogen selenide cannot be expected.

From the data in Table I it is seen that titration in 0.1 *N* hydrochloric acid yields low results. In 1 to 9 *N* hydrochloric acid accurate results are

TABLE I

TITRATION OF SELENIUM (IV) WITH CHROMOUS SULFATE

Initial volume of solution was 150 cc. Calculated volume of chromous sulfate required was 25.52 cc. Solutions swept with CO_2

Initial acidity	Temp., °C.	Cr_2SO_4 required	Error, cc.
0.1 *N* HCl	25	25.35	−0.17
	70	25.26	− .26
1.0 *N* HCl	25	25.49	− .03
	70	25.47	− .05
6.0 *N* HCl	25	25.52	.00
		25.45	− .07
		25.57	+ .05
	70	25.48	− .04
		25.56	+ .04
		25.53	+ .01
9.0 *N* HCl	70	25.55	+ .03
		25.55	+ .03
1.0 *N* H_2SO_4	70	25.48	− .04
6.0 *N* H_2SO_4	70	25.48	− .04
		25.52	.00
		25.62	+ .10
		25.67	+ .15

obtained at both 25° and 70°. The higher acid concentrations are preferable because of the very large potential change at the e. p., and because the reaction is more rapid the higher the acidity.

Titration curves in 1 to 6 *N* sulfuric acid are very similar to those in the same concentration of hydrochloric acid. Titration in sulfuric acid solution is not as satisfactory as in hydrochloric acid because the reaction is slower, although it is feasible if the titration is performed at 70°. The data in Table I show a somewhat poorer precision in sulfuric acid than in hydrochloric acid.

+4 Tellurium.—Typical titration curves in various concentrations of hydrochloric and sulfuric acids are shown in Fig. 2. The titration reaction is

$$TeOOH^+ + 4Cr^{++} + 3H^+ = Te + 4Cr^{+++} + 2H_2O$$

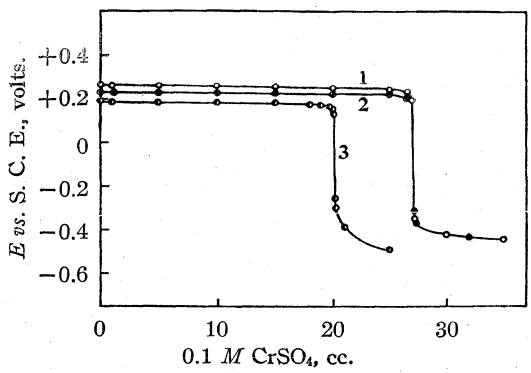


Fig. 2.—Titration of +4 tellurium: (1) 0.3 and 1 *N* hydrochloric acid, and 1 and 6 *N* sulfuric acid, at 25°; (2) 6 *N* hydrochloric acid at 25°; (3) 9 *N* hydrochloric acid at 70°.

The potential change at the e. p., although quite large, is smaller than that in the titration of +4 selenium. This is understandable from the following potential data[13] (referred to the standard hydrogen electrode). The standard potential

$H_2SeO_3 + 4H^+ + 4e = Se + 3H_2O$; $E^0 = +0.74$ v.

$TeOOH^+ + 3H^+ + 4e = Te + 2H_2O$; $E^0 = +0.529$ v.

$TeCl_6^{=} + 4e = Te + 6Cl^-$; $E^0 = +0.55$ v.

of the half reaction $Te + 2H^+ + 2e = H_2Te$ (−0.69 v.) is more reducing than that of the chromic–chromous couple (−0.40 v.), which precludes reduction to hydrogen telluride.

The reduction of +4 tellurium proceeds more rapidly than that of +4 selenium; at 70° establishment of the potential is almost instantaneous.

The data in Table II show that the titration is very accurate in all concentrations of hydrochloric acid between 0.3 and 9 *N*, and in 1 and 6 *N* sulfuric acid.

+6 Tellurium.—The standard potential of the half reaction

$H_6TeO_6 + 3H^+ + 2e = TeOOH^+ + 4H_2O$; $E^0 = +0.96$ v.

is 0.43 v. greater than that of the $TeOOH^+$–Te

(13) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938.

TABLE II

TITRATION OF TELLURIUM (IV) WITH CHROMOUS SULFATE

Initial volume of solution was 150 cc. Calculated volume of chromous sulfate required was 26.99 cc. All titrations at room temperature. Solutions swept with carbon dioxide

Initial acidity	Cr_2SO_4 required, cc.	Error, cc.
0.3 *N* HCl	26.94	−0.05
	26.91	− .08
1.0 *N* HCl	26.96	− .03
	26.97	− .02
6.0 *N* HCl	26.98	− .01
	26.96	− .03
	26.96	− .03
	27.03	+ .04
9.0 *N* HCl	26.97	− .02
	27.06	+ .07
1.0 *N* H_2SO_4	26.94	− .05
	26.96	− .03
	27.09	.00
	27.03	+ .04
6.0 *N* H_2SO_4	26.86	− .13
	26.86	− .13
	27.04	+ .05
	26.96	− .03

couple, so that a two stage reduction of telluric acid, first to the +4 state and then to the element, is possible. However, the reduction of telluric acid by chromous ion in either hydrochloric or sulfuric acid medium is so slow that a determination of tellurium based on reduction from the +6 to the +4 state is not feasible.

The first addition of chromous ion produces elemental tellurium which is only slowly reoxidized to the +4 state by the remaining telluric acid. In 6 *N* hydrochloric acid at 70° it is possible to obtain a titration curve with two inflection points if a long time is allowed for establishment of equilibrium between each addition of chromous ion until the first end-point has been reached. However, under these conditions a considerable part of the telluric acid is reduced by chloride ion

$$H_6TeO_6 + 2Cl^- + 3H^+ = TeOOH^+ + Cl_2 + 4H_2O$$

and since much of the resulting chlorine escapes from the solution, too little chromous solution is required. In a typical case, 9.75 cc. of chromous solution was required to reach the first end-point, compared to a theoretical 10.04 cc.

Titration of telluric acid to the elemental state is not feasible in any concentration of either hydrochloric or sulfuric acid up to 6 *N* at room temperature, nor in hot sulfuric acid solutions, because of the slow reduction. Although the reduction of telluric acid to the element proceeds at a more rapid rate in hot hydrochloric acid, the reduction by chloride ion precludes the use of this medium during the first stage of the titration. It is possible to obtain accurate results in the titration to the element by starting the titration in 6 *N* hydrochloric acid at room temperature, gradually heating the solution to 70° over a period of about ten minutes as the chromous solution is slowly added, and finally completing the titration at 70°. About one-half the total required volume of chromous solution should be added during the heating period. In five such titrations the volumes of chromous solution required ranged from 30.09 to 30.22 cc., the average being 30.14 ± 0.04 cc., in good agreement with the theoretical volume 30.13 cc. In this procedure the only oxidized form of tellurium that remains near the end-point is the +4 state, and the titration can be completed quickly.

+6 Selenium.—The titration of selenic acid is more difficult than telluric acid because the reaction is slower. Titration to the elemental state in 6 *N* hydrochloric acid at 70° led to results that were about 5% low, apparently because of partial reduction of the selenic acid by chloride ion. Starting the titration in 6 *N* hydrochloric acid at room temperature, slowly heating to 70° as the chromous solution was added, and finally completing the titration to the elemental state at 70°, yielded results accurate to about 0.5%. However, the titration requires such a long time that it is not practical.

Simultaneous Determination of Selenium and Tellurium.—Since in strongly acid solutions the oxidation potential of the Se(IV)–Se couple is about 0.3 v. greater than that of the Te(IV)–Te couple it is possible to determine both elements by a single titration with chromous ion.

Titration curves of mixtures of +4 selenium and +4 tellurium under various conditions of acidity and temperature are shown in Fig. 3.

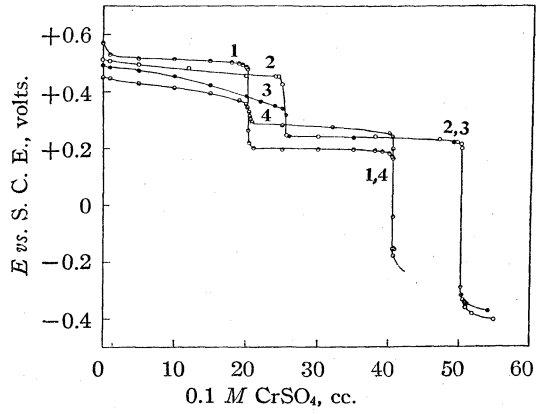


Fig. 3.—Titration of mixtures of +4 selenium and +4 tellurium under various conditions: (1) 9 *N* hydrochloric acid at 70°; (2) 6 *N* hydrochloric acid at 70°; (3) 6 *N* hydrochloric acid at 25°; (4) 6 *N* sulfuric acid at 70°.

In all cases the first inflection point corresponds to the reduction of Se(IV) to the elemental state, and the second occurs after the reduction of Te(IV) to the metal. Since the reduction of Te(IV) by chromous ion is more rapid than that of Se(IV),

addition of chromous ion causes some transient precipitation of elemental tellurium during the selenium stage of the titration, and equilibrium is established via the reduction of Se(IV) by the elemental tellurium.

In 6 *N* sulfuric acid at 70°, and in 6 *N* hydrochloric acid at room temperature the potential change at the selenium equivalence point is small and a long time is required for the attainment of equilibrium. In 9 *N* hydrochloric acid at 60° to 70° the titration is very satisfactory; a large potential break occurs at the selenium e. p. and equilibrium is established quickly. Under these conditions the titration yields accurate results. In three titrations, 25.55 ± 0.05 cc. of 0.1 *M* chromous sulfate solution was required to titrate the selenium, and 25.29 ± 0.09 cc. was used to titrate the tellurium, compared to theoretical values of 25.52 cc. and 25.30 cc., respectively.

Fairly accurate determinations of selenium may also be obtained in the presence of a large amount of tellurium. In two titrations in which 1.2 g. of tellurium (as TeO_2) was present, the selenium titration required 25.64 ± 0.02 cc. of 0.1 *M* chromous sulfate solution, compared to a theoretical 25.52 cc. The amount of selenium present was 6% of the amount of tellurium.

Selenium in Presence of Copper.—Since selenium frequently occurs in association with copper, the possibility of simultaneously determining both elements by titration with chromous ion was investigated.

Titration curves of solutions containing approximately equimolar concentrations of Se(IV) and Cu(II) are shown in Fig. 4. In all cases the Se(IV) is reduced first. In sulfuric acid medium the cupric copper is reduced to the metal, but in hydrochloric acid the copper exists as a chlorocuprate ion (probably $CuCl_4^=$) which is reduced to a chlorocuprite complex (probably $CuCl_2^-$).[12]

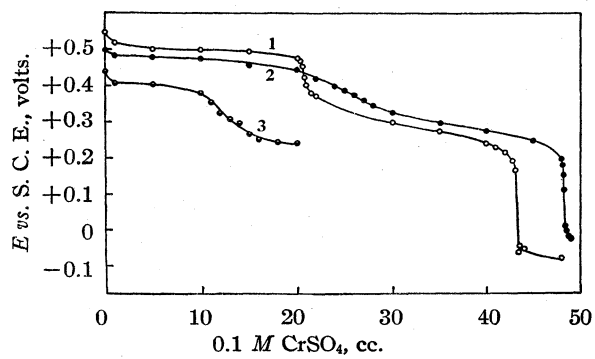


Fig. 4.—Titration of mixtures of +4 selenium and copper: (1) 9 *N* hydrochloric acid at 70°; (2) 6 *N* hydrochloric acid at 25°; (3) 6 *N* sulfuric acid at 70°.

In 6 *N* sulfuric acid at 70° (Curve 1 in Fig. 4) co-reduction of the copper takes place along with the reduction of the Se(IV), and the small gradual inflection in the titration curve occurs when only about half the Se(IV) is reduced.

In 6 *N* hydrochloric acid at room temperature (Curve 2) there is no distinct inflection at the completion of the Se(IV) reduction, although the completion of the reduction of both the Se(IV) and the Cu(II) is marked by a large potential change.

The optimum conditions appear to be 9 *N* hydrochloric acid and a temperature of 70°, as shown by curve 3. Under these conditions a small but distinct potential change occurs when the Se(IV) has been reduced, and both elements can be determined with fair accuracy. In one such titration, 20.8 cc. of 0.1 *M* chromous solution was used to reach the first inflection point, which was 2% greater than the theoretical 20.38 cc., and 22.5 cc. was required to titrate the copper, compared to a theoretical 22.71 cc.

Summary

In solutions acidified with sulfuric or hydrochloric acid Se(IV) and Te(IV) can be titrated accurately with standard chromous solution. The optimum conditions are 6 to 9 *N* hydrochloric acid and a temperature of about 70°. In both cases reduction proceeds to elemental selenium and tellurium.

Although it is quite possible to obtain titration curves for the stepwise reduction of both Se(VI) and Te(VI), first to the +4 states and then to the elements, the slow establishment of equilibrium renders impractical the determination of these elements by titrimetric reduction to the +4 states.

Accurate determinations of Se(IV) and Te(VI) in mixtures were obtained by a single titration with chromous ion in 9 *N* hydrochloric acid at 60° to 70°. A small amount of selenium can be determined accurately in the presence of large amounts of tellurium under these conditions.

Se(IV) and Cu(II), in mixtures containing approximately equal amounts of the two, can be determined with an accuracy of about 2% when the titration is performed in hot 9 *N* hydrochloric acid.

CAMBRIDGE 38, MASS. RECEIVED JANUARY 14, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF MONTANA STATE COLLEGE]

Vapor Pressure of Methyl Sulfoxide from 20 to 50°. Calculation of the Heat of Vaporization

BY THOMAS B. DOUGLAS[1]

For the calculation of bond energies from the previously reported[2] heats of two reactions involving liquid methyl sulfoxide, the heat of vaporization of this substance near room temperature must be known. It seemed that this quantity could be most conveniently determined with the required accuracy by measuring the vapor pressure at several temperatures. There was adopted a modification of the gas-saturation method used by Baxter and co-workers[3] to determine the vapor pressure of iodine. The amount of methyl sulfoxide evaporated was determined by chemical analysis.

Experimental Procedure

Methyl sulfoxide, prepared as previously described,[2] was finally purified in a closed system (J in Fig. 1) by four recrystallizations, the last of which did not appreciably change the freezing point (18.42°). The amount of impurity remaining was estimated to be 0.1 mole %, and the vapor pressure values were corrected accordingly.

Air, entering at A, was purified in train B by successive passage over the solids ferrous sulfate, potassium hydroxide, chromium trioxide, potassium hydroxide, and phosphorus pentoxide. Passing through a thermostat over two layers of liquid methyl sulfoxide C (each layer being 5 mm. wide and 25 cm. long) at a rate of two liters per hour (measured by a flowmeter K) and at a pressure 0.1 mm. below atmospheric, the air then bubbled through mercury (D), which completely prevented contamination of the liquid sulfoxide by backward diffusion of water vapor. The saturated sulfoxide vapor was absorbed in two tubes each containing 15 ml. of water (E). The air then emerging from the thermostat, after being thoroughly redried in the train F, was admitted through a system of capillaries (G) to one or two thirteen-liter highly evacuated glass bulbs (H) whose volumes had been (1) determined by filling with water and (2) checked by admittance of dry air and use of its data of state. The final pressure of the collected air was compared with the barometric pressure by means of a butyl phthalate manometer (L).

The temperatures of the thermostat and the collected air were periodically measured to ±0.01° by single-junction copper–constantan thermocouples,[4] using a calibrated Type K potentiometer and correcting for extraneous potentials. (The five thermocouple wells are designated in Fig. 1 by P.) The thermostat temperature remained constant to ±0.005°, and the total gradient averaged 0.03° at the highest temperatures. The combined absorption solutions produced in each run were withdrawn through tube M (sealed by mercury (N) during runs) and were accurately analyzed for their total content of methyl sulfoxide by the method previously developed,[2] with use of blanks and the other usual precautions.

Experimental Errors.—Tests were made to determine whether certain suspected sources of systematic error appreciably affected the results.

The contamination of the methyl sulfoxide during the series of runs was found to be inappreciable. After the completion of half the runs, involving the passage of 170 liters of air, the freezing point of the remaining sulfoxide was redetermined and found to have changed not more than 0.03°. This result indicated also the lack of appreciable reaction between the sulfoxide and oxygen of the air at the temperatures used. Nor did a removal of appreciable sulfoxide vapor by adsorption seem to occur before it reached the absorber tubes. For the various temperatures were run in random order and no chronological trend of vapor pressure values was detectable after three preliminary runs, each of whose values was about 0.5% low on the basis of the remaining fifteen runs.

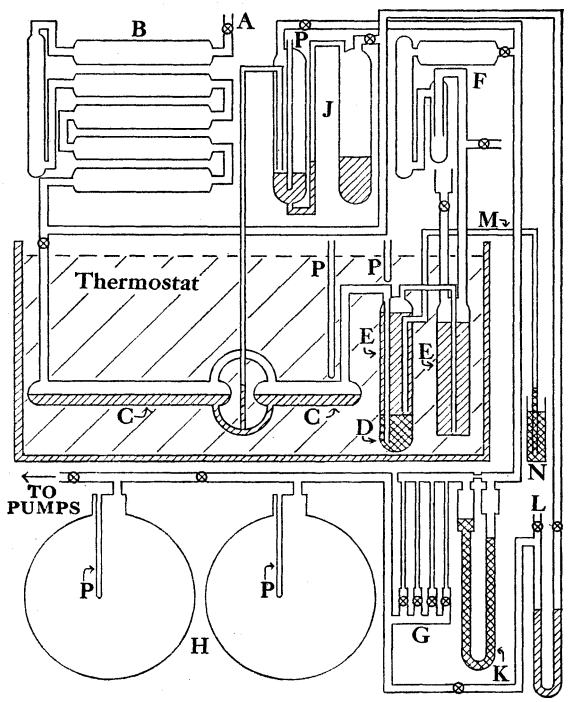


Fig. 1.—Apparatus used for determining the vapor pressure of methyl sulfoxide. No disassembling between runs was necessary. The arrangement permitted the liquid being frozen in J to be stirred by a stream of dry air.

Tests were made to establish whether the normal rate of air flow of two liters per hour was slow enough to permit complete saturation of the air with sulfoxide vapor, and a subsequent complete absorption of the vapor. One extra run at 30° and one at 50° were made at twice[5] the normal rate of air flow, yielding vapor pressure values which were, respectively, 0.1 and 0.3% lower than at the normal rate, which latter thus appears to be sufficiently slow.

Within the experimental error, all the sulfoxide vapor was found to be retained by the first of the two absorber tubes. One extra run at 30° and one at 50° in which water was present in only the first absorber tube gave vapor

(1) Present address: National Bureau of Standards, Washington, D. C.

(2) Douglas, THIS JOURNAL, **68**, 1072 ff (1946).

(3) Baxter, Hickey and Holmes, *ibid.*, **29**, 127 ff (1907); Baxter and Grose, *ibid.*, **37**, 1061 ff. (1915).

(4) Calibrated at the ice-point, the steam-point, and the transition temperatures of $Na_2SO_4 \cdot 10H_2O$, $NaBr \cdot 2H_2O$, and $MnCl_2 \cdot 4H_2O$ [Richards and Wrede, *Z. physik. Chem.*, **61**, 313 (1907)].

(5) Doubling the rate of flow should provide a more rigorous test than halving it, since the change in observed vapor pressure due to lack of saturation should be much greater in the former case.

pressure values which were respectively 0.1% lower and 0.2% higher than the values obtained using two absorbers. As a check the total water collected from the emerging air from all the runs was found to contain only a mere trace of sulfoxide.

It was feared that some mercury may have been carried into the water absorbing the sulfoxide vapor, causing the subsequent titration of the solution with permanganate to run high. One solution from a 30° run and one from a 50° run were each tested for mercury, which, if present at all, was shown to be insufficient in amount to raise the experimental value of the vapor pressure by more than 0.1%.

The departure of the saturated methyl sulfoxide vapor, mixed with air, from gas ideality is probably small, but seems too uncertain to justify its estimation. During one purification of the sulfoxide a sample was observed to boil at 79° at 16.5 ± 1 mm., whereas extrapolation of the calculated vapor pressure values to this temperature gives 15.5 mm. This comparison indicates that the vapor density does not differ widely from that calculated using the formula $(CH_3)_2SO$. Nor is departure from this formula, through dissociation or association, to be expected on theoretical grounds.

An estimation of individual errors indicated that the experimental vapor pressure values, as represented by the empirical equation below, are probably accurate in the temperature range of the measurements to within ±1%.

Results

Each value of the vapor pressure was calculated from the experimental data by use of the equation

$$p = \frac{0.9977\ P_1}{N\left(\frac{P_2 V_2}{nRT_2}\right) + 1}$$

where p is the vapor pressure of pure methyl sulfoxide, P_1 the average total pressure in the saturator (about 635 mm.), N the estimated mole fraction of methyl sulfoxide in the liquid used, P_2 the pressure of collected air at absolute temperature T_2, V_2 the volume of collected air, n the moles of methyl sulfoxide evaporated (assuming the formula $(CH_3)_2SO$), and R the gas constant. 0.9977, the ratio of the fugacity of liquid methyl sulfoxide at pressure p to its fugacity at pressure P_1,[6] corrects the vapor pressure to the value which should be obtained in the absence of the air. Two independent measurements of vapor pressure were made at each temperature at 5° intervals from 20 to 50°. These duplicates at the same temperature agreed on the average to within 0.15% and the maximum difference was 0.5%.

Using the method of least squares and giving each value of log p equal weight, the following equation was found for the vapor pressure of methyl sulfoxide from 20 to 50°.[7] This equation

$$\log_{10} p = 26.49558 - (3539.32/T) - 6.00000 \log_{10} T \quad (1)^8$$

represented the experimental values of vapor pressure with an average deviation of ±0.15%, the maximum discrepancy being 0.4%. Values calculated from equation (1) in this temperature range are given in Table I.

TABLE I

VAPOR PRESSURES OF METHYL SULFOXIDE AT ROUNDED TEMPERATURES

(Calculated from equation (1))

Temp., °C.	Vapor pressure, mm.	Temp., °C.	Vapor pressure, mm.
20	0.417	40	1.656
25	.600	45	2.27
30	.853	50	3.07
35	1.195		

Equation (1) yields a value of 12.64 kcal. for the molal heat of vaporization of methyl sulfoxide at 25°. This figure was estimated to have an uncertainty of ±0.1 kcal. It is of interest that equation (1) leads to a normal boiling point of 192° and a Trouton constant of 22.9 cal./mole/deg., but these two figures are naturally not highly reliable, because of the wide extrapolations involved.

Summary

The vapor pressure of methyl sulfoxide has been determined by a gas-saturation method at 5° intervals from 20 to 50°.

The values found are expressed, with an average deviation of ±0.15%, by the equation

$$\log_{10} p = 26.49558 - (3539.32/T) - 6.00000 \log_{10} T$$

which gives 12.64 ± 0.1 kcal. for the molal heat of vaporization at 25°.

Various sources of error are discussed. It is estimated that correct vapor pressures are given by this equation, in the temperature range of the measurements, to within ±1%.

BOZEMAN, MONTANA RECEIVED JANUARY 30, 1948

(6) Using $(\partial \ln f/\partial P)_T = v/RT$, where v is the molal volume of the liquid, 71 ml. The ratio of fugacities is practically independent of temperature in the range investigated.

(7) Although the constants given are accurately interconsistent, it was first necessary to find by trial a value for the coefficient of log T which would approximately minimize the sum of the squares of the deviations. No value of this coefficient between −8 and −4 produces any particular trend of deviations with temperature.

(8) p in mm., T in deg. absolute, and 0°C. = 273.16°K.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Hydrogen Exchange of Phenols and Phenol Ethers with Deutero-alcohol[1]

BY PHILIP F. TRYON,[2] WELDON G. BROWN AND M. S. KHARASCH

The experiments described herein were performed in an attempt to set up a quantitative basis for the comparison of variously constituted phenols and phenol ethers in respect to the rates of exchange of nuclear hydrogen atoms. Whereas previous investigators have examined the hydrogen exchange of phenol[3] with aqueous alkali, and of anisole with aqueous sulfuric acid,[3a] our work has been done with deutero-ethanol as solvent and reactant, thereby avoiding heterogeneous reaction mixtures. Moreover, although we have used sulfuric acid to promote the exchange of nuclear hydrogens, it has been under such mild conditions, as compared to the above-mentioned experiments on anisole, that the exchange is limited to those positions which are known to be active in ordinary electrophilic substitutions.

Briefly, the significant features of our results are the following. First, it is noted that the partition coefficient for the distribution of deuterium in a nuclear exchange reaction differs appreciably from unity, the deuterium favoring the hydroxyl group of ethanol as might be expected from zero-point energy considerations. Thus the limiting values of the "exchange number" in experiments on mixtures which were allowed to approach exchange equilibrium fall short of the integer representing the number of participating hydrogen atoms by nearly 10%. Such an effect is not observed in exchange reactions involving only the hydroxyl group of phenols (*cf.* Table I).[4]

TABLE I

EXCHANGE OF HYDROXYL HYDROGEN OF PHENOLS WITH DEUTEROALCOHOL[a]

Compound	Obs. exch.
p-Cresol	1.02
β-Naphthol	1.01
3,5-Dimethyl-4-chlorophenol	1.06
3,4-Dimethylphenol	1.09
6-Hydroxytetralin	1.10
5-Hydroxyhydrindene	1.06

[a] Experiments carried out by dissolving 0.008 mole of the phenol in 5 ml. of deuteroalcohol and recovering the alcohol immediately thereafter by vacuum distillation.

Referring next to the naphthols and naphthol ethers, the data presented in Table II show that whereas α-naphthol and its ethyl ether exchange two nuclear hydrogens, β-naphthol and its ether exchange only one. That this is the α-hydrogen is strongly supported by the observation that α-methyl-β-naphthyl ethyl ether exhibits no exchange under comparable conditions. The non-occurrence of exchange at the 3-position of β-naphthol and derivatives is readily explained on the basis of a mechanism similar to that established for the acid-catalyzed exchange reactions of tertiary aromatic amines.[5] Of the two possible transition states which could arise from the attachment of a deuteron at a carbon atom adjacent to the hydroxyl or alkoxyl group, I is fixed in electronic configuration and must correspond to an activation energy several kilocalories higher than II in which a benzenoid ring is preserved.

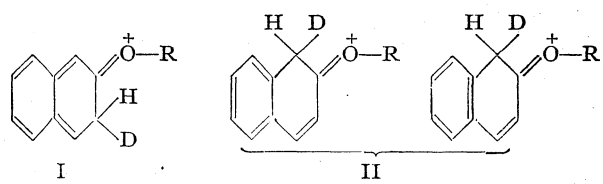


TABLE II

ACID CATALYZED EXCHANGE OF HYDROGEN ATOMS OF PHENOLS AND PHENOL ETHERS WITH DEUTEROALCOHOL AT 110°

Compound	Reaction time, hours	Observed exchange	Active H atoms (theor.)
α-Naphthol	0.25	1.74	
	0.5	2.67	
	3.5	2.93	
	9	2.85	
	22	2.89	3
β-Naphthol	0.25	1.80	
	0.5	2.10	
	3.5	2.01	
	16.5	1.90	
	51.5	1.97	2
p-Cresol	24	1.63	
	52	2.63	
	213	2.82	
	235	2.80	3
α-Naphthyl ethyl ether	22	0.18	
	83	1.46	
	119	1.72	
	206	1.89	2
β-Naphthyl ethyl ether	24	0.49	
	112	0.92	
	190	1.00	
	410	0.97	1
α-Methyl-β-naphthyl ethyl ether	142	0.03	0

(1) Abstracted from a Ph.D. thesis by Philip F. Tryon, Chicago, 1939.

(2) Present address: Commercial Solvents Corporation, Terre Haute, Indiana.

(3) (a) Ingold, Raisin and Wilson, *J. Chem. Soc.*, 1637 (1936); (b) Small and Wolfenden, *ibid.*, 1811 (1936); (c) Best and Wilson, *ibid.*, 28 (1938); (d) Munzberg, *Z. physik. Chem.*, **B33**, 23, 39 (1936).

(4) This work was carried out prior to the discovery that significant changes in isotopic composition occur when ethanol is fractionally distilled and that precautions are necessary to avoid errors due to this effect (Brown and Widiger, THIS JOURNAL, **61**, 2453 (1939)). The exchange numbers herein reported, being subject to such errors, may be too high by as much as 5%.

(5) Brown, Widiger and Letang, *ibid.*, **61**, 2597 (1939).

In experiments which were carried out at a lower temperature (Table III), and in which exchange equilibrium was not attained, there is revealed the rather surprising effect of the β-methyl group in ethers of β-methyl-α-naphthol. The lower reactivity of these compounds, in which the hydrogen atoms in the 4-position should still be active, is perhaps an example of a steric effect which should arise in di-*ortho*-substituted phenol ethers because of hindrance to coplanarity in the quinonoid transition state.[6]

TABLE III

ACID CATALYZED EXCHANGE OF HYDROGEN ATOMS AT 60°

Compound	Reaction time, hours	Observed exchange	Active H atoms (theor.)
p-Cresol	15	1.11	
	20	1.15	3
α-Naphthyl methyl ether	70	0.36	
	238	1.15	2
α-Naphthyl isopropyl ether	213	1.18	2
β-Methyl-α-naphthyl methyl ether	238	0.08	1
β-Methyl-α-naphthyl isopropyl ether	213	0.07	1

The results shown in Table IV for phenols having two non-equivalent free ortho positions are of interest in connection with the Mills–Nixon effect. It is clear from these results that each of these substances exchanges two nuclear hydrogen atoms, and if one exchanges faster than the other the differences are not great enough to be readily discernible in the rate curves. These curves are similar in form to that shown by the symmetrical phenol, 3,5-dimethyl-4-chlorophenol, except that the time scale is somewhat more extended for this compound because of its lower reactivity.

Experimental

The experimental procedure employed in this Laboratory for following exchange reactions with deuteroalcohol has been described in previous papers.[7] In all of the experiments here reported the extent of exchange has been determined from the decrease in deuterium content of the alcohol.

The experiments on sulfuric acid catalyzed reactions fall into two groups according to the temperature employed. At 60° the acid is present as ethyl hydrogen sulfate and it was determined that there is no loss of catalyst by further reaction to form diethyl sulfate within a period of eight days. At 110° the loss of catalyst is appreciable within a few hours and the experiments carried out at this temperature therefore do not represent steady conditions with respect to catalyst concentration.

In the presence of small amounts of sodium ethylate, neither α-naphthyl ethyl ether nor β-naphthyl ethyl ether showed any measurable exchange in periods up to twelve days at 110°.

The reaction mixtures generally contained 5 cc. of deuteroalcohol (0.085 mole) and about 0.009 mole of the phenol or ether. Where sulfuric acid was to be used, it was added to the alcohol so as to provide a stock solution containing 10 mg. of sulfuric acid per 5 cc. of alcohol. However, in the series of experiments summarized in Table IV, a more dilute stock solution, containing 0.5 mg. of sulfuric acid per 5 cc. of alcohol, was used and the quantity of phenol was accurately adjusted to 0.00818 mole.

TABLE IV

UPTAKE OF DEUTERIUM FROM DEUTEROALCOHOL, AT 60°, BY 3,4-DIMETHYLPHENOL (I), 5-HYDROXYHYDRINDENE (II), 6-HYDROXYTETRALIN (III) AND 3,5-DIMETHYL-4-CHLOROPHENOL

Time, hours	Exchange number[a] (I)	(II)	(III)	(IV)
0[b]	1.05	1.02	1.06	1.02
1	1.11	1.16	1.18	
3	1.26	1.37	1.40	
5	1.60	1.56	1.56	
6				1.13
10	1.70	1.85	1.99	
13				1.26
15	1.99	1.99	2.15	
20	2.25	2.09	2.27	1.34
25	2.40	2.21	2.28	
30	2.39	2.25	2.41	1.46
35	2.52	2.28	2.47	
40	2.54	2.40	2.44	1.54
45	2.60	2.43	2.54	
50		2.49	2.56	
55		2.50		
60			2.56	1.68
90		2.63		
100				1.97
120	2.71			
140	2.70	2.68		2.25
180			2.68	
200			2.68	
216				2.39
265				2.49
342				2.56

[a] For each experiment a solution was prepared containing 0.085 mole of deuteroalcohol (14.77 mole % C_2H_5-OD), 0.001 equivalent of sulfuric acid, and 0.00818 mole of phenol. The exchange numbers were calculated from the analyses on recovered alcohol, taking into account dilution of deuterium by hydrogen from the sulfuric acid. [b] The experimental results entered for zero time were obtained by recovering the alcohol, by distillation, immediately after preparing the mixture. Actually the separations required several minutes to perform. The observed exchange is obviously the exchange of the hydroxyl hydrogen atoms of the phenols.

Except as noted below the materials used were prepared and purified by methods described in the literature.

β-Methyl-α-naphthyl Methyl Ether.—This compound was obtained in 50% yield on treatment of an alkaline solution of β-methyl-α-naphthol[8] with dimethyl sulfate: colorless liquid, b. p. 129–130° at 9 mm., $n^{20}D$ 1.6007, d^{25}_4 1.056. It was characterized by nitration, following a procedure similar to that used by Heermann[9] in the nitration of α-naphthol ether, which furnished a mononitro derivative (1-methoxy-2-methyl-4-nitronaphthalene), light yellow needles, m. p. 104°. *Anal.* Calcd. for $C_{12}H_{11}O_3N$: N, 6.45; Found: N, 6.82.

β-Methyl-α-naphthyl Isopropyl Ether.—A suspension of the sodium salt of β-methyl-α-naphthol in a solution

(6) Further evidence concerning possible steric effects was sought by examining the hydrogen exchange of 2-methylanisole and 2,6-dimethylanisole, but both of these compounds showed some decomposition (positive ferric chloride test) under the conditions of the exchange experiments and the results were therefore inconclusive.

(7) (a) Kharasch, Brown and McNab, *J. Org. Chem.*, **2**, 36 (1937); (b) Brown, Kharasch and Sprowls, *ibid.*, **4**, 442 (1939).

(8) Prepared by the method of Lesser, *Ann.*, **402**, 38–43 (1914).

(9) Heermann, *J. prakt. Chem.*, **44**, 238 (1891).

containing 150 cc. of dioxane, 32 g. of isopropyl bromide, and 2 g. of potassium iodide was refluxed for fourteen hours. After distilling off most of the dioxane, ether and water were added, and the ether layer, after washing with alkali and with water and then drying over calcium chloride, yielded on distillation 13 g. (38% yield) of the desired product; b. p. 147–148° at 12 mm., n^{20}D 1.5764, d^{25}_4 1.017. Nitration yielded a mononitro derivative (1-isopropoxy-2-methyl-4-nitronaphthalene), light yellow needles, m. p. 45°. *Anal.* Calcd. for $C_{14}H_{15}O_3N$: N, 5.71; Found: N, 5.69.

α-Naphthyl Isopropyl Ether.—This was prepared by a procedure similar to the preceding, from the sodium salt of α-naphthol and isopropyl bromide in 21% yield; b. p. 139–140° at 9 mm., n^{20}D 1.5848, d^{25}_4 1.025. On nitration a mononitro derivative was obtained which yielded 4-nitro-1-naphthol on treatment with alcoholic potassium hydroxide for one hour on the steam-bath and is thus identified as 1-isopropoxy-4-nitronaphthalene; dark yellow needles, m. p. 69°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: N, 6.06; Found: N, 6.15.

Summary

It is shown that hydrogen atoms *ortho* and *para* to the hydroxyl or alkoxyl group in phenols and phenol ethers exchange with deuteroalcohol in the presence of small amounts of sulfuric acid. Exceptions are β-naphthol and derivatives thereof in which exchange occurs only at the α-position. The unsymmetrical phenols, 5-hydroxyhydrindene and 6-hydroxytetralin, which couple at a preferred *ortho* position (Mills–Nixon effect), show two active nuclear hydrogens in the exchange reaction.

CHICAGO, ILLINOIS RECEIVED DECEMBER 31, 1947

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

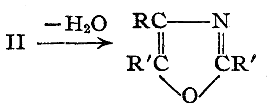
Conversion of α-Amino Acids to Acylamido Ketones and Oxazoles

BY RICHARD H. WILEY AND OLIN H. BORUM[1]

A previous communication[2] described a method for the conversion of α-amino acids (I) to acetamidoketones (II, R′ = CH_3) by reaction with acetic anhydride in pyridine, and of the acetamidoketones to oxazoles (III).

$$\underset{\text{I}}{RCH(NH_2)CO_2H} + 2(R'CO)_2O \xrightarrow{\text{pyr.}}$$

$$\underset{\text{II}}{RCH(NHCOR')COR'} + 2RCO_2H + CO_2$$



III

The present paper describes the anomalous course of this reaction with glycine, the substitution of propionic for acetic anhydride in the formation of a propionamidoketone, and a modified procedure for obtaining yields of 70–90% of the acylamidoketone.

The reaction product obtained on refluxing glycine and acetic anhydride in pyridine can be fractionated to give a principal fraction boiling at 105–108° at 2 mm. The analytical data show that this compound is not acetamidoacetone, the product which would be formed if the reaction were analogous to that with alanine. The data agree with values calculated for an acetyl derivative of acetamidoacetone. This is substantiated by the hydrolysis of this acetyl derivative to acetamidoacetone b. p. 101–105° (0.5 mm.) in 76% yield. The structure of the acetyl derivative cannot be assigned on the basis of the available information. It is noted in this connection that previous attempts to bring about this reaction with glycine[3] were less successful because the reaction is very slow at steam-bath temperatures.

Improved yields of 3-acetamido-2-butanone are obtained by stirring during the reaction period to aid in evolution of carbon dioxide. The preferred procedure, in which the product is separated by fractionation of the reaction mixture, gives 88% of redistilled product as described in the experimental part. Using this procedure aminophenylacetic acid and propionic anhydride give a 75% yield of 1-phenyl-1-propionamido-2-butanone.

Dehydration of the acylamidoketones to oxazoles with potassium bisulfate and other reagents has been accomplished but with no advantage over the previously described[2] sulfuric acid dehydration.

Experimental Part

3-Acetamido-2-butanone (II, R = CH_3, R′ = CH_3).—A mixture of 159 ml. (1.98 moles) of pyridine (J. T. Baker C. P.), 224 ml. (2.35 moles) of acetic anhydride (95% min. assay), and 35.11 g. (0.39 mole) of vacuum-dried alanine (Merck) was heated with stirring on the steam-bath for six hours after solution was complete. The excess pyridine and acetic anhydride were removed at reduced pressure and the residue distilled through a short column to obtain 47.5 g., 93.2% of the theoretical amount of crude 3-acetamido-2-butanone, b. p. 110–125° at 3 mm. On refractionation 88% of the theoretical amount, 45 g., b. p. 102–106° at 2 mm., was obtained, n^{25}D 1.4558.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.81; H, 8.48; N, 10.90.

Without stirring the yield dropped to 46%. Reducing the molar ratio of pyridine or anhydride also reduced the yield.

1-Phenyl-1-propionamido-2-butanone (II, R = C_6H_5, R′ = C_2H_5).—A mixture of 60 g. (0.4 mole) of aminophenylacetic acid (E. K. Co.), 250 ml. (2.0 moles) of propionic anhydride (Carbide and Carbon Co.), and 165

(1) The work reported in this paper was taken in part from the Master's Thesis submitted by Olin H. Borum to the Graduate School of the University of North Carolina.

(2) Richard H. Wiley, *J. Org. Chem.*, **12**, 43 (1947).

(3) Dakin and West, *J. Biol. Chem.*, **78**, 91–105 (1928).

ml. of pyridine were heated to solution and then at gentle reflux for one and a half hours. On vacuum distillation a fraction, b. p. 159–162° at 3–4 mm., weighing 66 g., 75% of the theoretical amount of 1-phenyl-1-propionamido-2-butanone, was collected. This fraction solidified on standing and was recrystallized from xylene, m. p. 69.7–70.7 (cor.).

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.33; H, 7.89; N, 6.65.

Acetyl Acetamidoacetone.—A mixture of 1.1 liters (11 moles) of acetic anhydride (95% min. assay), 485 ml. (6 moles) of pyridine (J. T. Baker C. P.), and 75 g. (1 mole) of vacuum-dried glycine (E. K. Co) was refluxed with stirring for six hours. The excess pyridine and acetic anhydride were removed at reduced pressure and the residue distilled to obtain 95 g., 60% of the theoretical amount, of crude acetyl acetamidoacetone, b. p. 118–128° at 3 mm. On refractionation 85 g., 54% of the theoretical amount of purified acetyl acetamidoacetone, b. p. 105–108° at 2 mm., was separated, $n^{25}D$ 1.4668; d^{25}_{25} 1.1275.

Anal. Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.54; H, 7.17; N, 9.17.

Acetyl acetamidoacetone reacts immediately with neutral potassium permanganate solution to give a heavy precipitate. Acetamidoacetone does not. Both decolorize bromine in carbon tetrachloride solution.

Acetamidoacetone (II, R = H, R′ = CH_3).—Thirty-two grams of acetyl acetamidoacetone was dropped into 500 ml. of boiling water over a thirty-minute period. The mixture was steam distilled for five hours, the remaining water and acetic acid removed under reduced pressure, and the residue fractionated to give 17.8 g., 76% of the theoretical amount of acetamidoacetone, b. p. 104–109° (1–2 mm.), $n^{25}D$ 1.4600 (supercooled). This fraction solidified to an extremely hygroscopic solid, m. p. 39–41°.

Anal. Calcd. for $C_5H_9O_2N$: C, 52.16; H, 7.88; N, 12.16. Found: C, 51.87; H, 7.92; N, 12.10.

Acetamidoacetone was converted to 2,5-dimethyloxazole by the process previously described.[2] Ten to fifteen per cent. of 2,5-dimethyloxazole, b. p. 116–117°, $n^{25}D$ 1.4365 was obtained. The reported[4] boiling point is 117°.

Anal. Calcd. for C_5H_7ON: N, 14.42. Found: N, 14.60.

2,5-Dimethyloxazole picrate, m. p. 122–122.5°, was prepared in alcohol solution. The reported m. p. is 124°.[4]

Anal. Calcd. for $C_{11}H_{10}O_8N_4$: N, 17.17. Found: 17.34.

Dehydration of 3-Acetamido-2-butanone to 2,4,5-Trimethyloxazole.—Thirty grams of 3-acetamido-2-butanone was dropped over a thirty-minute period onto 87.5 g. of potassium bisulfate in a distilling flask at 220°. A total of 21.10 g. of distillate was collected in the receiver. This material on fractionation gave a total of 17.8 g., b. p. 70–147°. A center cut of 7.8 g., b. p. 141–143°, $n^{25}D$ 1.4280 gave a picrate, m. p. 110–111.5°, which did not lower the m. p. when mixed with a sample of previously prepared[2] picrate. When 11.7 g. of the crude reaction mixture, b. p. 142–150°, was washed with 33% aqueous sodium hydroxide and dried over solid potassium hydroxide 1.7 g. of oxazole, b. p. 133–135°, $n^{25}D$ 1.4391, was obtained. Other pyrolyses with alumina, anhydrous zinc sulfate, lime, boron oxide and phosphorus pentoxide at 200–300°, but not thermal pyrolysis at 500°, dehydrate the ketone to the oxazole in low yields.

Summary

Glycine reacts with acetic anhydride in pyridine to form acetyl acetamidoacetone which is readily hydrolyzed to acetamidoacetone. Improved yields in the conversion of alanine to 3-acetamido-2-butanone, the conversion of aminophenylacetic acid to 1-phenyl-1-propionamido-2-butanone, and a potassium bisulfate dehydration of 3-acetamido-2-butanone to 2,4,5-trimethyloxazole are reported.

(4) Wrede and Feuerriegel, *Z. physiol. Chem.*, **218**, 129 (1933).

CHAPEL HILL, N. C. RECEIVED SEPTEMBER 6, 1947

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, COMMERCIAL SOLVENTS CORPORATION]

Some Chloromethyl Ethers of Nitro Alcohols and the Preparation of Mixed Acetals from Them

BY E. B. HODGE

The reaction between formaldehyde, hydrogen chloride and an alcohol to form a chloromethyl ether was first reported by Henry.[1] Since then, the reaction has become very well known and is frequently used in synthetic work. The chlorine atom in these compounds is quite reactive, and it was thought to be of interest to see if the chloromethyl ethers of nitro alcohols would form. These compounds would make available a new tool in the preparation of derivatives containing aliphatic nitro groups. The aromatic nitro group is known to hinder the chloromethylation reaction.[2]

The success of the chloromethylation reaction as applied to nitro hydroxy compounds was found to vary with the structure of the nitro hydroxy compound. The chloromethyl ethers prepared were mobile liquids with sharp odors. They were soluble in benzene and the usual oxygenated solvents, but were insoluble in petroleum ether and water. On being shaken for a short time with water they decomposed.

Properties and yields of the chloromethyl ethers prepared are listed in Table I. The yields are based on the nitro alcohol.

The chloromethyl ethers prepared were found to react smoothly with sodium phenoxide and alkoxides to give mixed acetals. The nitro group in these could be reduced catalytically to the amino group. Properties and yields of these mixed acetals are given in Table II.

Yields of the nitro acetals and of the amino acetals from phenol are based on the chloromethyl

(1) L. Henry, *Bull. acad. roy. Belg.*, 3, **25**, 439 (1893).

(2) "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 65.

TABLE I

CHLOROMETHYL ETHERS OF NITRO ALCOHOLS

Nitro hydroxy compound	Chloromethyl ether	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_{20}	Analyses, % Nitrogen Calcd.	Nitrogen Obs.	Chlorine Calcd.	Chlorine Obs.
2-Methyl-2-nitro-1-propanol	1-Chloromethoxy-2-methyl-2-nitropropane	75	85	4	1.4498	1.206	8.37	8.5	21.2	21.0
2-Methyl-2-nitro-1-butanol	1-Chloromethoxy-2-methyl-2-nitrobutane	70	98	3	1.4548	1.175	7.72	7.9	19.5	19.3
2-Nitro-1-butanol	1-Chloromethoxy-2-nitrobutane	69	95	1	1.4510	1.208	8.37	8.6		

TABLE II

MIXED ACETALS

Acetal	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_{20}	Analyses, % Neut. eq. Calcd.	Neut. eq. Obs.	Nitrogen Calcd.	Nitrogen Obs.
2-Methyl-2-nitro-4,6-dioxaheptane	68	65	2	1.4206	1.084			8.59	8.68
2-Methyl-2-nitro-4,6-dioxaoctane	30	72	1	1.4248	1.049			7.92	8.18
3-Methyl-3-nitro-5,7-dioxaoctane	55	75	1	1.4309	1.068			7.92	8.01
2-Amino-2-methyl-4,6-dioxaheptane	72	56	20	1.4158	0.917	133	134.3		
3-Amino-3-methyl-5,7-dioxaoctane	82	60	10	1.4242	0.917	147	148		
2-Methyl-1-(phenoxymethoxy)-2-propanamine	28	100	1	1.4983	1.018	195	196		
2-Methyl-1-(phenoxymethoxy)-2-butanamine	40	102	1	1.500	1.011	209	208		

ether, while the yields of the other amino acetals are based on the nitro acetals.

When the chloromethylation of 2-methyl-2-nitro-1,3-propanediol was attempted, only the acetal, 5-methyl-5-nitro-1,3-dioxane was obtained.[3]

The cyclic acetal was too stable to be split by hydrogen chloride. Support for this hypothesis is given by the fact that bis-(2-methyl-2-nitropropoxy)-methane was found to react with hydrogen chloride and formaldehyde to give 1-chloromethoxy-2-methyl-2-nitropropane.

The effect of structure on the formation of chloromethyl ethers of nitro alcohols is shown by the relative ease of preparation of the chloromethyl ethers. 2-Methyl-2-nitro-1-propanol and 2-methyl-2-nitro-1-butanol reacted smoothly and gave a product which could be distilled at reduced pressure without apparent decomposition. However, the chloromethyl ether of 2-nitro-1-butanol could not be distilled without some decomposition, while no product could be isolated from 2-methyl-2-nitro-3-hexanol.

Experimental

The preparation of the chloromethyl ethers is illustrated by the reaction between hydrogen chloride, formaldehyde and 2-methyl-2-nitro-1-propanol.

(3) The fact that this acetal was formed from the diol while chloromethyl ethers were formed from the monohydroxy compounds suggests that the chloromethyl ethers were formed through the acetals as intermediates and that the cyclic acetal was too stable to be split by hydrogen chloride. Thus the equations might be written to account for the formation of the chloromethyl ethers. Support for this hypothesis is given by the fact that bis-(2-methyl-2-nitropropoxy)-methane was found to react with hydrogen chloride and formaldehyde to give 1-chloromethoxy-2-methyl-2-nitropropane.

$$2ROH + HCHO \xrightarrow{H^+} (RO)_2CH_2 + H_2O$$
$$(RO)_2CH_2 + HCl \longrightarrow ROCH_2Cl + ROH$$

Into a mixture of 238 g. of 2-methyl-2-nitro-1-propanol, 90 g. of trioxymethylene and 175 ml. of concentrated hydrochloric acid in a 1-liter beaker was passed a rapid stream of HCl from a cylinder of liquefied hydrogen chloride. The beaker was in an ice-bath which kept the temperature below 30° during the addition of the hydrogen chloride. The contents of the beaker were stirred vigorously and the hydrogen chloride was added through a disperser of sintered glass. After about one hour the addition was stopped, 50 ml. of benzene was added, and the layers were separated. Dry air was passed through the top layer until no more hydrogen chloride was evolved and then the product was distilled, first at atmospheric pressure and then at 5 mm. to remove the chloromethyl ether. This came off at 90–94°, wt. 228 g.

The preparation of a mixed acetal is illustrated by the following experiment.

One-hundred and sixty grams of methanol was placed in a 500 ml. round-bottomed flask equipped with a sealed stirrer, a dropping funnel and a reflux condenser. One mole (23 g.) of sodium was added slowly and when all had reacted, 145 g. (0.8 mole) of 1-chloromethoxy-2-methyl-2-nitrobutane was added dropwise to the refluxing mixture. After one-half hour of refluxing the mixture was cooled and filtered. Then 500 ml. of water was added and the methanol was stripped off. The oil which separated from the water was distilled. The main cut (81.4 g.) came off at 75° at 1–1.5 mm.

Reduction of the nitro mixed acetals is illustrated by the following experiment.

2-Methyl-2-nitro-4,6-dioxaheptane (78.6 g.) was dissolved in 400 ml. of methanol and reduced with hydrogen in a rocking bomb at 50–60° and 1000 lb. pressure in the presence of 5 g. of Raney nickel. The methanol was stripped off and the product was distilled at 10 mm. The weight of the product was 53.5 g.

Reaction between an acetal and hydrogen chloride was carried out as follows.

To 63 g. (0.25 mole) of bis-(2-nitroisobutoxy)-methane was added 1 mole of formalin. Dry hydrogen chloride was passed into this mixture at room temperature for three hours. The mixture was then extracted with benzene and the high boiling product was rectified under reduced pressure. A middle cut of 27 g. was taken which boiled at 104–106° at 13 mm. and contained 21.5% of chlorine. Theory for 1-chloromethoxy-2-methyl-2-nitropropane is 21.2%.

Summary

The chloromethyl ethers of three nitro alcohols have been prepared.

Evidence suggests that the formation of these chloromethyl ethers takes place through the formal as an intermediate.

Several mixed acetals have been prepared from chloromethyl ethers of nitro alcohols and the nitro groups in these compounds have been reduced to amino groups.

TERRE HAUTE, INDIANA RECEIVED JANUARY 2, 1948

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. VI.[1] The Reaction of Vanillin with Mercuric Oxide[2,3]

BY IRWIN A. PEARL

The high yields of vanillic acid obtained when vanillin is treated with alkali and 0.5 mole of silver oxide in aqueous solution[4,5] and the interesting reactions of vanillin with alkali in the presence of silver oxide and silver metal[6] led to a study of the reaction of vanillin with alkali and other metallic oxides. This paper reports the study with mercuric oxide.

Vanillin gradually reacts with an excess of mercuric oxide in a boiling aqueous solution containing at least two moles of alkali to give a clear alkaline solution which may be treated by various procedures to give several different reaction products. All forms of mercuric oxide are operative, but the more reactive, freshly precipitated forms require less time. The reaction time is also dependent, to a considerable extent, upon the temperature of boiling which, in turn, is dependent upon dilution. The reaction of vanillin with mercuric oxide is much slower than that with silver oxide.

Acidification of the alkaline reaction mixture with a non-reducing acid (such as sulfuric acid) gives a high yield of 5-hydroxymercurivanillin and minor amounts of oxidized mercurated compounds. Acidification with hydrochloric acid yields 5-hydroxymercurivanillin as the chief product, together with minor quantities of 5-chloromercurivanillin and other mercurated compounds, including oxidized and bis derivatives.

Treatment of the alkaline solution with sulfur dioxide, followed by short boiling, decomposes the organic mercury compounds and gives a 60–70% yield of vanillic acid and a 25–35% yield of recovered vanillin. No mercurated products are obtained after the sulfur dioxide treatment, and most of the mercury is recovered as the free metal.

When only one mole of vanillin is employed in the above reaction, the vanillic acid yield is very low, and almost all the initial vanillin is recovered after the sulfur dioxide treatment.

Long boiling of vanillin with technical dry mercuric oxide and excess alkaline solution resulted in considerable decarboxylation of the originally formed vanillic acid to yield 11% of guaiacol. This was an unexpected result, because earlier work[7,8] on the caustic fusion of vanillin to yield protocatechuic acid indicated that the carboxyl group was much more resistant to removal by drastic alkaline treatment than was the methoxyl group. All attempts to oxidize vanillin by means of mercuric oxide without alkali in a non-aqueous solvent were unsuccessful.

5-Hydroxymercurivanillin was identified by converting it successively to 5-acetoxymercurivanillin, 5-chloromercurivanillin, and 5-iodovanillin, which compounds were compared with the corresponding compounds prepared according to Paolini,[9] who obtained acetoxymercurivanillin by treating vanillin with mercuric oxide in boiling glacial acetic acid. Paolini's compound was proved to be 5-acetoxymercurivanillin by Henry and Sharp.[10] 5-Iodovanillin was also compared with the iodovanillin prepared according to Carles[11] which Raiford and Wells[12] proved to be 5-iodovanillin.

Paolini's[9] 5-acetoxymercurivanillin, upon boiling with *N* potassium hydroxide solution and acidifying with hydrochloric acid, yielded 5-chloromercurivanillin, but all attempts to isolate 5-hydroxymercurivanillin from 5-acetoxymercurivanillin failed.

5-Hydroxymercurivanillin possesses remarkable toxicity toward representative microörganisms, such as sporeforming and non-sporeforming aerobic bacteria and molds and compares favorably with such outstanding antiseptics as ethylmercury and phenylmercury derivatives. On the other

(1) For paper V of this series, see Pearl and McCoy, THIS JOURNAL, **69**, 3071 (1947).

(2) Presented before the Division of Organic Chemistry at the 112th meeting of The American Chemical Society, New York, N. Y., September 15–19, 1947.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) Pearl, THIS JOURNAL, **68**, 429 (1946).

(5) Pearl, *ibid.*, **68**, 1100 (1946).

(6) Pearl, *J. Org. Chem.*, **12**, 79 (1947).

(7) Tiemann, *Ber.*, **8**, 512 (1875).

(8) Pearl, THIS JOURNAL, **68**, 2180 (1946).

(9) Paolini, *Gazz. chim. ital.*, **51**, II, 188 (1921).

(10) Henry and Sharp, *J. Chem. Soc.*, 8288 (1930).

(11) Carles, *Bull. soc. chim.*, **17**, 14 (1872).

(12) Raiford and Wells, THIS JOURNAL, **57**, 2500 (1935).

hand, 5-hydroxymercurivanillin is much less toxic toward fish than the ethylmercury and phenylmercury compounds and, therefore, its use as a mill disinfectant or slime control agent is indicated. 5-Hydroxymercurivanillin also appears to have medicinal uses.

Experimental

All melting points given are uncorrected.

Reaction of Vanillin with Alkali and Mercuric Oxide.—To a solution of 136 g. of mercuric chloride in 400 cc. of hot water was added a hot solution of 100 g. of sodium hydroxide in 100 cc. of water. The mixture was vigorously stirred and treated with 25 g. of vanillin. The reaction mixture was heated to boiling under a reflux with mercury-sealed stirring for ten hours and allowed to cool.

Acidification with Sulfuric Acid. Preparation of 5-Hydroxymercurivanillin.—The above reaction mixture was filtered and the inorganic precipitate was washed with water. The combined filtrate and washings were acidified with 1:3 sulfuric acid. The thick white precipitate which separated was filtered, washed with water, and dried in a vacuum desiccator. The yield was 40 g. Recrystallization from water, ethanol, methanol, acetone, or dioxane gave colorless needles of 5-hydroxymercurivanillin melting at 235°. 5-Hydroxymercurivanillin is very slightly soluble in the above solvents, but is soluble in dilute alkali, glacial acetic acid, and concentrated sulfuric acid.

Anal. Calcd. for $C_8H_8O_4Hg$: CH_3O, 8.4. Found: CH_3O, 8.4.

A sample was dissolved in the minimum amount of boiling acetic acid. On cooling a fine crystalline powder of 5-acetoxymercurivanillin separated, which melted at 196–198°.

Anal. Calcd. for $C_{10}H_{10}O_5Hg$: CH_3O, 7.56. Found: CH_3O, 7.61.

A suspension of 5-acetoxymercurivanillin in a solution of excess sodium chloride was boiled several hours and cooled. The glistening precipitate was filtered and recrystallized from methanol to yield 5-chloromercurivanillin melting at 242–243° and not depressing a mixed melting point with Paolini's compound.[9]

Anal. Calcd. for $C_8H_7O_3HgCl$: C, 24.8; H, 1.83; Cl, 9.17. Found: C, 24.2; H, 1.89; Cl, 9.2.

5-Chloromercurivanillin was warmed with a solution of iodine in ethanol and cooled. The light yellow crystals were recrystallized twice from water and twice from 50% ethanol to give colorless crystals of 5-iodovanillin which melted at 176° and did not depress a mixed melting point with Carles'[11] authentic 5-iodovanillin.

Acidification with Sulfur Dioxide. Preparation of Vanillic Acid.—A hot solution of 80 g. of sodium hydroxide in 500 cc. of water was treated with stirring with 108 g. of C. P. dry yellow mercuric oxide and then with 25 g. of vanillin. The mixture was boiled under a reflux with mercury-sealed stirring for seven hours and allowed to cool. The precipitate was filtered and washed with water. The filtrate and washings were acidified with sulfur dioxide, which caused the separation of a granular white precipitate. This precipitate was filtered, washed with water, dried, and washed with ether. The filtrate was thoroughly extracted with ether and the combined ether extracts were extracted with 8% sodium bicarbonate solution; the extract yielded 17.9 g. (65%) of vanillic acid melting at 207–208°. Recrystallization from water or ethanol yielded colorless crystals which melted at 209–210° and did not depress a mixed melting point with authentic vanillic acid.[4]

The sulfur dioxide-saturated aqueous solution was acidified with sulfuric acid, aspirated with air, and extracted with ether. The ether was extracted successively with 21% sodium bisulfite, 8% sodium bicarbonate, and 5% sodium hydroxide solutions. No bisulfite extract was obtained. A little more vanillic acid was obtained from the bicarbonate extract. Approximately 30% vanillin was recovered by acidification of the sodium hydroxide extract. The occurrence of vanillin in the sodium hydroxide extract, rather than in the bisulfite extract in this experiment, has not been satisfactorily explained, although it is apparent that the aldehyde group must be protected in some manner until treated with strong alkali.

In an alternate procedure, the original sulfur dioxide-saturated reaction mixture containing the granular white precipitate was boiled for a short while and filtered. The clear solution deposited needles of vanillic acid upon cooling and the rest was secured by ether extraction.

The granular white precipitate appears to be a hydrated mercuric bisulfite or bisulfate. The ether-extracted white crystals, when boiled with water, yielded metallic mercury and sulfur dioxide.

Anal. Calcd. for $Hg(HSO_4)_2 \cdot 2H_2O$: Hg, 46.8; S, 14.8. Calcd. for $Hg(HSO_3)_2 \cdot 4H_2O$: Hg, 46.0; S, 14.8. Found: Hg, 46.20, 46.73; S, 14.83, 14.64.

In a similar experiment employing technical dry mercuric oxide, the sulfited reaction mixture was boiled, cooled, and extracted with ether. The ether was extracted with 8% sodium bicarbonate solution, which was acidified to yield 35.4% vanillic acid. The ether was dried and distilled. The oily residue, on distillation, yielded 11.0% of guaiacol boiling at 203–207°. The benzoate melted at 57° and did not depress a mixed melting point with authentic guaiacol benzoate. The original sulfited aqueous solution yielded 53.3% of recovered vanillin.

Reaction of Vanillin with Mercuric Oxide in Anhydrous Solvent.—A mixture of 15.2 g. of vanillin, 21.6 g. of C. P. dry mercuric oxide, and 250 cc. of dry benzene was boiled under reflux with occasional shaking for seven hours. No reduction of the oxide took place and all the vanillin was recovered.

Reaction of 5-Acetoxymercurivanillin with Alkali.—A mixture of 20 g. of 5-acetoxymercurivanillin and 400 cc. of *N* potassium hydroxide solution was boiled for two hours. The clear solution was filtered from a trace of metallic mercury, cooled, and acidified with sulfur dioxide. The acidified solution was heated to boiling with continued sulfur dioxide introduction for ten minutes. The sulfur dioxide introduction was discontinued, and boiling was continued for ten minutes. The mercury which separated was filtered, and the cooled filtrate was extracted with ether. The ether solution, when dried and distilled, gave 7 g. of vanillin melting at 78–79° and not depressing a mixed melting point with authentic vanillin.

In a similar experiment, the original filtered alkaline reaction mixture was acidified with dilute hydrochloric acid. The white flocculent precipitate was filtered, washed with water, dried, and recrystallized from methanol to yield white crystals of 5-chloromercurivanillin melting at 241°.

Anal. Calcd. for $C_8H_7O_3HgCl$: Cl, 9.2; CH_3O, 8.1. Found: Cl, 9.2; CH_3O, 8.4.

Solution of the 5-chloromercurivanillin in dilute potassium hydroxide and acidification with sulfur dioxide yielded vanillin.

Similar acidification of the 5-acetoxymercurivanillin-potassium hydroxide reaction mixture with dilute sulfuric acid yielded only a yellow brittle solid which contained 8.3% methoxyl and which would not melt. All attempts to isolate 5-hydroxymercurivanillin failed.

Toxicity Studies.—The toxicity of 5-hydroxymercurivanillin was determined for the representative micro-organisms, *Aerobacter aerogenes* (non-sporeforming bacteria), *Bacillus mycoides* (sporeforming bacteria), and *Aspergillus niger* (molds), by the method of Appling and McCoy[13] and compared with commercial samples of Merfenel (phenylmercuric acetate), Lignasan (ethylmercuric phosphate), and Santobrite (sodium

(13) Appling and McCoy, *Paper Trade J.*, **119**, No. 11, 116 (1944).

pentachlorophenate). The results are given in Table I.

TABLE I

INHIBITING CONCENTRATIONS FOR THREE TEST ORGANISMS (IN PER CENT. BY WEIGHT)

	A. aerogenes (increment 0.0001%)	*B. mycoides* (increment 0.0004%)	*A. niger* (increment 0.0004%)
5-Hydroxymercurivanillin	0.0004	0.0002	0.0010
Merfenel[a]	.0001	.00001	.0001
Lignasan[b]	.0010	.00016	.0006
Santobrite[c]	.0225	.0004	.0016

[a] Technical phenylmercuric acetate. [b] Contains 6.25 ethylmercury phosphate. [c] Technical sodium pentachlorophenate.

TABLE II

TOXICITY TOWARD LAKE EMERALD SHINER (*Notropis atherinoides*)

	Critical concn., p. p. m.	Survival period, min.
5-Hydroxymercurivanillin	5–7	600 (7.5 p. p. m.)
Merfenel[a]	0.02	15 (5.0 p. p. m.)
Lignasan[b]	0.8	128 (5.0 p. p. m.)
Santobrite[c]	0.4	16 (5.0 p. p. m.)

[a] Technical phenylmercuric acetate. [b] Contains 6.25 ethylmercury phosphate. [c] Technical sodium pentachlorophenate.

Fish toxicity tests were run according to the method of Van Horn[14] employing the lake emerald shiner (*Notropis atherinoides*) as the test fish. Van Horn has shown this fish to be one of the most sensitive for toxicity studies. The data are given in Table II.

Acknowledgment.—The author is indebted to the Analytical, Biology, and Microbiology Departments of The Institute of Paper Chemistry for the analyses and toxicity tests reported in this paper.

Summary

Reaction of vanillin with excess mercuric oxide and alkali in aqueous solution and acidification of the filtered reaction mixture with sulfur dioxide yields 60–70% vanillic acid. Similar reaction of vanillin with one or more moles of mercuric oxide and acidification with a non-reducing acid yields 5-hydroxymercurivanillin as the chief reaction product. 5-Hydroxymercurivanillin has demonstrated remarkable toxicity toward representative microorganisms, but was found to be much less toxic to fish than other well-known comparable antiseptics. Its use as a mill disinfectant or slime control agent is indicated.

(14) Van Horn, *Paper Trade J.*, **117**, No. 24, 33 (1943).

APPLETON, WISCONSIN RECEIVED JANUARY 23, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Bromination of Zein

BY W. W. BINKLEY[1]

Investigations of the chemical nature of zein have been largely indirect. Extensive studies have been made of the hydrolytic products of this corn protein.[2] Few reagents are selective enough to reveal any part of the intimate structure of this molecule. Neuberger,[3] using iodine and ammoniacal methanol, prepared an undegraded iodozein which indicated the combination of 0.064 g. atom of iodine with 100 g. of zein. The iodine was shown to be combined with the tyrosine residues in the protein. The halogenation of zein has been extended using chlorine and bromine.

The direct titration of zein with chlorine in acetic acid did not show the formation of a definite compound (Fig. 1). Bromine reacted with zein to form an undegraded or slightly degraded bromozein (Fig. 1). Iodine did not react with zein in the presence of acetic acid.

Dry ethyl ether and 0.25% aqueous sodium chloride were used as the precipitation media for the brominated zein. The product of the ether precipitation was acidic, reacted with sodium hydroxide, silver nitrate, and liberated iodine from potassium iodide; this compound was called bromozein hydrobromide. The other product was neutral, and did not react with sodium hydroxide, silver nitrate or potassium iodide; it was named bromozein.

A total of 0.24 g. atom of bromine was required to brominate 100 g. of zein (Fig. 1). Bromozein hydrobromide possessed 0.20 g. atom of this bromine (Table I).[4] Sodium hydroxide or silver nitrate reacted readily with 0.13 g. atom of the bromine in bromozein hydrobromide, while 0.07 g. atom of the bromine was firmly bound. The amino acids which occur in zein were titrated with bromine in acetic acid. Two of these amino acids reacted under these conditions, *viz.*, tyrosine and histidine (Table II). Folin and Ciocalteu[5] established the presence of 0.033 mole of tyrosine residues in 100 g. of zein. The bromination of these tyrosine residues would produce 0.066 g. atom of the alkali labile bromines and an equal number of the firmly bound bromines in bromozein hydrobromide. Osborne and Liddle[6] found

(1) Research Associate of The Ohio State University Research Foundation.

(2) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, p. 358.

(3) A. Neuberger, *Biochem. J.*, **28**, 1892 (1934).

(4) Gram atoms of bromine are expressed per 100 g. of zein.

(5) O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

(6) T. B. Osborne and L. M. Liddle, *Am. J. Physiol.*, **26**, 295 (1910).

0.005 g. mole of histidine residues in 100 g. of zein. The bromine uniting with the histidine residues would account for all the firmly combined bromine in bromozein hydrobromide. An amount of 0.037 g. atom of the labile bromines of bromozein hydrobromide liberated iodine from potassium iodide.

TABLE I

DISTRIBUTION OF THE ELEMENTS IN ZEIN, BROMOZEIN AND ITS HYDROBROMIDE[a]

Elements		Zein, g. atoms / 100 g. zein	Bromozein hydrobromide, g. atoms / 100 g. zein residue	Bromozein, g. atoms / 100 g. zein residue	Bromozein from bromozein hydrobromide, g. atoms / 100 g. zein residue
Carbon		4.60		4.32	4.31
Nitrogen	Total	1.15	1.13	1.06	1.06
	Amide	0.33	0.33	0.31	
Bromine			0.20	0.07	0.07

[a] Calcd. as follows

$$\frac{\%\text{ of element present}}{100 - \%\text{ Br present}} \times \frac{1}{\text{at. wt. of element}} \times 100 = \frac{\text{g. atoms element}}{100\text{ g. zein residue}}$$

TABLE II

TITRATION OF THE AMINO ACID RESIDUES WHICH OCCUR IN ZEIN WITH BROMINE IN ACETIC ACID

Amino acid[a]	Bromine consumed, g. atoms / mole of amino acid	Bromide ion formed, g. ions / mole of amino acid	Bromine combined with amino acid, g. atoms / mole of amino acid
Tyrosine	4.1	2.1	2.0
Histidine	2.3	1.2	1.1

[a] The other amino acids which occur in zein had no significant bromine titration.

Bromozein hydrobromide was converted readily into bromozein with silver nitrate or sodium hydroxide. A total of 0.07 g. atom of bromine was found in bromozein (Table I).

The solubility characteristics of the bromozein and its hydrobromide were similar to those of zein itself but, unlike the latter substance, they showed only a slight tendency toward gelation.

Experimental

Materials.—The zein was obtained from the Corn Products Refining Co., Argo, Ill.

Anal. Moisture, 6.6; ash, 0.5; fat, 1.0; N, 14.70 (16.00, cor. for moisture, ash and fat); amide N, 4.58.

Titration of Zein with Chlorine, Bromine and Iodine.—Chlorine was passed into 1 liter of glacial acetic acid in an ambered-colored glass bottle surrounded by an ice-and-water-bath. After the addition of 4–5 g. of chlorine, 25-ml. aliquots of the resulting solution were titrated with 0.1 *N* sodium thiosulfate in the presence of an excess of potassium iodide using starch as the indicator. Four samples, each containing 5 g. of zein in 100 ml. of 90% acetic acid (10% water), were treated with 50, 100, 200, 300 ml., respectively, of the standardized chlorine solution and allowed to stand one hour at room temperature in diffuse daylight. After the addition of an excess of potassium iodide, the solutions were titrated with 0.1 *N* sodium thiosulfate using starch as the indicator.

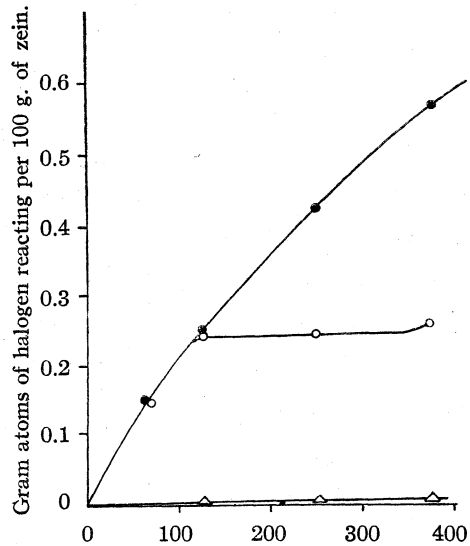


Fig. 1.—Titration of zein with chlorine, bromine and iodine in acetic acid: ●, chlorine; ○, bromine; △, iodine.

An amount of 10 g. of bromine was made up to 1 liter with glacial acetic acid and titrated with 0.1 *N* sodium thiosulfate as previously indicated. Zein was allowed to react with bromine under the conditions already described for chlorine.

An amount of 15.9 g. of iodine was made up to 1 liter with glacial acetic acid and titrated with 0.1 *N* sodium thiosulfate as previously indicated. Zein was treated with iodine under the conditions already described for chlorine. The analytical results are shown graphically in Fig. 1.

Titration of Amino Acids with Bromine.—An amount of 100 mg. of amino acid[7] in 20 ml. of 90% acetic acid was allowed to react with 40 ml. of 0.125 *N* bromine in glacial acetic acid for one hour at room temperature. The excess bromine was titrated with 0.1 *N* sodium thiosulfate as previously indicated.

An amount of 100 mg. of amino acid was allowed to react with bromine as indicated above. The excess bromine in the reaction was reduced to bromide ion with 0.1 *N* sodium bisulfite. This solution was diluted with 100 ml. of water and titrated with 0.1 *N* silver nitrate using eosin as the indicator. Analytical data are collected in Table II.

Preparation of Dibromotyrosine Hydrobromide.—An amount of 100 mg. of tyrosine was allowed to react with bromine as described above. The solvents and excess bromine were removed under reduced pressure with a bath temperature of 50°. The crystalline residue was washed with cold dry ethyl ether; yield, 232 mg. These crystals were recrystallized from ethanol–ethyl ether solution; m. p. 213–215° (dec.). They were soluble in water, ethanol and acetic acid; they were not soluble in ethyl ether. They were acid to methyl red and reacted with aqueous silver nitrate.

Anal. Calcd. for $C_9H_9O_3NBr_2 \cdot HBr$: total Br, 57.11; Br as HBr, 2.38 ml. of 0.1 *N* $AgNO_3$ per 100 mg. Found: total Br, 57.02; Br as HBr 2.40 ml. $AgNO_3$ per 100 mg. These data are summarized in Table II.

Bromination of Histidine.—Histidine dihydrobromide (150 mg.) was allowed to react with bromine as indicated previously. The solvents and excess bromine were removed almost completely under reduced pressure in the presence of carbon dioxide with a bath temperature of 30°.

(7) The amino acids were obtained from the Eastman Kodak Co. Rochester, N. Y.

The residue was poured into 20 ml. of cold, dry ethyl ether with vigorous stirring. The pink precipitate which formed, was collected on a filter, washed with 20 ml. cold, dry ethyl ether and dried in the absence of air at 25°; yield, 150 mg. The brominated histidine decomposed rapidly on exposure to air. It was soluble in water, ethanol and acetic acid, insoluble in ethyl ether. It was acid to methyl red and reacted with aqueous silver nitrate.

Anal. Calcd. for $C_6H_8O_2N_3Br \cdot 2HBr$: total Br, 60.57; Br as HBr, 5.95 ml. 0.1 *N* $AgNO_3$ per 100 mg. Found: total Br, 57.8; Br as HBr, 5.40 ml. 0.1 *N* $AgNO_3$ per 100 mg. These data are summarized in Table II.

Preparation of Bromozein Hydrobromide.—Ten grams of bromine in 500 ml. of glacial acetic acid was added slowly to a solution of 50 g. of zein in 450 ml. of 90% acetic acid. The reaction mixture was allowed to stand twenty-four hours at 25° in diffuse daylight and then poured slowly into 7 liters of dry ethyl ether with vigorous stirring. The white precipitate which formed, was collected on a filter, washed with 3 to 4 liters of dry ethyl ether and dried forty-eight hours at 50°; yield, 55.00 g. This solid was soluble in 90% acetic acid and 70% ethanol. It reacted with sodium hydroxide and silver nitrate in ethanol and liberated iodine from potassium iodide in acetic acid. An accelerated gelation test of bromozein hydrobromide in 70% ethanol showed only a slight tendency toward gel formation.

Anal. Moisture, 5.2; N, 12.90; amide N, 3.96; Br, 13.10; three samples, each of 500 mg., required 5.25 ml. 0.1 *N* NaOH, 5.25 ml. 0.1 *N* $AgNO_3$, and 1.50 ml. 0.1 *N* $Na_2S_2O_3$, respectively.

Preparation of Bromozein.—Zein was allowed to react with bromine as described in the preparation of bromozein hydrobromide. The reaction mixture was poured into 20 liters of 0.25% aqueous sodium chloride with vigorous stirring. The bromozein coagulated readily and the supernatant liquid was removed with a siphon. The product was resuspended in 20 liters of distilled water and allowed to settle. This washing process was repeated twice. The bromozein was collected on a filter and dried forty-eight hours at 50° and two hours at 105°; yield, 47.63 g. It was soluble in acetic acid and 70% ethanol but did not react with sodium hydroxide, silver nitrate, or potassium iodide. An accelerated gelation test of bromozein in 70% ethanol showed only a slight tendency toward gel formation.

Anal. N, 14.10; amide N, 4.06; Br, 5.34; C, 49.10.

The first supernatant liquid from the precipitation of bromozein was concentrated to 200 ml. and filtered. The addition of sodium hydroxide to this concentrate produced ammonia before and after digestion with sulfuric acid.

Conversion of Bromozein Hydrobromide into Bromozein.—An amount of 5 g. of bromozein hydrobromide was dissolved in 500 ml. of 0.05 *N* sodium hydroxide. The addition of 100 ml. of 2.5 *N* acetic acid to this solution resulted in the precipitation of a nearly white solid which was collected on a filter, dissolved in 10 ml. of glacial acetic acid, reprecipitated in dry ether, collected on a filter, washed free of acetic acid and dried forty-eight hours at 50° and two hours at 105°; yield, 4.3 g. It was soluble in acetic acid and 70% ethanol, but did not react with sodium hydroxide, silver nitrate, or potassium iodide.

Anal. N, 14.04; Br, 5.30; C, 49.02.

Control Experiment with Zein.—Five grams of zein was dissolved in 45 ml. of 90% acetic acid, allowed to stand twenty-four hours at 25° in diffuse daylight, and then poured into 2 liters of 0.25% aqueous sodium chloride with vigorous stirring. The zein was washed and dried as described in the preparation of bromozein: yield, 4.51 g.

Anal. N, 16.04.

The first supernatant liquid from the precipitation of zein was concentrated to 100 ml. and filtered. The addition of sodium hydroxide to this concentrate did not produce ammonia before or after digestion with sulfuric acid.

Acknowledgment.—This work was supported by the American Maize-Products Co., and the A. E. Staley Manufacturing Co. Acknowledgment is made of the counsel of Mr. W. L. Morgan.

Summary

1. A bromozein and its hydrobromide have been prepared.

2. Bromozein hydrobromide is acidic, reacts with silver nitrate and liberates iodine from potassium iodide. Sodium hydroxide converts it to bromozein.

3. Bromozein is neutral and does not react with silver nitrate or potassium iodide.

4. Bromozein and its hydrobromide have only a slight tendency toward gel formation.

COLUMBUS, OHIO RECEIVED NOVEMBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Preparation of Stable Ketimines from 2,2,6-Trimethylcyclohexanecarbonitrile

BY H. L. LOCHTE, JOE HORECZY,[1] P. L. PICKARD[2] AND A. D. BARTON[3]

In 1942 Horeczy isolated the very highly hindered 2,2,6-trimethylcyclohexanecarboxylic acid from California petroleum.[4] Shortly thereafter an attempt was made to synthesize the corresponding ketone by reaction of phenylmagnesium bromide with the nitrile of this acid. The usual Grignard synthesis yielded a very stable ketimine instead of the ketone.[5]

Since this ketimine is not hydrolyzed even on prolonged heating with acids or bases either in aqueous or alcoholic solution, and since it possesses other interesting properties, the corresponding methyl ketimine was prepared.[6] This ketimine is equally stable to hydrolysis, thus indicating that the abnormal stability is due mainly to the 2,2,6-

(1) Present address: Humble Oil and Refining Co., Baytown, Texas.

(2) General Aniline Fellow 1944–1946. Present address: Department of Chemistry, University of Oklahoma, Norman, Oklahoma.

(3) Du Pont Fellow 1947–1948.

(4) Shive, Horeczy, Wash and Lochte, THIS JOURNAL, **64**, 385 (1942).

(5) The observation that reaction of the nitrile with phenylmagnesium bromide produced a basic compound instead of a ketone was first made by William Shive in this Laboratory.

(6) P. L. Pickard, Ph.D. Dissertation, University of Texas, 1947.

trimethylcyclohexane group, rather than to the combination of the phenyl group and this group.[7]

It was thought that the corresponding aldimine (2,2,6-trimethylcyclohexanecarboxaldimine) might also be stable. Attempts to prepare this aldimine by partial hydrogenation of the nitrile have led only to complete reduction of the nitrile, the corresponding primary amine being the only product isolated.

It seemed possible that the unusual stability of these ketimines might be due to the fact that they possess an ene-amine structure. Accordingly, attempts were made to determine whether these compounds are primary or secondary amines. When treated with nitrous acid, no nitrogen is liberated, and each ketimine yields a neutral liquid compound which contains two atoms of nitrogen per molecule. Although attempts to purify these compounds were unsuccessful, they appear to be nitroso derivatives. Treatment of either ketimine with chloroform, ethanol and sodium hydroxide solution does not produce an isonitrile odor; each ketimine gives a monobenzenesulfonamide derivative which is insoluble in 10% (or more dilute) sodium hydroxide solution. However, since these ketimines are unusually unreactive, and since the hydrochloride of the phenyl ketimine is extremely insoluble in water, the results of the amine tests given above did not appear to be entirely conclusive. Therefore, attempts were made to prepare the corresponding primary amines by reduction of the ketimines.

On hydrogenation in the presence of Adams platinum catalyst, the phenyl ketimine takes up three moles of hydrogen but the reduction product gives the same amine reactions as the starting material. Apparently, only the benzene ring is hydrogenated. The methyl ketimine does not take up hydrogen in the presence of Adams catalyst. In alcoholic solution, neither compound is reduced by 3% sodium amalgam. When treated with sodium in liquid ammonia containing 5% methanol, each ketimine yields a reduction product which reacts as follows: when treated with nitrous acid each reduction product liberates the calculated volume of nitrogen; when treated with chloroform, ethanol and sodium hydroxide solution each gives a characteristic isonitrile odor; but each gives a monobenzenesulfonamide derivative insoluble in sodium hydroxide solution.

On hydrogenation with Adams catalyst or on reduction with sodium in liquid ammonia containing methanol, the nitrile (2,2,6-trimethylcyclohexanecarbonitrile) gives the same reduction product; this reduction product gives the same primary amine reactions as the reduction products of the ketimines.

Since these two ketimines react like secondary amines in the isonitrile and nitrous acid tests before they are reduced and since they yield reduction products which react like primary amines, it is probable that these compound do possess the ketimine structure which is abnormally stable due to steric hindrance.

(7) Quite recently, the preparation of a stable ketimine was reported by Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947).

Experimental

2,2,6-Trimethylcyclohexanecarbonitrile.—This nitrile was prepared from the corresponding acid *via* the acid chloride and the amide as described previously.[4]

Phenyl 2,2,6-Trimethylcyclohexyl Ketimine.—Phenylmagnesium bromide was prepared by the addition of 20.4 g. of bromobenzene to 3.15 g. of magnesium in anhydrous ether; 18.6 g. of 2,2,6-trimethylcyclohexanecarbonitrile dissolved in anhydrous ether was added and the mixture was refluxed for twelve hours. When the reaction mixture was poured into cold, dilute sulfuric acid, 22 g. of a solid sulfate salt of a base separated; 9 g. of unreacted nitrile was recovered from the ether layer. When the sulfate salt was treated with dilute sodium hydroxide solution a liquid was obtained which on fractionation yielded 13.2 g. (90% based on nitrile not recovered) of a compound characterized by the following data: b. p. 310° (750 mm.); d^{20}_4 0.9842; $n^{20}D$ 1.5406; MR_D calcd. 72.87; found 73.18.

Anal. Calcd. for $C_{16}H_{23}N$ as a secondary amine: C, 83.83; H, 10.12; N, 6.05; primary amino N, none; mol. wt., 229. Found: C, 83.47; H, 10.21; N, 6.11; primary amino N (Van Slyke), none; mol. wt. (in acetone), 236.

The ketimine dissolved readily in concentrated hydrochloric acid; when the resulting solution was neutralized most of the ketimine separated in the form of a hydrochloride salt which was extremely insoluble in water. The ketimine was liberated very slowly from this salt even in the presence of a strongly alkaline solution.

One drop of the ketimine, 3 drops of chloroform and 5 drops of ethanol were mixed and shaken continuously with 5 ml. of 10% sodium hydroxide solution and heated intermittently on a steam cone for five minutes. Even after the mixture had been allowed to stand for some time, no isonitrile odor was detected.

The benzenesulfonamide derivative was prepared by heating the ketimine with a slight excess of benzenesulfonyl chloride in pyridine solution on a steam cone for two hours. The mixture was then poured into a large volume of water and the material which separated was recrystallized from 50% aqueous alcohol, yielding small colorless needles: m. p. 114.5–116°. All of the benzenesulfonamide derivatives described in this paper are insoluble in 10% or more dilute sodium hydroxide solution.

Anal. Calcd. for $C_{22}H_{27}NO_2S$: N, 3.79. Found: N, 3.76.

The nitroso derivative was prepared by adding an aqueous sodium nitrite solution to a solution of the ketimine in ethanol containing hydrochloric acid. The solution was evaporated and the residue was extracted with ether. The ether extract was washed with dilute aqueous acetic acid and then with water. After the solution was dried with Drierite (anhydrous calcium sulfate) the ether was evaporated and the viscous residue was dried *in vacuo* over calcium chloride. Analysis indicated 8.27% nitrogen, whereas the value calculated for the pure nitroso derivative, $C_{16}H_{22}N_2O$, is 10.64. Although attempts to prepare this nitroso derivative (as well as the nitroso derivative of the methyl ketimine) in pure form were unsuccessful, it is evident that the treatment with nitrous acid introduced a second nitrogen atom into the molecule, whereas the nitrogen atom already present should have been eliminated had the compound been an eneamine.

Methyl 2,2,6-Trimethylcyclohexyl Ketimine.—Methylmagnesium iodide was prepared by the addition of 23.1 g. of methyl iodide to 3.96 g. of magnesium in anhydrous ether; 7.38 g. of 2,2,6-trimethylcyclohexanecarbonitrile in 100 ml. of anhydrous toluene was added, the ether was distilled off and the mixture was heated on a steam cone

for twenty hours. The resulting solution was poured on a mixture of chipped ice and ammonium chloride and was then extracted with ether. The ether layer was extracted with hydrochloric acid and the acid layer was then made strongly basic with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, leaving a liquid residue which, when distilled, yielded 7.5 g. (94%) of a compound with the following characteristics: b. p. 79–80° (4 mm.); d^{20}_4 0.8957; $n^{20}D$ 1.4730; MR_D calcd. 53.15, found 52.72.

Anal. Calcd. for $C_{11}H_{21}N$ as a secondary amine: N, 8:37; primary amine N, none. Found: N, 8.60; primary amino N, none.

When tested, this ketimine produced no isonitrile odor.

The benzenesulfonamide derivative was prepared by shaking a few drops of the ketimine with a slight excess of benzenesulfonyl chloride in 10% aqueous sodium hydroxide solution. Since the product did not crystallize, it was extracted with ether and the ether extract was washed with dilute acid, then with dilute alkali and finally with water; after the solution was dried, the ether was evaporated and the liquid residue was dried *in vacuo*.

Anal. Calcd. for $C_{17}H_{25}NO_2S$: N, 4.55. Found: N, 4.27.

The picrate of the ketimine was prepared in ethanol solution and recrystallized from aqueous ethanol: m. p. 143–144°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.06. Found: N, 14.21.

The nitroso derivative was prepared by adding a solution of the ketimine hydrochloride to a solution of sodium nitrite. The red liquid which separated was extracted with ether and the ether solution was washed with dilute acid, then with dilute alkali and finally with water. After the solution was dried and treated with charcoal, the ether was evaporated and the yellow viscous residue was dried *in vacuo*. Analysis indicated 12.12% nitrogen; the value calculated for the pure nitroso derivative, $C_{11}H_{20}N_2O$, is 14.26.

Attempted Hydrolysis of the Ketimines.—Each ketimine was refluxed for eight to ten hours with aqueous hydrochloric acid solution (37%) and with aqueous (33%) and alcoholic (10%) potassium hydroxide solutions without showing any evidence of hydrolysis.

Each ketimine was refluxed for eight hours with 50% aqueous potassium hydroxide solution containing 10% ethanol; each mixture was then steam distilled and the distillate was tested for ammonia with Nessler reagent. In each case the distillate contained some unchanged ketimine but no trace of ammonia was detected.

A small sample of each ketimine was dissolved in concentrated sulfuric acid and heated on a steam cone for one hour. Each solution was then cooled and poured into a large volume of water. The resulting solutions were made strongly alkaline with 50% potassium hydroxide solution and then steam distilled. Each distillate contained some unreacted ketimine but showed no trace of ammonia present when tested with Nessler reagent. The nitrile (2,2,6-trimethylcyclohexanecarbonitrile) was converted quantitatively to the corresponding amide (2,2,6-trimethylcyclohexanecarboxamide) when heated with concentrated sulfuric acid on a steam cone for one hour, and poured into a large volume of water.

Reduction of Phenyl 2,2,6-Trimethylcyclohexyl Ketimine. (a) **Hydrogenation with Adams Catalyst.**—When 317.4 mg. (1.38 millimoles) of phenyl 2,2,6-trimethylcyclohexyl ketimine dissolved in 50 ml. of methanol containing 1 ml. of glacial acetic acid was shaken with 14 mg. of Adams platinum catalyst in an atmosphere of hydrogen at room temperature and pressure, 94.0 cc. (4.20 millimoles) of hydrogen were absorbed. The catalyst was filtered off and the filtrate was evaporated to one fifth of its original volume; 20 ml. of water was added, the mixture was made strongly alkaline with sodium hydroxide and then extracted with ether. One portion of the ether solution was evaporated and the liquid residue was used for the isonitrile test and to prepare the benzenesulfonamide derivative of the reduction product. The other portion of the ether solution was shaken with the calculated quantity of concentrated hydrochloric acid solution. The cyclohexyl 2,2,6-trimethylcyclohexyl ketimine hydrochloride, which separated as a white solid, was washed with ether and with water and was dried *in vacuo*. Analysis indicated no primary amino nitrogen present.

When tested, this catalytic reduction product produced no isonitrile odor.

The benzenesulfonamide derivative of the catalytic reduction product was prepared in pyridine solution. This derivative proved to be a liquid, and it was purified in the same manner as the benzenesulfonamide derivative of methyl 2,2,6-trimethylcyclohexyl ketimine.

Anal. Calcd. for $C_{22}H_{33}NO_2S$: N, 3.73. Found: N, 3.82.

The picrate of the catalytic reduction product was prepared in ethanol solution and recrystallized from aqueous ethanol: m. p. 168–170°.

Anal. Calcd. for $C_{22}H_{32}N_4O_7$: N, 12.06. Found: N, 12.15.

(b) **Reduction with Sodium Amalgam.**—A sample of phenyl 2,2,6-trimethylcyclohexyl ketimine in 95% ethanol was stirred for twelve hours with 3% sodium amalgam. The ketimine was recovered unchanged and there was no evidence to indicate that any of the ketimine had been reduced.

(c) **Reduction with Sodium and Methanol in Liquid Ammonia.**—Reduction by means of sodium in liquid ammonia containing methanol was carried out under the conditions described by Watt, Knowles and Morgan.[8] To 100 ml. of liquid ammonia containing 5 ml. of anhydrous methanol was added 1.0 ml. of phenyl 2,2,6-trimethylcyclohexyl ketimine. Over a period of an hour, approximately 1.5 g. of sodium was added in small pieces and the mixture was stirred continuously. The gummy ketimine slowly disappeared and a copious white precipitate accumulated. The ammonia was allowed to evaporate, water was added and the mixture was extracted with ether. The reduction product and its hydrochloride were obtained in the same manner as the catalytic reduction product of phenyl 2,2,6-trimethylcyclohexyl ketimine.

Anal. Calcd. for α-phenyl-2,2,6-trimethylcyclohexanemethylamine hydrochloride, $C_{16}H_{26}NCl$: primary amino N, 5.23. Found: primary amino N, 5.40, 5.14.

When tested, this reduction product gave a characteristic isonitrile odor.

The benzenesulfonamide derivative was prepared in pyridine solution. The crude product was recrystallized three times from 95% ethanol, yielding small colorless needles: m. p. 193–195°. This sulfonamide, like the others, was insoluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: N, 3.77. Found: N, 3.94.

On hydrogenation in the presence of Adams catalyst, 60.0 mg. (0.224 millimole) of the reduction product (hydrochloride) absorbed 15.7 cc. (0.70 millimole) of hydrogen, apparently indicating that the benzene ring was not attacked when the phenyl ketimine was treated with sodium in liquid ammonia containing methanol.

Reduction of Methyl 2,2,6-Trimethylcyclohexyl Ketimine. (a) **Hydrogenation with Adams Catalyst.**—When a small quantity of methyl 2,2,6-trimethylcyclohexyl ketimine dissolved in methanol containing acetic acid was shaken with Adams catalyst in an atmosphere of hydrogen at room temperature and pressure, no hydrogen was absorbed.

(b) **Reduction with Sodium Amalgam.**—A small quantity of methyl 2,2,6-trimethylcyclohexyl ketimine was treated with 3% sodium amalgam in the manner described above. The ketimine was recovered unchanged and there was no evidence to indicate that any of the ketimine had been reduced.

(8) Watt, Knowles and Morgan, THIS JOURNAL, **69**, 1657 (1947).

(c) Reduction with Sodium and Methanol in Liquid Ammonia.—Methyl 2,2,6-trimethylcyclohexyl ketimine in liquid ammonia containing methanol was treated with sodium and the reduction product was isolated according to the procedure described above. The ether solution containing the reduction product was washed repeatedly with water, dried with Drierite and evaporated. The liquid residue was dried *in vacuo* over calcium chloride.

Anal. Calcd. for α-methyl-2,2,6-trimethylcyclohexanemethylamine, $C_{11}H_{23}N$: primary amino N, 8.27. Found: primary amino N, 8.31, 7.99.

When tested, this reduction product gave a characteristic isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution. The solid material which separated was recrystallized twice from 50% aqueous ethanol to yield colorless needles: m. p. 121–122°.

Anal. Calcd. for $C_{17}H_{27}NO_2S$: N, 4.53. Found: N, 4.68.

Reduction of 2,2,6-Trimethylcyclohexanecarbonitrile. (a) Hydrogenation with Adams Catalyst.—2,2,6-Trimethylcyclohexanecarbonitrile was hydrogenated with Adams catalyst and the reduction product and its hydrochloride salt were isolated according to the procedure described above; 156.5 mg. (1.03 millimoles) of the nitrile absorbed 47.4 cc. (2.12 millimoles) of hydrogen.

Anal. Calcd. for 2,2,6-trimethylcyclohexanemethylamine hydrochloride, $C_{10}H_{22}NCl$: primary amino N, 7.31. Found: primary amino N, 7.42, 7.32.

When tested, this reduction product produced an isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in sodium hydroxide solution. The product was recrystallized twice from 50% ethanol, to give colorless needles: m. p. 111–112°.

Anal. Calcd. for $C_{16}H_{25}NO_2S$: N, 4.77. Found: N, 4.74.

Attempts were made to achieve partial hydrogenation of the nitrile by carrying out the hydrogenation in a small volume of methanol containing an excess of concentrated hydrochloric acid. In all cases, the only compounds isolated were the unreacted nitrile and the fully hydrogenated primary amine described above.

(b) Reduction with Sodium and Methanol in Liquid Ammonia.—2,2,6 - Trimethylcyclohexanecarbonitrile in liquid ammonia containing methanol was treated with sodium in the manner described above. The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution: m. p. and mixed m. p. with the benzenesulfonamide derivative of the catalytic reduction product of 2,2,6-trimethylcyclohexanecarbonitrile, 111–112°, indicating that the two methods give the same reduction product, 2,2,6-trimethylcyclohexanemethylamine.

Summary

1. Phenyl 2,2,6-trimethylcyclohexyl ketimine and methyl 2,2,6-trimethylcyclohexyl ketimine have been prepared by treating 2,2,6-trimethylcyclohexanecarbonitrile with phenylmagnesium bromide and methylmagnesium iodide, respectively. These ketimines are not hydrolyzed even on prolonged heating in the presence of concentrated acid or alkali.

2. It appears that these compound possess the ketimine structure because, before reduction, they react like secondary amines to the isonitrile and nitrous acid tests and they yield reduction products which react like primary amines.

3. It is concluded that the abnormal stability of these compounds is due to steric hindrance.

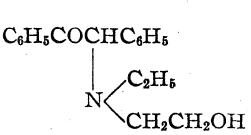
AUSTIN, TEXAS RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

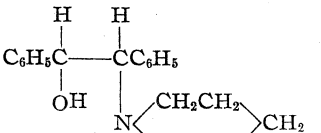
Secondary and Tertiary Amino Ketones and Alcohols Derived from Desoxybenzoin and 1,2-Diphenylethanol.[1] Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino) Ketones[2]

BY ROBERT E. LUTZ, JAMES A. FREEK[3a] AND ROBERT S. MURPHEY[3b]

This investigation was initiated in the fall of 1942 in connection with the search for new types of antimalarials.[2a] The compounds obtained,[4] however, showed no significant activity against avian malaria. At the instigation of Dr. J. L. Hartwell they were then tested at the National Cancer Institute for activity against mammalian tumors, because of their relationship to the nuclear - substituted 1,2 - diphenylethylamines,[5] $ArCH_2CH(NH_2)Ar$, which had already been under investigation as tumor-necrotizing agents. Two of the new compounds when tested in mice gave evidence,[6] at high dosage, of damage to sarcoma 37; these two compounds were α-[N-ethyl-N-(β-hydroxyethyl)-amino]-desoxybenzoin [supposed at the time to have the open-chain structure (I)],



I



II

(1) Agents Causing Necrosis in Tumors. I. This is the first of a series of papers dealing with the search for compounds which may have significance in the chemical treatment of tumors.

(2) (a) The smaller part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia; (b) the larger part of this work was carried out under a Grant-in-Aid from the National Cancer Institute.

(3) (a) Present location, Department of Pharmacology, University of Virginia Medical School, Charlottesville, Va.; (b) at present holder of a National Cancer Institute Junior Research Fellowship.

(4) These compounds, fourteen in number, which were tested against avian malaria, are listed in the Tables I and II, and are designated by SN numbers which locate them in the "Survey of Antimalarial Drugs, 1941–1945" (by F. Y. Wiselogle, published by J. W. Edwards, 1946).

(5) Hartwell and Kornberg, THIS JOURNAL, **67**, 1606 (1945).

(6) Unpublished work of Shear, Downing, MacCardle, Hartwell, *et al.*, at the National Cancer Institute.

TABLE I

α-(SECONDARY AND TERTIARY-AMINO)-DESOXYBENZOINS OF THE TYPE V AND VIII

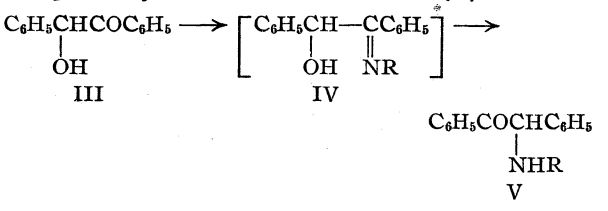
SN[2] or REL[a] no.	NR_2 (base, salt or deriv.)	Prep.[b]	React. time, hr.	Yield, %	Crystallized from[c]	M. p.,[d] °C.	Empirical formula	Analyses,[e,f] Carbon (or N) Calcd.	Found	Hydrogen (or Cl⁻) Calcd.	Found
6429	NH(*n*-butyl)·HCl	1a	2	51	Acet.–EtOH	184–186	$C_{18}H_{21}NO\cdot HCl$	71.16	70.90	7.30	7.17[k]
6649	NH(*n*-octyl)·HCl	1a	4	67	Acet.–EtOH	180–182	$C_{22}H_{29}NO\cdot HCl$	73.41	73.12	8.40	8.28[l]
6415	NH(*n*-dodecyl)·HCl	1c	6	55	Acet.–EtOH	153–156	$C_{26}H_{37}NO\cdot HCl$	N, 3.37	3.49	...	....
6648	$NHCH_2C_6H_5\cdot HCl$	1b	4.5	64	Acet.–EtOH	219–222	$C_{21}H_{19}NO\cdot HCl$	N, 4.15	3.94	...	....
6328	$NHCH_2CH_2C_6H_5\cdot HCl$	1b	4.5	72	Acet.–EtOH	230–232	$C_{22}H_{21}NO\cdot HCl$	N, 3.98	4.22	...	....
617[a]	$NHCH_2CH_2OH\cdot HCl$	1d	3	20[j]	*i*-PrOH–H_2O[i]	188–189	$C_{16}H_{17}NO_2\cdot HCl$	65.86	65.83	6.22	6.30
639[a]	$NHCH_2CH(OH)CH_3\cdot HCl$	1d	10	6[j]	Ethanol	173–174.5	$C_{17}H_{19}NO_2\cdot HCl$	66.77	66.76	6.59	6.50
..	$NHC_2H_4(C_2H_5)_2$(p)	..	..	..	60% EtOH	72– 74	$C_{24}H_{26}N_2O$	N, 7.82	7.67	...	....
612[a]	(hydrochloride)	1a	2	97	EtOH–H_2O	208–209	$C_{24}H_{26}N_2O\cdot HCl$	72.98	73.17	6.89	7.08
..	Piperidyl[10a]	..[g]	..	..	Ethanol	82– 83	.....	...	..	...	....
3636	(hydrochloride)	2[g]	..	..	EtOH–Ether	225–227[h]	$C_{19}H_{21}NO\cdot HCl$	N, 4.44	4.29	Cl, 11.23	11.37
3634	$N(C_2H_5)CH_2CH_2OH$	..	..	..	Ethanol	96– 97	$C_{18}H_{21}NO_2$	76.29	76.60	7.47	7.25
..	(hydrochloride)	2	3	43	EtOH–ligr.	204–205	$C_{18}H_{21}NO_2\cdot HCl$	67.59	67.39	6.93	6.67[m]
3101	$N(n\text{-butyl})CH_2CH_2OH$	2	2.5	24	Ligroin	75– 76.5	$C_{20}H_{25}NO_2$	N, 4.50	4.75	...	....
..	(hydrochloride)	..	..	..	.....	159–161.5	$C_{20}H_{25}NO_2\cdot HCl$	71.15	71.02	7.30	7.18[n]
643[a]	$N(CH_2CH_2OH)_2$	2	4	44	Ethanol	135–136	$C_{18}H_{21}NO_3$	72.21	73.31	7.07	7.14[p]
..	(hydrochloride)	..	..	..	.....	190–191	$C_{18}H_{21}NO_3\cdot HCl$	71.15	71.02	7.30	7.18

[a] The three-digit numbers are code numbers from this Laboratory. [b] Preparative methods A, B and C, are described in the experimental part, together with notes dealing with variations in the procedures and manipulations involved. [c] Acet. = acetone; *i*-PrOH = isopropanol; EtOH = 95% ethanol, or absolute ethanol where used with other solvents; ligr. = ligroin. [d] All melting points are "corrected." [e] Extra analyses: see footnotes *k* to *p*. [f] N = analysis for nitrogen. Cl = analysis for chloride ion by Mohr titration. [g] See experimental part. [h] Melts with decomposition. [i] With a little ether added. [j] In some cases where the yields listed are low, enough material was obtained in the preliminary experiments for testing, and no attempts were made in those cases to repeat the experiments because of the lack of time. [k] Calcd. for N, 4.61; Cl, 11.67. Found: N, 4.62; Cl, 11.88. [l] Calcd. for N, 3.89; Cl, 9.85. Found: N, 4.29; Cl, 9.84. [m] Calcd. for N, 4.38; Cl, 11.08. Found: N, 4.48; Cl, 11.18. [n] Calcd. for N, 4.03. Found: 4.11. [p] Calcd. for N, 4.68. Found: 5.11.

and the related 1,2-diphenyl-2-N-piperidylethanol (II).

Because of these findings the synthetic work in this series was extended. The results are summarized in Tables I and II where the various mono- and disubstituted-amino ketones and alcohols are listed.[7] The discussion of new chemistry incidental to the preparation of these compounds follows. The pharmacological results will be reported elsewhere.[6]

The Reaction between Benzoin and Primary Aliphatic Amines.—This condensation was used to prepare a series of seven monoalkylamino and the *p*-diethylaminoanilino ketones (V).

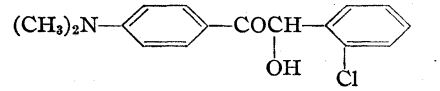


III IV V

It was adapted from the Voigt reaction[8] which up to this time had been applied only to aromatic amines. One attempt had been made to use an aliphatic amine in this reaction,[8b] but it was unsuccessful, perhaps because no catalyst was employed. In the present work phosphorus pentoxide or hydrochloric acid was used as the condensing agent and the reaction appeared to be general and proceeded with good yields.

Two aliphatic N-monoalkylamino desoxybenzoins have already been made in small yields by the palladium-catalyzed hydrogenation of benzil in the presence of cyclohexylamine and 3-aminopentane.[9] The first of these (V, R = cyclohexyl) has now been made in a second way by the Voigt reaction.

Some observations in the present work are pertinent to the mechanism proposed for the Voigt reaction, which involves first the formation of the Schiff base of benzoin (IV) followed by rearrangement to the monoarylamino ketone.[8c,d,e] The highly branched-chain amines, tris-(hydroxymethyl)-methylamine and 2-amino-1,3-dihydroxymethyl-2-methylpropane, do not undergo the reaction under the conditions applicable to ordinary primary amines, presumably because of steric interference with addition at the carbonyl groups.



VI

Furthermore 2′-chloro-4-dimethylaminobenzoin does not undergo this reaction with *n*-butyl and *n*-octylamines under the usual conditions, presumably also because of lowered activity of the carbonyl group, lowered in this case chemically by the *p*-dimethylamino group.

The monoalkylamino ketones are unstable in the form of the free bases and only the hydrochlorides have been isolated. In many cases it was observed that the bases underwent facile

(7) *Cf.* also Lutz and Murphey, the 4,4′-dichloro series, a paper to be published shortly.

(8) (a) Voigt, *J. prakt. Chem.*, [2] **34**, 2 (1886); (b) *cf.* also Cameron, Nixon and Basterfield, *Trans. Roy. Soc. Can.*, **3**, 25, Sect. 3, 145 (1931); (c) Cowper and Stevens, *J. Chem. Soc.*, 374 (1940); *cf.* also (d) Strain, THIS JOURNAL, **51**, 269 (1929); (e) Julian, Meyer, Magnani and Cole, *ibid.*, **67**, 1203 (1945).

(9) Skita and Keil, *Ber.*, **66**, 858 (1933).

TABLE II

2-(SECONDARY AND TERTIARY-AMINO)-1,2-DIPHENYLETHANOLS OF THE TYPE IX

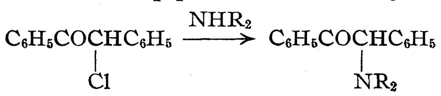
REL[a] or SN[2] no.	NR_2 (base or deriv.)	Prep. method[c]	Time heating, hrs.	Yield, %	Crystallized from[d]	M. p., °C. (cor.)	Empirical formula	Analyses/ Carbon (or N) Calcd.	Found	Hydrogen (or Cl⁻) Calcd.	Found
..	NH_2[15,16,17,18]	2a[k]	10	92	EtOH	165–166	$C_{14}H_{15}NO$	N, 6.57	6.54	...	....
677[a]	(hydrochloride)	...	..	..	CH_3OH	233–234	$C_{14}H_{15}NO{\cdot}HCl$	N, 5.61	5.41	...	....
..	NH_2[b,16,17]	2a[k]	6	92	EtOH	127–128	$C_{14}H_{15}NO$	N, 6.57	6.49	...	....
673[a]	(hydrochloride)[b]	...	..	..	CH_3OH	209–211	Base·HCl·CH_3OH	N, 4.97	5.16	...	....
..	NH(*n*-butyl)	1a	7	26	EtOH	135–136.5	$C_{18}H_{23}NO$	80.25	80.18	8.61	8.62
		2a[h]	8	44	EtOH	134–135	$C_{18}H_{23}NO$	N, 5.20	5.22	...	....
6413	(hydrochloride)	1a	..	..	.....	215–216	$C_{18}H_{23}NO{\cdot}HCl$	...	...	Cl, 11.60	11.76
..	(picrate)	...	..	..	Dil.EtOH	154.5–155	Base·$C_6H_3N_3O_7$	57.82	57.96	5.46	5.60
..	NH(*n*-butyl)[b]	2a	18	83	90% EtOH	63– 64	$C_{18}H_{23}NO$	80.25	80.51	8.61	8.79[n]
633[a]	(hydrochloride)[b]	2a	..	..	Acetone	181–182	$C_{18}H_{23}NO{\cdot}HCl$	N, 4.58	4.37	...	....
..	(picrate)[b]	...	..	..	Dil.EtOH	176–177.5	Base·$C_6H_3N_3O_7$	57.82	57.33	5.46	5.47
..	NH(2-heptyl)	2b	3.5	59	EtOH	97– 99	$C_{21}H_{29}NO$	N, 4.50	4.27	...	....
653[a]	(hydrochloride)	2b	..	..	Lig.–But.	138–140	$C_{21}H_{29}NO{\cdot}HCl$	72.49	72.38	8.69	8.64[p]
..	NH(*n*-octyl)	2b	0.5	85	EtOH	120–121	$C_{22}H_{31}NO$	81.18	80.88	9.60	9.67[q]
654[a]	(hydrochloride)	2b	..	..	But.–CH_3OH	193–194	$C_{22}H_{31}NO{\cdot}HCl$	N, 3.87	3.61	...	....
..	NH(*n*-dodecyl)	1a	11	56	Acetone	112–115	$C_{26}H_{39}NO$	81.84	81.52	10.30	10.33[r]
		2b[h]	7.5	48	Acetone	112–114	$C_{26}H_{39}NO$	N, 3.67	3.71	...	....
6426	(hydrochloride)	1a	..	..	Acet.–EtOH	145.5–148	$C_{26}H_{39}NO{\cdot}HCl$	...	...	Cl, 8.48	8.52
..	NH(cyclohexyl)[g]	3	..	71	Benz.–EtOH	163–164	$C_{20}H_{25}NO$	...	..	...	....
		2a[h]	1.5	76	EtOH	163–164	$C_{20}H_{25}NO$	N, 4.74	4.69	...	....
681[a]	(hydrochloride)	...	..	..	EtOH	239–240[j]	$C_{20}H_{25}NO{\cdot}HCl$	72.38	72.42	7.90	8.16
..	NH(cyclohexyl)[b]	2a	2	62	Dil.EtOH	71– 73	$C_{20}H_{25}NO$	N, 4.74	4.85	...	....
657[a]	(hydrochloride)[b]	...	..	..	But.–CH_3OH	251–252	$C_{20}H_{25}NO{\cdot}HCl$	N, 4.22	4.50	...	....
6427	$NHCH_2C_6H_5$[14]	1a[e]	24	38	Acet.–EtOH	154–155.5	$C_{21}H_{21}NO$	N, 4.62	4.38	...	....
		2b[h]	2	83	But.–EtOH	154–155	$C_{21}H_{21}NO$	N, 4.62	4.33	...	....
..	(hydrochloride)	...	..	..	.....	228–229	$C_{21}H_{21}NO{\cdot}HCl$	...	...	Cl, 10.43	10.60
..	(dibenzoate)	...	..	..	EtOH	166–167.5	$C_{35}H_{29}NO_3$	N, 2.74	2.78	...	....
..	$NHCH_2CH_2C_6H_5$	1a	24[i]	41	Acet.–EtOH	154–155	$C_{22}H_{23}NO$	N, 4.41	4.11	...	....
		b[h]	10	69	.....	153–154	$C_{22}H_{23}NO$	N, 4.41	4.54	...	....
6653	(hydrochloride)	...	..	..	EtOH	245–246	$C_{22}H_{23}NO{\cdot}HCl$	...	..	Cl, 10.02	10.16
634[a]	$NHCH_2CH_2OH$	2b	2	48	Benzene	105–105.5	$C_{16}H_{19}NO_2$	74.68	74.90	7.44	7.56
..	(hydrochloride)	1a	8	83	Acet.–Ether	237–238.5	$C_{16}H_{19}NO_2{\cdot}HCl$	N, 4.77	5.10	...	....
..	$NHCH_2CH_2CH_2N(C_2H_5)_2$	1a	2	61	Ligroin	136–137	$C_{21}H_{30}N_2O$	77.25	76.92	9.26	8.85[s]
271[a]	(dihydrochloride)	...	..	..	.....	228–229	$C_{21}H_{30}N_2O{\cdot}2HCl$	N, 7.38	7.16	...	....
..	$NHC_6H_4(C_2H_5)_2(p)$	1b	3.5	99	70% EtOH	108–109.5	$C_{24}H_{28}N_2O$	N, 7.78	7.62	...	....
618[a]	(dihydrochloride)	...	..	..	But.–CH_3OH	202–202.5	$C_{24}H_{28}N_2O{\cdot}2HCl$	66.50	66.21	6.98	7.05
..	$N(Ethyl)_2$	2a	12	17	Dil.EtOH	71– 72	$C_{18}H_{23}NO$	N, 5.20	5.22	...	....
661[a]	(hydrochloride)	...	..	..	But.–CH_3OH	218–219	$C_{18}H_{23}NO{\cdot}HCl$	N, 4.58	4.62	...	....
..	$N(butyl)_2$	2c	11	22	Dil.EtOH	45– 46	$C_{22}H_{31}NO$	N, 4.30	4.26	...	....
656[a]	(hydrochloride)	...	..	..	But.–CH_3OH	146–148	$C_{22}H_{31}NO{\cdot}HCl$	N, 3.87	4.03	...	....
..	Piperidyl	1	6.5	26	EtOH	109–110	$C_{19}H_{23}NO$	81.10	81.15	8.24	8.26
		2a[h]	12	84	EtOH	109–110	$C_{19}H_{23}NO$	N, 4.98	5.17	...	....
6423	(hydrochloride)	...	..	..	EtOH	259–260[l]	$C_{19}H_{23}NO{\cdot}HCl$	71.80	71.67	7.61	7.56
..	(benzoyl deriv.)	...	..	..	EtOH	166.5–167	$C_{26}H_{27}NO_2$	81.00	80.74	7.06	7.19
..	(methiodide)	...	..	..	H_2O	227–228.5	$C_{20}H_{26}INO$	56.74	56.74	6.19	6.32
..	Piperidyl[b]	1	6.5	25	EtOH	101–102[g]	$C_{19}H_{23}NO$	81.10	80.86	8.24	8.23
		2a[h]	8	63	EtOH	101–102	$C_{19}H_{23}NO$	N, 4.98	5.16	...	....
620[a]	(hydrochloride)[b]	...	..	..	EtOH	202–203	$C_{19}H_{23}NO{\cdot}HCl$	N, 4.41	4.32	...	....
..	(benzoyl deriv.)[b]	...	..	..	EtOH	143–144	$C_{26}H_{27}NO_2$	81.01	81.22	7.06	6.84
..	2-Methylpiperidyl	2a	12	79	EtOH	107–108	$C_{20}H_{25}NO$	81.31	81.41	8.53	8.24[t]
649[a]	(hydrochloride)	...	..	..	But.–CH_3OH	204–206	$C_{20}H_{25}NO{\cdot}HCl$	N, 4.22	3.99	...	....
..	3-Methylpiperidyl	2	12	67	EtOH	91– 93	$C_{21}H_{25}NO$	N, 4.74	4.98	...	....
648[a]	(hydrochloride)	...	..	..	But.–CH_3OH	217–219	$C_{21}H_{25}NO{\cdot}HCl$	N, 4.22	4.12	...	....
..	4-Methylpiperidyl	2	4	84	EtOH	112–113.5	$C_{20}H_{25}NO$	81.31	81.24	8.53	8.41[u]
645[a]	(hydrochloride)	...	..	..	But.–CH_3OH	245–246	$C_{20}H_{25}NO{\cdot}HCl$	N, 4.22	4.15	...	....
..	2-Hexylpiperidyl	2c	18	20	Dil.EtOH	47– 48	$C_{25}H_{35}NO$	N, 3.83	4.08	...	....
658[a]	(hydrochloride)	...	..	..	Acet.–ligr.	181–182	$C_{25}H_{36}NO{\cdot}HCl$	N, 3.48	3.63	...	....
..	2,4-Dimethylpiperidyl	2c	4	47	.....	Oil	.....	...	...	...	....
646[a]	(hydrochloride)	...	..	..	But.–CH_3OH	274–249	$C_{21}H_{27}NO{\cdot}HCl$	72.92	72.64	8.16	8.20[v]
..	Tetrahydroisoquinolyl	2c	1	43	EtOH	99–100	$C_{23}H_{23}NO$	N, 4.25	4.02	...	....
655[a]	(hydrochloride)	...	..	..	But.–CH_3OH	223–225	$C_{23}H_{23}NO{\cdot}HCl$	75.50	75.23	6.61	6.62[w]
635[a]	$N(C_2H_5)CH_2CH_2OH$	...	..	..	EtOH	80– 81	$C_{18}H_{23}NO_2$	N ,4.91	4.81	...	....
..	(hydrochloride)	2a	12	47.5	But.–EtOH	183–184	$C_{18}H_{23}NO_2{\cdot}HCl$	67.17	66.91	7.52	7.64
6422	Morpholinyl·HCl	1b	..	..	EtOH	155–157	$C_{18}H_{21}NO_2{\cdot}HCl$	N, 4.38	4.24	...	....

[a] Three-digit numbers are code numbers from this laboratory. [b] These are the B-stereoisomers which are made from *cis*-stilbene oxide and where the configuration is considered to be "threo." [c] Referring to preparative methods 1 and 2 which are described in the experimental part. [d] But. = butanone; Acet. = acetone; Benz. = benzene. [e] We were unable to obtain a "benzoyl" derivative of the melting point reported.[14] However, this dibenzoyl derivative melted at the point reported[14] at one stage of the purification. [f] N = analysis for nitrogen. Cl = analysis for chloride ion by Mohr titration. [g] A mixture melting point with the A-isomer showed a significant depression. [h] The two samples made by the two different methods were identified by mixture melting points. [i] Time of heating, ten hours. [j] Melting point reported

by Skita and Keil,[9] 264–265°. [k] See experimental part. [l] *In vacuo.* [m] Methanol of crystallization. Additional analyses: [n] Calcd. for N, 5.20; found, 5.16. [p] Calcd. for N, 4.03; found, 3.99. [q] Calcd. for N, 4.30; found, 4.24. [r] Calcd. for N, 3.67; found, 3.69. [s] Calcd. for N, 8.58; found, 8.42. [t] Calcd. for N, 4.74; found, 4.85. [u] Calcd. for N, 4.74; found, 4.78. [v] Calcd. for N, 4.05; found, 4.10. [w] Calcd. for N, 3.83; found, 3.84.

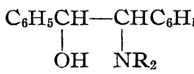
hydrolysis and oxidation during preparation of the hydrochlorides with the resulting formation of the primary amine and benzil. This secondary reaction often caused considerable loss in yield during purifications. The interesting question as to whether this formation of benzil was due to initial oxidation of the amino ketone to the mono-Schiff base of benzil followed by hydrolysis, or to hydrolysis to benzoin followed by oxidation (or to both of these as competing reactions) has not been answered. It is noteworthy, however, that in one case the γ-diethylaminopropylamino ketone [V, R = $NHCH_2CH_2CH_2N(C_2H_5)_2$, obtained as an oil and not characterized, but successfully reduced nevertheless to the diamino alcohol] was hydrolyzed readily by moist ethereal hydrogen chloride to benzoin.

Condensation of Desyl Chloride with Secondary Amines.—Three new dialkylamino desoxybenzoins (VIII) have been made by this method, and also α-piperidyldesoxybenzoin (VIII, NR_2 = piperidyl) which had previously been made by the action of N-chloropiperidine on desoxybenzoin.[10]



VII VIII

The Preparation of β-Mono and Dialkylamino Alcohols by Reductions.—Reductions of the mono- and dialkylaminodesoxybenzoins were accomplished by means of aluminum isopropoxide. In all but one case moderate yields of only one of the two possible diastereoisomeric amino alcohols were obtained. Doubtless the



IX

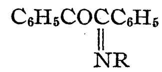
other diastereoisomers were also formed in many of these reductions but escaped detection because they were the minor and the more soluble forms.

The probabilities are that the amino alcohols obtained as the chief products from these reductions, are of the same type-configuration (arbitrarily designated as type-A) because in each of five cases, namely, the butyl, cyclohexyl, dodecyl, benzyl and phenylethylamino, these same compounds were isolated as the sole products, respectively, when *trans* stilbene oxide was condensed with the appropriate amines, and because in two cases studied, namely, the butyl and cyclohexylamino, the stereoisomeric lower-melting amino alcohols were obtained as the sole products, respectively, of the condensations with *cis* stilbene oxide.

Although the platinum-catalyzed reduction of α-piperidyldesoxybenzoin hydrochloride gave chiefly the one stereoisomer-A and appears to be consistent stereochemically with the other reductions described above, the reduction of either the base or the hydrochloride by means of aluminum isopropoxide gave difficultly separable mixtures of the two diastereoisomers. This constitutes the only case in the 1,2-diphenyl series where the B-type stereoisomer has actually been isolated as a reduction product, and the result is to be compared with the reduction of the amino ketone $C_6H_5COCH(CH_3)NHCH_3$ to ephedrine where, however, only a relatively smaller amount of the stereoisomer is formed.[11]

The second and lower-melting stereoisomeric piperidyl alcohol was subsequently obtained as the sole product of condensation of *cis*-stilbene oxide with piperidine.

The methylamino and cyclohexylamino alcohols, which are described in the literature, were made in a second way by platinum-catalyzed hydrogenation of a mixture of benzil and the primary amine.[12] It has been suggested that this reaction proceeds through the monoalkimine (X). It is



X

conceivable however that reduction of benzil to benzoin occurs first, and that this is followed by the formation of the benzoin-alkimine (IV) and/or the alkylamino ketone (the Voigt reaction) and reduction to the alkylamino alcohol. This alternative mechanism is suggested by the fact that the acyloin, $C_6H_5CHOHCOCH_3$, undergoes reductive amination to ephedrine,[13] and it has been tested as follows. The platinum-catalyzed hydrogenation of a mixture of benzil and cyclohexylamine (analogously to Skita's experiment[12a]) gave a cyclohexylamino alcohol corresponding in properties and evidently identical with that obtained by Skita. The product was shown to be of the type-A configuration by synthesis also from *trans*-stilbene oxide. Repetition of this hydrogenation experiment using benzoin in place of benzil, however, produced only *meso* hydrobenzoin in nearly quantitative yield. Therefore benzoin and the Voigt reaction could not have been involved here.

The Preparation of β-Mono and Dialkylamino Alcohols by Condensation of the Stilbene Oxides with Primary and Secondary Amines.—Of the compounds listed in Table II, ten sec-

(10) (a) Rabe, *Ber.*, **45**, 2169 (1912); (b) for the α-(N-morpholinyl)-desoxybenzoin (SN 2594), see *C. A.*, **33**, 6527 (1939) [German Patent 671,786].

(11) Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

(12) (a) Skita and Keil, *Ber.*, **62**, 1142 (1929); *C. A.*, **24**, 1119 (1930) [British Patent 313,617 (1928)]; the 4,4'-dimethoxy-N-methyl analog was made also.

(13) Hildebrandt and Klavehn, *C. A.*, **26**, 3623 (1932) [German Patent 548,459 (1930)]; *C. A.*, **28**, 4072 (1934) [U. S. Patent 1,956,950 (1934)].

ondary-amino and eleven tertiary-amino alcohols (*cf.* IX) have been made by condensation of *trans* stilbene oxide (XI) with appropriate amines. Because five of these compounds were identical with the products of reduction of the substituted-amino ketones, all of these compounds which clearly belong to the same stereochemical system are classified as type-A. The five stereoisomeric secondary- and tertiary-amino alcohols made similarly from *cis*-stilbene oxide (XII) have been designated configurationally as type-B.

It is noteworthy that *trans*-stilbene oxide was successfully condensed with three typical 2-substituted piperidines (the 2-methyl, 2-hexyl and 2,4-dimethyl), but that 2,4,6-trimethylpiperidine did not undergo this condensation, presumably because of excessive steric hindrance at the nitrogen.

Incidentally it should be mentioned at this point that the various condensations of β-ethanolamine with the stilbene oxides have been shown actually to involve the NH-group rather than the hydroxyl, as would be expected. The evidence is the fact that in one case the resulting β-(β-ethanolamino) alcohol (IX, NR_2 = $NHCH_2CH_2OH$) is obtainable in a second way by reduction of the α-(β-ethanolamino) ketone (V, NHR = $NHCH_2CH_2OH$) the structure of which is certain from the mode of synthesis from benzoin by the Voigt condensation with ethanolamine.

All of the secondary amino alcohols listed in Table II are new except the two with indicated references. One of these, the benzylamino compound, was first made by a complex reaction from benzaldehyde through the action of sodium nitrite, formic or acetic acid and zinc.[14] The properties reported for this compound, both the free base and the hydrochloride, agree with those of the samples we have prepared from *trans*-stilbene oxide. The configuration therefore appears to correspond to type-A.

For the purpose of comparative tests the two aminohydrins (known[15]) (IX, NR_2 = NH_2) were made in a new way by the ammonolysis of the *trans* and *cis* stilbene oxides. The higher-melting isomer (m. p. 165–166°) obtained from the *trans* oxide, is the one obtained by hydrolysis of the *trans* imine,[16] and is the one obtained in the reductions of aminodesoxybenzoin,[17] the benzilmonoximes[17] and benzoin oxime[18]; it evidently corresponds in configuration to the type-A. The lower-melting isomer (m. p. 127–128°) obtained from the *cis* oxide, is the one obtained by hydrolysis of the *cis* imine[16] and corresponds therefore to type-B. Thus the stereochemical picture here corresponds exactly to that described above for the mono and dialkylamino alcohols.

(14) Ogato and Hirano, *J. Pharm. Soc. Japan*, **50**, 1141 (1930) [*C. A.*, **25**, 1819 (1931)].

(15) McKenzie and Pirie, *Ber.*, **69**, 876 (1936).

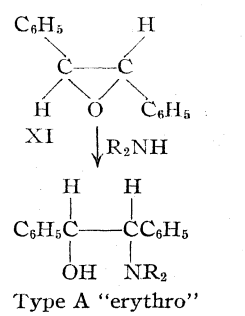
(16) Weissberger and Bach, *ibid.*, **65**, 631 (1932).

(17) Polonowska, *ibid.*, **21**, 488 (1888); Erlenmeyer, *ibid.*, **29**, 295 (1896).

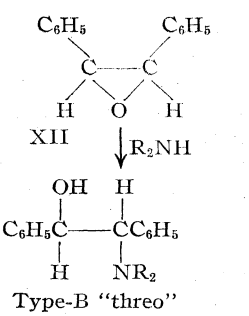
(18) Söderbaum, *ibid.*, **28**, 2523 (1895); Erlenmeyer, *ibid.*, **30**, 1525 (1897); Polonowska, *ibid.*, **20**, 493 (1887).

The Assignment of Relative and Specific Configurations to the Amino Alcohols.—The condensations between primary, secondary amines and ammonia, and the *cis* and *trans* stilbene oxides (XI and XII) have proceeded consistently in each case in only one of the two possible stereochemical senses, and in this respect they are comparable with three types of stereochemically consistent reactions (a) the hydrochlorination of the stilbene oxides,[19] (b) the formation of the stilbene oxides from the halohydrins[19] and aminohydrins,[20] and (c) the hydrolysis of the *cis* and *trans* imines.[16] The normal or chief products of reductions in which the two-asymmetric-carbon system is generated correspond in so far as has been tested, to the compounds obtained from the *trans* oxide; and the two synthetic methods therefore serve as independent means of assignment of type-configurations. However, because in one isolated case in this investigation a reduction actually did give simultaneously both of the two possible stereoisomeric products, the synthesis from the stilbene oxides where no such exception has appeared, is clearly the more reliable and is the preferred basis for stereochemical classification. Those compounds obtained in reductions which have not been directly or indirectly related by synthesis to the stilbene oxides are to be regarded as probably of the type-A configuration, and the assignment of configurations in these cases is tentative.

The specific configurations of these products have been assigned tentatively (a) on the assumption that the oxide ring-opening is consistently *trans* as has been demonstrated in the hydrochlorination and hydrolysis[21] of maleic and fumaric acid oxides, and (b) on the basis of analogy to the consistent stereochemical mode of reductions, namely, the catalytic, sodium amalgam or aluminum isopropoxide reductions[22] of benzoin which give chiefly the *meso* hydrobenzoin, and the reduction of benzil dioxime predominantly to *meso*



Type A "erythro"
XIII



Type-B "threo"
XIV

(19) (a) Reulos, *Compt. rend.*, **216**, 774 (1943); (b) Reulos and Collin, *C. A.*, **40**, 3743 (1946) [*Compt. rend.*, **218**, 795 (1944)].

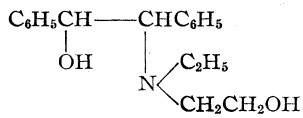
(20) Reid and Campbell, *J. Chem. Soc.*, 2377 (1930).

(21) (a) Kuhn and Zell, *Ber.*, **59**, 2514 (1926); (b) Kuhn and Wagner-Jaureg g, *ibid.*, **61**, 504 (1928).

(22) (a) See experimental part; (b) Irvine and Weir, *J. Chem. Soc.*, **91**, 1390 (1907); (c) Breuer and Zincke, *Ann.*, **198**, 141 (1879); (d) Lund, *Ber.*, **70**, 1520 (1937); (e) Hayashi, *C. A.*, **41**, 6561 (1947) [*Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **39**, 107 (1941)].

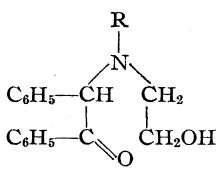
stilbenediamine.[22e] Thus the type-A compounds are presumed to be "erythro" as formulated (XIII) and the type-B compounds are tentatively formulated as "threo" (XIV).

Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino)-desoxybenzoins.—One negative result in the earlier aluminum isopropoxide reductions of the various substituted-amino desoxybenzoins stood out as striking; the reductions had proceeded effectively in all cases except one, namely, α-[N-ethyl-N-(β-ethanol)-amino]-desoxybenzoin (I). This compound either as the base or as the hydrochloride was recovered unchanged after prolonged treatment, yet the corresponding ethylethanolamino alcohol (XV), could easily be made through condensation of *trans*-stilbene oxide with ethylethanolamine.

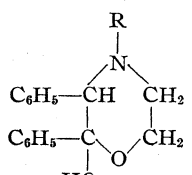


XV ("erythro")

It was of significance that this exceptional compound was the only one of the group of compounds reduced up to that time, which carried a β-hydroxyethyl group on the nitrogen. The unexpected resistance to reduction by the carbonyl-specific reagent, aluminum isopropoxide, suggested that the compound exists in the tautomeric ring form, XVIBa.



XVIA



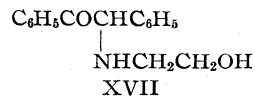
XVIB

(a) R = C_2H_5
(b) R = *n*-butyl
(c) R = CH_2CH_2OH

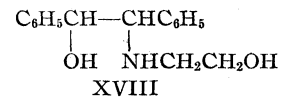
The ability of compounds of this type to function in the tautomeric cyclic sense is already implied in the conversion of one N-benzoyl compound of this type into a dehydromorpholine (dihydro-1,4-oxazine)[23] under the action of alcoholic hydrogen chloride. However, the present results indicate more than this, namely, that the cyclic hemiacetal form of these compounds actually can exist and in some cases is the stable tautomer. This phenomenon, of ring-chain tautomerism, if it has been correctly interpreted, might have been predicated from the probable influence of the α-amine nitrogen atom on the carbonyl group, an influence which should be to some extent analogous to that exerted by the δ-hydroxyl group in the ketone sugars and related compounds where the cyclic structures are the stable ones.

(23) (a) Hill and Powell, THIS JOURNAL, **67**, 1462 (1945); *cf.* also (b) Knorr, *Ber.*, **32**, 729 (1898); (c) Wolff and Marburg, *Ann.*, **363** 169 (1908); (d) Coghill, THIS JOURNAL, **59**, 801 (1937).

In order to explore the β-hydroxyethylamino ketones further in respect to reducibility by aluminum isopropoxide, three other compounds of the type were made. The β-hydroxyethylamino compound itself (XVII) in which the nitrogen is secondary, was reduced, with normal ease, to the dihydroxyamine (XVIII), whereas the tertiary



XVII

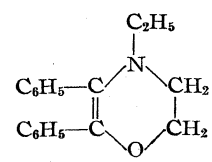


XVIII

N-butyl-N-(β-hydroxyethyl)-amino and di-(β-hydroxyethyl)-amino compounds (XVIBb and c) failed to undergo reduction. It is to be concluded from this that the latter two compounds which carry tertiary nitrogens are cyclic under these conditions like the ethylethanolamino compound (XVIBa), but that the monoethanolamino compound itself, which is secondary with respect to the nitrogen, either is open-chain (XVII) or involves a relatively labile ring-chain tautomerism. It thus seems that cyclization or stability of the cyclic tautomer is favored by N-substituents.

There are, of course, other though unlikely interpretations of these failures of aluminum isopropoxide reductions; for example, some special or peculiar influence of the hydroxyl group located β to the nitrogen and δ to the carbonyl, through chelation, hydrogen-bonding or aluminum-complex formation, perhaps through enolization. However, it should be stressed that many and various of the ordinary N-substituted secondary and tertiary desylamines (of the type V and VIII) have now been made and have been reduced successfully by means of aluminum isopropoxide, and that a close analog which is not represented in Tables I and II, the N,N-diethyl, has been made in the 4,4′-dichlorodesoxybenzoin series and has proved to be readily reducible in this same way.[7] Furthermore the simple monoethanolamino ketone (XVII) is readily reducible by aluminum isopropoxide. In view of these facts, no influence other than ring-chain tautomerism is apparent which might account for the diminished reactivity of these compounds toward aluminum isopropoxide.

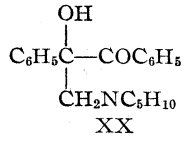
As a consequence of this phenomenon of ring-chain tautomerism it was anticipated that dehydration of the ethanolamino ketones could be accomplished easily (*cf.* ref. 23) by heating these compounds above their melting points. β-(Ethylethanolamino)-desoxybenzoin (XVIBa) at 160° with a trace of acid actually did give the dehydromorpholine (dihydro-1,4-oxazine) (XIX) which was readily hydrolyzed by dilute aqueous acid to regenerate the original compound.



XIX

Further work is in progress in respect to other kinds of evidence dealing with these phenomena,[24] and in exploration of the influence of various structural factors and substituents in this and other series on the tendency to cyclize and on the stability of the cyclic forms.

Products of the Mannich Reaction.—A few Mannich-reaction products were made for comparison with respect to possible tumor-necrotizing activity (see experimental part). One of these of particular interest is the piperidyl hydroxyketone (XX) which was made from benzoin.



XX

There are analogies for this reaction in the Mannich reaction on tartronic acid[25] and in the condensation between formaldehyde and benzoin.[26]

Acknowledgment.—The preparation of the piperidyl alcohol-A (II) was first carried out by Dr. M. T. Clark.

Experimental[27]

The Preparation of the Secondary-Amino Desoxybenzoins (V) (Method 1).—(*cf.* Refs. 8). A mixture of 0.2 mole of benzoin, 0.22 mole of the appropriate amine and 2 g. of phosphorus pentoxide was heated on a water-bath for two to ten hours. The sirupy mixture was cooled, treated with water, stirred until crystallization of the base occurred, and filtered.

The hydrochlorides were prepared in one of the following ways: by dissolving the moist filter-cake in (a) ether or (b) an ether–acetone mixture, and adding ethereal hydrogen chloride; or (c) by triturating the moist filter-cake with dilute hydrochloric acid until the yellow color associated with the free base disappeared, followed by filtering, washing with hot water and then with acetone, and recrystallizing.

(d) In two preparations 2 ml. of concentrated hydrochloric acid was used as the catalyst instead of phosphorus pentoxide. The hydrochloride was precipitated as a resin by means of ethereal hydrogen chloride, digested with water and crystallized. Significant amounts of benzil were recovered from the mother liquors.

(e) In one preparation using diethylaminopropylamine, the reaction mixture (heated for two hours) was dissolved in ether. After washing with 10% sodium hydroxide and then with water, and after drying over sodium sulfate, the amino ketone was obtained as a clear yellow oil which resisted attempts to obtain a crystalline form; it was reduced successfully without purification and was readily hydrolyzed to benzoin by moist ethereal hydrogen chloride.

Preparation of the Tertiary-Amino Ketones (VIII) from Desyl Chloride (VII) (Method 2).—A mixture of desyl chloride and three equivalents of the secondary amine was heated at 60–65°. The resulting brown sirupy product was dissolved in ether and the solution was washed with water and dried over sodium sulfate. The hydrochloride was precipitated by addition of ethereal hydrogen chloride. In the case of the di-(β-ethanol)-amino compound, the crude product was washed with water, digested with a small amount of cold ether and crystallized as the base.

α-Piperidyldesoxybenzoin, which had been obtained previously in low yield by Rabe,[10] has now been made by allowing 0.5 mole of desyl chloride to react in ether solution with 1.5 moles of piperidine (twenty-four hours at room temperature). The precipitated piperidine hydrochloride was filtered and the ether evaporated. The crude yellow product was not pure after repeated crystallizations and though nearly colorless it gave low yields of the amino alcohol upon reduction. Purification was effected by washing several times with water, dissolving in 2 l. of 0.5 *N* hydrochloric acid, filtering from an orange-colored residue, extracting by a small amount of benzene, and neutralizing carefully with ammonium hydroxide. It crystallized as white fibrous needles of m. p. 82–83° (Rabe,[10] 82°).

Preparation of Amino Alcohols (IX) by Reduction of the Amino Ketones (Method 1).—A solution of the amino ketone hydrochloride and four equivalents of 3 *N* aluminum isopropoxide in an excess of isopropanol was refluxed until the test for acetone in the distillate became negligible. The excess solvent was distilled under reduced pressure and the residue was treated with an excess of 30% sodium hydroxide, and then with water. The precipitated, crude amino alcohol was filtered, washed, dried and recrystallized. (a) In one case the oily diethylaminopropylamino alcohol was taken up in ether, dried over sodium sulfate and precipitated as the dihydrochloride by ethereal hydrogen chloride; the base was then liberated by means of ammonium hydroxide and was recrystallized. (b) In another case, the oily morpholinyl derivative was precipitated as the hydrochloride from benzene by means of ethereal hydrogen chloride.

The 1,2-Diphenyl-2-piperidylethanols-A and B. (II) Reduction of α-Piperidyldesoxybenzoin.—A solution of 67 g. (0.24 mole) of purified α-piperidyldesoxybenzoin in 400 ml. of 1.8 *N* aluminum isopropoxide was refluxed for 6.5 hours and evaporated to a volume of about 100 ml. under reduced pressure. The viscous residue was hydrolyzed by shaking for one hour with 240 ml. of 4 *N* sodium hydroxide. Extraction with ether, washing, drying over sodium sulfate, and evaporation of the ether, gave a solid which was digested with cold ethanol; yield 59 g.; m. p. 79–81°. Crystallizations from ethanol raised the melting point of this mixture only slightly. It was dissolved in acetone and converted into the hydrochlorides by addition of ethereal hydrogen chloride. Crystallization of this mixture (51 g.) from 95% ethanol gave 20 g. (30%) of pure isomer-A hydrochloride; m. p. 260° (*in vacuo*); it was shown by mixture melting point to be identical with the compound obtained from *trans* stilbene oxide. The mother liquor upon evaporating to crystallization gave 19 g. of solid isomer-B hydrochloride (m. p. 202–203°) which was converted into the base by means of ammonium hydroxide. This base was recrystallized from ethanol; 18 g. (27%); m. p. 101–102°. It was identified by mixture melting point as the same isomer (B) that was obtained from *cis*-stilbene oxide.

Isomer-A ("erythro") methiodide was prepared by the action of methanolic methyl iodide at room temperature (twelve hours).

Isomer-A ("erythro") benzoate was prepared by shaking together 2 g. of the amino alcohol, 2.9 g. of benzoyl chloride and 10 ml. of 20% sodium hydroxide. The viscous oil which separated soon solidified as the temperature rose to 60°. Recrystallization twice from ethanol gave 0.8 g. of m. p. 166.5–167°.

Isomer-B ("threo") benzoate was made by heating a mixture of the isomer-B (base) with a slight excess of benzoyl chloride (65°) for two minutes, adding dilute sodium carbonate, filtering and crystallizing from ethanol; m. p. 143–144°.

Catalytic hydrogenation of the amino ketone hydrochloride in 95% ethanol with platinum oxide catalyst was stopped after one molecule had been absorbed. The

(24) Lutz and Jordan, papers in preparation on the acetophenone analogs and nuclear-halogenated derivatives.

(25) Mannich and Bauroth, *Ber.*, **55**, 3504 (1922).

(26) (a) Langenbeck, *C. A.*, **39**, 278 (1945) [*Oel. u. Kohle*, **40**, 206 (1944)]; (b) Schauenstein and Stampfer, *Ber.*, **77**, 19 (1944).

(27) (a) All melting points are "corrected"; (b) microanalyses were performed by Miss Geraldine Alley and Mrs. Joyce Blume Caliga.

products included some unchanged amino ketone, a 30% yield of the amino alcohol, isomer-A, and a large amount of non-basic by-products which were not further investigated.

In a 100:22 by volume mixture of 95% ethanol and concd. hydrochloric acid, reduction did not occur.

The dibenzoyl derivative of 1,2-diphenyl-2,N-benzylaminoethanol was made from the base by the action of pyridine and benzoyl chloride for fifteen minutes at 80–90°.

Preparation of the Amino Alcohols from *cis* and *trans* Stilbene Oxides (Method 2).—A mixture of *cis*[28a] or *trans*[28b] stilbene oxide (XII–XI) and an excess (20% or more) of the appropriate primary or secondary amine, was refluxed for one to eight hours, or, if the boiling point of the amine was above 150°, the reaction temperature was maintained at this point to avoid the decomposition which resulted at higher temperatures. The product was purified in one of the following ways:

(a) If the amine used was water soluble the reaction mixture was taken up in alcohol-free ether. The ether solution was washed with water, dried over sodium sulfate, and treated with ethereal hydrogen chloride to obtain the salt.

(b) If the product crystallized from the reaction mixture upon cooling it was filtered and recrystallized. The hydrochloride could then be obtained in the usual way.

(c) If the amine was water insoluble and the product did not crystallize directly on cooling, the mixture was taken up in ether and the unreacted amine was extracted with 1 *N* hydrochloric acid in which the reaction product was relatively insoluble. The ether solution containing the suspended water-insoluble salt of the reaction product was shaken with 10% sodium carbonate and was dried over sodium sulfate, and the salt was regenerated by addition of ethereal hydrogen chloride.

Reductive amination of benzil with cyclohexylamine (Method 3) was carried out using a mixture of 0.1 g. of platinum oxide (pre-reduced in the solvent), 75 ml. of absolute ethanol, 11 g. (0.1 mole) of cyclohexylamine and 10 g. (0.052 mole) of benzil. These conditions approximated those employed by Manske and Johnson in the synthesis of ephedrine.[11] Hydrogenation at atmospheric pressure was complete in nine hours.

A similar reduction using benzoin instead of benzil gave only *meso* hydrobenzoin, and this in nearly quantitative yield.

Platinum-catalyzed hydrogenation of benzil in the presence of piperidine under the above conditions gave only *meso* hydrobenzoin.

Preparation of the 1,2-Diphenyl-2-aminoethanols[15] from the Stilbene Oxides.—A mixture of 15 g. (0.0765 mole) of *trans*-stilbene oxide (XI), 25 ml. of dioxane and 35 ml. of concentrated ammonium hydroxide was heated in a sealed tube at 120° for ten hours. On cooling, a white solid (isomer-A) separated; 15 g. (92%); m. p. 160–163°. The hydrochloride was obtained by dissolving the pure base in methanol and adding concentrated hydrochloric acid until acid to congo.

The preparation of the diastereoisomer (B) from *cis*-stilbene oxide (XII) was carried out similarly.

Attempts to reduce the N-substituted tertiary ethanolamino ketones (XVIa, b, c), carried out as follows, gave in each case only unchanged material which was recovered in good yield and identified. A mixture of the amino ketone (base) (and the hydrochloride also in the case of XVIa) in 0.7–0.8 *N* aluminum isopropoxide was heated at refluxing for seven to eight hours, and was worked up in the usual way as described above.

2,3-Diphenyl-5,6-dihydro-4-ethyl-1,4-oxazine (XIX).—Two grams of the amino ketone (XVIa) was heated at 120° for fifteen minutes. One drop of concentrated hydrochloric acid was added, and the yellow salt became orange-colored. The temperature was brought to 160° for five minutes. The product crystallized on cooling and was recrystallized from ethanol; yield 1.2 g.; m. p. 88–89°. After recrystallization it melted at 89–90°; a mixture with starting material melted at 75–84°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.42; H, 7.22; N, 5.33.

The hydrochloride was not obtained in crystalline form. When heated with dilute hydrochloric acid the amino ketone was regenerated.

1,2-Diphenyl-3-N-morpholinylpropanone Hydrobromide,[29] $C_6H_5COCH(C_6H_5)CH_2NC_4H_8O$.—A mixture of 30 g. (0.153 mole) of desoxybenzoin, 27 g. of morpholine hydrobromide and 9 g. of paraformaldehyde in 30 ml. of absolute ethanol was refluxed for seven hours. The amino ketone hydrobromide precipitated on cooling and was crystallized from absolute ethanol; 16 g. (28%); m. p. 182–183°.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HBr$: N, 3.72. Found: N, 3.69.

The **hydrochloride** (SN 2589) was made similarly, starting with morpholine hydrochloride, and was crystallized from absolute ethanol; yield 43%; m. p. 176–178°.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$: N, 4.22. Found: N, 4.02.

1,2-Diphenyl-2-hydroxy-3-N-piperidylpropanone (XX) (REL 644).—A solution of 21.2 g. (0.1 mole) of benzoin, 11 g. (0.13 mole) of piperidine, 11 g. (0.13 mole) of 35% formaldehyde in 75 ml. of ethanol was refluxed for seventy hours. (After two hours of heating an additional 5 g. of formaldehyde solution was added.) Cooling, filtering the precipitate and crystallization from ethanol gave 16.8 g. (55%); m. p. 68–69°. Recrystallizations did not raise the melting point.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.37; H, 7.43; N, 4.50.

The **hydrochloride** was precipitated from acetone by ethereal hydrogen chloride (slow crystallization); m. p. 178–180° (*in vacuo*).

Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.35; H, 6.84; N, 4.14.

Summary

Seven aliphatic α-secondary amino and the *p*-diethylaminoanilino desoxybenzoins have been made through the Voigt reaction by acid catalyzed condensation of benzoin with the appropriate primary amines. Three tertiary α-(β-hydroxyethylamino)-desoxybenzoins were made by condensing desyl chloride with the appropriate secondary amines.

Reductions of each of eight secondary and tertiary-aminodesoxybenzoins by means of aluminum isopropoxide gave one type (type-A) of amino alcohol except α-piperidyldesoxybenzoin which gave both of the two possible diastereoisomeric amino alcohols.

Six of the type-A amino alcohols including the parent aminohydrin itself, and also the compound obtained by reductive amination of benzil with cyclohexylamine, were obtained by condensation of *trans* stilbene oxide with the appropriate amines and ammonia, and four type-B stereoisomers, including the second isomer obtained in the reduction of α-piperidyldesoxybenzoin, were made similarly from *cis* stilbene oxide. The stereochemical mode of these reactions appears to be consistent.

(28) (a) Prepared according to Taylor and Crawford [*J. Chem. Soc.*, 1130 (1934)]; (b) prepared according to Tiffeneau and Levy [*Bull. soc. chim.*, **39**, 763 (1926)].

(29) *Cf.* piperidyl analog, Mannich and Lammering, *Ber.*, **55**, 3510 (1922).

The configurations of the amino alcohols have tentatively been assigned on the basis of the synthetic relation to the *cis* and *trans* stilbene oxides, assuming consistent *trans* reactions.

Because of the failure of α-(N-ethyl-N-ethanolamino)-desoxybenzoin and two related tertiary-nitrogen analogs to undergo reduction by aluminum isopropoxide, a cyclic structure for this type is suggested. Dehydration of one of these compounds was brought about by heating at 160°, and the reverse reaction was accomplished by the action of acid.

α-(Ethanolamino)-desoxybenzoin, in which the nitrogen is secondary, is reduced by aluminum isopropoxide and appears to be normal in its properties.

CHARLOTTESVILLE, VIRGINIA
RECEIVED DECEMBER 15, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Some Fluorinated Derivatives of Propane[1]

BY E. T. MCBEE, ANTHONY TRUCHAN AND R. O. BOLT[2]

This paper is one of a series[3] describing the synthesis of derivatives of fluoroalkanes; it offers an improved synthesis of $CF_3CH_2CF_3$ and describes new chlorofluoropropanes.

Hexachloropropene was subjected to the sequence

$$CCl_3CCl{=}CCl_2 \xrightarrow{SbF_3} CF_3CCl{=}CCl_2{}^{4} \xrightarrow{HF/SbCl_5}$$

$$CF_3CHClCClF_2 \xrightarrow{Zn/C_2H_5OH} CF_3CH{=}CF_2 \xrightarrow{HF} CF_3CH_2CF_3{}^{5}$$

No addition of hydrogen fluoride across the double bond or halide replacement occurred when $CF_3CCl{=}CCl_2$ was heated with anhydrous hydrogen fluoride at 240° in a pressure vessel, but in the presence of antimony(V) halides reaction did occur. Rectification of the product showed that $CF_3CCl{=}CCl_2$, $CF_3CHClCCl_2F$, $CF_3CHClCClF_2$, $CF_3CHClCF_3$, $CF_3CCl_2CCl_2F$ and $CF_3CCl_2CClF_2$ were present in the mixture. Two independent reactions may be viewed as taking place, (a) addition of hydrogen fluoride to the double bond followed by halogen exchange and (b) addition of chlorine (from antimony (V) chlorofluorides) to the double bond followed by halogen exchange. $CF_3CHClCCl_2F$ was formed but it could not be rectified from unreacted $CF_3CCl{=}CCl_2$ because the difference in boiling points is only one degree. For physical constants, $CF_3CHClCCl_2F$ was independently prepared by fluorination of $CF_3CHClCCl_3$, obtained by addition of chlorine to $CF_3CH{=}CCl_2$. The structure of $CF_3CHClCClF_2$ was established by dechlorination to $CF_3CH{=}CF_2$,[4] and dehydrochlorination to $CF_3CCl{=}CF_2$.[3]

The ratio of $CF_3CHClCClF_2$ to $CF_3CHClCF_3$ was controlled by varying the amount of hydrogen fluoride used. The use of a 100% excess of hydrogen fluoride gave high yields of $CF_3CHClCF_3$ with a corresponding decrease in the yield of $CF_3CHClCClF_2$. The amount of $CF_3CCl_2CCl_2F$ and $CF_3CCl_2CClF_2$ varied with the amount of antimony(V) chloride used. Further fluorination of $CF_3CHClCF_3$ with anhydrous hydrogen fluoride and antimony(V) chloride did not take place even at temperatures of 260°. The starting material was recovered.

Bromine was added to $CF_3CH{=}CF_2$ under pressure at 140° to give $CF_3CHBrCBrF_2$. Hydrogen bromide was eliminated readily from the latter compound to give $CF_3CBr{=}CF_2$.

Experimental

Starting Materials and Apparatus.—The $CF_3CCl{=}CCl_2$ used in this work was prepared by the method of Henne and co-workers[4] from hexachloropropene (Hooker Electrochemical Company). J. T. Baker, C. P. antimony(V) chloride and anhydrous hydrogen fluoride (prime commercial grade from Harshaw) were used for the fluorinations.

Fluorination of $CF_3CCl{=}CCl_2$.—A 2-liter, nickel-lined autoclave was assembled, evacuated and then chilled to 0°. $CF_3CCl{=}CCl_2$ (3.25 moles), antimony(V) chloride (0.3 mole) and hydrogen fluoride (18.4 moles) were sucked into the autoclave in the order mentioned through the needle valve. The charged autoclave was heated in a stationary, vertical position for one hundred hours at 250 ± 5°. After cooling to 150°, the contents were released through the needle valve into a recovery train consisting of a gallon bottle three-fourths full of water, drying tower and, finally, a receiver cooled with solid carbon dioxide. No alkali was used in the water scrubber because $CF_3CHClCClF_2$ is easily dehydrochlorinated to $CF_3CCl{=}CF_2$. The organic product was steam distilled, dried and rectified in a suitable column. The products from three similar runs were combined for rectification. Purification of the compounds for chemical analysis and determination of physical properties was accomplished by washing with water, drying and re-rectifying. The recovery of $CF_3CCl{=}CCl_2$ plus an unknown amount of $CF_3CHClCCl_2F$ was 21%. The conversions to $CF_3CHClCF_3$, $CF_3CHClCClF_2$, $CF_3CCl_2CClF_2$ and $CF_3CCl_2CCl_2F$ were 16%, 50%, 2% and 2%, respectively.

(1) Presented before the Symposium on Fluorine Chemistry as paper 24, Division of Industrial and Engineering Chemistry, 112th Meeting of the American Chemical Society, New York, New York. Taken in part from a doctoral thesis to be submitted by Anthony Truchan to the faculty of Purdue University in partial fulfillment of requirements for the degree of doctor of philosophy.

(2) Present address: California Research Corporation, a subsidiary of Standard Oil of California, Richmond, California.

(3) E. T. McBee and co-workers, THIS JOURNAL, **62**, 3340–3341 (1940); **69**, 944–947 (1947); *Ind. Eng. Chem.*, **39**, 409, 418, 420 (1947).

(4) A. L. Henne, A. M. Whaley and J. K. Stevenson, THIS JOURNAL, **63**, 3478–3479 (1941).

(5) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496–497 (1946).

TABLE I

NEW COMPOUNDS

Compounds	B. p., °C.	t, °C.	d_4^t	$n^{24}D$	Fluorine, % Calcd.	Fluorine, % Found	Chlorine, % Calcd.	Chlorine, % Found	Mol. wt. Calcd.	Mol. wt. Found
$CF_3CHClCCl_3$	125.1	24	1.6757	1.4180	24.1	24.8	60.2	60.3	...	...
$CF_3CHClCCl_2F$	87.0–87.3	23	1.6174	1.3699	34.6	35.4	48.5	48.8	...	...
$CF_3CHClCClF_2$	50.4	22	1.5564	1.3208	46.7	47.7	34.9	35.4	203	199
$CF_3CHClCF_3$	14.5–15.0	4	1.5415	....	61.1	61.4	19.1	20.6	186	183

In another experiment, a 2-liter, monel lined autoclave was charged with $CF_3CCl{=}CCl_2$ (3.3 moles) and anhydrous hydrogen fluoride (12 moles) and heated at 240° for sixty-seven hours. A pressure of 1225 lb./sq. in. was observed. The product was isolated in the usual manner and rectified. Five-hundred and sixty-six grams of the starting material, $CF_3CCl{=}CCl_2$, was recovered, indicating that substantially no fluorination had occurred.

Synthesis of $CF_3CH{=}CF_2$ and $CF_3CH_2CF_3$.—A 5-liter, 3-necked flask was fitted with a dropping funnel, a mercury sealed stirrer and a reflux condenser through which ice water was circulated. A receiver cooled by solid carbon dioxide was connected in series with the condenser. The flask was charged with zinc dust (7 moles) and absolute ethanol (1500 ml.). This mixture was heated to the temperature of refluxing alcohol and $CF_3CHClCClF_2$ (5.8 moles) was added dropwise to the zinc–alcohol suspension over a period of six hours. Upon rectification of the product, 655 g. $CF_3CH{=}CF_2$ (5.0 moles) and 122 g. $CF_3CHClCClF_2$ (0.6 mole) were obtained representing a conversion of 86% and a yield of 96%. $CF_3CH{=}CF_2$ was converted to $CF_3CH_2CF_3$ by addition of hydrogen fluoride.[5]

Synthesis of $CF_3CHClCCl_3$.—A Carius tube was charged with $CF_3CH{=}CCl_2$ (0.4 mole), liquid chlorine (0.75 mole) and antimony(V) chloride (0.04 mole) and the mixture heated at 140° for twenty-four hours. The product was washed with aqueous alkali, dried and purified by rectification. Fifty grams of $CF_3CHClCCl_3$ (0.21 mole) was obtained representing a yield and conversion of 53%.

Synthesis of $CF_3CHClCCl_2F$.—A mixture of $CF_3CHClCCl_3$ (0.18 mole), antimony(III) fluoride (0.13 mole) and antimony(V) chloride (0.06 mole) was refluxed for one hour. The product was steam distilled and purified by rectification. Twenty-three grams (0.10 mole) of $CF_3CHClCCl_2F$ was obtained representing a yield and conversion of 56%.

Synthesis of $CF_3CHBrCBrF_2$.—Two Carius tubes were charged with $CF_3CH{=}CF_2$ (0.7 mole) and bromine (0.72 mole) and heated at 140° for twenty-four hours. The products were combined, washed free of bromine with aqueous Na_2SO_3, dried and rectified. There was obtained 42 g. of $CF_3CBr{=}CF_2$, b. p. 24.7–25.0°, 216 g. of $CF_3CHBrCBrF_2$, b. p. 88.0°, d^{23}_4 2.1637, $n^{25}D$ 1.3780. Dehydrobromination of $CF_3CHBrCBrF_2$ during washing caused the formation of $CF_3CBr{=}CF_2$.

Acknowledgment.—The authors express their thanks to Mallinckrodt Chemical Works and to the Ethyl Corporation for making this work possible by their financial assistance.

Summary

A new series of reactions for the preparation of $CF_3CH_2CF_3$ is described. The fluorination of $CF_3CCl{=}CCl_2$ with anhydrous hydrogen fluoride and antimony(V) chloride gave $CF_3CHClCCl_2F$, $CF_3CHClCClF_2$, $CF_3CHClCF_3$, $CF_3CCl_2CCl_2F$ and $CF_3CCl_2CClF_2$. Several new compounds are reported.

LAFAYETTE, INDIANA RECEIVED JANUARY 8, 1948

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH, NEW YORK, THE NATIONAL RESEARCH COUNCIL OF CANADA, AND THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID CO.]

Studies in Steroid Metabolism. IV. The Characterization of Carbonyl and Other Functional Groups in Steroids by Infrared Spectrometry[1]

BY R. NORMAN JONES, V. Z. WILLIAMS, M. J. WHALEN AND KONRAD DOBRINER

Many organic compounds can be identified by the direct comparison of their ultraviolet, visible or infrared absorption spectra with the spectra of known substances measured under comparable experimental conditions. Such a procedure is strictly empirical and involves no premises as to the nature of the processes concerned in the absorption of the radiation. However, much more insight into the molecular structure of the compound can be derived from the spectrometric measurements if the location and the intensities of the absorption bands can be related to specific molecular structure. In the case of a new compound it is only through such correlations that information about the molecular structure can be derived from the spectrometric measurements.

The high specificity of the infrared absorption spectra of organic compounds has recently become generally appreciated,[2,3] and infrared spectrometry is now applied quite extensively for the qualitative and quantitative analysis of organic compounds. Thus infrared spectrometry was used as an aid in the establishment of the identity of synthetic folic acid with that isolated from natural sources,[4] and the application of infrared spectrometry to the analysis of the steroid constituents of human urine has been described in an

(1) Presented in part at The Laurentian Hormone Conference, St. Adele, Quebec, September, 1946, and at a Meeting of the Optical Society of America, New York, February, 1947. Published as contribution No. 1546 from the Laboratories of the National Research Council of Canada.

(2) "The Application of Infrared Spectra to Chemical Problems. A General Discussion," *Trans. Faraday Soc.*, **41**, 171 (1945).

(3) R. B. Barnes, R. C. Gore, U. Liddel and V. Z. Williams. "Infrared Spectroscopy, Industrial Applications and Bibliography," Reinhold Publishing Corp., New York, N. Y., 1944.

(4) Angier, *et al.*, *Science*, **102**, 227 (1945).

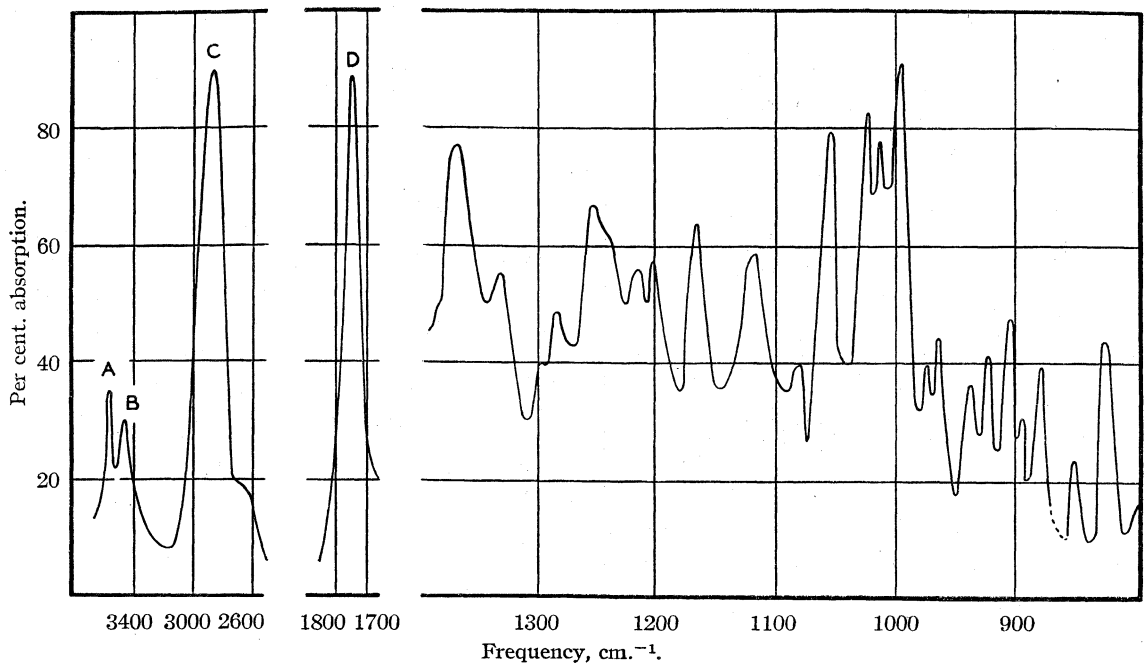


Fig. 1.—Infrared absorption spectrum of androsterone in carbon disulfide solution: A, O–H stretching motion of hydroxyl group; B, carbonyl overtone band; C, C–H stretching maxima; D, C=O stretching maximum of carbonyl group.

earlier paper of this series.[5] In such investigations the spectrometric curves have been used in an empirical manner as "molecular fingerprints."

The dependence of the infrared absorption spectrum on the molecular structure has been investigated very thoroughly for simple symmetrical molecules which are susceptible to mathematical treatment[6] and numerous studies of more complex molecules have been made by many observers following up the pioneer work of Coblenz.[7] In spite of this, comparatively little use has yet been made of infrared absorption data in the elucidation of molecular structure, although the possibilities of the method have been demonstrated by recent work on the structure of the penicillins.[8]

Infrared Absorption Spectra of Steroids.—In this paper an attempt is made to correlate the position of certain infrared absorption bands with the presence of specific molecular groupings in steroids. The infrared spectrum of a typical steroid, androsterone, is shown in Fig. 1. For the purposes of subsequent discussion it is convenient to consider this spectrum in two parts; a high frequency region from 4000 to about 1200 cm.$^{-1}$, and a lower frequency region extending down from 1200 cm.$^{-1}$ to the lower limit of measurement.

In the lower frequency region all steroids exhibit very complex absorption. This part of the spectrum is exceedingly sensitive to minor changes in chemical structure or steric configuration and has been utilized principally for empirical identification purposes.[5]

In the higher frequency region a smaller number of bands is observed. These are associated with hydrogen motions, or the stretching vibrations of doubly or triply bonded atoms from the second row of the periodic table. Such motions usually give rise to absorption bands in specific frequency ranges since they are little subject to perturbing interactions. For example, in the spectrum in Fig. 1, the band at 1742 cm.$^{-1}$ can be correlated with the stretching vibration of the carbon-oxygen bond of the carbonyl group. It is this higher region of the spectrum which offers the most encouraging prospect of yielding information concerning molecular structure.

The investigation described here was carried out in an endeavor to supplement the chemical methods available for the elucidation of the structure of new steroids isolated from biological material. In such compounds interest is centered mainly on the carbonyl group, the hydroxyl group and the double bond. Information is desired as to the presence or absence of these functional groups in the molecule, and if present it is important to locate their position in the ring system or on the side chain. It has been shown by Lecomte[9] and

(5) Dobriner, Lieberman, Rhoads, Jones, Williams and Barnes, *J. Biol. Chem.*, **172**, 297 (1948).

(6) Gerhard Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand Co., New York, N. Y., 1945.

(7) Coblenz, *Publ. Carnegie Inst. of Washington*, No. 35, Part 1, 1905.

(8) Fowler and Randall, Symposium on Molecular Structure and Spectroscopy, Ohio State University, June, 1946.

(9) J. Lecomte, "Spectres dans l'Infra-rouge," Traîté de Chimie Organique, sous le direction de V. Grignard, Secrétaire General, Paul Baud, Tome II, Fascicule 1, Masson et Cie, Paris, 1936, p. 143.

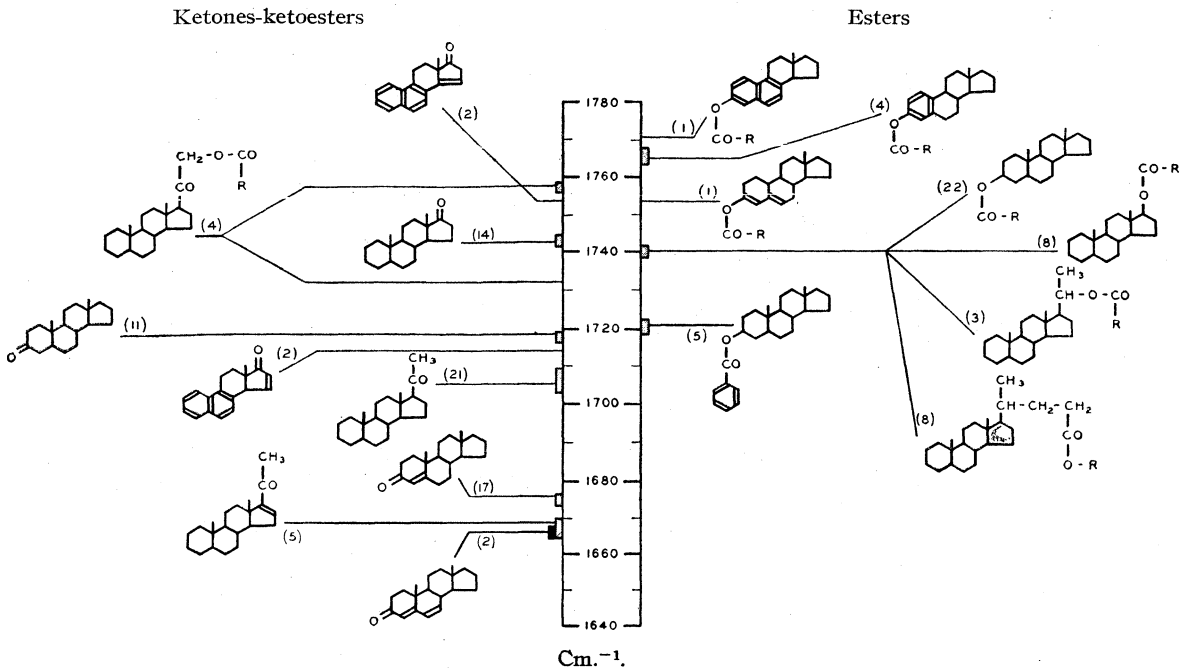


Fig. 2.—Diagram illustrating the relation between the frequency at the maximum of the carbon–oxygen stretching vibration and the location of the carbonyl group in steroid molecules (solvent carbon disulfide). The figures in parentheses indicate the number of individual compounds on which the frequency assignment is based.

others[3] that in certain types of organic compounds all of these groups may give rise to characteristic infrared absorption bands, and Furchgott, Rosenkrantz and Shorr[10,11,12] have demonstrated the presence of these absorption bands in the spectra of certain crystalline steroids.

The Carbonyl Group.—The carbon–oxygen stretching vibration of the carbonyl group may occur between 1550 and 2150 cm.$^{-1}$ and it has been observed in the spectra of ketones, aldehydes, carboxylic esters, acids, and ions, acid anhydrides, lactones and amides. The range of frequencies encompassed by this band varies somewhat for the different types of carbonyl groups.[3]

A comparison has been made of the infrared absorption spectra of carbon disulfide solutions of some one hundred and thirty steroids, and the positions of the maxima in the region between 1660 and 1780 cm.$^{-1}$ are listed for the monocarbonyl compounds in Table I, and for di- and polycarbonyl compounds in Table II. It is to be noted that an absorption band is seen only in the spectra of those steroids which contain a carbonyl group, so that the appearance of a strong band in this region of the spectrum of an unknown steroid is indicative of the presence of a carbonyl group in the molecule.

The carboxylic esters included in Tables I and II are mainly the acetates or propionates of steroid alcohols, although a few methyl esters of bile acid derivatives and some benzoates are also included. These esters give rise to a single absorption maximum between 1719 and 1771 cm.$^{-1}$. The position of the carbonyl maximum in the ketosteroids may be between 1666 and 1754 cm.$^{-1}$ so that it is not always possible to distinguish with certainty between a ketosteroid and a steroid ester from measurements in this region of the spectrum as some overlap in the band positions can occur.[13a]

A more precise consideration of the position of this carbonyl absorption band shows it to be closely dependent on the molecular environment of the carbonyl group in the molecule. The monoketosteroids and mono-steroid esters in Table I are grouped according to the position of the substituent, and the characteristic frequency positions derived from this analysis are summarized diagrammatically in Fig. 2.

For a given position of substitution, the carbonyl stretching vibration occurs at a sharply defined frequency. The frequencies of the maxima in steroids containing more than one carbonyl group are listed in a similar manner in Table II, and here, with certain exceptions to be considered later, the two carbonyl groups do not appear to exert any significant interaction effects, and the bands occur at the same positions as in the monocarbonyl compounds. The four ketonic positions of main significance in the steroid hormones are at carbon atoms 3, 11, 17 and 20 (I). In eleven steroids containing a non-conjugated ketonic carbonyl group at position 3 there is a maximum at

(10) Furchgott, Rosenkrantz and Shorr, *J. Biol. Chem.*, **163**, 375 (1946).

(11) Furchgott, Rosenkrantz and Shorr, *ibid.*, **164**, 621 (1946).

(12) Furchgott, Rosenkrantz and Shorr, *ibid.*, **167**, 627 (1947).

(13a) *Vide* page 2029.

TABLE I

CARBON–OXYGEN STRETCHING VIBRATION IN STEROIDS CONTAINING NOT MORE THAN ONE CARBONYL GROUP

Compound	Max.[w] ($cm.^{-1}$) CS_2	Source
A. Non-carbonyl compounds		
The following showed no absorption maxima between 1660 and 1780 $cm.^{-1}$ (Source of compound is indicated in parentheses): androstane (d), etiocholane (d), pregnane (d), allopregnane (d), cholestane (c), $\Delta^{2 \text{ or } 3}$-cholestene (j), cholestanol-3α (l), cholestanol-3β (l), androstanol-3α (o), androstanol-3β (o), androstanol-17α (o), Δ^5-androstenol-3β (o), Δ^5-androstenediol-3β,17α (o), Δ^5-androstenediol-3β,17β(o),cholestenetriol-3β,5β,6α (l).		
B. Non-conjugated 3-ketones		
Androstanone-3	1719	*o*
Etiocholanone-3	1719	*d*
Cholestanone-3	1719	*c*
Coprostanone-3	1718	*l*
Androstanol-17α-one-3 (*trans*-dihydrotestosterone)	1718	*o*
Androstanol-17β-one-3 (*cis*-dihydrotestosterone)	1718	*o*
C. Conjugated 3-ketones		
Δ^4-Androstenone-3	1677	*o*
Δ^4-Cholestenone-3	1674 (1656)[w]	*l*
Δ^4-Androstenol-17α-one-3 (testosterone)	1675 (1656)[w]	*p*
Δ^4-Androstenol-17β-one-3 (*cis*-testosterone)	1674 (1652)	*o*
Δ^4-17-Methylandrostenol-17α-one-3	1675 (1663)	*o*
Δ^4-17-Ethylandrostenol-17α-one-3	1675	*o*
Δ^4-17-Vinylandrostenol-17α-one-3	1675 (1660)	*o*
Δ^4-20,21-Epoxypregnenol-17α-one-3	1674[u]	*o*
D. $\Delta^{4,6}$-Diene-one-3		
$\Delta^{4,6}$-Cholestadiene-one-3	1666	*l*
E. Non-conjugated 17-ketones		
Androstanone-17	1745	*o*
$\Delta^{3,5}$-Androstadiene-one-17	1742	*b*
3-Chloroandrostanone-17	1743	*j*
Androstanol-3α-one-17 (androsterone)	1745 (1737)	*l*
Androstanol-3β-one-17 (isoandrosterone)	1745 (1735)	*o*
Etiocholanol-3α-one-17	1743 (1735)	*l*
Etiocholanol-3β-one-17	1742	*q*
Δ^5-Androstenol-3β-one-17 (dehydroisoandrosterone	1745	*o*
$\Delta^{9:11}$-Androstenol-3α-one-17	1742	*k*
$\Delta^{9:11}$-Etiocholenol-3α-one-17	1745	*n*
$\Delta^{11:12}$-Etiocholenol-3α-one-17	1742	*l*
Androstanediol-3α,11β-one-17	1742	*a, k*
F. $\beta\gamma$-Unsaturated 17-ketones		
$\Delta^{1,3,5:10,6,8,14}$-Estrahexaene-one-17	1754	*g*
3-Methoxy-$\Delta^{1,3,5:10,6,8,14}$-estrahexaene-one-17	1754	*g*
G. Conjugated 17-ketones		
$\Delta^{1,3,5:10,6,8,15}$-Estrahexaene-one-17	1716	*g*
3-Methoxy-$\Delta^{1,3,5:10,6,8,15}$-estrahexaene-one-17	1716	*g*
H. Non-conjugated 20-ketones		
Pregnanol-3α-one-20	1706	*l*
Allopregnanol-3α-one-20	1710	*l*
Allopregnanol-3β-one-20	1706 (1706)	*l*
17-Iso-pregnanol-3α-one-20	1706	*f*
Δ^5-Pregnenol-3β-one-20	1707 (1702)	*p*
Δ^{11}-Pregnenol-3β-one-20	1706	*c*
Pregnanediol-3α,11α-one-20	1706[u]	*c*
Pregnanediol-3β,12β-one-20	1706[u]	*o*
Δ^5-Pregnenediol-3β,21-one-20	1706	*p*
$\Delta^{2(\text{ or } 3?)}$-Allopregnenone-20	1706	*l*
I. Conjugated 20-ketones		
Δ^{16}-Pregnenol-3α-one-20	1666	*j*
$\Delta^{5,16}$-Pregnanedienol-3β-one-20	1669[v]	*h*
J. 3-Acyl esters		
Cholestanol-3α-acetate	1739	*c*
Cholestanol-3β-acetate	1739	*l*
Δ^5-Cholestanol-3β-acetate	1739	*t*
$\Delta^{8:14}$-Cholestanol-3β-acetate	1739	*t*
Δ^{14}-Cholestenol-3β-acetate	1739	*t*
$\Delta^{5,7}$-Cholestadienol-3β-acetate	1739	*t*
Androstanediol-3α,17α-acetate-3	1739	*o*
Δ^5-Androstenediol-3β,17α-acetate-3	1739	*o*
K. 3-Aryl esters		
$\Delta^{8:14}$-Cholestenol-3β-benzoate	1719	*t*
Δ^{14}-Cholestenol-3β-benzoate	1719	*t*
L. 17-Acyl ester		
Δ^5-Androstendiol-3β,17α-acetate-17	1739	*j*
M. Cholanate and cholenate methyl esters[x]		
3α-Hydroxycholanic acid m. e.[x]	1742 (1730)	*c*
3α-Hydroxy-$\Delta^{9:11}$-cholenic acid m. e.[x]	1742 (1732)	*c*
3α-Hydroxy-Δ^{11}-cholenic acid m. e.[x]	1742 (1732)	*c*
3α-Hydroxy-11α,12α-epoxycholanic acid m. e.[x]	1742	*c*
3α-Hydroxy-12β-methoxy-$\Delta^{9:11}$-cholenic acid	1742 (1732)	*r*
3β,12β-Dihydroxycholanic acid m. e.[x]	1742	*f*
3α,12β-Dihydroxy-$\Delta^{9:11}$-cholenic acid m. e.[x]	1742 (1732)	*r*

[a] R. I. Dorfman, Western Reserve U., Cleveland, Ohio. [b] L. Engel, Mass. General Hosp., Boston, Mass. [c] T. F. Gallagher, Sloan–Kettering Inst., New York, N. Y. [d] R. D. H. Heard, McGill U., Montreal. [e] E. B. Hershberg, The Schering Corp., Bloomfield, N. J. [f] W. H. Hoehn, G. A. Breon and Co., Kansas City, Mo. [g] W. S. Johnson, U. of Wisconsin. [h] O. Kamm, Parke, Davis & Co., Detroit, Michigan. [i] E. C. Kendall, Mayo Clinic, Rochester, Minn. [j] R. E. Marker, Pennsylvania State College, Penna. [k] H. L. Mason, Mayo Clinic, Rochester, Minn. [l] S. Lieberman, Memorial Hosp., New York, N. Y. [m] T. Reichstein, U. of Basel, Switzerland. [n] H. P. Sarett, Merck and Co., Rahway, N. J. [o] C. R. Scholz, Ciba Pharm. Prod. Inc., Summit, N. J. [p] E

Schwenk, The Schering Corp., Bloomfield, N. J. [q] H. Selye, U. Montreal. [r] R. Turner, Harvard U., Cambridge, Mass., E. C. Kendall, Mayo Clinic, Rochester, Minn. [s] Compound acetylated at Memorial Hosp., by Dr. S. Lieberman from alcohol supplied by H. P. Sarett. [t] D. K. Fukushima, Memorial Hosp., New York, N. Y. [u] Suspension of crystalline material in saturated solution in carbon disulfide. [v] Weak absorption band at 1719 cm.$^{-1}$ attributed to trace of impurity. [w] Figures in parentheses refer to maximum in chloroform solution. [x] In the names of these compounds "m. e." is used as an abbreviation for "methyl ester."

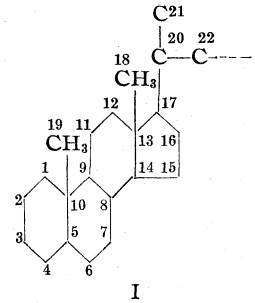
TABLE II

CARBON–OXYGEN STRETCHING VIBRATION IN STEROIDS CONTAINING TWO OR MORE CARBONYL GROUPS

Compound	Max. in CS_2[a] (cm.$^{-1}$)		Source[a]
A. 3,17-Diketones			
Androstanedione-3,17	1745	1719	*l*
Etiocholanedione-3,17	1745	1719	*l*
Δ^4-Androstanedione-3,17	1745 (1739)	1674 (1663)	*o*
B. 3,20-Diketones			
Allopregnanedione-3,20	1719	1710	*h*
Pregnanedione-3,20	1719	1710	*l*
Δ^5-Pregnenedione-3,20	1719	1710	*l*
Δ^4-Pregnenedione-3,20 (progesterone)	1708 (1706)	1677 (1669)	*p*
Δ^4-Pregnenol-17α-dione-3,20	1710	1674	*o*
Δ^4-Pregnenol-21-dione-3,20 (desoxycorticosterone)	1710	1677	*o*
$\Delta^{4,6}$-Pregnenediene-dione-3,20	1710	1669	*l*
Δ^{16}-Pregnenedione-3,20	1717 (1710)	1669 (1666)	*h*
C. Diacyl esters			
Androstanediol-3α,17α-diacetate	1742		*l*
Δ^5-Androstenediol-3β,17α-diacetate	1742		*o*
$\Delta^{3,5}$-Androstadienediol-3,17α-dipropionate	1754	1742	*o*
Pregnanediol-3α,12α-amine-20-hydrochloride diacetate	1742[c]		*o*
Pregnanediol-3α,20α-diacetate	1739		*l*
Pregnanediol-3α,20β-diacetate	1739		*j*
Pregnanediol-3β,20β-diacetate	1739		*j*
3α-Acetoxy-$\Delta^{9:11}$-cholenic acid m. e.[b]	1739		*o*
$\Delta^{1,3,5:10}$-Estratriendiol-3,17α-diacetate (estradiol diacetate)	1767	1742	*l*
D. 3-Ketoesters			
Androstanol-17α-one-3-acetate	1742	1719	*l*
Androstanol-17β-one-3-acetate	1739	1719	*l*
Δ^4-Androstenol-17α-one-3-acetate (testosterone acetate)	1742	1677	*o*
Δ^4-Androstenol-17α-one-3-propionate (testosterone propionate)	1742	1677	*p*
Δ^4-Androstenol-17β-one-3-acetate	1739	1677	*l*
E. 17-Ketoesters			
Androstanol-3α-one-17-acetate (androsterone acetate)	1742		*l*
Androstanol-3β-one-17-acetate (isoandrosterone acetate)	1742		*l*
Etiocholanol-3α-one-17-acetate	1742		*l*
Etiocholanol-3β-one-17-acetate	1742		*h*
Δ^5-Androstenol-3β-one-17-acetate (dehydroisoandrosterone acetate)	1742		*l*
Δ^5-Androstenol-3β-one-17-propionate (dehydroisoandrosterone propionate)	1742		*o*
$\Delta^{9:11}$-Androstenol-3α-one-17-acetate	1742		*a*
$\Delta^{9:11}$-Etiocholenol-3α-one-17-acetate	1742		*s*
5α,6α-Epoxyetiocholanol-3β-one-17-acetate	1742		*c*
5β,6β-Epoxyetiocholanol-3β-one-17-acetate	1742		*c*
$\Delta^{1,3,5:10}$-Estratrienol-3-one-17-acetate (estrone acetate)	1764	1742	*l*
$\Delta^{1,3,5:10,7}$-Estratetraenol-3-one-17-acetate (equilin acetate)	1764	1742	*l*
$\Delta^{1,3,5:10,6,8}$-Estrapentaenol-3-one-17-acetate (equilenin acetate)	1770	1742	*l*
Androstanol-3α-one-17-benzoate (androsterone benzoate)	1745	1723	*l*
Etiocholanol-3α-one-17-benzoate	1745	1719	*l*
Δ^5-Androstenol-3β-one-17-benzoate (dehydroisoandrosterone benzoate)	1745	1719	*l*
Δ^4-Androstenol-17α-one-3-benzoate (testosterone benzoate)	1724	1674	*o*
F. 20-Ketoesters			
Allopregnanol-3β-one-20-acetate	1739	1708	*j*
17-Iso-pregnanol-3α-one-20-acetate	1739	1706	*f*
Δ^5-Pregnenol-3β-one-20-acetate	1739	1706	*o*
Δ^{11}-Pregnenol-3α-one-20-acetate	1739	1706	*c*
Pregnanediol-3α,17α-one-20-acetate-3	1735	1710	*l*
Δ^{16}-Pregnenol-3α-one-20-acetate	1742	1670	*j*
$\Delta^{5,16}$-Pregnadienol-3β-one-20-acetate	1739	1669	*j*
Δ^5-Pregnenediol-3β,21-one-20-acetate-21	1756	1732[c]	*o*
Pregnanetriol-3α,12β,21-one-20-acetate-21	1756	1732	*o*
G. Polyesters			
Δ^5-Androstenetriol-3β,16,17-triacetate	1740		*k*
$\Delta^{1,3,5:10}$-Estratrienetriol-3,16,17-triacetate (estriol triacetate)	1767	1742	*l*
$\Delta^{17:20}$-Pregnenetriol-3β,12β,20-triacetate	1758[d]	1740	*c*
H. Poly-ketoesters			
Pregnanediol-3α,11α-one-20-diacetate	1739	1710	*c*
Δ^4-Pregnenol-21-dione-3,20-acetate (desoxycorticosterone acetate)	1758 1674	1732	*o*
Pregnanediol-12β,21-dione-3,20-acetate-21	1758 1703	1732	*o*

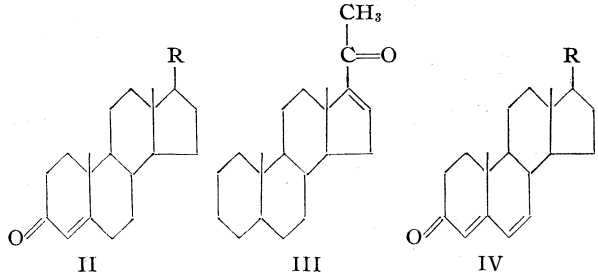
[a] See footnotes to Table I. [b] "m. e." is abbreviation for "methyl ester." [c] Measurements made on a suspension of crystalline material in a saturated solution in carbon disulfide. [d] Inflection only.

1717–1719 cm.$^{-1}$. Twenty-one ketosteroids with a non-conjugated carbonyl group at position 20 have a maximum at 1706–1710 cm.$^{-1}$, while in fourteen non-conjugated 17-ketosteroids the maximum is at 1742–1745 cm.$^{-1}$.

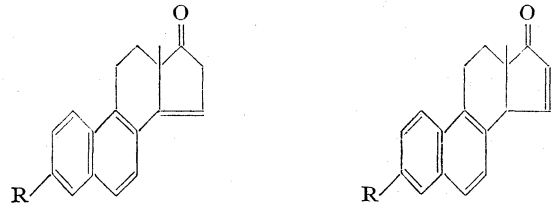


I

The introduction of a double bond in the α,β-position to the ketonic carbonyl group shifts the maximum by about 40 cm.$^{-1}$ to lower frequencies. In seventeen Δ^4-3-ketosteroids (II) there is a band at 1674–1677 cm.$^{-1}$ while in five Δ^{16}-20-ketosteroids (III) the maximum occurs at 1666–1670 cm.$^{-1}$. Two compounds containing the $\Delta^{4,6}$-diene-one-3 system (IV) also possess a maximum at 1666–1669 cm.$^{-1}$. Data on the effect of ethylenic unsaturation in ring D on the 17-carbonyl group is at present limited to the four synthetic equilenin derivatives V–VIII.[13] It is curious to note that in V and VI the introduction of the $\beta\gamma$- double bond shifts the position of the



II III IV



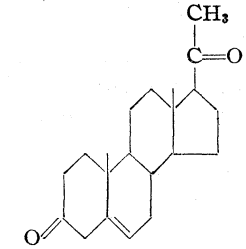
V (R = —H)
VI (R = OCH_3)

VII (R = —H)
VIII (R = —OCH_3)

carbonyl maximum about 10 cm.$^{-1}$ to higher frequencies from its position in the 17-ketosteroids in which ring D is saturated. A change in the force constants in the carbon–oxygen bond may be brought about by the shortening of the bond between carbon atoms 14 and 15 in the unsaturated compound with a resultant strain effect on the valence angles at carbon atom 17.[14]

Few data are yet available concerning the location of the carbonyl band in steroids containing a ketone group at positions other than 3, 17 or 20. The effects of carbonyl groups at 11 and 12, which are of considerable interest in connection with the adrenocortical steroids will form the subject of a separate publication.

In the non-conjugated 3,17-diketosteroids two maxima occur at 1745 and 1719 cm.$^{-1}$, positions normal to the corresponding monocarbonyl compounds. The same is true also of the 3,20-diketones which have two maxima at 1719 and 1710 cm.$^{-1}$. In the latter case the separation between the maxima is about the limit of resolution possible under the experimental conditions employed.[15]



IX

The carbonyl group of the non-conjugated carboxylic ester tends to be less sensitive than the ketonic carbonyl group to the position of substitution in the sterol ring system, and the acetates and propionates of 3-, 17- and 20-hydroxysteroids all absorb at 1739–1742 cm.$^{-1}$. The methyl esters of cholanic acid derivatives also absorb at the same position. This lies quite close to the position of the maximum in non-conjugated 17-ketosteroids so that it is not possible to distinguish 17-ketosteroids from certain steroid esters by this criterion alone. However, the acetate esters possess a strong band near 1240 cm.$^{-1}$ (see Table III) which is lacking from the spectra of ketosteroids, so that a supplementary examination of the absorption in the region near 1240 cm.$^{-1}$ permits a

(13) Johnson, Petersen and Gutsche, THIS JOURNAL, **69**, 2942 (1947).

(14) The possibility that this shift to higher frequency results from effects of the aromatic system in rings A and B cannot be excluded on the basis of this evidence. However, the interpretation given above seems most probable when the data on the band positions in the acetates of estrone, equilin and equilenin are also taken into consideration. These three compounds all possess a band at 1742 cm.$^{-1}$ which can be attributed most reasonably to the unperturbed 17-ketosteroid absorption. These compounds contain a second band at 1764–1771 cm.$^{-1}$ which is attributed to the phenolic acetate group. In estradiol diacetate two maxima are observed at 1767 and 1742 cm.$^{-1}$ indicating clearly that the carbonyl of the phenolic ester absorbs at a position different from that of the simple carbinol ester.

(15) Better resolution of these absorption maxima might be achieved by the use of higher dispersion, as may result from the substitution of a calcium fluoride prism or a grating in place of the sodium chloride prism used in these measurements. Measurements of the band intensity for standard conditions of concentration and sample thickness, or determination of the band width at half the maximum intensity may also yield more information about the nature of the absorbing group, and make possible a distinction between absorption caused by one or two carbonyl groups at the same frequency.

distinction to be made between a 17-ketosteroid and a steroid acetate ester. Some significance may be attached to the observation that in compounds containing the partial structure XI this maximum is displaced by 10–12 cm.$^{-1}$ to lower frequencies as indicated by the last four compounds in Table III.

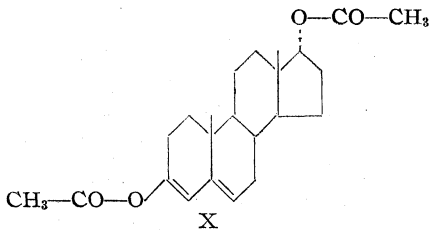
TABLE III

POSITION OF STRONG "ACETATE BAND" IN REPRESENTATIVE GROUP OF STEROID ACETATE ESTERS

Compound	Max. (cm.$^{-1}$) CS_2	Source[a]
Androstanol-3α-one-17-acetate	1240	*l*
Androstanol-3β-one-17-acetate	1240	*l*
Androstanol-17α-one-3-acetate	1245	*l*
Androstanol-17β-one-3-acetate	1238 1245	*l*
Δ^4-Androstenol-17α-one-3-acetate	1242	*o*
Δ^4-Androstenol-17β-one-3-acetate	1245	*l*
Δ^5-Androstenol-3β-one-17-acetate	1240	*l*
Androstanediol-3α,17α-acetate-3	1238	*o*
Androstanediol-3α,17α-diacetate	1242	*l*
Δ^5-Androstenediol-3β,17α-acetate-3	1242	*o*
Etiocholanol-3α-one-17-acetate	1240	*l*
Pregnanol-3α-one-20-acetate	1240	*l*
Allopregnanol-3β-one-20-acetate	1240	*j*
17-Iso-pregnanol-3α-one-20-acetate	1242	*f*
Δ^{16}-Pregnenol-3α-one-20-acetate	1235 1255	*j*
Δ^5-Pregnenediol-3β,21-one-20-acetate-21	1228	*o*
Δ^4-Pregnenol-21-dione-3,20-acetate	1230	*o*
Pregnenediol-3α,21-dione-11,20-acetate-21	1228	*n*
Pregnanol-21-trione-3,11,20-acetate	1228	*n*

[a] See footnotes to Table I.

Where the esterified hydroxyl group is phenolic in character, as in the 3-acetates of compounds in the estrone and equilenin series, the carbonyl ester absorption maximum is shifted to higher frequencies (Fig. 2). This is true also when the esterified hydroxyl group is associated with a conjugated system as in the enol ester X. It is interesting to observe that this type of attachment of the ester carbonyl group to an ethylenic double bond through the oxygen atom, shifts the carbonyl maximum in the opposite direction from that brought about by direct conjugation with the carbonyl bond, as is seen in the steroid benzoates and the conjugated ketosteroids (Fig. 2).

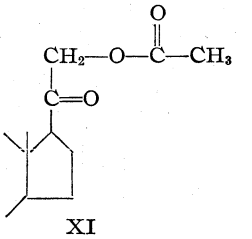


X

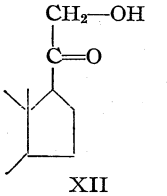
The above observations are all based on measurements in carbon disulfide solution. The positions of the carbonyl stretching maxima have been determined also in a few cases using chloroform as solvent, and the results are listed in Tables I and II. In chloroform the band maxima tend to be displaced to lower frequencies; the effect is least (0–5 cm.$^{-1}$) for non-conjugated 20-ketosteroids, somewhat greater for carboxylic esters and 17-ketosteroids (7–10 cm.$^{-1}$) and greatest for conjugated 3-ketosteroids (12–20 cm.$^{-1}$).

Interaction Effects.—In dicarbonyl compounds it might be anticipated that some interactions involving the vibrations of the two carbonyl groups would be encountered and result in the displacement of the bands from the positions observed in comparable monocarbonyl compounds.

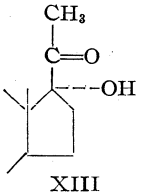
As has been shown above, such interactions have not been detected between carbonyl groups at positions 3 and 17 and 3 and 20. An example of such a displacement is seen in the spectra of the 21-acetoxy-20-ketosteroids which contain the partial structure XI. Such compounds would be expected to possess a band at 1706–1710 cm.$^{-1}$ for the 20-ketone group and at 1739–1742 cm.$^{-1}$ for the acetate ester. Actually all of the four such compounds examined possess bands at 1732 cm.$^{-1}$ and 1756–1758 cm.$^{-1}$. Four compounds containing the partial structures XII or XIII on the contrary show the normal 20-ketosteroid band at 1706–1710 cm.$^{-1}$ from which it may be argued that the displacements associated with structure XI involve carbonyl group interactions, and are not due merely to steric or other non-specific effects of the large oxygen atoms adjacent to the 20-ketone.



XI



XII



XIII

Other evidence of the influence of the molecular environment on the frequency of the carbon–oxygen stretching vibration in cyclic compounds has been reported in the literature. Biquard[16] has measured the position of the analogous band in the Raman spectra of a series of mono- and dicyclic ketones and noted quite similar displacements of the band positions. Thus in the Raman spectrum of cyclopentanone there is a band at $\Delta\nu$ = 1744 cm.$^{-1}$ which is displaced to $\Delta\nu$ = 1714 cm.$^{-1}$ in cyclohexanone. Furchgott, Rosenkrantz and Shorr[12] have reported that in the crystalline state non-conjugated 3-ketosteroids absorb at 1739 cm.$^{-1}$, 17-ketosteroids at 1738–1740 cm.$^{-1}$ and 20-ketosteroids at 1703–1715 cm.$^{-1}$ and that a 17-ketosteroid could not be distinguished from a 3-ketosteroid. This latter observation is contrary to our experience, based on measurements in solu-

(16) Biquard, *Bull. soc. chim. France*, **7**, 894 (1940); **8**, 55, 725 (1941).

tion. Measurements made on solutions would also appear preferable for the purposes of structural identification since the spread of the absorption maximum for a given substituent position seems to be less than for crystalline films or powder suspensions.

In addition to the carbon–oxygen stretching vibration, discussed above, the ketosteroids containing a double bond in the $\alpha\beta$-position to the carbonyl group possess another strong absorption band between 1580 and 1615 cm.$^{-1}$. Both carbon disulfide and carbon tetrachloride absorb appreciably in this region but satisfactory measurements can be made in chloroform solution as has been shown recently by Blout, Fields and Karplus.[17] Measurements on a few unsaturated ketosteroids in this region are summarized in Table IV. These are in agreement with the observation of Furchgott, Rosenkrantz and Shorr[12] who have suggested that the Δ^4-3-ketosteroid and the Δ^{16}-20-ketosteroid systems might be distinguished on the basis of the difference in the position of this band in the two types of $\alpha\beta$-unsaturated compounds.

TABLE IV

ABSORPTION AT 1580–1620 CM.$^{-1}$ ASSOCIATED WITH THE CONJUGATED CARBONYL GROUP

Substance	Max. (cm.$^{-1}$) $CHCl_3$ soln.	Max. (cm.$^{-1}$) film or mull	Source[a]
A. Δ^4-3-Ketosteroids			
Δ^4-Androstanol-17α-one-3 (testosterone)	1615	1615	*p*
Δ^4-Androstanol-17β-one-3- (*cis*-testosterone)	1613	1615	*o*
Δ^4-Androstenol-17α-one-3-propionate	..	1615	*p*
Δ^4-17-Methylandrostanol-17α-one-3	1615	1620	*o*
Δ^4-17-Vinylandrostanol-17α-one-3	1615	..	*l*
Δ^4-Androstenedione-3,17	1615	1620	*o*
Δ^4-Pregnenedione-3,20 (progesterone)	1615	1618	*p*
Δ^4-Cholestenone-3	1612	1615	*l*
B. Δ^{16}-20-Ketosteroids			
Δ^{16}-Pregnenol-3α-one-20	..	1588	*j*
$\Delta^{5,16}$-Pregnadienol-3β-one-20-acetate	..	1585	*j*
Δ^{16}-Pregnenedione-3,20	1588	..	*h*

[a] See footnotes to Table I.

Carbonyl Harmonic Band.—In addition to the fundamental carbonyl stretching vibration discussed above, another weak absorption band attributed to the carbonyl group occurs between 3300 and 3475 cm.$^{-1}$. This is an overtone of the fundamental carbon–oxygen stretching vibration. It should occur at twice the frequency of the main carbonyl maximum or at a frequency slightly lower than this. The position of this band in the spectrum of androsterone is indicated as B in Fig. 1. This carbonyl harmonic is not likely to be of appreciable value in the elucidation of sterol structure, since it is much weaker than the fundamental band. However its occurrence should be noted, since in certain instances it may be confused with the hydrogen–oxygen stretching vibration of the hydroxyl group (*vide infra*).

The Non-Conjugated Double Bond.—The presence or absence of a non-conjugated ethylenic double bond in a steroid cannot always be determined with certainty by infrared measurements. Several investigators[3,17,18] have shown that in many organic compounds there is an absorption band near 1650 cm.$^{-1}$ associated with a longitudinal vibration of the carbon–carbon double bond. It is difficult to observe this band in the spectra of carbon disulfide solutions since the solvent absorbs appreciably in this region. In only a few instances of solutions in carbon tetrachloride or in crystalline films and suspensions has this band been seen in the spectra of unsaturated steroids. It may be seen more readily in chloroform solutions, but when present it is of low intensity and its detection is rendered more difficult by the fact that atmospheric water vapor produces considerable background absorption in this region of the spectrum. Its detection would be facilitated by the use of a double beam instrument.

At higher frequencies, near 3000 cm.$^{-1}$ there is a group of strong bands associated with the stretching vibration of the carbon–hydrogen bond. Several observers have reported[19] that when the C–H bond forms part of an unsaturated system, this band occurs at a frequency greater than 3000 cm.$^{-1}$ whereas in a saturated group it is normally below 3000 cm.$^{-1}$. In all steroids there are strong bands in the region between 3000 and 2800 cm.$^{-1}$ due to the —C—H vibrations of the ring and side chain aliphatic system. In carbon disulfide solutions of several unsaturated steroids, a band or inflection is seen also on the high frequency side of this band group. A particularly favorable example is illustrated in curves A and B of Fig. 3,

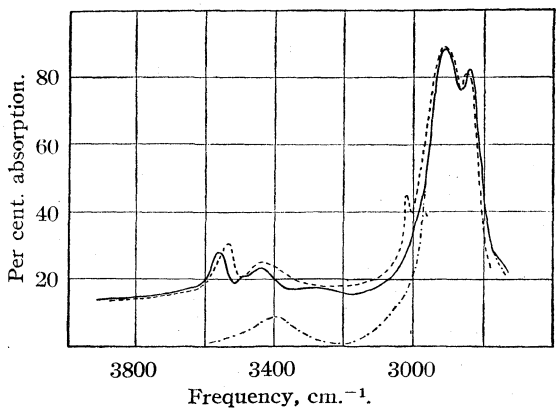


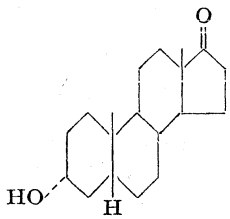
Fig. 3.—Infrared absorption spectra in carbon disulfide solution: A, —, etiocholanol-3α-one-17 (XIV); B, – – –, Δ^{11}-etiocholenol-3α-one-17 (XV); C, ·—·—, etiocholanol-3α-one-17-acetate.

(17) Blout, Fields and Karplus, THIS JOURNAL, **70**, 194 (1948).

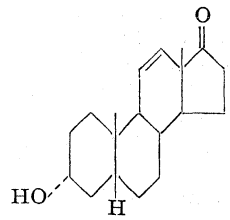
(18) Thompson and Torkington, *Trans. Faraday Soc.*, **41**, 246 (1945).

(19) See Fox and Martin, *Proc. Roy. Soc.* (*London*), **A175**, 208 (1940).

where the spectrum of etiocholanol-3α-one-17 (XIV) is compared with that of the unsaturated derivative with a double bond at the 11,12 position (XV).



XIV



XV

In column A of Table V the positions of this band in the spectra of some 47 steroids in carbon disulfide solution are recorded. Among these compounds are nineteen containing the =C—H group and a band or inflection near 3020 cm.$^{-1}$ is observed in the spectra of fourteen of them. No band was detected in this neighborhood in the spectra of any of the saturated steroids included in this survey. In these compounds the band attributed to the =C—H group is weak and as in many cases it occurs on the rising slope of the —C—H band group, the frequency at the maximum cannot be determined with much certainty. In many cases it fails to appear unless the concentration of the solution is increased considerably above the 10 mg. per ml. which is adequate for the determination of the remainder of the spectrum in a 1 mm. cell. In some instances the concentration cannot be increased sufficiently because of the low solubility of the steroid and this may account

TABLE V

ABSORPTION BETWEEN 3000 AND 4000 CM.$^{-1}$ ASSOCIATED WITH C=C—H AND C—O—H GROUPS

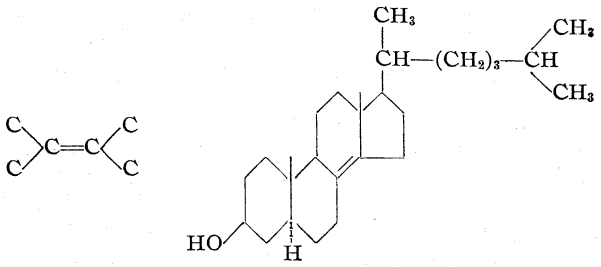
Compound	Maxima[b] (cm.$^{-1}$) C=C—H, CS_2 soln. A	C=C—H, Solid B	C—O—H, CS_2 soln. C	C—O—H, Solid D	Source[a]
A. Steroids Containing Neither C=C—H Nor C—O—H Groups					
The following showed no bands at positions attributable to the above groups (source of compounds is indicated in footnotes): androstane,[d] etiocholane,[d] allopregnane,[d] pregnane,[d] allopregnanedione-3,20,[h] pregnanedione-3,20,[l] androstanol-3α-one-17-acetate,[l] 3-choloroandrostanone-17,[l] cholestanone-3,[c] coprostanone-3,[e] sitostanedione-3,6.[j]					
B. Steroids Containing —C=C—H but not —C—O—H Group					
Δ^4-Androstenedione-3,17	3020	3028	a	a	*o*
Δ^4-Cholestenone-3	n. o.	3020	a	a	*l*
Δ^5-Androstenol-3β-one-17-acetate (dehydroisoandrosterone acetate)	3050	n. o.	a	a	*l*
Δ^5-Androstenol-3β-one-17-propionate	3000	3050	a	a	*o*
Δ^5-Androstenol-3β-one-17-benzoate	3025	3080, 3050	a	a	*l*
Δ^5-Androstenediol-3β,17α-dipropionate	n. o.	3010	a	a	*o*
Δ^5-Pregnenol-3β-one-20-acetate	3040	3035	a	a	*o*
Δ^4-Pregnenedione-3,20 (progesterone)	3020	3025	a	a	*l*
Δ^{5,16}-Pregnanedienol-3β-one-20-acetate	3020	3065, 3040	a	a	*j*
C. Steroids Containing —C—O—H but not C=C—H Group					
Androstanol-17	a	a	3570	3200, 3270b	*j*
Androstanediol-3α,17α	a	a	3575	3375b	*o*
Androstanediol-3β,17β	a	—	3575		*o*
Cholestanol-3β	a	a	3600	3200, 3350, 3450	*l*
Cholestanediol-3,4	a	a	3600	3270, 3370, 3435	*j*
Etiocholanediol-3α,17α	a	a	3600	3290, 3370	*j*
Pregnanediol-3α,20α	a	a	3610	3260, 3310b	*j*
Pregnanediol-3β,20β	a	a	3610	3355b	*j*
Androstanol-3α-one-17 (androsterone)	a	a	3610	3500s	*l*
Androstanol-3β-one-17	a	—	3610	..	*o*
Etiocholanol-3α-one-17	a	—	3610	..	*l*
Etiocholanol-3β-one-17	a	a	3620	3425s	*q*
Allopregnanol-3α-one-17	a	a	3620	3280b	*l*
17-Iso-pregnanol-3α-one-20	a	—	3605	..	*f*
Cholestanol-3β-one-6	a	a	3600	3420, 3490b	*j*
D. Steroids Containing both —C—O—H and —C=C—H Groups					
Δ^5-Androstenediol-3,17	ins.	3030	ins.	3310b	*o*
Δ^6-Androstenediol-3,17	n. o.	n. o.	3560	3350 3200b	*o* *l*
Δ^5-Cholestanol-3	3020	3040	3600	3360 3175b	
Δ$^{1,3,5:10}$-Estratrienediol-3,17-α(α-estradiol)	ins.	3055 3020	ins.	3450 3235b	*p*
Δ^4-Androstenol-3-one-17 (dehydroisoandrosterone)	3045	3020	3600	3430 3370	*o*
Δ^4-Androstenol-17β-one-3 (testosterone)	3020	3000	3610	3300b	*p*
Δ^4-Androstenol-17β-one-3 (*cis*-testosterone)	3010	3010	3610	3410b	*o*
Δ^4-17-Methylandrostenol-17α-one-3	3010	3020	3600	3450b	*o*
Δ^5-Pregnenol-3β-one-20	3020	3030	3605	3455 3420b	*p*
Δ^{16}-Pregnenol-3α-one-20	3040	3050	3600	3365b	*j*

[a] See footnotes to Table I. [b] b = broad band; s = sharp band; a = band absent; — = spectrum not measured; n. o. = spectrum measured but band not observed; ins. = compound insoluble in carbon disulfide.

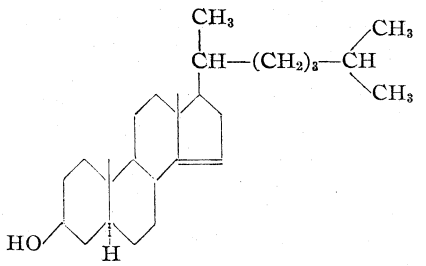
for the failure to detect this band in certain of the compounds in Table V. In column B of Table V similar data are listed for crystalline films or suspensions of these steroids. The possibility of introducing a thicker sample layer into the radiation beam in the form of a crystalline film or suspension in a "Nujol" mull favors the use of films rather than solutions for the investigation of this particular band.

In a molecule containing the partial structure XVI in which there are no hydrogen atoms attached to the unsaturated carbon atoms, this band would not be expected to appear. An example is given in Fig. 4 where the spectra of Δ$^{8:14}$-cholestenol-3β (XVII) and Δ^{14}-cholestenol-3β (XVIII) are compared over the region between 2500 and 4000 cm.$^{-1}$. The absence of the band near 3000 cm.$^{-1}$ from the spectrum of XVII is clearly in evidence.

The Conjugated Diene Systems.—The number of compounds containing this system which have been measured is comparatively small. Absorption associated with the conjugated diene group occurs between 1580 and 1620 cm.$^{-1}$ and the steroids must be examined as crystalline films,



XVI XVII



XVIII

powder suspensions, or in chloroform solution. In view of the fact that a system of conjugated ethylenic bonds can be detected and characterized with facility by ultraviolet spectrometry[20,21] the identification of this group from infrared measurements is of comparatively small importance. The same is true also of the aromatic systems present in the estrogens.

The Hydroxyl Group.—The longitudinal vibration of the hydrogen–oxygen bond of the hydroxyl group is responsible for an absorption band at the high frequency end of the spectrum. The position of this band may vary considerably with the experimental conditions under which the measurements are made, thus it may shift as a result of change in solvent or change in concentration, and may appear quite different (usually broadened, intensified and displaced to lower frequencies) when examined in a crystalline state.

Some data on the frequencies of the hydroxyl band in carbon disulfide solutions and in films of a number of steroids are listed in columns C and D of Table V. Displacement of the absorption band to lower frequency with increase in intensity and band width is associated with a lowering of the strength of the oxygen–hydrogen bond occasioned by inter- or intra-molecular hydrogen bonding. Where the hydroxyl group is not subject to such effects a maximum is observed near 3600 cm.$^{-1}$, a condition most favored in dilute solution.

It has not proved possible to associate the exact frequency of this absorption maximum with the position of the hydroxyl group in the steroid molecule. However, the presence or absence of a hydroxyl group in a steroid can be determined with certainty by examination of this region of the spectrum. This is illustrated in curves A and C of Fig. 3 where the spectra of etiocholanol-3α-one-17 and that of its acetate are compared. Twenty-five of the compounds included in Table V contain a hydroxyl group. When examined as crystalline films, most of these showed absorption bands of varied width between 3200 and 3500 cm.$^{-1}$. In carbon disulfide or carbon tetrachloride solution they showed a much weaker narrow absorption band between 3575 and 3610 cm.$^{-1}$. The two hydroxy steroids which failed to exhibit hydroxyl absorption in solution were poorly soluble and it is most probable that in these cases insufficient of the solute was present in the radiation path for the band to be manifested. Under conditions where association takes place, the spectrum of a compound containing a single hydroxyl group may exhibit two or more broad bands between 3200 and 3500 cm.$^{-1}$ and the relative intensities of these maxima may vary with the conditions of sample treatment. This behavior is suggestive of the presence of two or more types of hydrogen bonding or different modes of packing of the hydroxyl group in two or more crystalline forms.

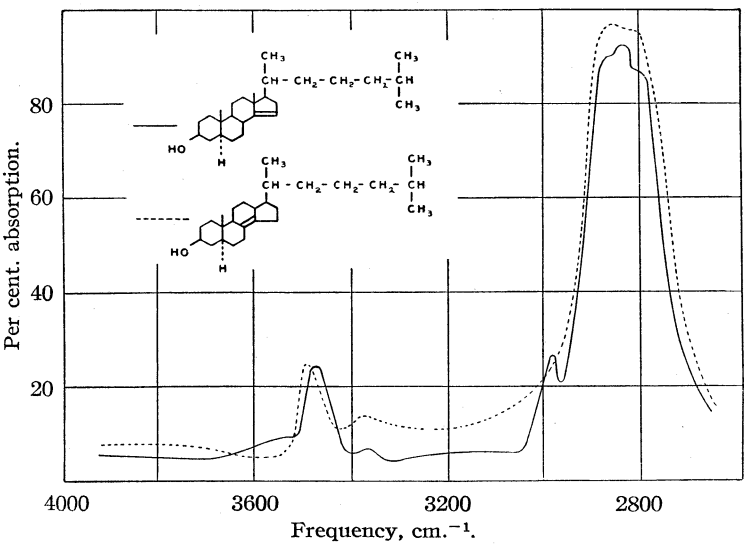


Fig. 4.—Infrared absorption spectra in carbon disulfide solution: —, Δ^{14}-cholestenol-3β; – – – – –, $\Delta^{8,14}$-cholestenol-3β.

General Discussion

While the absorption associated with the carbonyl group is influenced by the molecular environment in such a manner as to permit of the close correlation of absorption frequency with molecular structure, this would appear not to be the case with regard to absorption associated with the double bond and hydroxyl group. The analytical treatment developed in this paper has been

(20) Woodward, THIS JOURNAL, **64**, 72 (1942).
(21) Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940).

concerned almost exclusively with the high frequency region of the infrared spectrum, but it must be kept in mind that structural variations such as the introduction of a double bond also give rise to very large changes in the appearance of the absorption curves at frequencies less than 1200 cm.$^{-1}$. Similar modifications are produced also by stereochemical inversions; studies in the higher frequency region have given no indication of spectral variations which can be related to the stereochemical structure, and this is an important factor in the elucidation of steroid structure. It is reasonable to assume that the variations in the spectra in the lower frequency region should also be subject to regulation and correlatable with specific differences in molecular structure, and it is probably in this region that spectral features relatable to specific stereochemical configurations will be observed. Furchgott, Rosenkrantz and Shorr[10,11,12] have drawn attention to this and pointed out certain relationships, between the stereochemical configurations at positions 3 and 5 and absorption in the neighborhood 1000 cm.$^{-1}$. While we also have noted that absorption near 1000 cm.$^{-1}$ is highly susceptible to structural and stereochemical changes involving the 3 and 5 positions, we have as yet been unable to establish any specific correlations between structure and spectra in this region which are of general application.

Experimental

The data given in this work were obtained at the Sloan–Kettering Institute and at the Stamford Research Laboratories of the American Cyanamid Co. using Perkin–Elmer instruments with either galvanometer or electronic systems of automatic recording; both sodium chloride and lithium fluoride prisms were employed.

Because of the correlations for the carbonyl groups, the region between 1660 and 1780 cm.$^{-1}$ was subjected to special study at the Sloan–Kettering Institute. The positions of the absorption maxima in the carbonyl region were obtained directly by measurement of the displacement of the bands from the water vapor absorption bands at 1830 and 1637 cm.$^{-1}$ which appeared on every curve and were used as external standards of frequency. The estimated accuracy of the frequency measurements in this region is ± 3 cm.$^{-1}$. Most of the measurements were made in a cell of approximately 1 mm. thickness, although a 3 mm. cell was also used in certain instances. The solutions were made up to an initial concentration of 10 mg. per ml. and then diluted so as to obtain an absorption of about 50–75% in the region of the maximum. Under these conditions no appreciable error in the position of the maximum is caused by the slope of the background radiation over the width of the band.

Acknowledgments.—The authors wish to express their indebtedness to the several investigators, listed individually in a footnote to Table I, whose collaboration in supplying many of the compounds made these studies possible. The help of L. D. Marinelli, Sloan-Kettering Institute, with certain problems of instrumentation and the technical assistance of P. Humphries is gratefully acknowledged. This investigation was aided by grants from the American Cancer Society (on recommendation of the Committee on Growth of the National Research Council), Ayerst, McKenna and Harrison, Ltd., the Jane Coffin Childs Memorial Fund for Medical Research, the Commonwealth Fund, the Anna Fuller Fund, the Lillia Babbitt Hyde Foundation, International Cellucotton Products Company, the Albert and Mary Lasker Foundation, the Adele R. Levy Fund, the National Cancer Institute of the National Institute of Health, U. S. Public Health Service, the New York Foundation, and the Sidney Rheinstein Fund.

Summary

A comparative study has been made of the infrared absorption spectra of one hundred and thirty steroids in solution in carbon disulfide, or chloroform. Particular attention has been given to the region between 1660 and 1780 cm.$^{-1}$ where prominent absorption bands occur which are associated with the presence of carbonyl groups in the molecule. The exact location of the maxima of these bands can be employed to locate the position of the carbonyl group in ketosteroids and to distinguish conjugated from non-conjugated ketosteroids. Absorption bands in other regions of the spectrum associated with the presence of ethylenic double bonds and hydroxyl groups have been similarly investigated.

OTTAWA, CANADA RECEIVED SEPTEMBER 12, 1947

[CONTRIBUTION FROM THE HAYDEN MEMORIAL LABORATORIES OF NORTHEASTERN UNIVERSITY]

The Solubility of Tetraethylammonium Iodide in Benzene–Ethylene Dichloride Mixtures

BY ARTHUR A. VERNON AND JOHN L. SHEARD[1a]

Introduction

As part of the program to study solubility effects in solvents of low dielectric constant, it was decided to determine the effect of dielectric constant on the solubility of tetraethylammonium iodide. Investigation has shown that in solvents of dielectric constant higher than ten the single ion concentration is high enough so that within certain limits a common-ion effect can be observed. To study the effect in liquids with lower dielectric constant, the system benzene–ethylene dichloride is useful: data for this have been published by Vernon, Wyman and Avery.[1] Tetraethylammonium iodide was selected for the solute since it has a reasonable solubility in ethylene dichloride.

Experimental

Materials.—C. P. thiophene-free benzene, after standing for several days over anhydrous calcium chloride, was distilled from activated alumina, the first and last fifth portions being discarded. The refractive index was 1.4978 at 25.2°; the "International Critical Tables" value is 1.49779 at 25.2°.

Ethylene dichloride was dried over anhydrous calcium chloride to an index of refraction of 1.4422 at 25.2° as compared with the "International Critical Tables" value of 1.44225 at 25.2°.

Tetraethylammonium iodide was prepared by mixing equimolar quantities of ethyl iodide (Merck) and triethylamine (Eastman Kodak Co.) and allowing to stand overnight. The crude product was dried, washed with petroleum ether, dissolved in boiling 95% ethyl alcohol, and treated with alcoholic potassium hydroxide until pink to phenolphthalein. The mixture was then cooled in an ice-bath, the solid filtered off and recrystallized twice from 95% ethyl alcohol. Finally, the pure product was dried in a vacuum desiccator. Since decomposition of the pure solid occurred at 280°, no melting point could be obtained; the analysis of the material for iodine gave 49.61% as compared with the theoretical iodine per cent. of 49.63.

Procedure.—Excess solute was added to 600 cc. of a benzene–ethylene dichloride mixture in a bottle with a ground glass cap which was wired on and coated with paraffin. The bottles were rotated in a water-bath at 35° for twenty-four hours and then at 25 ± 0.02° long enough to establish equilibrium. For the 93.5% ethylene dichloride, rotation at 25° for one hundred and twenty hours gave essentially the same solubility as rotation for twenty-four hours at 35° followed by seventy-two hours at 25°.

After the required rotation time, the bottles and a calibrated 500-cc. volumetric flask were supported in the water-bath at 25 ± 0.02°. The solution, after settling, was forced out by dry air through a glass wool filter into a volumetric flask. Then the solution was poured into a beaker and the flask was washed out with 95% ethyl alcohol, the wash solution being added to the benzene–ethylene dichloride solution. Silver iodide was precipitated by adding excess silver nitrate solution, stirred for five minutes, allowed to settle four hours in the dark, filtered into a Gooch crucible, and dried at 120° to constant weight. This method applied to known amounts of solute was shown to be consistently accurate to within 1.9%.

Results

The solubility results given in Table I are the averages of two or more determinations as shown.

TABLE I

SOLUBILITY OF TETRAETHYLAMMONIUM IODIDE IN ETHYLENE DICHLORIDE–BENZENE MIXTURES AT 25°

Ethylene dichloride, %	Dielectric constant	No. of detns.	Moles per liter of iodide × 10^4
35.5	3.85	4	0.865 ± 0.009
48.0	4.55	3	2.18 ± .02
56.6	5.20	6	3.80 ± .04
68.0	6.07	5	8.51 ± .08
80.0	7.26	2	18.06 ± .14
85.0	8.01	2	30.6 ± .3
93.5	9.02	4	55.6 ± .3
100.0	10.36	5	91.9 ± .2

The average deviation of the individual determinations from the mean is no greater than 1.05% for any solvent mixture. Figure 1 shows a plot of the log of solubility against the log of the dielectric constant.

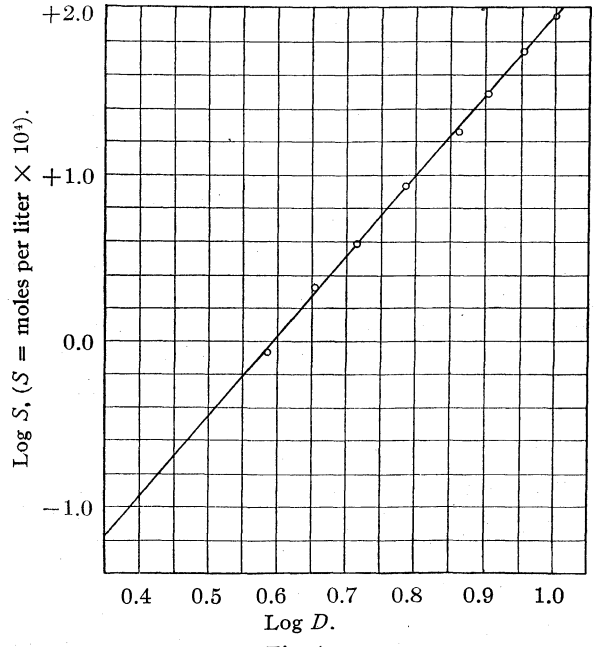


Fig. 1.

Discussion

Tucker and Kraus[2] studied the conductivity of tetraethylammonium picrate in ethylene dichloride at 25° and found that triple ion formation became important at $3.4 \times 10^{-4} N$. Luder, Kraus, Kraus and Fuoss[3] found this effect to be significant

(1a) Present address: University of Minnesota, Minneapolis, Minnesota.

(1) Vernon, Wyman and Avery, THIS JOURNAL, **67**, 1422 (1945).

(2) Tucker and Kraus, *ibid.*, **69**, 454 (1947).

(3) Luder, Kraus, Kraus and Fuoss, *ibid.*, **58**, 255 (1946).

at 1×10^{-5} N for tetrabutylammonium perchlorate in benzene at 25°. For tetraethylammonium iodide the triple ion formation should take place at a lower concentration than for the above reported salts since such an effect increases with decrease in ion size. The solubilities here reported are of the order of 10^{-2} N in pure ethylene dichloride and 10^{-4} N in 35.5% ethylene chloride. Therefore, it seems likely that multiple ion formation exists in all the solutions studied; straight line extrapolation to pure benzene is justified if such conditions continue to exist down to a dielectric constant of 2.274. Extrapolation of Fig. 1 gives a solubility of 6.918×10^{-6} mole per liter for the solubility of tetraethylammonium iodide in benzene at 25°. At this solubility, triple ions may reasonably be expected to exist. Further evidence of ion association would be obtainable from studies of the effect of a common ion upon the solubilities reported in this paper. It is planned to study this as well as the solubility relation in solvents of higher dielectric constant.

Ricci and Davis[4] proposed an empirical equation to relate solubility to dielectric constant of the solvent which showed that a plot of log S against log D should be a straight line with a slope of three. This equation assumed that the Debye–Hückel limiting law applied and that the activity coefficient of an electrolyte at saturation is a constant independent of the dielectric constant of the solvent medium. They further showed that approximate equality of activity coefficients could be expected between solvent dielectric constants of 80 and 40. This, together with the evidence of triple ion formation, seems to indicate that a slope of 3 should not be expected with our data. The explanation of the slope of 5 of Fig. 1 will have to wait until more data are available.

The dielectric constant of benzene is 2.274 and $\log D = 0.3568$. By extrapolation of Fig. 1, assuming a straight line relation, a value of log S of -1.160 is obtained. This gives 6.918×10^{-6} mole per liter for the solubility of tetraethylammonium iodide in benzene at 25°.

(4) Ricci and Davis, THIS JOURNAL, **62**, 407 (1940).

Summary

The solubility of tetraethylammonium iodide in pure ethylene dichloride and ethylene dichloride–benzene mixtures has been determined. A plot of log S *versus* log D follows closely a straight line with a slope of 5 in contrast to the value of 3 found in solvents with higher dielectric constant.

BOSTON, MASSACHUSETTS RECEIVED OCTOBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF SANITARY ENGINEERING, HARVARD GRADUATE SCHOOL OF ENGINEERING]

Equilibrium Studies on N-Chloro Compounds. I. The Ionization Constant of N-Chloro-*p*-toluenesulfonamide[1]

BY J. CARRELL MORRIS, J. ALFREDO SALAZAR[2] AND MARGARET A. WINEMAN

The N-chloro compounds, those substances in which it may be considered that one or more chlorine atoms in the +1 oxidation state are bound to nitrogen, are of considerable interest because of the widespread use of a number of them as disinfecting agents. In many cases it is believed that their efficiencies as disinfecting agents are related to the magnitudes of their hydrolytic and other equilibrium reactions in water solution, but quantitative data on the equilibria with which disinfection results might be compared are available for only one or two isolated systems. The present series of papers is therefore concerned with the quantitative evaluation of equilibrium relationships for water solutions of certain important N-chloro compounds and with the use of the equilibrium constants so determined for predicting the disinfectant power of solutions of the N-chloro compounds under various conditions.

The system selected for primary study was that in which the substances Dichloramine-T, and Chloramine-T are participants. These two substances are, respectively, N,N-dichloro-*p*-toluenesulfonamide (I) and sodium N-chloro-*p*-toluenesulfonamide, the latter being the sodium salt of N-chloro-*p*-toluenesulfonamide (II). A number of equilibria are established in solutions of these materials, which can be described most conveniently in terms of the following processes:

I. The hydrolysis equilibrium for Dichloramine-T

$$\underset{(I)}{C_7H_7SO_2NCl_2} + H_2O = \underset{(II)}{C_7H_7SO_2NHCl} + HOCl \quad (1)$$

for which the equilibrium constant equation is[3]

$$K_h = \frac{(HOCl)(C_7H_7SO_2NHCl)}{(C_7H_7SO_2NCl_2)} \quad (1a)$$

II. The exchange or disproportionation reaction

$$2\underset{(II)}{C_7H_7SO_2NHCl} = \underset{(I)}{C_7H_7SO_2NCl_2} + C_7H_7SO_2NH_2 \quad (2)$$

(1) This work was carried out under a research contract with the Office of the Quartermaster General, U. S. Army.

(2) Now with the West Virginia State Department of Health, Charleston, W. Va.

(3) In all of the equations of this paper parentheses, except when they are used just to set off mathematical terms, indicate molar activities of the substances concerned and square brackets indicate molar concentrations. For non-ionic substances the two are assumed to be the same within the experimental accuracy of the determinations.

with the equilibrium constant equation

$$K_d = \frac{(C_7H_7SO_2NCl_2)(C_7H_7SO_2NH_2)}{(C_7H_7SO_2NHCl)^2} \quad (2a)$$

III. The ionization of the hypochlorous acid produced in equation (1)

$$HOCl = H^+ + OCl^- \quad (3)$$

for which

$$K_1 = \frac{(H^+)(OCl^-)}{(HOCl)} \quad (3a)$$

IV. The ionization of N-chloro-*p*-toluenesulfonamide

$$C_7H_7SO_2NHCl = H^+ + C_7H_7SO_2NCl^- \quad (4)$$

giving an ionization constant

$$K_2 = \frac{(H^+)(C_7H_7SO_2NCl^-)}{(C_7H_7SO_2NHCl)} \quad (4a)$$

A fifth reaction, the acid ionization of $C_7H_7SO_2NH_2$ occurs under some conditions, and must eventually be included for a complete depiction of the system. However, preliminary studies indicate that the ionization constant is so small, perhaps 10^{-10}, that this reaction is a measurable factor only above *p*H 9. Other possible pertinent reactions, such as the hydrolysis of $C_7H_7SO_2NHCl$, need not be included, for they can be obtained by appropriate combination of the listed reactions.

The first two of these equilibria have been studied quantitatively by Soper.[4] By measuring the apparent solubility of Dichloramine-T[5] in 0.001 M H_2SO_4, by itself and in the presence of a known large excess of hypochlorous acid to repress the hydrolysis, he was able to calculate a value of 8.0×10^{-7} for K_h. The disproportionation constant, K_d, was evaluated, with the aid of the value for K_h, by measuring the apparent solubility of Dichloramine-T in 0.001 M sulfuric acid solutions containing known added amounts of *p*-toluenesulfonamide to displace reaction (2) to the left. These latter measurements have been repeated in connection with the present research and results in good agreement with the values given by Soper have been obtained. A combined average of the two sets of data yields $K_d = 6.1 \times 10^{-2}$.

The ionization constant for hypochlorous acid has been the subject of a number of studies which give as a probable best value $K_1 = 3.3 \times 10^{-8}$ at 25°.[6] The magnitude of this value is such that the ionization of hypochlorous acid did not occur to a measurable extent under the conditions of the present study, but it is concerned in the application of the results to disinfecting problems.

Although the compound $C_7H_7SO_2NHCl$ has not been isolated, its existence was demonstrated in Soper's studies and it is known that it must be a fairly strong acid because its sodium salt, Chloramine-T, gives only slightly basic solutions in water. However, no quantitative studies of the ionization constant have been reported. The simultaneous occurrence of the other listed equilibria and particularly of the disproportionation equilibrium introduces complicating factors into the standard procedures for determining ionization constants. In the present study these difficulties have been taken care of by appropriate mathematical treatment and the ionization constant has been determined in two ways: by measurement of the apparent solubility of Dichloramine-T in solutions buffered to *p*H 4.5 and containing known added amounts of *p*-toluenesulfonamide, and by potentiometric titration of solutions of Chloramine-T with standard hydrochloric acid.

Experimental

Reagents.—Purified Chloramine-T, furnished by the Monsanto Chemical Company, was recrystallized from distilled water under such conditions that only about 25% yield was obtained. The product was filtered with suction through a sintered-glass funnel and was dried at room temperature in a vacuum desiccator. The resulting product was the trihydrate, $NaC_7H_7SO_2NCl \cdot 3H_2O$, and was found to contain 12.56% Cl, the theoretical value being 12.58%.

Dichloramine-T was prepared by passing gaseous chlorine into water solutions of purified Chloramine-T and filtering out the precipitated Dichloramine-T with suction through a sintered-glass funnel. The material thus obtained was resuspended in a dilute chlorine solution (about 5 p. p. m.) agitated overnight and refiltered; this process was repeated two or three times to ensure complete removal of incompletely chlorinated products. After the final filtration the moist product was used for the solubility studies without drying.

The *p*-toluenesulfonamide was an Eastman Kodak Co. product, which was recrystallized from glacial acetic acid, filtered with suction through a sintered-glass funnel, washed several times with small quantities of cold water to remove adherent acetic acid and then dried in a vacuum desiccator over sulfuric acid. The recrystallized compound had a melting point of 137.0–137.5°.

Solubility Studies.—Samples of Dichloramine-T weighing 1–2 g. (several times the amount required for saturation) were placed in 500-ml. glass-stoppered Pyrex bottles and the bottles were then filled approximately three-quarters full with conductivity water. To these solutions were then added the desired amounts of *p*-toluenesulfonamide and either sufficient sulfuric acid to make the solutions 0.001 M in that reagent or a sufficient quantity of an equimolar solution of acetic acid and sodium acetate to give about 0.05 M concentration of each substance. The bottles were then stoppered and placed in a rotating frame in a constant-temperature water-bath held at 25.0 ± 0.2°. The rotation of the frame caused the bottles to be inverted about four times a minute. Samples were taken from the bottles at six to eight hour intervals by pressure filtration through a microfilter stick and were analyzed for their concentrations of oxidizing chlorine. The shaking and sampling procedures were continued until constant values for the apparent solubility of the Dichloramine-T were obtained. Constancy within the precision of the analytical determinations was generally obtained after about twenty-four hours of shaking and was maintained for at least forty-eight hours longer. Analyses for oxidizing chlorine were conducted by adding excess potassium iodide to the sample and titrating with 0.01 N sodium thiosulfate.

(4) Soper, *J. Chem. Soc.*, **125**, 1899 (1924).

(5) The "apparent solubility of Dichloramine-T" is evaluated by determining that oxidizing chlorine in solutions in equilibrium with solid Dichloramine-T which is attributable to dissolved Dichloramine-T itself or which, existing in other forms, has been produced from Dichloramine-T by any of the previously listed reactions.

(6) See, for example, Ingham and Morrison, *J. Chem. Soc.*, 1200 (1933), and Hagisawa, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **19**, 1220 (1940). A complete summary of the data on this ionization constant is given in Final Report, Contract OEMcmr-251, Disinfection of Water and Related Substances, Dec. 31, 1945.

Titration Studies.—For these determinations accurately weighed samples of recrystallized Chloramine-T were dissolved in conductivity water to make solutions ranging in concentration from 0.01 to 0.08 *M*. The solutions were then titrated potentiometrically with 0.5 *N* hydrochloric acid, the *p*H after each addition being measured by means of a Beckman Model G *p*H meter equipped with glass and saturated calomel electrodes. The meter and electrodes were calibrated before and after each titration against solutions of potassium acid phthalate and of phosphate buffer mixture prepared from Bureau of Standards salts according to their directions. Since these calibrations checked within 0.02 *p*H unit, it is believed that *p*H measurements during the course of the titration were accurate to a similar figure. The amounts of hydrochloric acid added were measured with a calibrated 10-ml. Exax buret, so that volumes could be measured with a precision of 0.01 ml. The necessity for refilling the buret for volume readings greater than 10 ml. made the measurement of the larger volumes less precise, but this did not affect the experimental results since the factor limiting the accuracy of the results for all volume measurements greater than a few ml. was the determination of the *p*H.

Because of the slight solubility of Dichloramine-T in water, precipitation of this substance occurred during the titrations, the first permanent precipitate appearing after the addition of 1–2 ml. of hydrochloric acid. When additional amounts of hydrochloric acid were added to solutions containing the precipitate, particularly in those instances in which only a small amount of precipitate was present, the *p*H showed an initial decrease greater than expected and a following slow increase for a period as long as ten minutes before stabilization resulted. The total amount of this shift was generally about 0.1 *p*H unit. It is believed to have been caused by a temporary supersaturation of the solution with Dichloramine-T upon the addition of the hydrochloric acid followed by a slow precipitation to equilibrium saturation conditions. As the amount of precipitate in the solution increased, the time for stabilization decreased until at the equivalence point it was complete in less than a minute. In the range in which this phenomenon was exhibited *p*H readings were not recorded until equilibrium conditions had been attained and the *p*H readings were constant for several minutes.

An example of the curves obtained showing the typical features of the titrations is shown in Fig. 1. Section A of the curve shows the region in which the solution was not yet saturated with Dichloramine-T and was therefore clear. At the point corresponding to the addition of 1 ml. of hydrochloric acid a break in the curve is noted, coincident with the appearance of a precipitate of Dichloramine-T. The next three points, shown as section B, presumably correspond to a region of supersaturation with Dichloramine-T in which the supersaturation was being relieved so slowly that no drift in the *p*H values was observed. At the point corresponding to the addition of 2 ml. of hydrochloric acid a second break occurs, this being the first point for which the previously discussed shift in *p*H with time was observed. For the region beyond this, section C, the recorded points represent the *p*H readings obtained after stable conditions in the solution were attained and are assumed to correspond to an equilibrium saturation state for the Dichloramine-T present.

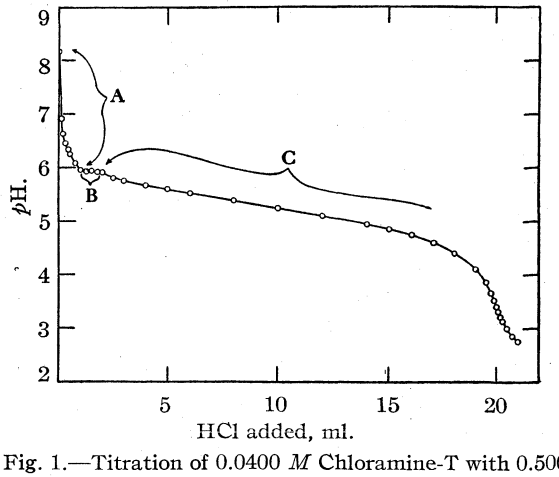


Fig. 1.—Titration of 0.0400 *M* Chloramine-T with 0.500 *M* HCl. Volume of solution 250 ml.: A, region with no precipitate, solution unsaturated with Dichloramine-T; B, region of supersaturation with Dichloramine-T; C, region with precipitate of Dichloramine-T in equilibrium with saturated solution.

The most concentrated solution titrated, 0.08 *M*, showed a fourth section just before the equivalence point. It was possible to calculate that in this region a large enough quantity of *p*-toluenesulfonamide had been produced to exceed its solubility, so that in this range both Dichloramine-T and *p*-toluenesulfonamide were being precipitated by the addition of further hydrochloric acid. This section was not used for any of the calculations.

Theory and Results

Solubility Studies.—In sufficiently acid solutions (0.002 *N*) of Dichloramine-T only the equilibria represented by reactions (1) and (2) are analytically significant, for the ionization of the weakly acidic compounds, hypochlorous acid and $C_7H_7SO_2NHCl$ is substantially completely repressed. Under these conditions the equivalents of oxidizing or "titratable" chlorine per liter, T_a, in the solution can be represented by the equation

$$T_a = 2[HOCl] + 2[C_7H_7SO_2NHCl] + 4[C_7H_7SO_2NCl_2] \quad (5)$$

When the concentration of titratable chlorine in acid solutions in equilibrium with an excess of solid Dichloramine-T, to which various amounts of *p*-toluenesulfonamide have been added, is measured, T_a is found to increase with increase in the concentration of added *p*-toluenesulfonamide because of the displacement of reaction (2) to the left. The accompanying decrease in the Dichloramine-T concentration is compensated for by additional solution of solid Dichloramine-T. On the assumption that the activity of the dissolved Dichloramine-T and hence its true solubility is constant regardless of the presence of the other dissolved substances and with a knowledge of the hydrolysis constant, K_h, it is possible to evaluate the disproportionation constant, K_d, from the increase in the titratable chlorine of the saturated solutions with increase of added *p*-toluenesulfonamide. This is the procedure which was followed by Soper.[4]

If the acidity at which these studies are carried out is changed to a *p*H of 4 to 5, the titratable chlorine level in the solution is further measurably increased over that obtained for the same concentration of added *p*-toluenesulfonamide in the more acid solutions because of the ionization of $C_7H_7SO_2NHCl$, which displaces reaction (2) even more to the left. At *p*H values less than 5 the ionization of hypochlorous acid is still not a factor. For solutions at *p*H 4 to 5 the equation for the

equivalents of oxidizing chlorine in the saturated solutions becomes

$$T_b = 2[HOCl] + 2[C_7H_7SO_2NHCl] + 2[C_7H_7SO_2NCl^-] + 4[C_7H_7SO_2NCl_2] \quad (6)$$

Since the concentration of hypochlorous acid is negligibly small for solutions in which the added *p*-toluenesulfonamide is 0.001 *M* or greater, and since the concentration of dissolved $C_7H_7SO_2NCl_2$ may be considered to be constant, equations (5) and (6) may be reduced to the forms

$$T_a = T_2 + 2[C_7H_7SO_2NHCl] \quad (7)$$

$$T_b = T_2 + 2[C_7H_7SO_2NHCl] + 2[C_7H_7SO_2NCl^-] \quad (8)$$

where T_2 is the saturation concentration of $C_7H_7SO_2NCl_2$ in equivalents per liter, determined by Soper to be 0.310×10^{-3}. Now if equations (7) and (8) be taken to apply to solutions to which the same number of moles, N, of *p*-toluenesulfonamide have been added per liter of solution, then the expressions for K_d for the two conditions may be written

$$K_d = \frac{(C_7H_7SO_2NHCl)^2}{(C_7H_7SO_2NCl_2)(C_7H_7SO_2NH_2)} = \frac{(T_a - T_2)^2}{T_2\left(N - \frac{T_a - T_2}{4}\right)} = \frac{(T_b - T_2 - 2[C_7H_7SO_2NCl^-])^2}{T_2\left(N - \frac{T_b - T_2}{4}\right)}$$

the second term in the denominator of each expression being derived from the stoichiometry of reaction (2). Solution of these expressions for the concentration of $C_7H_7SO_2NCl^-$ yields the equation

$$[C_7H_7SO_2NCl^-] = \frac{T_b - T_2}{2}\left(1 - \frac{T_a - T_2}{T_b - T_2}\sqrt{\frac{4N - T_b + T_2}{4N - T_a + T_2}}\right) \quad (9)$$

The ionization constant for $C_7H_7SO_2NHCl$ expressed in terms of the concentration of $C_7H_7SO_2NCl^-$ and the measured properties of the saturated buffer solutions is given by the following expression derived from equations (4a) and (8)

$$K_2 = \frac{(H^+)[C_7H_7SO_2NCl^-]f}{\frac{1}{2}(T_b - T_2 - 2[C_7H_7SO_2NCl^-])}$$

where f is the activity coefficient of the $C_7H_7SO_2NCl^-$ in the buffer solution. Substitution of equation (9) and simplification lead to the equation

$$K_2/f = (H^+)\left(\frac{T_b - T_2}{T_a - T_2}\sqrt{\frac{4N - T_a + T_2}{4N - T_b + T_2}} - 1\right) \quad (10)$$

Data obtained in the solubility studies and values of the term, K_2/f, calculated from them by means of equation (10) are shown in Table I. The ionic strength in these experiments, made up of the buffer ions and the ions produced in the reactions, was about 0.06.

Titration Studies.—If to a solution of $NaC_7H_7SO_2NCl$ of molar concentration B, is added a quantity of hydrochloric acid equivalent to a molar concentration A, both terms including a correction for the diluting effect of the added hydrochloric acid, then a simple application of equation (4) would indicate that the concentration of $C_7H_7SO_2NHCl$ formed is $A - [H^+]$, and that the remaining concentration of $C_7H_7SO_2NCl^-$ is $B - A + [H^+]$, where $[H^+]$ is the measured concentration of hydrogen ions in the solution after the addition of the acid. Then by substitution of these quantities in the ionization constant equation, the constant might be calculated. Actually, because the $C_7H_7SO_2NHCl$ formed undergoes further reaction according to equation (2), this procedure overestimates the concentration of that substance and gives an apparent ionization constant considerably smaller than the true one. Two sets of calculations are necessary to correct for this additional reaction, one for the early part of the titration in which the solution is not saturated with respect to Dichloramine-T formed by reaction (2) and one for the later part in which the precipitation of Dichloramine-T has caused a further shift of reaction (2) to the right.

TABLE I

DETERMINATION OF THE IONIZATION CONSTANT FOR $C_7H_7SO_2NHCl$ FROM THE APPARENT SOLUBILITY OF DICHLORAMINE-T IN BUFFERED *p*-TOLUENESULFONAMIDE SOLUTIONS AT 25°

Added sulfonamide, moles/l. $\times 10^3$	Saturation concentration, of oxidizing chlorine, equiv./l. $\times 10^3$ in 0.001 *M* $H_2SO_4 = T_a$	in acetate buffer $= T_b$	*p*H of buffer solution	$K_2/f \times 10^5$
1.00	1.97	3.27	4.52	5.06
2.00	2.90	5.03	4.54	3.84
5.00	4.70	9.22	4.51	4.35
8.00	6.17	11.66	4.50	3.73
10.00	6.89	12.99	4.51	3.49
15.00	8.70	16.90	4.48	3.82

Average, excluding first value, 3.85

A. Region with no Precipitate of Dichloramine-T.—The term $A - (H^+)$ still represents the concentration of added acid which has reacted and so $B - A + [H^+]$ is still equal to the remaining concentration of $C_7H_7SO_2NCl^-$. However, $A - [H^+]$ is equal to the sum of the concentrations of the $C_7H_7SO_2NHCl$ and its subsequent reaction products. This may be expressed by the equation

$$A - [H^+] = [C_7H_7SO_2NHCl] + 2[C_7H_7SO_2NCl_2] \quad (11)$$

Since the concentrations of $C_7H_7SO_2NCl_2$ and $C_7H_7SO_2NH_2$ formed by reaction (2) are equal, the equilibrium constant for the reaction may be written in the form

$$K_d = \frac{[C_7H_7SO_2NCl_2]^2}{[C_7H_7SO_2NHCl]^2} \quad (12)$$

from which

$$[C_7H_7SO_2NCl_2] = \sqrt{K_d}[C_7H_7SO_2NHCl] \quad (13)$$

Substitution in equation (11) and solution for the concentration of $C_7H_7SO_2NHCl$ gives

$$[C_7H_7SO_2NHCl] = \frac{A - [H^+]}{1 + 2\sqrt{K_d}} \quad (14)$$

This and the expression for the concentration of $C_7H_7SO_2NCl^-$, $B - A + [H^+]$, substituted in the ionization equation (4a) yield

$$K_2 = (1 + 2\sqrt{K_d}) \frac{(H^+)(B - A + [H^+])f}{A - [H^+]} \quad (15)$$

which, upon substitution of the value 0.061 for K_d, reduces to

$$K_2/f = 1.494 \frac{(H^+)(B - A + [H^+])}{A - [H^+]} \quad (16)$$

B. Region of Saturation with Dichloramine-T.—As soon as Dichloramine-T begins to precipitate, equations (11) and (12) are no longer true in terms of the dissolved Dichloramine-T concentration. However, the $C_7H_7SO_2NCl_2$ term in equation (11) may be replaced by $C_7H_7SO_2NH_2$, since this latter substance remains in solution, to give the modified equation

$$A - [H^+] = [C_7H_7SO_2NHCl] + 2[C_7H_7SO_2NH_2] \quad (17)$$

Also, since the concentration of dissolved $C_7H_7SO_2NCl_2$ can now be considered constant at its molar solubility value, S, the disproportionation equation takes the form

$$K_d = \frac{[C_7H_7SO_2NH_2]S}{[C_7H_7SO_2NHCl]^2} \quad (18)$$

Solution of equations (17) and (18) for the concentration of $C_7H_7SO_2NHCl$ gives

$$[C_7H_7SO_2NHCl] = \frac{S}{4K_d}\left[\left(\frac{8K_d(A - [H^+])}{S} + 1\right)^{1/2} - 1\right] \quad (19)$$

Substitution of this expression and of $B - A + [H^+]$ for $[C_7H_7SO_2NCl^-]$ in the ionization constant equation (4a) gives

$$K_2/f = \frac{4K_d}{S} \frac{(H^+)(B - A + [H^+])}{\left(\frac{8K_d}{S}(A - [H^+]) + 1\right)^{1/2} - 1} \quad (20)$$

Upon substitution of the numerical values, $K_d = 0.061$ and $S = 0.775 \times 10^{-4}$, equation (20) reduces to

$$K_2/f = \frac{3150(H^+)(B - A + [H^+])}{(6300(A - [H^+]) + 1)^{1/2} - 1} \quad (21)$$

A typical example of the results obtained is shown in Table II, which gives the data obtained for a titration of 0.02 M Chloramine-T with 0.5 M hydrochloric acid, together with the ionization constants calculated from the data by means of equations (16) and (21) for the regions to which each is applicable. Table III presents a summary of the average ionization constants determined from this and the other titrations which were carried out. It is apparent from Table II that the calculated values of K_2/f showed a good constancy during the course of a titration and that satisfactory agreement between the constants for the region without precipitation and that with precipitation was obtained. The values calculated for the period before the beginning of precipitation are probably less reliable because of the greater errors involved in the measurement of the small amounts of acid added and also because the presence of very small amounts of acid or basic impurity in the Chloramine-T would have had a much more pronounced effect on the data in this region than in the later stages of the titration. On the other hand, because of the possible uncertainty as to the attainment of a constant equilibrium saturation concentration of Dichloramine-T during the latter part of the titrations, it is reassuring to have the values obtained for the initial additions of HCl check the later ones so well.

TABLE II

TITRATION OF 0.02 M CHLORAMINE-T WITH HYDROCHLORIC ACID

500 ml. of 0.02000 M Chloramine-T titrated with 0.5000 N HCl; activity coefficient for H^+ in solution taken as 0.95

HCl added, ml.	pH	Concn. of added acid, A moles/l. $\times 10^{3a}$	$A - [H^+] \times 10^3$	Unreacted $C_7H_7SO_2NCl^-$, $B - A + [H^+] \times 10^{3a}$	$K_2/f \times 10^5$
A. No precipitate; equation 16 used for calculations					
0.00	7.68	0.000	0.000	20.00	..
.10	6.81	.100	.100	19.90	4.62[b]
.25	6.48	.250	.250	19.74	3.91[b]
.50	6.23	.500	.499	19.48	3.43
.75	6.04	.749	.748	19.22	3.50
1.00	5.92	.998	.997	18.96	3.41
1.25	5.82	1.247	1.245	18.70	3.39
1.50	5.73	1.496	1.494	18.45	3.43
2.00	5.61	1.992	1.989	17.93	3.31
B. Dichloramine-T precipitated, but not in equilibrium					
3.00	5.49	2.982	2.979	16.90	..
C. Solution saturated with Dichloramine-T; equation 21 used for calculations					
4.00	5.52	3.968	3.965	15.87	3.68
5.00	5.48	4.950	4.947	14.85	3.31
7.00	5.30	6.900	6.895	12.82	3.57
9.00	5.16	8.845	8.838	10.81	3.61
11.00	5.04	10.76	10.75	8.82	3.47
13.00	4.89	12.67	12.66	6.83	3.47
15.00	4.70	14.57	14.55	4.87	3.55
17.00	4.50	16.44	16.41	2.93	3.16
18.00	4.31	17.38	17.33	1.98	3.22
19.00	4.02	18.31	18.21	1.06	3.27
19.50	3.79	18.77	18.60	0.65	3.36
19.75	3.66	19.00	18.77	.47	3.27[c]
20.00	3.48	19.23	18.88	.35	3.66[c]
20.25	3.33	19.46	18.97	.25	3.69[c]
20.50	3.19	19.69	19.01	.20	4.07[c]
21.00	2.98	20.15	19.04	.15	4.96[c]
				Averages A	3.41
				C	3.42

[a] Corrected for dilution of sample by added hydrochloric acid. [b] Omitted from average because of lack of precision in volume of hydrochloric acid. [c] Omitted from average because of lack of precision in $B - A + [H^+]$ term.

In computing the term, $A - [H^+]$, it was necessary to convert the hydrogen ion activities calcu-

TABLE III

SUMMARY OF IONIZATION CONSTANT VALUES FOR N-CHLORO-*p*-TOLUENESULFONAMIDE OBTAINED BY TITRATION OF CHLORAMINE-T SOLUTIONS

Molar concn. of chloramine-T[a]	Section of titration curve and equation used	Average $K_2/f \times 10^5$	$-\log K_2/f$, pK_2'
0.01	A, equation 16	3.28	4.48
.01	C, equation 21	3.15	4.50
.02	A, equation 16	3.41	4.47
.02	C, equation 21	3.42	4.47
.04	A, equation 16	3.33	4.48
.04	C, equation 21	3.42	4.47
.08	A, equation 16	3.27	4.49
.08	C, equation 21	3.86	4.41

[a] This term also represents the ionic strength, μ, at which the titration was carried out.

lated from the *p*H measurements by the equation $p\mathrm{H} = -\log(\mathrm{H}^+)$ to hydrogen ion concentrations. The activity coefficients used for this purpose were taken from the chart of individual ion activities given by Chapin and Steiner.[7] The application of these corrections or the exact value of the activity coefficient used for them made very little difference over the greater part of the titration, but by including them it was possible to calculate consistent values for the ionization constant up to and even past the equivalence point.

In Fig. 2 a plot of the negative logarithms of K_2/f, pK_2' values, obtained in the various experiments against the square roots of the ionic strengths at which the experiments were conducted is shown, the circles having been drawn with radii corresponding to an error of 0.02 unit in *p*H measurement. The extrapolation line drawn through the points has a slope of 0.5, corresponding to that given by the simple Debye–Hückel expression in the form $pK_2 = pK_2' - 0.5\sqrt{\mu}$.

(7) Chapin and Steiner, "Second Year College Chemistry," John Wiley and Sons, Inc., New York, N. Y., 5th edition, 1947, pp. 390–393.

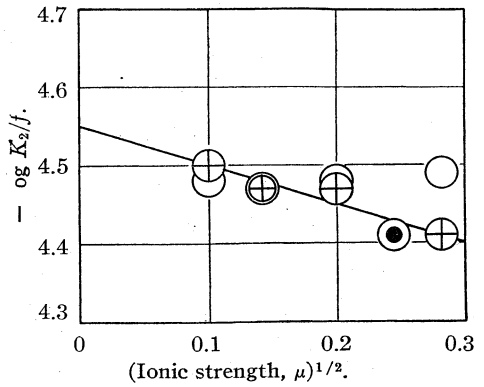


Fig. 2.—Variation of experimental ionization constants for $C_7H_7SO_2NHCl$ with ionic strength: O, titration values for solutions unsaturated with Dichloramine-T; ⊕, titration values for solutions containing precipitate of Dichloramine-T; ◉, value from solubility studies. Line corresponds to equation $-\log f = 0.5\sqrt{\mu}$.

The value of pK_2 determined from the extrapolation is 4.55 ± 0.02. This leads to a value for K_2, the activity ionization constant of $C_7H_7SO_2NHCl$, of $2.8 \pm 0.2 \times 10^{-5}$.

Summary

The ionization constant for N-chloro-*p*-toluenesulfonamide has been determined by potentiometric titration of solutions of Chloramine-T with acid and by measurement of the solubility of Dichloramine-T in solutions at *p*H 4.5 containing added quantities of *p*-toluenesulfonamide. Suitable mathematical equations have been developed to overcome the complications caused by the simultaneous occurrence of other equilibrium processes along with the ionization equilibrium.

The value obtained for the activity ionization constant of $C_7H_7SO_2NHCl$ at 25° is $K_2 = 2.8 \pm 0.2 \times 10^{-5}$, corresponding to $pK_2 = 4.55 \pm 0.002$.

CAMBRIDGE, MASS. RECEIVED DECEMBER 19, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Salts of an Aquoammonomolybdic Acid[1,2]

BY GEORGE W. WATT AND DARWIN D. DAVIES

In 1906, Rosenheim and Jacobsohn[3] prepared molybdenum(VI) oxide 3-ammonate by the interaction of the oxide and liquid ammonia. They considered the compound to be the diammonium salt of "imidomolybdic acid" and attempted to convert it to a lead(II) salt by reaction with lead(II) iodide in liquid ammonia at 108–109°, but their results were inconclusive.

In terms of Franklin's nitrogen system of compounds,[4] molybdenum(VI) oxide 3-ammonate may be looked upon as a salt of a mixed aquoammonomolybdic acid. As such, this acid salt should be unreactive toward liquid ammonia solutions of ammonium salts (acids in liquid ammonia), but in the same medium should react, for example, with potassium amide (a base in liquid ammonia) to form a tripotassium salt which in turn should be convertible by metathesis to other

(1) This work was supported in part by grants from The University Research Institute, Project No. 25.

(2) Presented at the first Southwestern Regional Meeting of The American Chemical Society, Austin, Texas, December 7, 1945.

(3) Rosenheim and Jacobsohn, *Z. anorg. allgem. Chem.*, **50**, 297 (1906).

(4) Franklin, "The Nitrogen System of Compounds," A. C. S. Monograph No. 68, Reinhold Publishing Corporation, New York, N. Y., 1935, pp. 86–199.

metal salts. These properties have been demonstrated by the work described below.

The formation of the yellow tripotassium salt by the reaction,

$$(NH_4)_2(HMoO_3N) + 3KNH_2 \longrightarrow K_3(MoO_3N) + 5NH_3$$

goes to completion only very slowly even in the presence of a large excess of potassium amide. A red-brown dipotassium salt appears to be formed as an intermediate. Conversion by metathesis to the silver salt, $Ag_3(MoO_3N)$, or the lead salt, $Pb_3(MoO_3N)_2$, is more rapid and apparently quantitative.

Experimental

Materials.—With the exceptions noted below, all chemicals employed were of analytical reagent grade and of purity demonstrated by analyses prior to use.

Molybdenum(VI) Oxide.—A Schering–Kahlbaum product was dried for six hours at 110°, stored *in vacuo* over concentrated sulfuric acid, and used without further purification.

Anal. Calcd. for MoO_3: Mo, 66.65. Found: Mo, 66.60.

This oxide was also prepared by partial evaporation of a solution of sodium molybdate in concentrated nitric acid.

Anal. Calcd. for MoO_3: Mo, 66.65. Found: Mo, 66.35.

Experimental Methods.—Unless otherwise specified, all reactions in liquid ammonia employed the familiar faraday tube technique[5,6] and were effected at or near 25°. It is important here only to recognize that these techniques permit one to conduct reactions out of contact with the atmosphere under strictly anhydrous conditions and to form, purify, and isolate ammonia-insoluble reaction products.

Diammonium Aquoammonomolybdate.—Molybdenum(VI) oxide (0.6842 g.) was treated with about 15 ml. of liquid ammonia and agitated frequently over a period of one hour. The insoluble product was washed five times with liquid ammonia. Following evaporation of the solvent, the tube was evacuated by means of an oil pump for a period of two hours, filled with dry nitrogen and samples of the white crystalline solid (d^{25}_4 4.04) were removed for analysis.

Anal. Calcd. for $MoO_3 \cdot 3NH_3$: Mo, 49.98; N, 21.87. Found: Mo, 49.78; N, 21.65.

This compound loses ammonia slowly when exposed to the atmosphere and is rapidly and completely deammonated when heated to 110°.

Attempts to demonstrate the presence of ammonium ions in terms of hydrogen liberated upon treatment with liquid ammonia solutions of potassium led to results that were inconclusive.

Treatment of Diammonium Aquoammonomolybdate with Ammonium Salts.—To the diammonium salt produced (as above) from 0.2918 g. of molybdenum(VI) oxide and about 10 ml. of liquid ammonia was added an eight-fold excess (2.3738 g.) of ammonium chloride dissolved in liquid ammonia. After frequent agitation at 25° over a period of eighteen hours, the white solid was washed and removed for analysis in the manner indicated above.

Anal. Calcd. for $MoO_3 \cdot 3NH_3$: Mo, 49.98; N, 21.87. Found: Mo, 49.80; N, 21.75.

Substantially identical results were obtained using an excess of ammonium nitrate at 25° and ammonium chloride or ammonium nitrate at 100°. The experiments at 100° employed a modified Faraday tube[7] so constructed that it could be heated in an autoclave identical with that described by Bergstrom.[8]

Tripotassium Aquoammonomolybdate.—Preliminary experiments showed that the reaction between diammonium aquoammonomolybdate and potassium amide in liquid ammonia at 25° is slow and leads initially to mixtures of products. Accordingly, known weights of molybdenum(VI) oxide and potassium were placed in separate legs of a faraday tube, ammonia was condensed in the tube and the oxide and potassium were converted, respectively, to diammonium aquoammonomolybdate and potassium amide. The amide solution was then added to the suspension of the ammonium salt and the reaction mixture agitated intermittently prior to decantation of the supernatant solution and washing of the insoluble product preparatory to opening the tube for analysis. In a series of experiments of this type, the reaction ratio and time of contact were varied in an effort to obtain a product of reproducible composition. The resulting data are given in Table I. The tripotassium salt (d^{25}_4 4.59) hydrolyzes slowly upon exposure to the atmosphere. When treated with water, the salt hydrolyzes rapidly and yields an alkaline solution containing molybdate ion.

TABLE I

PREPARATION OF TRIPOTASSIUM AQUOAMMONOMOLYBDATE

MoO_3, g.	K g.	K equiv.	Time, hr.	Insoluble product[a,b] Color	Mo, %	N, %
0.6317	0.5878	3.42	0.5	Red-brown	39.12	6.15
.3986	.3575	3.60	0.5	Red-brown	38.48	5.77
.5172	.4671	3.32	2.0	Slate-gray	34.50	5.32
.8590	.9402	4.07	12	Yellow	34.79	5.25
.5620	.9313	6.10	12[c]	Yellow	34.71	5.22

[a] Calcd. for K_2HMoO_3N: Mo, 40.46; N, 5.90. [b] Calcd. for K_3MoO_3N: Mo, 34.86; N, 5.09. [c] Reaction times as long as twenty-six hours (using four to six equivalents of potassium amide) were employed without substantial change in the character of the results.

Silver(I) Aquoammonomolybdate.—The tripotassium aquoammonomolybdate equivalent to 0.7160 g. of molybdenum(VI) oxide was prepared and purified as described above. Thereafter, it was agitated (in the faraday tube in which the tripotassium salt was prepared) with a liquid ammonia solution containing excess silver(I) nitrate (3.1612 g.) until there was no further evidence of reaction (*ca.* one hour). Excess silver(I) nitrate and by-product potassium nitrate were separated from the black insoluble solid product by repeated washing with liquid ammonia.

Anal. Calcd. for Ag_3MoO_3N: Ag, 67.20; Mo, 19.95; N, 2.91. Found: Ag, 67.03; Mo, 19.73; N, 3.18.

This salt (d^{25}_4 7.64) underwent no change in appearance or composition during exposure to the atmosphere for twenty-four hours.

Lead(II) Aquoammonomolybdate.—In an entirely analogous manner, the lead salt was formed by the reaction between a liquid ammonia solution containing excess lead(II) iodide (2.4200 g.) in the potassium salt derived from 0.4877 g. of molybdenum(VI) oxide. The purified product was a light brown ammonia-insoluble solid (d^{25}_4 6.93) which is stable under ordinary atmospheric conditions.

Anal. Calcd. for $Pb_3Mo_2O_6N_2$: Pb, 66.25; Mo, 20.24; N, 2.86. Found: Pb, 65.98; Mo, 20.39; N, 2.82.

X-Ray Diffraction Data.—By the powder technique, X-ray diffraction patterns (Cu K_α radiation) were obtained for the diammonium, tripotassium, and trisilver salts. The interplanar spacings (d) in ångström units and the relative intensities (I/I_0) of the lines are given in Table II. The pattern for the lead salt (twenty-four hour exposure) showed only one line (d = 2.010).

(5) Reference 4, pages 319–330.

(6) Johnson and Fernelius, *J. Chem. Education*, **6**, 441–450 (1929).

(7) Holt and Watt, THIS JOURNAL, **65**, 988 (1943); for full details see R. B. Holt, M. A. Thesis, The University of Texas, June, 1942.

(8) Bergstrom, *J. Org. Chem.*, **2**, 424 (1937).

TABLE II

DATA FROM X-RAY DIFFRACTION PATTERNS

$(NH_4)_2(HMoO_3N)$		$K_3(MoO_3N)$		$Ag_3(MoO_3N)$	
d	I/I_0	d	I/I_0	d	I/I_0
1.678	0.28	0.875	0.04	1.260	0.19
1.798	.85	0.941	.06	1.312	.21
1.891	.12	0.965	.07	1.665	.22
2.070	.09	1.001	.08	1.795	.31
2.167	.18	1.240	.09	1.920	.21
2.236	.20	1.453	.08	2.240	.49
2.458	.30	1.550	.08	2.615	.62
2.648	.10	1.711	.11	3.030	.19
3.218	.87	1.750	.13	3.340	1.00
3.319	.95	1.920	.19	4.320	0.76
3.594	.90	2.200	.10		
4.901	.52	2.220	.21		
6.315	.98	2.615	.16		
7.145	1.00	2.453	1.00		
		3.001	0.42		
		3.156	.48		
		3.251	.91		
		3.501	.62		
		5.011	.18		

The same result was obtained using a sample of the lead salt that had been maintained for three hours at 300° (without change in composition) in an atmosphere of dry oxygen-free nitrogen.

Summary

1. The existence of a compound of molybdenum(VI) oxide and ammonia in a 1:3 mole ratio has been confirmed and the compound has been interpreted as the diammonium salt of an aquoammonomolybdic acid.

2. This salt has been shown to be unaffected by treatment with liquid ammonia solutions of ammonium chloride or ammonium nitrate at 25 and 100°.

3. By the use of excess potassium amide in liquid ammonia solution and long time of reaction, the diammonium acid salt has been converted to a yellow tripotassium salt.

4. By metathesis with solutions of silver(I) nitrate and lead(II) iodide in liquid ammonia, the tripotassium salt has been converted to the corresponding silver(I) and lead(II) salts.

AUSTIN, TEXAS RECEIVED JULY 19, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

X-Ray Diffraction Studies of Systems Involved in the Preparation of Alkaline Earth Sulfide and Selenide Phosphors[1]

BY WILLIAM PRIMAK[2a] HERMAN KAUFMAN AND ROLAND WARD

The methods of preparation and some of the properties of the alkaline earth sulfide and selenide infrared phosphors have recently been described.[2,3] It has been shown[4] that in most cases their formation involves a complex interaction between solid phases and a fused salt, or flux, during which the composition of the phases alters. It is important to know the solubility limits of the different base materials which are used in the preparation of phosphors. A knowledge of the ways in which solid solutions may be formed is also useful. This paper presents the results of a study of the intersolubility of some alkaline earth sulfides, selenides and oxides by means of X-ray analysis. The excellent back-reflection powder pictures given by the alkaline earth sulfides, selenides and oxides, all of which have the sodium chloride lattice, have permitted the determination of the lattice constant of these phases with high precision. Our results indicate that the simple Vegard law is applicable over a wide range of composition of mixed sulfides and selenides so that changes in composition of the base material can be determined from the lattice constant measurement.

Experimental

Procedure.—A symmetrical back-reflection focussing powder camera of 6 cm. radius was used for most of the pictures. Several were taken with a Philip's Straumanis type powder camera of 5.72 cm. radius, and these are indicated in footnotes. To obtain a precision lattice constant, the lattice constants computed from the back-reflection lines were plotted against the square of the sine of the Bragg angle and extrapolated to Bragg angle 90°.[5] The error in extrapolation was about $^1/_{10,000}$, but the reproducibility in different samples of supposedly pure material was not better than $^1/_{3000}$. Some of the chemical work did not warrant obtaining lattice constants of such precision. In these cases, lattice constants were computed from a single back-reflection line spacing. They were probably good to $^1/_{500}$.

Preparation of Materials.—All chemicals used were purified as for the preparation of phosphors.[6] Strontium and calcium sulfide were prepared by reducing the sulfates with ammonia, hydrogen or hydrogen sulfide at 850–1050°. They were then treated with hydrogen sulfide at a temperature of 1000°. Strontium selenide was prepared by the reduction of the selenite with ammonia at about 850°. Several preparations of sulfides and selenides were made by the reaction of sulfur or selenium on

(1) The work described in this paper was carried out in whole under contract NObs 28370 between the Bureau of Ships and the Polytechnic Institute of Brooklyn.

(2a) Present address: Argonne National Laboratory, P. O. Box 5207, Chicago 80, Ill.

(2) Reports of B. O'Brien, F. Urbach and R. Ward, *J. Optical Soc. Am.*, **36**, 351 (1946).

(3) R. T. Ellickson, *ibid.*, **36**, 261 (1946); R. T. Ellickson and W. L. Parker, *Phys. Rev.*, **69**, 534 (1946).

(4) W. Primak, R. K. Osterheld and R. Ward, THIS JOURNAL, **69**, 1283 (1947).

(5) M. J. Buerger, "X-Ray Crystallography," John Wiley and Sons, Inc., New York, N. Y., 1942, p. 393.

(6) A. L. Smith, R. D. Rosenstein and R. Ward, THIS JOURNAL, **69**, 1725 (1947).

the carbonates. These are specifically referred to. Magnesium sulfide was prepared by the action of hydrogen sulfide on magnesium chloride.[7] Strontium and calcium oxides were prepared by treating the carbonates with hydrogen at about 1000° and then with oxygen at the same temperature.

Fluxing Procedures.—Samples were prepared in two ways: (1) 10 to 15 g. of material was molded under a force of 10 tons to form a 7/8 inch diameter cylindrical block, which was then fired on a molded plate of magnesium oxide placed in a platinum boat; (2) 2 to 5 g. of material was placed into a small platinum boat and fired. In both cases the firing was performed by placing the boat into a quartz tube in which a purified nitrogen atmosphere was maintained, and the quartz tube was inserted for the desired length of time into the furnace maintained at a temperature of 1000–1100°.

Lattice Constants for Base Materials.—Precision lattice constants were determined for several different preparations of a number of alkaline earth oxides, sulfides, and selenides. They are given in Table I.

TABLE I

PRECISION LATTICE CONSTANTS

Base	Parts base	Flux	Parts flux	Minutes fluxed	Lattice constant "a" in Å.
SrS		None			6.0079
SrS	20	LiF	3	120	6.0080
SrS	100	LiF	9	90	6.0063
SrS	25	$SrCl_2$	3	90	6.0063
SrSe		None			6.2320
SrSe	10	LiF	1	30	6.228
SrSe	20	$SrSO_4$-SrF_2 (1:1 wt.)	3	30[a]	6.2309
CaS		None			5.6836
CaS	20	LiF	3	120	5.6835
CaSe		(Calculated)[b]			5.908
MgS		None			5.1913
MgS		None			5.1913
MgS	5	LiF	1	180	1.1900
MgS	5	NaCl	2	180	5.191
SrO	10	LiF[c]	1	120	5.1396
CaO		None			4.7990
CaO	10	LiF	1	30	4.799

[a] Phillip's Straumanis camera was used. [b] Calculated from the lattice constants given for strontium sulfide, strontium selenide and calcium sulfide, using Vegard's law. [c] Strontium oxide, unfluxed, gave diffuse lines which were attributed to poor crystallinity. When fluxed with sodium chloride or strontium chloride, a slight improvement was observed, but with lithium fluoride, rather sharp lines were obtained.

It is seen from these results that the flux does not affect the lattice constant within the limits of experimental error.

Solid Solutions of Strontium and Calcium Sulfides.—This system was previously investigated by Rumpf and Travnicek.[8] They used mixtures of strontium and calcium sulfides and sulfates prepared by the reaction of sulfur with a mixture of carbonates at high temperatures and observed large apparent deviations from Vegard's law, which they could not explain satisfactorily. For the work described here, practically pure sulfides were used. Two mixtures of strontium sulfide and calcium sulfide were prepared by grinding the constituents together in a ball mill. The one contained 75 mole per cent. strontium sulfide, the other 50 mole per cent. strontium sulfide. Several fluxes were used: (a) lithium fluoride; (b) mixtures of lithium fluoride, calcium fluoride, and strontium fluoride with the molar ratio of strontium to calcium ions the same as that of the respective sulfide mixtures. Lithium fluoride constituted one-third the weight of the mixture to give a mixture that was completely molten at the temperature of fluxing. (c) Mixtures of strontium fluoride, calcium fluoride and strontium sulfate with the molar ratio of strontium to calcium ions the same as that of the respective sulfide mixtures. The composition chosen was close to the line of two-fold saturation in the liquidus of the reciprocal salt system.[4]

The results obtained with these mixtures are given in Table II.

TABLE II

LATTICE CONSTANTS FOR FLUXED MIXTURES OF CALCIUM SULFIDE AND STRONTIUM SULFIDE

Base composition (mole% SrS)	Flux composition (Grams of flux for 10 g. sulfide) LiF	CaF_2	SrF_2	$SrSO_4$	Lattice constant ("a" in Å.)
75	1.5				5.9375
75	0.5	0.172	0.828		5.936
75		.205	.330	0.965	9.535
75	Calculated from the lattice constants given in Table I for SrS and CaS, using Vegard's law				5.927
50	1.5				5.853
50	0.5	0.384	0.616		5.854
50		.447		1.053	5.868
50	Calculated from the lattice constants given in Table I for SrS and CaS, using Vegard's law				5.846

These results show that complete solid solution of the two sulfides results on fluxing; and also that using a flux containing calcium and strontium ions in the same molar ratio as in the sulfide does not change the composition of such solid solutions. One would not expect any better agreement than is found above, because of the difficulty experienced in compounding solids quantitatively.

If having the same molar cation ratio in base and flux is the equilibrium condition for ion exchange between base and flux, it should be possible to reach this condition starting with a base containing the one cation and a flux containing the other. Accordingly, calcium sulfide was fluxed with a flux containing strontium fluoride; and strontium sulfide was fluxed with a flux containing calcium fluoride. The lattice constants given by these samples are given in Table III.

(7) V. Russo, M.S. Thesis, Polytechnic Institute of Brooklyn, 1947.

(8) Rumpf and Travnicek, *Ann. Physik*, [5] **4**, 725 (1930).

TABLE III

ION EXCHANGE BETWEEN BASE AND FLUX

Original base (10 g.)	Original flux (g.) LiF	SrF_2	CaF_2	"a," Å.	Mole per cent. SrS Found[a]	Calculated[b]
SrS	0.50		1.00	5.974	89.6	86.8
CaS	0.50	1.00		5.699	4.6	5.4

[a] Calculated from the lattice constant using Vegard's law. [b] Calculated from the composition, assuming ion exchange continues until the cation ratio is the same in flux and base.

Although complete transposition apparently did not occur in the time of fluxing, it is clearly established that cation exchange does take place. In applying this information to the study of phosphors, it could be assumed that cation exchange results in equal concentrations of these ions in base and flux.

The lattice constants obtained for calcium sulfide, strontium sulfide, and their solid solutions are plotted in Fig. 1 as a function of the composition. Contrary to the results obtained by Rumpf, which are plotted in the same figure for comparison, it is seen that our results obey Vegard's law very closely.

Conditions for the Formation of Solid Solutions.—In the above experiments, solid solutions were obtained by heating a mixture of sulfides with a flux. An attempt was made to obtain a solid solution by the reduction with hydrogen sulfide, of an intimate mixture of calcium and strontium sulfate. With a mixture containing 57 mole per cent. calcium sulfate, the product gave the patterns of the individual sulfides. When fluxed with lithium fluoride this mixture gave a lattice constant of 5.83 Å., corresponding to a composition of 56 mole per cent. calcium sulfide.

Quite different results were obtained when solid solutions of calcium and strontium carbonates were converted to sulfides. Three $(Ca,Sr)CO_3$ precipitates were prepared by adding a solution containing appropriate concentrations of Ca^{+2} and Sr^{+2} to a hot ammonium carbonate solution. They contained 81.7, 59.7 and 32.8 mole per cent. of calcium. Upon conversion to the sulfide by heating in hydrogen sulfide at 1000° the lattice constants of the solid solutions indicated 81.2, 57.7 and 31.0 mole per cent. of calcium, respectively, and on fluxing these products with lithium fluoride 80.5, 57.7 and 30.2 mole per cent. of calcium, respectively. The conversion to sulfide by heating with sulfur at 1000° gave somewhat similar results. The product from the mixture containing the highest percentage of calcium gave a very diffuse pattern before fluxing, and after fluxing a well-defined pattern corresponding to 73.8 mole per cent. calcium. The others yielded sulfides with calcium content 57.7 and 30.4 mole per cent. before fluxing and 59.0 and 30.8 mole per cent. after fluxing. The agreement is reasonably good considering that in the conversion of carbonate to sulfide with sulfur a considerable proportion of sulfate is formed.

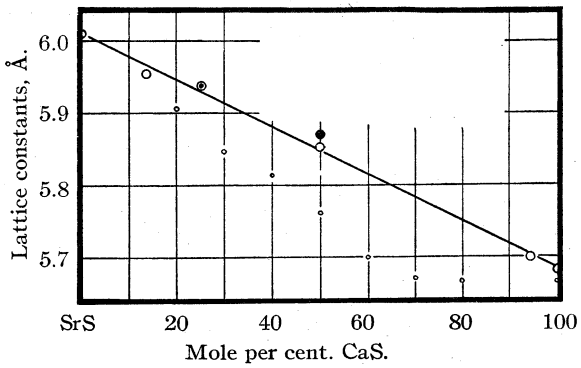


Fig. 1.—Lattice constants (Si,Ca)S: O, LiF fluxes, ●, $SO_4^=$ fluxes; ○, Rumpf.

Thus solid solutions of sulfides form when a mixture that is itself a solid solution is converted to sulfide. When the starting material is not a solid solution, appreciable solid solution is not obtained. This indicates a low rate of diffusion for these ions at 1000°.

These conclusions serve to explain some of the results previously obtained with mixtures of strontium selenite and other salts.[4] One of these systems ($SrSeO_3$–$CaSeO_3$) gave a lattice constant on reduction which differed widely from that predicted from the expected (Ca,Sr)Se solid solution. This experiment was repeated using a larger proportion (39 mole per cent.) of calcium selenite. The pattern of the selenide phase from the reduced mixture could barely be distinguished from the background but a strong set of lines corresponding to calcium oxide was present. Upon fluxing the mixture with lithium fluoride a distinct pattern of selenide phase appeared with lattice constant corresponding to about 14 mole per cent. calcium. The calcium oxide pattern was unaltered by the fluxing. It would appear, therefore, that the hydrolysis which always occurs when calcium selenite is reduced does not lead to the formation of strontium oxide or to a strontium–calcium oxide solution upon reduction of the mixture of strontium and calcium selenites.

The intersolubility of calcium and strontium oxides was accordingly tested by fluxing (a) a mixture of calcium oxide, strontium fluoride, and lithium fluoride in the proportions of 100:15:5, and (b) a similar mixture composed of strontium oxide, calcium fluoride, and lithium fluoride. From the powder picture of the former, a lattice constant 4.8020 Å. was computed. In the powder picture of the latter were found two sets of lines: from those that corresponded to a strontium oxide phase, the lattice constant 5.1312 Å. was computed; and from those that corresponded to a calcium oxide phase, the lattice constant 4.806 Å. It is obvious that ion exchange between base and flux had occurred in experiment b. The intersolubility of strontium and calcium oxides is apparently quite limited. According to Vegard's law, these results correspond to approximately 2.5

mole per cent. calcium oxide in strontium oxide, and 1 mole per cent. strontium oxide in calcium oxide.

The pronounced effect of oxide upon the luminescent properties of phosphors[9] suggested that solid solution with the sulfide or selenide might occur. The lattice constants obtained by fluxing strontium oxide and sulfide and oxide and selenide mixtures are shown in Table IV. It can be seen that the amount of oxide which disssolves in either selenide or sulfide is quite small and lies almost within the limits of determination by X-ray diffraction.

TABLE IV

LATTICE CONSTANTS OF MIXTURES CONTAINING OXIDE

Composition by weight Base	Flux	Fluxing time, hours	Lattice constant Å. SrO	Other base
SrSe 5, SrO 5	LiF 1	30	5.145	6.230
SrSe 100, SrO 0, 1, 2, 4[a]	SrF_2 7.5, $SrSO_4$ 7.5	0.75		6.232
SrS 2, SrO 1	LiF 0.3	30	5.140	6.0050
SrS 100, SrO 3	LiF 9	1.5		6.0075
SrS 100, SrO 10	LiF 9	1.5		6.0070
SrS 100, SrO 2	$SrCl_2$ 12	1.5		6.0065

[a] Phillip's Straumanis camera used.

The intersolubility of magnesium sulfide with calcium and strontium sulfides was also tested by the same procedures. The lattice constants for these mixtures are listed in Table V and should be compared with the values for the pure sulfides given in Table I. There is very little intersolubility in the MgS–SrS systems but with the CaS–MgS system about 11 weight per cent. magnesium sulfide dissolves in the calcium sulfide and about 15 weight per cent. of calcium sulfide in the magnesium sulfide lattice. This is perhaps a greater intersolubility than one would expect with a difference in cationic radii of some 50 per cent.

TABLE V

LATTICE CONSTANTS OF MIXTURES CONTAINING MAGNESIUM SULFIDE

Composition by weight Base	Flux	Fluxing time, hours	Lattice constant, Å. MgS	Other base
MgS 5, SrS 10	LiF 2.2	3	5.194	6.0058
SrS 10	LiF 0.5, MgF_2 1	3		6.0062
MgS 9, SrS 1	$SrCl_2$ 1	3		6.0012
MgS 6, SrS 4	$SrCl_2$ 1	1		6.0030
MgS 3, SrS 7	$SrCl_2$ 1	1		6.0020
MgS 1, CaS 5	NaCl 1.2	1		5.614
MgS 5, CaS 1	NaCl 1.2	1	5.251	

Acknowledgments.—The authors wish to thank Professor Fankuchen for his advice and Mr. Milton Schneider for his assistance in taking some powder diagrams. We are also indebted to Miss Hilda Texin and Messrs. Richard Hall and Kenneth Stripp for some of the samples used.

Summary

Precision lattice constants were determined for magnesium, calcium and strontium sulfides, strontium selenide, calcium and magnesium oxides. The extent of solid solution among these compounds and some of the methods for forming solid solutions were studied.

Complete intersolubility exists among calcium sulfide, strontium sulfide and strontium selenide. Magnesium and calcium sulfides are intersoluble to a limited extent. Solid solution formation among the other pairs appears to be negligible.

RECEIVED JANUARY 27, 1948

(9) K. Stripp and R. Ward, THIS JOURNAL, **70**, 401 (1948).

[CONTRIBUTION FROM RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION, KEARNY, NEW JERSEY]

Melting Points of Iron Oxides on Silica; Phase Equilibria in the System Fe–Si–O as a Function of Gas Composition and Temperature

BY L. S. DARKEN

The phase relations in the ternary system Fe–O–Si are of considerable interest to the steel industry, particularly in two respects: (1) the oxidation (scaling) of silicon steels produces in some cases a subscale and in other cases a so-called "silicon skin" (mainly metallic Fe + SiO_2). Since the primary requisite for scaling is the production of a gradient of the partial pressure of oxygen in the vicinity of the surface scaled, it is believed that a knowledge of the stability of the different oxides under various partial pressures of oxygen will aid in interpreting the observed phenomena. (2) The behavior of refractories is influenced in some cases by the form of iron oxide contained therein or deposited thereon. This is particularly so in blast furnace brick, in which metallic iron is thought to act as a catalyst for the deposition of carbon which in extreme cases disintegrates the brick. It has been observed that brick fired at high temperatures are less susceptible to this form of attack. It seems reasonable that higher temperatures effect fusion of the iron oxides forming silicates, etc., which are less easily reduced and less catalytic. The present investigation demonstrates that the temperature of fusion of iron oxides in contact with silica is a rather sensitive function of gas composition (varying from 1120 to 1447°), hence that fusion may be accomplished in some

cases by control of the gas atmosphere without changing the temperature.

Experimental Procedure and Data.—A number of the univariant equilibria in the oxide region of the ternary system Fe–Si–O are identical with those of the binary system Fe–O which have been investigated previously. Others may be estimated with sufficient precision from available data, though there are but few data on the influence of gas composition on the melting temperature of the oxides. The present experimental investigation was intended partially to fill this gap by determination of the relation between gas composition and temperature for the two univariant equilibria: silica, magnetite, melt, gas; and silica, fayalite, melt, gas.

In each experiment a silica rod (about 1 mm. diam., 5 cm. long) was coated with Fe_2O_3 by dipping it in an aqueous suspension of the latter. After the coated rod had dried, it was placed on a platinum suspension and hung in the gradient of a platinum-wound tubular furnace, which was controlled in the manner described previously,[1] the winding of the furnace acting as one arm of a bridge circuit which was automatically balanced. The desired atmosphere, usually delivered by a gas mixer, was introduced into the furnace (at atmospheric pressure) through the mercury seal at the bottom of the tube. The rate of flow of gas was about 50 cc. per minute, which is ample to avoid appreciable thermal separation of the gases. The time at temperature varied from fifteen minutes in some of the preliminary experiments to eighteen hours. If the temperature and gas composition were suitably chosen, the sample exhibited on removal a fairly sharp demarcation between the opaque fused region and the region in which no fusion had occurred. This transition is best seen by the naked eye using the sky as a background. In questionable cases, the demarcation was developed by immersing the rod in warm 6 *N* hydrochloric acid for a few minutes; the acid removed essentially all the iron from the unfused region, but had little effect on the fused portion. To determine the temperature, the position of the demarcation line was carefully measured and a thermocouple was inserted at the corresponding position in the furnace. If the temperature gradient in this region was too steep to yield the desired precision, the furnace temperature was readjusted so that on repetition of the experiment the transition occurred nearer the center of the furnace in a region of smaller temperature gradient.

After this temperature adjustment had been made, so that the transition in a given atmosphere occurred in a region where the gradient was about 10° per cm., the specimen was held at the determined position for different lengths of time to be sure that the observed demarcation line corresponded to equilibrium between the phases involved. Fusion of course proceeded from the hotter zone to the cooler. It was found that, within the limits of experimental measurement, motion of the boundary line between fused and unfused portions ceased after about one-half hour; however, the sharpness of the boundary line usually increased appreciably on longer treatment. For this reason, as well as to be sure of equilibration, all specimens were treated for sixteen hours. In each case a preliminary measurement was made, usually at the end of one hour, but at the lower temperatures, at a somewhat longer time. In all cases, the position of the demarcation line was the same at the end of sixteen hours as at the time of the previous preliminary measurement. The experimental data are recorded in Table I, and are presented graphically in Fig. 1 along with curves representing other equilibria subsequently discussed.

Since it is reasonable to expect a slight difference in equilibrium temperature depending on whether the solid silica phase is vitreous or crystalline, several determinations were made using a vitreous silica rod whose surface had been transformed to cristobalite. This conversion was accomplished by heating the rod at about 1500° for an hour; the success of this treatment was easily recognized by the shattering of the surface accompanying the high–low inversion of cristobalite (200–275°) as the specimen was cooled. From the data assembled by Mosesman and Pitzer[2] it is clear that the free energy difference between vitreous silica and any of the crystalline forms is greater, in the range covered, than the free energy difference between any two crystalline forms. Hence it is of negligible importance from the viewpoint of the present investigation that cristobalite was used, in spite of the fact that tridymite is the stable crystalline form in the temperature range investigated. Since the metastability of the vitreous form is greater at lower temperatures, it is evident that the observed temperature of the four phase equilibria would be most greatly influenced by the form of silica at the lower temperatures. For this reason, cristobalite was used in the case of all three measurements of the equilibrium between fayalite, silica, liquid and gas. Cristo-

TABLE I

MELTING POINT OF IRON OXIDES IN CONTACT WITH SILICA AND VARIOUS ATMOSPHERES AT ONE ATMOSPHERE TOTAL PRESSURE

Atmosphere	Form of silica	Temperature, °C.
(the univariant equilibrium; silica, magnetite, melt, gas)		
Oxygen[a]	Vitreous	1447
Air	Vitreous	1442
1/4% O_2 in CO_2	Vitreous	1411
CO_2, CO; CO_2/CO = 308	Vitreous	1369
CO_2, CO; CO_2/CO = 79.2	Vitreous	1279
CO_2, CO; CO_2/CO = 52.8	Vitreous	1230
CO_2, CO; CO_2/CO = 26.0	Cristobalite	1159
CO_2, CO; CO_2/CO = 20.8	Vitreous	1131
(the univariant equilibrium; silica, fayalite, melt, gas)		
CO_2, CO; CO_2/CO = 14.1	Cristobalite	1120
CO_2, CO; CO_2/CO = 11.2	Cristobalite	1129
CO_2, CO; CO_2/CO = 4.02	Cristobalite	1139

[a] Actually the phases in equilibrium at this point are silica, hematite, melt and gas as may be seen from Fig. 1. It is, however, very nearly identical with quintuple point 1.

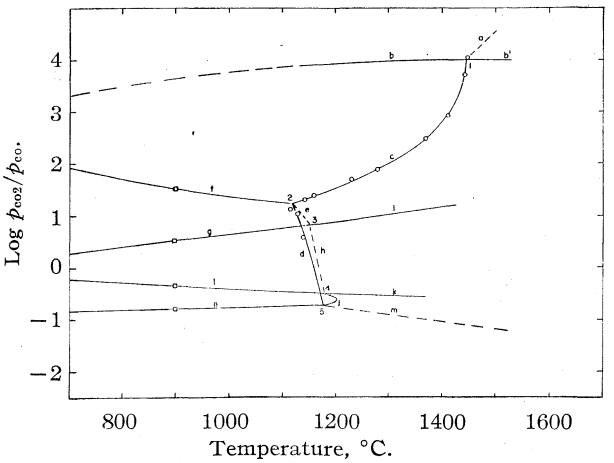


Fig. 1.—Relations between gas composition and temperature for the univariant equilibria of the system Fe–Si–O.

(1) Darken and Gurry, THIS JOURNAL, **67**, 1398 (1945).

(2) Mosesman and Pitzer, *ibid.*, **63**, 2348 (1941).

balite was also used in the case of one sample in the series determining the equilibrium between magnetite, silica, liquid, gas. Since this point falls on the same smooth curve as that for the points representing equilibrium with vitreous silica it is concluded that the influence of the form of silica is smaller than the experimental error, which is estimated to be about 5°.

Although the system investigated comprises four elements (iron, oxygen, silica, carbon) the solubility of carbon (or carbon monoxide or carbon dioxide) in the condensed phases is negligibly small in the region investigated; hence, the system may be regarded as a three component one. It is convenient, however, to give the pressure in terms of the ratio of carbon dioxide to carbon monoxide in the gas phase rather than in terms of the partial pressure of oxygen; it is clear that these are interconvertible by means of the equilibrium constant for the homogeneous gaseous reaction $CO + {}^1/_2O_2 = CO_2$. Values of this constant, calculated from the tabulated values of $(F^0 - E_0^0)/T$ for CO,[3] O_2,[4] and CO_2,[5] using the value of ΔE_0^0 given by Rossini,[6] were given by Darken and Gurry.[2] The uncertainty of this equilibrium constant is negligibly small compared to other errors involved in construction of the diagram.

Construction of the Remainder of the Diagram.—In order to construct the diagram (Fig. 1) showing the equilibrium ratio of carbon dioxide to carbon monoxide in the presence of various stable phases and at various temperatures the general procedure was as follows. The known invariant points (five phase equilibria) and the known univariant curves (four phase equilibria) or points thereon were plotted. A number of these are identical with the invariant curves of the binary system iron–oxygen. In general for a ternary system five univariant curves intersect at an invariant point; however, one of these univariant curves represents the small effect of pressure on the completely condensed system (no gas phase present), and does not appear in the representation chosen since the total pressure is essentially one atmosphere. Hence the construction consisted mainly of interconnecting the univariant curves to accord with this condition, using directly determined data together with indirect data related thermodynamically to the diagram.

There are five invariant points occurring in the region considered; at these points the following phases are in equilibrium (the numbers correspond to those in Fig. 1).

(1) hematite, magnetite, silica, melt, gas
(2) magnetite, fayalite, silica, melt, gas
(3) magnetite, wüstite, fayalite, melt, gas
(4) wüstite, fayalite, metal, melt, gas
(5) fayalite, metal, silica, melt, gas

Of the various stable phases listed, hematite (Fe_2O_3), fayalite ($2FeO{\cdot}SiO_2$), silica (SiO_2), and metal (Fe) are essentially of fixed composition; magnetite (Fe_3O_4) and wüstite ("FeO") are binary compounds containing no appreciable amount of silica, although the ratio of iron to oxygen is variable; the melt contains all three components in variable amounts.

(3) Clayton and Giauque, THIS JOURNAL, **55**, 5071 (1933).
(4) Johnston and Walker, *ibid.*, **57**, 682 (1935).
(5) J. S. Kassel, *ibid.*, **56**, 1838 (1934).
(6) F. D. Rossini, *J. Research Nat. Bur. Standards*, **22**, 407 (1939).

There are fifteen univariant curves derived from these five invariant points. In addition to the gas phase the following phases are present along the univariant curves shown in Fig. 1.

(a) hematite, silica, melt
(b) hematite, magnetite, silica
(b′) hematite, magnetite, melt
(c) magnetite, silica, melt
(d) fayalite, silica, melt
(e) magnetite, fayalite, melt
(f) magnetite, fayalite, silica
(g) magnetite, wüstite, fayalite
(h) wüstite, fayalite, melt
(i) magnetite, wüstite, melt
(j) metal, fayalite, melt
(k) wüstite, metal, melt
(l) wüstite, fayalite, metal
(m) metal, silica, melt
(n) metal, fayalite, silica

Of these fifteen equilibria b, b′, g, i, k, and l are essentially identical with those of the binary system iron–oxygen determined in part by Darken and Gurry.[1,7] Equilibrium c and part of d was determined by the present investigation. Invariant points 1 and 2 are thus established by the intersection of b and c and of c and d, respectively. The temperature of invariant point 4 was determined by Bowen and Schairer[8] as 1175°; its position is thus fixed by this temperature and the fact that it lies on the curves *l* and *k*.

The equilibria of this system at 900° have been investigated by Schenck, Franz and Laymann,[9] whose data on the various univariant equilibria are thermodynamically consistent and in good agreement with the data of Darken and Gurry on the binary system iron–oxygen. At this temperature the ratio p_{CO_2}/p_{CO} is 0.163 for equilibrium n, and is 34.5 for equilibrium f.[10] Curve f is thus reasonably well established by this point at 900° and quintuple point 2 at 1118°. It was constructed under the assumption that $\log p_{CO_2}/p_{CO}$ is linear with $1/T$. Curve n is determined by the point at 900° and a calculated point[11]

(7) Darken and Gurry, THIS JOURNAL, **68**, 798 (1946).
(8) Bowen and Schairer, *Am. J. Sci.*, **24**, 177 (1932).
(9) Schenck, Franz and Laymann, *Z. anorg. allgem. chem.*, **206**, 126 (1932).
(10) The thermodynamic consistency of these values may be demonstrated in the following manner. The chemical reaction corresponding to equilibria f, g, l and n may be written

(f) $3(2FeO{\cdot}SiO_2) + 2CO_2 = 2Fe_3O_4 + 3SiO_2 + 2CO$
(g) $3FeO$ (in wüstite) $+ CO_2 = Fe_3O_4 + CO$
(l) $Fe + CO_2 = FeO$ (in wüstite) $+ CO$
(n) $2Fe + SiO_2 + 2CO_2 = 2FeO{\cdot}SiO_2 + 2CO$

It will be noticed that these four equations are not independent but that any one may be expressed in terms of the others—for example (f) = 6(l) + 2(g) − 3(n). The following relation must then hold between the thermodynamic equilibrium constants: $K_f = K_l^6 K_g^2 / K_n^3$. The values of K_l and K_g (including the activity of (FeO) were taken from Darken and Gurry[1] and that for K_n from Schenck, *et al.*[9] The calculated value for the ratio p_{CO_2}/p_{CO} corresponding to (f) is 34.7 in agreement with the observed value[9] 34.5.

(11) At 1100° the logs of the ratio p_{CO_2}/p_{CO} are 1.28, 0.785 and −0.450, for the equilibria f, g and l, respectively. The log of the ratio of the activity of FeO in wüstite equilibrated with iron to the activity of FeO in wüstite equilibrated with magnetite is 0.124. Hence for equilibrium n at 1100°:

$$\log \frac{CO_2}{CO} = \frac{-1.28}{3} - 0.450 + \frac{0.785}{3} - 0.124 = -0.74$$

at 1100° where p_{CO_2}/p_{CO} is found to be 0.182.

Quintuple point 5 is established as the point on curve n at 1180°, the temperature determined by Bowen and Schairer.[8]

Curve j is constructed connecting quintuple points 4 and 5; it passes through a maximum at 1208°, the melting point of pure fayalite as determined by Bowen and Schairer.

Curve m, radiating from quintuple point 5, is estimated roughly in the following manner: Iron melts in contact with its molten oxide at about 1525°, at which temperature $\log p_{CO_2}/p_{CO} = -0.68$; it is estimated that the activity of ferrous oxide in the oxide phase in equilibrium with iron is depressed by saturation with silica to about one-third,[12] thus at 1525° on curve m the value of $\log p_{CO_2}/p_{CO}$ is $-0.68 - \log 3 = -1.16$. The remainder of the curve is determined approximately by these two points.

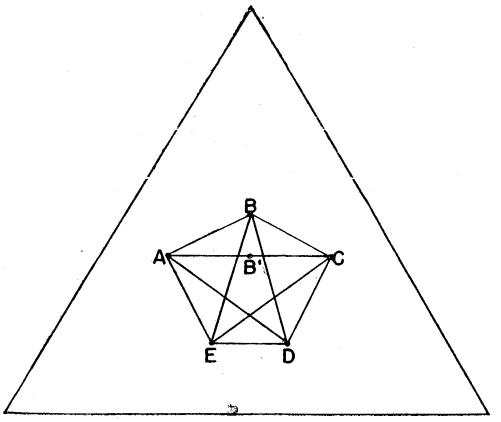
Estimation of Position of Quintuple Point 3.—Of the five quintuple points occurring in the region covered by Fig. 1 four have already been considered and their positions established; the position of quintuple point 3 remains to be determined. Of the fifteen univariant equilibrium curves only three remain to be considered. Curve a is of little interest since the corresponding equilibrium can exist only at pressures above one atmosphere; its general direction is indicated by a dotted line in the diagram. The positions of curves e and h, which connect quintuple point 3 to quintuple points 2 and 4, respectively, are undetermined since there are no available experimental data on either of these curves; also the position of quintuple point 3 is undetermined except that it must be on the curves g, i. Thus from the direct data available, the only facts known concerning curves e and h are that they start from quintuple points 2 and 4, respectively, and terminate at a common point on the curves g, i which is quintuple point 3.

Some insight into possible constructions of these curves is gained by consideration of a theorem relating the order of curves about a quintuple point to the isothermal (triangular) composition diagram. This theorem is due in part to Roozeboom, Schreinemakers and Smits. An original derivation for the general case was given by Morey and Williamson.[13] Since a quintuple point represents the equilibrium of five phases each of a definite composition, the representation of this point on a composition diagram consists of five points, each of which represents the composition of one of the five phases present. The five univariant equilibria derived from the quintuple point correspond to the five possible combinations of four of the five phases. Thus at quintuple point 3, the five phases are magnetite, wüstite, fayalite, melt and gas. It will be noted that the five univariant equilibria correspond to the absence from the five phases present at the quintuple point of wüstite, melt, magnetite, fayalite and gas, respectively. The theorem states that if the points representing the composition of any three phases are colinear on the composition diagram, the two pressure–temperature curves representing the two univariant equilibrium involving these three phases are identical, that is, one is the extension of the other. At quintuple point 3 it is obvious that the compositions of magnetite, wüstite and gas (oxygen) are colinear on the triangular composition diagram; (they all lie on the Fe-O edge of the triangle) hence the curves g and i in Fig. 1 are extensions one of the other, as already anticipated from the consideration that the equilibrium of wüstite, magnetite and gas is not influenced by a third substance which is not appreciably soluble in any of these three phases.

The theorem gives further information as to the more general case in which three points are not colinear. This extended part of the theorem may best be visualized by imagining that five pins are stuck in the composition diagram at the five points corresponding to the compositions of the five phases present at the quintuple point. These pins are then each connected to each of the other four by elastic strings as in Fig. 2a. This particular set of compositions A, B, C, D, E, may be regarded as derived from any one of a variety of sets of compositions (imaginary quintuple points) in which colinearity of three points does occur—for example, the set A, B′, C, D, E. The theorem states in effect that if the pin at B with its attached elastic strings may be moved to B′ without any of the interconnecting lines (elastic strings) crossing any of the points (or *vice versa*) then the two univariant curves corresponding to the equilibria ABCD and ABCE are adjacent at the quintuple point on the pressure–temperature diagram, *i. e.*, no other univariant curve lies between them at their intersection. In the present example B may be so moved to B′ colinear with A and C but may not be so moved as to be colinear with any other two of the five points. The same type of operation may be performed with each of the other points (A, C, D and E). Thus the order of all the univariant curves around a quintuple point may be established provided that the composition of the five phases is known. It is also necessary to establish the stable direction of each univariant curve since each curve is continuous through the quintuple point but represents a stable equilibrium in one direction and a metastable equilibrium in the other. Returning to the illustration, this matter is determined as follows: if the two points E and D lie on the same side of the line AB′C then the two univariant curves for equilibria ABCD

(12) This is based on the data of Körber and Oelsen [*Mitt. Kaiser-Wilhelm Inst. Eisenforsch Dusseldorf*, **15**, 271 (1933)] that at steel making temperatures the equilibrium oxygen content of iron under an iron-oxide slag saturated with silica is about 1/3 the oxygen content of iron under an iron oxide slag.

(13) Morey and Williamson, THIS JOURNAL, **40**, 59 (1918). Further discussion and applications are given by G. W. Morey in "Commentary on the Scientific Writings of J. Willard Gibbs," Yale University Press, New Haven, Conn., 1936.



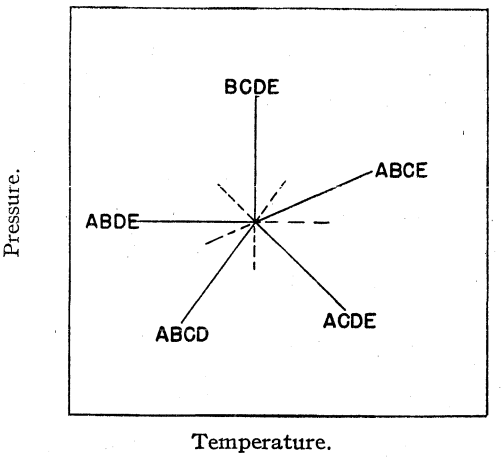


Fig. 2.—Schematic representation of the relation between *a* the composition of the five phases in equilibrium at the quintuple point and *b* the order of the univariant equilibrium curves about the quintuple point.

and ABCE are adjacent stable to metastable (*i. e.*, the stable portion of each, designated by a full line, is adjacent to the metastable portion of the other, designated by a dashed line). If E and D happened to lie on opposite sides of AB'C then these two univariant curves would be adjacent stable to stable. Application of this theorem to the postulated compositions shown in Fig. 2a leads to the order of univariant curves in the pressure temperature diagram as shown in Fig. 2b. Obviously the theorem is equally valid if the logarithm of the pressure is used as ordinate instead of the pressure itself.

Application of this theorem to quintuple point 4 in Fig. 1, using the composition data of Bowen and Schairer, leads to the conclusion that curve h radiates upward from this point and slightly to the left; this follows from the fact that the composition of the melt is very nearly colinear with that of wüstite and fayalite but is slightly higher in oxygen. It is assumed that the curvature of h is small. Quintuple point 3 is thus very roughly estimated as the point at 1150° lying on the curve g,i. The diagram is completed by constructing the short curve e connecting quintuple points 2 and 3.

Temperature Maxima and Minima of the Univariant Curves.—In the case of a univariant equilibrium in a ternary system involving three condensed (solid or liquid) phases and a gaseous phase it is rather unusual to find that all the condensed phases have fixed compositions independent of temperature. It is this variation of composition of the phases with temperature which introduces the most serious complexities into the treatment of such systems. Of the various equilibria here considered only two (f and n) of the truly ternary equilibria, *i. e.*, equilibria in which all components participate, as distinguished from equilibria which may be represented as binary since the third component is inert, consist exclusively of phases of reasonably fixed composition. Thus, equilibrium f may be represented by the chemical equation

$$3(2FeO\cdot SiO_2) + O_2 = 2Fe_3O_4 + 3SiO_2$$

The equilibrium constant may be written

$$K_f = \frac{a^2_{Fe_3O_4} a^3_{SiO_2}}{a_{2FeO\cdot SiO_2} a_{O_2}}$$

Since the solid phases involved are all of fixed composition, or very nearly so, the activities may be set equal to unity. The activity of oxygen is equal to its partial pressure in the gas phase and hence $K_f = 1/p_{O_2}$. The change of K_f and hence of $1/p_{O_2}$ is given by the simple equation: $d \ln K_f/d(1/T) = -\Delta H_f/R$. The treatment of this is relatively simple and leads to the well known linear relation between $\log K$ and $1/T$ if the heat of reaction (ΔH) is essentially independent of temperature. The use of carbon dioxide–carbon monoxide mixtures as the gas phase introduces no further complexities since the ratio CO_2/CO may be regarded as simply a measure of $p_{O_2}^{1/2}$ through the homogeneous gas equilibrium involving carbon monoxide, carbon dioxide, and oxygen. Hence for this equilibrium the plot of $\log p_{CO_2}/p_{CO}$ *versus* $1/T$ exhibits only the slight curvature occasioned by the difference in heat capacities. The use of temperature instead of $1/T$ as ordinate in Fig. 1 does not lead to any serious distortion of the relationship but simply produces a mild curvature.

A very different situation prevails, however, in the equilibria involving the molten oxide phase (curves a, c, d, e, h and j). In each of these cases it is impossible to write a chemical equation with integral or even constant coefficients to represent the reaction. The relation between $\log p_{O_2}^{1/2}$ (or $\log p_{CO_2}/p_{CO}$) and temperature is a function not only of the heats of reaction but also of the variable composition of the liquid phase. In general, these curves cannot be estimated even approximately by assuming $\log p_{O_2}^{1/2}$ to be linear with $1/T$; for example, curve j passes through a maximum temperature. The occurrence of such a temperature maximum (or minimum) may be

predicted, if the compositions are known, by aid of the theorem that at such a maximum (or minimum or stationary value) the composition of the three condensed phases is represented by three colinear points on the composition diagram[14]: The converse of this theorem is also true. Thus, at the maximum temperature of curve j the compositions of metal, fayalite and melt are colinear; the melt may be considered as molten fayalite from which some iron has been removed. It will be observed that the experimentally determined curve c is obviously approaching a maximum at its high temperature end. It does not actually pass through a maximum since it ends at quintuple point 1 first. It may, however, be inferred from the steep vertical rise of curve *c* near quintuple point 1 that the composition of the liquid oxide at this quintuple point is nearly colinear with the compositions of magnetite and silica; *i. e.*, this melt may be regarded approximately as composed of Fe_3O_4 and SiO_2.

Equilibria in Special Cases.—Although Fig. 1 shows the various possible univariant equilibria curves in the region under consideration, it is not possible to decide from this diagram alone what equilibria are pertinent for a given composition. In other words, the regions between the curves in this figure do not correspond to a unique set of phases. In general, the diagram may be applied to a specific case only if some composition data are available. In case a large amount of silica is present, the pertinent equilibria (taken from Fig. 1) are shown in Fig. 3. The stable phases, in addition to the gas, in the various fields are designated in this diagram. This diagram may be taken as a guide to the various iron oxide phases that may be present in contact with silica brick under different conditions of temperature and gas composition.

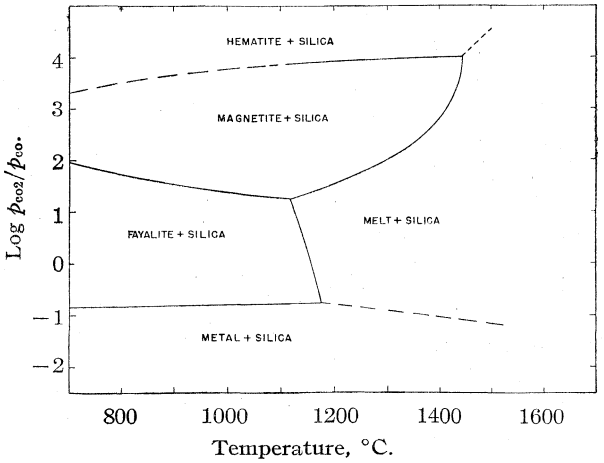


Fig. 3.—Stable phases of the system Fe–Si–O in the presence of solid silica.

(14) This theorem is similar to that of Morey and Williamson, used previously; a proof is given in the appendix. A less explicit derivation was given by Gibbs.

If the ratio of total silicon to total iron is low, as in the case of a silicon steel and the oxides formed therefrom, the stable phases under various conditions of temperature and gas composition are as shown in Fig. 4. The temperature of complete melting is not shown in either Fig. 3 or Fig. 4, since this temperature is a continuous function of composition and may not be readily expressed on this type of diagram. In the region on the right of the diagrams, designated as corresponding to melt plus a solid phase, the relative proportions of the two phases depend on the composition as does the temperature of complete melting corresponding to the complete disappearance of the solid phase.

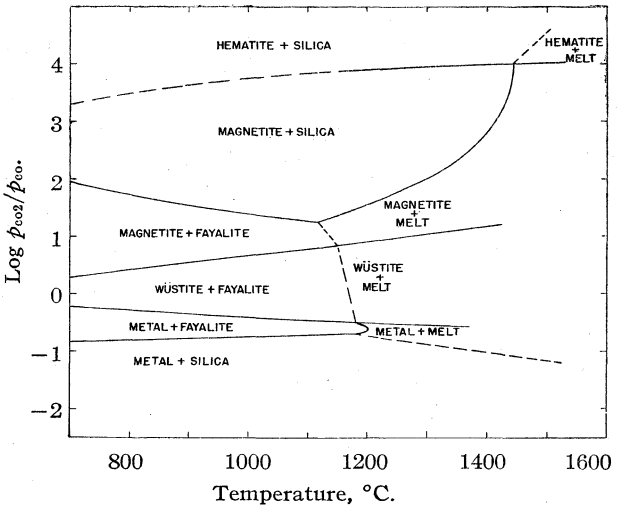


Fig. 4.—Stable phases of the system Fe–Si–O at low amounts of silicon.

The Migration of Silica During the Scaling of Steel.—It has been observed that the presence of a relatively small amount of silica or siliceous material on an iron or steel surface which is heated in an oxidizing atmosphere causes the scale to be more adherent to the metal than is the case in the absence of silica. The siliceous scale forms a very irregular boundary with the metal and is thus anchored so that it does not separate cleanly from the metal when bent, quenched or subjected to impact. The most peculiar part of the behavior is that the silica does not grow out appreciably with the scale, but remains principally near the scale–metal interface and spreads laterally so that the adherent zone increases with time of scaling. Clearly this phenomenon is very undesirable at any stage in the heat treatment of steel since it may occasion surface defects in the finished product.

In an elementary sense some insight is given by the consideration that silica forms a compound with ferrous though not with ferric oxide. It would be expected to migrate toward the region where it can form the most stable compound, which in this case is the scale–metal interface

where the composition of the iron oxide is nearest that corresponding to the formula FeO. This same line of reasoning may be developed in a quantitative manner by consideration of the activity of silica in the metal and various scale layers. At constant temperature silica will tend to move in such manner as to lower its free energy and hence its activity. The activity of silica differs appreciably from unity only when the silica is present in compound form, *i. e.*, combined as fayalite. From the equilibria (f) and (n)[9] it is found that at 900° in the presence of metallic iron and fayalite the activity of silica is given by the expression

$$a_{SiO_2} = 0.0268(p_{CO}/p_{CO_2})^2$$

and in the presence of magnetite and fayalite

$$a_{SiO_2} = 0.094(p_{CO_2}/p_{CO})^{2/3}$$

In the presence of wüstite and fayalite the activity of silica is inversely proportional to the square of that of ferrous oxide; a_{FeO} was taken from Darken and Gurry.[1] The variation of the activity of silica thus calculated with the degree of oxidation is shown in Fig. 5. The lowest activity is seen to be at the scale–metal interface, thus accounting for the observation that silica tends to move to and remain at this interface.

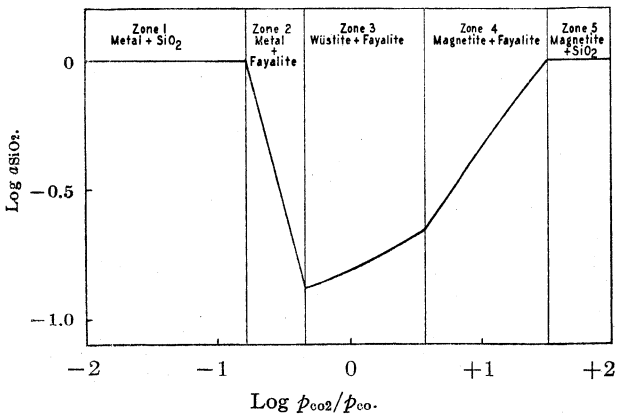


Fig. 5.—Activity of silica in iron and iron oxide systems at 900°.

Appendix

Proof of Theorem.—If a univariant equilibrium in a ternary system has a maximum (or minimum) temperature on a pressure temperature plot, then at this temperature the compositions of the three condensed phases, one of variable and two of fixed composition, are colinear. By the fundamental theorem of partial differentiation the total derivatives of the activities (at constant total pressure), of each of the three components may be written as follows

$$(1)\quad \frac{d\ln a_1}{d(1/T)} = \left(\frac{\partial \ln a_1}{\partial(1/T)}\right)_{N_2,N_3} + \left(\frac{\partial \ln a_2}{\partial N_2}\right)_{N_3,T}\frac{dN_2}{d(1/T)} + \left(\frac{\partial \ln a_1}{\partial N_3}\right)_{N_2,T}\frac{dN_3}{d(1/T)}$$

$$(2)\quad \frac{d\ln a_2}{d(1/T)} = \left(\frac{\partial \ln a_2}{\partial(1/T)}\right)_{N_2,N_3} + \left(\frac{\partial \ln a_2}{\partial N_2}\right)_{N_3,T}\frac{dN_2}{d(1/T)} + \left(\frac{\partial \ln a_2}{\partial N_3}\right)_{N_2,T}\frac{dN_3}{d(1/T)}$$

$$(3)\quad \frac{d\ln a_3}{d(1/T)} = \left(\frac{\partial \ln a_3}{\partial(1/T)}\right)_{N_2,N_3} + \left(\frac{\partial \ln a_2}{\partial N_2}\right)_{N_3,T}\frac{dN_2}{d(1/T)} + \left(\frac{\partial \ln a_3}{\partial N_3}\right)_{N_2,T}\frac{dN_3}{d(1/T)}$$

The a's refer to activities and the N's to mole fractions. If these three equations are multiplied by N_1, N_2 and N_3, respectively, and added, then all terms on the right-hand side except the first of each equation disappear by virtue of the Gibbs–Duhem relationship.

$$(4)\quad \frac{N_1 d\ln a_1 + N_2 d\ln a_2 + N_3 d\ln a_3}{d(1/T)} = N_1\left(\frac{\partial \ln a_1}{\partial(1/T)}\right)_{N_2,N_3} + N_2\left(\frac{\partial \ln a_2}{\partial(1/T)}\right)_{N_2,N_3} + N_3\left(\frac{\partial \ln a_3}{\partial(1/T)}\right)_{N_2,N_3}$$

If the liquid phase is in equilibrium with two solid phases of fixed composition and a gaseous phase, then the two solid phases may arbitrarily be selected as components (designated components 1 and 2). The standard state for these components is selected as the solid and hence the activity of each is unity and its total derivative is zero. Then

$$(5)\quad N_3\frac{d\ln a_3}{d(1/T)} = N_1\left(\frac{\partial \ln a_1}{\partial(1/T)}\right)_{N_2,N_3} + N_2\left(\frac{\partial \ln a_2}{\partial(1/T)}\right)_{N_2,N_3} + N_3\left(\frac{\partial \ln a_3}{\partial(1/T)}\right)_{N_2,N_3}$$

If component 3 be selected as a gaseous component (oxygen in the present case) then $p_{O_2}^{1/2}$ may be written for a_3; further the partial derivatives on the right multiplied by R are equal to the partial molal heats of solution $\overline{H}_1$, $\overline{H}_2$, $\overline{H}_3$, ($\overline{H}_1$ and $\overline{H}_2$ being heats of melting).

$$(6)\quad R\frac{d\ln p_{O_2}^{1/2}}{d(1/T)} = \frac{N_1}{N_3}\overline{H}_1 + \frac{N_2}{N_3}\overline{H}_2 + \overline{H}_3$$

In terms of the ratio p_{CO_2}/p_{CO}

$$(7)\quad R\frac{d\ln (p_{CO_2}/p_{CO})}{d(1/T)} = \frac{N_1}{N_3}\overline{H}_1 + \frac{N_2}{N_3}\overline{H}_2 + \overline{H}_3'$$

where $\overline{H}_3'$ is equal to the change of the heat content of oxygen on transfer from the gas phase to the liquid. Since N_3 occurs in the denominator it follows that whenever $N_3 = 0$ the expression becomes infinitely great. But by the choice of components, the equality of N_3 to zero is synonymous with the colinearity (on the composition triangle) of melt, component 1, and component 2. Hence whenever the composition of the melt is colinear with the composition of the two solid phases in equilibrium with it, it follows that the plot of log p_{CO_2}/p_{CO} (or log p_{O_2}) *vs.* $1/T$ (or *vs.* temperature) is vertical. Conversely, since the heats of solution are never infinite, any vertical portion of the plot corresponds to colinearity of the three phases on the composition diagram. A general proof of this theorem was given by Gibbs.[15]

(15) J. W. Gibbs, "Collected Works," Vol. I, Longmans Green & Co., New York, N. Y., 1928, pp. 99–100.

Summary

The melting point of iron oxides in contact with silica has been determined as a function of the partial pressure of oxygen or the ratio of carbon dioxide to carbon monoxide in the gas phase. With the aid of these and other available data, a large part of the diagram showing the stable phases under various conditions of temperature and gas composition has been constructed for the ternary system iron–silicon–oxygen. The data have been used to interpret the migration of silica through iron oxide to the scale–metal interface during the scaling of steel.

KEARNY, NEW JERSEY RECEIVED JANUARY 28, 1948

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

The Reactions of Diborane with Hydrocarbons[1]

BY DALLAS T. HURD

A number of experiments have been conducted to delineate the character of the complex reactions that occur between hydrocarbons and diborane at elevated temperatures. In these experiments the effect of the highly reactive diborane on the reaction products has been minimized by using only small amounts of diborane with relatively large amounts of hydrocarbon. Under these conditions several different reactions have been observed:

1. The addition of diborane to olefins occurs with saturation of the double bonds and the formation of trialkyls of boron.
2. Substitution on the benzene ring occurs with the formation of phenyl boron compounds.
3. Diborane reacts with paraffins to form polymeric reaction products containing boron, carbon, and hydrogen. Breakdown and synthesis of hydrocarbon chains effected by the diborane obscures the nature of the reaction.

Experimental

The general technique employed in studying the addition and substitution reactions was to seal mixtures of diborane with various hydrocarbons in heavy-walled Pyrex tubes. The tubes were frozen in liquid nitrogen and evacuated before sealing. The tubes then were encased in protecting tubes of steel pipe and either heated in an oven or allowed to stand at room temperature. After the time allotted for the reaction had elapsed the tubes were immersed in liquid nitrogen to freeze their contents, their tops were cracked off under a blanket of dry nitrogen, and the reaction products together with any unchanged materials were removed from the tubes, generally by distillation on a vacuum chain.

A. Reactions with Olefins. 1. Isobutylene.—The reaction of isobutylene with diborane was studied with mixtures containing from two to ten per cent. by weight of diborane. Within this range of composition no significant differences in the results were observed. Most of the reactions were conducted by heating the tubes at 100° for twenty-four hours but it also was noticed that the addition reaction took place at room temperature although somewhat more slowly. Since no pressure of noncondensable gas developed in the tubes during these reactions it was presumed that the addition of diborane to the olefin was rapid and almost quantitative. Otherwise the pyrolysis of unreacted diborane at the elevated temperature would develop a pressure of hydrogen that would become apparent when the tubes were opened.

Distillation of excess isobutylene from a reaction mixture left a clear colorless oil of low volatility. Upon exposure of this oil to the air it quickly became warm from spontaneous oxidation. Inflammation was observed if a few drops were placed on a filter paper or in a watch glass.

Fractionation of a fresh sample of the oil under a nitrogen atmosphere in a distillation column of approximately twenty plates separated the sample into two fractions of almost equal volume, one boiling at 181.5° and the other at 188.5°. The boiling point calculated from reduced pressure data for tri-*t*-butylboron is 182°[2] and the reported boiling point of tri-isobutylboron is 188°.[3] Each fraction was shaken individually in a separatory funnel with aqueous sodium hydroxide and air until the oil had been oxidized completely and had been dissolved as the sodium salt of the corresponding butylboric acid. The solutions were concentrated by boiling and, after cooling, were neutralized by the addition of hydrochloric acid. This caused the precipitation of the white crystalline butylboric acids. A determination was made of the melting points of the isomeric acids thus isolated and the values obtained checked very closely with those reported in the literature (*t*-butylboric acid, m. p. 113–114°; reported m. p. 113°[2]; isobutylboric acid, m. p. 112–113°; reported m. p. 112°[3]). Although these two butylboric acid isomers have melting points lying within one degree of each other it was clear that the original reaction product comprised a mixture of isomeric tributylboron compounds since oxidation of an unfractionated sample of the oil and isolation of the mixed butylboric acids by the technique described above yielded a crystalline white solid with no sharply defined melting point melting over the range from 80–90°.

2. Ethylene.—Ethylene containing two per cent. by weight of diborane was heated at 100° for four days. The tube then was opened and the unreacted ethylene was removed by distillation on the vacuum chain. A small amount of clear liquid remained in the tube. This liquid inflamed immediately upon exposure to air. Since the liquid had an appreciable volatility it could be analyzed most conveniently on the mass spectrometer. Strong maxima in the pattern indicated large amounts of triethylboron. Examination of a vapor sample taken during the last stages of the removal of ethylene from the sample revealed no volatile ethyldiborane compounds.[4]

B. Reaction with Benzene.—Pure benzene was heated with five per cent. by weight of diborane in sealed tubes or in a stainless steel bomb for twelve hours at 100°. During the course of the reaction it was observed that the benzene gradually developed a dark yellow color. Upon opening the tubes after freezing the contents in liquid nitrogen it

(1) Presented before the Physical and Inorganic Division, American Chemical Society, New York, September, 1947.

(2) E. Krause and P. Nobbe, *Ber.*, **64B**, 2112 (1931).

(3) E. Krause and R. Nitsche, *ibid.*, **54**, 2784 (1921).

(4) These analyses were performed by Dr. Francis J. Norton.

was noticed that a large pressure of non-condensable gas, presumably hydrogen, had developed. The benzene solution of the reaction products was removed from the tubes in a nitrogen atmosphere.

Evaporation of the unreacted benzene from a sample of the solution left a soft solid material. This solid partially dissolved in water with the evolution of gas to give a milky solution. When this solution was made alkaline with sodium hydroxide and boiled it eventually became clear. After cooling the solution it was neutralized, extracted with ether, and the ether extract was evaporated to yield a white crystalline solid, m. p. 214° (reported m. p. for phenylboric acid 216°[5]). The identity of this compound as phenylboric acid was verified by specific chemical tests for this material, *i. e.*, by the precipitation of white phenylmercuric chloride (m. p. 251°) with mercuric chloride from a very dilute solution, by the thermal dehydration of the acid to its cyclic anhydride (m. p. 190°), and by the slow deposition of a silver mirror from ammoniacal silver nitrate solution.[6]

This experiment established that a substitution reaction occurred between benzene and diborane with the formation of phenylboron compounds.

An examination of the yellow benzene solution removed from the reaction tubes was made with the aid of the mass spectrometer. Samples were concentrated to varying degrees by removing benzene on a vacuum distillation system and analyses were made of the residual solutions. It was found, surprisingly enough, that diborane continued to be given off by the solutions even when most of the benzene had been removed and the samples were highly concentrated. The mass spectrographic analyses showed no evidence of any volatile phenylborane compounds, *i. e.*, phenylboron hydrides. These were indicated indirectly however since the benzene volatilized *in vacuo* from the samples gave upon shaking with water, solutions which responded to the very sensitive mercuric chloride test for phenylboric acid (not shown by benzene or diborane alone).

The residue after complete removal of the benzene was found to be of quite high molecular weight. No mass numbers between 130 and 220 appeared on the mass spectrometer. It was possible to isolate a material crystallizing in long prismatic needles from this residue by sublimation *in vacuo* at 100°. This material, believed to be triphenylboron, reacted rapidly with air to form a substance readily soluble in dilute sodium hydroxide. After neutralization of this solution it was possible to extract phenylboric acid (m. p. 215°) which in turn was verified by the specific tests for this compound as mentioned previously.

C. Reactions with Paraffins.—Methane was heated with six per cent. by weight of diborane for seventy-three hours at 180° in a stainless steel bomb. At the end of this time the bomb was frozen in liquid nitrogen and the non-condensable gas was pumped off. Volatilization of the unreacted methane left a small amount of less volatile liquid residue and a solid material containing both boron and carbon. Mass spectrographic analysis of the liquid portion of the reaction product revealed the presence of ethane, propane and butane, in addition to some mass numbers considered explainable as volatile methylboron compounds. Solution of the solid reaction product in water produced a large evolution of gas. The presence of boron bonded carbon in this material could be demonstrated by qualitative analysis.

Thirty-five grams of *n*-pentane and 1.5 g. of diborane were heated in the bomb for sixty-five hours at 180°. The bomb then was cooled in liquid nitrogen to freeze the contents, the non-condensable gas was bled off, and the bomb was evacuated. The bomb then was allowed to warm up slightly and the most volatile fraction of the reaction product was distilled off in the vacuum chain. This volatile material was fractionated further and the components were analyzed in the mass spectrometer. The material comprised roughly 40% methane, 40% ethane, and smaller amounts of other hydrocarbons including pentane.[7] After the bomb had warmed up to room temperature the residual pressure of volatile material was vented and the contents of the bomb were removed. Filtration separated a clear liquid from 3.5 g. of a light yellow powder of unknown composition containing boron bonded carbon. The liquid material was distilled and, with the exception of a very small amount of higher boiling material, the whole amount of liquid boiled at 36° or under.

Diborane and butane reacted only slightly at 100° in twenty-four hours although considerable polymerization of the diborane to decaborane occurred. Analysis of the very small amount of solid residue left after removal of the excess butane revealed only 3% of carbon, the balance being boron and hydrogen. A mixture of butane and five per cent. by weight of diborane heated at 200° for twenty-four hours reacted to yield a light tan powder containing 66% carbon. No analyses were made of the liquid fractions. Large pressures of hydrogen were built up in the tubes during these reactions.

The above experiments show that some substitution to form boron–carbon bonds does occur with diborane and paraffin hydrocarbons although the reactions involving breakdown and synthesis of paraffin chains under the influence of the diborane may be of major importance.

Discussion

There is a considerable amount of evidence on record to show that diborane may take part in many reactions in its monomeric form, that is as borine (BH_3).[8] It seems reasonable, therefore, although not necessary, to assume that in the addition and substitution reactions which diborane undergoes with hydrocarbons the active agent is the BH_3 molecule.

The borine molecule has, like the boron halides and the alkylborons, a strong tendency to accept and coördinate electrons. Thus by a mechanism similar to that proposed for the boron trifluoride activation of olefins a borine molecule could coordinate to one carbon of a carbon–carbon double bond to form temporarily a complex negative ion. Migration of a negative hydride ion (H^-) from the complex ion to the other carbon, positively charged by the withdrawal of electrons from the double bond, would result in a neutral molecule, RBH_2. This process then could be repeated with the remaining hydrogens attached to the boron atom to form eventually a molecule of trialkylboron, R_3B. Alternatively, the newly formed alkylborine molecule (RBH_2) could undergo disproportionation with similar molecules into trialkylboron and borine, a process known to occur readily with the alkyl derivatives of diborane.

Since breakdown of paraffin chains into smaller molecules does occur to a considerable degree under the influence of diborane (such an effect is observed with other strong acceptor molecules such as boron trifluoride and aluminum chloride) the addition or substitution of borine on the hydro-

(5) E. Krause and R. Nitsche, *Ber.*, **55**, 1261 (1922).

(6) These tests are described in Krause and von Grosse, "Die Chemie der Metall-organischen Verbindungen," Borntraeger, Berlin, 1937, pp. 212–214.

(7) The author wishes to think Dr. Paul Zemany for these analyses.

(8) For example, diborane dissociates into monomeric borine in its reaction with carbon monoxide to form borine carbonyl. See A. Stock, "The Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N. Y., 1933.

carbon fragments could only result in a complicated mixture of compounds. The observed synthesis of paraffin hydrocarbons from methane and the formation of polymeric solids indicates the complexity of these reactions. It is suggested that in the reaction of diborane with olefins or aromatic hydrocarbons this effect will make isolation of the primary reaction products difficult or impossible if the reaction conditions are severe or if relatively large amounts of diborane are used.

The behavior of the reaction products from benzene and diborane suggests that the intermediate phenyldiboranes, if they are formed, are quite unstable and resemble chlorodiborane rather than the alkyldiboranes. Thus monophenyldiborane may exist at room temperature only in equilibrium with both diborane and triphenylboron. This behavior might be predicted in view of the electronegative character of the phenyl group.

This work has been directed toward outlining the general types of reactions that diborane and hydrocarbons may undergo. It is not unreasonable to assume that under different conditions reaction products other than those observed by the author may be obtained. For example, at lower reaction temperatures it may be possible to isolate intermediate alkylation products of diborane.

Summary

The reactions of diborane with hydrocarbons have been investigated at elevated temperatures using low concentrations of diborane. Under these conditions:

1. The addition of diborane to olefins results in the formation of trialkylborons.
2. A substitution reaction occurs with benzene to form phenylboron compounds.
3. The reactions of diborane with paraffins are complex and involve paraffin chain breakdown and paraffin chain synthesis as well as the formation of boron–carbon bonds.

SCHENECTADY, NEW YORK RECEIVED MARCH 3, 1948

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Spontaneous Ignition of Nickel Carbonyl Vapor. The Ignition of *n*-Butane[1]

BY ELMER J. BADIN, PAUL C. HUNTER AND ROBERT N. PEASE

Earlier papers[2] from this Laboratory have described the spontaneous ignition of zinc dimethyl and of boron triethyl vapors in oxygen, and the oxidation of *n*-butane induced thereby. Similar experiments with nickel tetracarbonyl are here reported.

The apparatus for these experiments was of conventional design.[2] It need only be mentioned that a clean, dry reaction bulb (6.5 cm. diameter) was used for each experiment, and that the bulb was thermostatted at 20°. Nickel carbonyl was obtained through the Matheson Company and fractionated in a nitrogen atmosphere before use (b. p. 43.5°). Oxygen and air were dried before using.

Precise measurements of explosion limits were prevented by the occurrence of long and variable induction periods (up to at least 1000 sec.). Thus, out of 6 experiments on 30 mole % nickel carbonyl in oxygen at 110 to 120 mm. total pressure, explosion occurred almost immediately on admitting the oxygen in two cases; after 30 and 325 seconds in two cases; while there was no explosion in 1000 seconds for two other trials. In another set of 12 experiments on 10% nickel carbonyl in dry air between 150 and 200 mm. total pressure, successes and failures (over 1000 seconds) were spread rather uniformly over the whole pressure range.

The reason for this irreproducible behavior is not clear. In some experiments with long induction periods, a film would form slowly at some point on the surface of the bulb. This could indicate dissociation of the carbonyl, since Mittasch's equilibrium data[3] indicate considerable dissociation at equilibrium even at 20° and 180 mm. A free nickel surface would seem to be ideal as a point from which inflammation could spread. Nevertheless, the formation of a white fog in the body of the gas always immediately preceded explosion, as if the initiating reaction were homogeneous. In this connection it is of interest that Berthelot[4] reported explosions of dry nickel carbonyl–oxygen mixtures at room temperature only if the mixture were abruptly expanded in a buret over mercury, or if the buret were shaken violently. This might suggest ionization due to friction between the mercury and the glass container. Though our mixtures were quiescent at the time of explosion, it is conceivable that an extraneous disturbance is involved. The behavior, however, might be still due to indeterminate differences or non-uniformity in the clean Pyrex surfaces used.

In Table I are reported the lowest pressures at which explosion was observed within 1000 seconds. Minimum values were quite low and only moderately different for oxygen as compared to air,

(1) The work described in this paper was done in connection with Contract NOrd 7920 with the United States Naval Bureau of Ordnance, as coördinated by the Applied Physics Laboratory, The Johns Hopkins University. Acknowledgment is due Dean Hugh S. Taylor, who has general supervision of this project.

(2) E. J. Badin, D. R. Walters and R. N. Pease, THIS JOURNAL, **69**, 2586 (1947); R. S. Brokaw, E. J. Badin and R. N. Pease, *ibid.*, **70**, 1921 (1948).

(3) Mittasch, *Z. physik. Chem.*, **40**, 1 (1902).

(4) Berthelot, *Ann. chim. phys.*, [6] **26**, 555 (1892).

except for mixtures with excess of carbonyl (40%). They are substantially below those reported by Garratt and Thompson[5] and by Bawn[6] at higher temperatures (40–60° 100–45 mm. nickel carbonyl) when oxygen was admitted slowly to the nickel carbonyl vapor. According to these authors, the induction period is still considerable even at the higher temperatures.

TABLE I

LOWEST OBSERVED EXPLOSION PRESSURES OF $Ni(CO)_4$ IN OXYGEN OR AIR AT 20°

Clean Pyrex bulb, 6.5 cm. diameter. Induction periods up to 1000 seconds

$Ni(CO)_4$, mole %	Total press., mm.	Part. press., $Ni(CO)_4$
In oxygen (Stoich. 28.5 mole % $Ni(CO)_4$)		
10	115	12
30	115	35
40	150	60
In air (Stoich. 7.8 mole % $Ni(CO)_4$)		
10	145	15
20	160	32
40	280	112

A summary of analytical data may be added. After explosion, the gas was found to be mainly carbon dioxide (CO_2/CO = 4 to 40). Solid residues varied in composition from 60 to 81.7% Ni (NiO, 79.7% Ni).

Although we are not in a position to suggest a detailed mechanism for nickel carbonyl oxidation, it is tempting to correlate the induction period with a preliminary dissociation of the carbonyl[5]

$$Ni(CO)_4 \rightleftarrows Ni(CO)_3 + CO$$

followed by addition of oxygen

$$Ni(CO)_3 + O_2 \longrightarrow Ni(CO)_3 \cdot O_2$$

This would be in contrast to the behavior of the metal alkyls[2] whose unsaturated nature seems to permit direct addition of oxygen with negligible induction periods.

It was also found that nickel carbonyl would cause the explosion of *n*-butane–oxygen mixtures at 20°. There were long induction periods, and occasional violent explosions. For example, a mixture of 36 mm. of nickel carbonyl, 24 mm. of *n*-butane, and 140 mm. of oxygen exploded after 550 seconds, shattering the reaction bulb. With somewhat less nickel carbonyl it was possible to preserve the exploded mixtures for analysis, but the temperature had to be raised to 40° in order to obtain explosion in a reasonable time. Analytical data for carbon dioxide, hydrogen and oxygen are reported in Table II, as partial pressures. Olefins and paraffins were found to be present only in negligible amounts. Deficits in the material balance represent nickel compounds, water and other condensable products. The large amounts of carbon monoxide and hydrogen formed from rich mixtures are of interest, and leave no question that the hydrocarbon reacted.

TABLE II

PRODUCTS FROM THE EXPLOSION OF *n*-BUTANE–OXYGEN MIXTURES INDUCED BY NICKEL CARBONYL

Clean Pyrex bulb, 6.5 cm. diameter. Explosion at 40°, pressures measured at 20°. Initial pressure 200 mm.

Partial pressures, mm.							
Initial			Final				Final[a] press., mm.
$Ni(CO)_4$	*n*-C_4H_{10}	O_2	CO_2	CO	H_2	O_2	
25	0	175	86	2	0	122	210
25	10	165	131	2	2	41	176
25	18	157	147	17	9	9	182
25	25	150	103	81	45	10	239
25	35	140	62	158	102	7	329
25	45	130	26	223	173	9	431

[a] Corrected for vapor pressure of water, except in first experiment.

Summary

1. Nickel carbonyl vapor explodes in air or oxygen at 20° and partial pressures as low as 15 mm. Explosion is preceded by a long and variable induction period.

2. The existence of an explosion limit and induction period suggests a chain process. The exact mechanism of initiation is not known.

3. Addition of nickel carbonyl to a *n*-butane–oxygen mixture causes the latter to react at 20–40°.

PRINCETON, NEW JERSEY RECEIVED OCTOBER 18, 1947

(5) A. P. Garratt and H. W. Thompson, *J. Chem. Soc.*, 1822 (1935).

(6) C. E. H. Bawn, *Trans. Faraday Soc.*, **31**, 440 (1935).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Inhibition of Lactic Acid Bacteria by Analogs of Pantothenic Acid[1]

BY WILLIAM DRELL[2] AND MAX S. DUNN

The synthesis of the sodium salt of N-(α,γ-dihydroxy-β,β-dimethylvaleryl)-β-alanine (Fig. 1, $R_1 = CH_3$, $R_2 = H$), hereafter referred to as ω-methylpantothenic acid, was reported recently.[3]

The study of ω-methylpantothenic acid was undertaken to determine the effect of R_1 substituents on the activity of pantothenic acid toward lactic acid bacteria. Although most analogs of pantothenic acid possess little or no activity, two are partially active as growth promoters. Thus, N-(α-hydroxy-β,β-dimethylolbutyryl)-β-alanine[4] (Fig. 1, $R_1 = H$, $R_2 = OH$) and N-(α-hydroxy-β-methyl-β-methylolvaleryl)-β-alanine[5] (Fig. 1, $R_1 = H$, $R_2 = CH_3$) exhibit growth activity which is significant but less than that of pantothenic acid. Compounds which inhibit competitively or non-competitively the growth of microörganisms include salicylol-β-alanine,[6] mandelyl-β-alanine,[6] analogs of pantothenic acid lacking the α-hydroxy group[7,8] and analogs with different modifications of the β-alanine moiety.[9]

There was no adequate basis on which to predict the type of activity of ω-methylpantothenic acid, although the competitive inhibition exhibited is somewhat analogous to that shown by the methyl homolog (ethionine) of methionine,[10,11] the methyl homolog (β-aminobutyric acid) of β-alanine[12] and the 2-*n*-butylpyrimidine analog of thiamine.[13] However, the lower homologs of thiamine retain growth activity.[13] That ω-methylpantothenic acid is inactive as a growth promoter for *Lactobacillus casei*[5] was not known until the present experiments were completed.

Since pantoyltaurine inhibits the growth of microörganisms,[14] it was considered desirable to test this and other analogs of pantothenic acid and ω-methylpantothenic acid. Pantoyltaurine, pantoylglycine, pantoyl-DL-α-amino-*n*-butyric acid,

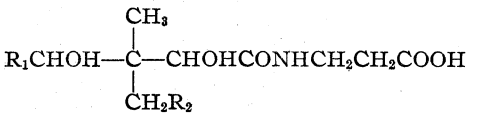


Fig. 1

pantoyl-DL-α-aminoisobutyric acid, pantoyl-DL-α-amino-α-ethyl-*n*-butyric acid, panto-DL-norvaline, ω-methylpantoyl-L-leucine and ω-methylpantoyltaurine were prepared by fusing the *dl*-pantolactones with the sodium salts of these amino acids or by refluxing the lactones and amino acid salts in methanol and precipitating the products with ether. It was found that ω-methylpantoyltaurine inhibited some lactic acid bacteria but that the other analogs were essentially inactive toward *Lactobacillus arabinosus* 17-5. That the α-amino acid analogs were inactive is in agreement with the observations on related α-amino acids reported by earlier workers.[7,15] While this work was in progress, it has been reported that pantoylglycine is inactive toward *Leuconostoc mesenteroides*[16] and that pantoylglycine and related analogs act as antivitamins for *Streptobacterium plantarum*.[17]

Experimental

α,α-Dimethyl-β-hydroxybutyraldehyde.—The method employed is essentially that of Lilienfeld and Tauss.[18] To a cold solution of 102 g. (2.31 moles) of acetaldehyde were added 166 g. (2.31 moles) of isobutyraldehyde and 200 ml. of a saturated aqueous solution of potassium carbonate. The mixture was stirred continuously and maintained below 30°. At the end of an hour the temperature began to rise rapidly and after two hours the reaction appeared to be complete. The viscous mixture was extracted with three 100-ml. portions of ether. The ether solution was washed with *N* acetic acid and saturated sodium bicarbonate solution and dried over sodium sulfate. The ether was removed and the fraction which distilled at 74–76° under 15 mm. (88–90°(22 mm.))[18] was collected in 30% yield.

α-Hydroxy-β,β-dimethyl-γ-valerolactone.—The method employed is essentially that of Stiller, *et al.*[19] To 74.5 g. (0.64 mole) of freshly distilled α,α-dimethyl-β-hydroxybutyraldehyde was added 200 ml. (20% excess) of sodium bisulfite solution. The mixture was stirred and heated on the steam-bath but a small amount of viscous material remained undissolved. The mixture was cooled to 5° and an aqueous solution of potassium cyanide (equivalent to the bisulfite) was added in small portions with stirring while maintaining the mixture between 5 and 10°. Stirring was continued for an hour at 10° and for an additional hour at room temperature. The aqueous and oily (cyanohydrin) layers were separated and the aqueous layer was extracted with three 75-ml. portions of ether. The combined solution of cyanohydrin and ether extracts was added

(1) Paper 44. For Paper 43, see Dunn, Camien, Shankman and Block, *Archiv. Biochem.*, in press. This work was aided by grants from the National Institute of Health of the U. S. Public Health Service and the University of California. Some of the material in this paper was presented before the Division of Biological Chemistry of the American Chemical Society at the New York City meeting in September, 1947.

(2) Junior Fellow, National Institute of Health.

(3) Drell and Dunn, THIS JOURNAL, **68**, 1868 (1946).

(4) Mitchell, Snell and Williams, *ibid.*, **62**, 1791 (1940).

(5) Nease, Dissertation, University of Texas, 1943.

(6) Martin, Lewis and Urist, Abstracts of Papers, 109th Meeting, Amer. Chem. Soc., 21B (1946).

(7) Barnett and Robinson, *Biochem. J.*, **36**, 357 (1942).

(8) McIlwain, *ibid.*, **36**, 417 (1942).

(9) An excellent review article has been presented by Roblin, *Chem. Rev.*, **38**, 255 (1946).

(10) Dyer, *J. Biol. Chem.*, **124**, 519 (1938).

(11) Harris and Kohn, *J. Pharmacol.*, **73**, 383 (1941).

(12) Nielson, *Compt. Rend. Lab. Carlsberg, Ser. physiol.*, **23**, 107 (1940).

(13) Emerson and Southwick, *J. Biol. Chem.*, **160**, 169 (1945).

(14) Snell, *J. Biol. Chem.*, **139**, 975 (1941); **141**, 121 (1941).

(15) Williams, *Advances in Enzymol.*, **3**, 253 (1943).

(16) Snell and Shive, *J. Biol. Chem.*, **158**, 551 (1945).

(17) Nielsen and Roholt, *Acta Pharmacol. Toxicol.* (*Copenhagen*), **1**, 207 (1945); *C. A.*, **40**, 6127 (1946).

(18) Lilienfeld and Tauss, *Monatsh.*, **19**, 77 (1898).

(19) Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1785 (1940).

with stirring to 250 ml. of concentrated hydrochloric acid maintained below 15°. The resulting solution was allowed to stand overnight at room temperature, the ether was removed and the acid solution was refluxed for three hours. The acid was neutralized to *p*H 7 and extracted 12 times with ether. The ether solution was evaporated to a volume of one liter and dried over sodium sulfate. The ether was removed and the fraction which distilled at 94–96° under 2 mm. (120–122° (9 mm.))[5] was collected. The yield was 58.5 g. (63%).[20] The lactone was crystallized by dissolving the sirup in dry ether, adding petroleum ether to the point of cloudiness and cooling the solution below 0°. Two recrystallizations from an ether–petroleum ether mixture gave white needles, m. p. 60–60.5°.

Anal. Calcd., for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.57; H, 8.54.

3,5-Dinitrobenzoate of ω-Methylpantolactone.—This derivative was prepared from approximately equivalent quantities of ω-methylpantolactone and freshly prepared 3,5-dinitrobenzoyl chloride in freshly distilled dry pyridine by the procedure of Stiller, *et al.*[21] After two recrystallizations from ethanol the compound melted at 123–124°.

Anal. Calcd. for $C_{14}H_{14}O_8N_2$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.83; H, 4.30; N, 8.61.

Sodium Salt of ω-Methylpantothenic Acid.—The sodium salt of β-alanine was prepared by adding an equivalent of base to the amino acid, evaporating the solution to dryness, and powdering the solid. A mixture of 1.58 g. of freshly distilled ω-methylpantolactone and 1.11 g. of the sodium salt of β-alanine was maintained for two hours at 110–120° with occasional stirring. The product was dissolved in 100 ml. of absolute isopropanol, the solution was cooled and the small quantity of white solid which settled was separated.

To about half the isopropanol solution was added 250 ml. of absolute ether. The resulting suspension was filtered and the precipitate was washed with ether and dried for five days at room temperature *in vacuo* over phosphorus pentoxide; yield, 1.3 g. This product contained isopropanol of crystallization.

Anal. Calcd. for $C_{10}H_{18}O_5NNa \cdot C_3H_8O$: N, 4.44. Found: N, 4.43, 4.46.

Two samples (160 and 190 mg.) of this product heated for three weeks at 70° *in vacuo* over phosphorus pentoxide changed from a pure-white to a light-tan color and attained nearly constant weight (loss <1 mg. in four days). The products appeared to be anhydrous and nearly pure.

Anal. Calcd. for $C_{10}H_{18}O_5NNa$: N, 5.49. Found: N, 5.45 (sample 1), 5.43 (sample 2).

It is of interest that Levy, *et al.*,[22] obtained calcium pantothenate with isopropanol of crystallization which could not be removed by drying *in vacuo* at 100°.

The remainder of the isopropanol solution was evaporated to about 15 ml. and preserved at 0°. The almost solid cake of precipitate which formed after two weeks was filtered and the precipitate was washed first with cold isopropanol and then with ether. The product was dried at room temperature *in vacuo* over phosphorus pentoxide. Yield of product, m.p. 160–161.5°, was 0.9 g. It was less hygroscopic and easier to handle than the sodium salts prepared in other ways. It has been observed that crystalline sodium *d*-pantothenate behaves similarly.[23]

Anal. Calcd. for $C_{10}H_{18}O_5NNa$: C, 47.05; H, 7.11; N, 5.49; Na, 9.01. Found: C, 47.65; H, 7.28; N, 5.48, 5.50; Na, 9.02.

Products obtained by fusion of the lactone and the sodium salt of β-alanine were dissolved in water and used directly in determining inhibitory effects of the analog. These materials were from 70 to 85% condensed according to Van Slyke amino nitrogen determinations.

Sodium Salts of Pantoyltaurine and ω-Methylpantoyltaurine.—These salts were prepared in crude form by fusing equivalent quantities of the lactone and the dry sodium salt of taurine for five hours at 110–120°.[14] According to amino nitrogen analyses, 55 to 85% condensation occurred. The compounds were purified by dissolving the fused products in absolute ethanol, filtering to remove the unreacted amino acid salts, precipitating the analogs with ether, and drying the products *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_8H_{16}O_6NSNa$ (pantoyltaurine): N, 5.05; Na, 8.30. Found: N, 5.12; Na, 8.36. Calcd. for $C_9H_{18}O_6NSNa$ (ω-methylpantoyltaurine): N, 4.81. Found: N, 4.59.

Some of the fusion products were used without purification since the presence of the uncondensed components was found to have relatively little effect on the response of the microörganisms.

Sodium Salt of ω-Methylpantoyl-L-leucine.—The analog was prepared by fusing equivalent amounts of ω-methyl pantolactone and the dry sodium salt of L-leucine for two hours at 110°. Amino nitrogen determinations before and after acid hydrolysis indicated 64% condensation. The product was used without further purification.

Sodium Salts of the α-Amino Acid Analogs of Pantothenic Acid.—These analogs were prepared[7] by refluxing equivalent quantities of *dl*-pantolactone and the amino acid salts in absolute methanol for two hours, filtering the solutions, and precipitating the compounds with ether. The nitrogen (Kjeldahl) of the products, dried *in vacuo* over phosphorus pentoxide, is shown below:

Analog (sodium salt) Name	Formula	Nitrogen, % Calcd.	Found	% Condensation
Pantoylglycine	$C_8H_{14}O_5NNa$	6.16	6.58, 6.61	85
Pantoyl-DL-α-aminobutyric acid	$C_{10}H_{18}O_5NNa$	5.49	5.58, 5.62	98
Pantoyl-DL-α-aminoisobutyric acid	$C_{10}H_{18}O_5NNa$	5.49	5.62, 5.68	97
Pantoyl-DL-norvaline	$C_{11}H_{20}O_5NNa$	5.20	6.40	77
Pantoyl-DL-α-amino-*d*-ethylbutyric acid	$C_{12}H_{22}O_5NNa$	4.95	6.46, 6.41	65

Testing Procedure.—The methods commonly employed in the authors' laboratory were used to determine the microbiological activity of the present compounds. The basal medium was Medium B given in Table I of a previous paper[24] modified in that amino acids, ammonium chloride and pantothenic acid were omitted and the following supplements were added per liter of diluted medium: casein hydrolysate,[25] 7.5 g. (solids); natural asparagine, 100 mg.; L-tryptophan, 50 mg.; L-cysteine hydrochloride, 200 mg.; and xanthine, 12 mg. Four-inch test tubes containing final 3-ml. volumes of solutions were covered with toweling, sterilized, inoculated with a syringe or automatic pipet, and incubated at 35° for seventy-two hours. The acid produced was titrated with standard approximately 0.04 *N* sodium hydroxide using brom thymol blue as indicator.

Results

The growth-promoting activity of ω-methylpantothenic acid for *Lactobacillus casei*, *Lactobacillus arabinosus* 17-5, *Lactobacillus fermenti* 36 and *Leuconostoc mesenteroides* P-60 was investigated in the present experiments but the data have been omitted to conserve space. There was no stimula-

(20) A large scale synthesis (9 moles) was carried out without purification of the intermediate aldol in an over-all yield of 38% based on acetaldehyde.

(21) Stiller, Keresztesy and Finkelstein, THIS JOURNAL, **62**, 1779 (1940).

(22) Levy, Weijlard and Stiller, *ibid.*, **63**, 2846 (1941).

(23) Parke and Lawson, *ibid.*, **63**, 2869 (1941).

(24) Dunn, Shankman, Camien, Frankl and Rockland, *J. Biol. Chem.*, **156**, 703 (1944).

(25) Green, Black and Howland, *Ind. Eng. Chem., Anal. Ed.*, **15**, 77 (1943).

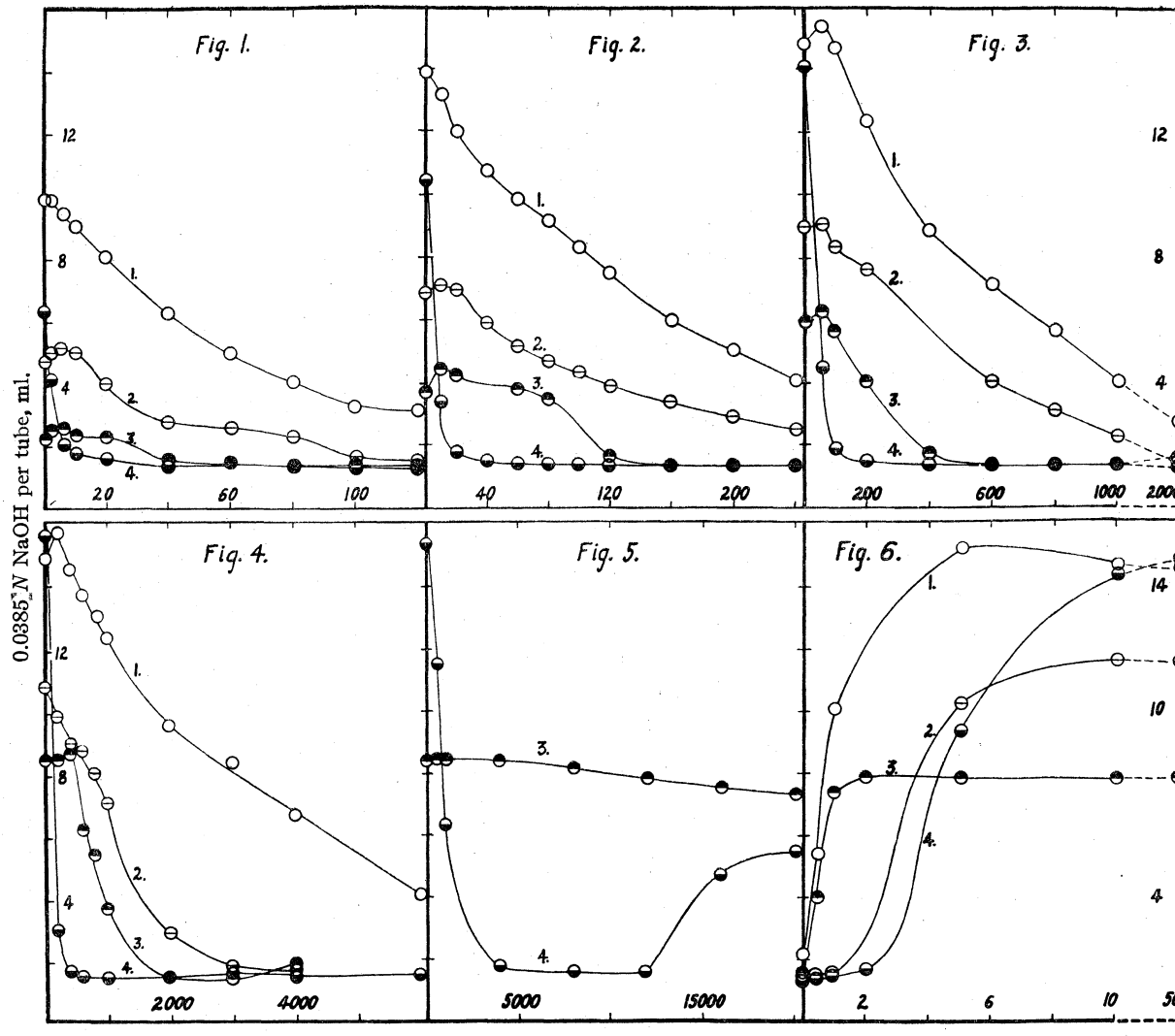


Plate I: Figs. 1–6.—The volumes of base consumed are plotted against γ of sodium ω-methylpantothenate added per tube in the presence of the following amounts of calcium *d*-pantothenate: 0.02γ (Fig. 1), 0.06γ (Fig. 2), 0.2γ (Fig. 3), 0.6γ (Fig. 4), and 2.0γ (Fig. 5). Figure 6 shows the response to increasing concentrations (γ) of pantothenic acid in the presence of 10,000 γ of sodium ω-methylpantothenate. The values at zero γ of pantothenic acid were obtained by extrapolation from other (not shown) data. The responses of four lactic acid bacteria are plotted as: (1) *Lactobacillus arabinosus* 17–5, (2) *Leuconostoc mesenteroides*, P-60, (3) *Lactobacillus fermenti* 36, and (4) *Lactobacillus casei*. Their "blank" titrations were 4.05, 2.33, 1.55 and 1.80 ml., respectively. The uninoculated blank was 1.15 ml. Points are averages of duplicate tubes.

tion at any level (0.01 to 1000 γ per tube) of analog and the "blank" acid production was suppressed. ω-Methylpantoyl-L-leucine was inactive except that at high levels (above 4000 γ) it diminished the blank titration values.

As shown in plate I, ω-methylpantothenic acid repressed the growth of the four lactic acid bacteria. The concentrations of analog required to inhibit the organisms were proportional to the concentrations of pantothenic acid in the medium, and the inhibition was competitive over a wide range in concentrations both of inhibitor and nutrilite. The direct reversal by pantothenic acid of the effects of ω-methylpantothenic acid is shown in Fig. 6, Plate I. Since growth of the organisms was normal in the presence of sufficient pantothenic acid, even at the highest level (20 mg./3 ml.) of inhibitor tested, it appears that ω-methylpantothenic acid is non-toxic for the bacteria investigated.

That the analog is stimulatory for some organisms under certain conditions is indicated by the data in Plate I. Examples of this effect at concentrations below the inhibition range are the stimulation of *L. fermenti* and *L. mesenteroides* (at 0.02, 0.06, and 0.2 γ of pantothenic acid) and *L.*

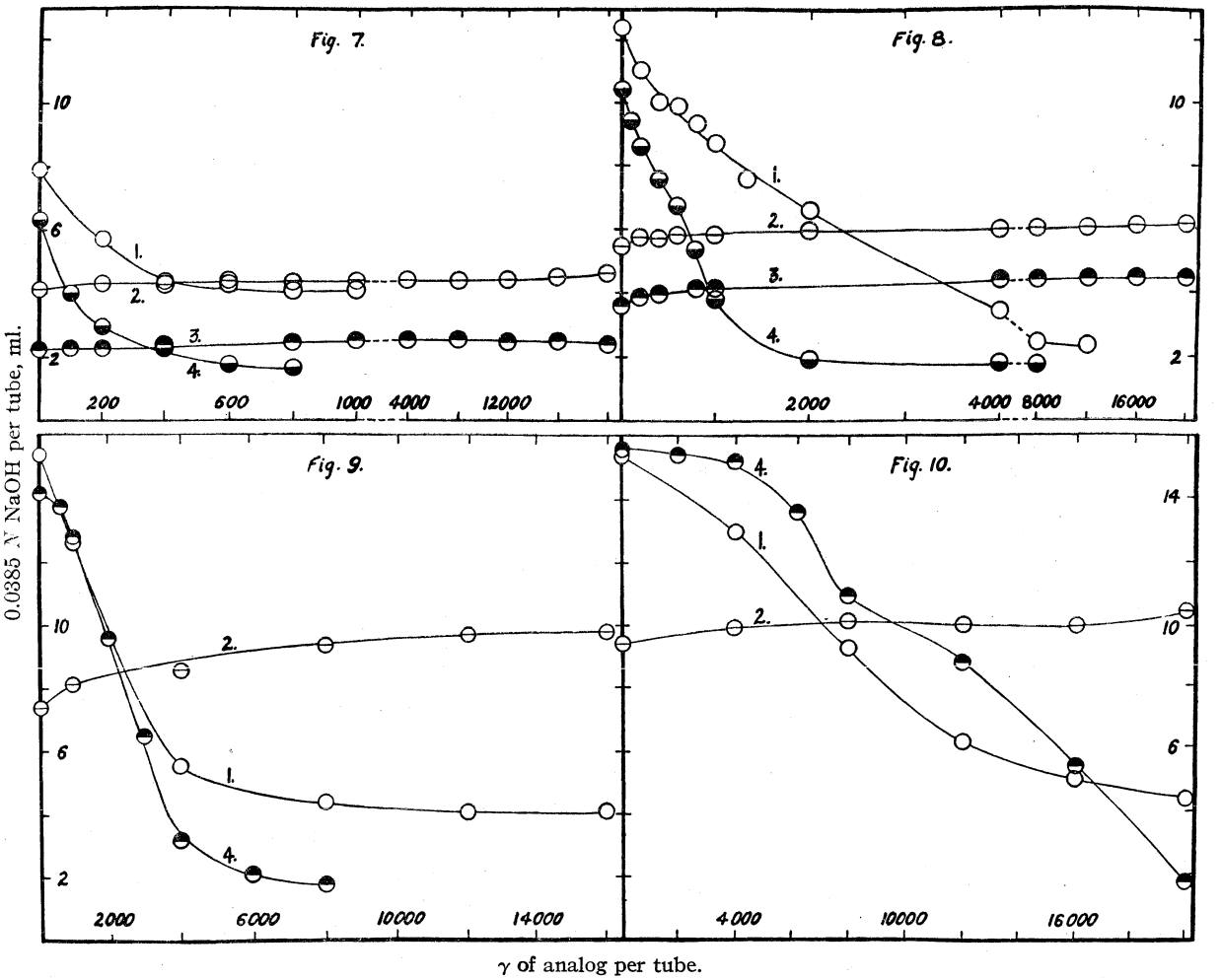


Plate II: Figs. 7–10.—The volumes of base consumed are plotted against γ of the sodium salt of ω-methylpantoyltaurine added per tube in the presence of the following amounts of calcium *d*-pantothenate: 0.02γ (Fig. 7), 00.6γ (Fig. 8), 0.2 γ (Fig. 9), and 0.6 γ (Fig. 10). The lactic acid bacteria are numbered as in Plate I and the blank titration values are the same except for *L. mesenteroides* P-60 (3.70 ml.). The values for *L. mesenteroides* and *L. fermenti* beyond 1000 γ and 8000 γ (Figs. 7 and 8, respectively) were calculated from data obtained in a separate experiment. Points are averages of duplicate tubes.

arabinosus (at 0.2 and 0.6 γ). After complete inhibition has been reached stimulation is observed in the cases of *L. casei* (at 2 γ) and *L. fermenti* (at 0.2 and 0.6 γ). That *L. arabinosus* and *L. fermenti* are not completely inhibited at 0.5 γ of pantothenic acid and 10000 γ of analog (Fig. 6), as would be expected, may be explained by this effect.

ω-Methylpantoyltaurine was found (Plate II) to inhibit the growth of only two of the four lactic acid bacteria. In both cases (*L. casei* and *L. arabinosus*) it was considerably less active than ω-methylpantothenic acid. *L. fermenti* and *L. mesenteroides* were stimulated by the analog, with growth increasing as the level was raised. No inhibition was observed at any concentration tested.

A study of pantoyltaurine under the same conditions was carried out for comparative purposes. It was observed (unpublished work[26]) that both *L. fermenti* and *L. mesenteroides* were stimulated up to high levels (2000–4000 γ) by the inhibitor. Stimulation was maximum at 1000 and 600 γ, respectively, and decreased thereafter as the level was raised leading to inhibition and complete cessation of growth. The degree of stimulation exerted by pantoyltaurine was nearly approached but not exceeded by its homolog.

The activities of the analogs described above are compared in Table I expressed in terms of the antibacterial index[8] (the molar ratio of inhibitor to growth promoter which inhibits completely the growth of the organisms.). It may be noted that the antibacterial indices of the analogs remained essentially constant over a wide range in

(26) Some of the data are summarized in the Thesis by W. Drell submitted in partial fulfillment of the requirements for the Master of Arts in Chemistry, June, 1946.

concentration of pantothenic acid in almost all cases. That the values rose significantly at the highest levels of nutrilite particularly at 2.0 γ with *L. casei* and *L. fermenti* probably was not due to differences in assay conditions.[27]

TABLE I

ANTIBACTERIAL INDICES OF PANTOTHENIC ACID ANALOGS AT VARYING CONCENTRATIONS OF PANTOTHENIC ACID

Analog	Ca *d*-pantothenate γ per tube	Antibacterial index[a] *Lactobacillus casei* 7469[c]	*Lactobacillus rabinosus* 17-5 8014[c]	*Lactobacillus fermenti* 36 9338[c]	*Leuconostoc mesenteroides* P-60 8042[c]
ω-Methylpantothenic acid	0.02	350	3000	1500	3000
	.06	260	3000	1600	3300
	.20	450	3900	1600	3900
	.60	450	5200	2200	3300
	2.0	950		>7500	
ω-Methylpantoyltaurine	0.02	12500	16500	[b]	[b]
	.06	16500	22000	[b]	[b]
	.20	14500	25000		[b]
	.60	16500	22000		[b]
Pantoyltaurine	0.02	13000	4000	150000	300000
	.06	15000	4700	130000	250000
	.20	15000	6200		

[a] Corrected for the per cent. condensation of the *dl*-analogs. [b] Stimulation observed. [c] American Type Culture Collection Number.

The relative concentrations of the analogs required for half-maximum inhibition and for complete inhibition were compared. In the case of ω-methylpantothenic acid, the ratio was approximately two for *L. fermenti* and *L. mesenteroides* and between two and three for *L. arabinosus*. With pantoyltaurine this ratio was about two for all three organisms. ω-Methylpantoyltaurine was required in larger than twofold amounts to achieve complete inhibition with *L. arabinosus*. *L. casei* required threefold or higher concentrations of all analogs.

In view of the results obtained, it was of interest to investigate further the comparative activity of these analogs against a large number of lactic acid bacteria particularly with reference to the mutual influence of the two combined inhibitory groups (ω-methyl and sulfonic acid). The responses of 19 organisms are summarized in Table II. All lactic acid bacteria tested were susceptible to inhibition by ω-methylpantothenic acid. The antibacterial indices ranged from 80 to 13000. Stimulation was observed in those cases (five) where concentrations of analog were sufficiently small to lie below the inhibitory level.

(27) Shive and Snell[28,29] have showed that time of incubation and concentration of inocula modify the responses of organisms to inhibitors of pantothenic acid. An example of the latter effect is illustrated by *L. arabinosus*. When, under otherwise uniform assay conditions, the density of the washed inoculum was increased markedly (from a blank titration value of 4.05 to 6.08 ml. of 0.0385 *N* sodium hydroxide) the antibacterial index of ω-methylpantothenic acid increased from 3000 to 12000. This difference cannot be due to an increase in nutrilite concentration alone. The synthetic ability of *L. arabinosus* (Shankman, Camien, Block, Merrifield and Dunn, *J. Biol. Chem.*, **168**, 23 (1947)) may play a more prominent role under these conditions.

(28) Shive and Snell, *Science*, **102**, 401 (1945).

(29) Shive and Snell, *J. Biol. Chem.*, **160**, 287 (1945).

TABLE II

ACTIVITY OF ANALOGS OF PANTOTHENIC ACID AGAINST LACTIC ACID BACTERIA

Organism	Antibacterial index[a] ω-Methylpantothenic acid	ω-Methylpantoyltaurine	Pantoyltaurine
Leuconostoc citrovorum 8082[b]	80[c]	2400[c]	4200[c,d]
Lactobacillus fermentatus 4006	150	51000[d]	113000
Lactobacillus pentoaceticus 367	270	175000	85000[g]
Lactobacillus brevis 8257	270	75000	140000
Leuconostoc citrovorum 797	330	7300[c]	8500[c,d]
Leuconostoc citrovorum 7013	330	6000[c,d]	5100[c,d]
Streptococcus faecalis R 8043	330	26000	35000
Lactobacillus helveticus 335	500[d]	51000[d]	42500[d]
Lactobacillus helveticus 6345	550[d]	44000[d]	57000[d]
Lactobacillus lycopersici 4005	800	[e]	51000
Leuconostoc dextranicum 8358	900	2200[c]	850
Leuconostoc dextranicum 8086	900	5000[c]	1350[c]
Leuconostoc mesenteroides 9135	900[c]	[e]	1350[c]
Leuconostoc mesenteroides 8293	1100	4400	7000[c,d]
Lactobacillus gayoni 8289	2200[d]	[e]	225000[d]
Leuconostoc dextranicum 8359	2700[d]	3500[c]	1400[c]
Lactobacillus pentosus 124-2	4000	[f]	[f]
Lactobacillus brassicae 8041	7500	[f]	[f]
Lactobacillus mannitopoeus	13000[c,d]	[e]	225000[d]

[a] Based on average values of duplicate tubes. Corrected for the per cent. condensation of the *dl*-analogs. [b] American Type Culture Collection Number. [c] The half-maximum point was achieved at a concentration of analog approximately half that required for complete inhibition of growth. [d] Stimulation was observed at concentrations below the inhibitory range. [e] Stimulation only was observed. Levels up to 20,000 γ in the presence of 0.06 γ of calcium *d*-pantothenate were tested. [f] Relatively little effect was observed at levels up to 20,000 γ in the presence of 0.06 γ of calcium *d*-pantothenate. [g] Half-maximum inhibition; growth was not completely repressed at the analog–metabolite molar ratio of 280,000.

Pantoyltaurine inhibited the growth of all but two (*L. pentosus* and *L. brassicae*) of the lactic acid bacteria tested. In most cases the activity was considerably less than that of ω-methylpantothenic acid. Two organisms (*Leuconostoc dextranicum* 8358 and 8359) were more susceptible to the latter than to pantoyltaurine. At levels below the inhibitory range, eight organisms were found to be stimulated and five (*L. fermentatus*, *L. pentoaceticus*, *L. brevis*, *L. pentosus*, and *L. brassicae*) appeared unaffected by pantoyltaurine. The responses of the remaining organisms were not determined in the experiment.

ω-Methylpantoyltaurine was less active than the β-alanine analog against all organisms tested, but in many cases it was more inhibitory than pantoyltaurine. Four organisms (*L. lycopersici*, *L. mesenteroides* 9135, *L. gayoni*, and *L. mannitopoeus*) exhibited stimulation with the analog of the type described previously for *L. fermenti* and *L. mesenteroides* P-60. With these bacteria inhibition was not observed at the levels tested (up to 20 mg. in the presence of 0.06 γ of pantothenic acid). In the cases of *L. pentosus* and *L. brassicae* neither stimulatory nor strong inhibitory effects were noted. At concentrations below the inhibitory level, four lactic acid bacteria were stimulated and one, *L. pentoaceticus*, was not. The responses of the other organisms inhibited by ω-methylpan-

toyltaurine were not determined at these low levels.

The relative concentrations of analogs required for half-maximum and complete inhibition were calculated for these organisms. Of the fourteen bacteria for which data at the half-maximum inhibition level were obtained with ω-methylpantothenic acid, a ratio of two was observed with three organisms. In the case of pantoyltaurine, seven of the sixteen organisms observed were of this type. With ω-methylpantoyltaurine, seven of thirteen organisms showed this behavior. The responses of these bacteria to pantoyltaurine had a high correlation to those obtained with ω-methylpantoyltaurine.

ω-Methylpantoylleucine showed relatively little inhibitory activity against four lactic acid bacteria (those listed in Table I were used) at levels as high as 20,000 γ in the presence of 0.02 γ of pantothenic acid. The uncondensed amino acids, β-alanine, L-leucine and taurine were inactive except for a slight inhibition of *L. casei* and *L. mesenteroides* by leucine (4000 γ) and of *L. arabinosus* by taurine (8000 γ). Somewhat greater inhibition, reversed by the nutrilite, was observed for ω-methylpantolactone in the absence, or at low levels, of pantothenic acid. The behavior of mixtures of the lactone and an amino acid resembled that of the lactone alone.

Discussion

That substitution at the ω-hydroxymethyl group of pantothenic acid leads to compound possessing inhibitory properties has been shown by the results given above and by investigations with other analogs.[30] This is in contrast to substitution at one of the ω-methyl groups whereby significant growth promoting ability is retained. It would seem therefore that methyl substitution in the former case produces a more significant change in the steric configuration, interfering in some manner with the normal functioning of the ω-hydroxy group. The relatively high activity of ω-methylpantothenic acid toward all lactic acid bacteria studied in comparison with the varying effectiveness of inhibitors such as pantoyltaurine and others is noteworthy. Of these β-methylpantothenic acid (N-pantoyl-β-aminobutyric acid)[28] although it shows a somewhat different bacterial spectrum, is the most similar to ω-methylpantothenic acid. The two inhibitors resemble each other further in that both contain methyl groups substituted in positions adjacent to functional groups.[31]

Lipmann and co-workers[32,33] have clearly demonstrated that the pantothenic acid in living organisms is largely bound in the form of a coenzyme. They have shown further that two distinct enzymes, phosphatase and liver enzyme, are required to liberate pantothenic acid for bacterial use, indicating that at least two groups of the growth factor are tied up. The work of Williams[34] has indicated that a point of attachment in the coenzyme is probably at the carboxyl group through an amide linkage, while the activity of phosphatase denotes phosphorylation of a hydroxy group. From the inhibitory activity of ω-methylpantothenic acid it might appear that the ω-hydroxy is the group so concerned. However, it is of interest that methyl substitution at the 2-hydroxyethyl group of thiamine, which is the site of phosphorylation, results in an analog which is entirely active upon the pea root, slightly so upon *Phycomyces blakesleeanus* and inactive upon the rat.[35]

It appears that ω-methylpantothenic acid and pantoyltaurine may interfere with the metabolism of pantothenic acid at different loci either in the same or in different reaction steps. This could account for their greatly different inhibitory activities as well as for the results observed with the hybrid, ω-methylpantoyltaurine. With the latter no synergism was encountered and its observed activity could be correlated in general with the relative inhibitory powers of its two parent compounds. In those cases where ω-methylpantothenic acid was considerably more active than pantoyltaurine, the hybrid was intermediate in strength between the two. If the parent analogs were of approximately equal activity the hybrid was weaker than either. In instances where pantoyltaurine was very weakly inhibitory and (very frequently) stimulatory at concentrations below the range of inhibition, the hybrid was found to exhibit only stimulatory activity. The effect might be one of further weakening in activity, in which case inhibitory effects would be encountered at much higher concentrations of inhibitor than those tested. The hybrid appears to be more sensitive to the variations induced by the sulfonic acid than by the ω-methyl group. In comparing the relative concentrations of inhibitor to produce half-maximum or complete inhibition with these organisms, greater correlation was obtained between pantoyltaurine and ω-methylpantoyltaurine than between the latter and ω-methylpantothenic acid. Against *L. brassicae* and *L. pentosus*, pantoyltaurine and likewise ω-methylpantoyltaurine were almost completely without effect. Further, neither analog was stimulatory at any of the levels tested. This response is similar to that observed with inactive pantoylleucine and ω-methylpantoylleucine.

The stimulation effects observed above have been reported with other inhibitory analogs of

(30) Drell and Dunn, Abstracts of Papers, 112th Meeting, American Chemical Society, 5C (1947).

(31) The inhibition of the growth of yeast by β-amino-*n*-butyric acid[12] presumably through interference in the utilization of β-alanine for the synthesis of pantothenic acid, may be considered a more direct analogy.

(32) Lipmann, Kaplan, Novelli, Tuttle and Guirard, *J. Biol. Chem.*, **167**, 869 (1947).

(33) Novelli and Lipmann, Abstracts Amer. Soc. Bact., Philadelphia, G-43 (1947); Lipmann, Kaplan and Novelli, *Fed. Proc.*, Part II, **6**, 272 (1947).

(34) Williams, in Evans, "Biological Action of the Vitamins," University of Chicago Press, Chicago, 1942, p. 122.

(35) Bonner and Erickson, *Amer. J. Bot.*, **25**, 685 (1938); Buchman and Richardson, THIS JOURNAL, **67**, 395 (1945).

pantothenic acid including phenylpantothenone,[36] N-pantoyl-β-aminoisobutyric acid[28,37] and N-pantoylisoserine.[28] The latter two compounds possessed weak growth-promoting properties in the absence of pantothenic acid, and in the presence of the nutrilite were inhibitory, but only to the level at which they had been stimulatory. Higher levels of the analog diminished the inhibitory effect. This type of behavior is comparable to that observed for ω-methylpantothenic acid particularly with *L. casei* at the 2 γ level of pantothenic acid. However, *L. casei* was not stimulated by the inhibitor in the absence of the nutrilite at any level tested.

Investigations of the pantothenic acid requirements and of the responses to ω-methylpantothenic acid for a large number of microorganisms (unpublished experiments) have shown that the analog inhibits only those bacteria which require the preformed nutrilite or are stimulated by it. Similar observations have been reported with other pantothenic acid analogs in cases of reversible inhibitions. It has been suggested[38] that the ineffectiveness of pantoyltaurine and related analogs in inhibiting microörganisms which might utilize pantoic acid or lactone may be due to the availability of these components in solution. This explanation is not tenable for ω-methylpantothenic acid although the possibility of inactivation of the analog through hydrolysis cannot yet be ruled out. However, it appears more likely that, as indicated by McIlwain,[8] pantothenic acid may be produced and utilized by these organisms in a form with which these analogs cannot compete.

Streptococci are susceptible to ω-methylpantothenic acid both *in vitro* and *in vivo*. In preliminary experiments it was found that mice were protected from an 80% fatal infection of a β-hemolytic streptococcus (Group A, type 23, no. 1072)[39] when the inhibitor was incorporated in a characterized diet at a molar analog–pantothenic acid ratio of 200 for four days prior to inoculation. Substituted amides of pantoyltaurine have been prepared which are effective against Group A *Streptococcus hemolyticus in vivo*.[40,41]

In view of the stereochemical specificity of the pantolactone moiety in pantothenic acid required for growth,[19] or in analogs which exhibit inhibitory activity,[14,16,41,42,43] it would be of interest to investigate the relative activities of the resolved isomers of ω-methylpantothenic acid. Presumably, at least one of the four possible isomers will show greater activity than the *dl*-compound.

Summary

ω-Methylpantolactone (α-hydroxy-β,β-dimethyl-γ-valerolactone) has been synthesized and condensed with β-alanine, taurine and L-leucine. It has been found that ω-methylpantothenic acid inhibits the growth of twenty-three strains of lactic acid bacteria which require pantothenic acid. That the inhibitory action is reversed competitively by pantothenic acid over wide ranges in concentrations has been shown with four lactic acid bacteria. The taurine analog has been shown to be less active than the β-alanine derivative, but more inhibitory than that containing L-leucine. The comparative activity of pantoyltaurine has been determined. The contributions of ω-methylpantothenic acid and pantoyltaurine to the activity of ω-methylpantoyltaurine have been discussed.

(36) Woolley and Collyer, *J. Biol. Chem.*, **159**, 263 (1945).

(37) Pollack, THIS JOURNAL, **65**, 1335 (1943).

(38) Stansly and Alverson, *Science*, **103**, 398 (1946).

(39) Obtained from the collection of Dr. Alice C. Evans, National Institute of Health, through the courtesy of Dr. M. V. Veldee, Chief of the Biologics Control Laboratory (see Evans, *J. Immun.*, **46**, 399 (1943)).

(40) White, Lee, Jackson, Himes and Alverson, *Fed. Proc.*, Part II, **5**, 214 (1946).

(41) Winterbottom, Clapp, Miller, English and Roblin, THIS JOURNAL, **69**, 1393 (1947).

(42) Kuhn, Wieland and Moller, *Ber.*, **74**, 1605 (1941).

(43) Lutz, Wilson, Deinet, Harnest, Martin and Freek, *J. Org. Chem.*, **12**, 96 (1947).

LOS ANGELES 24, CALIFORNIA

RECEIVED NOVEMBER 15, 1947

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

2-Thenyl Substituted Diamines with Antihistaminic Activity

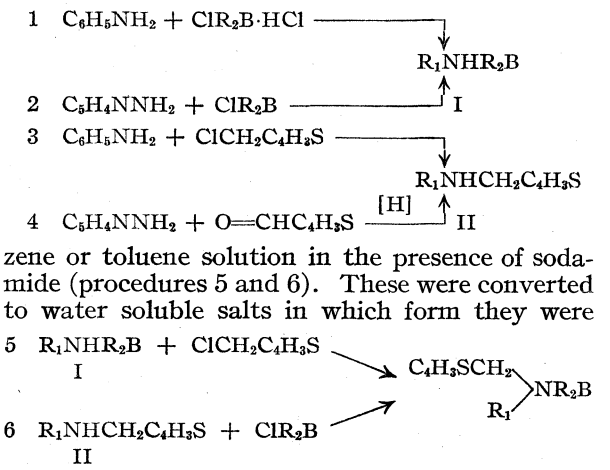
BY FREDERICK LEONARD AND ULRICH V. SOLMSSEN

A number of aminoalkyl ethers and alkylenediamines which exhibit antihistaminic activity have been discovered[1] and several have been adopted for clinical use. Since these substances are not without their undesirable side effects we prepared a series of 2-thenyl substituted alkylenediamines which conform to the general type $C_4H_3SCH_2$(R$_1$)N—R_2B, where R_1 is phenyl or 2-pyridyl, R_2 is a straight or branched alkylene chain containing two or three carbon atoms and B is a dimethylamino or piperidino group.

In a recent note[2] we reported the preparation and pharmacological activity of one of the compounds described herein, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-thenyl)-ethylenediamine,[3] the 2-thienyl analog of Pyribenzamine. Another of our compounds, N,N-dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine, the thiophene analog of Antergan has been described in the chemical literature.[4] However, prior to these publications we had prepared and evaluated it in these laboratories.

The intermediate secondary amines (I) and (II) were prepared by condensing aniline with a dialkylaminoalkyl chloride hydrochloride or 2-thenyl chloride (procedures 1 and 3), and 2-aminopyridine with dialkylaminoalkyl chlorides[1f,5] or 2-thiophenealdehyde followed by reduction[6] (procedures 2 and 4).

The tertiary amines were obtained by the alkylation of the intermediates (I) and (II) in benzene or toluene solution in the presence of sodamide (procedures 5 and 6). These were converted to water soluble salts in which form they were evaluated under the direction of Dr. N. Ercoli in the pharmacological laboratories of this institute.[7] Preliminary results have shown that several of the compounds described here have a range of antihistaminic activity similar to that of preparations now on the market. One of these N,N-dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine is characterized by a very low toxicity and a high order of activity. Viaud[4] found this compound to be inactive while Kyrides, *et al.*,[4] reported an activity which apparently is lower than that found in our laboratories.



All attempts to form either hydrochlorides or drobromides of N^2,N^2-dimethyl-N^1-phenyl-N^1-(2-thenyl)-1,2-propanediamine and N^2,N^2-dimethyl-N^1-(2-pyridyl-(2-pyridyl)-N^1-(2-thenyl)-1,2-propanediamine (amines 3 and 7, respectively) resulted in their decomposition.[8] Analytical data on amine 3 (obtained using both procedures 5 and 6) and its picrate and the picrate of amine 7 agreed with the theory. Since we were able to obtain stable picrates we attempted the formation of water soluble salts of organic acids and found that succinic acid gave stable bisuccinates.

The decomposition of N^2,N^2-dimethyl-N^1-phenyl-N^1-(2-thenyl)-1,2-propanediamine (amine 3)[9] under conditions of hydrochloride formation was observed when the removal of solvents from the

(1) (a) Aryloxyethyldialkylamines, Staub, *Ann. Inst. Pasteur*, **63**, 400, 485 (1939); (b) Benadryl, β-dimethylaminoethyl benzhydryl ether, Rieveschl and Huber, Paper 41 presented before the Medicinal Division of the American Chemical Society, Atlantic City, April, 1946; (c) Antergan, N,N-dimethyl-N′-phenyl-N′-benzylethylenediamine, Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942); (d) Neo-Antergan, N,N-dimethyl-N′-(2-pyridyl)-N′-*p*-methoxybenzylethylenediamine, Bovet, Horclois and Walthert, *Compt. rend. soc. biol.*, **138**, 99 (1944); (e) Antistin, 2-(N-benzyl-N-phenylaminomethyl)-imidazoline, Miescher, Urech and Klarer, *cf.* Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946); (f) Pyribenzamine, N,N-dimethyl-N′-(2-pyridyl)-N′-benzylethylenediamine, Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946); (g) N-(beta-dialkylaminoalkyl)-phenothiazines, Halpern, *J. Allergy*, **18**, 263 (1947).

(2) Ercoli, Schachter, Leonard and Solmssen, *Arch. Biochem.*, **13**, 487 (1947).

(3) The same compound has also been described by Weston, (THIS JOURNAL, **69**, 980 (1947)) and Clapp, Clark, Vaughan, English and Anderson (*ibid.*, **69**, 1549 (1947)) and its pharmacology studied by Lee, Dinwiddie and Chen (*J. Pharmacol. Exptl. Therap.*, **90**, 83 (1947)), Roth, Richards and Sheppard (*Federation Proc.*, **6**, I, 366 (1947)) and Litchfield, Adams, Goddard, Jaeger and Alonso, *Bull. Johns Hopkins Hosp.*, **81**, 55 (1947)).

(4) Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947); Kyrides, Meyer and Zienty, THIS JOURNAL, **69**, 2239 (1947).

(5) Whitmore, Mosher, Goldsmith and Rytina, *ibid.*, **67**, 393 (1945).

(6) General method of Tschitschibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

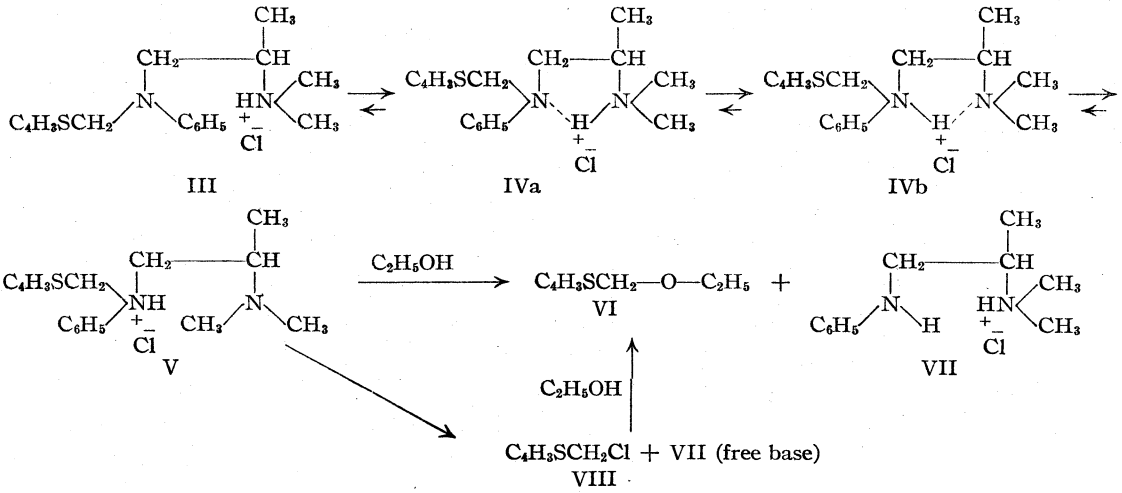
(7) A detailed account of these studies will be published in another journal.

(8) The work of Brode and Hill (THIS JOURNAL, **69**, 724 (1947)) and Schulz, Robb and Sprague (*ibid.*, **69**, 2455 (1947)) on the rearrangement of the isomeric 1,2-dimethylaminopropyl chlorides suggests that the condensation product of any alkylation involving the use of either of these halides would be a mixture of the desired substance and its isomer. We employed one of these halides in our investigation but made no effort to determine the amount of isomer obtained along with the 1,2-propanediamines reported here.

(9) It would seem that N^1,N^1-dimethyl-N^2-phenyl-N^2-(2-thienyl)-1,2-propanediamine may undergo the same type of decomposition as amine 3. The secondary amine (VII), therefore, was probably contaminated with its isomer.

neutralization mixture left a sirup which possessed an unexpected, strong sweet odor. Fractionation of the sirup yielded 2-thenyl ethyl ether (VI), N^2,N^2-dimethyl-N^1-phenyl-1,2-propanediamine (VII) and recovered tertiary amine.

We feel that this decomposition can be accounted for by the formulation[10]



The monohydrochloride (III)[11] which is obtained upon neutralization of amine 3 can be in equilibrium, because of intramolecular hydrogen bonding with the quasi-five-membered ring systems (IVa and IVb) which may open to yield (V). Since the electronegativity of the N^1-atom in amine 3 is small, due to the phenyl substituent, the localization of the proton at this point will further decrease the charge to such a low value that the strongly electropositive 2-thenyl radical will only be weakly bound. (V) will therefore be able to enter into metathetical reactions of the type $A^+B^- + C^+D^- \rightarrow AD + BC$ in much the same manner as esters of toluene sulfonic acids and some of the quaternary ammonium halides. In our case (III) was formed in the presence of ethanol (which was used as a solvent) with which its isomer (V) may have reacted to form 2-thenyl ethyl ether (VI) and N^2,N^2-dimethyl-N^1-phenyl-1,2-propanediamine hydrochloride (VII). The formation of these stable products would then shift the equilibrium of all the intermediate forms to the right. Another route to (VI) and (VII) may involve a decomposition of (V) to 2-thenyl chloride (VIII) and the free base of (VII). Subsequent reaction of (VIII) with ethanol would produce the ether (VI) and cause a shift of the equilibrium to the right as before.

Since all of our straight chain diamine monohydrochlorides are stable compounds it would seem that the instability of the hydrochlorides of amines 3 and 7 can be related to their C-methyl branch. It is conceivable that this substituent crowds the dimethylamino hydrochloride group at least close enough to the N-thenylanilino group for intramolecular hydrogen bonding, rearrangement and subsequent decomposition to occur. The degree of stability of all of these hydrochlorides therefore probably depends directly upon the internitrogen distance in the "horseshoe shaped" rotational configuration. This distance and the stability appear to be at a minimum in the branched chain diamines (III).

The stability of the picrate and bisuccinate salts of bases 3 and 7 may be due to the greater bulk of their anions which are unable to approach closely enough the nitrogen bearing the large phenyl and 2-thenyl groups to form an intermediate corresponding to (V). This would have the effect of keeping the electrical center of the molecule in the neighborhood of the nitrogen bearing the two methyl radicals and result in a stable configuration.

Experimental[12]

2-Thenyl chloride,[13] γ-dimethylaminopropyl chloride[14,15] and hydrochlorides of β-dimethylaminoethyl chloride,[16] β-piperidinoethyl chloride[17] and β-dimethylaminopropyl chloride[15,18] were obtained by methods described in the literature.

Procedure 1: N^2,N^2-Dimethyl-N^1-phenyl-1,2-propanediamine.—A mixture of 37.2 g. (0.40 mole) of aniline, 31.6 g. (0.20 mole) of β-dimethylaminopropyl chloride hydrochloride, 55.2 g. (0.40 mole) of anhydrous potassium carbonate and 100 cc. of dry toluene was stirred and refluxed for seven hours, cooled, water added and the organic

(10) This formulation can be applied equally well to the possible decomposition of the isomeric N^1,N^1-dimethyl-N^2-phenyl-N^2-(2-thenyl)-1,2-propanediamine.

(11) Since the *Kb* of dialkylamines is in general of the order of magnitude of 10^{-4} to 10^{-5} while that of N-alkylanilines is 10^{-10} it is reasonable to assume that the dimethylamino is more basic than the N-(2-thenyl)-anilino group and will be involved in the primary neutralization of the diamine.

(12) Microanalyses by Mr. L. Dorfman and Miss B. Baumgarten of this institute.

(13) Blicke and Leonard, THIS JOURNAL, **68**, 1936 (1946).

(14) Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

(15) Prepared by Dr. G. C. van Wessem.

(16) Slotta and Behnish, *Ber.*, **68**, 754 (1935).

(17) Blicke and Kaplan, THIS JOURNAL, **65**, 1967 (1943); Dunlop, *J. Chem. Soc.*, **101**, 2002 (1912).

(18) Office of The Publication Board, Department of Commerce, Report P. B. 981, p. 96-A.

TABLE I

HYDROCHLORIDES OF TERTIARY AMINES $C_4H_3SCH_2$(R1)$NR_2B \cdot HCl$

Compound 1 was recrystallized from alcohol, compound 3 from a mixture of ethyl methyl ketone and ether, compound 7 from ethyl methyl ketone. All of the others were recrystallized from a mixture of absolute ethanol and ether.

				Bases			Hydrochlorides		Analyses, %			
				B. p.					Nitrogen		Chlorine	
	R1	R2B	Procedure	°C.	Mm.	Yield, %	Formula	M. p., °C.	Calcd.	Found	Calcd.	Found
1	C_6H_5	$CH_2CH_2N(CH_3)_2$	5	183–185	7	69.8	$C_{15}H_{21}SN_2Cl$	186–187	9.44	9.44	11.95	11.90
2	C_6H_5	$CH_2CH_2NC_5H_{10}$	6	215–218	5	58.0	$C_{18}H_{25}SN_2Cl$	187–188	8.32	8.11	10.52	10.75
3	C_6H_5	$CH_2CH(CH_3)N(CH_3)_2$	5, 6	164–171	3	44.7, 77.0	$C_{20}H_{28}O_4SN_2$	99–100[a]	7.14	7.15		
4	C_6H_5	$CH_2CH_2CH_2N(CH_3)_2$	6	158–161	3	78.6	$C_{16}H_{23}SN_2Cl$	138–139	9.01	9.13	11.40	11.47
5	2-C_5H_4N	$CH_2CH_2N(CH_3)_2$	5	166–168	2	64.8	$C_{14}H_{20}SN_3Cl$	162–163	14.11	14.05	11.90	11.87
6	2-C_5H_4N	$CH_2CH_2NC_5H_{10}$	5	189–194	1	67.5	$C_{17}H_{24}SN_3Cl$	135–136	12.44	12.71	10.49	10.49
7	2-C_5H_4N	$CH_2CH(CH_3)N(CH_3)_2$	5	162–169[b]	1.5	53.2	$C_{20}H_{27}O_4SN_3$	101–102[a,b]	10.68	10.90		
8	2-C_5H_4N	$CH_2CH_2CH_2N(CH_3)_2$	6	171–174	4	33.1	$C_{15}H_{22}SN_3Cl$	122–124	13.43	13.28	11.33	11.54

[a] Bisuccinate. [b] Prepared by Dr. C. P. Huttrer.

layer separated. The aqueous phase was extracted with ether, the combined organic layers washed with water and dried. Solvents were removed and the residual oil fractionated. The amine was obtained as a yellow oil, b. p. 97–102° (3 mm.), $n^{25}D$ 1.5300; yield 26.1 g. (73.3%). It was characterized by conversion to a monopicrate, m. p. 158–159° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.20. Found: C, 49.83; H, 5.44; N, 16.91.

Procedure 2: N²,N²-Dimethyl-N¹-(2-pyridyl)-1,2-propanediamine.—A suspension of 14.16 g. (0.36 mole) of sodamide, 28.2 g. (0.30 mole) of 2-aminopyridine and 250 cc. of dry toluene was stirred and refluxed for two hours. Heating was stopped and a solution of 40.1 g. (0.33 mole) of β-dimethylaminopropyl chloride in 40 cc. of dry toluene added dropwise with stirring. The mixture was refluxed for five hours, cooled, water added, the organic layer separated, washed with water and dried. Fractionation gave 46.4 g. (86.5%) of the secondary amine, b. p. 128–131° (5 mm.), $n^{25}D$ 1.4969. The dipicrate melted at 210°.

Anal. Calcd. for $C_{22}H_{23}N_9O_4$: C, 41.44; H, 3.61; N, 19.78. Found: C, 40.92; H, 3.79; N, 19.78.

Procedure 3: N-(2-Thenyl)-aniline.—Aniline, 93.0 g. (1.0 mole) was dissolved in 150 cc. of dry benzene, 24.5 g. (0.25 mole) of anhydrous potassium carbonate added to the solution, the mixture heated to boiling and a solution of 33.0 g. (0.25 mole) of 2-thenyl chloride in 50 cc. of dry benzene added dropwise with constant stirring. The mixture was stirred and refluxed for four hours, cooled and worked up as in procedure 1. Fractionation at 12 mm. gave 34.0 g. (72.3%) of a product which boiled at 174–177°, solidified to a tan solid, m. p. 37–39°, and yielded a hydrochloride melting from 170–171°.

Anal. Calcd. for $C_{11}H_{12}NSCl$: N, 6.21; Cl, 15.71. Found: N, 6.32; Cl, 15.93.

Procedure 4: 2-(2-Thenylamino)-pyridine.—Freshly distilled 2-thiophenealdehyde,[19] 45.9 g. (0.41 mole) was added to a solution of 37.6 g. (0.40 mole) of 2-aminopyridine in 75 cc. of 95% formic acid. The mixture was refluxed for seventeen hours, diluted with water and neutralized from sodium hydroxide. The precipitate was washed with water and dried, m. p. 73–76°; yield 40.7 g., (53.5%). A sample recrystallized from a toluene–petroleum ether (b. p. 90–110°) mixture, melted at 78–80°.

Anal. Calcd. for $C_{10}H_{10}SN_2$: C, 63.12; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.16; N, 14.57.

Procedure 5: N,N-Dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine Hydrochloride.—A solution of 32.4 g. (0.198 mole) of N,N-dimethyl-N′-phenylethylenediamine[20] in 50 cc. of dry toluene was added to a suspension of 8.5 g. (0.217 mole) of sodamide in 100 cc. of dry toluene. The mixture was stirred and heated at 100° for three hours, heating discontinued and a solution of 28.8 g. (0.217 mole) of 2-thenyl chloride in 30 cc. of dry toluene added dropwise. After refluxing for two hours, the mixture was cooled and worked up in the usual way. Distillation *in vacuo* yielded 36.17 g. (69.8%) of a dark yellow oil, b. p. 183–185° (7 mm.), $n^{25}D$ 1.5902. Hydrochloride formation was generally effected by solution of the amine in ether and treatment of the resulting solution with a slight excess of ethanolic hydrochloric acid with cooling. In a number of instances the salt precipitated at once in crystalline form, in others it oiled out or remained in solution. In these cases it was necessary to remove the solvents *in vacuo* and crystallize the residual sirups. This amine was dissolved in 85 cc. of absolute alcohol and treated with 74.5 cc. (1% excess) of 1.885 *N* alcoholic hydrochloric acid. The monohydrochloride was filtered off, washed with alcohol and ether and dried; yield 35.6 g., m. p. 185–186°. Recrystallized from ethanol the salt melted at 186–187°.

Anal. Calcd. for $C_{15}H_{21}SN_2Cl$: C, 60.69; H, 7.13; Cl, 11.95. Found: C, 60.49; H, 7.11; N, 9.44; Cl, 11.90.

N²,N²-Dimethyl-N¹-(2-pyridyl)-N¹-(2-thenyl)-1,2-propanediamine Bisuccinate.—A stirred suspension of 8.5 g. (0.22 mole) of sodamide and 35 g. (0.20 mole) of N²,N²-dimethyl-N¹-(2-pyridyl)-1,2-propanediamine and 320 cc. of dry toluene was refluxed for two hours, heating stopped and a solution of 2-thenyl chloride in 30 cc. of toluene added dropwise. The mixture was refluxed for two hours, cooled and worked up as before to give the tertiary amine, b. p. 162–169° (1.5 mm.), $n^{25}D$ 1.5755, in 53.2% yield (29.3 g.). The dipicrate, recrystallized from acetone melted at 136–138°.

Anal. Calcd. for $C_{27}H_{27}N_9O_{14}S$: C, 44.20; H, 3.70; N, 17.18; S, 4.37. Found: C, 44.36; H, 3.89; N, 17.23; S, 4.68.

The bisuccinate formed in the same manner as that of the phenyl analog (see procedure 6) melted at 101–102° after recrystallization from ethyl methyl ketone.

Anal. Calcd. for $C_{19}H_{27}O_4SN_3$: C, 57.99; H, 6.92; N, 10.68. Found: C, 57.88; H, 6.93; N, 10.90.

Procedure 6: N²,N²-Dimethyl-N¹-phenyl-N¹-(2-thenyl)-1,2-propanediamine Bisuccinate.—A sodium salt prepared by stirring and refluxing for two hours a mixture of 29.8 g. (0.157 mole) of N-(2-thenyl)-aniline, 6.15 g. (0.157 mole) of sodamide and 240 cc. of dry benzene was treated dropwise with 19.2 g. (0.157 mole) of β-dimethylaminopropyl chloride in 45 cc. of dry benzene. The material was stirred and refluxed for eight hours and the product obtained in the usual way; b. p. 164–171° (3 mm.), $n^{25}D$ 1.5792; yield 34.5 g. (77.0%).

Anal. Calcd. for $C_{16}H_{22}SN_2$: C, 70.02; H, 8.08; N, 10.21; S, 11.68. Found: C, 70.13; H, 8.34; N, 10.09; S, 11.98.

(19) Dunn, Waugh and Dittmer, THIS JOURNAL, 68, 2118 (1946).

(20) Prepared in 81.5% yield by procedure 1. We found b. p. 100–104° (6 mm.), $n^{25}D$ 1.5395. Huttrer, Djerassi, Beears, Mayer and Scholz (ref. 1f) reported b. p. 103–107° (0.2 mm.), $n^{25}D$ 1.5380.

The base gave a monopicrate which melted at 139–140° after recrystallization from benzene.

Anal. Calcd. for $C_{22}H_{25}O_7SN_5$: C, 52.47; H, 5.00; N, 13.91; S, 6.37. Found: C, 52.39; H, 5.26; N, 14.09; S, 6.43.

The bisuccinate was formed by adding 11 cc. of a saturated alcoholic solution of succinic acid to a solution of 2.328 g. of the base in 10 cc. of ether. The mixture was kept at room temperature overnight, concentrated to a sirup *in vacuo* and crystallized under ether. Recrystallized twice from an ethyl methyl ketone–ether mixture, the salt melted at 99–100°.

Anal. Calcd. for $C_{20}H_{28}O_4SN_2$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.35; H, 7.37; N, 7.15.

Attempted Hydrochloride Formation of Amine 3 and Identification of Decomposition Products.—N^2,N^2-Dimethyl-N^1-phenyl-N^1-(2-thenyl)-1,2-propanediamine, 18.28 g. (0.059 mole) was dissolved in 27 cc. of dry ether, treated with 27.6 cc. of 2.15 *N* ethanolic hydrochloric acid, let stand at room temperature overnight and placed in the refrigerator. After several days the solution was evaporated and the sirupy residue found to have a strong, sweet odor. Water was added to the sirup, the solution made strongly alkaline with sodium hydroxide, the oily layer taken up in ether and the solution dried. After removal of ether the residual oil was fractionated *in vacuo*. Three definite fractions were obtained.

Fraction 1, b. p. 52° (3 mm.), $n^{25}D$ 1.5061, was the sweet smelling component. It was redistilled, b. p. 58.7° (5 mm.). 184–185° (760 mm.), $n^{25}D$ 1.5061 and analyzed.

Anal. Found: C, 58.69; H, 6.79; S, 23.00; N, 0.35.

Disregarding the nitrogen as a trace impurity the analysis indicates an empirical formula of C_7H_8SO or $C_7H_{10}SO$. The analytical and physical data agree reasonably well with that of 2-thenyl ethyl ether,[21] $C_7H_{10}SO$, which has the following constants: b. p. 84–86° (22 mm.), 181–182° (740 mm.), $n^{20}D$ 1.5062, and percentage composition C, 59.12; H, 7.09; S, 22.54.

Fraction 2, b. p. 106–108° (3 mm.), $n^{25}D$ 1.5321, was redistilled (b. p. 111–113° (4 mm.)) with no change in refractive index and gave a monopicrate which melted at 155–156°. This data and the analysis of the base was in good agreement with that of N^2,N^2-dimethyl-N^1-phenyl-1,2-propanediamine (see procedure 1).

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.72. Found: C, 74.33; H, 10.28; N, 15.56.

Fraction 3, b. p. 163–165° (3 mm.), $n^{25}D$ 1.5800. These constants showed that this fraction was recovered tertiary amine.

(21) Leonard, Ph. D. Thesis, University of Michigan, 1946.

Acknowledgment.—The authors wish to express their appreciation to Drs. H. M. Wuest and J. A. King for their interest in this project and to Mr. I. Ehrenthal for his help in a number of the preparations.

Summary

Six new and two previously reported 2-thenyl substituted diamines, $C_4H_3SCH_2(R_1)NR_2B$, have been synthesized in which R_1 is a phenyl or 2-pyridyl radical, R_2 is a straight or branched alkylene chain of two or three carbon atoms and B is a dimethylamino or piperidino group. An interesting decomposition of one of these in the presence of hydrogen halides has been observed, the products identified and a mechanism suggested.

113 WEST 18th STREET
NEW YORK, N. Y. RECEIVED DECEMBER 10, 1947

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

The Resolution of *dl*-Arterenol

BY B. F. TULLAR

Recently the resolution of *dl*-arterenol, α-aminomethyl-3,4-dihydroxybenzyl alcohol, was announced together with a brief description of the physiological characteristics of the active *l*-isomer.[1] The present paper deals with the method of effecting this resolution.

An observation that *dl*-arterenol is almost quantitatively converted to its methyl ether by evaporating *in vacuo* a solution of the hydrochloride in methanol[2] suggested that ether formation might occur during resolution attempts in anhydrous alcohols. Accordingly, aqueous alcohols seemed to offer more promise as resolution solvents.

The presence of water in the resolution mixture afforded an additional advantage since only the *l*-arterenol forms a *hydrated* salt with *d*-tartaric acid. This *l*-arterenol *d*-bitartrate monohydrate possesses greater solubility in aqueous methanol and considerably lower water solubility than does the *non-hydrated* *d*-arterenol *d*-bitartrate, permitting an easy separation of the diastereomers.

The bitartrates were purified by repeated recrystallization from water (*l* isomer) and from 95% methanol (*d* isomer) and converted to the free bases by treatment with ammonium hydroxide. The hydrochlorides were prepared by dissolving the base in isopropanol with slightly more than the calculated amount of concentrated hydrochloric acid and crystallizing by cooling.

d-Arterenol was racemized by heating at 90° for two hours in dilute hydrochloric acid solution with an 83% recovery of the racemic base.

Experimental

Resolution. (a) In Aqueous Methanol.—In a solution of 155 g. of *d*-tartaric acid in 100 ml. of water 169 g. of *dl*-arterenol was dissolved by vigorous stirring. The solution was diluted slowly with methanol to one liter. Crystallization was induced by scratching and after several hours at room temperature there was a nearly solid mass of crystals which was separated and washed with a little 90% methanol. After drying *in vacuo* at

(1) Tainter, Tullar and Luduena, *Science*, **107**, 39–40 (1948).

(2) A similar reaction of epinephrine was described by Öppinger and Vetter, *Med. u. Chemie*, **4**, 343–367 (1942), see *C. A.*, **58**, 5928 (1944). Johnson, *et al.*, THIS JOURNAL, **69**, 2945 (1947), reported alkylation of a hydroxymethylene group under quite similar conditions.

25° the white crystalline *d*-arterenol *d*-bitartrate[3] weighed 110 g., had m. p. 161–163° and $[\alpha]^{23}D$ +31.4° (*C* = 6% water).

***d*-Arterenol *d*-Bitartrate.**—The crystalline fraction was recrystallized twice from 95% methanol. After drying *in vacuo* at 25° the product weighed 58 g. and had m. p. 164–165° (cor.), $[\alpha]^{25}D$ +39.9° (*C* = 1.5% in water). A portion recrystallized from one-half its weight of hot water had the same constants. The solubility of this salt in water is greater than 20% at 25°.

Anal. Calcd. for $C_{12}H_{17}O_8N$: N, 4.40; C, 45.20; H, 5.33. Found: N, 4.30; C, 45.38; H, 5.44.

***l*-Arterenol *d*-Bitartrate Monohydrate.**—The resolution liquor was evaporated to dryness *in vacuo*. The residue was dissolved in 150 ml. of water at 60° and cooled to 2–3° for several hours with occasional stirring and scratching to induce crystallization. The heavy, crystalline precipitate was collected, washed with 95% alcohol and dried *in vacuo* at 25°. The crude salt amounted to 80 g. and had m. p. 90–115°. A portion was converted to base as described below and had $[\alpha]^{25}D$ −20° (*C* = 1.5% in water with 1 equiv. hydrochloric acid).

After three recrystallizations from equal weights of water, drying finally at 50° *in vacuo*, 28 g. of *l*-arterenol *d*-bitartrate monohydrate was obtained with the following constants: m. p. 102–104° (cor.) $[\alpha]^{25}D$ −11° (*C* = 1.6% in water). Recrystallization from 95% ethanol or from water did not change these values. This salt is soluble to more than 20% in water at 25°.

Anal. Calcd. for $C_{12}H_{17}O_8N \cdot H_2O$: H_2O, 5.35; N, 4.15; C, 42.48; H, 5.68. Found: H_2O, 5.34; N, 4.10; C, 42.73; H, 5.65.

(b) **Resolution in Water.**—The same quantities of *dl*-arterenol and *d*-tartaric acid as in (a) were dissolved in 300 ml. of water. By cooling to 3–5° and inducing crystallization by stirring and scratching there was a heavy precipitate after several hours. This was filtered off, washed with 30 ml. of ice-water and with 2 × 100 ml. of 95% alcohol and air-dried. The product weighed 135 g. and had m. p. 88–95°.

Recrystallization by dissolving in 135 ml. of water at 50° and after decolorizing with charcoal cooling to 2–3° for several hours gave 80 g. of nearly pure *l*-arterenol *d*-bitartrate, m. p. 94–98°. After two more such recrystallizations, 43 g. was obtained having m. p. 102–104.5° (cor.) and $[\alpha]^{26}D$ −10.8°.

From the aqueous resolution liquors by concentration and crystallization from aqueous methanol 110 g. of *d*-arterenol *d*-bitartrate having m. p. 161–165° was recovered.

***d*-Arterenol.**—A solution of 10 g. of the *d*-arterenol bitartrate of maximum rotation in 100 ml. of de-ionized water containing a trace of sodium bisulfite was cooled to 10° and treated slowly while stirring with 4 ml. of ammonium hydroxide solution. After fifteen minutes at 10° the microcrystalline precipitate was collected, washed with water, methanol and finally with ether. After drying *in vacuo* at 25° the colorless base weighed 5.2 g. and had m. p. 215–217°, dec., and $[\alpha]^{26}D$ +37.4° (*C* = 5% in water + 1 equiv. hydrochloric acid).

Anal. Calcd. for $C_8H_{11}O_3N$: N, 8.28; C, 56.75; H, 6.54. Found: N, 8.12; C, 56.77; H, 6.47.

***l*-Arterenol.**—*l*-Arterenol *d*-bitartrate monohydrate of maximum rotation was treated exactly as above. The colorless *l*-arterenol base from 10 g. of the salt amounted to 4.9 g. and had m. p. 216.5–218°, dec., and $[\alpha]^{25}D$ −37.3° (*C* = 5% in water with 1 equiv. hydrochloric acid).

Anal. Calcd. for $C_8H_{11}O_3N$: N, 8.28; C, 56.75; H, 6.54. Found: N, 8.21; C, 56.37; H, 6.61.

(3) When equivalent amounts of *l*-malic acid or of N-benzoyl-*l*-threonine were substituted for tartaric acid the corresponding salts of *d*-arterenol separated in about the same yield and degree of purity.

***d*-Arterenol Hydrochloride.**—To 10 ml. of isopropanol and 1.5 ml. of concentrated hydrochloric acid at 25° was added 1.69 g. of *d*-arterenol. The mixture was stirred until a clear solution was formed and then cooled to −10°. After fifteen minutes the crystalline precipitate was collected, washed with ether and dried *in vacuo* at 25°. The colorless *d*-arterenol hydrochloride weighed 1.4 g. and was very readily soluble in water. It had m. p. 146.8–147.4° and $[\alpha]^{27}D$ +39° (*C* = 6% in water). Recrystallization of this hydrochloride did not raise the melting point or rotation. Exposure of solutions of this salt to elevated temperatures (higher than 50°) during crystallization for even a few minutes lowers the melting point and rotation. This is also true of the *l*-arterenol hydrochloride.

Anal. Calcd. for $C_{11}H_{11}O_2N \cdot HCl$: N, 6.80; C, 46.72; H, 5.88. Found: N, 6.75; C, 46.95; H, 5.99.

***l*-Arterenol Hydrochloride.**—*l*-Arterenol was treated as above. One and sixty-nine one hundredths grams yielded 1.3 g. of colorless *l*-arterenol hydrochloride, having m. p. 145.2–146.4° and $[\alpha]^{25}D$ −40° (*C* = 6% in water).

Anal. Calcd. for $C_6H_{11}O_2N \cdot HCl$: N, 6.80; C, 46.72; H, 5.88. Found: N, 6.73; C, 46.98; H, 5.83.

Racemization of *d*-Arterenol.—One hundred and twenty grams of *d*-arterenol was dissolved in one liter of de-ionized water with 100 ml. of concentrated hydrochloric acid at 90°. After two hours at this temperature in a nitrogen atmosphere the solution was cooled to 20°, treated with Darco and filtered. The filtrate was made alkaline with 80 ml. of concentrated ammonium hydroxide at 10° and let stand until precipitation was complete. The base was collected, washed with water, alcohol and ether and dried *in vacuo* at 25°. One hundred grams of *dl*-arterenol was recovered, m. p. 190–191°, $[\alpha]^{22}D$ +0.6° (*C* = 5% in water as the hydrochloride).

***dl*-Arterenol Methyl Ether Hydrochloride,** [β-(3,4-Dihydroxyphenyl)-β-methoxyethylamine hydrochloride]. —One-hundred grams of *dl*-arterenol was suspended in 800 ml. of methanol and hydrogen chloride was passed in with stirring at 10° until a slight excess had dissolved and a clear solution resulted. The solution was concentrated at the water pump at 30–35° to a volume of 300 ml. when heavy crystallization occurred. The precipitate was collected at 0°, washed with cold methanol and ether and dried *in vacuo*, yielding 72 g. of a hydrochloride which was very easily soluble in water and had m. p. 170–171°. A sample of this salt in aqueous solution gave a green coloration with ferric chloride as does arterenol. *dl*-Arterenol hydrochloride has m. p. 141° (dec.).

Anal. Calcd. for $C_9H_{12}O_3N \cdot HCl$: OCH_3, 14.13; N, 6.38. Found: OCH_3, 13.41; N, 6.25.

A portion of the hydrochloride was converted to the free base as described above for *d*-arterenol. The base, which was appreciably soluble in water and methanol, had m. p. 109–112°.

Acknowledgment.—The author is indebted to M. E. Auerbach of these laboratories for determination of physical constants and analyses.

Summary

1. *dl*-Arterenol has been resolved through the acid tartrates.

2. The *d*- and *l*-base and hydrochloride were prepared.

3. *d*-Arterenol was racemized by heating with dilute acid.

RENSSELAER, NEW YORK RECEIVED JANUARY 3, 1948

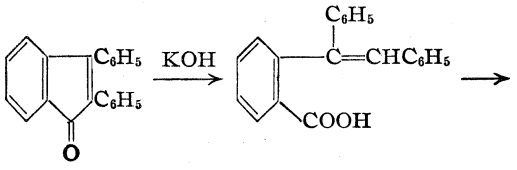
[COMMUNICATION NO. 1176 FROM THE KODAK RESEARCH LABORATORIES]

The Formation of 1,3-Diphenylisobenzofuran from 2,3-Diphenylindone

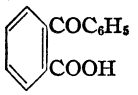
BY C. F. H. ALLEN AND J. A. VANALLAN

In earlier papers[1,2] it has been shown that alcoholic alkaline reagents give two types of reaction with carbonyl bridge compounds, depending on the nature of the substituent groups at the ends of the bridge. When these groups are phenyl, the bridge is cleaved at one end, a carboxylic acid resulting, whereas the presence of methyl groups favors a reduction of the carbonyl to carbinol. It seemed desirable to learn the behavior of a simpler phenylated ketone with the same sort of reagent.

2,3-Diphenylindone (I) was selected for study, since so many of the possible reaction products were at hand from our earlier work. It was previously known that, upon fusion with potassium hydroxide, the ring is cleaved, with consequent formation of *o*-α,β-diphenylvinylbenzoic acid (II).[3]



I II

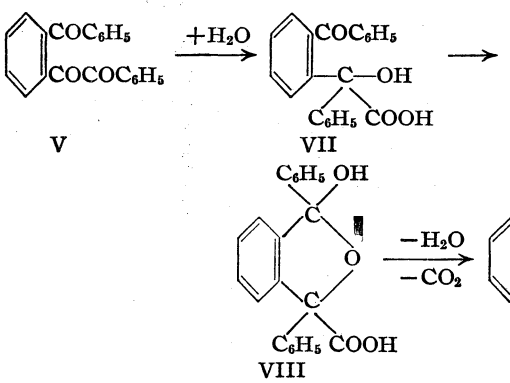


III

We found that cleavage takes place at the same point when a cymene solution of 2,3-diphenylindone is boiled with sodium amide. Under these conditions, however, the unsaturated acid was not isolated; instead, degradation proceeds to *o*-benzoylbenzoic acid (III).

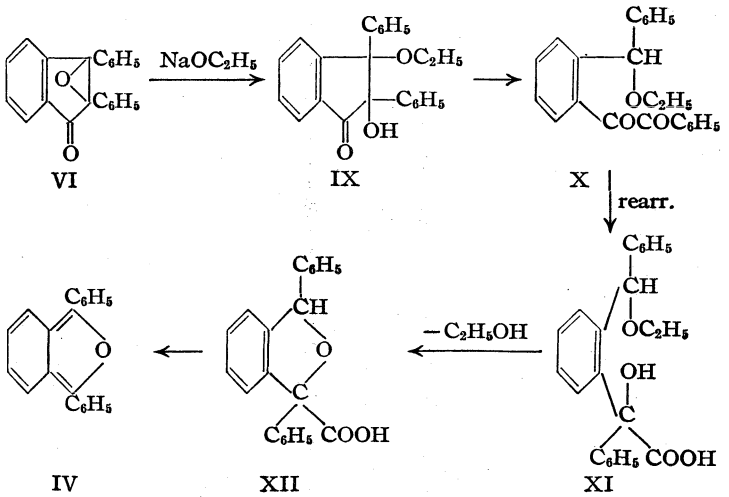
In view of these observations, it was anticipated that alkaline reagents in solvents such as water or alcohol would bring about the same result. Much to our surprise, however, after acidification, the principal reaction product was found to be 1,3-diphenylisobenzofuran (IV). This same furan was also formed in reactions between ethanolic potassium hydroxide and related substances such as *o*-benzoylbenzil (V) and 2,3-diphenylindone epoxide (VI). In the latter case, the yield is small. It is, thus, apparent that not only has there been a different mode of cleavage, but that it has been accompanied by a rearrangement, for in the furan one phenyl group is attached to each carbon atom directly connected to the ring. The route followed cannot be a simple reaction, since the empirical formulas of the indone and isobenzofuran differ by only one carbon atom.

The mechanism of the formation of a diphenylisobenzofuran (IV) from *o*-benzoylbenzil (V) seems obvious. The first step is probably a benzilic acid rearrangement to (VII); this is followed by intramolecular addition, to give the isomeric lactol which is a dihydrofuran (VIII); the last step is the elimination of carbon dioxide and water. The facile elimination of groups from the 1,3-positions of dihydrofurans is well known.[4]



V VII VIII IV

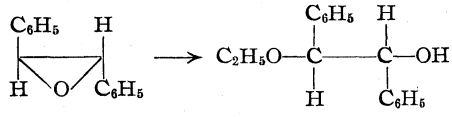
The mechanism of isobenzofuran formation from the epoxide (VI) and alcoholic potassium hydroxide is more complex. A plausible sequence of reactions is as follows: The oxide ring is opened in the presence of the potassium ethoxide, with consequent formation of the glycol ether (IX). The latter, by the reverse of an aldol reaction,[5] forms a benzil (X), which, in the alkaline alcoholic solution, undergoes a benzilic acid rearrangement



VI IX X XI XII IV

(1) Allen, Jones and VanAllan, THIS JOURNAL, **68**, 708 (1946).
(2) Allen, Jones and VanAllan, *J. Org. Chem.*, **11**, 268 (1946).
(3) Meyer and Weil, *Ber.*, **30**, 1281 (1897).
(4) Guyot and Catel, *Bull. soc. chim.*, [3] **35**, 1126 (1906).
(5) Allen and Gates, THIS JOURNAL, **65**, 1230 (1943).

to give (XI); elimination of alcohol closes the dihydrofuran ring (XII), from which formic acid is lost, to give 1,3-diphenylisobenzofuran (IV).[6] An analogy for the ring opening (VI–IX) is furnished by Read and Campbell's observation[7] that *l-trans*-diphenylethylene oxide, on standing in ethanolic solution, gave the monoethyl ether of *l*-isohydrobenzoin.



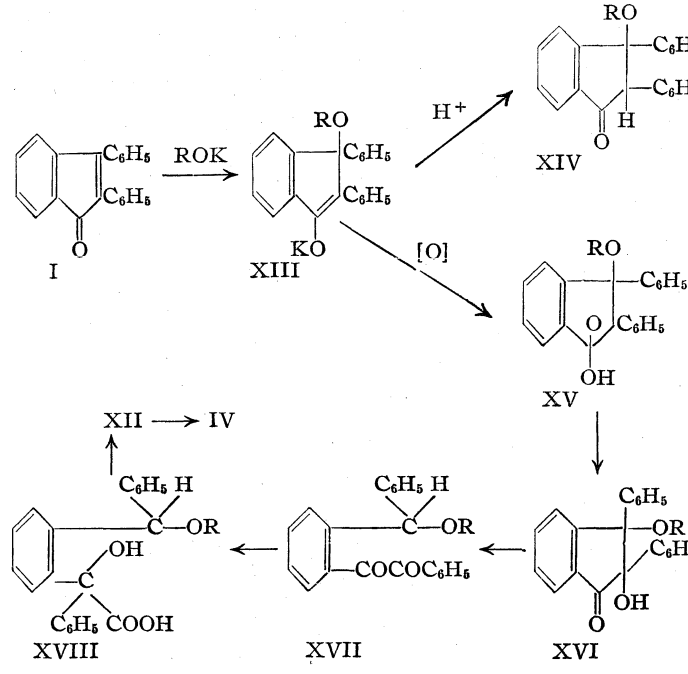
Since 2,3-diphenylindone likewise gives 1,3-diphenylisobenzofuran under the same conditions, it would seem that by some obscure process it must be first converted to either *o*-benzoylbenzil or the epoxide (VI). This indone has been reported to form an epoxide[5] when treated with alkaline hydrogen peroxide in aqueous alcoholic solution, and to form *o*-benzoylbenzil on permanganate oxidation.[8] However, there is no indication of the presence of either in the reaction mixture.

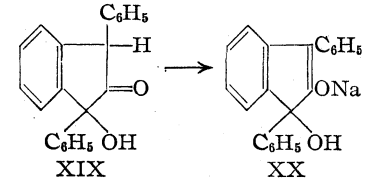
The yield of the isobenzofuran which is isolated from the reaction mixture is 50–55%. Upon concentration, the filtrate deposits two colorless substances. The one obtained in larger amount (25%), upon analysis, gave figures indicating that a molecule of the solvent, isopropyl alcohol, had been added to the indone. The second substance, isolated in a yield of 2–5%, analyzes for a glycol (XXI).

While there are several ways in which an alcohol might be added to the indone (I), it seems highly probable that 1,4-addition of the potassium alkoxide to the conjugated systems of double bonds has occurred, with consequent formation of an enolate (XIII). The free enol would undoubtedly isomerize to the isomeric β-alkoxyketone (XIV), which is the product isolated in 25% yield. This alkoxyketone gives a green color with concentrated sulfuric acid; the alcohol is lost and 2,3-diphenylindone regenerated.

Now it is well known that many enolates undergo spontaneous oxidation to oxanols.[9] In this instance, the oxanol (XV) can be considered as undergoing two successive reactions, each of which is the reverse of an aldol condensation (XV → XVII), to give an ether (XVIII) of a benzilic acid corresponding to (XI); the subsequent ring closure to a dihydroisobenzofuran (XII) and loss of formic acid then proceeds exactly as just outlined. The proposed sequence of reactions, as indicated by formulas XIII–IV, is supported by the observation that when one equivalent of alkoxide is used and the time decreased to one hour, only a very small amount of the isobenzofuran is formed, but the alcohol addition product can be isolated in a good yield.

Dufraisse[10] recently announced that 1,3-diphenylisobenzofuran (IV) resulted when an alkaline solution of 1,3-diphenyl-1-hydroxy-2-indanone (XIX)[11] was treated with air or oxygen (no reaction *in vacuo*); the gas was absorbed very rapidly, which led the authors to assume intermediate formation of an enolate.





In view of our conclusions, it is suggested that his observations can be correctly explained by a similar mechanism, involving oxidation of the metallic enolate (XX) to an oxanol, and so forth, through a dihydrofuran to the isobenzofuran (IV). By an alternative interpretation, the double bond in the enolate could be cleaved by oxidation to give the ketobenzilic acid (VII), with the subsequent steps as already outlined.

The glycol (XXI) is an isomer of one previously described.[5] It exhibits the same halochromism

(6) In footnote 22 [Bissinger, *et al.*, THIS JOURNAL, **69**, 2955 (1947)], it is noted that 3,4-epoxy-1-butene is opened in both possible ways by methanol under alkaline conditions. Other products that are formed from the 2,3-diphenylindone epoxide are retained in the untractable resinous material that is formed; this probably accounts for the low yield of furan.

(7) Read and Campbell, *J. Chem. Soc.*, 2379 (1930).

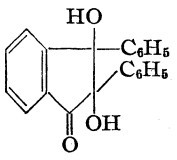
(8) Ivanov and Dalev, *Ann. univ. Sofia, II, faculté phys.-math.*, Livre 2, **33**, 305 (1937) [*Chem. Abs.*, **32**, 3371 (1938)].

(9) Kohler and Mydans, THIS JOURNAL, **54**, 4668 (1932).

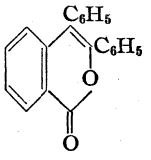
(10) Dufraisse and Ecary, *Compt. rend.*, **223**, 1143 (1946).

(11) Koelsch, THIS JOURNAL, **58**, 1324 (1936).

with sulfuric acid, and, like its isomer, is easily converted to the lactone (XXII). It, thus, appears that this is an instance of geometrical isomerism. The new glycol has a much higher melting point and is therefore assigned a *trans* structure. Its origin is not clear, but it probably arises from a *trans* ring opening of a little epoxide formed in the alkaline solution.



XXI

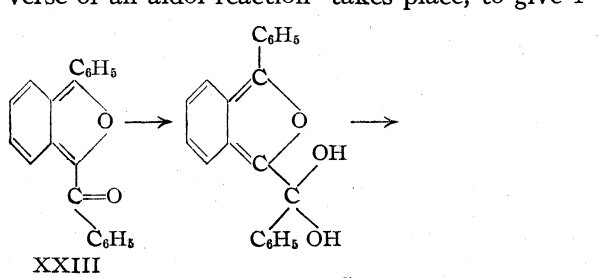


XXII

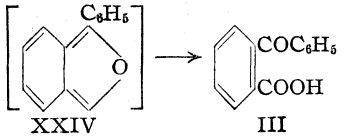
It has been reported[4] that 1,3-diphenylisobenzofuran in alcoholic solution is oxidized by air alone to *o*-dibenzoylbenzene. This observation has been checked and the time required found to be thirty-four hours. Since a high yield is obtained, the reaction makes available this hitherto relatively inaccessible diketone. The furan can be prepared either from 2,3-diphenylindone (I)[12] as described in this paper, or through Adams and Gold's procedure[13] which starts with a diene synthesis.

This remarkably easy oxidation procedure was applied to 1 - phenyl - 3 - benzoylisobenzofuran (XXIII).[5] The same type of reaction took place, and *o*-benzoylbenzil (V) was obtained in high yield.

It seemed that if potassium hydroxide were added to a solution of 1-phenyl-3-benzoylisobenzofuran before aeration the reaction should not stop with formation of the diketone, but should continue, as described earlier in this paper, to 1,3-diphenylisobenzofuran; the latter would, thus, be obtained in a single operation from 1-phenyl-3-benzoylisobenzofuran. However, *o*-benzoylbenzoic (III) and benzoic acids were formed in excellent yield. Two mechanisms could account for such a result. In the first, an equivalent of water adds to the carbonyl group, after which the reverse of an aldol reaction[5] takes place, to give 1-phenylisobenzofuran (XXIV) and benzoic acid. The furan is then oxidized by air, as in the other instances. By the second mechanism, *o*-benzoylbenzil is produced by aerial oxidation, whereupon the 1,2-diketone is cleaved by further alkaline oxidation. This suggestion seems less likely, for 1,2-diketones are cleaved by alkaline peroxides, rather than through aerial oxidation.



XXIII



XXIV III

An apparent exception to the easy oxidation of isobenzofurans has been noted in the case of the 1,3-dibenzoyl derivative.[14] This deep red substance was reported as not being further oxidized. Such a discrepancy, along with the unusual color of the substance, suggests that a reinvestigation is in order.

Experimental

Formation of 1,3-Diphenylisobenzofuran (IV). A. From 2,3-Diphenylindone.—To a solution of 1.6 g. of potassium hydroxide in 75 ml. of isopropyl alcohol was added 4 g. of 2,3-diphenylindone,[12] and the mixture was refluxed for ten hours. The red solid slowly dissolved, giving a brownish solution. After pouring into water, the cooled solution was extracted with ether to remove alkali-insoluble material, treated with Norite, and acidified. The yellow solid was taken up in benzene, the solvent evaporated, and the residue triturated with methanol and recrystallized from alcohol. It melted at 127° and showed no depression when mixed with an authentic sample. The yield was 51%; with ethanol as solvent, the yield dropped to 44%, while it was less than 2% with methanol.

From a similar-sized run, in which one equivalent of sodium isopropoxide was used, and the time reduced to one hour, under 0.1 g. of isobenzofuran was obtained. The oily material is easily separated from 0.2 g. (3%) of the glycol (XXI) but crystallizes very reluctantly. The solid that does separate is a mixture of the alcohol addition product (XIV) (31%) and unchanged starting material (5%).

B. From *o*-Benzoylbenzil.—A mixture of 1.2 g. of *o*-benzoylbenzil[8] and 10 ml. of 10% potassium hydroxide in ethanol was refluxed for one and one-half hours, and worked up as in A. It gave an 85% yield of the 1,3-diphenylisobenzofuran.

C. From the Epoxide (VI).—Following the same procedure, but using 2 g. of the epoxide, resulted in formation of the isobenzofuran in a yield of only 10–11%.

3-Isopropoxy-2,3-diphenylindanone (XIV; R = i-C_3H_7).—The ethereal extract from A (above) was evaporated to dryness and the residue extracted twice with ligroin (b. p. 90–120°). The crude crystals deposited from the ligroin were recrystallized from a mixture of petroleum ether and benzene, when the melting point was 127–128°.

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.3; H, 6.4. Found: C, 84.8; H, 5.8.

When 0.2 g. of this ether was added to 2 ml. of concentrated sulfuric acid, it gave a green solution; after a half hour this was poured into water. The bright red crystals were removed and found to be 2,3-diphenylindone by mixed melting point.

2,3-Dihydroxy-2,3-diphenylindanone (XXI).—The residue, insoluble in ligroin, was triturated with benzene, filtered, and recrystallized from benzene. It melted to a red liquid at 233–235° with decomposition; the yield was 4.2%.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.7; H, 5.1. Found: C, 79.4; H, 5.1.

This is the *trans* glycol, corresponding to the *cis* form obtained from the epoxide.[5]

Both the *cis* and *trans* glycols give a red halochromism with concentrated sulfuric acid, which soon changes to

(12) Allen, Gates and VanAllan, "Organic Syntheses," **27**, 30 (1947).

(13) Adams and Gold, THIS JOURNAL, **62**, 56 (1940).

(14) Weiss and Sonnenschein, *Ber.*, **58**, 1043 (1925).

pale yellow. On dilution and appropriate manipulation, the same lactone (XXII) is obtained from both; it was identical with a previously prepared specimen.[5]

Formation of 1-Phenyl-3-benzoylisobenzofuran (XXIII).—The yield of this substance from the glycol (XXI)[5] has been improved (90%) by modifying the procedure as follows: A mixture of 8 g. of the glycol, 0.3 g. of potassium hydroxide, and 50 ml. of alcohol is refluxed for three hours and worked up as usual.

Formation of *o*-Benzoylbenzoic Acid. A. From the Indone.—A mixture of 1.4 g. of 2,3-diphenylindone, 0.39 g. of sodium amide, and 10 ml. of xylene was refluxed for twelve hours. It was then diluted first with alcohol, then with water, and 1 ml. of 40% sodium hydroxide, and the xylene distilled with steam. The residual alkaline solution was treated with Norite and acidified. After some time, *o*-benzoylbenzoic acid separated in a yield of 50%, and was identified by comparison with an authentic specimen.

B. From 1-Phenyl-3-benzoylisobenzofuran (XXIII).—A mixture of 1.5 g. of the furan, 0.5 g. of potassium hydroxide, and 75 ml. of absolute alcohol was heated in a current of oxygen for five hours. The next day the solvent was removed *in vacuo*, the residue taken up in water, treated with Norite, acidified, and extracted with benzene. The acid was caused to crystallize by the addition of ligroin; the yield was 0.98 g. (93%); it was shown to be *o*-benzoylbenzoic acid by mixed melting point.

Oxidation of Isobenzofurans to 1,2-Aroylbenzenes. A. *o*-Dibenzoylbenzene.—A solution of 0.4 g. of 1,3-diphenylisobenzofuran in 15 ml. of benzene was refluxed for thirty-four hours in a slow current of oxygen. When the fluorescence had disappeared, the solvent was evaporated and the residue recrystallized from methanol. The yield of *o*-dibenzoylbenzene was 0.37 g. (86%); m. p. 145–147°. It was identified by comparison with a sample at hand.

B. *o*-Benzoylbenzil (V).—A solution of 1 g. of 1-phenyl-3-benzoylisobenzofuran in 20 ml. of alcohol was refluxed in a current of air for seven hours, the solvent removed, and the residue crystallized from acetic acid. The yellow crystals (0.55 g.) melted at 96°; a mixed melting point with a stock sample was not depressed.

Summary

1,3-Diphenylisobenzofuran is easily obtained by the action of alcoholic potassium hydroxide upon 2,3-diphenylindone, its epoxide, and *o*-benzoylbenzil. Mechanisms are proposed to account for the reactions.

1,3-Disubstituted isobenzofurans are slowly but completely oxidized by air or oxygen, in refluxing alcoholic solutions, to *o*-diaroylbenzenes.

1-Phenyl-3-benzoylisobenzofuran, in an alkaline alcoholic refluxing solution, is oxidized to *o*-benzoylbenzoic acid. This same acid also results when 2,3-diphenylindone is cleaved by sodium amide in boiling xylene.

ROCHESTER 4, NEW YORK RECEIVED FEBRUARY 2, 1948

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Morphine Studies. 2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone

BY E. C. HORNING, M. G. HORNING AND E. J. PLATT[1]

One of the chief structural characteristics of morphine and many of its derivatives is the presence of a quaternary carbon, identified in the Gulland–Robinson formula as C-13 of the octahydrophenanthrene system. Methods for the synthesis of octahydrophenanthrenes of this kind are quite limited; few such compounds have been made, and attempted applications of known methods to the synthesis of morphine derivatives have not been successful.

It was recognized by Cook[2] that octahydrophenanthrenes could be obtained from 2-arylcyclohexanones by an apparently general method involving a Reformatsky reaction, followed by dehydration, hydrogenation and cyclization. This method was applied by the English workers to 2-phenylcyclohexanone, and we have used it with 2-(2′,3′-dimethoxyphenyl)-cyclohexanone.[3]

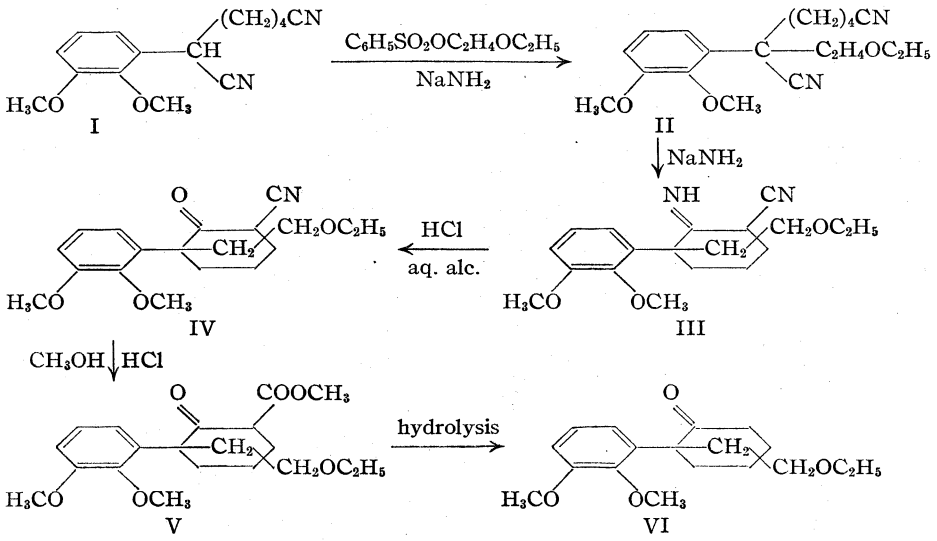
We have been interested in the application of Cook's procedure to the synthesis of certain morphine derivatives, and for this purpose it has first been necessary to investigate the preparation of a dimethoxyarylcyclohexanone containing an appropriately substituted carbon in the 2-position. The reactions employed are indicated on the diagram; the starting material was prepared by the sodamide alkylation of 2,3-dimethoxyphenylacetonitrile with δ-chlorovaleronitrile. Continued study of this reaction has led to the inclusion of certain apparently minor modifications which result in consistent yields of 80–83%. The product, 2-(2′,3′-dimethoxyphenyl)-pimelonitrile, is a dinitrile which can undergo cyclization to a six-membered β-iminonitrile, but which can also be alkylated directly by the sodamide method. This situation apparently arises through the structural factors which affect the cyclization. In the case of pimelonitriles, cyclization does not occur so readily as in the case of adiponitriles, and structural modifications may impose added difficulty in the way of the reaction. In the cyclization of α-(2,3-dimethoxyphenyl)-pimelonitrile (I) with sodium,[3] the cyclizing agent will produce a carbanion by removal of the most acidic hydrogen, which in this case is that associated with the phenylacetonitrile system. If a carbanion of this structure is formed, however, cyclization may follow directly only by addition of a completely substituted carbanion carbon to the nitrile group at the other end of the chain. The effective steric hindrance presented toward this addition is a barrier which in similar cases usually is sufficient to prevent cyclization. It is not known whether

(1) Rohm and Haas Research Assistant.

(2) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(3) Horning, Horning and Platt, THIS JOURNAL, 69, 2929 (1947).

the cyclization which occurs here takes place in spite of this steric effect, or whether a partial replacement of one of the α-hydrogens at the other end of the chain leads to cyclization in the other direction; this would also be possible, but it would represent a condition not easily arrived at in the presence of the more acidic hydrogen of the phenylacetonitrile system. These effects, which retard cyclization, are fortunately the same effects which are needed to allow alkylation of I in the desired position. With β-ethoxyethyl benzenesulfonate as the alkylating agent, an 80% yield of 2-(2′,3′-dimethoxyphenyl)-2-(β-ethoxyethyl)-pimelonitrile (II) may be obtained.

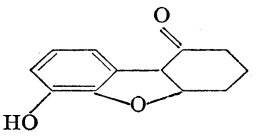


The cyclization of this pimelonitrile (II) can occur in only one fashion, and the structure of the resulting β-iminonitrile is that of III. Sodamide (in boiling benzene) was used as the cyclizing agent; a nitrogen atmosphere must be employed. The iminonitrile was isolated in crystalline form, and was converted into the β-ketonitrile IV in quantitative yield by acid hydrolysis in aqueous ethanol. Treatment of IV with hydrogen chloride in dry methanol gave the β-ketoester V.

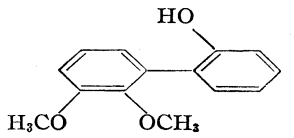
Under appropriate conditions, it might be expected that either III, IV or V would undergo hydrolysis-decarboxylation to yield the desired product, 2-(2′,3′-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone (VI). Three methods were investigated; the best proved to lie in the hydrolysis of the β-ketoester (V) with a dilute alcoholic solution of potassium hydroxide, followed by brief heating of the acidified solution to effect decarboxylation. The ketone (VI) was obtained from (V) in 83% yield as a colorless viscous oil.

The removal of the carbomethoxy group of (V) by ester interchange-decarboxylation with ethyl hydrogen adipate, following the general method of Fourneau[4] was also investigated. It was not possible to obtain material of analytical purity by this method, although the reaction apparently proceeded without difficulty. The yield was slightly lower than that obtained by direct hydrolysis-decarboxylation.

The use of a boiling hydrochloric acid–acetic acid mixture for hydrolysis led to an unexpected result. When this hydrolysis method was applied to the iminonitrile (III), with a reflux period of three hours, a crystalline phenolic product was isolated. While demethylation under such circumstances is not unusual, analytical data for the phenol indicated that the β-ethoxyethyl chain was no longer present. The structure of this compound is under investigation; the analytical results correspond to structure VII.



(VII)



(VIII)

The possibility that the product was 2,3-dimethoxy-2′-hydroxybiphenyl (VIII) was excluded both by analysis and by synthesis of (VIII) by dehydrogenation of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone.

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-pimelonitrile (I).—By the introduction of several apparently minor modifications into the procedure described previously,[3] the yield has been raised to 80–83%. After addition of the solvent (toluene), the ammonia was allowed to evaporate, with little or no warming, over several hours. The addition of δ-chlorovaleronitrile was started while the mixture was at room temperature, and was carried out as rapidly as possible. Good stirring and spraying of water on the flask during the addition were necessary to allow continued control of the vigorous exothermic reaction. Under these circumstances, 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile yielded 106.5 g. (83%) of the dinitrile, b. p. 191–199° (0.5–0.7 mm.).

β-Ethoxyethyl Benzenesulfonate.—A mixture of 180 g. of ethylene glycol monoethyl ether, 360 g. of benzenesulfonyl chloride, 200 ml. of water, and 200 ml. of chloroform was stirred in an ice-bath while a solution of 120 g. of sodium hydroxide in 700 ml. of water was added dropwise over one hour. The mixture was then stirred for one hour longer at room temperature. The chloroform layer was separated and washed with 200 ml. of water. After drying over magnesium sulfate the solvent was removed and the residue distilled under reduced pressure. There was obtained 232 g. (50%) of the ester, as a nearly colorless oil, b. p. 136–144° (0.7 mm.).

(4) Fourneau, *Bull. soc. chim.*, [4] **43**, 859 (1928); Stoll, *Helv. Chim. Acta*, **30**, 1401 (1947).

α-(2,3-Dimethoxyphenyl)-α-(β-ethoxyethyl)-pimelonitrile (II).—Sodamide was prepared from 8.85 g. (0.38 mole) of sodium in approximately 350 ml. of ammonia. With the aid of 40 ml. of dry ether, 89.0 g. (0.35 mole) of α-(2,3-dimethoxyphenyl)-pimelonitrile was added with stirring. After ten minutes, 200 ml. of dry benzene was added, and the mixture was allowed to stand until the ammonia had evaporated. There was then added with good stirring, at a rate compatible with the ensuing vigorous reaction, 97.6 g. (0.42 mole) of β-ethoxyethyl benzenesulfonate. The mixture was heated and stirred for two and one-half hours; methanol (30 ml.) and water (150 ml.) were added to the cooled mixture, and the benzene layer was separated. The aqueous layer was extracted with 100 ml. of benzene and two 50-ml. portions of ethyl acetate. The combined extracts were washed with 100-ml. portions of 5% sodium hydroxide solution, water, 5% hydrochloric acid, water, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvents were removed by distillation and the residue distilled under reduced pressure. The product was collected as a light yellow viscous oil at 210–220° (0.5–0.7 mm.); yield 91.2 g. (80%).

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: C, 69.00; H, 7.87. Found: C, 69.00; H, 7.77.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-cyanocyclohexanone Imine (III).—Sodamide was prepared from 4.6 g. (0.20 mole) of sodium. There was added to the sodamide-ammonia mixture 59.0 g. (0.18 mole) of α-(2,3-dimethoxyphenyl)-α-(β-ethoxyethyl)-pimelonitrile in 50 ml. of dry ether, and this was stirred for fifteen minutes. After providing a nitrogen atmosphere, 175 ml. of dry benzene was added and the ammonia was evaporated with slight warming. The mixture was heated under reflux for two and one-half hours, cooled, and treated with methanol (15 ml.) and water (100 ml.). The benzene layer was separated, and the aqueous layer washed with 50 ml. of benzene and four 50-ml. portions of ethyl acetate. The combined extracts were washed with 100-ml. portions of 5% sodium hydroxide solution, water, 2% aqueous acetic acid, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvents were removed by distillation; the product was collected at 191–200° (0.2–0.3 mm.) as a very viscous light-yellow oil; yield, 47.3 g. (80%).

The distillate solidified immediately, but was apparently composed of both oil and solid. Trituration with ether–pentane (2:1) gave 32.5 g. of colorless crystalline material; evaporation of the solvents returned an oil which crystallized in part on standing. The nature of the oily product obtained here has not been determined; it may have been unchanged starting material.

Recrystallization from cyclohexane–ethyl acetate provided an analytical sample, m. p. 116–117°.

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: C, 69.09; H, 7.88; N, 8.48. Found: C, 69.24; H, 7.64; N, 8.54.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-cyanocyclohexanone.—A mixture of 3.0 g. of the iminonitrile, 45 ml. of ethanol (95%), 9 ml. of concentrated hydrochloric acid, and 9 ml. of water was heated under reflux for one hour. The solution was diluted with 300 ml. of water, and the product was extracted with five 100-ml. portions of ether. The ethereal extract was washed well with water and with two 30-ml. portions of saturated sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of the ether gave a crystalline residue of crude, slightly discolored ketonitrile; yield, 3.0 g.; m. p. 97–99°.

A small sample was recrystallized from ether–pentane to give a colorless crystalline product, m. p. 98–99°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60. Found: C, 69.11; H, 7.74.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-carbomethoxycyclohexanone (V).—A solution of 2.00 g. of crude ketonitrile in 25 ml. of methanol was saturated with hydrogen chloride, without cooling. After standing at room temperature for twelve hours, the mixture was poured into 300 ml. of water, and the product extracted with four 50-ml. portions of ether. The ether solution was washed with water and with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to yield 1.68 g. of crude ketoester. This material was used directly for decarboxylation.

Additional purification by evaporative distillation at 110–130° (0.1 mm.) gave the ketoester as a colorless, viscous oil.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.49; H, 7.67.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone (VI).—A solution was prepared from 1.50 g. of potassium hydroxide, 3 ml. of water, and 27 ml. of absolute ethanol. To this was added 2.00 g. of β-ketoester (V), and the mixture was heated under reflux for three hours. It was acidified by the addition of 5 ml. of concentrated hydrochloric acid in 5 ml. of water, and refluxing was continued for fifteen minutes. The solution was diluted with 200 ml. of water and the product extracted with four 60-ml. portions of ether. The combined extracts were washed with two 30-ml. portions of 5% sodium hydroxide solution, and with 30-ml. portions of water and 2% aqueous acetic acid. After drying, the ether was removed and the residue evaporatively distilled at 110–120° (0.07 mm.) to yield 1.40 g. (83%) of the ketone as a colorless, viscous oil.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.69; H, 8.25.

Ester Interchange Method.—A solution of 1.68 g. of crude ketoester (V) in 9.0 ml. of ethyl hydrogen adipate was heated under gentle reflux in an apparatus arranged for sweeping with dry nitrogen. The rate of evolution of carbon dioxide was followed by means of an attached anhydrone–ascarite absorption tube. About forty minutes were required for the collection of 210 mg. (theoretical, 202 mg.) of carbon dioxide.

Hydrolysis of the mixture was carried out by adding 90 ml. of ethanol and a solution of 20 g. of potassium hydroxide in 50 ml. of water. The solution was heated under reflux for two hours, and most of the ethanol was removed by distilling until 90 ml. of distillate was obtained. The residue was diluted with 250 ml. of water and extracted with five 60-ml. portions of ether. The combined ether extracts were washed well with water and with 50 ml. of 2% aqueous acetic acid, and dried over magnesium sulfate. After evaporation of the ether, the remaining oil was evaporatively distilled at 105–110° (0.05 mm.) to provide 0.99 g. of the cyclohexanone as a colorless viscous oil. Material obtained in this way was not of analytical purity (about 0.5% or more from the calcd. values) although it was evidently the same compound as that obtained by hydrolysis-decarboxylation.

Hydrolysis with Hydrochloric Acid–Acetic Acid.—A mixture of 1.00 g. of the iminonitrile (III), 10 ml. of acetic acid, 10 ml. of concentrated hydrochloric acid, and 3 ml. of water was heated under reflux for three hours. After dilution with 100 ml. of water, 30 ml. of saturated sodium bicarbonate solution was added and the mixture was extracted with three 30-ml. portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, and with four 30-ml. portions of Claisen alkali. The combined Claisen solution was diluted with water and treated with 20 ml. of concentrated hydrochloric acid, followed by saturation with carbon dioxide. After chilling, the crystalline phenol was removed by filtration and air dried. The product, 290 mg., was recrystallized twice from ether–ethyl acetate to give a colorless product, m. p. 134–135°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.56; H, 5.92. Found: C, 70.78; H, 5.71.

In separate experiments, it was established that a noncrystalline fraction, insoluble in sodium bicarbonate solution, which was isolated as a reaction product after a reflux period of twenty minutes, had a composition by analysis indicating that one nitrogen atom had been lost, and that the β-ethoxyethyl chain was largely intact. A

reflux period of six hours resulted in a lowered yield of phenolic product.

2,3-Dimethoxy-2-hydroxybiphenyl.—A mixture of 500 mg. of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone, 5 ml. of triethylbenzene, and 1.0 g. of 5% palladium–charcoal catalyst[5] was heated under reflux for one hour. The warm solution was filtered and the catalyst washed with warm benzene. The organic solution was extracted with one 25-ml. and one 15-ml. portion of Claisen alkali. The Claisen solution was washed with benzene, and the benzene added to the organic solvents. The combined organic solution was extracted with three 15-ml. portions of Claisen alkali, and the combined Claisen solution was washed with 40 ml. of pentane. The alkaline solution was diluted with 100 ml. of water. A 40-ml. portion of concentrated hydrochloric acid was added and neutralization was completed with carbon dioxide (Dry Ice). After chilling, the crystalline product was removed by filtration and air dried. The yield of phenol, m. p. 102–104°, was 225 mg. Recrystallization from cyclohexane gave a colorless sample, m. p. 103–104.5°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.22; H, 6.07.

(5) "Organic Syntheses," **26**, 77 (1946).

Acknowledgment.—The authors are indebted to Miss Sarah H. Miles for carrying out the analyses reported here.

Summary

The synthesis of 2-(2′,3′-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone is described.

PHILADELPHIA 4, PENNA. RECEIVED FEBRUARY 2, 1948

[CONTRIBUTION FROM THE KERCKHOFF LABORATORIES OF BIOLOGY OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY AND THE EMERGENCY RUBBER PROJECT, BUREAU OF PLANT INDUSTRY, U. S. DEPARTMENT OF AGRICULTURE]

Chemical Investigation in Guayule. II. The Structure of Partheniol, A Sesquiterpene Alcohol from Guayule

BY A. J. HAAGEN-SMIT AND C. T. O. FONG[1]

In studies conducted in this Laboratory on the constituents of guayule, *Parthenium argentatum, Gray*, it was found that cold alcohol extracted from the plant a cinnamate of an optically active sesquiterpene alcohol previously isolated by Alexander.[2] The yield of the alcohol from the plant was approximately 0.03%. Later, the same ester was obtained by chromatographic adsorption of guayule extracts on silicic acid. Further studies showed that guayule resin obtained from Mexico as a by-product of guayule rubber refining would serve as a convenient source of this alcohol, yielding as much as 0.3% of the desired substance.

The physical constants of this alcohol and its cinnamate are listed below and are compared with those given by Alexander[2] and by Walter.[3]

Parthenyl cinnamate: empirical formula, $C_{24}H_{30}O_2$,[4,2] $C_{24}H_{32}O_2$[3]; m. p. 125–126°[4,2,3]; molecular weight by saponification of ester, 355[4], 354.[3]

Partheniol: empirical formula, $C_{15}H_{24}O$,[4,2] $C_{15}H_{26}O$[3]; m. p. 127–128°,[4,2] 131°[3]; mol. wt. 215,[4] 222[2]; $[\alpha]^{26}D$ 116.5° ($CHCl_3$, *c* 1.29%),[4] $[\alpha]^{24}D$ + 88.7° ($CHCl_3$, *c* 1.566%)[3]; parthenyl *p*-phenylazobenzoate, m. p. 162.5–164°[4]; parthenyl 3,5-dinitrobenzoate, m. p. 143–144°.[4]

Our data for the alcohol are in agreement with those of Alexander and the empirical formula $C_{15}H_{24}O$ for the alcohol was substantiated throughout this work. Also the melting point of partheniol repeatedly recrystallized from different solvents agrees with that of Alexander. The chromatographic separation of the phenylazobenzoate showed only traces of compounds other than the partheniol derivative. The presence of isomeric forms of partheniol might explain the melting point of 131° found by Walter[3] since we have observed that heating partheniol with alcoholic potassium hydroxide resulted in a raise of melting point to 132–132.5°. Similar observations were made in preparing a maleic anhydride addition compound.

Catalytic hydrogenation of the alcohol indicated the presence of two double bonds. The absorption spectrum of partheniol, together with the failure of partheniol to form an adduct with maleic anhydride or to be reduced by sodium in alcohol, indicates that the two double bonds are not conjugated.

The relative ease of dehydration with potassium bisulfate confirms the presence of an alcoholic hydroxyl group and indicates that the hydroxyl group is probably tertiary. The failure of esterification with phthalic anhydride under conditions described by Ruzicka, *et al.*,[5] as well as the failure to form a xanthate indicated that partheniol is a tertiary alcohol.[6]

Dehydration of partheniol with potassium bisulfate resulted in the formation of a mixture of isomeric hydrocarbons, $C_{15}H_{22}$, which we shall call dehydroparthenene.[7] These hydrocarbons contain three double bonds, which physical and chemical methods show are not conjugated.

Dehydrogenation of dehydroparthenene with sulfur gave blue S-guaiazulene which was identified by its 1,3,5-trinitrobenzene addition product, its picrate and its trinitrotoluene addition prod-

(1) Present address, Lederle Research Laboratories, Pearl River, N. Y.

(2) Alexander, *Ber.*, **44**, 2320 (1911).

(3) Walter, THIS JOURNAL, **66**, 419 (1944).

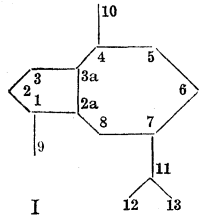
(4) Data of Haagen-Smit and Fong.

(5) Ruzicka, Pontalti and Balas, *Helv. Chim. Acta*, **6**, 858 (1923).

(6) Feigl, "Spot Tests," Nordemann Publishing Co., New York, N. Y., 1937, p. 251.

(7) Conforming to sesquiterpene nomenclature: parthenene is $C_{15}H_{24}$.

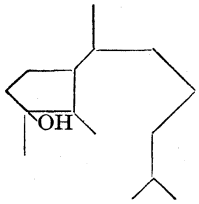
uct. The adsorption spectrum of the S-azulene obtained from partheniol correspond with those reported for S-guaiazulene by Willstaedt[8] and by Plattner.[9] Dehydration of dehydroparthenene with selenium gives a violet azulene. This behavior is similar to that shown by the dehydrogenation of a crystalline sesquiterpene alcohol, guaiol obtained from the wood of *Guaiacum officinale* (family *Zygophyllacae*).[10] These data show that the carbon skeleton of partheniol is that of 1,4 - dimethyl - 7 - isopropyl - decahydrocyclopentacycloheptene (I).



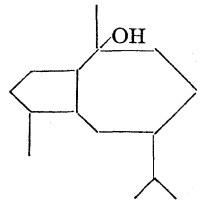
I

Tetrahydropartheniol, $C_{15}H_{28}O$, is formed by hydrogenating both double bonds of partheniol. Dehydration of tetrahydropartheniol with potassium bisulfate gives dihydroparthenene, $C_{15}H_{26}$, a hydrocarbon containing one double bond. In the ozonization of dihydroparthenene formaldehyde was formed, indicating the presence of a methylene group. Since the double bond in this methylene group arose from the removal of the hydroxyl group in tetrahydropartheniol, we may conclude that the hydroxyl group in partheniol is situated on a carbon atom to which a methyl group is attached.

If the hydroxyl group were located at carbon atom 7 or 11 dehydration of tetrahydropartheniol to dihydroparthenene would have given a mixture of isomers yielding acetone and formaldehyde upon ozonization. As no trace of acetone could be detected in the ozonization products, only two structures are possible for tetrahydropartheniol. They are shown in II and III.

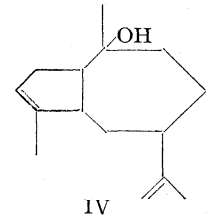


II

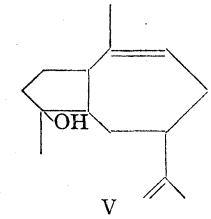


III

The position of the hydroxyl group at carbon atom 1 or carbon atom 4 is confirmed by the results of ozonization experiments on partheniol, since a neutral product, $C_{14}H_{22}O_4$, containing an aldehyde and two methyl ketone groups was obtained. The presence of formaldehyde among the volatile oxidation products demonstrated that one of the double bonds is exocyclic and present in a methylene group. The oxidation of the double bond located in the isopropenyl group explains the formation of formaldehyde and one of the methyl ketone groups. The other double bond has given rise to the aldehyde and second methyl ketone group. This limits the position of the second double bond to one adjoining a methyl group and one not connected with the bridge between the 5 and 7 membered ring. The fourth oxygen in $C_{14}H_{22}O_4$ is present as in the original tertiary hydroxyl group. This leaves out of the numerous possible isomers only the following two structures for partheniol.



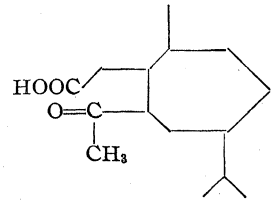
IV



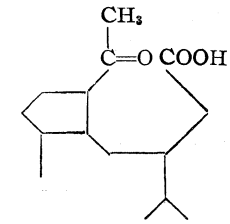
V

These structures are in harmony with the absence of conjugation of the double bonds in partheniol and its dehydration product dehydroparthenene. To secure a possible check of the exact position of the hydroxyl group the dicarboxylic acid, which was formed from the ozonization of dihydroparthenene followed by hypobromite oxidation, was treated with acetic anhydride according to Blanc's method.[11]

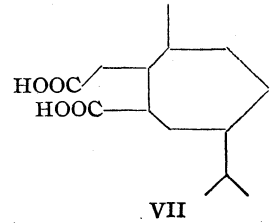
In the removal of the hydroxyl group from tetrahydropartheniol, a mixture of isomers is formed, which upon ozonization gives rise to a ketone, a diketone and a keto acid (VI or VIII) or keto aldehyde. On hypobromite oxidation of the keto acid, a dicarboxylic acid is formed which would be, in the case of structure II, a substituted glutaric acid (VII), and in the case of structure III, a substituted pimelic acid (IX). With acetic anhydride, ketone formation was not detected, indicating the presence of a glutaric acid derivative rather than a pimelic acid derivative. Also, our



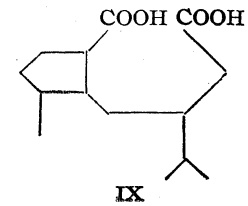
VI



VIII



VII



IX

(8) Willstaedt, *Ber.*, **68**, 333 (1935).
(9) Plattner, *Helv. Chim. Acta*, **24**, 283E (1941).
(10) Ruzicka and Haagen-Smit, *ibid.*, **14**, 1104 (1931).
(11) Blanc, *Compt. rend.*, **144**, 1356 (1907).

analytical data show that an anhydride rather than a ketone was formed. These facts indicate that the hydroxyl group in partheniol is attached to carbon atom 1, as shown in structure V.

Experimental[12]

Isolation of Partheniol.—Twenty-five gallons of crude resin was extracted three times with five-gallon portions of ether and twice with seven-gallon portions of a 5:2 ether–methanol mixture. After the removal of the solvents from the extract, the ether-soluble portion of the guayule resin was saponified with *N* alcoholic solution of sodium hydroxide for three hours at a bath temperature of 90°. After neutralization and extraction with ether, the residue (about five gallons) was distilled at 0.01 mm. pressure. Approximately two liters of material boiling below 150° collected. Redistillation through a short helix-packed column fitted with a variable take-off still head yielded 1.2 liters of viscous oil boiling at 100–125° at 0.01 mm. pressure. This distillate was then diluted slightly with petroleum ether and inoculated with a few crystals of partheniol. After standing for several days, this solution became a solid mass of partheniol crystals.

These were recrystallized from petroleum ether to constant melting point: 150 g. of purified crystalline partheniol, m. p. 127–128°, was obtained. This melting point stayed constant after recrystallization from petroleum ether, from acetone and from benzene as well as after sublimation.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.77, 81.73; H, 10.92, 10.98.

Attempt at Reduction of Partheniol with Sodium and Alcohol.—Two grams of partheniol in 10 ml. of amyl alcohol was heated in a 40-ml. flask at a bath temperature of 135° for six and one-quarter hours. Sodium (4.5 g.) was gradually added; at periodic intervals, more amyl alcohol was introduced until all the sodium had reacted. The residue was recrystallized twice from low-boiling petroleum ether; the substance melted at 132–132.5°.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.85; H, 11.06.

Reaction of Partheniol with Maleic Anhydride.—The reaction of partheniol with maleic anhydride or ethyl maleate dissolved in benzene and refluxed for ten hours gave no adduct. The recovered partheniol melted at 129.5°, no depression with original partheniol.

Absorption Spectrum of Partheniol.—The absorption spectrum of a solution of 1.76 mg. of partheniol in 100 ml. of absolute alcohol was determined with the Beckman photoelectric spectrophotometer. The spectrum did not show any characteristic maxima or minima within the range of the spectrophotometer.

Parthenyl *p*-Phenylazobenzoate.—To 2 g. of partheniol in 15 ml. of dry pyridine 2.4 g. of *p*-phenylazobenzoyl chloride in 20 ml. of anhydrous benzene was added. The reaction mixture was heated at a bath temperature of 90° for half an hour and worked up in the usual manner. The residue was recrystallized first from a mixture of benzene and petroleum ether, then from acetone.

One gram of this benzoate dissolved in a mixture of 10 ml. of benzene and 50 ml. of petroleum ether (85–100°) was chromatographed on a silicic acid–celite column (2:1) 4.5 cm. × 20 cm., which had been initially washed with 250 ml. of petroleum ether. The column was developed with 400 ml. of petroleum ether (85–100°) and post-washed with 50 ml. of 30–60° petroleum ether. The chromatogram showed two very faint bands near the top. The main zone *ca.* 10 cm. below the top was cut out from the extruded column and was recovered by eluting with ether; after recrystallizing three times from acetone, m. p. 163–164°.

(12) All melting points are corrected; microanalysis by Dr. G. Oppenheimer and G. Swinehart.

Anal. Calcd. for $C_{28}H_{32}O_2N_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.42; H, 7.53; N, 6.66.

Parthenyl 3,5-Dinitrobenzoate.—A solution of approximately 150 mg. of partheniol and an equal amount of 3,5-dinitrobenzyl chloride in a mixture of 2 ml. of dry benzene and 5 ml. of anhydrous pyridine was gently refluxed for 0.75 hour. The reaction mixture was worked up according to Reichstein.[13] The turbid solution was allowed to stand in the refrigerator for several days: the crystals formed were recrystallized from acetone and washed with alcohol, m. p. 143–144°.

Anal. Calcd. for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.31; N, 6.76. Found: C, 63.88, 63.97; H, 6.61, 6.51; N, 6.67, 6.90.

Dihydropartheniol.—A 5.04-g. sample of partheniol dissolved in 55 ml. of absolute ethanol was hydrogenated with approximately 2 g. of Raney nickel as catalyst at 25° and 760 mm. pressure.

The rate of hydrogenation was fairly rapid for the first fifteen hours, decreasing rapidly thereafter. The hydrogenation was terminated after the required amount of hydrogen for one double bond was taken up. After the removal of the Raney nickel and the alcohol, the remaining oil was distilled at 92–102° at 0.1 mm.; a total of 3.5 g. of dihydropartheniol was obtained. The dihydropartheniol gave the constants: $n^{26}D$ 1.5035, $d^{23.6}_4$ 0.9614; calcd. MD for $C_{15}H_{26}O$ with one double bond and one hydroxyl group is 68.15; found 68.5; *p*-phenylazobenzoate, m. p. 121.5–122.5°.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.05; H, 11.96.

Dehydroparthenene.—A mixture of 5 g. of partheniol and 3.5 g. of fused potassium acid sulfate was refluxed at a bath temperature of 180–190° for one-half hour. Extraction was carried out with ether and the recovered oil was distilled twice over potassium. In the second distillation at 60–65° and 0.1 mm., 1.1 g. of dehydroparthenone was obtained: $n^{25}D$ 1.15120, $d^{23.6}_4$ 0.9194. Calcd. MD is 65.67 calcd. for three double bonds; found 66.04.

Anal. Calcd. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.90; H, 11.15.

Dehydrogenation of Dehydroparthenene.—Fifteen grams of crude dehydroparthenene was heated with 4.7 g. of sulfur at a pressure of 30–50 mm. and a bath temperature of 180–185°, for three hours.[14] The blue azulene which was formed was distilled directly from the reaction flask. The fraction obtained at 70–100° and 10–15 mm. was 7 g. The distillate was taken up in petroleum ether and the azulene was extracted with 85% phosphoric acid following the procedure of Ruzicka, *et al.*[15] The crude azulene distilled at 140–150° (bath temperature) and 0.05 mm. The yield based on crude parthenene is 1.7%. The purification was carried out as indicated by Plattner and St. Pfau[16] by converting the azulene to its trinitrobenzene addition compound.

The addition compound was decomposed and the azulene liberated through chromatographic adsorption on an aluminum oxide column. The trinitrobenzene forms a zone at the top of the column while the azulene is less strongly adsorbed. After development with petroleum ether the azulene was eluted with a mixture of 1:1 benzene–petroleum ether. A trinitrobenzene addition product was again prepared and the cycle of the decomposition and the regeneration of the azulene was repeated. The final product was distilled under reduced pressure. Approximately 125 mg. of the purified blue azulene was obtained.

Anal. Calcd. for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.93; H, 9.24.

The addition products of the azulene with picric acid, trinitrobenzene and trinitrotoluene were prepared following the methods of Plattner and St. Pfau.[16]

(13) Reichstein, *Helv. Chim. Acta*, **9**, 799 (1926).

(14) Melville, THIS JOURNAL, **55**, 2462 (1933).

(15) Ruzicka and Rudolph, *Helv. Chim. Acta*, **19**, 858 (1936).

(16) Plattner and St. Pfau, *ibid.*, **20**, 224 (1937).

Picrate, m. p. 120–121°. *Anal.* Calcd. for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83. Found: C, 58.79; H, 4.88; N, 10.09.

Trinitrobenzene addition compound, m. p. 150–151°. *Anal.* Calcd. for $C_{21}H_{21}N_3O_6$: C, 61.34; H, 5.14; N, 10.21. Found: C, 61.61; H, 4.99; N, 10.12.

Trinitrotoluene addition compound, m. p. 88–89°. *Anal.* Calcd. for $C_{21}H_{21}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.30; H, 5.74; N, 10.06.

The melting points found in the literature are: picrate m. p. 120–121°, trinitrobenzene compound 150–151.5° and trinitrotoluene compound 88–89°.[10,17]

Absorption Spectrum of the S-Azulene.—The absorption spectrum of the S-azulene in hexane, with a concentration of 3.62 mg. per 10 ml., was determined with a Beckman photoelectric spectrophotometer using a slit width of 0.02 to 0.3 mm. The spectrum was characterized by three maxima at 603, 659 and 735 mμ and undulations at 557, 582, 630 and 698 mμ.

Reported for S-guaiazulene are strong bands at 604, 663, 736 mμ and weak bands at 557, 581, 633 and 697 mμ.[18,19]

Tetrahydroparthenio l.—32.8 g. of partheniol was hydrogenated at room temperature and at a pressure slightly above atmospheric in 200 ml. of glacial acetic acid with 0.4 g. of platinum dioxide as a catalyst. After removal of the catalyst and the solvent, the hydrogenated product distilled at 70–85° at 0.01 mm.: $n^{25}D$ 1.4820, $d^{25.4}_4$ 0.9342; *MR* calcd., 68.60 for one hydroxyl group; found, 68.47.

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.16; H, 12.72.

Dihydroparthenene.—A mixture of 38.5 g. of tetrahydropartheniol and 24 g. of fused powdered potassium bisulfate was heated for forty-five minutes at a bath temperature of about 160°. After washing the ether extract with dilute sodium hydroxide and with water until neutral, the hydrocarbon was distilled twice over potassium. The dihydroparthenene had the following constants: b. p. (0.02 mm.) 59–60°; $n^{25}D$ 1.4880; d^{25}_4 0.9025; *MR* calcd. 66.6 for one double bond; found, 65.9.

Anal. Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.31; H, 12.83. Microhydrogenation: Found: uptake 1.0 mole H_2, calcd. for $C_{15}H_{26}$.

Ozonization of Partheniol.—Five grams of partheniol was ozonized in glacial acetic acid. The ozonide was decomposed by hydrogenation in 1:1 acetic acid–ether with a platinum catalyst (Adams). The reaction mixture was cooled in an ice–salt-bath during the first phase of the hydrogenation in order that a secondary reaction of "acid rearrangement" of the ozonide would not occur to any appreciable extent. The hydrogenation was later allowed to proceed at room temperature till the required amount of hydrogen was taken up. A test for formaldehyde on the volatile products with dimedon reagent was positive, while a test for acetone with *p*-nitrophenylhydrazine was negative. From the ozonized products was separated a neutral fraction, by making the solution alkaline and extracting with ether. An acid fraction was obtained by acidifying the alkaline solution and extracting with ether. A qualitative test for methyl ketone in the neutral fraction was positive; a qualitative test for aldehyde with Schiff reagent was also positive.

The amount of acid fraction was negligible. A greater portion of the neutral fraction was not distillable. By distilling at 0.6 mm. and 98–100°, 0.5 g. of the neutral fraction was collected with the following constants: $n^{24}D$ 1.4762; d^{24}_4 1.0624.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01; for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.74; H, 8.69. Micro-Zerewitinoff: Found: 0.9 mole act. H and 1.8 moles carbonyl, when calcd. for $C_{14}H_{22}O_4$. Methyl ketone determination. Found: 1.9 moles CH_3CO group, calcd. for $C_{14}H_{22}O_4$.

Quantitative Ozonization of Partheniol and of Dihydroparthenene.—Following the procedure and using the apparatus described by Grignard, Doeuvre and Escourrou,[20,20a] a 1.5-g. sample of partheniol was ozonized in 25 ml. of acetic acid (30% water) at 17° for forty minutes (ozone concn. 1.24 g./hr.). Decomposition of the ozonide was carried out by adding 50 ml. of water and heating at 100° for three hours. A suspension of mercuric oxide in water was then added and the reaction mixture was heated in a boiling water-bath for one hour. The wash-bottles did not contain formaldehyde when tested with dimedon. The amount of carbon dioxide formed by oxidation of the formic acid present was 180 mg. or 60% of the theoretical amount if one exocyclic double bond were present.

Following the same procedure 0.85 g. of dihydroparthenene was ozonized in 25 ml. of acetic acid containing 30% water for forty minutes (O_3 concentration 1.24 g./hr.). The amount of formaldehyde which was precipitated was negligible; the quantity of carbon dioxide after oxidation of the formic acid with mercuric oxide was 111 mg. or 65% of the theoretical if one exocyclic double bond were present. This result was confirmed by ozonizing 0.4 g. of dihydroparthenene in carbon tetrachloride. The ozonide was decomposed by adding 10 ml. of water and heating on a boiling water-bath. A test with dimedon for formaldehyde on the volatile products was positive; a test for acetone with *p*-nitrophenylhydrazine was negative.

Ozonization of Dihydroparthenene and Reduction of Ozonides.—An 18.2-g. sample of dihydroparthenene in 40 ml. of glacial acetic acid was ozonized at about 15° for three hours. To decompose the ozonide, 18 g. of zinc dust suspended in a small amount of water was slowly added; the reaction temperature was kept at 50–70° for approximately one hour. A test for peroxides was made with titanic sulfate and dilute sulfuric acid; no peroxides were found. After the removal of the excess zinc and zinc salts, the acetic acid solution was neutralized with dilute potassium hydroxide and the neutral solution was extracted with ether. An acid fraction was obtained by acidifying the ether-extracted aqueous phase with dilute sulfuric acid and extracting with ether. Fractionation of neutral fraction at 0.125 mm. gave the following fractions: 68–78°, 6.4 g.; 78–93°, 1.4 g.; 93–108°, 2.4 g.; 108–120°, 2.8 g.

Anal. Calcd. Fr. b. p. (0.125 mm.) 68–78°. Found: C, 83.83; H, 12.51. Fr. b. p. (0.125 mm.) 78–93°. Found: C, 77.56; H, 11.36. Fr. b. p. (0.125 mm.) 93–108°. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. For $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 75.17; H, 11.37.

Ozonization of Dihydroparthenene and Oxidation of Ozonides.—A 10.5-g. sample of dihydroparthenene was ozonized in 20 ml. of glacial acetic acid for 1.5 hours (1.45 g. O_3/hour). Since a maximum yield in acid fraction was desired, the ozonide was decomposed with a 5–7% solution of hydrogen peroxide, heating in a water-bath for an hour. The excess hydrogen peroxide was removed by heating for half an hour in the presence of a few mg. of platinum black. The mixture was concentrated in order to remove the excess acetic acid. A neutral and acid fraction were obtained by making the concentrate basic and acidic, respectively, and extracting with ether. The total acid fraction obtained was 2.5 g.; the neutral fraction 4.5 g. Distillation of the acid fraction at 0.1 mm. gave the following fractions: 176–190°, 0.65 g.; 190–210°, 0.5 g.

Anal. Fraction b. p. (0.1 mm.,) 176–190°, calcd. for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30; for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 66.51; H, 9.70.

Oxidation of Acid Fractions with Sodium Hypobromite.—Fraction b. p. (0.1 mm.) 176–190° was treated with

(17) St. Pfau and Plattner, *Helv. Chim. Acta*, **19**, 870 (1936).

(18) Willstaedt, *Ber.*, **68**, 333 (1935).

(19) Susz, St. Pfau and Plattner, *Helv. Chim. Acta*, **20**, 469 (1937).

(20) Grignard, Doeuvre and Escourrou, *Compt. rend.*, **177**, 669 (1923).

(20a) Escourrou, *Bull. soc. chim.*, [4] **43**, 1088 (1928).

sodium hypobromite (1.7 g. of sodium hydroxide, 2 g. of bromine in 23 ml. of water) for two hours. The excess sodium hypobromite was decomposed with a small amount of sodium bisulfite. After removing the neutral fraction containing bromoform, the alkaline solution was acidified with sulfuric acid and an acid fraction was extracted with ether. The major portion (0.39 g.) distilled at 0.1 mm. and a bath temperature of 190–200°.

Anal. Fr. b. p. (0.1 mm.) 190–200° after redist.: calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44 (dicarboxylic acid). Found: C, 64.34; H, 9.52.

Reaction of Dicarboxylic Acid with Acetic Anhydride.[5]—A mixture of 0.3 g. of dicarboxylic acid obtained from fraction b. p. (0.1 mm.) 190–200° and 0.5–0.7 ml. of acetic anhydride was heated in a sealed tube for half an hour at 240° (bath temperature).

After removal of the acetic anhydride, the reaction mixture was distilled under high vacuum. A fraction of approximately 50 mg. which distilled at 0.01 mm. pressure and a bath temperature of 200–210° was obtained.

Anal. Calcd. for $C_{14}H_{24}O_4$ (acid): C, 65.60; H, 9.44. For $C_{14}H_{22}O_3$ (anhydride): C, 70.55; H, 9.30. For $C_{13}H_{20}O$ (ketone): C, 80.35; H, 11.41. Found: C, 68.17; H, 9.17.

Acknowledgment.—The authors appreciate the coöperation and interest of Dr. A. C. Hildreth, Dr. H. Trent and Dr. J. Kirchner during the course of this work.

Summary

The structure of partheniol, a sesquiterpene alcohol isolated from guayule, *Parthenium argentatum, Gray*, has been determined.

PASADENA, CALIFORNIA RECEIVED DECEMBER 22, 1947

[CONTRIBUTION FROM HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Resin Acids. III. The Isolation of Dextropimaric Acid and a New Pimaric-type[1] Acid, Isodextropimaric Acid

BY GEORGE C. HARRIS AND THOMAS F. SANDERSON

The history of the discovery and isolation of dextropimaric[2] acid parallels that of levopimaric[2] acid by virtue of one property common to both acids, namely, the insolubility of their crystalline sodium salts. In other physical and chemical properties, they are significantly different. Dextropimaric acid is not susceptible to oxidation by air or isomerization by heat or dilute mineral acid, whereas levopimaric acid is relatively sensitive to both changes.

Previous methods of isolation of dextropimaric acid depended on fractional crystallization as its insoluble sodium salt from mixtures of resin acids such as "galipot"[3] or on recrystallization after oxidation of the more susceptible acids.[4] We have obtained a fraction containing dextropimaric acid and related acids by removal of the two-double-bond abietic-type acids by reaction with maleic anhydride after acid isomerization. The unreacted acids were separated from the maleic anhydride adduct by precipitation from aqueous alkaline solution by adjustment of the *p*H to 6.2.[5] Ultraviolet absorption spectra showed the absence of two-double-bond abietic-type acids in this fraction.

Further fractionation of this mixture has not only given relatively large amounts of dextropimaric acid but also yielded a new pimaric-type acid. When this resin acid fraction was dissolved in acetone and treated with butanolamine, an insoluble salt was obtained and recrystallized to constant rotation $[\alpha]^{20}D$ 0°. When the salt was decomposed with mineral acid, the resin acid was obtained which was crystallized first from alcohol and water as thin plates and finally as needles after standing in the mother liquor; $[\alpha]^{24}D$ 0°; m. p. 162–164°; neutral equivalent 302. The yield was 8% of the total oleoresin acids of *Pinus palustris*. The physical constants indicated a new resin acid. The isolation of formaldehyde as its "dimedon" derivative, m. p. 190–191°, on ozonolysis at −60° and of pimanthrene as its trinitrobenzolate,[6] m. p. 158–160°, on dehydrogenation with palladium–carbon catalyst at 330° proved it to be a pimaric-type acid. The homogeneity of the acid was proved by the preparation and purification of the methyl ester, m. p. 61.5–62°, and the butanolamine salt, $[\alpha]^{24}D$ 0°, and the regeneration of the acid with the same physical constants. The ultraviolet absorption spectrum, like that of dextropimaric acid, showed no maximum, indicating the absence of a conjugated double bond system.[7] This new pimaric-type acid has been termed isodextropimaric acid.

Dextropimaric acid was isolated from the acids regenerated from the residual salts, after that of isodextropimaric acid was separated, by crystallization first from acetone and then from glacial acetic acid in 4% yield with rotation, $[\alpha]^{24}D$ + 79°, m. p. 213–215°. The isolation of dextro-

(1) We wish to designate by this term that type of resin acid which yields pimanthrene (1,7-dimethylphenanthrene) upon complete dehydrogenation, and that has the gem configuration of methyl and vinyl groups at C-7. Evidence for this will be shown in a subsequent publication: G. C. Harris and T. F. Sanderson, Resin Acids. IV. THIS JOURNAL, **70**, 2081 (1948). The abietic-type acids are those that yield retene (1-methyl-7-isopropylphenanthrene) upon complete dehydrogenation and have an isopropyl or isopropylidene group at C-7.

(2) These words have purposely been written as one word since the compounds are not stereoisomers as the prefixes *levo-* and *dextro-* would imply.

(3) A. Vesterberg, *Ber.*, **20**, 3248 (1887).

(4) E. Knecht and E. Hibbert, *J. Soc. Dyers Colourists*, **38**, 221 (1922).

(5) A method developed by W. P. Campbell of this Laboratory.

(6) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **23**, 124 (1940).

(7) V. N. Krestinskii, S. S. Malevskaya, N. F. Komshilov and E. V. Kazeeva, *J. Applied Chem. (U. S. S. R.)*, **12**, 1840 (1939).

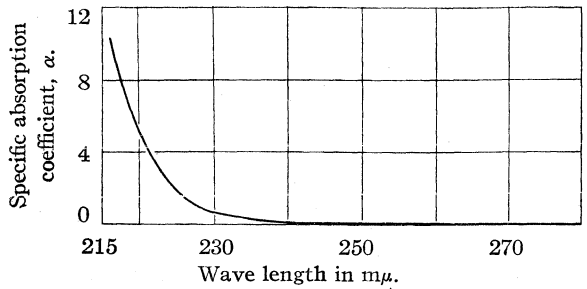


Fig. 1.—Ultraviolet absorption spectra (identical) of dextropimaric and isodextropimaric acids.

pimaric acid of high purity from this source supports the supposition that two-double-bond pimaric-type acids were not altered by the action of mineral acid in boiling benzene, the conditions used in the removal of the two-double-bond abietic-type acids.

The separation of both dextropimaric and isodextropimaric acid from wood or gum rosin was possible after observation was made of their very high volatility. It was found that in the course of the fractional distillation of rosin, these acids distilled with the more volatile constituents, the neutral bodies, at 136–200° with 1.0 mm. pressure. The total acids were separated by an alkaline extraction to obtain a mixture of resin and non-resin acids from which the isodextropimaric acid was separated as the insoluble butanolamine salt, and the dextropimaric acid crystallized as in the foregoing mixture of oleoresin acids in about 4 and 2% yield, respectively.

Experimental[8]

Isolation of Resin Acids from Oleoresin.—The procedure for the isolation of the resin acids from oleoresin was described in a previous publication.[9] It is carried out in the same manner with the exception that the temperature can be raised above 50° and dilute hydrochloric acid, *ca.* 10%, can be used in place of boric acid solution.

Separation of the Two-Double Bond Abietic-Type Acids.—A solution of 200 g. of oleoresin acids and 200 g. of maleic anhydride in one liter of dry benzene was saturated with dry hydrogen chloride and refluxed for forty-eight hours. At the end of this time, the benzene was steam distilled and the residue washed twice with hot water to remove the excess maleic anhydride. It was dissolved in a concentrated solution of 67 g. of sodium hydroxide, and, after complete solution, diluted to 6 liters. This solution was titrated to a *p*H of 6.2 with dilute hydrochloric acid and the precipitated resin acids were filtered, dissolved in ether, the ether solution washed free of acid, dried over sodium sulfate, and the ether evaporated. To assure the complete removal of two-double-bond abietic-type acids, the reaction with maleic anhydride was repeated to obtain 48 g. (24% yield) of maleic anhydride–unreactive acids with neutral equivalent of 304. An ultraviolet absorption curve showed the absence of these abietic-type acids.

Isolation of Isodextropimaric Acid.—The resin acids (48 g.) were dissolved in 96 g. of acetone and treated with a solution of 14.7 g. of butanolamine (2-amino-2-methyl-1-propanol, Commercial Solvents, Inc.) in 14.7 g. of acetone. A very vigorous reaction resulted with the simultaneous precipitation of the crystalline salts. In subsequent experiments, methyl acetate was used as the precipitating solvent. The salts were filtered and recrystallized three times from large volumes of methyl acetate to the constant rotation, $[\alpha]^{24}D$ 0°.[10,11] A few drops of amine were added after the salts were dissolved and the solution concentrated to compensate for that lost by evaporation. This was found necessary for complete recovery.

The salts were then suspended in ether and decomposed by shaking with 10% hydrochloric acid. To assure complete decomposition, two fresh portions of acid were used after the salts were in solution. The ether solution containing the resin acid was washed free of mineral acid with water, dried over sodium sulfate, and the ether evaporated. The residue was dissolved in acetone and crystallized from the hot solution by the addition of water to incipient turbidity, first as thin platelets and then, on long standing in the solution, as shiny needles, with rotation $[\alpha]^{24}D$ 0°, melting point 162–164°, and neutral equivalent 302 (theory 302). The yield was 8% (16.0 g.) based on the total oleoresin acids.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.37; H, 10.00. Found: C, 79.48, 79.40; H, 9.90, 9.95.

Preparation of the Methyl Ester of Isodextropimaric Acid.—A 20-g. sample of isodextropimaric acid was dissolved in 100 cc. of ether and the solution treated with an excess of an ether solution of diazomethane. The isolation was carried out in the usual manner to obtain an excellent yield (20 g.) of the ester melting at 61.5–62°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.70, 79.65; H, 10.27, 10.30.

The purity and homogeneity of the acid was established in the following manner. Material with rotation $[\alpha]^{24}D$ 0° and melting point 162–164° was used to prepare the butanolamine salt which was recrystallized three times to constant rotation $[\alpha]^{24}D$ 0°. The resin acid was regenerated in the usual manner with no change in rotation, $[\alpha]^{24}D$ 0°, or melting point, 162–164°. The methyl ester prepared as above was recrystallized to the constant melting point of 61.5–62°. Saponification in alcoholic alkali with subsequent acidification with mineral acid resulted in the isolation of isodextropimaric acid with rotation $[\alpha]^{24}D$ 0° and melting point 162–164°.

Ozonization of Isodextropimaric Acid; Isolation of Formaldehyde.—A 1.0-g. sample of pure isodextropimaric acid, rotation $[\alpha]^{24}D$ 0°, was dissolved in 50 cc. of dry ethyl chloride and treated with 3–5% ozone at −60° for two hours. The solvent was evaporated over water at room temperature and the ozonide decomposed in boiling water in an apparatus so arranged that the escaping gases were passed through an aqueous alcohol solution of "dimedon" (dimethyldihydroresorcinol). Upon standing, needles of the dimedon derivative of formaldehyde precipitated, m. p. 190–191°. A mixed melting point with an authentic sample showed no depression.

Dehydrogenation of Isodextropimaric Acid.—A 1.0-g. sample was mixed with 1.0 g. of 5% palladium–carbon catalyst and heated at 300–330° for four hours using carbon dioxide gas to sweep the gaseous products out of the reaction flask. After cooling, the catalyst was filtered from an ether solution of the reaction product and the ether evaporated. The trinitrobenzolate of pimanthrene, melting point 158–160°, crystallized upon heating the residue with a saturated alcoholic solution of trinitrobenzene.

Isolation of Dextropimaric Acid.—The acetone solution of the residual salts was evaporated to dryness, the residue dissolved in ether, and washed with dilute (10%) aqueous hydrochloric acid to decompose the salts. The ether solution containing the resin acids was washed free of mineral acid and water, dried over sodium sulfate, and the ether evaporated to obtain 32 g. of resin acids. The latter were dissolved in 30 cc. of acetone and cooled to

(8) All melting points are corrected.

(9) G. C. Harris and T. F. Sanderson, THIS JOURNAL, **70**, 338 (1948).

(10) All rotations are of 1% solutions in absolute ethanol.

(11) Same rotation, $[\alpha]^{24}D$ 0°, in chloroform and dry benzene.

−20° to obtain crystals of dextropimaric acid. Recrystallization from glacial acetic acid gave 8.0 g. (4% yield) of pure acid with rotation $[\alpha]^{24}D$ +79°, and melting point 217–219°.

Isolation of the Pimaric Acids from Wood or Gum Rosins.—A 1000-g. charge of wood or gum rosin was distilled fractionally at 1.0-mm. pressure in a 10-plate column and the fraction, 120 g., boiling between 136 and 200° was taken. It was found to be composed of nonacidic material and of resin and nonresin acids. The total acids were separated from the neutral bodies by extraction with a 2% aqueous alkaline solution from an ether solution of the mixture. The alkaline solution was acidified, the resin acids dissolved in ether, and the ether solution washed free of mineral acid, dried, and the ether evaporated.

The total acids (65 g.) were dissolved in 200 cc. of acetone and treated with 20 g. of butanolamine in 20 g. of acetone. The pure salt of isodextropimaric acid, $[\alpha]^{24}D$ 0°, was isolated and decomposed with mineral acid as before to obtain 39 g. (*ca.* 4%) of isodextropimaric acid. The acetone solution of the residual salts was evaporated, the salts decomposed, and dextropimaric acid crystallized as above to obtain 20 g. (2%) of the pure acid with rotation $[\alpha]^{24}D$ +79°, and melting point 217–219°.

Summary

1. A new, pimaric-type resin acid, termed isodextropimaric acid, has been isolated from the oleoresin of *Pinus palustris* and from wood or gum rosin.

2. Dextropimaric acid has also been isolated from these sources.

WILMINGTON 99, DELAWARE RECEIVED[12] AUGUST 9, 1947

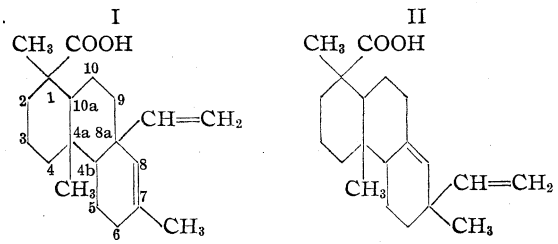
(12) Original manuscript received August 9, 1946.

[CONTRIBUTION FROM HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Resin Acids. IV. The Position of the Ring Double Bond in Dextropimaric[1] Acid and the Structure of Isodextropimaric[1] Acid

BY GEORGE C. HARRIS AND THOMAS F. SANDERSON

Ruzicka and Sternbach[2] have recently advanced Formula I and suggested Formula II as possible structures for dextropimaric acid.



Their argument against the latter was the fact that upon dehydrogenation of tetrahydrodextropimaric acid only pimanthrene (1,7-dimethylphenanthrene and no 1-methyl-7-ethylphenanthrene) was obtained. However, Formula II cannot be eliminated on this basis because the latter hydrocarbon may have been formed in such low yield as to escape detection. Experience shows that the isolation of pure hydrocarbons even as their solid derivatives from dehydrogenation mixtures is difficult, and especially so, if they are only minor constituents.

Formula II was proposed and preferred by Fleck and Palkin[3] in explaining the structure of a lactone obtained from dextropimaric acid treated with sulfuric acid at −20 to −30°. Lactonization at 4b position was suggested by the comparable stability of this lactone to that of hydroxytetrahydroabietic acid. If Formula I is assumed for dextropimaric acid, the necessary shift of the double bond to the bridgehead position, 4b,8a, is not possible; whereas if Formula II is assumed, the shift can be brought about by mineral acid so that lactonization of the carboxyl group can occur at C-4b.

Ruzicka and co-workers[4] have shown on the basis of experimental results that the vinyl group must be on a tertiary carbon atom, either 7 or 8a, however, not 4b, and still be compatible with the isoprene rule. Since the endocyclic double bond can be at the 7,8 or 8,8a position, the vinyl group must be on C-8a carbon atom for the former and on C-7 carbon atom for the latter position. The experimental evidence described herein will show the vinyl group to be at C-7 carbon atom, and, hence, the endocyclic double bond at 8,8a position.

Dextropimaric acid, I or II, $[\alpha]^{24}D$ + 75°, melting point 217–219°,[5] was hydrogenated selectively to the dihydro stage in absolute ethanol with 5% palladium–carbon catalyst. The reaction proceeded smoothly to the absorption of 1.0 mole of hydrogen yielding the insoluble dihydro acid, III or VII, in excellent yield.[6] The dihydro acid was ozonized in dilute carbon tetrachloride solution at −20° and the ozonide decomposed in boiling water in the presence of zinc powder to obtain a ketoaldehyde, IV or VIII. If the endocyclic double bond in dextropimaric acid is in 7,8 position, Formula I, a methyl ketone, IV, would be obtained and detected by the liberation of iodo-

(1) These words have purposely been written as one word since the compounds are not stereoisomeric with levopimaric acid as the prefixes *levo-*, *dextro-*, and *isodextro-* would imply.

(2) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **23**, 124 (1940).

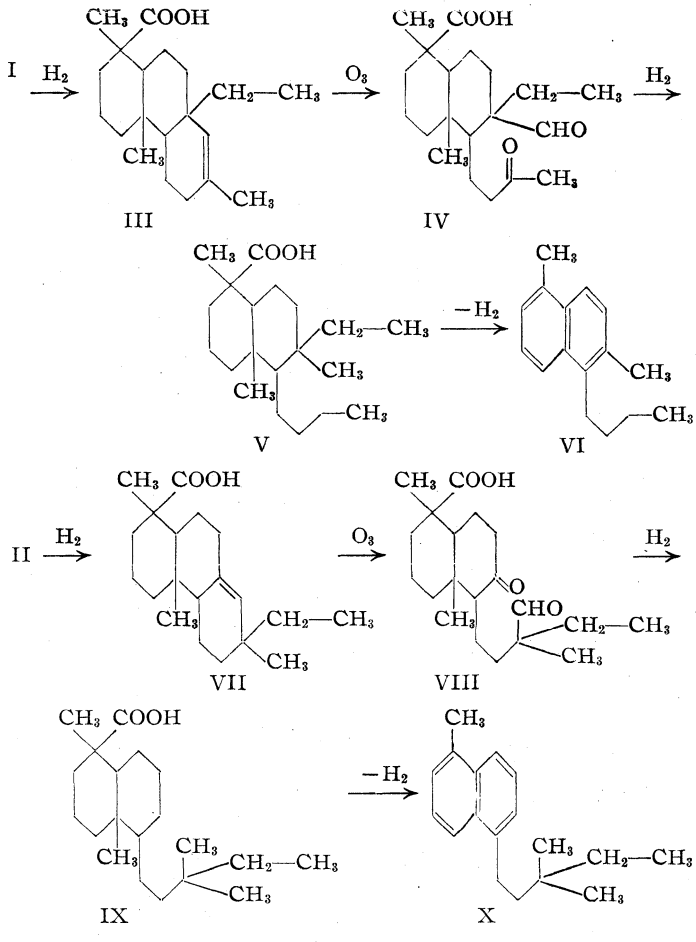
(3) E. E. Fleck and S. Palkin, THIS JOURNAL, **62**, 2044 (1940).

(4) L. Ruzicka, G. B. R. de Graaff, M. W. Goldberg, and B. Frank, *Helv. Chim. Acta*, **15**, 915 (1932).

(5) G. C. Harris and T. F. Sanderson, Resin Acids III, THIS JOURNAL, **70**, 2079 (1948).

(6) It was also found (reference below) that the crystals formed from rosin hydrogenated in the presence of platinum oxide were those of the dihydrodextropimaric acid. This afforded an abundant source of the material. T. Hasselstrom and B. L. Hampton, *ibid.*, **61**, 967 (1939).

form from a sodium hypoiodite solution of the substance. A negative iodoform test indicated that the endocyclic double bond is at 8,8a position, Formula II, hence a ketoaldehyde of structure VIII.



The latter compound, VIII, was reduced to the hydrocarbon by the Wolff–Kishner method. The non-crystalline product was dehydrogenated, the hydrocarbon isolated, and its trinitrobenzolate prepared and recrystallized to a constant melting point, 113–116°. Analyses for carbon, hydrogen, and nitrogen content and molecular weight determinations, obtained ebullioscopically with acetone as solvent, of the solid derivative showed it to be conclusively the trinitrobenzolate of a C_{18} hydrocarbon. The derivative was decomposed over activated alumina and the hydrocarbon isolated. Carbon and hydrogen analyses and molecular weight determination showed it to be a C_{18} hydrocarbon. Attempts to oxidize the hydrocarbon to the 1,5-dicarboxylic acid with potassium ferricyanide were unsuccessful, possibly because of the long alkyl chain at the 5 position. The ultraviolet absorption curve[7] of the isolated hydrocarbon, Fig. 1, Curve 2, demonstrates absorption that is characteristic of dialkylated naphthalenes, with intense band at 228 mμ, for example, 1,5-dimethylnaphthalene, Fig. 1, Curve 1 (see below). The height of the maxima of the C_{18} hydrocarbon is not so intense as those of the 1,5-dimethylnaphthalene because of the larger molecular weight of the former.

If the vinyl group is on C-8a carbon atom, Formula I, dehydrogenation of V should give a C_{16} hydrocarbon, VI; whereas, if the vinyl group were on C-7 carbon atom, Formula II, dehydrogenation of IX would give a C_{18} hydrocarbon. Since a C_{18} hydrocarbon was isolated, the vinyl group is placed at 7 position and the endocyclic double bond at 8,8a position. Hence Formula II is concluded to be that for dextropimaric acid.

The same series of experiments was carried out with pure isodextropimaric acid, $[\alpha]^{24}D$ 0°, and melting point 162–164°,[5] to obtain the trinitrobenzolate of the same hydrocarbon, X, with melting point 113–116°. A mixed melting point with the corresponding derivative from dextropimaric acid showed no depression, 113–116°. The identity of the two substances was *further* supported by the identity of their X-ray diffraction patterns and identity of their ultraviolet absorption spectra (Fig. 1, Curve 2).

From this, it was concluded that the two acids, isodextropimaric and dextropimaric acid, are dissimilar only with regard to the difference in the configuration of the methyl and vinyl groups about the asymmetric C-7 carbon atom. If this is the case, a similar decomposition product, in which the asymmetry at C-7 carbon atom was destroyed, should be obtained from each acid. Formula IX represents such a compound; how-

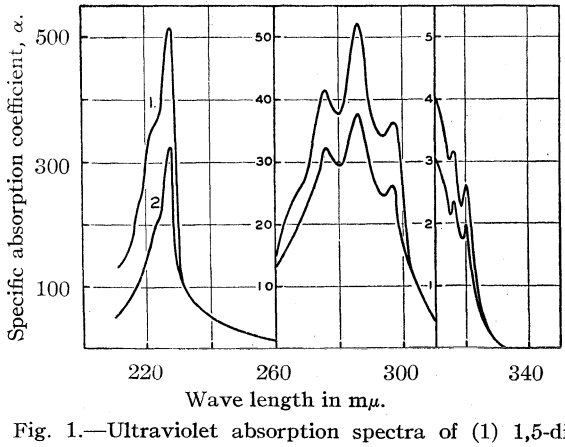
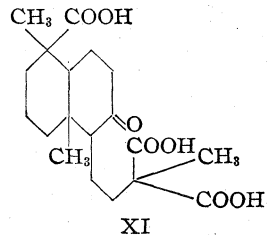


Fig. 1.—Ultraviolet absorption spectra of (1) 1,5-dimethylnaphthalene, and (2) the C_{18} hydrocarbon (X) from both dextropimaric and isodextropimaric acids.

(7) The ultraviolet absorption data were determined by Dr. Evelyn V. Cook of this Laboratory.

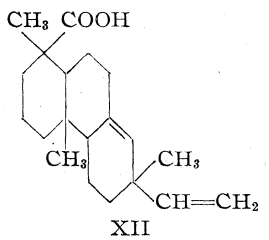
ever, it was not possible to crystallize either it or an acid derivative thereof.

Another approach for eliminating the asymmetry at 7 position is to ozonize the intact acids to obtain a tricarboxylic acid of Formula XI.



XI

This scheme was followed successfully to obtain the crystalline 2,4-dinitrophenylhydrazones and semicarbazones of triacids XI, which were proved to be identical by comparison of X-ray diffraction patterns and mixed melting points that showed no depression as compared with those of the individual derivatives. Therefore, the indication is that isodextropimaric and dextropimaric acids are dissimilar only with respect to the configuration of the methyl and vinyl groups at C-7 carbon atom. If Formula II is assumed for dextropimaric acid, Formula XII is that for isodextropimaric acid.



XII

Further evidence for Formula II as that for dextropimaric acid was obtained by the partial dehydrogenation of the pure acid.

The dehydrogenation was carried out in the usual manner at 300–330° with palladium–carbon catalyst, but the products were isolated by fractionation through a column of silica gel with hexane as solvent. The first product of dehydrogenation was a trisubstituted naphthalene, a C_{18} hydrocarbon (XIII). Its most intense band in the near ultraviolet (Fig. 2) is at 232 mμ, characteristic of trialkylated naphthalenes,[8] a shift of 4 millimicrons from that of dialkylated naphthalenes (Fig. 1). An intense band at 325 mμ, absent in the spectrum of the dialkylated naphthalenes, is also characteristic of the trisubstituted naphthalenes. If Formula I is that for dextropimaric acid, a C_{16} hydrocarbon would be isolated with only one substituent, a methyl group, at C-7. This structure would not be expected to be stable so that further dehydrogenation would give pimanthrene (XV) at once.

The C_{18} hydrocarbon was further dehydrogenated under the same conditions to obtain pimanthrene (XV).

(8) The characteristic absorption maxima of mono- and polyalkylated naphthalenes will be the subject of a future publication.

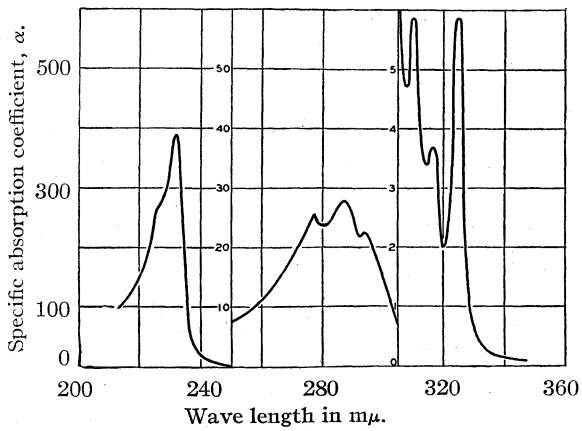
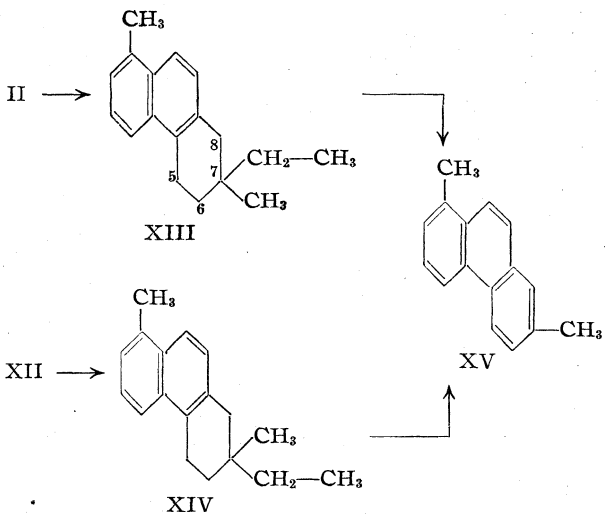


Fig. 2.—Ultraviolet absorption spectrum of C_{18} hydrocarbon (XIII and/or XIV).



Isodextropimaric acid (XII) was treated in a similar manner to obtain the C_{18} hydrocarbon, XIV, whose trinitrobenzolate had the same melting point as that of hydrocarbon XIII, m. p. 122–123°. Further dehydrogenation of hydrocarbon XIV also gave pimanthrene in good yield. No difference in spatial configuration of the two hydrocarbons (XIII and XIV) was detected by a mixed melting point of their trinitrobenzolates, optical rotation of the pure substances, or X-ray diffraction patterns of the trinitrobenzolates. It, therefore, can be assumed that racemization took place during the dehydrogenation so that hydrocarbons XIII and XIV are identical. Racemization during partial dehydrogenation is further evidence for the asymmetry at C-7. The identity of the hydrocarbon derivatives was substantiated by identical X-ray diffraction patterns. The synthesis of the C_{18} hydrocarbon is now in progress.

The known and new derivatives of the two acids and their melting points are:

		Melting point, °C.
1	Methyl isodextropimarate	61–62
2	Methyl dextropimarate	68–69
3	Dihydroisodextropimaric acid	173–175
4	Dihydrodextropimaric acid	243–245
5	Lactone of 3	109–110
6	Lactone of 4	98–99
7	Methyl ester of 3	75–76[a]
8	Methyl ester of 4	78–79

[a] Mixed melting point with 8 shows a marked depression.

Experimental[9]

Hydrogenation of Dextropimaric Acid (II).—A 5.0-g. sample of dextropimaric acid, $[\alpha]^{24}D$ +75°,[10] melting point 217–219°, was dissolved in 50 cc. of absolute ethanol and the solution agitated in a hydrogen absorption apparatus in the presence of 1.0 g. of 5% palladium–carbon catalyst until 408 cc. (1.0 mole) of hydrogen was absorbed. The reaction was carried out at room temperature and atmospheric pressure and stopped completely after the absorption of 1.0 mole of hydrogen. The catalyst was removed by filtration, and the dihydro acid watered out of the warm alcoholic solution to obtain 4.9 g. of acid (98% yield) with rotation, $[\alpha]^{24}D$ +19°, and melting point 243–245°.

Hydrogenation of Isodextropimaric Acid (XII).—The reaction was carried out in the same manner to obtain the dihydroisodextropimaric acid in the same yield with rotation, $[\alpha]^{24}D$ 0°, and melting point 173–175°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.88; H, 10.54. Found: C, 78.91, 78.95; H, 10.66, 10.60. Hydrogen absorption calcd. 0.66; found, 0.66.

Ozonization of Dihydrodextropimaric Acid (VII).—A 1.0-g. sample of dihydrodextropimaric acid, $[\alpha]^{24}D$ 0°, was dissolved in 50 cc. of boiling carbon tetrachloride and the solution allowed to cool to room temperature and eventually to −20° in an acetone–Dry Ice-bath. The ozonolysis reaction was carried out for two hours with an oxygen throughput of 20–25 liters per hour using a generator issuing 3–5% ozone. At the end of this time, the solvent was evaporated in vacuum at room temperature, the residue dissolved in a minimum amount of ether, water added, and the suspension boiled for four hours in the presence of 1.0 g. of powdered zinc. The reaction product was isolated in ether, the ether solution washed, dried, and the ether evaporated to obtain 0.80 g. (77% yield) of the ketoaldehyde, VIII, with neutral equivalent 330 (theory 336). It was not possible to crystallize the ketoaldehyde or a derivative thereof.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.38; H, 9.60. Found: C, 70.40, 70.49; H, 9.41, 9.38.

The product gave a negative iodoform test.

Ozonization of Dihydroisodextropimaric Acid.—The results with this acid were almost identical with those of dihydrodextropimaric acid. A non-crystalline substance was obtained giving approximately the same analytical data and a negative iodoform test.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.38; H, 9.60. Found: C, 70.20, 70.43; H, 9.45, 9.50.

Wolff–Kishner Reduction of the Ketoaldehyde, VIII, and of the Corresponding Product from Isodextropimaric Acid.—The disemicarbazones were prepared by dissolving 2 g. of the ketoaldehyde in an alcoholic solution of semicarbazide acetate, adding a few drops of pyridine and allowing the solution to stand for two days. The non-crystallizable derivative was then extracted in ether after the reaction solution was poured into a large volume of water. The ether was evaporated, the residue taken up in 35 cc. of alcohol containing 3.0 g. of sodium metal, and the solution heated at 200° for eight hours under 1800 p. s. i. of nitrogen pressure.

(9) All melting points are corrected.

(10) All rotations are of 1% solutions in absolute ethanol.

The solution was poured into water and acidified with dilute mineral acid, and the organic material was dissolved in ether. The ether solution was washed free of mineral acid, dried, and the ether evaporated. The crude product, IX, 0.9 g. (50% yield) was dehydrogenated.

The corresponding product from isodextropimaric acid was treated in a similar manner to obtain a crude product in the same yield.

Dehydrogenation of the Crude Product IX.—A 2.0-g. sample of the powdered material was mixed intimately with 2.0 g. of 5% palladium–carbon catalyst and heated at 300–325° for four hours under a stream of carbon dioxide gas. At the end of this time, the dehydrogenated product was dissolved in ether and the catalyst filtered. The residue was dissolved in 1 cc. of 95% ethanol and treated with 10 cc. of a saturated solution of trinitrobenzene. Upon concentrating to 5-cc. volume and cooling, light-yellow needles of the trinitrobenzolate of hydrocarbon X precipitated in 35–40% yield. The derivative was recrystallized to a constant melting point of 113–116°.

Anal. Calcd. for $C_{18}H_{24}$ (X) + $C_6H_3N_3O_6$, $C_{24}H_{27}N_3O_6$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.76, 63.43; H, 5.75, 5.67; N, 9.14, 9.20. Molecular weight Calcd.: 227. Found (ebullioscopic method): 225, 229. Calcd. for $C_{16}H_{20}$ (VI) + $C_6H_3N_3O_6$, $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.44; N, 9.88. Molecular weight calcd.: 213.

Dehydrogenation of Compound, Corresponding to IX, from Isodextropimaric Acid.—This reaction was carried out in the same manner to obtain a trinitrobenzolate of the hydrocarbon that melted at 113–116°. The identity of the two substances was shown by a comparison of their X-ray diffraction patterns, ultraviolet absorption curves, and a mixed melting point that showed no depression.

Anal. Calcd. for $C_{18}H_{24}$ + $C_6H_3N_3O_6$ or $C_{24}H_{27}N_3O_6$: C, 63.56; H, 6.00; N, 9.27; mol. wt., 227. Found: C, 63.60, 63.40; H, 5.85, 5.65; N, 9.22, 9.17; mol. wt., 227, 230.

Isolation of Hydrocarbon X.—The trinitrobenzolate derivative (2.0 g.) was dissolved in 5 cc. of benzene and placed on a column of alumina (30 × 320 mm.). Upon elution with benzene, the hydrocarbon was washed through the column and the trinitrobenzene remained adsorbed. The benzene was evaporated under vacuum to obtain 1.0 g. (95% yield) of a fluorescent hydrocarbon that could not be made to crystallize.

Anal. Calcd. for $C_{18}H_{24}$: C, 89.92; H, 10.08; mol. wt., 240. Found: C, 89.84, 89.87; H, 10.10, 10.10; mol. wt., 237, 242.

Complete Ozonization of Dextropimaric Acid, II.—A 1.0-g. sample was dissolved in 30 cc. of ethyl chloride and the solution cooled to −60° in an acetone–Dry Ice-bath. The reaction was carried out for two hours with an oxygen throughput of 20–25 liters per hour using a generator issuing 3–5% ozone. At the end of this time, the solvent was evaporated in vacuum, the residue dissolved in a minimum amount of ether, water added, and the suspension boiled for four hours in the presence of 1.0 g. of powdered zinc. Upon isolation in ether, the decomposed ozonide was dissolved in 5% alkali, and 2% hydrogen peroxide solution was added to oxidize the aldehyde to carboxyl groups, XI.

The aqueous solution was acidified and the precipitate dissolved in ether. The ether solution was extracted with bicarbonate solution and the product isolated in ether upon careful acidification of the bicarbonate solution. It could not be made to crystallize, so the data were obtained on the powdered material.

Anal. Calcd. for $C_{19}H_{28}O_7$ (XI): C, 61.82; H, 7.89. Found: C, 62.29, 62.89; H, 8.28, 8.00. Molecular weight, calcd.: 368. Found: 373 (ebullioscopically).

Its 2,4-dinitrophenylhydrazone was prepared in the usual manner, melting point 185–188°. The semicarbazone was also prepared, m. p. 223–225°, and analyzed for nitrogen content. Calcd., 9.9; found, 10.35, 10.12.

Complete Ozonization of Isodextropimaric Acid, XII.—The reaction was carried out in the same manner to obtain

a product of the same nature. Its dinitrophenylhydrazone also melted at 185–188° and its semicarbazone at 223–225°. The identity of the two derivatives with the corresponding ones from dextropimaric acid was shown by mixed melting points that showed no depression and also by the fact that their X-ray diffraction patterns were identical.

Dehydrogenation of Dextropimaric and Isodextropimaric Acids.—A 2.0-g. sample of the pure acid was mixed intimately with 1.0 g. of 5% palladium–carbon catalyst and heated at 300–330° for four hours. The catalyst was filtered from an ether solution of the mixture of hydrocarbons.

Isolation of the Trinitrobenzolate of C_{18} Hydrocarbon (XIII or XIV).—The dehydrogenation product (1.4 g.) was dissolved in 10 cc. of hexane and transferred to a column of silica gel. The chromatogram was developed with hexane and followed with ultraviolet light. The fraction (0.6 g.) taken was that which preceded the blue fluorescence due to pimanthrene.

The same trinitrobenzolate, m. p. 122–123°, was isolated from the corresponding fraction obtained from each of the two resin acids as shown by identical X-ray diffraction patterns and no depression in a mixed melting point. Once their identity was established, they were mixed and analytical data obtained.

Anal. Calcd. for $C_{18}H_{22}$ + $C_6H_3N_3O_6$ (T. N. B.), $C_{24}H_{25}N_3O_6$: C, 63.56; H, 6.00; N, 9.27. Found: C, 64.16, 64.10; H, 5.75, 5.75; N, 9.18, 9.34.

Isolation of Hydrocarbon XIII or XIV.—The procedure is the same as that described for the isolation of hydrocarbon X. The first experiments were done with the pure trinitrobenzolates of the hydrocarbons obtained from each acid. Each was found to have a rotation of 0° in absolute ethanol or benzene.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.65; H, 9.35. Found: C, 90.23, 90.64; H, 9.30, 9.35.

Dehydrogenation of Hydrocarbon XIII or XIV.—The same procedure was used as in the section on the dehydrogenation of the free acids. The trinitrobenzolate of pimanthrene, m. p. 158–160°, was isolated in good yield.

Summary

The positions of the vinyl group and of the endocyclic double bond of dextropimaric acid have been established, hence the structure of the acid completed.

The structure of isodextropimaric acid has been determined and the stereoisomerism of the two acids demonstrated.

WILMINGTON, DELAWARE RECEIVED[11] AUGUST 12, 1947

(11) Original manuscript received August 9, 1946.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Streptomyces Antibiotics. XVI. The Structures of bis-Desoxystreptose, Dihydrodesoxystreptose and Tetraacetyl-bis-desoxystreptobiosamine

BY NORMAN G. BRINK, FREDERICK A. KUEHL, JR., EDWIN H. FLYNN AND KARL FOLKERS

Treatment of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal,[1,2] I, with Raney nickel catalyst gave tetraacetyl-bis-desoxystreptobiosamine, II, and tetraacetyldesoxystreptobiosamine, III. Acid hydrolysis of tetraacetyl-bis-desoxystreptobiosamine yielded N-methyl-L-glucosamine,[3] IV, and bis-desoxystreptose, a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran,[4] V. Details of these investigations and an account of the analogous degradation of pentaacetyldihydrodesoxystreptobiosamine[5,6] to dihydrodesoxystreptose are described herein.

When a solution of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal in 70% ethanol was refluxed in the presence of Raney nickel catalyst (not freshly prepared) and the products of the reaction were chromatographed on alumina, two compounds were isolated. The first crystalline fractions from the chromatogram consisted of tetraacetyl-bis-desoxystreptobiosamine, m. p. 159–160°, $[\alpha]^{25}D$ − 85°. The second product melted at 166–167°, $[\alpha]^{25}D$ − 81°, and was isolated from later fractions. It differed by the presence of one additional oxygen atom, and was designated tetraacetyldesoxystreptobiosamine. A mixture of the two compounds did not give a mixed melting-point depression, and the close correspondence of their physical properties added to the difficulties of separation. The bis-desoxy derivative was unchanged by acetylation treatment, but the desoxy derivative on acetylation gave a pentaacetyl derivative, VI, which melted at 111–112°. The pentaacetyldesoxystreptobiosamine was considerably more soluble than either of the tetraacetates. This observation was of value for the purification of tetraacetyl-bis-desoxystreptobiosamine, because after acetylation it could be separated readily from pentaacetyldesoxystreptobiosamine by recrystallization. Crude tetraacetyldesoxystreptobiosamine was purified by repeated chromatography.

The conversion of tetraacetyldesoxystreptobiosamine to pentaacetyldesoxystreptobiosamine indicated that the additional oxygen atom in the desoxy compound was present as a hydroxyl group, and it seemed likely that this group had been introduced by hydrolysis which competed with the hydrogenolysis during the treatment with Raney nickel catalyst. In support of this interpretation was the observation that when the reaction was carried out with Raney nickel catalyst which had been prepared immediately before use,

(1) Kuehl, Flynn, Brink and Folkers, THIS JOURNAL, **68**, 2096 (1946).

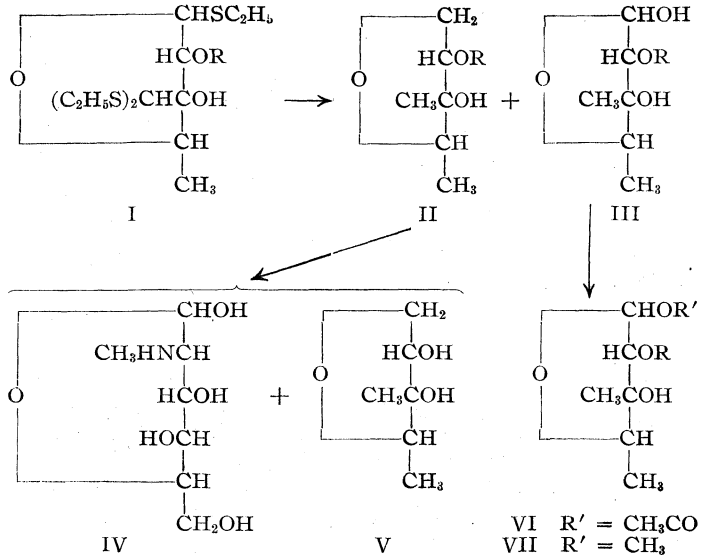
(2) Hooper, Klemm, Polglase and Wolfrom, *ibid.*, **68**, 2120 (1946).

(3) Kuehl, Flynn, Holly, Mozingo and Folkers, *ibid.*, **68**, 536 (1946).

(4) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2405 (1946).

(5) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2557 (1946).

(6) Lemieux, Polglase, DeWalt and Wolfrom, *ibid.*, **68**, 2747 (1946).



R = tetraacetyl-N-methyl-L-glucosoaminido

the yield of the bis-desoxy derivative was greatly increased and no appreciable amount of the desoxy derivative could be isolated. Tetraacetyldesoxystreptobiosamine gave a precipitate with 2,4-dinitrophenylhydrazine and reacted with one mole of hydroxylamine, as determined acidimetrically.[7] Treatment of tetraacetyldesoxystreptobiosamine with methanol containing hydrogen chloride, followed by reacetylation, gave crystalline methyl tetraacetyldesoxystreptobiosaminide, VII. These observations establish that the hydroxyl group in tetraacetyldesoxystreptobiosamine is glycosidic, rather than alcoholic, and that this hydroxyl group marks the location of the thioglycosidic ethylmercapto group in the original ethyl thiostreptobiosaminide diethyl mercaptal.

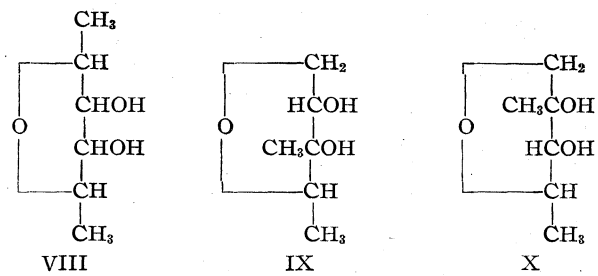
The partial deacetylation of tetraacetyl-bis-desoxystreptobiosamine with methanolic ammonia to N-acetyl-bis-desoxystreptobiosamine has been described.[1] In like manner, N-acetyldesoxystreptobiosamine was prepared from tetraacetyldesoxystreptobiosamine. Kuhn–Roth determinations on both of these N-acetyl derivatives indicated the presence of three C-methyl groups. In each case, the N-acetyl group accounted for one C-methyl group, and another C-methyl group was known to be present in the streptobiosamine skeleton.[5] Hence, an additional C-methyl group had been introduced during the hydrogenolysis reaction.

When the infrared spectrum of a sample of tetraacetyl-bis-desoxystreptobiosamine, which had been purified by reacetylation and recrystallization and carefully dried, was determined at high concentration (*ca.* 50%) in tetrachloroethane solution, a well-defined absorption band at 2.85 μ (–OH region) was observed. Further, in a Zerewitinoff determination, the compound gave one mole of methane. The presence in the bis-desoxy derivative of a free hydroxyl group, resistant to acetylation, was indicated. Tetraacetyl-bis-desoxystreptobiosamine was stable to chromic acid in 90% acetic acid solution. In view of the resistance of this hydroxyl group to acetylation and its stability to chromic acid, it was presumed to be tertiary.

When a solution of pure tetraacetyl-bis-desoxystreptobiosamine in 5% sulfuric acid was refluxed for six hours, and the acid solution then extracted continuously with chloroform, the chloroform extract yielded crystalline bis-desoxystreptose, $C_6H_{12}O_3$. From the sulfuric acid solution after chloroform extraction, N-methyl-L-glucosamine was isolated as the pentaacetyl derivative.

Bis-desoxystreptose melted at 90–91° and was dextrorotatory. Kuhn–Roth determinations showed the presence of two C-methyl groups. No carbonyl group could be detected in the compound. That two of the three oxygen atoms were present as hydroxyl groups was demonstrated by the preparation of a bis-*p*-nitrobenzoate. Bis-desoxystreptose reacted with one mole of periodic acid, from which it followed that the two hydroxyl groups were on adjacent carbon atoms. The periodic acid cleavage product was characterized as a dicarbonyl compound of formula $C_6H_{10}O_3$ by conversion to the crystalline bis-*p*-nitrophenylhydrazone.

Three structures (VIII, IX and X) were to be considered for bis-desoxystreptose. Structure

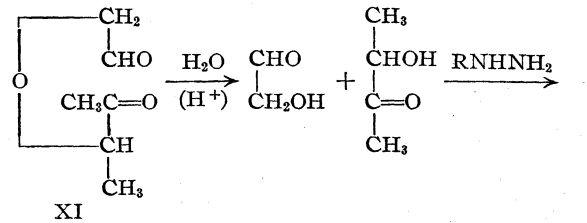


VIII seemed to be unlikely, because it did not contain a tertiary hydroxyl group. In order to decide which of these three structures was correct, the reactions of the periodic acid cleavage product $C_6H_{10}O_3$ were studied.

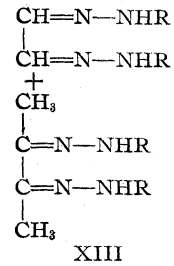
Compounds of structures IX and X on treatment with periodic acid should yield products XI and XII, respectively; and these in turn, being ethers of α-hydroxy carbonyl compounds, should be readily hydrolyzed by acid, as shown. Further, treatment of the acid hydrolysis products with excess hydrazines would be expected to give osazones of biacetyl (XIII) and osazones of pyruvaldehyde (XIV), respectively. A similar degradation of a compound of structure VIII would also

(7) Bryant and Smith, THIS JOURNAL, **57**, 57 (1935).

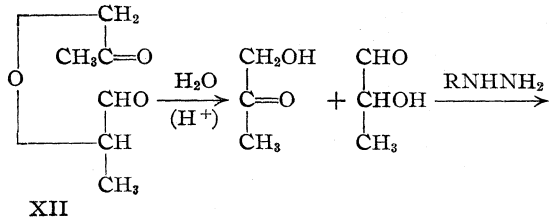
be expected to yield osazones of pyruvaldehyde (XIV).



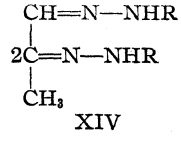
XI



XIII



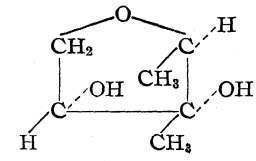
XII



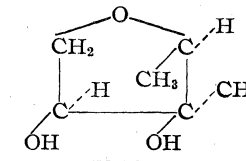
XIV

Bis-desoxystreptose was allowed to react with one mole of periodic acid, the inorganic products were removed, and the solution was warmed briefly on the steam-bath with 50% acetic acid to effect the hydrolysis of the dicarbonyl compound. Portions of the hot solution were then added to solutions of phenylhydrazine, *p*-nitrophenylhydrazine and *p*-bromophenylhydrazine in hot dilute acetic acid. In each case, the corresponding osazone of biacetyl (XIII) was obtained. The products were identified by comparison with authentic specimens and, in the case of the phenyl compound, by oxidation to 5,6-dimethyl-2,3-diphenylosatetrazine.[8] These results show that the structure of bis-desoxystreptose is as represented by formula IX and that the compound is a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran.

The acidity of a dilute boric acid solution was strongly increased by the addition of a slight excess of bis-desoxystreptose. The formation of such an acidic complex with boric acid indicates that the two hydroxyl groups are in the *cis* configuration.[9] The isolation of the phenylosazone of 4-desoxy-L-erythrose from streptobiosamine[10] showed that carbon atom five of the tetrahydrofuran ring of streptose possessed the L-configuration. Bis-desoxystreptose is thus a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran having a configuration XV or XVI.



XV

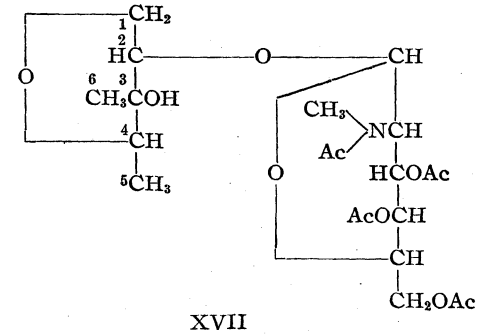


XVI

In tetraacetyl-bis-desoxystreptobiosamine, the presence of a free tertiary hydroxyl group requires that N-methyl-L-glucosamine be attached through the secondary hydroxy group of the bis-desoxystreptose. That the two portions of the disaccharide are linked glycosidically through the aldehydic carbon atom of the methylamino hexose has already been established.[1,2,4]

When N-acetyl-bis-desoxystreptobiosamine was treated with an excess of sodium periodate in aqueous solution, one mole of oxidant was rapidly consumed, the reaction then proceding more slowly. At the time that one mole of periodate had reacted, a potentiometric titration of the reaction solution showed the presence of 0.25 mole of a weak acid, presumably acetic acid formed by partial deacetylation. No formic acid could be detected. In another experiment, N-acetyl-bis-desoxystreptobiosamine was oxidized with exactly one mole of sodium periodate. No formaldehyde could be isolated from the reaction solution. The rapid primary reaction of the disaccharide with one mole of periodate without the formation of either formaldehyde or formic acid is consistent only with a pyranose ring structure for the N-methyl-L-glucosamine moiety.

The structure of tetraacetyl-bis-desoxystreptobiosamine, on the basis of this evidence, is represented by formula XVII.



XVII

Since carbon atom four (structure XVII) has been shown to have the L-configuration,[10] streptose is an L-sugar by definition.

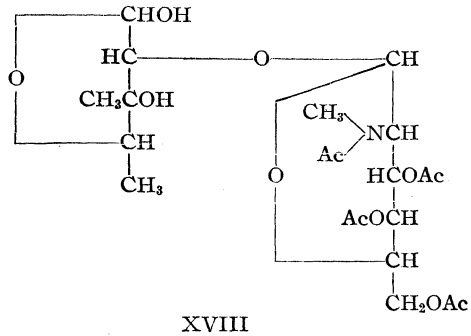
Tetraacetyldesoxystreptobiosamine, on the basis of this evidence, is represented by formula XVIII.[4,11] Since the free hydroxyl group is gly-

(8) H. v. Pechmann, *Ber.*, **21**, 2751 (1888).

(9) Böeseken, *Rec. trav. chim.*, **40**, 553 (1921).

(10) Fried, Walz and Wintersteiner, THIS JOURNAL, **68**, 2746 (1946).

(11) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).

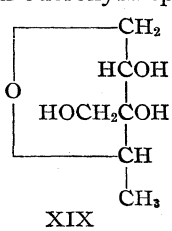


XVIII

cosidic, it must be located either at carbon atom one or four; from the structure of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal,[11] it is evident that the group is at carbon atom one.

It can be seen that in bis-desoxystreptose the methyl group adjacent to the tertiary hydroxyl group must have been the one formed during the hydrogenolysis reaction. However, it was felt that a direct proof of this, and consequently of the position of the original streptomycin aldehyde group, would be of interest. For this reason, the hydrolysis of pentaacetyldihydrodesoxystreptobiosamine[5,6] was studied.

Pentaacetyldihydrodesoxystreptobiosamine was hydrolyzed with acid under conditions used for the cleavage of tetraacetyl-bis-desoxystreptobiosamine, but in this case the products could not be separated by chloroform extraction. Treatment of the neutralized acid hydrolysate with ion-exchange resins served, however, to remove N-methyl-L-glucosamine, and crystalline dihydrodesoxystreptose, $C_6H_{12}O_4$, was isolated from the eluates. Dihydrodesoxystreptose consumed two moles of periodate with the liberation of one equivalent of an acid. One equivalent of formaldehyde was also formed upon periodate cleavage as demonstrated by the isolation of the dimedone derivative. These results are consistent with the structure XIX of dihydrodesoxystreptose, and support



XIX

the previously assigned position of the linkage of streptidine to streptobiosamine.[11]

Experimental

Tetraacetyl-bis-desoxystreptobiosamine (II) and Tetraacetyldesoxystreptobiosamine (III).—A solution of 10 g. of ethyl thiostreptobiosaminide diethyl mercaptal hydrochloride in 20 ml. of pyridine was cooled in an ice-bath, and 15 ml. of acetic anhydride was added. The mixture was allowed to warm slowly to room temperature and stand overnight. Water was added to decompose the excess acetic anhydride, and the solution was concentrated *in vacuo* to a sirup which was dissolved in chloroform. The chloroform solution was washed with water, 5% sulfuric acid, and twice with water. The chloroform was removed under reduced pressure and 12.6 g. (95%) of crude tetraacetate remained.

A solution of the tetraacetate in 1.4 l. of 70% ethanol was refluxed for one and one-half hours in the presence of 350 g. of Raney nickel catalyst which had been prepared some weeks previously. The nickel was removed by centrifugation and washed repeatedly with portions of hot methanol. The combined supernatant and washings were concentrated under reduced pressure to a volume of about 150 ml. The organic material was removed by extraction with chloroform. The chloroform was distilled *in vacuo* giving 9.3 g. of oily residue. This oil was dissolved in 265 ml. of a 78% benzene–22% petroleum ether mixture, and the solution was poured on a column which was prepared with 91 g. of acid-washed alumina and petroleum ether. The material was eluted by solvents and solvent mixtures of increasing polarity. Details of the chromatographic separation are shown in Table I.

TABLE I

CHROMATOGRAPHIC SEPARATION OF HYDROGENOLYSIS PRODUCTS

Fraction	Solvents	Products,[a] mg.	M. p., °C.
I	78% Benzene–22% petroleum ether (265 ml.)	Oil	
II	100% Benzene (120 ml.)	Oil	
III	80% Benzene–20% chloroform (120 ml.)	Oil	
IV	60% Benzene–40% chloroform (120 ml.)	273	155–159
V	40% Benzene–60% chloroform (120 ml.)	967	158–160
VI	20% Benzene–80% chloroform (120 ml.)	717	161–165
VII	100% Chloroform (120 ml.)	724	162–164
VIII	50% Chloroform–50% acetone (480 ml.)	1460	166–167

[a] Yields and melting points refer to material crystallized from ether and recrystallized from chloroform–ether.

Fractions IV and V consisted of nearly pure tetraacetyl-bis-desoxystreptobiosamine. For final purification, 980 mg. of this material was reacetylated with pyridine and acetic anhydride. The product was worked up in the usual manner and crystallized from a chloroform–ether mixture, giving 846 mg., m. p. 158–160°. Two recrystallizations of this product from chloroform–ether gave pure tetraacetyl-bis-desoxystreptobiosamine, m. p. 159–160°, $[\alpha]^{25}D$ −85° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_{13}H_{21}NO_7(CH_3CO)_4$: C, 53.04; H, 7.00; N, 2.95; O-acetyl, 27.2. Found: C, 52.98; H, 6.75; N, 2.87; O-acetyl, 27.7.[12]

In a Zerewitinoff determination carried out in anisole solution at room temperature on a sample dried in a weighing pig, 0.94 mole of methane was liberated from tetraacetyl-bis-desoxystreptobiosamine.

In tetrachloroethane solution at ordinary concentration (10–15%), tetraacetyl-bis-desoxystreptobiosamine showed absorption of 5.75 μ (ester) and 6.12 μ (disubstituted amide). However, a very concentrated solution (about 50%) showed a strong absorption band at 2.85 μ (hydroxyl group region).

Fractions VI and VII contained mixtures of tetraacetyl-bis-desoxystreptobiosamine and tetraacetyldesoxystreptobiosamine. These mixtures could not be separated by crystallization methods, but rechromatographing on alumina afforded some further separation.

Fraction VIII appeared to be pure tetraacetyldesoxystreptobiosamine. Its properties could not be changed by recrystallization, nor did repeated chromatography give material of higher melting point. A sample for analysis was recrystallized from ether containing a small amount of chloroform. It melted at 166–167°, and had a specific rotation of $(\alpha)^{25}D$ −81° (*c*, 1.04 in chloroform).

Anal. Calcd. for $C_{13}H_{21}NO_8(CH_3CO)_4$: C, 51.32;

(12) Determined by the method of Kunz and Hudson, THIS JOURNAL, **48**, 1982 (1926).

H, 6.77; N, 2.85; CH_3CO, 35.0. Found: C, 51.29; H, 6.94; N, 2.81; CH_3CO, 33.6.

There was no appreciable lowering of the melting point of a mixture of the two pure products. The desoxy compound (m. p. 166–167°) admixed with the bis-desoxy compound (m. p. 159–160°) melted at 162–165°.

Improved Preparation of Tetraacetyl-bis-desoxystreptobiosamine (II).—The acetylation product of 4.0 g. of ethyl thiostreptobiosaminide diethyl mercaptal hydrochloride was treated with Raney nickel catalyst exactly as described above, except that the catalyst was prepared immediately before use. The reaction products were isolated and chromatographed on alumina as in the previous example. The crystalline fractions were recrystallized separately from chloroform–ether. The lowest melting fraction melted at 153–156°; the highest melting fraction melted at 158–160°. The total weight of the recrystallized fractions was 1.91 g. They were combined and reacetylated, yielding 1.46 g. (33%) of tetraacetyl-bis-desoxystreptobiosamine, m. p. 157–159°.

In subsequent preparations, it was found that the chromatographic analysis of the reduction products could be omitted if freshly prepared Raney nickel catalyst had been used. The total organic material from the reduction was reacetylated and once recrystallized. This consistently afforded essentially pure tetraacetyl-bis-desoxystreptobiosamine in yields of 30–35%.

N-Acetyldesoxystreptobiosamine.—A solution of 212 mg. of tetraacetyldesoxystreptobiosamine in 8 ml. of methanol was cooled in an ice-bath and saturated with anhydrous ammonia. The solution was allowed to warm gradually to room temperature, and after two hours the solvent was removed *in vacuo*. The residue was dissolved in 10 ml. of water and the aqueous solution extracted with three 5-ml. portions of chloroform to remove acetamide. The aqueous solution was concentrated to dryness, the product dissolved in 1 ml. of isopropyl alcohol, and 15 ml. of chloroform added. The resulting gel was warmed gently, giving an oil which crystallized on standing. The product, 122 mg., melted at 224–226°. Pure N-acetyldesoxystreptobiosamine, m. p. 224–225°, was obtained by recrystallization from chloroform–methanol mixtures.

Anal. Calcd. for $C_{13}H_{24}NO_8(CH_3CO)$: C, 49.30; H, 7.45; N, 3.84; CH_3CO, 11.7; C-methyl, 8.2 (2 moles) 12.3 (3 moles). Found: C, 49.34; H, 7.20; N, 4.19; CH_3CO, 10.8; C-methyl, 9.8 (2.4 moles).

Pentaacetyldesoxystreptobiosamine (VI).—One hundred milligrams of tetraacetyldesoxystreptobiosamine was acetylated overnight at room temperature with 1 ml. of acetic anhydride in 5 ml. of pyridine. The solvents were removed *in vacuo* and the residue was dissolved in ether. The solution deposited 40 mg. of needle-like crystals on standing, m. p. 60–63°. Several recrystallizations of the product from ether gave pure pentaacetyldesoxystreptobiosamine, m. p. 111–112°, $[\alpha]^{25}D$ −132° (*c*, 0.62 in chloroform).

Anal. Calcd. for $C_{13}H_{20}NO_8(CH_3CO)_5$: C, 51.78; H, 6.61; N, 2.63; CH_3CO, 40.2. Found: C, 51.90; H, 6.56; N, 2.99; CH_3CO, 36.0.

Methyl Tetraacetyldesoxystreptobiosaminide (VII).—A solution of 200 mg. of tetraacetyldesoxystreptobiosamine in 5 ml. of absolute methanol containing 1% of hydrogen chloride was allowed to stand overnight at room temperature. The solvent was removed *in vacuo* and benzene was added and distilled. The residue was evacuated on the oil pump for two hours and was then dissolved in 3 ml. of pyridine, cooled to 0°, and treated with 2 ml. of acetic anhydride. After standing overnight at room temperature, the acetylation mixture was treated in the usual manner, giving a colorless oil. This oil was dissolved in ether containing a small amount of chloroform. On standing for three hours, the solution deposited crystals; 68 mg., m. p. 152–165°. Recrystallization of the product from a small volume of cold methanol gave 25 mg. of material, m. p. 176–180°. The combined mother liquors were chromatographed on 3 g. of alumina. An additional 36 mg. of crystalline material, m. p. 177–181° and 172–175° (two fractions), was eluted by benzene–chloroform mixtures. The two highest melting fractions were recrystallized from methanol yielding pure methyl tetraacetyldesoxystreptobiosaminide; m. p. 179–180.5°, $[\alpha]^{25}D$ −129° (*c*, 0.925 in chloroform).

Anal. Calcd. for $C_{13}H_{20}NO_7(CH_3O)(CH_3CO)_4$: C, 52.27; H, 6.98; N, 2.77; CH_3O, 6.1. Found: C, 52.21; H, 6.87; N, 2.65; CH_3O, 5.0.

Volumetric Determination of Carbonyl in Tetraacetyldesoxystreptobiosamine.—Sixty-seven milligrams (0.136 millimole) of tetraacetyldesoxystreptobiosamine, m. p. 165–167°, was added to a dilute alcohol solution containing pyridine, brom phenol blue, and an excess of hydroxylamine hydrochloride. After the solution had stood overnight, titration with 0.105 *N* sodium hydroxide in 90% methanol according to the method of Bryant and Smith[7] required 1.27 ml. to match the color of a blank prepared with hydroxylamine hydrochloride, pyridine, and brom phenol blue. This amount corresponded to 0.133 millimole of pyridine hydrochloride formed, or 0.98 mole of carbonyl function in the compound tested.

Treatment of Tetraacetyl-bis-desoxystreptobiosamine with Chromic Acid.—Twenty-seven milligrams of tetraacetyl-bis-desoxystreptobiosamine, m. p. 159–160°, was dissolved in 0.5 ml. of acetic acid and treated with a solution of 14 mg. of chromic anhydride in 0.5 ml. of 80% acetic acid. After two hours at room temperature, no appreciable color change could be detected. The chromic acid was then reduced with methanol. The solution yielded 18 mg. of crystals, m. p. 155–158°. Recrystallization of this material from a chloroform–ether mixture gave pure starting material, m. p. and mixed m. p. 159–160°.

bis-Desoxystreptose (3,4-Dihydroxy-2,3-dimethyltetrahydrofuran) (V).—A solution of 1.52 g. of tetraacetyl-bis-desoxystreptobiosamine in 95 ml. of 5% sulfuric acid was refluxed for six hours. The solution was then extracted continuously with chloroform for six hours. The chloroform solution was shaken with solid sodium bicarbonate, filtered, and the chloroform distilled, leaving a mixture of crystals and red tar. The crystalline material sublimed readily at 50–60° and 10^{-4} mm. pressure. The sublimate was recrystallized from an ether–petroleum ether mixture, giving 98 mg. (22%) of needle-like crystals, m. p. 90–90.5°. After recrystallization of this material from ether–petroleum ether and from ether, the product melted constantly at 90–91°; $[\alpha]^{25}D$ +32° (*c*, 0.975 in chloroform); $[\alpha]^{25}D$ +21° (*c*, 1.02 in water).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16; 2 C-methyl, 22.7; mol. wt., 132. Found: C, 54.63; H, 8.93; C-methyl, 19.4; mol. wt., 141 (ebullioscopic in carbon tetrachloride).

In tetrachloroethane solution, bis-desoxystreptose showed 3 μ (—OH group) absorption in the infrared; no carbonyl absorption could be detected. The compound did not react with a solution of 2,4-dinitrophenylhydrazine hydrochloride, nor was it affected by treatment with hydroxylamine hydrochloride in the presence of pyridine.

The pure bis-desoxystreptose did not reduce Tollens reagent in the cold. Fehling solution was not reduced, even when boiled for several minutes.

Bis-*p*-nitrobenzoate of Bis-desoxystreptose.—Sixty milligrams of bis-desoxystreptose, m. p. 89–91°, was converted to the bis-*p*-nitrobenzoate by treatment with a large excess of *p*-nitrobenzoyl chloride in pyridine solution. The crude crystalline product (89 mg.) was recrystallized from ether and then twice from methanol, giving the pure ester, m. p. 141–142°.

Anal. Calcd. for $C_{20}H_{18}N_2O_8$: C, 55.81; H, 4.22; N, 6.51. Found: C, 55.58; H, 4.00; N, 6.72.

Hydrolysis of Tetraacetyl-bis-desoxystreptobiosamine to Pentaacetyl-N-methyl-L-glucosamine and N-Methyl-L-glucosamine Hydrochloride.—The 5% sulfuric acid solution from the hydrolysis of 1.52 g. of tetraacetylbis-

desoxystreptobiosamine, after continuous chloroform extraction to remove the bis-desoxystreptose, was neutralized with barium carbonate and the filtrate concentrated to dryness. A solution of the residue in 10 ml. of concentrated hydrochloric acid was refluxed for two hours, and the hydrolysis mixture was twice extracted with chloroform. The aqueous solution was concentrated to dryness *in vacuo* and the product acetylated. Three recrystallizations of the crude acetylated product from chloroform–ether mixtures gave 707 mg. of pentaacetyl-N-methyl-L-glucosamine,[3] m. p. 160–160.5°. Hydrolysis of the pentaacetyl derivative with 10% hydrochloric acid gave 330 mg. of crude product,[3] m. p. 151–155° (dec.), and recrystallization gave the pure N-methyl-L-glucosamine hydrochloride, m. p. 161–165° (dec.), $[\alpha]^{25}D$ −103° (four minutes) → 88.5° (twelve hours, constant) in aqueous solution (*c*, 0.61).

Periodic Acid Oxidation of Bis-desoxystreptose. bis-*p*-Nitrophenylhydrazone of Oxidation Product $C_6H_{10}O_3$ (Glycolic Aldehyde Ether of Acetoin).—To a solution of 30.3 mg. of bis-desoxystreptose in 2 ml. of dioxane was added 2.19 ml. (1.0 equivalent) of a 0.105 *M* solution of periodic acid in 90% dioxane. A white crystalline precipitate of iodic acid appeared immediately. After one hour at room temperature, the precipitate was removed by centrifugation and washed twice with dioxane. To the combined supernatant and washings was added dropwise 0.1 *N* barium hydroxide until the solution was neutral. The small precipitate was removed and the filtrate concentrated *in vacuo* to a sirup. A solution of the sirup in 1 ml. of 50% acetic acid was added to a solution of 73 mg. of *p*-nitrophenylhydrazine in 1 ml. of 50% acetic acid. An orange crystalline precipitate formed and was centrifuged and washed with warm 50% acetic acid. The crude product, 55 mg., melted at 188–193°. Two recrystallizations of the product from alcohol gave tiny orange needle-like crystals, m. p. 204–206° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_6O_5$: C, 53.99; H, 5.04; N, 20.99. Found: C, 53.95; H, 4.92; N, 21.42.

Hydrolysis of the Oxidation Product $C_6H_{10}O_3$ (Glycolic Aldehyde Ether of Acetoin). Preparation of Phenylosazone of Biacetyl.—The freshly isolated product from the periodic acid cleavage of 37.6 mg. of bis-desoxystreptose was dissolved in 1.5 ml. of 50% acetic acid and the solution was heated in the steam-bath for ten minutes. The solution was then added to a hot solution of 0.15 ml. of phenylhydrazine in 2 ml. of 50% acetic acid, giving a clear light brown solution. A crystalline precipitate began to form after about two minutes at 95–100°. The heating was continued in the steam-bath for one-half hour, after which the hot solution was centrifuged and the precipitate washed with dilute acetic acid, twice with water, and once with ethanol. The product, light tan, feathery needle-like crystals, weighed 28 mg., m. p. 226–237°. Two recrystallizations of this material from ethanol–pyridine (10:1) gave material melting constantly at 247–249°. A mixture of this product and an authentic sample of the phenylosazone of biacetyl[13] (m. p. 246–250°) melted at 246.5–250°.

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.65; H, 6.69; N, 21.34.

5,6-Dimethyl-2,3-diphenylosatetrazine.—A solution of 21 mg. of sodium dichromate in 1 ml. of 20% acetic acid was added to 22 mg. of the phenylosazone isolated from the hydrolysis of the dicarbonyl compound $C_6H_{10}O_3$. The suspension was heated at 100° for one hour. The mixture was cooled and the precipitate separated and washed with water and ethanol. Recrystallization of the material from 1 ml. of acetone gave red crystals; 14 mg., m. p. 153–155° (dec.). No depression of melting point was observed when this product was mixed with an authentic sample of 5,6-dimethyl-2,3-diphenylosatetrazine[8] of m. p. 151–155°.

***p*-Bromophenylosazone of Biacetyl.**—The hydrolysis products of the glycolic aldehyde ether of acetoin gave, with excess *p*-bromophenylhydrazine hydrochloride in hot 50% acetic acid solution containing sodium acetate, a crystalline compound which melted, after recrystallization from chloroform, at 210–215° (dec.). Similar treatment of an authentic sample of biacetyl gave crystals of m. p. 212–216° (dec.). A mixture of the "natural" and synthetic products melted at 209–215°.

***p*-Nitrophenylosazone of Biacetyl.**—In a manner similar to that described for the preparation of the phenylosazone, a *p*-nitrophenylosazone of biacetyl was prepared. After two recrystallizations from pyridine, the product melted at 312–316° (dec.), varying somewhat with the rate of heating. Melting points of 316°[14] and 326°[15] are reported for the *p*-nitrophenylosazone of biacetyl.

Anal. Calcd. for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.53; N, 23.59. Found: C, 53.82; H, 4.39; N, 23.77.

Bis-desoxystreptose–Boric Acid Complex.—The acidity of an aqueous boric acid solution was greatly increased by the addition of a small molecular excess of the 3,4-dihydroxy-2,3-dimethyltetrahydrofuran. When the solution was titrated with alkali, the general region of binding was at about *p*H 7.5, instead of at about *p*H 9, as is the case with boric acid alone.

Periodate Oxidation of N-Acetyl-bis-desoxystreptobiosamine.—To a solution of 36.3 mg. (0.104 millimole) of N-acetyl-bis-desoxystreptobiosamine in water was added 3.00 ml. of 0.0955 *M* sodium periodate solution, and water was added to make exactly 10 ml. of solution. The course of the reaction was followed by withdrawing 1.00-ml. aliquot portions, adding sodium bicarbonate and potassium iodide, and titrating the iodine with standard arsenite solution. The results are presented in Table II. After one and eight-tenths hours, a portion of the reaction solution was titrated with alkali. There was found to be present 0.25 equivalent of a weak acid (*pK* 4.8), apparently acetic acid, since the *pK* of acetic acid is 4.85, while that of formic acid is 3.8.

TABLE II

TITRATION RESULTS

Time, hours	Periodate consumed, equivalents
0	0
0.10	0.21
0.50	0.53
1.36	1.08
2.25	1.17

A solution of 99.8 mg. (0.286 millimole) of N-acetyl-bis-desoxystreptobiosamine in 3 ml. of 0.07 *M* phosphate buffer (*p*H 7) was treated with 61 mg. (0.286 millimole) of sodium periodate. After one and one-half hours, all of the periodate had been consumed. Water was added to a volume of 15 ml., and 10 ml. of the solution was distilled into 5 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. Centrifugation of the mixture gave 4 mg. of a gummy orange solid. In a control experiment, two-thirds of a solution of 9 mg. of formaldehyde in 15 ml. of very dilute *p*H 7 phosphate buffer was distilled into 2,4-dinitrophenylhydrazine hydrochloride solution, yielding 24 mg. of yellow, crystalline formaldehyde 2,4-dinitrophenylhydrazone.

Dihydrodesoxystreptose (XIX).—Nine-tenths gram of pentaacetyldihydrodesoxystreptobiosamine was dissolved in 75 ml. of 5% sulfuric acid and the solution was refluxed for eight hours. It was then neutralized by stirring with barium carbonate, filtered, and the filtrate (*p*H 8) concentrated *in vacuo* to a volume of 15 ml. This solution was passed over a column of 17 g. of freshly regenerated and washed Amberlite IR-100. The first 10 ml. of eluate was discarded. Washing was continued with water until 65 ml. of eluate had been collected. The eluate was concentrated *in vacuo* to a volume of 12 ml., and passed over a column of 5 g. of Amberlite IR-4B.

(13) Neuberg and Reinfurth, *Biochem. Z.*, **143**, 563 (1923).

(14) Hirsch, *ibid.*, **131**, 184 (1922).

(15) Neuberg and Kobel, *ibid.*, **160**, 255 (1925).

The column was washed with water. In all, 30 ml. of eluate was collected and lyophilized.

The solid product was triturated with boiling chloroform, and the chloroform solution filtered. Concentration of the filtrate to a small volume gave crystals which were filtered and washed with cold chloroform. The yield of crystalline product, m. p. 75–77°, was 35 mg. Recrystallization of the product from chloroform gave pure dihydrodesoxystreptose, m. p. 78–79°.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found: C, 48.53; H, 7.96.

Periodate Oxidation of Dihydrodesoxystreptose.—A solution of 15.2 mg. (0.102 millimole) of dihydrodesoxystreptose and 55.3 mg. (0.259 millimole) of sodium periodate in 10 ml. of water was allowed to stand at room temperature for one hour. Titrations of aliquot portions showed the presence of 0.047 millimole of periodate and of 0.098 millimole of acid, corresponding to a consumption of 2.07 equivalents of periodate with formation of 0.96 equivalent of acid.

In another experiment, 6.7 mg. of dihydrodesoxystreptose in 2 ml. of water containing 14 mg. of sodium bicarbonate was oxidized with 19.3 mg. (2 equivalents) of sodium periodate. After one hour, no periodate could be detected, and a solution of 81 mg. of dimedone in 2 ml. of ethanol was added. The crystalline precipitate which formed rapidly was collected, washed with 50% ethanol and dried. It weighed 11.6 mg. (88%) and melted at 182–189°. One recrystallization of this material from dilute ethanol gave pure dimedone–formaldehyde condensation product, m. p. and mixed m. p. 191–194°.

Acknowledgment.—The authors wish to thank Dr. N. R. Trenner and his associates for the infrared absorption measurements and potentiometric titrations, Dr. J. B. Conn for the molecular weight determination, and Mr. Richard N. Boos and his associates for microanalyses.

Summary

Treatment of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal with Raney nickel catalyst has given two products, tetraacetyl-bis-desoxystreptobiosamine and tetraacetyldesoxystreptobiosamine.

The additional oxygen atom of the desoxy compound is present as a glycosidic hydroxyl group. Tetraacetyldesoxystreptobiosamine was characterized by the preparation of N-acetyldesoxystreptobiosamine, pentaacetyldesoxystreptobiosamine and methyl tetraacetyldesoxystreptobiosaminide.

Acid hydrolysis of tetraacetyl-bis-desoxystreptobiosamine yielded N-methyl-L-glucosamine and bis-desoxystreptose.

Bis-desoxystreptose has been determined by periodic acid oxidation studies to be a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran. The two hydroxyl groups of bis-desoxystreptose appear to be in a *cis* configuration. The structure of tetraacetyl-bis-desoxystreptobiosamine is given.

Pentaacetyldihydrodesoxystreptobiosamine was hydrolyzed with acid to give dihydrodesoxystreptose. The periodate degradation of dihydrodesoxystreptose to yield formaldehyde and an acid was in agreement with the proposed structure of this product, and offered further evidence for the position of the linkage of streptidine to streptobiosamine.

RAHWAY, N. J. RECEIVED FEBRUARY 11, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Alkaloids of *Dichroa Febrifuga* Lour.

BY FREDERICK A. KUEHL, JR., CLAUDE F. SPENCER AND KARL FOLKERS

The tests on extracts of about six hundred plants have shown that several plants possess interesting unknown principles which exibit antimalarial activity.[1] Of those plants containing active principles which were investigated, *Dichroa febrifuga* Lour. was particularly interesting because of the high antimalarial activity of the alkaloidal fraction isolated from it. Extractions were made on dried roots, stems and leaves of the plant obtained from both India and China. Unfortunately, the samples of *Dichroa febrifuga* Lour. from India, the material available when most of this work was done, contained only about one-tenth of the alkaloidal fraction present in the Chinese samples.

A number of extraction procedures was investigated. The best yields of the alkaloidal fraction from the Chinese root material were 0.1 to 0.15%. The yield of alkaloids from stem and leaf material was invariably much lower.

(1) Spencer, Koniuszy, Rogers, Shavel, Easton, Kaczka, Kuehl, Phillips, Walti and Folkers, *Lloydia*, **10**, 145 (1947).

Nothing crystallized directly from the crude alkaloidal fraction. A solution of this material and oxalic acid, however, gave a characteristic crystalline oxalate, which represented more than 75% of the antimalarial activity of the crude fraction. The yield of crude oxalate was 0.05% from the Chinese root sample and 0.005% from the Indian root sample. The recrystallized oxalate, m. p. *ca.* 212–214° (dec.), $(\alpha)^{25}D$ +18° (*c*, 1.5 in water), had a composition which was in agreement with the formula $(C_{16}H_{19}N_3O_3)_2 \cdot C_2H_2O_4$.

When a sample of a recrystallized oxalate was converted to the free base, two different crystalline alkaloids appeared which were not separated satisfactorily by crystallization. Chromatography of the mixture over alumina gave crystalline alkaloid I, m. p. 131–132°, $(\alpha)^{25}D$ +31° (*c*, 1.5 in ethanol), $(\alpha)^{25}D$ +120° (*c*, 0.8 in chloroform) and the properties of this alkaloid were not changed after repeated crystallization. The results of analytical data, potentiometric titration and ebullioscopic molecular weight determination were in-

dicative of the formula $C_{16}H_{19}N_3O_3$ for this alkaloid.

A sample of alkaloid I was chromatographed over a mixture of Norite and filter paper pulp. The specific rotation of all twenty eluates was about the same, but the value was somewhat lower than that of the starting material. After the eluates were allowed to stand for two days, they acquired a yellow color. The combined fractions 1–16 yielded alkaloid I upon crystallization, and the mother liquor yielded alkaloid II, m. p. 140–142°, $(\alpha)^{17}D$ +21° (*c*, 1.4 in ethanol). The composition of alkaloid II was also indicative of the formula $C_{16}H_{19}N_3O_3$.

These results were interpreted as indicating that alkaloid I is unstable under certain conditions and may be converted to some extent into alkaloid II. To test for this reaction or conversion, an alcoholic solution of alkaloid I was refluxed for twleve hours, and it was observed that the specific rotation decreased and approximated that of alkaloid II. In contrast, the specific rotation of alkaloid II was unchanged after this treatment. In the extraction of the plant material, where the alkaloid undoubtedly exists as a salt, alkaloid I was isolated after the root was extracted for three days with hot methanol. It is of interest that despite the instability of alkaloid I in solution, reference samples of the crystalline alkaloid have been on hand for almost three years without evidence of change.

Not only do alkaloids I and II appear to have the same formula $C_{16}H_{19}N_3O_3$, they also have indistinguishable ultraviolet and infrared absorption spectra. The ultraviolet absorption spectrum of alkaloid I in ethanol solution showed maxima at 2250 Å. (*E*% 900), 2650 Å. (*E*% 267), 3020 Å. (*E*% 125), and 3140 Å. (*E*% 101); the spectrum of alkaloid II showed maxima at 2250 Å. (*E*% 895), 2660 Å. (*E*% 246), 3010 Å. (*E*% 109), and 3130 Å. (*E*% 98). The infrared absorption spectra of both compounds showed bands at 6.03, 6.26, 6.45 and 6.78 μ.

We are indebted to Dr. A. O. Seeler and Miss Christine Malanga of the Merck Institute for Thereapeutic Research for the antimalarial tests. The crude alkaloidal fraction at a level of 20 mg./kg. orally showed an activity equivalent to a dose of 40 mg./kg. of quinine for essentially complete suppression of the trophozoite-induced infections of *Plasmodium gallinaceum* in chicks according to the described procedure.[2,3] Alkaloid I at a level of 5 mg./kg. and alkaloid II at a level of 2.5 mg./kg. orally were equivalent to a dose of 40 mg./kg. of quinine. The toxicity of these alkaloids to chicks was rather high since doses only twice the above-mentioned levels were toxic. A communication[4] has appeared which announced the isolation of two alkaloids from *Dichroa febrifuga* Lour. The melting points, compositions, and ultraviolet absorption spectra of these two alkaloids correspond closely with the properties of the two alkaloids which we have isolated. Our supply of alkaloids, as well as plant material, is exhausted and further comparisons are not possible at present. It was also mentioned[4] that isofebrifugine (alkaloid I) was converted to febrifugine (alkaloid II) by heat. Febrifugine showed approximately one hundred times the activity of quinine and isofebrifugine showed relatively slight activity against *P. lophurae* in ducks.

We also found[4] no evidence of the two alkaloids dichroine A and dichroine B which were described[5] as being derived from *Dichroa febrifuga* Lour. (Ch'ang Shan).

Experimental

Crystalline Alkaloidal Oxalate from *Dichroa febrifuga* Lour. from China.—A 2467-g. portion of finely ground root material of *Dichroa febrifuga* Lour., W. M. Clark 18634,[6] was moistened with water and extracted in a Soxhlet with methanol for three days. The methanol extract was evaporated *in vacuo*, and the aqueous solution remaining (*ca.* 800 ml.) was adjusted to *p*H 3 with dilute hydrochloric acid. The aqueous solution was extracted continuously with chloroform for twenty hours to remove impurities, and then the solution was adjusted to *p*H 8 with sodium bicarbonate and the alkaloids were removed by continuous chloroform extraction for twenty hours. The alkaloidal fraction was obtained as a brown residue, 3.78 g. (0.15%), after removal of the chloroform. It was dissolved in 25 ml. of 50% methanol and oxalic acid was added to *p*H 3. The resulting solution was warmed, filtered and concentrated. The gummy residue was dissolved in methanol and treated with acetone, and 1.453 g. (0.052%) of a crystalline oxalate, m. p. 199–201°, was obtained. After recrystallization from 50% methanol, the oxalate melted at 215–218° (dec. temperature somewhat dependent upon the rate of heating), $(\alpha)^{25}D$ +17° (*c*, 1.0 in water).

Extraction of *Dichroa febrifuga* Lour. from India.—An alternative extraction procedure to obtain the alkaloidal fraction was carried out as follows. A 4901-g. portion of ground root of *Dichroa febrifuga* Lour., National Institute of Health (Kaleshan) 18629, was moistened with water, added to *ca.* 15 l. of methanol and then the mixture was boiled for three hours. The extract was removed by filtration and the extraction was repeated two more times with fresh solvent. The combined extract was concentrated *in vacuo* to a volume of *ca.* 2 l. and the solution was adjusted to *p*H 8 and continuously extracted with chloroform. After distillation of the chloroform, the residue weighed 9.845 g. It was dissolved in 150 ml. of chloroform and the solution was extracted with 5–40 ml. portions of 3.5% hydrochloric acid. The aqueous extract was then adjusted to *p*H 8 and continuously extracted with chloroform to give 1.424 g. (0.029%) of the alkaloidal fraction.

Crystalline Alkaloidal Oxalate from *Dichroa febrifuga* Lour. from India.—Two kilograms of ground root material of *Dichroa febrifuga* Lour., Biswas 18637, was extracted in a Soxhlet and the methanol extract was processed in the manner described above. The alkaloidal fraction yielded 98 mg. of crude oxalate, m. p. 195–210°. After two recrystallizations from 50% methanol, the oxalate melted at 213–214° (dec.), $(\alpha)^{25}D$ +18° (*c*, 0.5 in water).

Anal. Calcd. for $(C_{16}H_{19}N_3O_3)_2 \cdot C_2H_2O_4$: C, 58.85; H, 5.83; N, 12.10. Found: C, 58.97; H, 6.06; N, 12.37.

(2) Seeler, Malanga and Pierson, *Proc. Soc. Exp. Biol. Med.*, **59**, 291 (1945).

(3) Seeler and Malanga, *ibid.*, **63**, 194 (1946).

(4) Koepfli, Mead and Brockman, THIS JOURNAL, **69**, 1837 (1947).

(5) Jang, Fu, Wang, Huang, Lu and Chou, *Science*, **103**, 59 (1946).

(6) The collector's names and specimen numbers were assigned by Mr. B. A. Krukoff.

Alkaloids I and II from the Oxalate from a Chinese Sample.—An aqueous solution of 4.38 g. of the oxalate, $(\alpha)^{25}D$ +17° (*c*, 1.0 in water), was treated with sodium bicarbonate to *p*H 8, and extracted continuously for three hours with chloroform. The chloroform extract was concentrated to a residue *in vacuo*. An alcohol solution of this residue deposited 2.74 g. of crystalline alkaloid I, m. p. 131–132° (softening at 127°), $(\alpha)^{25}D$ +33.6° (*c*, 1.7 in alcohol). On standing, the mother liquor deposited crude crystalline alkaloid II, m. p. 135–142°, $(\alpha)^{25}D$ +21° (*c*, 0.9 in ethanol).

Upon recrystallization of the first crop, two distinct fractions were obtained, the first crystallizing immediately in small needles, 1.700 g., m. p. 124–130°, $(\alpha)^{25}D$ +31° (*c*, 1.1 in alcohol), and the second crystallizing in long needles on standing overnight, 0.359 g., m. p. 135–142°, $(\alpha)^{25}D$ +23° (*c*, 0.9 in alcohol).

Separation of Alkaloid I and II by Chromatography.—A solution of 2.487 g. of a mixture of the two alkaloids in 25 ml. of chloroform was passed through a column containing 35 g. of acid-washed alumina. Elution with 800 ml. of chloroform gave 1.604 g. of residue, $(\alpha)^{25}D$ +31° (*c*, 2.6 in ethanol). A second elution with 200 ml. of chloroform containing 5% methanol gave 749 mg. of residue, $(\alpha)^{25}D$ +21° (*c*, 2.0 in ethanol). Finally, elution with 200 ml. of methanol gave 106 mg. of material, $(\alpha)^{25}D$ +20° (*c*, 1.3 in ethanol). The first eluted fraction, after recrystallization from benzene, gave 376 mg. of alkaloid I, m. p. 131–132°, $(\alpha)^{25}D$ +31° (*c*, 1.5 in ethanol). Concentration of the mother liquor yielded a second crop of 0.984 g., m. p. 124–130°. Recrystallization of this second crop gave 0.775 g., m. p. 128–132°, $(\alpha)^{25}D$ +31° (*c*, 1.9 in alcohol). This was combined with the first crop and recrystallized again from benzene, giving 0.829 g., m. p. 131–132°, $(\alpha)^{25}D$ +31° (alcohol), $(\alpha)^{25}D$ +120° (*c*, 0.8 in chloroform). The melting point of this material did not alter after further recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.8; H, 6.4; N, 14.0, mol. wt., 301. Found: C, 63.91; H, 6.50; N, 14.10, eq. wt. (potentiometric titration) 314; mol. wt., 281 (ebullioscopic in benzene).

Chromatography of Alkaloid I.—A solution of 1.6 g. of alkaloid I, $(\alpha)^{25}D$ +33.6° (*c*, 1.7 in ethanol), in 5 ml. of ethanol was diluted with chloroform and the solution was concentrated *in vacuo* to a gum. This gum was dissolved in chloroform and the concentration was repeated to yield an alcohol-free gum. A solution of this gum in 10 ml. of chloroform was poured onto a column composed of 25 g. of Norite and 2 g. of pulverized filter paper. The column was developed with 200 ml. of chloroform and then eluted with chloroform containing 2% ethanol. The data are shown in Table I.

The eluates were allowed to stand for two days, during which time they acquired a yellow color. Fractions 4, 6, 8, 10 and 12 were combined to give 0.435 g. of residue, a total of 1.24 g. in all (78%). Fractions 1 to 16 were combined and concentrated *in vacuo* to a residue, which was dissolved in a small amount of alcohol and decolorized with a little charcoal. Upon cooling, 560 mg. of alkaloid I deposited as colorless needles, m. p. 131–132°, $(\alpha)^{25}D$ +32° (*c*, 1.7 in ethanol). After standing for several days, the mother liquor deposited 170 mg. of alkaloid II. After several recrystallizations, alkaloid II melted at 140–142°, $(\alpha)^{25}D$ +21° (*c*, 1.4 in ethanol).

Anal. Calcd. for $C_{19}H_{16}N_3O_3$: C, 63.80; H, 6.40; N, 14.00. Found: C, 63.42; H, 6.56; N, 14.33.

TABLE I

CHROMATOGRAPHIC DATA ON ALKALOID I

Fraction	Volume, ml.	Weight of residue, mg.	$[\alpha]^{25}D$ (in ethanol)
1	10	11	+29°
2	10	38	
3	10	65	+30°
4	10		
5	10	85	+29°
6	10		
7	10	78	+31°
8	10		
9	10	83	+29°
10	10		
11	10	84	+32°
12	10		
13	20	85	+31°
14	30	57	+32°
15	30	37	+31°
16	50	45	+29°
17	50	41	+27°
18	50	35	+26°
19	50	28	+26°
20	50 (methanol)	29	+23°

Stability Tests in Ethanol.—A solution of 22 mg. of alkaloid I, m. p. 130–132°, $(\alpha)^{25}D$ +32° (*c*, 1.7 in ethanol), in 25 ml. of ethanol was boiled for twelve hours. The solvent was then removed *in vacuo*. The residue showed $(\alpha)^{25}D$ +24° (*c*, 1.5 in ethanol).

A solution of 23 mg. of alkaloid II, m. p. 140–142°, $(\alpha)^{25}D$ +20.5° (*c*, 1.4 in ethanol) in 25 ml. of ethanol was boiled for twelve hours. The residue showed $(\alpha)^{25}D$ +20° (*c*, 1.5 in ethanol).

Preparation of the Oxalate of Alkaloid I.—A mixture of 33 mg. of alkaloid I, m. p. 131–132°, $(\alpha)^{25}D$ +31° (*c*, 1.1 in ethanol) and 14 mg. of oxalic acid was heated in 1 ml. of 50% methanol until the components dissolved. After standing in ice, 19 mg. of the oxalate salt deposited which, when recrystallized from 50% methanol to constant melting point, was obtained as colorless crystals, m. p. 212–213° (dec.), $(\alpha)^{25}D$ +19° (*c*, 0.3 in water).

Acknowledgment.—We wish to express our appreciation to Mr. B. A. Krukoff of the New York Botanical Garden for obtaining certain plant materials, for determining specimens, and for advice on botanical matters. We also wish to thank Dr. N. R. Trenner and his associates for the ultraviolet and infrared analyses, and Mr. Richard Boos and his associates for the microanalyses.

Summary

Two crystalline alkaloids have been isolated from *Dichroa febrifuga* Lour. which show antimalarial activity. These two alkaloids appear to be isomeric, both having the composition $C_{16}H_{19}N_3O_3$.

RAHWAY, N. J. RECEIVED JANUARY 8, 1948

[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY, THE HEBREW UNIVERSITY]

Poly-condensation of α-Amino Acid Derivatives. III. Poly-lysine[1]

BY EPHRAIM KATCHALSKI, ISAAC GROSSFELD AND MAX FRANKEL

In the previous papers of this series we have described the preparation and properties of some polymers of glycine[2a] and *d,l* alanine.[2b] As an extension of this work the study of the polymerization of poly-functional α-amino acids was undertaken. In the present paper the formation of poly-lysine by the polymerization of a 1-lysine derivative is described.

The following considerations had to be taken into account in the choice of a suitable monomer for polymerization: (a) the ε-amino group of the lysine had to be masked in order to prevent its participation in the polymerization and thus to insure that all the —CONH— bonds in the polymer are derived from the α-amino groups of the monomer. The ε-amino group was masked by Bergmann's method of introducing the carbobenzoxy group; (b) the monomer must consist of a lysine derivative having a pronounced tendency to polymerize. ε-Carbobenzoxylysine itself is comparatively stable owing to its zwitterionic structure, while its methyl ester yields mainly the corresponding diketopiperazine on heating;[3] both these lysine derivatives did not appear therefore to be the proper starting material. A more suitable monomer was eventually found in ε-carbobenzoxy-α-carboxyl-lysine anhydride.[4] It was found that this substance polymerizes on heating with the evolution of carbon dioxide in a manner similar to the polymerization of N-carboxyl anhydrides of other amino acids.[5]

The steps of preparation of poly-lysine from the chosen monomer are summarized in the first part of the scheme: ε-carbobenzoxy-α-carboxyl-1-lysine anhydride (I), yields on heating, under the catalytic action of water, poly-carbobenzoxylysine (II), carbon dioxide being evolved. The carbobenzoxy groups of (II) were removed by phosphonium iodide, and poly-lysine hydriodide (III) obtained.

For each polymerization experiment, the starting material, ε-carbobenzoxy-α-carboxyl-1-lysine anhydride, had to be freshly prepared from α,ε-carbobenzoxy-1-lysine kept in stock. This was necessary, as it was found that while the freshly prepared substance undergoes rapid polymerization at its melting point (100°), the same substance after having been allowed to stand for several weeks did not polymerize even at higher temperatures (160–170°), but decomposed slowly under such conditions. In this connection the observation of Bergmann, Zervas and Ross,[4] may be recalled that the melting point of freshly prepared ε-carbobenzoxy-α-carboxyl-1-lysine anhydride rises on standing several months to above 250°. Our attempts to recover the ε-carbobenzoxy-α-carboxyl-1-lysine anhydride with a melting point of 100° from the preparation having a high melting point by recrystallization were unsuccessful as no solvent for the latter was found.

During search for other precautions to be taken in the polymerization of ε-carbobenzoxy-α-carboxyl-1-lysine anhydride, the following findings were useful: (a) pure α,ε-di-carbobenzoxy-1-lysine, as well as pure carbobenzoxy-glycine, give no amino N values on using Van Slyke's[6] manometric method for amino N determination.

(b) ε-Carbobenzoxy-1-lysine yields practically the theoretical amount (96%) of carboxyl nitrogen in Van Slyke, MacFadyen and Hamilton ninhydrin–CO_2 method[7] when the reaction is carried out at *p*H 2.5.

(c) ε-Carbobenzoxy-α-carboxyl-1-lysine anhydride evolved an amount of carbon dioxide equivalent only to about 50% of its total α-nitrogen when analyzed by the usual ninhydrin–CO_2 method. The samples were boiled, after addition of citrate buffer, *p*H 2.5, for thirty seconds to remove performed carbon dioxide. The solution was chilled and the N-carboxyl determination carried out as usual after addition of ninhydrin.

Finding (a) shows that during the carrying out of the amino nitrogen determinations, no cleavage of the NH-carbobenzoxy bond, leading to the liberation of free NH_2 groups, occurs. It is thus possible to determine the free amino-N in materials containing NH-carbobenzoxy bonds, without fear that additional free amino groups, not present in the original material will be liberated on analysis. Finding (b) permits the determination of ε-carbobenzoxy-lysine in the presence of poly-carbobenzoxy-lysine. Furthermore, in view of (b) and (c), it is clear that high values of carboxyl-N (determined according to the ninhydrin–CO_2 method) indicate the presence of a considerable amount of either or both ε-carbobenzoxy lysine and ε-carbobenzoxy-α-carboxyl lysine anhydride. This conclusion enables us to estimate roughly the amount of "monomer" derivatives in the prepara-

(1) A manuscript under this title was received from these authors on January 21, 1946, for publication in the Journal. It was returned to them on February 21, 1946, for revision and further data.—The Editor.

(2) (a) Frankel and Katchalski, THIS JOURNAL, **64**, 2264 (1942); (b) Frankel and Katchalski, *ibid.*, **64**, 2268 (1942).

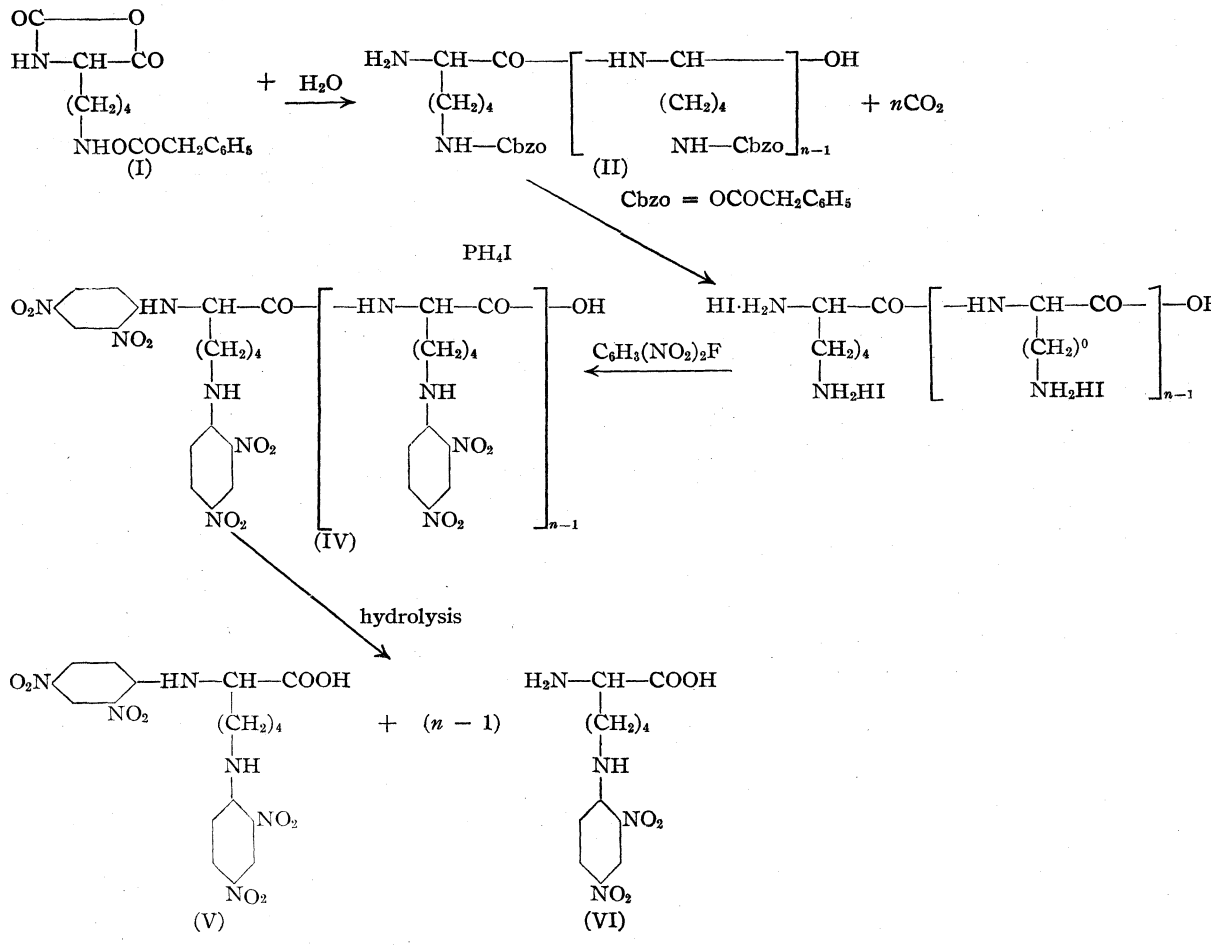
(3) Katchalski, Grossfeld and Frankel, *ibid.*, **68**, 879 (1946).

(4) Bergmann, Zervas and Ross, *J. Biol. Chem.*, **111**, 245 (1935).

(5) Leuchs, *Ber.*, **39**, 857 (1906); Leuchs and Manasse, *ibid.*, **40**, 3243 (1907); Leuchs and Geiger, *ibid.*, **41**, 1721 (1908); Curtius and Sieber, *ibid.*, **55**, 1543 (1922); Wessely, *Z. physiol. Chem.*, **146**, 72 (1925); Sigmund and Wessely, *ibid.*, **157**, 91 (1926); Wessely and Sigmund, *ibid.*, **159**, 102 (1926); Wessely and John, *ibid.*, **170**, 38 (1927); Meyer and Go, *Helv. Chim. Acta*, **17**, 1488 (1934); Go and Tani, *Bull. Chem. Soc. Japan*, **14**, 510 (1939); Woodward and Schramm, THIS JOURNAL, **69**, 1551 (1947).

(6) Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(7) Van Slyke, MacFadyen and Hamilton, *ibid.*, **141**, 671 (1941).



tions obtained on heating ε-carbobenzoxy-α-carboxyl lysine anhydride, even before removal of the carbenzoxy groups.

In Table I we summarize various analytical data concerning preparations obtained on heating ε-carbobenzoxy-α-carboxyl-lysine anhydride, purified in different ways and using different conditions of polymerization. Table II contains data concerning products derived on reduction of the corresponding preparations described in Table I.

TABLE I

ANALYTICAL DATA ON PREPARATIONS OBTAINED ON HEATING ε-CARBOBENZOXY-α-CARBOXYL-LYSINE ANHYDRIDE UNDER VARIOUS CONDITIONS

	Mg. of element (or group) per 100 mg. preparation					
Prepn.	N	Amino N	Carboxyl N	Total C	H	Remarks
(a)	2.00	1.09	10.7	63.5	6.9	Transparent brittle film, readily soluble in cold glacial acetic acid, insoluble in water
(b)	1.08	0.092	10.7	..	...	
(c)	0.22	0.025	10.8	64.2	6.8	Transparent film soluble in hot glacial acetic acid, insoluble in water
(d)	0.17	0.017	1.3	63.9	7.1	

(a) Obtained from ε-carbobenzoxy-α-carboxyl-1-lysine anhydride recrystallized once from ethyl acetate and petroleum ether and then dried for several days over sulfuric acid. The dried anhydride was left to polymerize in an open vessel at 105° for twenty-four hours.

(b) Obtained from ε-carbobenzoxy-α-carboxyl-1-lysine anhydride recrystallized twice from ethyl acetate and petroleum ether and dried in a 20-mm. vacuum over phosphorus pentoxide for forty-five minutes. Polymerization was carried out in the drying apparatus by raising the temperature to 104°, and maintaining this temperature for several hours.

(c) Obtained from ε-carbobenzoxy-α-carboxyl-1-lysine anhydride recrystallized three times from ethyl acetate and petroleum ether, and introduced immediately after the last recrystallization into a high vacuum apparatus containing phosphorus pentoxide and liquid air trap. The monomer was dried in this apparatus for three hours at 50° and then the temperature raised to 104° for two hours. A high vacuum (10^{-4} mm.) was maintained throughout. The polymeric preparation represents a hard, colorless transparent substance.

(d) The preparation of this product is described in detail under the heading preparation of poly-carbobenzoxy-lysine (*n* average = 32 carbobenzoxy-lysine units).

Table I shows clearly that the purification of the ε-carbobenzoxy-α-carboxyl-lysine anhydride by recrystallization from ethyl acetate and petroleum ether and the thorough drying of freshly prepared monomer leads on heating to prepara-

TABLE II

ANALYTICAL DATA ON PRODUCTS DERIVED FROM THE CORRESPONDING PREPARATIONS DESCRIBED IN TABLE I, ON REDUCTION WITH PHOSPHONIUM IODIDE

Product	Mg. of element (or group) per 10 mg. preparation: Amino, N	Carboxyl, N	Total, N	C	H	I	Remarks	Mg. group per 100 mg. preparate after hydrolysis: Amino, N	Carboxyl, N
(a′)	5.40	1.120	10.8	28.4	5.3	50.8	Soluble in water	..	...
(b′)	5.61	0.101	10.2	27.0	5.5	52.0		10.1	5.0
(c′)	5.32	0.023	10.8	27.6	5.3	49.9	Transparent brittle film,	10.6	5.5
(d′)	5.30	0.019	10.7	27.6	5.2	50.0	soluble in water	10.7	5.4

tions with a small percentage of free amino-N and carboxyl-N. In accordance, Table II shows that products obtained on reduction of the preparations prepared by heating purified and thoroughly dried ϵ-carbobenzoxy-α-carboxy-lysine anhydride, contain small amounts of free lysine. Some of the bulk products, (*cf.* b′c′d′, Table II) obtained on reduction of the corresponding polycarbobenzoxylysine preparations, were totally hydrolyzed by boiling with 20% hydrochloric acid for twenty-seven hours. In the hydrolyzate, practically a quantitative yield of lysine was found.

The loss in weight of highly purified and thoroughly dried ϵ-carbobenzoxy-α-carboxyl-1-lysine anhydride during polymerization was measured. It was found that this loss is equivalent to 98–100% of the theoretical amount of carbon dioxide which could evolve on polymerization.

The presence of amino nitrogen in the preparations described in Table I and the fact that the amino N content of these preparations is considerably higher than that of the corresponding carboxyl-N's seems to indicate that water plays a certain role in the carbon dioxide cleavage of ϵ-carbobenzoxy-α-carboxyl-1-lysine anhydride, and its polymerization.

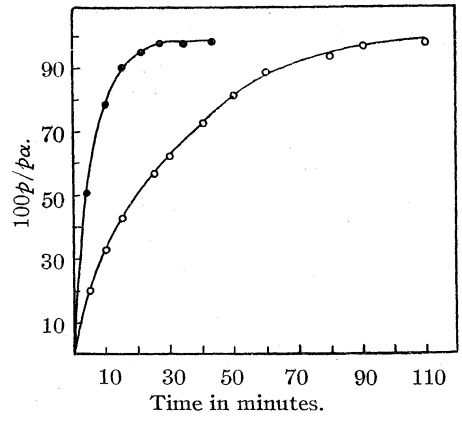


Fig. 1.—Per cent. of theoretical carbon dioxide, evolved on polymerization of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride *versus* time at 102°: ●, monomer kept over water for forty minutes; O, monomer dried over phosphorus pentoxide.

In order to evaluate the role of water in our case, the rate of carbon dioxide evolution of two samples of ϵ-carbobenzoxy-α-carboxyl-1-lysine anhydride containing different amounts of water was measured at 102° (*cf.* Fig. 1).

From these experiments, details of which are given in the experimental part, it became obvious that water acts as a catalyst during the polymerization of ϵ-carbobenzoxy-α-carboxyl-1-lysine anhydride. Catalytic action, but to a smaller extent, was found with methanol. This conclusion is in agreement with the findings of several previous authors,[5] who found that N-carboxyl anhydrides of various amino acids, while relatively stable in dry atmosphere, undergo rapid polymerization when exposed to moist air.

By taking into account the previously discussed precautions, we could obtain poly-carbobenzoxy-lysine polymers and poly-lysines virtually free of monomer and possessing a considerable chain length.

In the following, we describe in some detail the preparation and properties of one such polymer.

ϵ-Carbobenzoxy-α-carboxyl-lysine anhydride recrystallized six times, and dried in high vacuum (10^{-4} mm.) over phosphorus pentoxide at 60° for three hours, in an apparatus equipped with a liquid air trap, yielded on heating to 105° in high vacuum (10^{-4} mm.) for one hour, a transparent glassy hard polycarbobenzoxy-lysine. This polymer is insoluble in water and dissolves in hot glacial acetic acid. It contains free terminal amino groups determinable by Van Slyke's manometric method. Assuming that the above polymer is a mixture of poly-carbobenzoxy-lysine peptides of various chain lengths, an average chain length of 32-lysine units was calculated from the values of free terminal amino-N.

The carbobenzoxy groups of the poly-carbobenzoxylysine (*n* average = 32) were removed by reduction with phosphonium iodide according to the procedure used by Harington and Mead[8]; attempted reductions by the usual catalytic methods were unsatisfactory. Poly-lysine hydriodide (III) thus obtained, is very readily soluble in water, gives positive ninhydrin and biuret reactions, and negative picric acid test. The latter negative test indicated the absence of lysine anhydride in the poly-lysine hydriodide polymer obtained.

By making use of the ninhydrin–carbon dioxide method for determination of free amino acids it was found that (III *n* average = 32) contains a

(8) Harington and Mead, *Biol. Chem. J.*, **29**, 1603 (1935).

very small amount of free lysine (0.2 mg. free lysine per 100 mg. (III)).

Elementary analyses of poly-lysine hydriodide (*n* average = 32) and ratio of amino nitrogen to total nitrogen (found to be 1 to 2) are in agreement with the formula suggested. On hydrolysis, poly-lysine, yields lysine quantitatively.

Independent support for the proposed constitution for poly-lysine hydriodide (*n* average = 32) was obtained by using the procedure worked out by Sanger,[9] who found that 2,4-dinitrofluorobenzene reacts with the free amino groups of α-amino acids, peptides and proteins in the presence of sodium bicarbonate at room temperature with elimination of hydrogen fluoride. The dinitrophenyl-N-bond formed is relatively stable to acid hydrolysis. Thus, in the case of insulin, he was able, after coupling with 2,4-dinitrofluorobenzene and following acid hydrolysis, to isolate and determine quantitatively the 2,4-dinitrophenyl derivatives of those amino acids which in insulin bear the free amino groups.

On coupling poly-lysine hydriodide (*n* average = 32) with 2,4-dinitrofluorobenzene at room temperature, a yellow substance was obtained in almost quantitative yields. The low value of amino N (Van Slyke 0.03%) in the polymer (IV) indicates the blocking of all amino groups by 2,4-dinitrophenyl groups. Dinitrophenyl-poly-lysine (IV) was hydrolyzed in 50% (w/w) sulfuric acid during ten hours. The acid hydrolysate contains the α,ε-di-(2,4-dinitrophenyl)-lysine and ε-dinitrophenyl-lysine. The former is derived from the terminal lysine units of the poly-lysine containing two (α and ε) free amino groups, the latter from the other lysine units containing only one (ε) free amino group.

The α,ε-di-(2,4-dinitrophenyl)-lysine contained in this hydrolyzate was quantitatively extracted with ether, while the ε-2,4-dinitrophenyl-lysine remained in the aqueous acid solution. Both lysine derivatives were purified chromatographically; α,ε-di-(2,4-dinitrophenyl)-lysine by using butanol–chloroform 1% as developing solvent and ε-2,4-dinitrophenyl-lysine by using methyl ethyl ketone–ether (66%) as developing solvent. Water was the stationary phase in both cases. The R values found for α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine obtained from the acid hydrolyzate, were 0.6 and 0.2, respectively, under our conditions. The same values were obtained for the corresponding substances prepared from l-lysine. When each of the 2,4-dinitrophenyl-lysine derivatives, obtained from the polymer hydrolysate, was mixed with the corresponding synthetic substance, and each of the mixtures developed chromatographically by the suitable developing solvent only one yellow band was obtained which in each case showed the characteristic R value.

The quantitative estimations of α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine were carried out colorimetrically according to Sanger. Sanger found that during acid hydrolysis of 2,4-dinitrophenyl derivatives of α-amino acids, partial decomposition occurs. This is taken into account in the evaluation of the amount of the terminal amino acids with free amino groups in the insulin molecule. In order to determine the percentage decomposition of the two dinitrophenyl lysine derivatives, under the hydrolytic conditions applied in the present case, parallel experiments were carried out with the corresponding 2,4-dinitrophenyl-lysine derivatives obtained synthetically. It was found that on boiling with 50% (w/w) sulfuric acid for ten hours, 38% of α,ε-di-(2,4-dinitrophenyl)-lysine and 25% of ε-2,4-dinitrophenyl-lysine were decomposed. After correcting for the decomposition of each of the 2,4-dinitrophenyl-lysine derivatives during hydrolysis of 2,4-dinitrophenyl-poly-lysine, the amounts and ratio between α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine were determined; 4.80 mg. of α,ε-di-(2,4-dinitrophenyl)-lysine, and 98 mg. of ε-2,4-dinitrophenyl-lysine per 100 mg. of 2,4-dinitrophenyl-poly-lysine, were found. The ratio of the two compounds as determined in the hydrolysate was therefore: 31 moles of ε-2,4-dinitrophenyl-lysine per 1 mole of α,ε-di-(2,4-dinitrophenyl)-lysine.

The above data indicate that poly-lysine hydriodide from which the 2,4-dinitrophenyl-poly-lysine was obtained, is built up on the average of 31 lysine units. This conclusion is in satisfactory agreement with the average chain length ascribed to the above poly-lysine hydriodide from the value of the amino-N of the poly-carbobenzoxy-lysine from which it had been derived by reduction.

It must be emphasized, however, that the considerable destruction of both dinitrophenyl-lysine derivatives during hydrolysis on the one hand, and the low amino nitrogen content of poly-carbobenzoxy-lysine on the other, may lead to some uncertainty in the estimation of the average chain length. Nevertheless, the agreement between the two analytical methods justifies, in our opinion, the drawing of a conclusion concerning the order of magnitude of the average chain length of the poly-lysine derivatives synthesized.

From poly-lysine hydriodide (*n* average = 32), the picrate, picrolonate, hydrochloride and benzoyl derivatives were prepared.

An indication for the presence of polymers of various chain lengths was found by carrying out a rough fractionation experiment. Poly-carbobenzoxy-lysine, containing a very small amount of monomeric lysine derivatives, yielded three fractions which differed in terminal amino nitrogen content.

Preliminary enzymatic experiments were carried out with poly-lysine and lysine anhydride. It was found that poly-lysine is split by glycerol

(9) Sanger, *Biochem. J.*, **39**, 507 (1945).

extract of pancreatin as well as by crystalline trypsin. About 50% of the peptide bonds were split. Lysine anhydride is not split by pepsin.

Experimental

Preparation of ϵ-Carbobenzoxy-α-carboxyl-l-lysine Anhydride.—l-Lysine was prepared from the red corpuscles of ox blood according to Rice[10]; from it ϵ-carbobenzoxy-α-carboxyl-lysine anhydride was prepared according to Bergmann, Zervas and Ross.[4] The anhydride was recrystallized several times from ethyl acetate and petroleum ether, and the purified starting material used at once for polymerization experiments. The freshly purified product dissolves readily in ethyl acetate, and its m. p. is 100°.

Estimation of Carbon Dioxide from ϵ-Carbobenzoxy-carboxyl-lysine Anhydride on Heating to 102°.—1.140 g. of twice recrystallized ϵ-carbobenzoxy-α-carboxyl-lysine anhydride dried over phosphorus pentoxide *in vacuo* was kept at 102° for two hours. Carbon dioxide evolution started on melting and a transparent, glassy polymer residue was obtained. The weight of polymer residue was found to be 0.979 g. The weight of carbon dioxide evolved (161 mg.) represents 98.5% of the theoretical.

Rate of Carbon Dioxide Evolution at 102° from ϵ-Carbobenzoxy-α-carboxyl-lysine Anhydride (a) Kept over Phosphorus Pentoxide; (b) Kept over Water.—The rate of carbon dioxide evolution at 102° was measured in an apparatus similar to that described by Hinshelwood.[11] ϵ-Carbobenzoxy-α-carboxyl-lysine anhydride twice recrystallized was dried over phosphorus pentoxide *in vacuo* during two days at room temperature. One sample from the dried preparation was put at once into Hinshelwood's apparatus, the apparatus sealed, and placed in a constant temperature bath at 102°. The rate of carbon dioxide evolution was calculated from the manometric readings of the apparatus.

The second sample of the dried ϵ-carbobenzoxy-α-carboxy-lysine anhydride, weighing 67.85 mg., was put into a desiccator over water for forty minutes. After this period it was found to have gained in weight 0.870 mg. The wet product was put into Hinshelwood's apparatus and the rate of carbon dioxide evolution at 102° measured as above.

A comparison of the rate of carbon dioxide evolution in both cases is given in Fig. 1.

The increase in rate of carbon dioxide evolution in the presence of water may be at least partly explained by the catalytic action of water on the polymerization of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride according to the first step of the general scheme. Nevertheless, it should be borne in mind that water may open the anhydride bond of the N-carboxyl anhydride, and thus lead to carbobenzoxy-lysine with carbon dioxide evolution. Regarding the latter possibility, it should be remarked, that for quantitative transformation of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride into ϵ-carbobenzoxy-lysine, water in an amount of 5.9% of the weight of the anhydride is needed, whereas only 1.3% of water was taken up by ϵ-carbobenzoxy-α-carboxyl-lysine anhydride in our case. The fact that this amount of water is sufficient to shorten the time of cleavage, involving the loss of 95% of the theoretical amount of carbon dioxide in ϵ-carbobenzoxy-α-carboxyl-lysine anhydride, from ninety-five minutes to twenty minutes, justifies the conclusion that water acts under our experimental conditions mainly as polymerization catalyst. This is borne out also by the polymeric properties of the reaction products.

Preparation of Poly-carbobenzoxy-lysine (*n* average = 32 Carbobenzoxy-lysine Units).—The starting ϵ-carbobenzoxy-α-carboxyl-lysine anhydride for the polymerization, was recrystallized six times from ethyl acetate and petroleum ether. The purified product was introduced immediately into a glass vessel connected to an apparatus with phosphorus pentoxide and a liquid air trap and dried in high vacuum (10^{-4} mm.) at 60° for three hours. The temperature was then elevated to 105°; carbon dioxide evolution started at once with the melting of the anhydride. After one hour no further gas evolution was observed; a transparent, glassy hard residue remained in the reaction vessel.

The poly-carbobenzoxy-lysine preparation thus obtained is insoluble in water, ether or toluene. It is soluble in hot glacial acetic acid, and slightly soluble in hot alcohol. Part of the polymer precipitates from its solution in acetic acid on cooling, and from the supernatant solution a further precipitate of polymer may be obtained on adding water.

On heating the mixture of poly-carbobenzoxy-lysine in water with ninhydrin for half an hour, the polymers turn deep blue, while the water remains almost colorless.

The analytical data obtained correspond to a polymer having formula (II) with an average chain length $n = 32$.

Anal. Calcd. for (II) (*n*-average = 32 units): C, 64.0; H, 6.9; N, 10.6; amino N, 0.17. Found: C, 63.9; H, 7.1; N, 10.3; amino N, 0.17. The total nitrogen determinations, in this case as in other analytical data given in this paper, were carried out by the micro Dumas method.

Poly-lysine Hydriodide (*n* average = 32).—One gram of the above poly-carbobenzoxy-lysine (*n* average = 32) was dissolved in 25 ml. of hot glacial acetic acid and the solution kept at 50°, while a stream of dry hydrogen was passed through it; 4 g. of phosphonium iodide was added in portions of about 1 g. during one to one and one-half hours. The reduction of the carbobenzoxy groups was accompanied by a strong evolution of carbon dioxide. During the reduction, the phosphonium iodide dissolved, and a voluminous precipitate formed on the walls of the vessel. At the end of the reaction, the clear liquid was decanted off and the residue washed several times with dry ether and dissolved in 2 ml. of water; to this solution about 5 ml. of absolute alcohol and 70 ml. of ether were added. After standing overnight in the ice box, the supernatant fluid was decanted from the viscous material which had separated out. The latter was then dissolved in several ml. of water, and the solution filtered and evaporated to dryness in a vacuum desiccator over sulfuric acid and sodium hydroxide. The transparent, solid film-like polymer thus obtained was washed several times with ether and dried. It was obtained in almost quantitative yield. Poly-lysine hydriodide was dried in a micro vacuum desiccator over phosphorus pentoxide at 80° before analysis.

Anal. Calcd. for (III) (*n* average = 32): C, 27.7; H, 5.0; N, 10.7; amino N, 5.5; I, 50.2. Found: C, 27.6; H, 5.2; N, 10.7; amino N, 5.3; I, 50.0. The amino N value was obtained after shaking the polymer solution with HNO_2 for five minutes; this value was not altered on further shaking for half an hour.

Poly-lysine hydriodide dissolves very readily in water and its aqueous solution gives a positive ninhydrin reaction and a strong biuret reaction. A negative Abderhalden test was obtained on heating with an alkaline solution of picric acid.

Poly-lysine hydriodide does not dissolve in the usual organic solvents.

Search for Free Lysine in Poly-lysine Hydriodide (*n* average = 32).—The amount of free lysine in the poly-lysine hydriodide described above was determined by the ninhydrin-carbon dioxide method at *p*H 2.5. In 100 mg. of polymer product described in the previous section 0.2 mg. of free lysine was found.

Total Hydrolysis of Poly-lysine Hydriodide (*n* average = 32).—15.9 mg. of dried poly-lysine hydriodide was dissolved in 4 ml. of 20% hydrochloric acid and the solution boiled under reflux for twenty-four hours. The acid hydrolyzate was neutralized with sodium hydroxide and brought to 15 ml.

In 2 ml. of the final solution the amount of carboxyl N was determined by using the ninhydrin–carbon dioxide method[7]; in the other 2 ml., the total free amino N (Van

(10) Rice, *J. Biol. Chem.*, **131**, 1 (1941).

(11) Hinshelwood, *J. Chem. Soc.*, **117**, 156 (1920).

Slyke's manometric method—on shaking half an hour with nitrous acid—was determined. From the data obtained, the total amounts of carboxyl N and amino N in hydrolyzate were calculated. The amount of these groups per 100 mg. starting material are given below.

Anal. Calcd. for hydrolysis of 100 mg. poly-lysine hydriodide (*n* average = 32). Carboxyl-N 5.50 mg.; amino N, 10.60 mg. Found: carboxyl N, 5.4 mg.; amino N, 10.7 mg.; on hydrolysis of 100 mg. of starting material.

The analytical data show that the total amount of amino-N is equal to twice that of carboxyl N and thus indicates the presence of free lysine in the hydrolyzate. Furthermore, it is proved that the starting poly-lysine hydriodide is built up quantitatively of lysine units.

Preparation of 2,4-Dinitrophenyl-poly-lysine.—150 mg. of poly-lysine hydriodide (*n* average = 32) and 3.1 g. of sodium bicarbonate were dissolved in 30 ml. water; 30 ml. of ethanol and 5 ml. of 2,4-dinitrofluorobenzene were then added and the mixture mechanically shaken for two hours. A large excess of 2,4-dinitrofluorobenzene was necessary in order to assure complete coupling of the large number of free amino groups in poly-lysine hydriodide with the 2,4-dinitrophenyl reagent. The yellow precipitate of 2,4-dinitrophenyl-poly-lysine was centrifuged and washed several times with water and ethanol and dried in a vacuum desiccator. 2,4-Dinitrophenyl-poly-lysine is a yellow powder, insoluble in water, alcohol, ether, and glacial acetic acid. It is soluble in concentrated sulfuric acid, and can be precipitated from it by addition of water.

Anal. Calcd. for 2,4-dinitrophenyl-poly-lysine (*n* average = 32): amino N, 0.0; N, 18.9. Found: amino N, 0.03; N, 19.0.

The amino N value found indicates that practically all of the amino groups of poly-lysine reacted with 2,4-dinitrofluorobenzene.

Hydrolysis of 2,4-Dinitrophenyl-poly-lysine; Identification and Estimation of α,ε-Di-(2,4-dinitrophenyl)- and ε-2,4-Dinitrophenyl-lysine Formed.—2,4-Dinitrophenyl-poly-lysine is not hydrolyzed quantitatively in 20% hydrochloric acid even on boiling for extended periods, as clumps of polymer settle to the bottom of the vessel and do not enter into solution. We thus looked for another acid in which the polymer would dissolve more readily before hydrolysis. It was found that total hydrolysis of 2,4-dinitrophenyl-poly-lysine can be carried out in 50% (w/w) sulfuric acid; the following hydrolytic experiment was therefore carried out in this medium.

Twenty mg. of 2,4-dinitrophenyl-poly-lysine was boiled under reflux for ten hours in 20 ml. 50% (w/w) sulfuric acid. After cooling, the solution was extracted five times with ether. The first two ether extracts showed a clear yellow color which could be attributed to the presence of α,ε-di-(2,4-dinitrophenyl)-lysine in the hydrolyzate.

The ether extracts were washed with a small amount of water and the washings returned to the original aqueous solution. The collected ether extracts were reduced to dryness, and passed through an ether column prepared from 2 g. of silica, and again evaporated to dryness, and developed on a 1% butanol–chloroform column. There was a red band that moved rapidly ($R = 1.5$) and a yellow band which moved much more slowly ($R = 0.6$). After repeating the separation between the two bands on a 3 g. of 1% butanol–chloroform column, the red band was decanted and not explored further, as it seemed to represent a breakdown product of hydrolysis. The R of the yellow band was that found for synthetic α,ε-di-(2,4-dinitrophenyl)-lysine prepared from lysine and 2,4-dinitrofluorobenzene. Furthermore, in a parallel hydrolysis experiment, it was found that on mixing the fraction of yellow band with synthetic α,ε-di-(2,4-dinitrophenyl)-lysine, evaporating to dryness and developing with 1% butanol–chloroform one band only with the anticipated R was formed.

The solution of the yellow band is thus identified as the solution of α,ε-di-(2,4-dinitrophenyl)-lysine.

In order to estimate the α,ε-di-(2,4-dinitrophenyl)-lysine formed by the hydrolysis of 2,4-dinitrophenyl-poly-lysine quantitatively, the fraction of yellow band mentioned above was run out, taken to dryness, the residue dissolved in 50 ml. of chloroform and estimated colorimetrically, with a photoelectric absorptiometer after plotting the standard curve of synthetic α,ε-di-(2,4-dinitrophenyl)-lysine in chloroform; 0.596 mg. was found.

The acid solution, after extraction with ether, was diluted to 500 ml. with water, and the sulfuric acid removed quantitatively by means of barium chloride. The precipitate of barium sulfate was filtered off and washed several times with water. The combined filtrate and washings were made up to 1000 ml. A 100-ml. sample from this solution was withdrawn and evaporated to dryness. The residue was passed through a 66% methyl ethyl ketone ether column on silica gel. One yellow band was formed having $R = 0.2$. The same R was obtained when synthetic ε-2,4-dinitrophenyl-lysine prepared according to Sanger was passed through this column, and when the residue from aqueous solution of hydrolyzate, described above, in another hydrolytic experiment, was mixed with synthetic ε-2,4-dinitrophenyl-lysine and the mixture passed through a 66% methyl ethyl ketone ether column. The presence of ε-2,4-dinitrophenyl-lysine in the aqueous solution of hydrolyzate is thus proved.

In order to determine quantitatively the amount of ε-2,4-dinitrophenyl-lysine obtained, the yellow band in the original column was run out, taken to dryness and made up to 50 ml. with *N* hydrochloric acid. The amount of ε-2,4-dinitrophenyl-lysine in this solution was estimated colorimetrically. A total amount of 14.7 mg. of ε-2,4-dinitrophenyl-lysine was found in the 1000 ml. of aqueous solution.

In order to estimate the amount of α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine, decomposing under the conditions prevailing in the hydrolysis of 2,4-dinitrophenyl-poly-lysine, weighed amounts of synthetic α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine were kept in boiling 50% (w/w) sulfuric acid for ten hours. In the first case, the amount of α,ε-di-(2,4-dinitrophenyl)-lysine and in the second case, the amount of ε-2,4-dinitrophenyl-lysine which remained unaffected by the acid were determined as above.

A breakdown of 25% of ε-2,4-dinitrophenyl-lysine and a breakdown of 38% of α,ε-di-(2,4-dinitrophenyl)-lysine were observed under the hydrolytic conditions used.

If the values obtained on the hydrolysis of 2,4-dinitrophenyl-poly-lysine are corrected by the last data for the breakdown of ε-2,4-dinitrophenyl-lysine and α,ε-di-(2,4-dinitrophenyl)-lysine, the following yield from 100 mg. of 2,4-dinitrophenyl-poly-lysine of α,ε-di-(2,4-dinitrophenyl)-lysine and ε-2,4-dinitrophenyl-lysine, are obtained: 4.80 mg. of α,ε-di-(2,4-dinitrophenyl)-lysine and 98.0 mg. of ε-2,4-dinitrophenyl-lysine.

Although as already remarked by Sanger, "the correction may not be strictly valid, as the stability of the derivatives while still condensed in the protein or in peptide split products may not be the same as that found for the derivatives themselves," it seems that at least a good approximation for the real estimation of the two 2,4-dinitrophenyl-lysine derivatives is thus obtained.

It can be seen that 31 moles of ε-2,4-dinitrophenyl-lysine per 1 mole of α,ε-di-(2,4-dinitrophenyl)-lysine was obtained in the hydrolyzate. As pointed out previously, these data are in fair agreement with the suggested structure for poly-lysine hydriodide (*n* average = 32).

Proof for the Practical Absence of α,ε-Di-(2,4-dinitrophenyl)-lysine, in 2,4-Dinitrophenyl-poly-lysine.—In order to prove that the α,ε-di-(2,4-dinitrophenyl)-lysine is derived entirely from the original terminal lysine units of the 2,4-dinitrophenyl polymer, and does not partly originate from the coupling of 2,4-dinitrofluorobenzene with any free lysine monomer in the poly-lysine hydriodide (*n* average = 32), the following experiment was carried out.

A sample of 30 mg. of 2,4-dinitrophenyl-poly-lysine

was dissolved without heating in 10 ml. of concentrated sulfuric acid, 20 ml. of water was slowly added under strong cooling, and the mixture shaken vigorously with ether. No yellow color indicating the presence of α,ϵ-di-(2,4-dinitrophenyl)-lysine appeared in the ether extract.

On the other hand, when a sample of 2,4-dinitrophenyl-poly-lysine dissolved in 50% (w/w) sulfuric acid was boiled for about thirty minutes and the mixture then extracted with ether, the formation of small amounts of α,ϵ-di-(2,4-dinitrophenyl)-lysine due to hydrolysis was apparent from the faint yellow color of the ether extract.

Poly-lysine Picrate.—100 mg. of poly-lysine hydriodide (n average = 32) was dissolved in 2 ml. of hot water, and 2 ml. of hot saturated solution of picric acid added. After standing overnight in the ice box, the yellow picrate was filtered off and washed several times with cold water and ether. Yield was 85% of the theoretical.

The product was thoroughly dried in vacuum desiccator at 100° before analysis.

Anal. Calcd. for poly-lysine picrate (n average = 32): C, 40.5; H, 4.2; N, 19.5. Found: C, 40.1; H, 4.4; N, 19.4.

The picrate is soluble in hot water, slightly soluble in alcohol but insoluble in ether and benzene.

Poly-lysine Picrolonate.—100 mg. of poly-lysine hydriodide (n average = 32) was dissolved in 2 ml. of water, and 5 ml. of hot saturated solution of picrolonic acid in water added. A voluminous precipitate separated at once. After standing overnight in the icebox, the precipitate was filtered and washed several times with water and ether. The material was thoroughly dried in a vacuum desiccator at 100° before analysis.

Anal. Calcd. for polylysine picrolonate (n average = 32): C, 49.0; H, 4.9; N, 21.4. Found: C, 48.6; H, 5.1; N, 21.1.

It is sparingly soluble in water and insoluble in the usual organic solvents.

Benzoyl-poly-lysine.—100 mg. of poly-lysine hydriodide (n average = 32) was dissolved in 2 ml. of water, 400 mg. of sodium bicarbonate added and the mixture cooled to 0°. On further cooling, 0.5 ml. of benzoyl chloride in five portions was added with vigorous shaking. After forty-five minutes, the mixture was acidified to congo red with concentrated hydrochloric acid, and the white precipitate decanted and thoroughly washed with water, alcohol and ether. Benzoyl-poly-lysine was obtained in 80% yield as a white powder. It is soluble in hot glacial acetic acid and concentrated sulfuric acid, but insoluble in ether, alcohol and water. For analysis the polymer was dried in vacuum desiccator at 100°.

Anal. Calcd. for benzoyl poly-lysine (n average = 32): N, 11.86. Found: N, 11.60.

Poly-lysine Hydrochloride.—0.65 ml. of N hydrochloric acid was added to 150 mg. of poly-lysine picrate suspended in 5 ml. of water. The mixture was shaken several times with ether to remove the picric acid liberated. An equal volume of alcohol was then added to the aqueous solution and the mixture dried at room temperature in a vacuum desiccator over sulfuric acid and sodium hydroxide. The remaining hydrochloride was washed several times with dry ether and dried *in vacuo*. The yield was quantitative. The hydrochloride was further dried at 80° *in vacuo* over phosphorus pentoxide before analysis.

Anal. Calcd. for poly-lysine hydrochloride (n average = 32): Cl, 22.3. Found: Cl, 22.0.

Poly-lysine hydrochloride is very soluble in water and gives a strong violet biuret reaction. The ninhydrin reaction is positive, and when heated with an alkaline solution of picric acid, no red coloration is obtained. Polylysine hydrochloride is insoluble in usual organic solvents.

Preliminary Experiment in the Fractionation of a Poly-carbobenzoxy-lysine Preparation.—This experiment was carried out with the material described under Table IC; this preparation contains a very small percentage of carboxyl-N indicating a very small percentage of "monomers." 100 mg. of polymer was dissolved in 5 ml. of hot glacial acetic acid. The solution was allowed to cool and the precipitate (fraction 1) filtered. To the filtrate an equal amount of water was added and the turbid mixture formed allowed to stand overnight in the icebox. The white precipitate (fraction 2) was filtered off and the filtrate concentrated *in vacuo* to dryness (fraction 3). In the three fractions the free amino N (Van Slyke) was determined.

Fraction	Weight of fraction, mg.	Amino N, %
1	18	0.18
2	63	.23
3	19	.30

Discussion

The structure suggested for the polymeric derivatives obtained from ϵ-carbobenzoxy-α-carboxyl-lysine anhydride (*cf.* scheme) calls for proof of the presence of peptide bonds and free α-amino and α-carboxyl terminal groups.

The presence of the assumed –CONH– bonds is indicated by the positive biuret reaction, and proved by the formation of the expected equivalent amounts of α-amino and α-carboxyl groups on hydrolysis of poly-lysine hydriodide. The peptide structure of poly-lysine is also supported by the fact that crystalline trypsin causes cleavage of this polymer. This enzymatic result is in agreement with the findings of Bergmann and Fruton,[12] that a typical trypsin substrate has to contain lysine or arginine residues.

Furthermore, the method of synthesis of poly-lysine and the fact that it yields on hydrolysis lysine quantitatively, leave little doubt that the polymer is built up of lysine residues bound by normal peptide bonds.

The positive ninhydrin reaction in poly-lysine hydriodide and poly-carbobenzoxy-lysine indicates the presence of α-amino groups. The presence of the α-amino end-group in poly-carbobenzoxy-lysine is proved by the Van Slyke manometric amino nitrogen determination, while the presence of the same terminal group in poly-lysine hydriodide is proved by the isolation of α,ϵ-di-(2,4-dinitrophenyl)-lysine from 2,4-dinitrophenyl-poly-lysine. The formation of the terminal groups can be explained by the observed catalytic action of water on the polymerization of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride.

The above facts support our view that the poly-lysine derivatives described in this paper represent mixtures of straight chains of poly-lysine peptides probably of various chain length; nevertheless the presence of high rings in the polymeric mixtures cannot be excluded.

In connection with our previous work on the polycondensation of esters of α-amino acids,[1,2] the absence of diketopiperazine in the product obtained on polymerization of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride is of interest. While

(12) Bergmann and Fruton, "Advances in Enzymology," I, 75 (1941).

the methyl ester of ϵ-carbobenzoxy-lysine yields on heating mainly ϵ,ϵ′-dicarbobenzoxy-lysine anhydride,[3] the corresponding N-carboxyl anhydride yields a polymer without any diketopiperazine. This difference may be connected with the fact that polycondensation of α-amino acid esters proceeds slowly, while the polymerization of the corresponding N-carboxyl anhydrides is rapid. Thus the methyl ester of ϵ-carbobenzoxy-lysine condenses to ϵ,ϵ′-di-carbobenzoxy-lysine anhydride at 105° over a period of several days, while the polymerization of ϵ-carbobenzoxy-α-carboxyl-lysine anhydride is accomplished under the same conditions within an hour.

Summary

ϵ-Carbobenzoxy-α-carboxyl-lysine anhydride (I) when heated to 102–105° evolves carbon dioxide and yields a polymeric preparation to which the structure of poly-carbobenzoxy-lysine (II) is ascribed.

The products of polymerization of (I) obtained under various conditions were studied.

On polymerization of (I) under special precautions, a poly-carbobenzoxy-lysine was obtained with an average chain length of 32-carbobenzoxy-lysine units.

Poly-carbobenzoxy-lysine (II) (*n* average = 32) yields on reduction with phosphonium iodide poly-lysine hydriodide (III) (*n* average = 32).

Poly-lysine hydriodide (*n* average = 32) contains practically no free lysine or lysine anhydride. On hydrolysis it yields lysine quantitatively.

The following derivatives were prepared from (III) (*n* average = 32): picrate, picrolonate, hydrochloride, benzoyl and 2,4-dinitrophenyl-poly-lysine.

The suggested formula for poly-lysine (*n* average = 32) is supported by the analytical data, and by the fact that 2,4-dinitrophenyl-poly-lysine (*n* average = 32) yields the expected amounts of α,ϵ-di-(2,4-dinitrophenyl)-lysine and ϵ-2,4-dinitrophenyl-lysine on hydrolysis.

Independent support for the presence of peptide bonds in (III) is given by its cleavage with crystalline trypsin.

RECEIVED DECEMBER 9, 1947

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Phosphorylation of Proteins with Phosphoric Acid Containing Excess Phosphorus Pentoxide

BY ROBERT E. FERREL, HAROLD S. OLCOTT AND HEINZ FRAENKEL-CONRAT

When proteins are treated with cold concentrated sulfuric acid, the principal reaction is a transformation of the aliphatic hydroxyl groups to half-esters of sulfuric acid.[2,3] The present study was undertaken in order to determine whether analogous reactions occur when proteins are treated with phosphoric acid containing excess phosphorus pentoxide. Levene and Schormüller[4] had used such a reaction mixture for the preparation of *o*-phosphoric acid esters of serine, hydroxyproline and serine anhydride in small yield, and Plimmer,[5] using the same medium at elevated temperatures, had duplicated their findings and also reported the preparation of *o*-phosphoric acid esters of tyrosine, threonine and isoserine.

In general, the reaction was carried out by permitting a mixture of the material to be treated and the phosphoric acid–phosphorus pentoxide reagent to stand for three days at room temperature in a dry atmosphere (desiccator). The product was isolated by pouring the reaction mixture over cracked ice, neutralizing, and dialyzing, first against ion-free water, then against 10% sodium chloride, and finally against distilled water until free of inorganic phosphates. Recoveries ranged from 70 to 100% based upon nitrogen analyses. The extent of reaction was estimated from the phosphorus-to-nitrogen ratio of the product.

Of the many polar groups in proteins available for reaction, only the aliphatic hydroxyl groups of serine, threonine and hydroxyproline, and to some extent the aromatic hydroxyl group of tyrosine were found to bind phosphorus in a stable manner.[6]

The basic groups and the peptide bonds, however, appear to be responsible for an additional amount of phosphate, retained during dialysis against water but liberated by high salt concentration. Part of the peptide bonds were labile to

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Reitz, Ferrel, Fraenkel-Conrat and Olcott, THIS JOURNAL, **68**, 1024 (1946).

(3) The product obtained from wheat gluten was gel-forming and appeared to have possible industrial significance (Reitz, Ferrel and Olcott, *Ind. Eng. Chem.*, **36**, 1149 (1944)).

(4) Levene and Schormüller, *J. Biol. Chem.*, **105**, 547 (1934); **106**, 595 (1934).

(5) Plimmer, *Biochem. J.*, **35**, 461 (1941).

(6) This specificity contrasts with the non-specific action of other phosphorylating agents which are known to react with amines, guanidyl compounds, etc., as well as with alcohols and phenols. Mayer and Heidelberger[7] phosphorylated horse-serum albumin in alkaline solution with phosphorus oxychloride. The derivatives contained 2–3% phosphorus, approximately half of which was accounted for by reaction with the amino groups. The reaction of egg albumin under similar conditions was described by Heidelberger, *et al.*[8]

(7) Mayer and Heidelberger, THIS JOURNAL, **68**, 18 (1946).

(8) Heidelberger, Davis and Treffers, *ibid.*, **63**, 498 (1941).

hydrolysis when the lightly bound phosphate was present.

A considerable part of the ester-bound phosphorus was present as metaphosphate.

Reactivity of the Aliphatic Hydroxyl Groups.—That the aliphatic hydroxyl groups of proteins and model polypeptides bind phosphorus is shown in Table I, in which the amount of phosphorus introduced is compared with the β-hydroxyamino acid content. There is, in general, good correlation between the two values, although materials treated ranged in β-hydroxyamino acid content from sericin, which contains 37 equivalents per 10^4 grams (38% serine), to synthetic polypeptides containing none. Further evidence for the reactivity of the hydroxyl groups was the considerable amount of phosphorus bound by polyvinyl alcohol (18%).

TABLE I

COMPARISON OF STABLY-INTRODUCED PHOSPHORUS WITH THE ALIPHATIC HYDROXYAMINO ACID CONTENTS OF PROTEINS AND MODEL SUBSTANCES

	Equivalents per 10^4 g. original material		
	Phosphorus introduced[a]	Sulfate sulfur introduced[b]	Hydroxyamino acids[c]
Sericin	35.8	37.7	37.7
γ-Globulin	14.2	17.3	16.8
Gelatin	15.6	15.2	14.2[d]
Silk fibroin	16.5	16.9	12.8
Isinglass	13.7	13.7	10.2[d]
Bovine serum albumin	9.6[e]	..	10.0
Edestin	9.6[e]	..	9.3
Insulin	8.2	7.9	6.1
Globin	6.0	..	5.2
Gramicidin	6.1	5.9	4.8
Gliadin	7.4	7.9	4.6
Polyglutamic acid	0.2	1.6	..
Polyglutamine	0.3	0.7	..
Nylon	1.2[e]	0.5	..
Tyrosine–formaldehyde polymer	0.4	..	..
Polyglycine	0.8	0.5	..
Crystalline egg albumin	15.5[f]	13.6	10.0
Ovomucoid	16.7[f]	17.5	7.6
Gluten (soluble fraction)[g]	15.8[f]	7.5 (wt. av.)	5.6
Gluten (insoluble fraction)[g]	8.3[f]	..	..

[a] Calculated from the phosphorus-to-nitrogen ratio of the phosphorus derivative and the nitrogen content (dry basis) of the original material. Equivalents phosphorus introduced per 10^4 g. of original material = (% N (orig. material) P/N (derivative) × 100)/14. [b] For comparison, the results of previously reported sulfation experiments with cold concentrated sulfuric acid[2] have been included. [c] These data have been reported previously.[2] The total β-hydroxyamino acid content may be expected to be low by 10% because of the known sensitivity of serine to acid hydrolysis. Also, the method used for their determination yielded recoveries of ammonia corresponding to only about 90% of added serine or threonine. [d] The values 9.5 and 3.4 have been added for the hydroxyproline content of gelatin and isinglass, respectively. [e] In these samples significant amounts (over 10%) of the products were insoluble. Only trace amounts of phosphorus were bound in the insoluble fraction and values given here are for the soluble portion. [f] These derivatives are listed out of the normal order of decreasing hydroxyamino acid content, since they are the proteins known to contain significant amounts of carbohydrate, 26%, 10%, and 3%, respectively, for ovomucoid, gluten, and egg albumin. The role of carbohydrates in the reaction is discussed in the text. [g] Yield, approximately 50% by weight.

The large amounts of phosphorus introduced into gelatin and isinglass were evidence that the hydroxyl group of hydroxyproline was as available for phosphorylation as was that of serine and threonine.

It appears significant in this connection that those proteins that bound amounts of phosphorus in excess of the β-hydroxyamino acids present were generally the same proteins that bound excess sulfate sulfur when treated with concentrated sulfuric acid (Table I).[2] This result may be attributed to the presence of unknown amounts of hydroxyproline, other hydroxyamino acids, or carbohydrate in the proteins. Of these, only the amount of carbohydrate can be determined with any degree of accuracy. The role of carbohydrate is illustrated by ovomucoid (26% carbohydrate), which after phosphorylation was found to contain phosphorus much in excess of the hydroxyl groups present as β-hydroxyamino acids (16.7 equivalents P/10^4 g. as compared to 7.6 equivalents β-hydroxyamino acids).

Other Polar Groups.—The phenolic hydroxyl group appears to react to a limited extent only. Model experiments with tyrosine and *p*-cresol showed that these phenols were phosphorylated to the extent of 38 and 60%, respectively, (as determined colorimetrically with the Folin phenol reagent), after treatment with the phosphoric acid–phosphorus pentoxide reagent. The original chromogenic value was restored by acid hydrolysis. Conversely, a tyrosine–formaldehyde polymer[9] containing free phenolic groups bound only trace amounts of phosphorus. The extent to which the phenolic groups of proteins participate in the reaction was difficult to evaluate. Both insulin and silk fibroin bound phosphorus in excess of their known aliphatic hydroxyl groups. These same proteins had previously been found to bind similarly high amounts of sulfate upon treatment with concentrated sulfuric acid (Table I).[2] In that case, however, model experiments with tyrosine suggested that almost no phenol sulfates were formed with the usual sulfation procedure but only sulfonates, which did not yield sulfate upon hydrolysis. That the extent of phosphorylation of the phenolic groups was small was suggested by colorimetric measurements (Folin) on intact phosphorylated insulin and untreated insulin, which were found to correspond to 8.5 and 9.0% of tyrosine, respectively. The corresponding value for the water-soluble phosphorylated silk fibroin was 6.0% tyrosine, but the fibroin derivative could not

(9) Olcott, in preparation for press.

be compared with the original protein because of the insolubility of the latter.[10]

That the sulfhydryl groups did not react was suggested by the observation that the chromogenic activity (Folin uric acid reagent) of cysteine was not affected when this amino acid was exposed to the phosphorylating mixture. Confirming evidence for the comparative non-reactivity of the sulfhydryl groups was obtained with phosphorylated egg albumin, which, when prepared with special precautions[11] gave a strongly positive sulfhydryl test in the presence of guanidine hydrochloride. Titration indicated that slightly over half of the sulfhydryl groups were still present.

The non-participation of the guanidyl group was indicated with edestin, which contains 9.6 equivalents of guanidyl per 10^4 g. of protein. This protein bound phosphorus only to the extent of its hydroxyl groups (Table I). Further evidence was obtained with methylguanidine sulfate. No phosphorus appeared to be bound by this compound. An attempt was made to use salmine sulfate (approximately 66% arginine) as a further model. Precipitation techniques had to be used for the isolation of these reaction products. Although considerable amounts of phosphorus in excess of its hydroxyl groups were found in reacted salmine, it was possible to show that this excess was due to salt-linked metaphosphoric acid rather than to primary ester linkages (see Experimental).

That the amino group did not participate in the reaction was shown with the tyrosine–formaldehyde polymer (5% free amino nitrogen)[9] which bound almost no phosphate stably (see above). Further evidence was the fact that proteins rich in amino groups bound phosphorus only to the extent of their aliphatic hydroxyl groups, and showed unchanged or slightly increased amino nitrogen values. (Bovine serum albumin gave amino nitrogen values of 7.2 and 8.7% of the total nitrogen, respectively, before and after treatment.)

That the carboxyl group and peptide bond did not contribute to the stable fixation of phosphorus was shown with polyglutamic acid, nylon, polyglutamine and polyglycine. The labile fixation of phosphate by the peptide linkage will be discussed below.

The non-reactivity of the imidazole group was suggested by the fact that globin (approximately 9% histidine) bound phosphorus only to the extent of its hydroxyl groups (Table I).

Evidence that the indole group did not bind phosphorus was obtained with gramicidin which, although it contains almost 40% tryptophan, bound amounts of phosphorus only slightly in excess of its content of hydroxyl groups.

Nature of the Phosphate Bound.—Levene and Schormüller[4] and Plimmer[5] had found that the hydroxyamino acid phosphates prepared by reaction with phosphoric acid–phosphorus pentoxide reagent were acid esters of *o*-phosphoric acid. However, the phosphate bound in proteins and model systems appears to be a mixture of the meta and ortho and possibly other forms. Possibly the low yields obtained by these investigators were due to the presence of similar mixtures in the amino acid reaction products.

The first indication that the phosphate was not entirely in the ortho form was obtained from titration data (Table II). While synthetic monoesters of phosphoric acid and a phosphoprotein obtained from egg yolk[12] required approximately 2 equivalents of alkali for each equivalent of phosphorus present in order to bring a solution from *p*H 2 to *p*H 8, the phosphorylated proteins required only 0.7 to 1 equivalent of alkali under the same conditions.

TABLE II

EQUIVALENTS OF ALKALI REQUIRED TO TITRATE PHOSPHORYLATED PROTEINS AND MODEL SUBSTANCES FROM *p*H 2.0 TO *p*H 8.0[a]

Sample	Equivalents of alkali per equivalent of phosphorus
Phosphorylated polyvinyl alcohol	0.8
Phosphorylated gelatin	1.0[b]
Phosphorylated sericin	0.7[b]
Phosphorylated bovine serum albumin	0.8[b]
Phosvitin[d]	1.9
Sodium pyrophosphate[c]	2.1
Mono ethyl orthophosphoric acid[c]	1.9
Dimethyl orthophosphoric acid[c]	1.0

[a] Titrations were performed in 0.1 *M* potassium chloride. [b] Corrected for the titration of the untreated material over the same range. [c] Commercial preparations. [d] See footnote 12.

These findings were supported by acid group analyses by a dye method.[13] Orthophosphoric monoesters of proteins behave as dibasic acids in fixing 2 dye molecules, as was shown with the naturally occurring phosphoprotein.[12] In the artificial phosphoproteins, however, the acid group increase due to phosphorylation corresponded to only about 70% of the phosphorus, if the latter is

(10) Dispersion of both the phosphorylated and intact silk fibroin (5 mg.) in saturated lithium iodide (0.2 ml.) made a comparison possible by colorimetry immediately after dilution with water; but the accuracy of these analyses was small, since lithium iodide markedly augmented the chromogenic value of the standard tyrosine solution. The results obtained with the known samples were corrected by this apparent excess tyrosine. The tyrosine contents found by this technique were 11.5 and 12.7%, respectively, for phosphorylated and unreacted silk fibroin.

(11) In the first preparation of phosphorylated egg albumin no sulfhydryl groups could be detected. It was suspected that this might be due to the oxidizability of sulfhydryl groups of the denatured protein during prolonged dialysis in neutral solution. In an attempt to eliminate this factor, the reaction was repeated in an atmosphere of carbon dioxide and most of the acid was removed by dialysis without neutralization. The completely insoluble product was washed free of inorganic phosphorus, frozen, and dried from the frozen state *in vacuo* over sodium hydroxide flakes. Ten mg. of phosphorylated protein required 0.3 to 0.4 micromole of *p*-chloromercuribenzoate as compared with 0.7 to 0.8 for unreacted egg albumin for the abolishment of the nitroprusside test.

(12) Phosvitin, a protein containing 10.3% phosphorus; Mecham and Olcott, *Fed. Proc.*, **7**, 173 (1948).

(13) Fraenkel-Conrat and Cooper, *J. Biol. Chem.*, **154**, 239 (1944).

assumed to be present as the dibasic monoester (Table III). Therefore either most of the phosphorus introduced into proteins by this method must be present as the diester, or, more likely, a smaller fraction in an uncharged (presumably the meta ester) form.

TABLE III

APPARENT ORTHOPHOSPHATE CONTENT OF SOME PHOSPHATE DERIVATIVES BY ACID GROUP DETERMINATIONS

Samples	Equivalents per 10^4 g. original material: Acid groups, Derivative	Acid groups, Untreated	Acid groups, Increase	Phosphorus, As ortho	Phosphorus, Total
Phosphorylated bovine-serum albumin	28.8	14.6	14.2	7.1	9.1
Phosphorylated sericin	59.8	15.5	44.3	22.2	32.2
Phosphorylated polyvinyl alcohol	107.0	..	107.0	53.5	127.0
Phosvitin[a]	89.0	5.4	83.6	41.8	39.0

[a] Since phosvitin (footnote 12) is a naturally occurring phosphoprotein, the value of 5.4 acid groups in the untreated material was obtained by a determination on a 90% enzyme-dephosphorylated sample and correcting for the phosphorus still present. The other values for phosvitin are calculated on the basis of this dephosphorylated material.

To support this conclusion by elementary analytical means, polyvinyl alcohol, chosen as a simple model of a polyhydroxy compound, was phosphorylated. Complete analyses were obtained on the product, isolated both as the sodium salt and as the free acid after electrodialysis. The results corresponded to the following empirical formulas (per vinyl unit): $C_2H_{3.40}P_{0.55}Na_{0.379}O_{2.27}$, $C_2H_{3.60}P_{0.485}O_{2.04}$.

The phosphorus content indicated that about half of the vinyl alcohol units had reacted. Since titration data have shown that at *p*H 7.5 (sample neutralized to this *p*H) the ortho fraction is 90% neutralized, *i. e.*, $C_2H_{3.2}PO_4Na_{1.8}$, then the first analysis indicates that about one-fourth of the units contain orthophosphate (or the equivalent of pyrophosphate), one-third contain metaphosphate, and the rest are unreacted. The analysis of the electrodialyzed preparation indicates that about 8% of the hydroxyl groups are orthophosphate esters and about 40% are metaphosphate esters.

Salt-Labile Phosphorus.—The usual method of purifying protein derivatives by extensive dialysis was inadequate for phosphorylated proteins, in that it yielded materials having somewhat variable phosphorus contents, usually much higher than was to be expected from the β-hydroxyamino acid content of the material. In some cases phosphorus was found in model substances having no aliphatic hydroxyl groups (nylon, polyglutamine, polyglycine and tyrosine-formaldehyde polymers). This phosphorus, however, was shown to be only loosely held, since it was readily removed by dialyzing the material for five days against 10% sodium chloride (Table IV).

The results obtained with some model polypeptides (Table IV) suggested that the labile fixation of extra phosphorus might be due to the formation of salt linkages with the basic groups and to an unknown type of linkage at the peptide bond.

TABLE IV

EFFECT OF HIGH SALT CONCENTRATIONS UPON LABILE PHOSPHORUS BOUND BY SOME PROTEINS AND MODEL SYSTEMS[a]

	Equivalents phosphorus/10^4 g. original material: Before salt treatment[b]	After salt treatment[c]
Edestin	68	9.6
Sericin	41	35.8
Bovine-serum albumin	36	9.6
Polyglutamine	58	0.3
Nylon	56	1.2
Polyglycine	20	0.8
Tyrosine–formaldehyde polymer	13	0.4

[a] Dialysis for five days against 10% sodium chloride. [b] These values were not constant but varied markedly with various preparations. [c] Longer dialysis did not change these values significantly.

The participation of the peptide bonds was also suggested by Van Slyke amino nitrogen analyses on samples of phosphorylated bovine serum albumin. A preparation *not* exposed to salt dialysis (containing 36 phosphorus equivalents per 10^4 g.) seemed to contain more amino nitrogen (13.5% of the total nitrogen) than either the salt-dialyzed (8.8%) or the untreated protein (7.2%), even though no loss of nitrogen occurred during either type of dialysis. This finding could be interpreted as indicating that some peptide–phosphate bonds are labile to hydrolysis under the condition of the Van Slyke amino nitrogen analysis. Removal of the phosphate by salt dialysis restores the stability. The situation appears to be analogous to the lability toward dilute acid hydrolysis of proteins that have been exposed to concentrated sulfuric acid for several days.[2] Removal of the labily-bound sulfate by techniques that do not involve exposure to dilute acid avoids the hydrolysis. A plausible interpretation might be that phosphate or sulfate introduced on the peptide bond activates it in some manner so that under certain conditions the peptide bond is split concomitantly with the liberation of the inorganic acid.[14]

Stability of the Phosphate Bond.—A neutral solution of phosphorylated sericin was stable for four months at 4°. The phosphate bond was also stable at *p*H 2.2 and *p*H 11.5 for twenty-four hours at room temperature (23–25°). Exposure of the derivatives to 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide for twenty-four hours resulted

(14) Of interest in this respect is nylon, approximately 20% of which became water-soluble during the phosphorylation. This fraction contained large amounts of labily-bound phosphorus (Table IV). Subsequent salt dialysis not only liberated the phosphorus but split enough of the peptide linkages so that a major portion of the nitrogen was lost through the dialysis membrane.

in the liberation of 5–10% and 20–40%, respectively, of their phosphorus as orthophosphate, while incubation at 40° for twenty-four hours in 1% (0.25 *N*) sodium hydroxide caused the liberation of 60–80% of their total phosphorus as inorganic orthophosphate. Plimmer and Bayliss[15] and Rimington and Kay[16] reported that naturally occurring phosphoproteins were completely dephosphorylated in twenty-four hours at 37° by 0.25 *N* sodium hydroxide. Conversely, Plimmer[5] reported that the hydroxyamino acid phosphate monoesters were completely stable to both *N* hydrochloric acid and *N* sodium hydroxide at 37°.

Gel-Forming Property.—The neutral product of the reaction of wheat gluten with concentrated sulfuric acid possessed the property of absorbing large amounts of cold water rapidly to form gels.[2,3] The insoluble product obtained from wheat gluten and the phosphoric acid–phosphorus pentoxide reagent was also gel-forming but the gels were weaker than those obtainable with sulfuric acid. The hydration capacity[3] (ratio of grams water absorbed per gram gluten product) of the phosphorylated material was about 100 compared to 200–300 for gluten sulfates. Most of the products obtained from other proteins were soluble at neutrality. The insoluble fractions, except for those obtained from wheat gluten, did not form gels.

Specificity.—The observation that the phosphorylation procedure described here is even more specific for the hydroxyl groups of proteins than is sulfation with sulfuric acid suggested that the reagent might be useful for studying the role of the hydroxyl group in biologically-active proteins.[17] However, the reaction conditions are more drastic, with the result that more hydrolysis and denaturation occur. In contrast to sulfated insulin, which retains the biological potency of the untreated protein,[18] a phosphorylated insulin sample had decreased activity.[19]

Experimental

Materials.—Wheat gluten, gelatin, nylon molding powder and crystalline bovine serum albumin were commercial products. Crystalline egg albumin was prepared by the method of Kekwick and Cannan.[20] Sericin was prepared by the method of Rutherford and Harris.[21] The silk fibroin preparation was that portion of the raw silk remaining after four successive treatments with hot water. The sample of gliadin was obtained from D. K. Mecham of this Laboratory, who prepared it by fractional precipitation with alkali from dilute acid solution. Polyglutamic acid was obtained from a culture of a particular strain of *Bacillus brevis* by the method of Bovarnick.[22] The polyamide was synthesized from the peptide and has been characterized previously.[23] Protamine (salmine) sulfate and insulin were kindly furnished by the Eli Lilly Company, isinglass by the Connaught Laboratories, gramicidin by the Wallerstein Company, and edestin by D. M. Greenberg of the University of California. The tyrosine–formaldehyde polymer used was obtained by heating tyrosine with formaldehyde in acid solution.[9] The product contained approximately 5% amino nitrogen, 6.7% total nitrogen.

Phosphorylation Procedure.—Preliminary experiments showed that the following method introduced maximal amounts of phosphorus into proteins: The reagent was prepared by quickly weighing 75 g. of phosphorus pentoxide into a beaker containing 100 g. of 85% orthophosphoric acid and heating the mixture with stirring to dissolve. Ten grams of the cooled reagent was weighed into a small beaker[24] and 100 mg. of finely ground protein was dusted in with stirring to obtain a smooth dispersion. The beaker was then placed in a desiccator over phosphorus pentoxide to react for three days at room temperature.[25] The reaction mixture was stirred several times during the first twenty-four hours to disperse any lumps formed. After seventy-two hours, the viscous reaction mixture was diluted by adding finely crushed ice with vigorous stirring. The diluted mixture was then poured over more cracked ice and neutralized (*p*H 7.5–8.0) with 10 *N* sodium hydroxide, with stirring to prevent local overheating. More ice was added as needed to maintain the temperature at 5–10°. The neutralized mixture was transferred to dialysis tubing and dialyzed against running demineralized water[26] overnight and then against successive changes of distilled water until the dialysate had the same conductivity as distilled water. Some preparations were analyzed at this stage. Others were next concentrated to small volume by placing the dialyzing bags in a stream of warm air, and then dialyzing for five days against 10% sodium chloride solutions to remove all labile phosphorus. The solutions were dialyzed free of salts with distilled water, centrifuged to remove any insoluble material, frozen, and dried *in vacuo* from the frozen state. Soluble portions were either lyophilized or stored in the refrigerator after addition of a few drops of toluene to prevent bacterial action. The extent of reaction was estimated from phosphorus-to-nitrogen ratios.

Analytical Methods.—Nitrogen was determined by the Kjeldahl procedure. Total phosphorus was determined by the Allen[27] method. Inorganic orthophosphate was determined by the method of Lowry and Lopez.[28] Amino nitrogen was determined by the ninhydrin method of Harding and Maclean,[29] and by the Van Slyke manometric procedure (fifteen minutes).[30]

(15) Plimmer and Bayliss, *J. Physiol.*, **33**, 439 (1905–1906).

(16) Rimington and Kay, *Biochem. J.*, **20**, 777 (1926).

(17) Olcott and Fraenkel-Conrat, *Chem. Rev.*, **41**, 151 (1947).

(18) Glendenning, Greenberg and Fraenkel-Conrat, *J. Biol. Chem.*, **167**, 125 (1947).

(19) Fraenkel-Conrat and Fraenkel-Conrat, unpublished.

(20) Kekwick and Cannan, *Biochem. J.*, **30**, 227 (1936).

(21) Rutherford and Harris, *J. Research Nat. Bur. Standards*, **24**, 415 (1940).

(22) Bovarnick, *J. Biol. Chem.*, **145**, 451 (1942).

(23) Fraenkel-Conrat, Cooper and Olcott, THIS JOURNAL, **67**, 314 (1945).

(24) It was found advisable to use freshly prepared acid mixtures each time to prevent solidification during reaction. The composition of such mixtures has recently been elucidated, Bell, cited by Audrieth and Hill, *J. Chem. Ed.*, **25**, 80 (1948). A commercial phosphoric acid preparation containing 83–84% total phosphorus pentoxide is available under the name "phospholeum." The products obtained with this reagent were mostly insoluble (about 70%). The insoluble fractions contained very little phosphorus. The soluble fractions contained amounts of phosphorus similar to those obtained with the reagent prepared as described above (78% phosphorus pentoxide).

(25) Lower percentages of phosphorus pentoxide caused less phosphorus to be bound. Elevated temperatures could not be used to shorten the reaction time because of extensive protein degradation and losses on dialysis. The use of even traces of organic solvents as extenders and aids to dispersion of the protein led to lower phosphorus contents.

(26) Tap water could not be used, since insoluble calcium and magnesium phosphates were formed and most of the protein was rendered insoluble, complicating further purification and analysis.

(27) Allen, *Biochem. J.*, **34**, 858 (1940).

(28) Lowry and Lopez, *J. Biol. Chem.*, **162**, 421 (1946).

(29) Harding and Maclean, *ibid.*, **24**, 503 (1916).

(30) Van Slyke, *ibid.*, **83**, 425 (1929).

Tyrosine was determined colorimetrically by Herriott's modification[31] of the Folin method. Total acid groups were determined by a dye technique.[13] Cysteine was determined with the Folin uric acid reagent,[32] protein-SH groups were determined with *p*-chloromercuribenzoate[33] using nitroprusside as an external indicator.

Treatment of Low-Molecular-Weight Materials.—Several amino acids and other materials with molecular sizes too small to permit separation by dialysis were used as model systems. In general, they were handled in one of two ways: by colorimetric analyses performed on the complete, diluted reaction mixture or by measurements on the material isolated by precipitation techniques. Specific methods are cited below.

Phenols.—The reactivity of the aromatic hydroxyl group of tyrosine and *p*-cresol was ascertained as follows: 100 mg. each of tyrosine and *p*-cresol were treated for three days at room temperature with 10 g. of the phosphorylating reagent. Parallel controls (100 mg. each) were treated with 85% *o*-phosphoric acid. The reaction products were diluted with cracked ice and ice water and, in the case of tyrosine, were neutralized by the addition of the necessary amount of sodium hydroxide as calculated by titration of an aliquot to neutrality with brom thymol blue as an indicator. Tyrosine crystallized from the control solution. The diluted *p*-cresol reaction mixture had oily droplets present, hence alkali was cautiously added until these droplets were in solution. An aliquot was then titrated to neutrality and the main solution adjusted with the calculated amount of alkali. Colorimetric measurements on these solutions showed that the chromogenic values for phosphorylated tyrosine and *p*-cresol were reduced by 38 and 60%, respectively, while that for the *p*-cresol control (treated with 85% phosphoric acid) was not affected. Hydrolysis in 6 *N* hydrochloric acid at 120–125° for eighteen hours regenerated the full chromogenic activity.

Cysteine.—To ascertain whether the sulfhydryl group was phosphorylated, the amino acid cysteine was treated as follows: 100 mg. of cysteine hydrochloride was introduced into 10 g. of the phosphoric acid–phosphorus pentoxide reagent and 100 mg. was introduced into 10 g. of 85% orthophosphoric acid and run parallel as a control. The samples were allowed to react for three days at room temperature in a desiccator and then diluted with cracked ice and brought to a volume of 100 ml. with water. Nitrogen and cysteine determinations on aliquots of these solutions showed that the sulfhydryl group had not reacted.

Salmine Sulfate.—500 mg. of salmine sulfate was treated for three days with the regular phosphorylating mixture. Since it could not be dialyzed, the reaction mixture was poured into cold acetone. The water-insoluble precipitate was repeatedly dissolved in *M* sodium chloride and reprecipitated as an oil by addition of distilled water until there was no free phosphate in the supernatant fluid. The final material contained considerable quantities of phosphorus in excess of its hydroxyl groups (30.4 equivalents as compared to 4.3 equivalents per 10^4 g.), not present as free orthophosphate. However, indications were obtained that the phosphorus was present in a labile form, possibly as a salt of a metaphosphoric acid. That this explanation is a plausible one was shown with the ortho- and metaphosphoric acid salts of protamine. These were prepared by quantitatively removing the sulfate from solutions of protamine sulfate with the calculated equivalent amount of barium hydroxide and neutralizing the resulting free base with ortho- or metaphosphoric acids. The resultant orthophosphate salt showed solubility characteristics different from those of the treated material and all of its phosphorus could be determined as inorganic orthophosphate. Conversely, the meta salt had the same solubility characteristics and the same phosphorus content as the phosphorylated material, and its phosphorus could not be determined as inorganic orthophosphate.

(31) Herriott, *J. Gen. Physiol.*, **19**, 283 (1935).

(32) Anson, *ibid.*, **24**, 399 (1940).

(33) Hellermann, Chinard and Dietz, *J. Biol. Chem.*, **147**, 443 (1943).

In the light of these findings it was necessary to ascertain that the metaphosphate ion was quantitatively removed from typical proteins by our technique of dialysis against salt solution. To this end the meta salt of bovine serum albumin was prepared by acidifying a solution of the protein to *p*H 3.0 with dilute metaphosphoric acid and separating the precipitate. The 3.3% phosphorus originally present was completely removed by salt dialysis.

Methylguanidine Sulfate.—A 500-mg. sample of methylguanidine sulfate was treated in the usual manner and isolated by diluting the reaction product with approximately 4 volumes of cold acetone and pouring this diluted mixture into sufficient saturated barium hydroxide solution to keep the final mixture alkaline to brom thymol blue. The precipitate was separated and washed three times by centrifugation. Carbon dioxide was bubbled through the combined supernatants to remove excess barium. The suspension was then filtered and concentrated to a small volume. The extent of reaction was measured by nitrogen, total phosphorus, and inorganic orthophosphate determinations. No bound phosphorus was present.

Serine and Threonine.—Although the isolation in low yields of the orthophosphate esters of serine and threonine has been reported,[4,5] repeated attempts to obtain such preparations in a pure state, either by the methods previously described or by variations in the techniques of phosphorylation and isolation were unsatisfactory.

Titration Method.—The following titration method was used for the estimation of the amount of orthophosphoric acid monoester present in the phosphorylated proteins: A sample of the phosphorylated protein of suitable size to contain approximately 100 mg. original protein (calculated from nitrogen content) was placed in a 100-ml. beaker and water was added to give a volume of 18 ml. To prevent salt concentration changes from materially affecting the results, 2 ml. of *M* potassium chloride was added to make the solution 0.1 *M* with respect to salt. It was then adjusted with *N* hydrochloric acid to *p*H 2.0 as measured with a line-operated continuous-indicating *p*H meter. 0.1 *N* sodium hydroxide was then added in 0.20-ml. portions from a 5-ml. buret (graduated in 0.02 ml.) and the *p*H recorded after each addition. A titration blank was made in the same manner on an equal sample (based on nitrogen) of the untreated protein. Titration curves were prepared by plotting the equivalents of sodium hydroxide required per gram of original material against *p*H. The amount of alkali required to titrate from *p*H 2.0 to *p*H 8.0, as determined from the curve and corrected for the titration blank value, was used to determine the molar ratio of sodium consumed to phosphorus present. This value can be used then as an approximate measure of the amount of phosphorus present in the sample in the form of *o*-phosphoric acid monoester (for orthophosphate monoesters the theoretical value is 2.0). Sodium-to-phosphorus ratios for our preparations varied from 0.7 to 1.0 (Table II).

Stability.—A solution of phosphorylated sericin was stored for four months at 4° with toluene present to prevent bacterial action. It was then dialyzed against three changes of distilled water. The phosphorus-to-nitrogen was the same as that of the original derivative.

Stability at *p*H 2.2 and 11.5 was determined by adding 5 ml. of *p*H 2.2 citrate and *p*H 11.5 phosphate buffers[13] to 5-ml. samples of phosphorylated protein solutions and dialyzing the solutions against 100 ml. of the respective buffers for twenty-four hours at room temperature. The samples were then dialyzed against 10% sodium chloride for five days and finally against distilled water until the conductivity of the dialysate was equal to that of distilled water. Phosphorus-to-nitrogen ratios of the products permitted an estimate of the stability of the phosphate bonds.

Inorganic orthophosphate determinations were used to measure the extent of liberation of phosphorus in samples exposed to 0.1 *N* or stronger acid and alkali, since these conditions caused marked protein degradation leading to low nitrogen recoveries upon dialysis. Solutions of the

materials to be treated were introduced into 50-ml. Erlenmeyer flasks, and an equal volume of 0.2 *N* hydrochloric acid, 0.2 *N* sodium hydroxide, or 2% sodium hydroxide were added. The flasks were stoppered and held for twenty-four hours at room temperature in the case of the 0.1 *N* acid and alkali and at 40° in the case of the 1% sodium hydroxide. The samples were then neutralized with an equivalent amount of alkali or acid, and inorganic orthophosphate determinations were made on aliquots of the solutions.

The data obtained included only a part of the inorganic metaphosphate that may have been liberated. Control experiments with sodium metaphosphate indicated that 0.1 *N* sodium hydroxide and hydrochloric acid hydrolyzed only 11 and 22%, respectively, to orthophosphate at 23° in twenty-four hours; 28% was converted by 1% sodium hydroxide at 40° in the same length of time.

Summary

Proteins reacted with phosphoric acid containing excess phosphorus pentoxide (78% total phosphorus pentoxide) for three days at room temperature. After neutralization and dialysis, the products contained considerable amounts of phosphorus, much of which could be removed by dialysis against 10% sodium chloride solution. The remaining stably-bound phosphate was found to be present as esters of ortho- and metaphosphoric acids on the hydroxyl groups of the serine, threonine, and hydroxyproline residues. Possibly part of the phenolic hydroxyl groups, but probably no other type of protein group, participate in the stable fixation of phosphate.

The stability of the protein phosphate bonds in neutral and dilute acid and alkaline solutions has been determined.

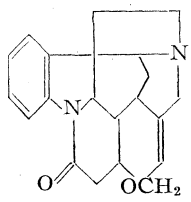
ALBANY 6, CALIFORNIA RECEIVED JANUARY 28, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

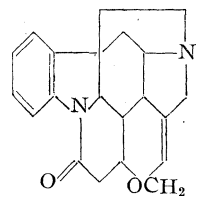
The Structure of Strychnine. Formulation of the *Neo* Bases

BY R. B. WOODWARD AND WARREN J. BREHM

Some years ago we were led to the view that strychnine was best represented by the expression[1] (I), rather than that (II) generally accepted at that time.[2] We considered *i.e.*: (i) that (I) was preferable on biogenetic grounds[3]; (ii) that (I) contains the skeletons of the main products of the drastic degradation of strychnine, *viz.*, tryptamine,[4] carbazole[5] and in particular, β-collidine,[4b,6] while the last could be formed from (II) only by rearrangement; (iii) that in any event little direct evidence was available concerning the mode of attachment of N^b to the carbazole ring.

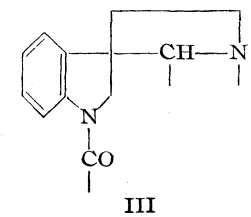


I



II

Since we have recently been able to provide evidence that the part structure (III) is present in the strychnine molecule,[7] only one major barrier



III

has remained in the way of the final acceptance of the expression (I) for strychnine. It will be clear that many of the reactions of the alkaloid will be as readily interpretable on the basis of (I) as of (II).[8] On the other hand, the acceptance of (I) has definite consequences in respect to the formulation of the *neo* series of strychnine derivatives, and the previous knowledge of the reactions of the *neo* bases has indicated strongly that these consequences did not obtain. In this communication, we describe experiments which provide conclusive proof in favor of particular expressions for relevant portions of the molecules of the *neo* bases, and show that the expressions derived are those to be expected if strychnine be formulated as (I).

The first of the *neo* bases, methoxymethyldihydro*neo*strychnidine, $C_{21}H_{24}ON(NCH_3)(OCH_3)$, was formed when strychnidine methosulfate was treated with methyl alcoholic potassium hydrox-

(1) This structure was proposed and discussed at length in the lectures by the senior author on the Chemistry of Natural Products during the summer term of 1944. It was discussed with Sir Robert Robinson in August of 1945, and since that time, investigations have been proceeding independently in the Oxford and Harvard Laboratories with the objective of final clarification of the structural situation. Professor Robinson has very generously kept us informed from time to time of the more important results of his program through private communications, and we in turn have let him know of ours.

(2) Holmes and Robinson, *J. Chem. Soc.*, 603 (1939).

(3) Woodward, *Nature*, in press.

(4) Kotake, *Proc. Imp. Acad. Tokyo*, **12**, 99 (1936); Clemo, *J. Chem. Soc.*, 1695 (1936).

(5) Perkin and Robinson, *J. Chem. Soc.*, 305 (1910); Clemo, Perkin and Robinson, *ibid.*, 1589 (1927).

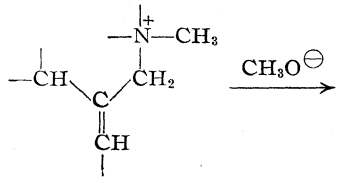
(6) Clemo and Metcalfe, *ibid.*, 1519 (1937); Oechsner de Coninck, *Ann. chim.*, [5] **27**, 507 (1882); *Bull. soc. chim.*, [2] **42**, 102 (1884).

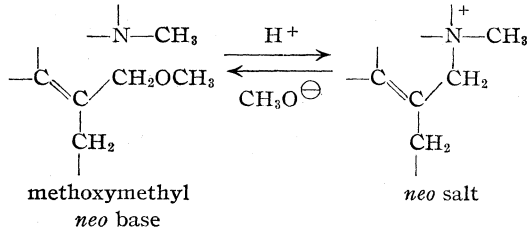
(7) Woodward, Brehm and Nelson, THIS JOURNAL, **69**, 2250 1947).

(8) A review of the enormous literature on the subject is outside the scope of this paper. An outline of the main facts is given in Henry's "Plant Alkaloids" (Blakiston's Son, 1939) and an excellent and very complete review by Professor H. L. Holmes will appear in the first volume of the forthcoming series of monographs on alkaloids, to be published by the Academic Press under the general editorship of Dr. R. H. F. Manske.

ide.[9] On boiling with dilute acids, the methoxy group of the new base was lost, and a new quaternary salt, isomeric with the original strychnidinium derivative, was formed.[9,10] The chloride of the new series, methyl *neo*strychnidinium chloride, lost methyl chloride on pyrolysis with the formation of *neo*strychnidine, an isomer of strychnidine.[9,10] Further, the methyl *neo*strychnidinium salts, on treatment with methyl alcoholic potassium hydroxide, were reconverted to the same methoxymethyldihydro*neo*strychnidine from which they were formed.[9,10] Subsequently, exactly parallel transformations were effected in the strychnine series,[11] and the important observations were made that *neo*strychnidine[10] and *neo*strychnine[11] could be reduced catalytically to dihydro derivatives identical with those obtained by the hydrogenation, respectively, of strychnidine and strychnine.[12]

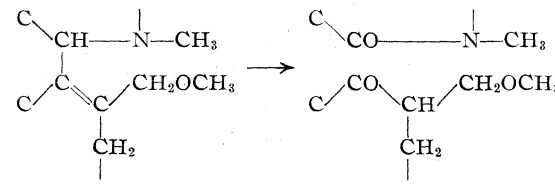
From these observations, it was clear that in the formation of the *neo* bases, no rearrangement of the carbon skeleton had occurred, and that the double bond of the normal series had migrated to a new position. Further, the cleavage of the quaternary salts of both series, as well as the ready reconstitution of the quaternary salts of the *neo* series, was explicable if the double bond present were assumed to be in the β,γ (*i. e.*, allylic) position with respect to the quaternary nitrogen atom, and the fundamental changes outlined above were formulated in this sense





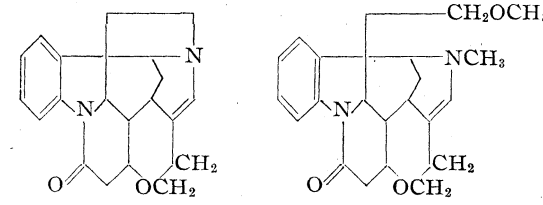
Support for this view was found in the relatively sluggish cyclization (to quaternary salts) of those methoxymethyl derivatives in which the double bond had been saturated.[13]

The validity of this scheme was challenged by facts which emerged from the further study of methoxymethyldihydro*neo*strychnine. It was found that the latter was converted by perbenzoic acid in excellent yield, with addition of two oxygen atoms, to a *neutral* oxidation product (named methoxymethyl*chano*dihydrostrychnone) containing a carbonyl group. It was clear that the new substance contained the group $-N^b-CO-$, and its formation was assumed to involve the change[13,14]:



When methoxymethyl*chano*dihydrostrychnone was reduced by the Clemmensen method, the oxygen atom of its carbonyl function appeared to be replaced by two hydrogen atoms, and a new substance, methoxymethyl*chano*dihydrostrychnane, was formed, which on Kuhn–Roth oxidation gave one mole of acetic acid.[15] This fact was explained by assuming that the new methylene group ($C-CH_2-C$) appeared as acetic acid during the Kuhn–Roth procedure; the assumption was hardly tenable in view of the fact that no such change had been observed even in more likely cases.[16] The simple inference from the above facts was that methoxymethyl*chano*dihydrostrychnone contained an aldehyde group (thus, $-\overset{|}{C}-CHO \longrightarrow -\overset{|}{C}-CH_3$), and although negative evidence was brought forward against that view,[13] no really convincing formulation of the substance was advanced; the recent demonstration[17] that the double bond in the *neo* series is adjacent to N^b served only further to compound the difficulty of the matter.

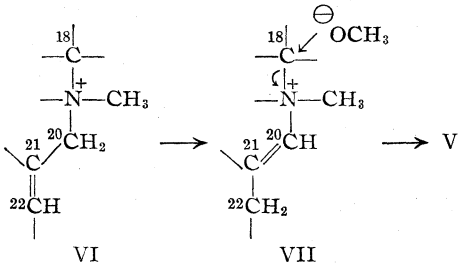
We turn now to a consideration of the structure of the *neo* bases in the light of the new strychnine



(9) Clemo, Perkin and Robinson, *J. Chem. Soc.*, 1589 (1927).
(10) Achmatowicz, Perkin and Robinson, *ibid.*, 486(1932).
(11) Achmatowicz, Clemo and Perkin, *ibid.*, 767 (1932).
(12) *Neo* bases have been prepared by other methods, of less structural interest, but of more preparative value. Kotake and Yokohama (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, **31**, 321 (1937)) isomerized strychnine to *neo*strychnine by heating with selenium. Recently Robinson and Chakravarti (*J. Chem. Soc.*, 78 (1947)) have confirmed Kotake's observation, and have shown that the strychnos alkaloids are smoothly converted to the corresponding *neo* isomers when heated in xylene in the presence of Raney nickel. This elegant method makes the *neo* bases readily accessible in quantity for the first time.
(13) Reynolds and Robinson, *J. Chem. Soc.*, 936 (1935).
(14) Briggs and Robinson, *ibid.*, 590 (1934).
(15) Reynolds and Robinson, *ibid.*, 592 (1934).
(16) *Cf.* Kuhn and L'Orsa, *Z. angew. Chem.*, **44**, 852 (1931), who show that even the methylene groups of malonic acid and 5,5-dimethyldihydroresorcinol (dimedon), do not appear as acetic acid in the C-methyl determination.
(17) Briggs, Openshaw and Robinson, *J. Chem. Soc.*, 903 (1946).

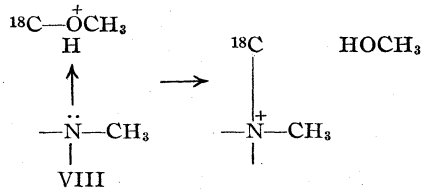
formula (I). It may be deduced at once that only one likely position is available for the double bond in the *neo* series if (I) be accepted.[18] Steric considerations prohibit the placement of unsaturation at Δ^{14-21}, Δ^{13-14}, Δ^{14-15}, or Δ^{15-16}, and no reasonable path is available for the migration of a double bond from Δ^{21-22} to Δ^{8-13} or Δ^{17-18}. Only Δ^{20-21} remains, and on the basis of (I), *neo*strychnine must be represented as (IV).

If *neo*strychnine be (IV), the views outlined above in connection with the formation of the methoxymethyl derivatives must be abandoned. An alternate scheme is available in the following terms: (i) the double bond of the methyl strychninium salt (VI) migrates into juxtaposition with the quaternary nitrogen atom[19] (*cf.* VII); (ii)



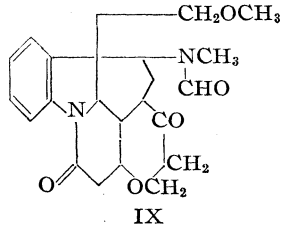
VI VII

the double bond in the new position facilitates[20] a direct bimolecular cleavage reaction (S_N2) involving attack by methoxide ion at C.18 (VII, arrows) to give (V).[21] The greater ease of reconstitution of quaternary salts from the unsaturated, as compared with the saturated methoxymethyl derivatives must be attributed to the lowering of the basicity of N^b in the former by the adjacent double bond. Thus the attack of N^b on C.18, with release of methyl alcohol (VIII, arrows) will be more or less facile as a smaller or greater proportion of the molecules contain a proton attached to N^b.



VIII

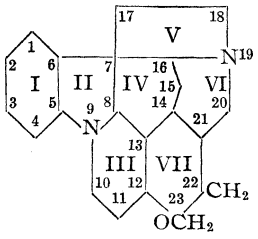
Ample analogy is now available[22] for the cleavage $-\overset{|}{N}-\overset{|}{C}=\overset{|}{C}- \longrightarrow -\overset{|}{N}-\overset{|}{C}O\ O\overset{|}{C}-$ by perbenzoic acid, and if (V) be methoxymethyldihydro*neo*strychnine, the expression (IX) must be accepted for methoxymethyl*chano*dihydrostrychnone. The facts hitherto available could only with the greatest difficulty be so construed as to commend this



IX

view. On the one hand it was necessary to assume that a formamide system survived boiling for twenty-eight hours with concentrated hydrochloric acid[15] (in the Clemmensen reduction of the strychnone), as well as heating for four hours with concentrated methyl alcoholic barium hydroxide[13]

(18) The following numbering of the strychnine skeleton is used in the sequel, and we should like to propose that it be adopted generally. Following general practice contiguous rings are numbered consecutively; the particular choice adopted has the distinct menmonic advantage that the designations of rings, V, VI and VII are identical with the respective ring sizes. The atoms have then been numbered consecutively, beginning with ring I, *etc.*



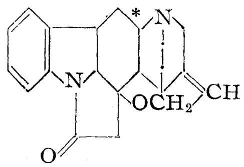
(19) The change is formally analogous in some respects to the well-known shift $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-\overset{|}{C}O \longrightarrow -\overset{|}{C}H-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}O,$ since the carbon atom of —CO bears a considerable formal charge. On the other hand, the first order conjugation effects present in the carbonyl system cannot be operative in the case described above, since $\equiv N^+$ is saturated. However, it may not be doubted that the positive charge in $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-\overset{+}{N}\equiv$ will facilitate the first step in the process, *viz.*, proton release from C*; the operation of the same effect is seen in the very ready elimination of hydrogen bromide from $BrCH_2CH_2N^+(CH_3)_3$ (Renshaw, THIS JOURNAL, **34**, 1618 (1912); Schmidt and Bode, *Ann.*, **267**, 311 (1892)).

(20) No relevant information is available for analogous simple unsaturated systems. However, it is abundantly clear that in the case in which a phenyl group replaces the C.20–C.21 double bond of (VII), cleavage analogous to that outlined above takes place with particular ease (von Braun and Seemann, *Ber.*, **55**, 3820 (1922); *cf. Ann. Rep. Chem. Soc.*, 103 (1920) for collected references to v. Braun's results). Cases strikingly analogous to that discussed above were studied by Vorländer and Spreckels (*Ber.*, **52**, 309 (1919)), who showed that the change $C_6H_5N^+R_3 + {}^-OEt \longrightarrow C_6H_5NR_2 + ROEt$ was readily brought about when the quaternary salt was heated with sodium ethoxide in ethanol for a few hours. Further, the ease of these reactions has a sound basis in theory, in that the breaking of the C—N bond will be facilitated as the environment of the nitrogen atom is such that the latter more readily accepts the released electron pair. The low basicity of nitrogen atoms attached to double bonds, and the ultraviolet absorption characteristics of such systems (*cf.* Bowden, Braude, Jones and Weedon, *J. Chem. Soc.*, 50 (1946)) are attributable to the same effect, which has its origin in the resonance $-\overset{|}{C}=\overset{|}{C}-\overset{|}{N}- \longleftrightarrow -\overset{|}{C}-\overset{|}{C}=\overset{|}{N}-$

(21) There is no direct evidence bearing on the point of attachment of the methoxyl group. It seems probable that a bimolecular substitution reaction of the type outlined above would take place most readily at C.18, which is primary, and possibly otherwise less hindered, than the alternative position (C.16). In any event, the point has no special relevance in connection with the demonstration which follows.

(22) Witkop, private communication. Dr. Witkop has made available to us a proof copy of a communication by himself and Fiedler which was submitted in 1946 for publication in the *Annalen;* we have been unable to determine whether it has appeared. In it the very smooth oxidation of a series of indole derivatives to *o*-acylaminophenyl ketones by perbenzoic acid is described.

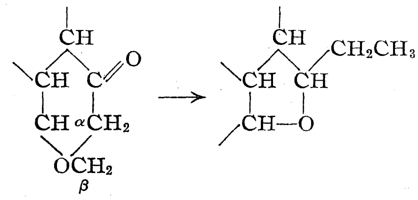
(in the transformation of methoxymethyl*chano*-dihydrostrychnane to the corresponding strychnanic acid, *by cleavage of the* N^a *lactam link*). On the other hand, the presence of the group $-\overset{|}{\underset{|}{C}}-CH_3$ in the Clemmensen reduction product of the strychnone suggested that the carbonyl group of the latter was present as $-\overset{|}{\underset{|}{C}}-CHO$. The obvious inference from these facts was that the *neo* bases contained $-\overset{|b}{N}-\underset{\underset{C}{|}}{C}=CH-C$ and indeed, these, taken with other considerations, led recently to the proposal of a strychnine formula (X) which permitted this feature[23] (double bond at * in the *neo* series).



X

We have now subjected these substances to further study. Methoxymethyl*chano*dihydrostrychnone was converted by ethyl mercaptan in the presence of hydrochloric and acetic acids to the corresponding mercaptal $\left(-\overset{|}{C}=O \longrightarrow -\overset{|}{C}(SEt)_2\right)$. Removal of the mercapto groups by treatment in alcohol with Raney nickel $\left(-\overset{|}{C}(SEt)_2 \longrightarrow -\overset{|}{C}H_2\right)$ gave a substance, $C_{23}H_{30}O_4N_2$, m. p. 136–139°, different from, but isomeric with methoxymethyl*chano*dihydrostrychnane (m. p. 163°). *The new compound contained no* $-\overset{|}{\underset{|}{C}}-CH_3$ *group.*

It is now clear that methoxymethyl*chano*dihydrostrychnone contains the group $C-\overset{C}{\overset{|}{C}}=O$, and that the formation of methoxymethyl*chano*dihydrostrychnane[24] must be accompanied by rear-



XI XII

rangement. It is not difficult to envisage the nature of this change. Thus, in the part structure (XI), present in the strychnone, the opportunity exists for: (i) reductive cleavage of the ether linkage in the reactive β-position to a carbonyl group (this change may well proceed through β-elimination, followed by reduction of the resultant α,β-unsaturated carbonyl system); (ii) reduction of $-\overset{|}{C}=O$ to $-\overset{|}{C}HOH$; (iii) ether formation involving the two hydroxyl groups formed in (i) and (ii). The strychnane, then, contains the part structure (XII), and the presence of $-\overset{|}{\underset{|}{C}}-CH_3$ no longer constitutes a problem.

We turned next to an examination of the nature of the amide function in methoxymethyl*chano*dihydrostrychnone. Since this compound undergoes deep-seated changes in the presence of acid or base, it seemed unlikely that the isolation or characterization of simple hydrolysis products would be possible. (We attribute these changes to the presence of the labile system $-COCH_2CH_2O-$, which can readily suffer elimination, with the formation of the very reactive grouping $-COCH=CH_2$). Consequently, we studied the behavior with hydrolytic reagents of (*a*) methoxymethyl*chano*dihydrostrychnane, (*b*) desoxomethoxymethyl*chano*dihydrostrychnone, m. p. 136–139°, from the Raney nickel desulfurization (see above), and (*c*) a dihydroderivative $\left(-\overset{|}{C}=O \longrightarrow -\overset{|}{C}HOH\right)$ m. p. 225–226°, obtained by the catalytic hydrogenation of the strychnone. As might have been expected from earlier work with the strychnane, none of these substances liberated formic acid even on prolonged treatment with concentrated bases. On the other hand, *each of them readily gave exactly one mole of formic acid on hydrolysis with 2N sulfuric acid.* After hydrolysis of methoxymethyl*chano*dihydrostrychnane ($C_{23}H_{30}$-

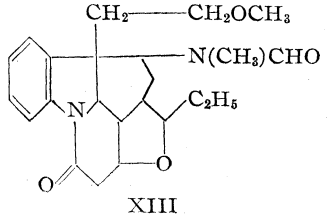
(23) Robinson, *Nature*, **159**, 263 (1947). The supporting evidence involved the formation from the *neo* bases of oxidation products containing one additional oxygen atom by the action of bromine and water. The products are basic, and contain a carbonyl group; the change was assumed to be $-\overset{|}{N}-\underset{|}{C}=CH-C \longrightarrow -\overset{|}{N}-\underset{|}{C}H-CO-C$. In a still more recent note, Robinson and Chakravarti (*Nature*, **160**, 18 (1947)) indicate that the substances are aldehydes, and that a rearrangement accompanies their formation. The opinion is further expressed that while the new evidence does not exclude the structure (X) (presumably in view of the possibility $-\overset{|}{N}-\underset{\underset{C}{|}}{C}=CH-C \longrightarrow -\overset{|}{N}-\overset{C}{\overset{|}{\underset{\underset{C}{|}}{C}}}-CHO$), it removes the necessity for its proposal in so far as the oxidation reaction is concerned (since $-\overset{|}{N}-CH=\overset{|}{C}-$ is transformable with rearrangement to $-\overset{|}{N}\ \ OHC-\overset{|}{C}-$). In these circumstances, Robinson and Chakravarti, as "the best hypothesis to guide future work," revert to the expression (I), which for some years has been under consideration independently in the Harvard and in the Oxford laboratories.

(24) Actually the new substance, m. p. 136–139°, now properly deserves this name, but the adoption of the change would create unnecessary confusion. Consequently, we propose the designation desoxomethoxymethyl*chano*dihydrostrychnone for the new isomer.

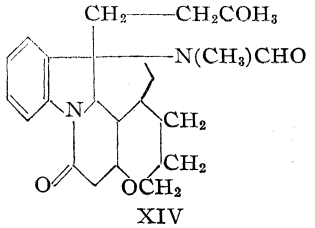
O_4N_2), the corresponding base, $C_{22}H_{30}O_3N$, m. p. 86–86.5° was isolated. In view of the special circumstances *vis-a-vis* the stability of $-\overset{|b}{N}-CO$ in these substances, it was necessary to eliminate the possibility that the formic acid owed its origin to an acid-catalyzed rearrangement (*e. g.*, of an α-hydroxy (*or* alkoxy) amide). This was done by formylating the above base, m. p. 85–86°, through treatment with anhydrous formic acid and acetic anhydride. The formylation product was identical in all respects with methoxymethyl*chano*dihydrostrychnane.

These facts are explicable only if in all of these compounds the presence of the group $-\overset{|b}{N}-CHO$ be accepted. The marked resistance to alkaline cleavage must be attributed to steric hindrance of the approach of hydroxide ion (models indicate the plausibility of this view), while the stability under the strongly acid conditions of the Clemmensen reduction is probably a consequence of the relatively low activity of water in highly acid and concentrated salt (in this case zinc chloride) solutions.[25]

Taken all together our new observations provide conclusive proof of the presence of $-\overset{|b}{N}-CH=\overset{C}{\overset{|}{C}}-C$ in the *neo* bases; we may now assign with confidence the structures (IV), (V), (IX), (XIII) and (XIV),[21] respectively, to *neo*strychnine, methoxymethyldihydro*neo*strychnine, methoxymethyl*chano*dihydrostrychnone, methoxymethyl*chano*dihydrostrychnane and desoxomethoxymethyl*chano*dihydrostrychnone. Since these are precisely the expressions required by the structure (I) for



XIII

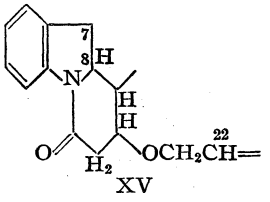


XIV

strychnine, it is clear that the last major barrier in the way of the acceptance of (I) has collapsed.

(25) In any event, the slowing down of amide hydrolysis as the acid concentration is increased beyond a certain point appears to be a general phenomenon. *Cf.* Hammett, "Physical Organic Chemistry," p. 365 (McGraw-Hill Book Co., Inc., 1940). Further it should be mentioned that the formamide link of the strychnane is not completely stable under the above conditions, since we have been able to isolate some of the base $C_{22}H_{30}O_3N_2$ from Clemmensen reduction reaction-mixtures.

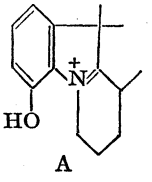
It is therefore now pertinent to examine the general situation in order to determine whether the formula (I) represents a necessary as well as a sufficient solution to the structural problem. We take as the basis for the structural discussion the expression (XV), which follows from (i) the presence in strychnine of an *o*-substituted N-acylaniline system[8]; (ii) Robinson's deduction, from the Leuchs degradations, of the nature of ring III and of the presence of the chain $-OCH_2CH=$ at C.12[26]; (iii) the presence of a dihydroindole sys-



XV

tem, suggested by a number of independent lines of evidence,[8] and definitely confirmed by our recent elucidation of the changes accompanying the formation of strychnone.[7] We now examine evidence which necessitates the elaboration of three independent chains of atoms, each of which originates at N^b and terminates at some atom of (XV): (*a*) the nature of the changes involved in the formation of strychnone requires[7] that in strychnine the β position of the dihydroindole ring be linked by a methine bridge to N^b; (*b*) the formation of tryptamine by the alkaline degradation of strychnine necessitates a chain of two carbon atoms between C.7 and N^b. *We make the reasonable assumption that this chain bears four hydrogen atoms*[27]; (*c*) the results of the present

(26) Robinson, *Proc. Roy. Soc.* (*London*), **130**, 431 (1931). The original demonstration did not include the placing of a hydrogen atom at C.8 but, subsequently, Briggs, Openshaw and Robinson (ref. 17, footnote, p. 903) deduced the presence of this feature through the formulation of one of the colorless benzal derivatives of the (*iso*) strychnine series as an (11-) benzyl α-pyridone. Further, the formation of strychnone (ref. 7) requires a hydrogen atom either at C.7 or C.8, and the lack of reactivity toward bromine of diketonucidine (ref. 2) provides evidence against C.7. We reach a similar conclusion through a consideration of certain changes in the vomicine series (part formulation of the salts of the catalytic hydrogenation products from desoxyvomicidine, isovomicidine and dihydrodesoxyvomicidine (Wieland and Huisgen, *Ann.*, **556**, 161, 166 (1944)) as (A)–note



A

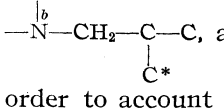
that the typical color reactions of the *o*-aminophenol system are not given by these bases with oxidizing agents in weakly acid solution!).

17 18

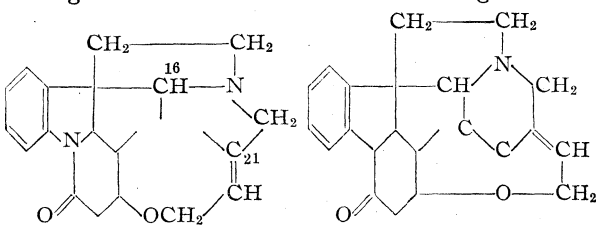
(27) The presence of such a chain ($-CH_2CH_2-$) has been accepted generally (*cf.* ref. 8). No conclusive direct proof of that feature is available but it may be considered unlikely that tryptamine (ref. 4) would be a product of degradative processes involving the scission of carbon-carbon bonds to these positions. The presence of $=CH_2$ in dimethyl*dess*trychnidine D (Achmatowicz and Dybowski, *J. Chem. Soc.*, 1483 (1938)) has also been put forward

18 |b

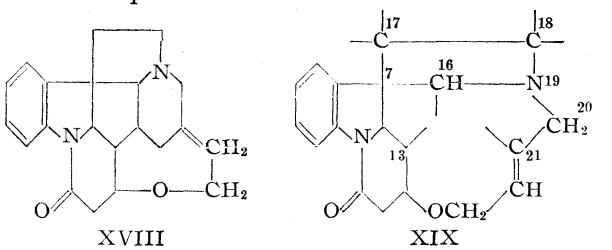
as evidence in support of the presence of $-CH_2-N-$ in strychnine.

paper demonstrate that strychnine contains  , and it is further clear that in order to account for the formation of strychninonic acid, one of the starred carbon atoms must be identical with C.22 (see XV).[28]

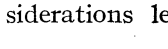
These considerations extend the development of the partial structure of strychnine to (XVI). Now Prelog's recent demonstration[29] that ring VI is six-membered, from which a certain amount of ambiguity is removed by our new results,[30] necessitates the incorporation of the two carbon atoms lacking from XVI in a chain bridging C.16 and C.21. The resulting expression (XVII) can be elaborated in only two ways, *viz.*, to (I) or to XVIII, and the latter is excluded in view of the formation from N-methyl*chano*pseudostrychnine of a dibenzal derivative[31] and by the failure of strychninonic acid to be attacked by bromine at the position α to the carbonyl group.[32] It is now clear that (I) provides a unique solution to the structural problem.

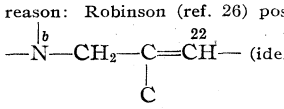


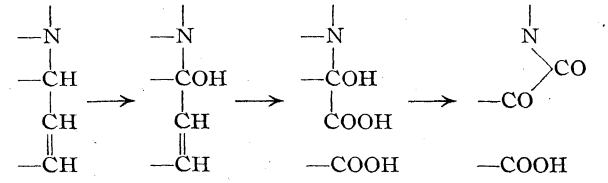
XVI XVII



XVIII XIX

On the other hand, it is necessary to examine the consequences of rejecting the one assumption[27] in the above demonstration for which unambiguous experimental evidence is not available. In that event the structural argument is more complicated, but in our opinion is equally conclusive. Thus, if the four hydrogen atoms at C.17 and C.18 be omitted, it is first possible to show that  cannot be co-extensive with either of the chains of (*a*) or (*c*), above, since: (i) if C.16 were identical with either C.17 or C.18, pseudostrychnine must be a (potential) cyclopropanone or α-iminoketone, and these possibilities may safely be discarded; (ii) C.20 cannot be identical with C.18, since the latter must be contained in a five-membered ring, and it has been shown earlier that C.20 cannot be so situated.[29,30] These considerations lead to the part structure (XIX). Now the chain  must be part of a six-(or seven)-membered ring[29,30]; this ring cannot be constructed from the chain 21-20-19-16-7-17, nor by the interpolation of a bridge containing one or both of the carbon atoms lacking from (XIX) between C.21 and C.17, since in that event the formation and properties of strychninonic acid (and to a greater extent, the formation of the lactam of cunine carboxylic acid[33]) would be inexplicable.[34] Precisely the same circumstances bar construction of the necessary ring by the union of C.13 and C.21. Finally, the ring cannot be constructed by bridging C.21 and C.18 by a chain of two carbon atoms, since in that event, N-methyl*chano*pseudostrychnine could not form a dibenzal derivative,[31] and the stable (and consequently five- or six-membered) N^b-lactam ring of strychnone[7] could not be accounted for. The only remaining possibility, *viz.*, the interpolation of two carbon atoms, to one of which two hydrogen atoms must be attached,[31] between C.16 and

(28) We have presented the situation in the above terms for this reason: Robinson (ref. 26) postulated the presence of the system  (identical with that derived above) on the basis of interpretations of (*a*) the methoxylating cleavage of strychninium salts, and (*b*) the formation of strychninonic acid. It will be clear from the earlier sections of this paper that the considerations involved in (*a*) must now be rejected, but the alternative now adopted yields the same part structure. Beyond that, in our opinion the interpretation of the formation of strychninonic acid has not hitherto been free of ambiguity. Thus, the scheme

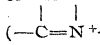


is *a priori* in no wise less satisfactory than that originally proposed by Robinson (the concomitant formation of dihydrostrychninonic acid can also be encompassed). The results of the present work, however, permit the unequivocal rejection of the alternative scheme.

(29) Prelog and Szpilfogel, *Helv. Chim. Acta*, **28**, 1669 (1946).

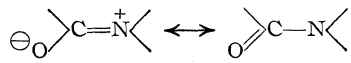
(30) Thus, the work of the Swiss workers indicated that *strychninonic acid* contains a six (or seven) membered ring. The considerations advanced in ref. 28 indicate that hitherto the possibility was definitely present that a five-membered ring in strychnine itself might be transformed into a six-membered ring in strychninonic acid.

(31) Blount and Robinson, *J. Chem. Soc.*, 2305 (1932).

(32) Leuchs, *Ber.*, **72**, 1588 (1939); *cf.* also Robinson, ref. 2, and Leuchs and Grunow, *Ber.*, **72**, 679 (1939). The phenomenon is explicable on the basis of (I) through the steric blocking of enolization, which necessitates a double bond at C.14–C.21. It is worthy of note that pseudostrychnine does not form anhydro salts () for a similar reason (Δ^{16-19} impossible).

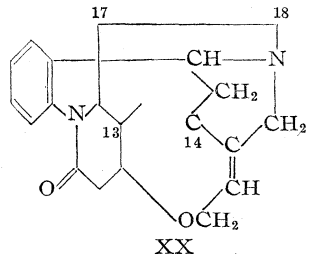
(33) Holmes, Openshaw and Robinson, *J. Chem. Soc.*, 908 (1946).

(34) Since the amide link is stabilized by the resonance



amides do not form at the bridgeheads of bicyclic systems which prohibit double bonds to the bridgehead atoms; further, were such an amide obtainable by indirect means, it would be expected to open very readily and *irreversibly* to the corresponding amino acid. The situation is discussed in detail by one of us (R. B. W.) in Chapter XV of the forthcoming monograph on the chemistry of penicillin (Princeton University Press).

C.21, leads to (XX). Now bonds between C.14 and C.17 or C.18 are excluded by considerations already advanced.[34] Only three possibilities remain; of these, the first is I, and those obtained by linking C.13 to C.17 or to C.18 are excluded by the fact that strychninonic acid is not attacked by bromine at the position α to the carbonyl group,[32] and by the failure of pseudostrychnine to form anhydro salts.[35]



XX

We conclude that the structure (I) for strychnine is established.

Experimental

Methylstrychnine.—The method[36] employing strychnine and dimethyl sulfate in the absence of a solvent was found to be superior to the alternate method involving preliminary isolation of pure crystalline strychnine methosulfate.[37]

Methoxymethyldihydro*neo*strychnine (V).—Since, in our hands, both the yield and purity of product were similar whether methylstrychnine was treated with methanolic sodium methoxide or with sodium amalgam in methanol,[11] we favor the former method because of its greater simplicity.

In an early preparative attempt, before any material with the reported melting point of 143° had been obtained, there was isolated a white crystalline substance of m. p. 115–117°. Subsequent to the successful preparation of material with the higher melting point, this material was recrystallized and gave material, m. p. 139–141°, identical with the higher melting sample obtained directly from the reaction-mixture. Hence this is apparently a case of polymorphism.

Methoxymethyl*chano*dihydrostrychnone (IX).—This compound was prepared[14] in almost quantitative yield by treating a boiling ethereal solution of methoxymethyldihydro*neo*strychnine (V) with perbenzoic acid in ether. Ten recrystallizations from ethyl acetate–ether and acetone–ether were required to obtain a sample melting at 189–191°. This is in accord with the observations of the original workers. However, material melting at about 160° (after two recrystallizations from benzene–ligroin) was found to be suitable for use in subsequent reactions.

When (IX) was heated with concentrated sulfuric acid, carbon monoxide was detected in the evolved gases by the production of black metallic palladium from a neutral palladous chloride solution. Under the same conditions the gases from strychnine itself caused no reduction. *Anal.* Calcd. for $C_{23}H_{28}O_5N_2$: mol. wt., 412.5. Found (method of isothermal distillation):[38] 433.

Methoxymethyl*chano*dihydrostrychnone Semicarbazone.—Methoxymethyl*chano*dihydrostrychnone (IX) (2.0 g.), dissolved in the minimum amount of hot water (steam-bath), was treated with an aqueous solution of 2.0 g. of semicarbazide hydrochloride followed by 3.0 g. of anhydrous sodium acetate. After heating for one hour the solution was concentrated *in vacuo;* a yellowish gum precipitated. After a week crystals appeared, 0.65 g., m. p. 238–242°. After recrystallization from methanol the white needles melted at 242–244° (dec.). *Anal.* Calcd. for $C_{24}H_{31}O_5N_5$: C, 61.30; H, 6.60; N, 14.90. Found: C, 61.33; H, 6.70; N, 14.40.

Methoxymethyl*chano*dihydrostrychnol.—Methoxymethyl*chano*dihydrostrychnone (IX) (0.995 g.) was dissolved in 75 cc. of ethanol and was stirred with 0.04 g. of pre-reduced Adams catalyst in an atmosphere of hydrogen. In twenty-four hours only 13.5 cc. of hydrogen was absorbed. After addition of 0.25 g. of pre-reduced catalyst 42.7 cc. of hydrogen was consumed in eleven hours, followed by 6.2 cc. in four hours (theoretical consumption, 54 cc.). The solution was filtered through charcoal and concentrated *in vacuo*. When the concentrated solution was diluted with ether, crystallization occurred; 0.67 g. of white crystals, m. p. 223–226°. After two recrystallizations from ethanol–ether, 0.41 g. of short white needles, m. p. 225.5–226.5°, were obtained. *Anal.* Calcd. for $C_{23}H_{30}O_5N_2$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.37; H, 7.30; N, 6.73.

When a repetition of this preparation was attempted on a larger scale using a more concentrated ethanolic solution, a larger excess of hydrogen was consumed and only an amorphous product was obtained. This would not crystallize under the conditions described above even with seeding. Similarly, none of the eluted fractions from a chromatographic adsorption of this material could be made to crystallize.

Methoxymethyl*chano*dihydrostrychnone Diethylmercaptal.—Methoxymethyl*chano*dihydrostrychnone (IX) (4.12 g.), dissolved in 30 cc. of glacial acetic acid and 0.3 cc. of concentrated hydrochloric acid and cooled in ice, was treated with 4.4 g. of ethyl mercaptan. After standing in the refrigerator for three days the volatile materials were removed *in vacuo*. The yellowish oily residue crystallized to a pasty mass on standing. After crystallization from ethanol there was 2.6 g., m. p. 177–181°. After recrystallizations from benzene–ligroin, carbon tetrachloride and ethanol the white prisms melted at 183–184.5°. *Anal.* Calcd. for $C_{27}H_{38}O_4N_2S_2$: C, 62.51; H, 7.38; N, 5.40; S, 12.36. Found: C, 61.83; H, 7.64; N, 5.21; S, 12.35.

Desoxomethoxymethyl*chano*dihydrostrychnone (XIV).—About 5 g. of Raney nickel, suspended in 50 cc. of ethanol, was added to a boiling solution of 0.25 g. of methoxymethyl*chano*dihydrostrychnone diethylmercaptal in 50 cc. of ethanol. The reaction-mixture was boiled for thirty minutes and the nickel was filtered off and washed with fresh ethanol. When the solvent had been removed in an air stream on the steam-bath the residue weighed 0.13 g. This was dissolved in benzene and the solution diluted with ligroin. On standing, rosettes of crystals appeared, 100 mg., m. p. 140–143°. The melting point of a mixture with methoxymethyl*chano*dihydrostrychnane (XIII) was 129–131°. After recrystallizations from benzene–ligroin the white prisms melted at 136–139°. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59; N, 7.03; C—CH_3, 0.0. Found: C, 69.73; H, 7.73; N, 6.73; C—CH_3, 0.12.

Methoxymethyl*chano*dihydrostrychnane (XIII).—This material was prepared as reported[15] by the Clemmensen reduction of methoxymethyl*chano*dihydrostrychnone (IX). By strict adherence to the published procedure the reported yield was never obtained although the preparation was repeated many times (from 10 g. of IX yields were 0.2–0.9 g. instead of 3.5 g.). Better yields were obtained when the period of heating was shortened to five hours or when mechanical stirring of the reaction mixture was employed (1.0 and 1.9 g., respectively). However, in these cases, the reported difficulty in purification was observed. This had not been previously encountered in the reactions which gave lower yields. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C—CH_3, 6.8. Found: C—CH_3, 6.1, 6.0.

The acidic mother liquor from the Clemmensen reduction of 6.0 g. of methoxymethyl*chano*dihydrostrychnone

(35) Leuchs, Grunow and Tessmar, *Ber.*, **70**, 1701 (1937). *Cf.* also ref. 32.

(36) Clemo, Perkin and Robinson, *J. Chem. Soc.*, 1624 (1927).

(37) Clemo, Perkin and Robinson, *ibid.*, 1599 (1927).

(38) Clark, "Semimicro Quantitative Organic Analysis," Academic Press, New York, N. Y., 1943, p. 78.

Compound	Amount	Volume (in cc.) of 0.0137 *N* alkali consumed: 1st fraction	2nd fraction	Total	No. of N—CHO groups
N-Formylpenicillamine	0.0737 mmole. (13.0 mg.)	3.56	1.18	4.85 (4 fractions)	0.91
Methoxymethyl*chano*dihydrostrychnane (XIII)	0.0397 mmole. (15.8 mg.)	0.14[a]	..	....	..
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0482 mmole. (19.2 mg.)	0.14	0.14	0.79 (5 fractions)	0.22
Methoxymethyl*chano*dihydrostrychnol	0.0487 mmole. (20.2 mg.)	0.27	0.38	3.05 (9 fractions)	0.86
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0461 mmole. (18.4 mg.)	0.25[b]	0.34	2.39 (7 fractions)	0.71

[a] Here the amount of base consumed by the first fraction was so small that extra acid was added, and the solution refluxed for a while so as to bring about acidic hydrolysis of the amide linkage. [b] In this determination the hydrolysis mixture was refluxed overnight before acidification and distillation.

Compound	Amount	Volume (in cc.) of 0.0137 *N* alkali consumed: 1st fraction	2nd fraction	Total	No. of N—CHO groups
Desoxomethoxymethyl*chano*dihydrostrychnone (XIV)	0.0446 mmole. (18.0 mg.)	1.53	0.65	3.23 (4 fractions)	0.99
Methoxymethyl*chano*dihydrostrychnane (XIII)	0.0479 mmole. (19.1 mg.)	2.07	0.85	3.45 (6 fractions)	0.99
Methoxymethyl*chano*dihydrostrychnol	0.0397 mmole. (15.8 mg.)	1.91	0.86	3.06 (4 fractions)	1.03
Methoxymethyl*chano*dihydrostrychnone (IX)	0.0514 mmole. (21.2 mg.)	1.73	0.95	3.08 (4 fractions)[a]	0.56

[a] In this determination 0.00937 *N* alkali was used.

(IX) (after extraction of the desired product (XIII) with chloroform) was poured into excess concentrated ammonium hydroxide and extracted continuously with 300 cc. of ether. On evaporation the ether solution was found to contain 2.4 g. of orange-brown oil. In benzene solution this was chromatographed over alumina. Fractional elution with various solvents gave: (1) benzene, 0.67 g.; (2) benzene–ether (1:1), 0.37 g.; (3) ether, 0.20 g.; (4) methanol–ether (1:1), 1.09 g.; (5) methanol, 0.06 g.; (6) methanol–water (1:1), 0.10 g. None of these eluates was crystalline. On treating ethanolic solutions of fractions 2, 3 and 4 with an ethanolic solution of picric acid there was obtained a crystalline picrate, 0.55 g.; after recrystallizations from benzene and ethanol, 0.14 g., m. p. 174–177°. This showed no depression on mixed melting point determination with the picrate of desformylmethoxymethyl*chano*dihydrostrychnane (see below).

Desformylmethoxymethyl*chano*dihydrostrychnane.—Methoxymethyl*chano*dihydrostrychnane (XIII) (0.25 g.) was refluxed for five hours with 15 cc. of 3 *N* sulfuric acid. After cooling, the solution was extracted with chloroform to remove any unchanged starting material. The aqueous solution was made basic with 10 cc. of concentrated ammonium hydroxide, causing the precipitation of a whitish oil. This was extracted with chloroform. The second chloroform extract was dried over sodium sulfate and evaporated to dryness. The residual red oil was boiled with ligroin (b. p. 70–90°). After concentrating the ligroin solution crystallization was induced by cooling in Dry Ice and scratching the sides of the vessel with a glass rod. However, this material was still gummy, and it was found better to remove all the ligroin, dissolve the oil in ethanol and treat the solution with picric acid in ethanol. This gave 0.11 g. of picrate, m. p. 172.5–174°. After recrystallizations from benzene and ethanol the bright yellow wooly needles melted at 176–178°. *Anal.* Calcd. for $C_{28}H_{33}O_{10}N_5$: C, 56.09; H, 5.55; N, 11.68. Found: C, 55.91; H, 5.86; N, 11.92.

The picrate was suspended in benzene and extracted with dilute ammonium hydroxide. The benzene solution on evaporation gave 60 mg. of colorless oil. This was crystallized from ligroin, 50 mg., m. p. 84.8–86°. After recrystallization from ligroin the white needles melted at 86.0–86.6°. *Anal.* Calcd. for $C_{22}H_{30}O_3N_2$: C, 71.32; H, 8.16; N, 7.56. Found: C, 70.80; H, 8.08; N, 7.66.

When 40 mg. of this base was warmed with 2 cc. of 2 *N* perchloric acid, a crystalline perchlorate precipitated on cooling, 40 mg., m. p. 195–201°. After recrystallization from absolute ethanol, the white needles melted at 244.5–245.5°. *Anal.* Calcd. for $C_{22}H_{31}O_7N_2Cl$: C, 56.10; H, 6.64; N, 5.95; Cl, 7.53. Found: C, 56.58; H, 6.86; N, 6.05; Cl, 7.29.

Formylation of Desformylmethoxymethyl*chano*dihydrostrychnane.—Desformylmethoxymethyl*chano*dihydrostrychnane (40 mg., m. p. 83–84°) was dissolved in 10 cc. of anhydrous formic acid[39] and 4 cc. of acetic anhydride. After refluxing for fourteen hours the volatile materials were removed *in vacuo*, and the residue was dissolved in benzene. The benzene solution was twice extracted with dilute hydrochloric acid and then with water. After drying over sodium sulfate the benzene was evaporated leaving a tan-colored oily residue, 10 mg. This was dissolved in a little benzene, treated with charcoal, filtered and diluted with petroleum ether (b. p. 30–60°). On standing the cloudy solution deposited rosette-shaped clumps of crystals, m. p. 160–161.5° after washing with fresh petroleum ether. A sample, mixed with some methoxymethyl*chano*dihydrostrychnane of m. p. 163–164.5°, had a melting point of 161–162°.

An earlier attempt to effect this reaction omitting the use of acetic anhydride resulted in the isolation only of unchanged starting material.

N-Formyl Determinations.—About 20 mg. of the compound to be analyzed was refluxed for one hour with 2 cc. of reagent grade methanol, 1 cc. of 5 *N* sodium hydroxide and 2 cc. of water. The mixture was diluted with 5 cc. of water and the methanol distilled off. After acidification with 1 cc. of 33% sulfuric acid distillation was continued, and the volatile acid in the distillate determined by titration with standard alkali. The distillate was collected in 20-cc. fractions, water being added to the reaction-mixture at intervals to maintain its volume. These fractions were titrated separately, and the process continued until there was detected only a small constant

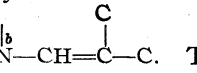
(39) Lorin, *Bull. soc. chim.*, [2] **5**, 10 (1866).

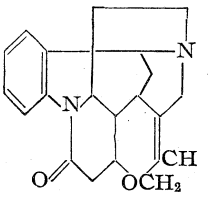
quantity of volatile acid consistent with that obtained from a blank determination.

The small volume of acid in the first fraction, and the constancy of the amount in successive fractions of distillate, led to the conclusion that hydrolysis of the amide linkage was occurring at the same time as the acid produced was being distilled.

When acidic hydrolysis was employed the sample was refluxed for two hours with 2 *N* sulfuric acid before distillation was started. Here again the collection of fractions of distillate was continued until they contained constant amounts of volatile acid of the same size as was found in a blank determination.

Summary

It has been shown that the *neo* bases derived from the strychnos alkaloids contain the part structure  . This demonstration resolves previous difficulties in the way of the acceptance of the structure (I) for strychnine. The general situation has now advanced to the point at which it is conclusive in favor of the expression (I), and the structure of the major strychnos alkaloids is regarded as established.



I

CAMBRIDGE, MASS. RECEIVED JANUARY 28, 1948

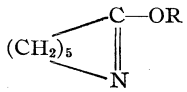
[CONTRIBUTION NO. 232 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & CO. INC.]

Chemical Reactions of Caprolactam

BY RICHARD E. BENSON AND THEODORE L. CAIRNS

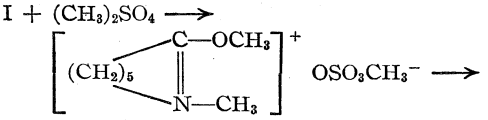
This paper reports the results of a general investigation of the chemistry of caprolactam with emphasis on the O-alkyl imino ethers and their reactions, and on nitrogen-substituted derivatives obtainable by alkylation and acylation. The general reactivity of caprolactam parallels that of related open-chain amides but several unusual transformations were observed and some discrepancies in the literature were clarified.

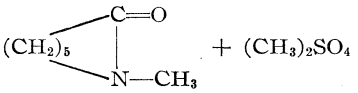
The preparation of O-methylcaprolactim (I) was accomplished by the direct action of dimethyl sulfate on caprolactam in benzene solution.[1a] Dur-



I, R = CH_3
II, R = C_2H_5

ing this preparative work, it was noticed that the proportion of N-methylcaprolactam formed along with the O-methylcaprolactim increased as the scale of the preparation was increased and that, in particular, the amount of N-methyl derivative formed was very much greater when all the dimethyl sulfate was added at once compared with the amount formed when a gradual addition over a long period of time was used. These observations lead to the hypothesis that dimethyl sulfate reacts with I to convert it to N-methylcaprolactam as shown in the equation





That this may actually be the case is demonstrated by the fact that treatment of O-methylcaprolactim in benzene solution with 0.1 mole equivalent of dimethyl sulfate brought about its conversion to N-methylcaprolactam in 80% yield. In addition, the action of excess dimethyl sulfate on the lactam gave the N-methyl derivative in 70% yield. The report[2] that the interaction of dimethyl sulfate and caprolactam leads only to the N-methyl derivative may well be accounted for by the assumption that a slight excess of the alkylating agent was used. O-Ethylcaprolactim (II)[1b] was prepared in an analogous fashion. It was found that heating caused rearrangement of both I and II to the corresponding N-alkyl compounds in a manner similar to that reported for open-chain imino ethers.[3]

O-Methylcaprolactim was found to be a water-insoluble basic material that could be converted by the action of boiling water into a mixture of caprolactam and ϵ-aminocaproic acid. Treatment of the imino ether with amines led to the corresponding amidines; these are listed in Table I. In the case of the unsubstituted amidine it was found that the action of ammonia on the imino ether was not a satisfactory preparative method, while the use of ammonium chloride readily yielded the desired amidine as the hydrochloride, in accord with the experience of Knorr[4]

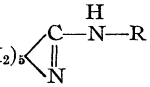
(1) (a) Schlack, U. S. Patent 2,356,622. Other methods for the preparation of this and related imino ethers may be found in (b) French Patent 673,628; Schmidt and Zutavern, German Patents 532,969 and 531,403.

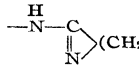
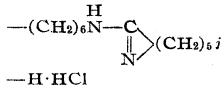
(2) Prochazka, *Chem. Listy*, **37**, 208 (1943); *C. A.*, **40**, 2113 (1946).

(3) Chapman, *J. Chem. Soc.*, 1992 (1925).

(4) Knorr, *Ber.*, **50**, 229 (1917).

TABLE I

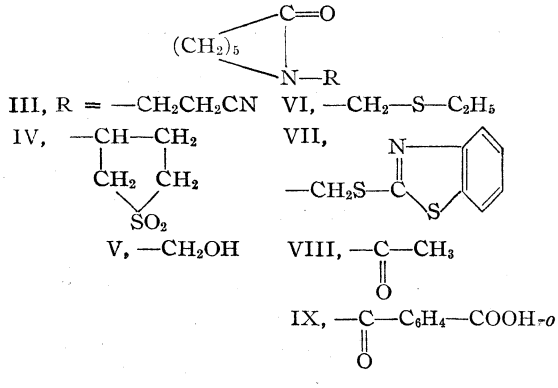
AMIDINES PREPARED BY THE CONDENSATION OF O-METHYLCAPROLACTIM WITH AMINES 

Product, R =	Yield, %	M. p., °C.[a]	Conditions	Formula	Analyses, % Calculated C	H	N	Found C[b]	H[b]	N[b]
—$C_6H_4OCH_3$-*o*	83	86–88[c]	175°, 3 hours	$C_{13}H_{18}N_2O$	71.52	8.31	12.83	71.70	8.66	12.98
—C_6H_4Cl-*o*	45	126–128[d]	190°, 3.5 hours 1 ml. 10% KOH	$C_{12}H_{15}N_2Cl$	64.71 (Cl, 15.92)	6.79	12.58	64.13 (Cl, 16.4)	6.88	12.26
	36	129–130[d]	100–110°, 65 hours	$C_{12}H_{22}N_2$	74.17	11.41	14.42	74.21	11.54	14.62
—$C_{18}H_{37}$[e]	85	73–74[f]	165°, 4 hours	$C_{24}H_{48}N_2$	79.05	13.27	7.68	79.05	12.67	6.72
—NH_2[g]	88	103.5–104.5[h]	Steam-bath 0.5 hour							
	50	125.5–126.5[d]	Steam-bath 0.5 hour							
	78	160–160.5[h]	Methyl alcohol, steam-bath, 17 hr.	$C_{18}H_{34}N_4$	70.54	11.18	18.28	70.37	11.22	18.31
—H·HCl	85	159.5–160.5[k]	NH_4Cl, abs. EtOH, room temp., 3 days	$C_6H_{13}N_2Cl$	48.48 (Cl, 23.85)	8.82	18.85	48.35 (Cl, 23.6)	8.70	18.80

[a] The m. p. values are uncorrected. [b] Average of two determinations. [c] From hexane–ether. [d] From acetone. [e] Oxalate salt, m. p. 105.5–107°, from ethanol. *Anal.* Calcd. for $C_{24}H_{48}N_2 \cdot C_2H_2O_4$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.56; H, 10.83; N, 6.82. [f] From ether. [g] Lit.[5] m. p. 112°. [h] From benzene. [i] Lit.[11] m. p. 126°. [j] Preparation described,[1a] but not isolated or characterized. [k] From absolute ethanol–ether.

with acetamidine. The hydrogenation of O-methylcaprolactim over Raney nickel, ruthenium oxide, or barium–copper chromite catalyst yielded hexamethylenimine, while the use of platinum gave the amidine derived from interaction of the O-ether and hexamethylenimine.

In addition to N-methyl- and N-ethylcaprolactam, it was found that other nitrogen-substituted derivatives could be prepared from caprolactam by the following types of reactions: (1) addition to active unsaturated compounds, (2) reaction with formaldehyde, and (3) reaction with acid anhydrides. Treatment of caprolactam with acrylonitrile gave the corresponding N-β-cyanoethyl derivative (III),[6] and 2,5-dihydrothiophene-1-dioxide gave an analogous product IV.



The N-methylol derivative V was obtained by the action of formaldehyde on caprolactam. Compound V with mercaptans, such as ethyl mercaptan and 2-mercaptobenzothiazole, yielded the corresponding alkylthiomethyl derivatives VI and VII. Refluxing caprolactam with acetic anhydride formed N-acetylcaprolactam (VIII) as reported by Prochazka.[2] The structure of the product obtained by Prochazka[2] from caprolactam and phthalic anhydride is not clear, but it was apparently regarded as the bisamide from two moles of caprolactam and one mole of the anhydride. Such a formulation is at variance with a German report[7] which states that the compound is the monoamide, N-(*o*-carboxybenzoyl)-caprolactam (IX), and that the bisamide could not be formed. In our work only the monoamide IX was obtained.

Hydrolysis of N-methylcaprolactam with concentrated hydrochloric acid has been reported by Ruzicka[8] to give the expected N-methyl-ϵ-aminocaproic acid, m. p. 130–131°, while the use of 10% sulfuric acid has been reported by Lukes and Smolek[9] to form N-methyl-α-aminocaproic acid, m. p. 66°. We have repeated the work of Lukes and Smolek and obtained a compound melting at 66–67° which has been shown conclusively to be the dihydrate of N-methyl-ϵ-aminocaproic acid and not the α-amino derivative. In view of the fact that the analytical data reported by Lukes and Smolek are correct for the free amino acid and not the dihydrate, it is believed that the water of hydration was lost during drying of their sample for analysis and that they failed to observe the change in melting point which accompanies this dehydration.

Experimental

O-Methylcaprolactim (I).—A modification of the procedure given in the literature[1a] gave increased yields on large runs. To a refluxing, stirred solution of 678 g. (6 moles) of caprolactam[10] in 2 l. of benzene was added 569 ml.

(5) Stolle, *Ber.*, **63B**, 1032 (1930).

(6) This compound is mentioned in Office of Publication Board Report 693 but no experimental details are given.

(7) Office of Publication Board Report 621.

(8) Ruzicka, *Helv. Chim. Acta*, **4**, 472 (1921).

(9) Lukes and Smolek, *Coll. Czech Chem. Commun.*, **11**, 506 (1939); *C. A.*, **34**, 7868 (1940).

(10) Obtained from Explosives Department, E. I. du Pont de Nemours & Company, Wilmington, Delaware.

(6 moles) of dimethyl sulfate over a period of two and one-half hours. The mixture was refluxed for sixteen hours longer. The cold mixture was made alkaline with excess 50% potassium carbonate, the organic layer was separated, and the product was distilled. There was obtained 517 g. (68% yield) of I, b. p. 65–67° (24 mm.), $n^{25}D$ 1.4610, d^{25}_4 0.9598; lit.[1a,b] b. p. 50–52° (4 mm.), 160°.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.10, 65.86; H, 10.44, 10.31; N, 10.87, 11.04.

There was also obtained 10 g. (1.3% yield) of N-methylcaprolactam, b. p. 133–135° (26 mm.).

O-Ethylcaprolactim (II).—In a manner similar to the preparation of I, O-ethylcaprolactim was prepared in 52% yield, b. p. 81–82° (26 mm.), $n^{25}D$ 1.4564, d^{25}_4 0.9440; lit.,[1b] b. p. 180°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.71, 67.67; H, 10.63, 10.62; N, 9.40, 9.56.

Hydrolysis of O-Methylcaprolactim.—A mixture of 15 g. of I and 50 ml. of water was refluxed for ten minutes, and the resulting homogeneous solution was then cooled and extracted with ether. Concentration of the ether extract by distillation gave 2 g. (15% yield) of caprolactam m. p. 69–70°, mixed m. p., 69–70°.

Concentration of the water solution gave, after crystallization from ethanol–water, 7 g. (45% yield) of ϵ-aminocaproic acid, m. p. 192–194°, mixed m. p. with authentic ϵ-aminocaproic acid, m. p. 196°. The authentic sample melts at 196.5°.

N-Methylcaprolactam (Method A).—The preparation was similar to that of I except that 0.32 molar excess of the dialkyl sulfate was used per mole of the lactam. There was obtained a 70% yield, b. p. 120° (19 mm.), $n^{25}D$ 1.4818, d^{25}_4 1.0154.

Anal. Calcd. for $C_7H_{13}NO$: N, 11.01. Found: N, 10.92, 11.02.

Ruzicka[8] has prepared this compound, b. p. 120° (15 mm.), by the reaction of N-sodiocaprolactam and dimethyl sulfate, while Prochazka[2] states that only N-methylcaprolactam could be prepared by the action of dimethyl sulfate and caprolactam.

Method B.—By action of dimethyl sulfate on I: A solution of 25.4 g. (0.2 mole) of I, 1.9 ml. (0.02 mole) of dimethyl sulfate and 50 ml. of benzene was refluxed for six hours. The solution was shaken with excess 50% potassium carbonate, the organic layer separated and distilled. There was obtained 20.5 g. of N-methylcaprolactam, b. p. 128° (32 mm.), $n^{25}D$ 1.4812.

Method C.—Thermal rearrangement of I: O-Methylcaprolactim was heated in a steel bomb at 285° for ten hours. Distillation of the product gave a 67% yield of the N-methyl compound, b. p. 110–112° (10 mm.), $n^{25}D$ 1.4833.

N-Ethylcaprolactam.—O-Ethylcaprolactim (25 g.) was heated for two hours at 180–250° in an atmosphere of nitrogen. Distillation gave 23.4 g. (85% yield) of N-ethylcaprolactam, b. p. 97° (5.5 mm.), $n^{25}D$ 1.4777, d^{25}_4 0.9850.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.42, 68.20; H, 10.85, 10.70; N, 9.48, 9.53.

Amidines.—The preparation of several cyclic amidines was achieved by heating I with the appropriate amine. The results are summarized in Table I. A typical example is given below.

A mixture of 25.4 g. (0.2 mole) of I and 24.6 g. (0.2 mole) of *p*-anisidine was heated at 175° for three hours, and the methanol continuously removed by distillation. The resulting 2-(*p*-anisidino)-1-aza-1-cycloheptene was crystallized from hexane-ether to give 36 g. (83% yield) of white needles, m.p. 85–87°. The analytical results are given in Table I.

2-(1′-Azacycloheptyl)-1-aza-1-cycloheptene. Method A.—A solution of 83.3 g. (0.657 mole) of I and 65 g. (0.657 mole) of hexamethylenimine was refluxed for nine hours and then the methanol was removed by distillation. The resulting product was fractionated through a 6″ Vigreux column to give 100 g. (78%) of the amidine, b. p. 165–170° (25–28 mm.), $n^{25}D$ 1.5242; methiodide, m. p. 194.5–196°.

Method B.—A solution of 50 g. (0.394 mole) of I in 125 ml. of absolute ethanol was shaken with platinum oxide catalyst under a hydrogen pressure of 20–30 lb./sq. in. for twenty-four hours. The total pressure drop corresponded to about 0.25 mole of hydrogen. The alcohol was removed by distillation and the product fractionated to give 27.3 g. of I, b. p. 33–35° (1 mm.) and 15.2 g. of the amidine, b. p. 98–105° (1 mm.) (87% yield at 45% conversion of I), $n^{25}D$ 1.5248, d^{25}_4 0.9956.

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.77, 73.92; H, 11.29, 11.34; N, 14.18, 14.03.

Methiodide, m. p. 193.5–194.5°: a mixed m. p. of methiodides of the amidine prepared by Methods A and B, m. p. 194–196°.

Anal. Calcd. for $C_{13}H_{25}N_2I$: N, 8.33; I, 37.74. Found: N, 8.99, 8.70; I, 37.67, 37.73.

Hexamethylenimine.—O-Methylcaprolactim was hydrogenated at 150° and 2000–3000 lb./sq. in. hydrogen pressure using barium–copper chromite catalyst to give 70% yield of the imine, b. p. 134–137°, $n^{25}D$ 1.4645, d^{25}_4 0.8806 (literature values,[11] b. p. 138°, $n^{23}D$ 1.4654, d^{25}_4 0.8770). The imine was converted to its picrate, m. p. 144–145°, lit.[11] m. p. 146.5°, and *p*-toluenesulfonamide, m. p. 75–76°, lit.[12] m. p. 76.5°. The hydrogenation of I at 3000 lb./sq. in. using Raney nickel catalyst at 140° gave 49% of the imine, while the use of ruthenium catalyst at 125° gave 31% yield.

N-(β-Cyanoethyl)-caprolactam (III).—To a solution of 113 g. (1.0 mole) of caprolactam in 300 ml. of dioxane and 6 ml. of "Triton" B (trimethylbenzylammonium hydroxide) was added dropwise with stirring 56 g. (1.0 mole) of acrylonitrile over a period of thirty-five minutes with the temperature maintained at 30–35°. Stirring was continued for two hours and the reaction mixture allowed to stand at room temperature for sixty-three hours. The solution was made slightly acid with hydrochloric acid, the dioxane and unreacted acrylonitrile removed by distillation, and the product fractionated through an 8″ Vigreux column to give 108 g. (65% yield) of III, b. p. 153–158° (1.5–1.8 mm.), $n^{25}D$ 1.4903, d^{25}_4 1.074. On standing, the product crystallized to give white needles, m. p. 32–34°, readily soluble in water and most organic solvents.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.97, 64.86; H, 8.49, 8.41; N, 17.11, 16.93.

N-(β-Cyanoethyl)-caprolactam was hydrolyzed to 4-azasebacic acid in 40% yield by refluxing with 25% sulfuric acid; m. p. 177–178° from 95% ethanol.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 52.86, 52.93; H, 8.52, 8.56; N, 6.82, 6.77.

N-(1,1-Dioxotetrahydro-3-thienyl)-caprolactam (IV).—A mixture of 56.5 g. (0.5 mole) of caprolactam and 1 g. of potassium hydroxide was heated to 65° and 59 g. (0.5 mole) of 2,5-dihydrothiophene-1-dioxide added in 2-g. portions over a period of thirty minutes with constant stirring. The temperature rose to 70° and the mixture was heated and stirred at 65–75° for seven hours. The product was crystallized from ethanol and then from ethanol–ether to give 19 g. (16.5% yield) of white needles, m. p. 107–108°. An analytical sample melts at 108–109.5°.

Anal. Calcd. for $C_{10}H_{17}NO_3S$: C, 51.92; H, 7.41; N, 6.06; S, 13.86. Found: C, 51.81, 52.06; H, 7.48, 7.59; N, 6.04, 5.92; S, 13.82, 13.78.

N-Methylolcaprolactam (V).[13]—A mixture of 339 g. (3.0 moles) of caprolactam, 135 g. of paraformaldehyde,

(11) Müller and Sauerwald, *Monatsh.*, **48**, 727 (1927).

(12) Müller and Bleier, *ibid.*, **50**, 399 (1928).

(13) Prepared by Dr. Clarence E. Denoon; present address, Rohm & Haas Co., Philadelphia, Pa.

5 g. of sodium hydroxide and 500 ml. of 95% ethanol was stirred and heated at 140–150° for three hours. The mixture was filtered from a small amount of insoluble material and cooled in a Dry Ice–acetone-bath. There was obtained 184 g. of white, microcrystalline solid, V. Concentration of the filtrate yielded an additional 105 g. of V, m. p. 62–64°, total yield 289 g. (67%). Recrystallization from methanol gave an analytical sample, m. p. 65–66°.

Anal. Calcd. for $C_7H_{13}NO_2$: N, 9.78. Found: N, 9.98.

N-(Ethylthiomethyl)-caprolactam (VI).[13]—A mixture of 113 g. (1.0 mole) of caprolactam, 45 g. of paraformaldehyde, 3 g. of sodium hydroxide, and 250 ml. of 95% ethanol was stirred and heated at 40–50° for fourteen hours. The mixture was cooled, 40 ml. of concentrated hydrochloric acid added and the precipitated sodium chloride removed by filtration. To the filtrate was added 93 g. (1.5 moles) of ethyl mercaptan and the resulting mixture allowed to stand overnight. To the mixture was added 100 ml. of ether, the resulting organic layer washed with 5% sodium hydroxide and finally with water. The oil was dried over sodium sulfate and then distilled to give 122 g. (65% yield) of VI, b. p. 138–141° (5–6 mm.), $n^{25}D$ 1.5189, d^{25}_4 1.0689.

Anal. Calcd. for $C_9H_{17}NOS$: S, 17.12. Found: S, 17.30.

N-(Benzothiazolyl-2-thiomethyl)-caprolactam (VII).[13]—A mixture of 113 g. (1.0 mole) of caprolactam and 30 g. of paraformaldehyde was heated at 80–90° for one-half hour. To this hot mixture was added 167 g. (1.0 mole) of 2-mercaptobenzothiazole and the mixture heated at 130–140° for two additional hours. The resulting liquid was poured into 2 l. of 5% sodium carbonate and stirred to give a yellow crystalline mass. The yellow product was ground, extracted again with sodium carbonate and finally with 1500 ml. of 95% ethanol. The ethanol filtrate was decolorized with activated carbon, filtered and cooled to give 150 g. (51% yield) of crystalline solid, m. p. 150–155°. An analytical sample from methanol melts at 157°.

Anal. Calcd. for $C_{14}H_{16}N_2OS_2$: S, 21.93. Found: S, 22.21.

N-Acetylcaprolactam (VIII).—A mixture of 678 g. (6.0 moles) of caprolactam and 670 g. (6.65 moles) of acetic anhydride was refluxed for four hours. After removal of the unreacted anhydride and acetic acid, there was obtained 775 g. (83.5% yield) of N-acetylcaprolactam, b. p. 134–136° (26–27 mm.); $n^{25}D$ 1.4885, d^{25}_4 1.094.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03; sapn. eq., 155.2. Found: C, 62.20, 61.90; H, 8.75, 8.70, N, 9.36, 9.06; sapn. eq., 159, 158.

This compound has been prepared previously[2] but physical constants other than b. p. 130–131° (13 mm.) were not given.

N-(*o*-Carboxybenzoyl)-caprolactam (IX).—A mixture of 113 g. (1.0 mole) of caprolactam and 148 g. (1.0 mole) of phthalic anhydride was heated at 180–195° for eighteen hours. The product was distilled through a short column to give 231 g. of IX, b. p. 206–208° (0.20–0.25 mm.), m. p. 104.5–106.5°. Recrystallization from hexane–ethanol gave 210 g. (80% yield) of product, m. p. 105–107°. Further recrystallization from benzene gave m. p. 107.5–108°. The product is soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36; neut. eq., 261.3. Found: C, 64.38, 64.44; H, 5.94, 5.97; N, 5.51, 5.46; neut. eq., 254.4, 253.6.

Prochazka[2] has reported that the above reaction using one-half mole of the anhydride per mole of lactam yields N-phthaloylcaprolactam, b. p. 279–282° (15 mm.), m. p. 108.5–109°; while a German report[7] states that only N-(*o*-carboxybenzoyl)-caprolactam, b. p. 250° (2–3 mm.), m. p. 109–110°, can be prepared. Since no analytical data were available and the reported physical constants are similar, it was necessary to repeat the reaction to determine the exact structure of the resulting compound. The directions of Prochazka were followed but only unchanged caprolactam and IX were obtained by distillation of the reaction mixture.

N-Methyl-ε-aminocaproic Acid Dihydrate.—A solution of 130 g. of concentrated sulfuric acid, 1170 ml. of water and 130 g. (1.025 mole) of N-methylcaprolactam was refluxed for ten hours. The hot solution was treated with a slight excess of barium hydroxide, filtered to remove the precipitated barium sulfate, the filtrate treated with solid carbon dioxide to remove the barium ions as barium carbonate and the solid removed by filtration. The resulting filtrate was concentrated by distillation to give a sirupy residue that was treated with benzene and heated to remove most of the remaining water. The resulting product was crystallized twice from absolute ethanol–ether to give a white, crystalline solid, m. p. 66–67°. The directions followed were those of Lukes and Smolek[9] who state that the product thus obtained was N-methyl-α-aminocaproic acid, m. p. 66°; however, Ruzicka[8] has stated that the hydrolysis of N-methylcaprolactam with concentrated hydrochloric acid yields N-methyl-ε-aminocaproic acid, m. p. 130–131°.

The product of m. p. 66–67° was identified as N-methyl-ε-aminocaproic acid dihydrate by analysis, dehydration to N-methyl-ε-aminocaproic acid, and ring closure to give N-methylcaprolactam.

Anal. Calcd. for $C_7H_{15}NO_2 \cdot 2H_2O$: C, 46.39; H, 10.57; N, 7.73; neut. eq., 181.23. Found: C, 46.95; 47.00; H, 10.44, 10.74; N, 7.37, 7.58; neut. eq., 180.4, 180.8.

To check the structure of the above compound, a weighed amount of the air-dried material was placed in a drying pistol, evacuated by means of a vacuum pump and heated by boiling alcohol for fifteen hours. The solid did not melt but the crystalline material slowly changed to an amorphous powder. A weighed sample (1.4868 g.) of the compound lost 0.3068 g.; the calculated loss for the dihydrate is 0.2956 g. In addition, the amorphous powder thus obtained melted at 129–131°, lit. m. p. 130–131° for N-methyl-ε-aminocaproic acid.[3]

The air-dried product was heated in a small distilling flask for fifteen minutes and most of the water collected. The temperature was raised and the major portion of the material distilled at 234°, $n^{25}D$ 1.4819. This is in good agreement with the values for N-methylcaprolactam, b. p. 234°, $n^{25}D$ 1.4818.

From the above data it is evident that the product obtained by Lukes and Smolek was the dihydrate of N-methyl-ε-aminocaproic acid rather than N-methyl-α-aminocaproic acid.

Summary

1. The reaction of caprolactam with dimethyl sulfate has yielded O-methylcaprolactim or N-methylcaprolactam depending on the amount of the sulfate used in the reaction. In addition, O-ethyl- and O-methylcaprolactim were rearranged thermally to the corresponding N-substituted derivatives.

2. The condensation of the methyl imino ether with amines yielded the corresponding cyclic amidines.

3. The reaction of caprolactam with active unsaturated compounds, with acid anhydrides and with formaldehyde gave other N-substituted compounds.

4. The hydrolysis of N-methylcaprolactam with 10% sulfuric acid was shown to yield the dihydrate of N-methyl-ε-aminocaproic acid rather than N-methyl-α-aminocaproic acid as previously reported.

WILMINGTON 98, DELAWARE RECEIVED JANUARY 13, 1948

[CONTRIBUTION NO 646 FROM THE RESEARCH LABORATORIES OF THE GOODYEAR TIRE AND RUBBER CO.]

The Preparation and Some Reactions of α-(ω-Cyanoethyl)-β-naphthol

BY A. F. HARDMAN

Hoesch[1] discovered that acetonitrile condenses with resorcinol in the presence of zinc chloride and hydrogen chloride to yield a compound which hydrolyzes to 2,4-dihydroxyacetophenone. Later Langley and Adams[2] attempting the same type of condensation with β-chloropropionitrile or acrylonitrile and resorcinol obtained not a ketone, but 2,4-dihydroxyphenylpropionic acid.

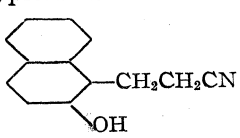
More recently, it was shown that various cyanoethyl aryl ethers are obtained by treating phenols with acrylonitrile in the presence of about 1% of metallic sodium as catalyst. This represents the usual reaction between acrylonitrile and a phenol.

It has now been found that β-naphthol and acrylonitrile in a solvent such as benzene condense in the presence of solid caustic soda. The caustic is used in equal or slightly more than equal molal quantities to the naphthol. Therefore, its function is not merely that of a catalyst. The product first obtained, as a viscous water-soluble layer under the organic solvent, is the sodium salt of α-(ω-cyanoethyl)-β-naphthol, from which the free naphthol is obtained by dissolution in water and acidification. This naphthol (I) is analogous to that obtained by Langley and Adams from resorcinol and acrylonitrile. However, resorcinol, treated with acrylonitrile and caustic under the conditions described, does not react. In fact, this reaction appears to be specific to β-naphthol; other phenols, including α-naphthol, failed to yield satisfactory products.

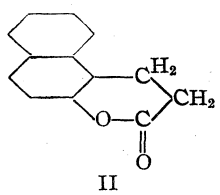
α-(ω-Cyanoethyl)-β-naphthol is readily hydrolyzed to the corresponding propionic acid which on heating forms a lactone (II).

The lactone reacts with ammonia and various amines to yield well-crystallized amides of 2-hydroxynaphthalenepropionic acid, and with alcohols to yield esters of the same acid. The esters cannot be distilled, but revert to lactones and free alcohols on heating.

α-(ω-Cyanoethyl)-β-naphthol also reacts like a typical nitrile to form amidines.



I



II

Experimental[3]

α-(ω-Cyanoethyl)-β-naphthol (1).—A mixture of 29 g. of β-naphthol, 12 g. of acrylonitrile, 50 cc. of benzene and 9 g. of sodium hydroxide pellets was refluxed. The mixture boiled vigorously at first, and the sodium hydroxide mostly went into solution. After about one-half hour the mixture began to separate into two layers. The heating was stopped after two hours, 100 cc. of cold water added and the water solution separated from the benzene, and acidified with acetic acid. The crude precipitate weighed 37 g. and after recrystallization from ethanol yielded white crystals melting at 142°.

Anal. Calcd. for $C_{13}H_{11}ON$: N, 7.1. Found: N, 6.85.

2-Hydroxy-1-naphthalenepropionic Acid.—A solution of 50 g. (I) in 222 g. of 10% aqueous sodium hydroxide was refluxed for eight hours, then cooled and stirred slowly into dilute hydrochloric acid. The crude 2-hydroxy-1-naphthalenepropionic acid melting at 115–117° weighed 54 g. and after recrystallization from benzene, melted at 121°.

Anal. Calcd. for $C_{13}H_{12}O_3$, neutral equivalent, 259. Found: neutral equivalent, 258.

Lactone of 2-Hydroxy-1-naphthalenepropionic Acid (II).—One hundred forty-three grams of crude acid, (m. p. 114–115°) was refluxed in 100 cc. of toluene under a water trap, until no more water collected, about one-half hour. The toluene was removed by distillation and the lactone distilled under 5 mm. pressure, coming over mostly between 210 and 220°. The viscous liquid, which weighed 115 g., crystallized after stirring and seeding. After recrystallization from benzene–petroleum ether, the lactone melted at 69–70°.

2-Hydroxy-1-naphthalenepropionamide.—Dry ammonia was bubbled through a solution of 20 g. of the lactone (II) in 200 cc. benzene. The solution became warm and in a few minutes crystals began to separate. After saturation, the mixture was allowed to stand overnight, then filtered, and the crystals washed with benzene. The yield was 21 g. of fine, white crystals melting with decomposition at 171–172°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: N, 6.52. Found: N, 6.46.

2-Hydroxy-1-naphthalene-N-cyclohexyl-propionamide.—Twenty grams of the lactone (II) was dissolved in 50 cc. of benzene and 10 g. of cyclohexylamine was added. The solution became warm on adding the amine, and in a short time crystals began to separate. After standing overnight, the fine white crystals were filtered off and washed with benzene. The yield was 28 g.; m. p. 172–173°.

Anal. Calcd. for $C_{19}H_{23}O_2N$: N, 4.72. Found: N, 4.81.

Table I below lists a number of other substituted amides which have been prepared by heating the lactone and the amine in an appropriate solvent.

TABLE I

Amine	Amide M. p., °C.	Nitrogen, % Calcd.	Found
Diethylamine	124	5.17	5.26
Monoethanolamine	142–143	5.40	5.14
Ethylenediamine	188	6.14	5.87
Aniline	173–174	4.81	4.48
p-Aminophenol	142–143	4.56	4.32
α-Naphthylamine	205–206	4.11	4.06
β-Naphthylamine	193–194	4.11	3.91
p,p'-Diaminodiphenylmethane	207	4.71	4.68

Methyl 2-Hydroxy-1-naphthalenepropionate.—A solution of 20 g. of the lactone (II) in 50 cc. of methanol to which

(1) Hoesch, *Ber.*, **48**, 1122 (1915).

(2) Langley and Adams, THIS JOURNAL, **44**, 2326 (1922).

(3) The melting points reported are uncorrected.

a pinch of sodium methylate was added was refluxed for one-half hour. On cooling, 16 g. of the ester precipitated. After recrystallization from methanol, the product melted at 122–123°.

Anal. Calcd. for $C_{14}H_{14}O_3$: sapn. equiv., 244. Found: sapn. equiv., 245.

2-Hydroxy-1-naphthalenepropio-N,N'-diphenylamidine.—One hundred grams of (I) was refluxed with 125 g. of aniline. Ammonia came off rapidly at first, then more and more slowly. After eight hours 86% of the theoretical ammonia had been driven off. The mixture was cooled and stirred into 400 cc. of ethanol and allowed to stand overnight. The product, which was removed by filtration and washed with ethanol weighed 123 g. and melted at 147°. After recrystallization from xylene, it melted at 150–151°.

Anal. Calcd. for $C_{25}H_{22}ON_2$: N, 7.64. Found: N, 7.87.

It has been discovered in preliminary tests that the 2-hydroxy-1-naphthalenepropionic acid is moderately effective as a root growth promoter when applied to chrysanthemum cuttings and is of some value as a spray material to reduce premature apple drop. It is hoped that this publication will stimulate investigation by others in various fields of possible utility.

Acknowledgment. The author is indebted to Miss Marion Treiber for assistance in preparing a number of the amides tabulated above.

Summary

1. A new reaction is described in which α-(ω-cyanoethyl)-β-naphthol is obtained in excellent yield from acrylonitrile and β-naphthol.

2. Derivatives prepared from α-(ω-cyanoethyl)-β-naphthol include 2-hydroxy-1-naphthalenepropionic acid, its methyl ester, various amides and the N,N'-diphenylamidine.

AKRON, OHIO RECEIVED NOVEMBER 26, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A New Synthesis of Atranol (2,6-Dihydroxy-4-methylbenzaldehyde) and the Corresponding Cinnamic Acid

BY ROGER ADAMS AND JEAN MATHIEU

In experiments designed to prepare products suitable for the synthesis of natural tetrahydrocannabinol,[1] techniques for certain reactions were developed which may be of general interest. A new synthesis of atranol was also discovered. The compounds desired are 2,6-dihydroxy-4-*n*-amylcinnamic acid and its ester. This preliminary work, however, has involved the synthesis of the corresponding 4-methyl derivatives, since orcinol is a much more readily accessible substance than olivetol (3,5-dihydroxy-*n*-amylbenzene).

Orcinol dimethyl ether can be formylated (I) in the position between the methoxyls by treating lithium orcinol dimethyl ether with methylformanilide.[1b] Demethylation of this product was attained only after an exhaustive study of different reagents. Anhydrous aluminum bromide proved successful and a 70% yield of 2,6-dihydroxy-4-methylbenzaldehyde (II) resulted. This product is known as atranol. It was first isolated by degradation of atranorin, a product occurring in various lichens, and its structure was determined by oxidation to *p*-orsellinic acid.[2] It has been synthesized by Pfau in low yields by the introduction of an aldehyde group into ethyl 2,4-dihydroxy-6-methylbenzoate (orcinol carboxylic ester), followed by saponification and decarboxylation.[3] The new method offers a much simpler and more satisfactory procedure. Anhydrous aluminum chloride under similar conditions gives primarily resins, although in very small runs (0.1 g.), a 30% yield of atranol could be isolated. With benzene as a solvent, aluminum chloride causes demethylation of only one methoxyl with formation of 2-hydroxy-6-methoxy-4-methylbenzaldehyde (atranol monomethyl ether). This compound has been described by Asahina,[4] who found it in the pyrolysate of stictinic acid and synthesized it from atranol.

Although atranol dimethyl ether (I) condenses with malonic acid in presence of piperidine with formation of an almost quantitative yield of the corresponding cinnamic acid,[1b] the unmethylated product, atranol(II), did not react similarly under the same conditions. The conversion of substituted aromatic aldehydes to the cinnamic acids by the Knoevenagel reaction has been exhaustively studied. In general the yields are excellent but previous investigators have noted the abnormally low yields of products when *o*- or *p*-hydroxybenzaldehydes were subjected to condensation under conditions entirely suitable to other substituted benzaldehydes.[5] The conditions found most satisfactory for the condensation of salicylaldehyde with malonic acid[5b] were (a) the use of a small amount of pyridine as catalyst resulting in a yield of 51% of 3-carboxycoumarin or (b) heating at 80° followed by twenty-four hours at room temperature in presence of trace amounts of a variety of tertiary bases such as lutidine, quinoline, etc. (methylacridine[1c] proved to be the best) resulting in a 66–77% yield of product. An explanation of the difficulty in the condensation of *o*- and *p*-hydroxybenzaldehydes was suggested by

(1) (a) Adams, McPhee, Carlin and Wicks, THIS JOURNAL, **65**, 356 (1943); (b) Adams and Carlin, *ibid.*, **65**, 360 (1943).

(2) Pfau, *Helv. Chim. Acta*, **9**, 650 (1926).

(3) Pfau, *ibid.*, **16**, 282 (1933).

(4) Asahina, *Ber.*, **66**, 943 (1933).

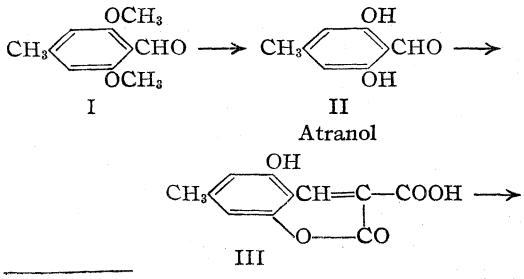
(5) (a) Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925); **9**, 309 (1932); (b) Kurien and Pandja, *ibid.*, **11**, 823 (1934); (c) *Proc. Indian Acad. Sci.*, **1A**, 440 (1935).

Vorsatz,[6] who pointed out that at the temperatures usually employed the *o*- and *p*-hydroxycinnamic acids readily decarboxylated with subsequent polymerization of the corresponding styrenes. He was able to overcome this side reaction by keeping the reactants at a relatively low temperature for a period of many days. He also observed that replacing the piperidine by aniline greatly accelerated the reactions. Thus, protocatechuic aldehyde, and 2,3,4-trihydroxybenzaldehyde condensed in better than 80% yield. In this investigation, the usual procedure with atranol and malonic acid failed but that described by Vorsatz using pyridine and aniline proceeded very satisfactorily to give a 75% yield of 3-carboxy-5-hydroxy-7-methylcoumarin (III). Aniline thus appears to be a catalyst of general utility for *o*- and *p*-hydroxybenzaldehyde condensations. Whether the mechanism involves intermediate formation of a Schiff base is now under investigation.

Sastry and Seshadri[7] have described the decarboxylation of 3,8-dicarboxy-5-hydroxy-7-methylcoumarin and report the formation of 8-carboxy-5-hydroxy-7-methylcoumarin. Since the melting point of their product is identical with that of the 3-carboxy derivative obtained in this research and prepared by an unequivocal method, it is probable that in the decarboxylation of the 3,8-dicarboxy derivative the 8-carboxyl group has been lost and that the product reported by Sastry and Seshadri is the 3-isomer.

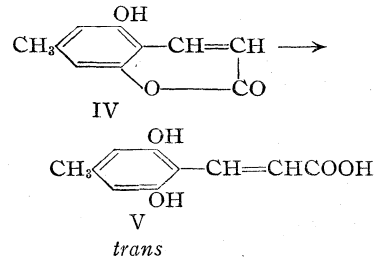
The decarboxylation of 3-carboxy-5-hydroxy-7-methylcoumarin could not be accomplished with quinoline and copper and only a low yield of impure product resulted when the metal alone was used. It was discovered that aqueous sodium bisulfite was an excellent reagent for this purpose and 75–90% yields of 5-hydroxy-7-methylcoumarin (IV) was readily obtained. Presumably the coumarin is opened and carbon dioxide is lost without transforming the *cis*-cinnamic acid intermediate to the *trans* form. Sodium sulfite could not be used in place of sodium bisulfite.

The 5-hydroxy-7-methylcoumarin was hydrated to the *trans*-2,6-dihydroxy-4-methylcinnamic acid (V) in 65–85% yields by means of aqueous sodium sulfite. In the esterification of the acid produced, difficulties were encountered and only diazomethane gave satisfactory results.



(6) Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936).

(7) Sastry and Seshadri, *Proc. Indian Acad.*, **12A**, 498 (1940).



Experimental

2,6-Dimethoxy-4-methylbenzaldehyde (Atranol Dimethyl Ether).—Modifications of Adams and Carlin's method[1b] were introduced to avoid special apparatus and to increase the yield. In a 200-ml. round-bottom flask provided with a dropping funnel, a mechanical stirrer and a reflux condenser fitted with a calcium chloride tube was placed 2.5 g. of lithium hammered to paper thickness under a layer of paraffin oil. The lithium was washed twice with anhydrous ether by decantation and covered with 100 ml. of anhydrous ether. The stirrer was started, 5 g. of *n*-butyl chloride was added all at once and the flask warmed gently to start the reaction. The reflux was maintained by dropwise addition of 15 g. of *n*-butyl chloride. Stirring was continued for about two hours when the lithium disappeared almost completely.

After addition dropwise of 25 g. of orcinol dimethyl ether, the stirrer was stopped and the flask placed in an oil-bath at 50° for eight hours. The oil-bath was removed, the stirrer started and a mixture of 25 g. of N-methylformanilide and 25 ml. of anhydrous ether introduced dropwise. At the end of the addition the mixture was heated for one more hour at 50°.

The product was poured over a mixture of 100 g. of crushed ice and 300 ml. of 3 *N* hydrochloric acid and extracted twice with ether (200 ml., 100 ml., 100 ml.). The combined ether extracts were washed with *N* hydrochloric acid, 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate.

The ether was distilled and the residue was dissolved in 100 ml. of boiling cyclohexane. On cooling the aldehyde crystallizes in white needles and was filtered, washed twice with a little cyclohexane and finally with petroleum ether (b. p. 60–100°). The product was pure enough for the next step. From the mother liquor, a little more product was obtained but had to be crystallized from cyclohexane to be of acceptable purity. The yield in ten runs was between 12–16 g. (45–55%).

The melting point after crystallization from cyclohexane was 91–92° (Adams and Carlin,[1b] 91–92°).

2,6-Dihydroxy-4-methylbenzaldehyde (Atranol).—To a solution of 5 g. of atranol dimethyl ether in 250 ml. of carbon disulfide in a 500-ml. round-bottom flask fitted with a mechanical stirrer, 22 g. of aluminum bromide (3 moles per mole of aldehyde) in 250 ml. of carbon disulfide was added quickly with stirring. The addition complex precipitated as a red gum. After stirring for one hour the carbon disulfide was decanted into a separatory funnel and 100 g. of crushed ice, 150 ml. of 3 *N* hydrochloric acid and 200 ml. of ether was added to the residual gum in the flask and stirred until it was completely dissolved (one to two hours). The carbon disulfide in the separatory funnel was washed with 50 ml. of 3 *N* hydrochloric acid, the carbon disulfide layer discarded and the acid layer added to the mixture in the flask. The ether layer was removed and the aqueous layer extracted with two 200-ml. portions of ether.

The combined ether solutions were extracted with three 50-ml. portions of *N* aqueous sodium hydroxide. The atranol was precipitated from the alkaline solution by addition of 15 ml. of concentrated hydrochloric acid. The product was filtered, washed with a little water and crystallized from 125 ml. of boiling water (Norit). Yield, (average of twelve runs), 2.9 g. (70%) of slightly yellow product of adequate purity for the next step.

The product can be purified by crystallization from water, or toluene, and sublimation. It forms white crystals which start shrinking at 117° and melt at 123°; Pfau[2] reports m. p. 121° for his synthetic product and m. p. 124° for that obtained by degradation.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.58; H, 5.40.

It was found that when working with larger runs, the yield was not as satisfactory. The conditions described were the best observed after careful study of many catalysts and solvents, modification of temperature and time.

Aluminum chloride, under similar conditions, gave only resins. In 0.1 g. runs, a yield of 30% could be obtained with this reagent.

2-Hydroxy-6-methoxy-4-methylbenzaldehyde (Atranol Monomethyl Ether).—A solution of 10 g. of atranol dimethyl ether in 200 ml. of benzene and 10 g. of aluminum chloride was placed in a 250-ml. round-bottom flask and stirred mechanically at room temperature. The complex, a dark liquid, formed in about ten minutes and the mixture was then heated for ten minutes at 85° without stirring.

The product was poured onto a mixture of 100 g. of crushed ice and 100 ml. of 3 *N* hydrochloric acid. The precipitate was not filtered but 250 ml. of 3 *N* aqueous sodium hydroxide was added which took it into solution. The alkaline solution was washed with ether, acidified and extracted twice with ether. The combined ether extracts were washed with 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The residue from the ether was distilled under reduced pressure; b. p. 110–112° (1 mm.); yield, 7.4 g. (80%). After purification from toluene, it has a m. p. of 82–83°; Asahina[4] reports a m. p. of 78°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.64; H, 6.24.

2-Hydroxy-6-methoxy-4-methylbenzaldoxime.—The oxime was prepared in the usual way and purified from ethanol, m. p. 150–151°.

Anal. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12. Found: C, 59.72; H, 6.06.

3-Carboxy-5-hydroxy-7-methylcoumarin.—A mixture of 10 g. of atranol, 15 g. of malonic acid (2 moles per mole of aldehyde), 20 ml. of pyridine and 0.4 g. of aniline was heated in an open flask on an oil-bath at 55°. After about four hours, the product crystallized as a yellow mass.

It was heated one more hour and decomposed by trituration with 200 ml. of *N* hydrochloric acid. The product was filtered with suction, dissolved in 200 ml. of *N* hydrochloric acid, and precipitated by addition of 20 ml. of concentrated hydrochloric acid. The yield was 11 g. (75%) of yellowish product of satisfactory purity for the next step. It may be purified by crystallization from acetophenone, m. p. 270–271°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 60.00; H, 3.80.

Aniline was the only catalyst used which resulted in a satisfactory yield of the desired product; pyridine, piperidine, pyridine with piperidine, pyridine with methylaniline, ammonia in alcohol, acetic acid and sulfuric acids failed as catalysts.

5-Hydroxy-7-methylcoumarin.—A mixture of 5 g. of 3-carboxy-5-hydroxy-7-methylcoumarin and 60 ml. of a 25% aqueous solution of sodium bisulfite was placed in a 250-ml., round-bottom flask fitted with a mechanical stirrer and a dropping funnel. The flask was warmed with a bare flame until the solution was complete, the mixture stirred for about five minutes and then boiled for about thirty seconds. To the solution 50 ml. of a 50% aqueous solution of potassium hydroxide was then introduced and at the end of the addition the solution was boiled for ten seconds.

The flask was cooled in a freezing mixture, and concentrated hydrochloric acid (about 40 ml.) was added dropwise which resulted in formation of an abundant white precipitate. After one hour in the freezing mixture, the product was filtered with suction, washed twice with water and dried. The yield was 3.0 to 3.5 g. (75–90%). The product was of satisfactory purity for the next step. It may be purified by crystallization from a 50% mixture of dioxane and water. The melting point was 215–216° identical with that reported by Sastry and Seshadri[7] for 8-carboxy-5-hydroxy-7-methylcoumarin. It is believed probable that Sastry and Seshadri had in hand the 3-carboxy derivative.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.57. Found: C, 68.67; H, 4.99.

Decarboxylation by means of copper gave only a 10% yield of the same product. The use of quinoline–copper failed completely.

2,6-Dihydroxy-4-methyl-*trans*-cinnamic Acid.—A mixture of 8 g. of 5-hydroxy-7-methylcoumarin and 60 ml. of a 25% aqueous solution of sodium sulfite in a 250-ml. round-bottom flask fitted with a mechanical stirrer and a dropping funnel was heated and stirred. When complete solution had taken place, the mixture was brought to boiling and the flask placed for one hour and a half in an oil-bath at 100° without stirring.

The stirrer was started again and 30 ml. of a 50% aqueous solution of potassium hydroxide was added dropwise after which the mixture was brought to boiling for about fifteen seconds. Upon cooling in a freezing mixture and dropwise addition of concentrated hydrochloric acid (about 30 ml.) an abundant white precipitate formed. The yield was 7 to 8.5 g. (65–85%) of product of satisfactory purity for the next step. The product may be purified by crystallization from glacial acetic acid, m. p. 200° with evolution of carbon dioxide.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.10; H, 5.40.

Methyl 2,6-Dihydroxy-4-methyl-*trans*-cinnamate.—A current of diazomethane, prepared by heating a solution of diazomethane in ether, was passed into a stirred solution of 6 g. of 2,6-dihydroxy-4-methyl-*trans*-cinnamic acid in 200 ml. of dried ether. The esterification was followed by dipping blue litmus first in the ether solution and "revealed" by dipping in water (one test per minute). After about twenty minutes the esterification was complete and 100 ml. of a 10% aqueous solution of sodium bicarbonate was added all at once to decompose the excess of diazomethane.

The liquid was placed in a separatory funnel and washed with *N* hydrochloric acid, 10% aqueous sodium bicarbonate, water and dried over anhydrous sodium sulfate. The yield was 6 g. (95%). It was purified by crystallization from 40 ml. of a mixture of water and ethanol (2:1), m. p. 184–185°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.82; H, 5.98.

The usual method of esterification with methanol and sulfuric acid, hydrogen chloride or *p*-toluenesulfonic acid was unsatisfactory. The use of silver oxide and methyl iodide also failed.

Summary

1. The preparation of 2,6-dimethoxy-4-methylbenzaldehyde has been simplified. By demethylation with aluminum bromide, 2,6-dihydroxy-4-methylbenzaldehyde, atranol, is produced.

2. Atranol condenses with malonic acid in presence of pyridine and aniline to give 3-carboxy-5-hydroxy-7-methylcoumarin.

3. Aqueous sodium bisulfite readily causes decarboxylation of 3-carboxy-5-hydroxy-7-methylcoumarin to 5-hydroxy-7-methylcoumarin.

4. For hydration of the coumarin, aqueous sodium sulfite is satisfactory and 2,6-dihydroxy-4-methyl-*trans*-cinnamic acid results. The acid can be esterified with diazomethane.

URBANA, ILLINOIS RECEIVED MARCH 8, 1948

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Hydrogen Transfer. I. Reaction of *p*-Cymene with Olefinic Hydrocarbons in the Presence of Sulfuric Acid and Hydrogen Fluoride Catalysts[1,2]

BY V. N. IPATIEFF, HERMAN PINES AND R. C. OLBERG[2a]

In the course of the study of terpenic hydrocarbons which is being carried out in our laboratory, the reaction of *para*-cymene with dihydrolimonene (1-methyl-4-isopropylcyclohexene) in the presence of either sulfuric acid or hydrogen fluoride at 0° was included. It was noticed that this reaction proceeded abnormally[3] inasmuch as a 60% yield of 1-methyl-4-isopropylcyclohexane was obtained. This could not be attributed to a conjunct polymerization[4] of dihydrolimonene since the product obtained, including the high-boiling fractions, did not contain any olefinic hydrocarbons as determined by means of a potassium permanganate test.[5] It was also noticed that the high-boiling fraction resulting from this reaction had a much higher index of refraction than that expected from a cycloalkylation reaction. This material corresponded, according to elementary analysis, to a tricyclic hydrocarbon of the formula $C_{20}H_{24}$ (I). On the basis of these preliminary results, it was tentatively concluded that *p*-cymene acted as a hydrogen donor and dihydrolimonene as a hydrogen acceptor.

It was difficult to substantiate this conclusion as long as *p*-cymene and dihydrolimonene, having the same skeletal arrangement, were used as reactants. For this reason 3-methylcyclohexene was substituted for dihydrolimonene.

It was found in the reaction of *p*-cymene with 3-methylcyclohexene in the presence of either sulfuric acid or hydrogen fluoride, 62–80% of the methylcyclohexene was converted to methylcyclohexane. The yield of the expected methylcyclohexyl-*p*-cymene was very small, whereas a large amount of the tricyclic hydrocarbon, $C_{20}H_{24}$, was obtained which was identical with compound I. It was also found that for each mole of $C_{20}H_{24}$ produced there was one mole of methylcyclohexane formed.

If, however, *p*-cymene and a branched open chain olefin, such as trimethylethylene, were contacted in the presence of hydrogen fluoride, both an alkylation and a hydrogen transfer reaction occurred; the latter reaction was the predominant one. Isopentane and decanes were found among the reaction products. The presence of decanes is attributed to the dimerization of the trimethylethylene, which through a subsequent hydrogen transfer reaction yields decanes. The major part of *p*-cymene which underwent reaction yielded the hydrocarbon, $C_{20}H_{24}$, identical with the one described above.

In order to determine whether the hydrogen transfer reaction which involves *para*-cymene and an olefinic hydrocarbon is of a general nature, a series of experiments was made using various olefins.

It was found that cyclohexene[6] or straight chain olefin such as 1-octene, react with *p*-cymene in the usual manner yielding the corresponding mono- and disubstituted *p*-cymene; hydrogen transfer reaction did not occur.

The Structure of the $C_{20}H_{24}$ Hydrocarbon (I).—The facts described below and the postulated mechanism of hydrogen transfer reaction suggested that the $C_{20}H_{24}$ hydrocarbon corresponds to 1,3,3,6-tetramethyl-1-*p*-tolylindan (I). In order to establish conclusively the structure of compound (I) 1,3,3,6-tetramethyl-1-*p*-tolylindan was synthesized. The physical constants, nitro derivatives, and ultraviolet absorption spectra of the synthetic sample were compared with the tricyclic hydrocarbon obtained from the hydrogen transfer reaction; the two compounds were identical.[7]

Infrared absorption spectra of the synthetically prepared compound I and that obtained from the hydrogen transfer reaction were taken (Graph I and II). The 1,3,3,6-tetramethyl-1-*p*-tolylindan prepared from the latter reaction solidified on standing, so for that reason the infrared spectrum was taken in a carbon disulfide solution. The spectra of both compounds were found to be basically the same; the synthetic sample seems to be only about 95% pure. Due to the small amount of synthetic sample prepared, no attempt was made to purify it.

Compound I yielded on nitration a tetranitro derivative $C_{20}H_{20}N_4O_8$ melting at 252–253°. A disulfonamide of the hydrocarbon was obtained melting at 227–228°. The tricyclic hydrocarbon yielded on oxidation a dicarboxylic acid, $C_{20}H_{20}O_4$, melting at 294–295°.

(1) This work was made possible through the financial assistance of Universal Oil Products Company.

(2) This paper was presented in part before the Organic Division of the American Chemical Society, September, 1946.

(2a) Present address: Paraffine Companies, Inc., Emeryville, Calif.

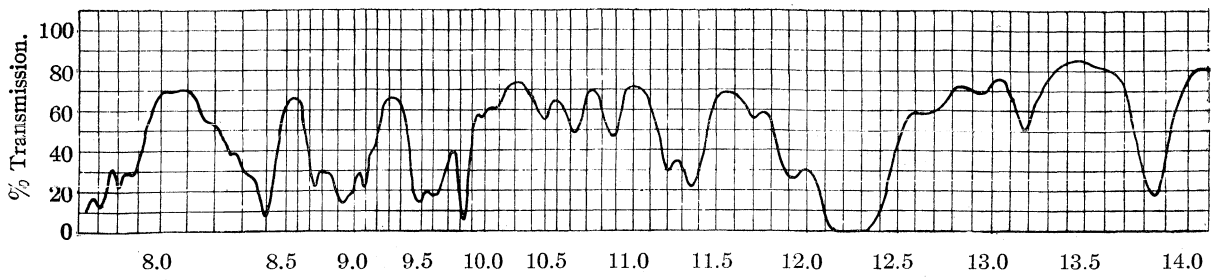
(3) For the literature references pertaining to the alkylation of aromatic hydrocarbons, see paper by V. N. Ipatieff, H. Pines and L. Schmerling, *J. Org. Chem.*, **5**, 253 (1940).

(4) V. N. Ipatieff and H. Pines, *J. Org. Chem.*, **1**, 464 (1936).

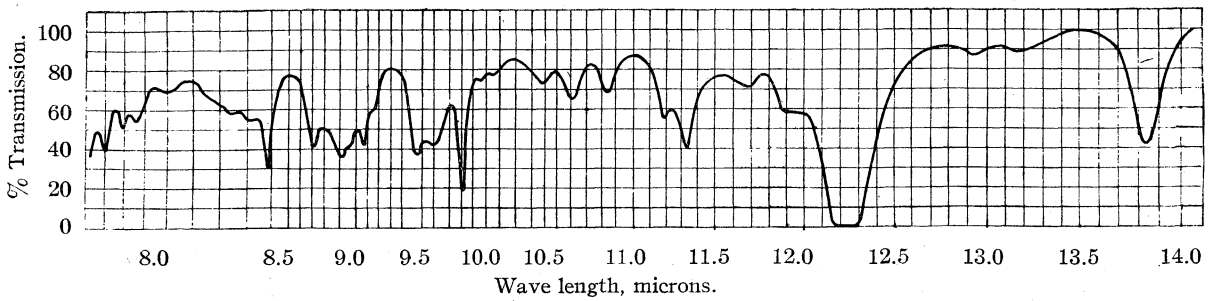
(5) V. N. Ipatieff, W. W. Thompson and H. Pines, THIS JOURNAL, **70**, 1658 (1948).

(6) H. Pines, A. Weizmann and V. N. Ipatieff, "Hydrogen Transfer II." Paper presented before the Organic Division of the American Chemical Society, New York, September 15–19, 1946.

(7) The same tricyclic hydrocarbon, $C_{20}H_{24}$, was reported by N. Puranen (*Ann. Acad. Sci. Fennicae*, **37A**, No. 10, 1–80 (1933); **C**, 1933 II, 856) to be formed by the treatment of *p*-cymene with nitrosylsulfuric acid in sulfuric acid. The melting point of the hydrocarbon and its nitro derivatives agrees with those obtained from the hydrogen transfer reaction. Puranen assigned to this compound the structure of 1,3,3,6-tetramethyl-1-*p*-tolylindan; he did not however prove the structure by either degradative or synthetic means.



Graph I.—1,3,3,6-Tetramethyl-1-*p*-tolylindan; prepared by synthetic means.



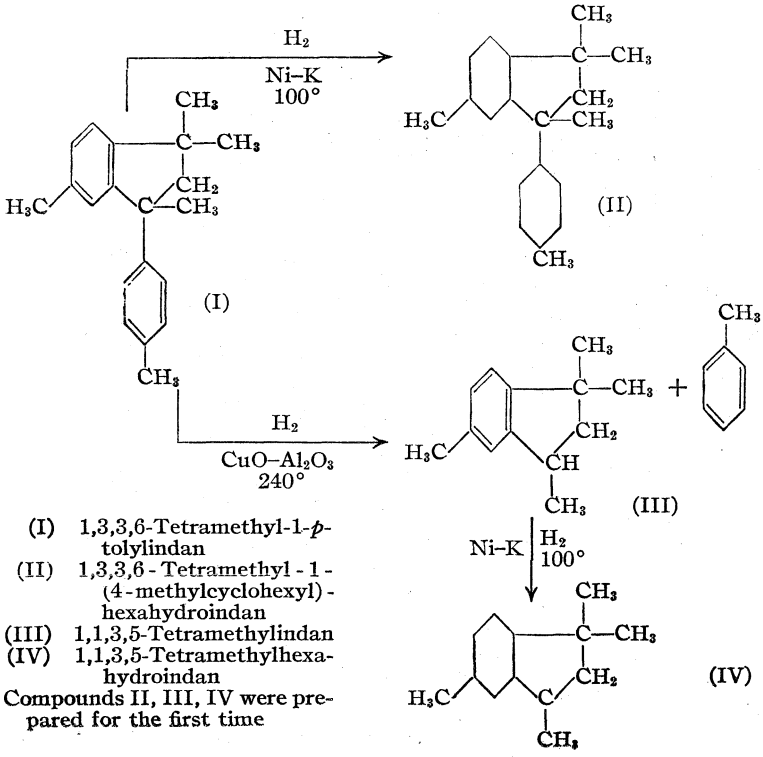
Graph II.—1,3,3,6-Tetramethyl-1-*p*-tolylindan; obtained from a hydrogen transfer reaction.

The $C_{20}H_{24}$ hydrocarbon (I), on hydrogenation in the presence of a nickel–kieselguhr catalyst at 100° and under an initial hydrogen pressure of 100 atmospheres, absorbed six moles of hydrogen per mole of hydrocarbons to yield a compound corresponding to $C_{20}H_{36}$ (II).

The tricyclic hydrocarbon (I) on destructive hydrogenation at 240° under pressure in the presence of a copper oxide–alumina catalyst yielded toluene and a bicyclic aromatic hydrocarbon corresponding to $C_{13}H_{18}$ (III); some of the original tricyclic hydrocarbon was recovered.

The bicyclic hydrocarbon, $C_{13}H_{18}$ (III), obtained from the destructive hydrogenation, was further hydrogenated under pressure at 100° in the presence of a nickel–kieselguhr catalyst. A bicyclic hydrocarbon corresponding to $C_{13}H_{24}$ (IV) was obtained.

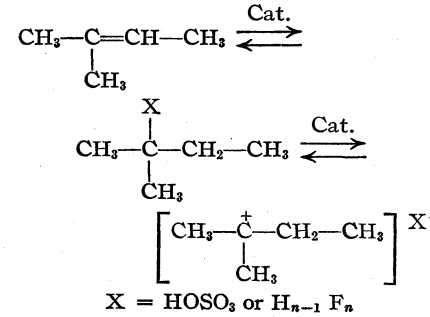
The tricyclic hydrocarbon $C_{20}H_{24}$ (I) did not undergo dehydrogenation when passed over platinized alumina at 300°.



(I) 1,3,3,6-Tetramethyl-1-*p*-tolylindan
(II) 1,3,3,6-Tetramethyl-1-(4-methylcyclohexyl)-hexahydroindan
(III) 1,1,3,5-Tetramethylindan
(IV) 1,1,3,5-Tetramethylhexahydroindan
Compounds II, III, IV were prepared for the first time

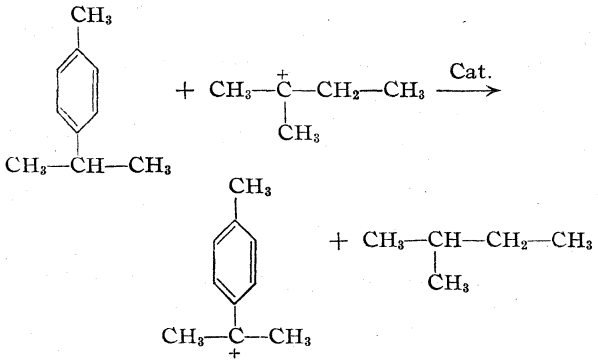
Mechanism of Reaction.—The following mechanism is suggested to explain the hydrogen transfer reaction between trimethylethylene and *p*-cymene:

1. The olefinic hydrocarbons react with the catalyst; a carbonium ion is probably formed.

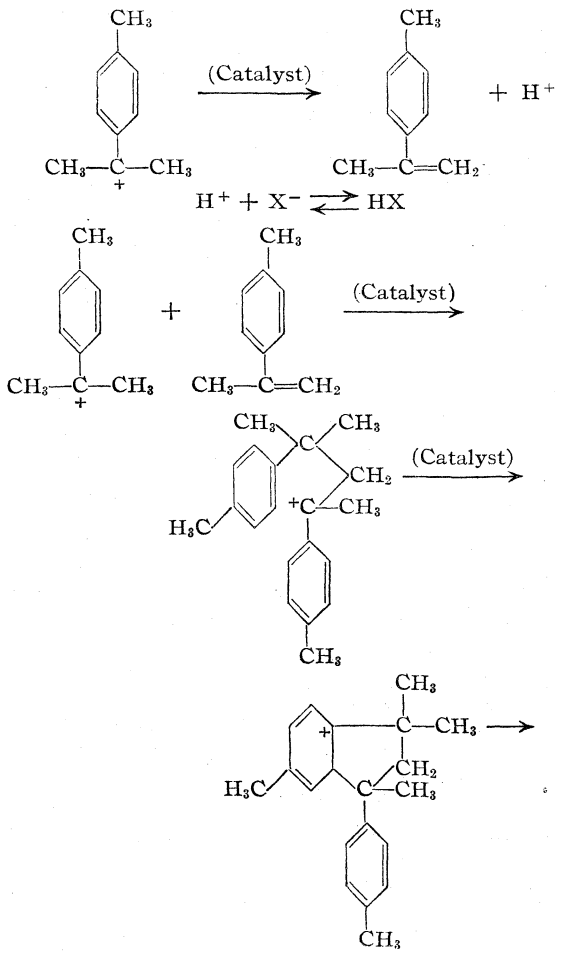


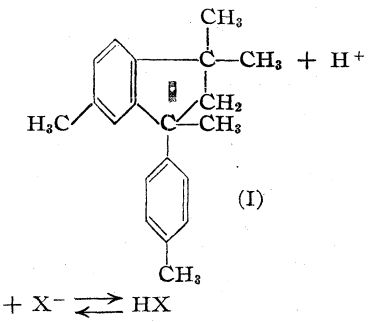
2. In the presence of an alkylating catalyst an exchange reaction

probably occurs similar to the type described by Bartlett, Condon and Schneider.[8]



3. Part of the dimethyl-*p*-tolyl carbonium ion formed may lose a proton to form 1-methyl-4-isopropenylbenzene; the latter on reaction with the dimethyl-*p*-tolylcarbonium ion forms probably 2,4-di-*p*-tolyl-4-methyl-2-pentylcarbonium ion. The latter through an internal addition to the benzene ring and a subsequent loss of a proton yields 1,3,3,6-tetramethyl-1-*p*-tolylindan (I).

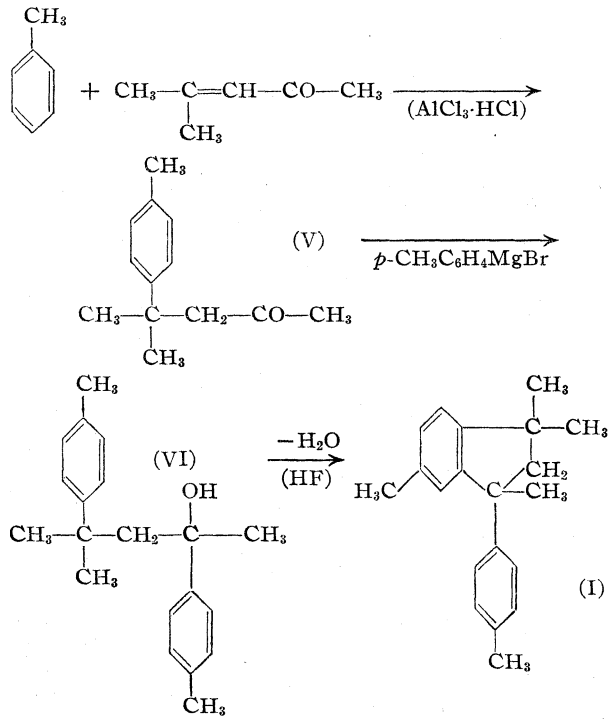




In order to prove that the formation of 1,3,3,6-tetramethyl-1-*p*-tolylindan (I) may proceed through the above indicated mechanism, 1-methyl-4-isopropenylbenzene was prepared and the compound treated with hydrogen fluoride under experimental conditions similar to those required for a hydrogen transfer reaction. The product of the reaction was 1,3,3,6-tetramethyl-1-*p*-tolylindane. This is in agreement with a similar result obtained by Bergmann, Taubadel and Weiss[9] who found that the dimerization of isopropenylbenzene in the presence of acid acting catalysts yields 1,3,3-trimethyl-1-phenylindan.

p-Cymene by itself does not undergo any changes when treated with either hydrogen fluoride or sulfuric acid under the experimental conditions used for the hydrogen transfer reaction.

1,3,3,6-Tetramethyl-1-*p*-tolylindan (I) was synthesized as follows.[9]



The para position of the substituents on the aro-

(8) P. D. Bartlett, F. E. Condon and A. Schneider, THIS JOURNAL, **66**, 1531 (1944).

(9) The general scheme of the synthesis was similar to the method of E. Bergmann, H. Taubadel and H. Weiss, *Ber.*, **64**, 1493 (1931).

TABLE I

Experiment number	1	2	3	4	5
Reagents used:					
p-Cymene, moles	2.0	4.8	4.0	0.8	1.0
Olefins, kind	Trimethylethylene	Methylcyclohexene		Dihydrolimonene	Octene
Olefins, moles	1.0	2.0	2.0	0.4	0.5
Catalyst, kind	HF	H_2SO_4	HF	HF	H_2SO_4
Catalyst, moles	8.4	2.4	6.6	3.3	0.6
Results obtained:					
Hydrocarbon layer, grams	318	800	696	154	175
Hydrocarbon wt. % yield	94	96	96	94	92
Composition of hydrocarbon layer; based on total product recovered					
Saturated product formed, kind	Isopentane	Methylcyclohexane		Paramenthane	Octane
Saturated product formed, moles	0.33[c]	1.31	1.69	0.17	0
p-Cymene recovered, moles	1.29	3.28	2.19	.59	0.55
Alkylated product,[a] grams	51	42	39	5[e]	88
moles	0.25	0.18	0.17	0.02	0.36
1,3,3,6-Tetramethyl-1-*p*-tolylindane, moles	.23	.58	.75	.15	0
Evaluation of yield: original aromatic hydrocarbon converted to[b]					
(1) Alkylated product,[a] mole %	25[f]	9	8.5	5.0	72[g]
(2) 1,3,3,6-Tetramethyl-1-*p*-tolylindan, mole %	46	58	75	75	0
Olefinic hydrocarbons converted to[b]					
(1) Saturated hydrocarbons, mole %	43[d]	65	84.5	42.5	0
(2) Alkylated product,[a] mole %	25[f]	9	8.5	5.0	72[g]

[a] Hydrocarbons corresponding to the interaction of a mole of olefins with a mole of aromatic hydrocarbons charged. [b] The yields were calculated on the basis of olefin reacted. [c] In addition to isopentane 0.05 mole of decanes was formed. [d] Includes decanes produced, which distilled at 145–155°, $n^{20}D$ 1.4182. *Anal.* Calcd. for $C_{10}H_{22}$: C, 84.41; H, 15.59. Found: C, 84.64; H, 15.65. [e] Estimated from the index of refraction. [f] It distilled at 94–96° at 4 mm., $n^{20}D$ 1.5021. *Anal.* Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.74; H, 11.42. [g] It distilled at 126–129° at 4 mm., $n^{20}D$ 1.4842. *Anal.* Calcd. for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 88.11; H, 11.78.

matic ring was proved by means of oxidation of compound (V) to terephthalic acid.

Experimental Part

The reactions of *p*-cymene with olefins in the presence of catalysts were carried out by the following procedure.

Sulfuric Acid Catalyzed Reaction.—The apparatus consisted of an appropriately sized three-neck flask equipped with a mercury sealed stirrer, reflux condenser and a water-cooled dropping funnel. The flask was surrounded by a cooling bath of ice and water. A thermometer was inserted into the reaction flask.

The sulfuric acid (96%) and one-half of the *p*-cymene were introduced into the flask and cooled at 0°. The olefinic hydrocarbon and the remainder of the *p*-cymene were mixed and added slowly with efficient stirring to the contents of the flask. The rate of addition was controlled so as to maintain the temperature inside the flask between 0° and 7°. After the addition was finished, the stirring was continued for a half hour.

The contents of the flask were poured into a separating funnel and allowed to stand for one to two hours in order to assure a complete separation of the acid and hydrocarbon layers.

The hydrocarbon layer was separated washed with water, with alkali, again with water, dried and distilled.

Hydrogen Fluoride Catalyzed Reaction.—The apparatus consisted of a copper flask provided with a copper stirrer and a dropping funnel. The flask was surrounded by a cooling bath of ice and water. The procedure was the same as that of sulfuric acid.

The contents of the flask were poured into a copper beaker containing ice precooled to about −30°. The hydrocarbon was separated and washed with dilute aqueous potassium hydroxide, followed by a water wash, then dried over calcium chloride and distilled.

The experimental results obtained are given in Table I.

As an example of the methods used for the identification of the reaction product, Experiment 2 is described in detail.

Experiment 2 (*p*-Cymene-methylcyclohexene–Sulfuric Acid).—Distillation of 700 g. of hydrocarbon mixture yielded the following fractions:

Fraction 1, b. p. 101°, $n^{20}D$ 1.4220, 114 g., corresponds to methylcyclohexane, since on dehydrogenation over platinized alumina (Pt 7%) at 260°,[10] it yielded toluene. The latter was identified by means of its dinitro derivative, which melted at 70°.

Fraction 3, b. p. 172–174°, $n^{20}D$ 1.4890, 378 g., consists of unreacted *p*-cymene, as determined by the ultraviolet absorption spectra.

Fraction 6, b. p. 124–126° at 4 mm., $n^{20}D$ 1.5305, d^{20}_4 0.9581, 28 g., corresponds to methylcyclohexyl-*p*-cymene.

Anal. Calcd. for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 89.40; H, 10.68.

Nitro Derivative.—One ml. of the product was treated with 5 ml. of nitrating mixture composed of 1 vol. 72% nitric acid and 2 vol. 96% sulfuric acid. The nitro compound was crystallized from ethanol. It melted at 152–153°.

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.75; H, 7.50; N, 8.75. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.74; H, 7.19; N, 9.15. Found: C, 62.53; H, 6.91; N, 8.79.

According to elementary analysis, the nitro compound corresponds to isopropyl-(methylcyclohexyl)-dinitrobenzene; it seems that a methyl group in the benzenoid ring was replaced by a nitro group. Such replacement is quite common.[11]

The sulfonamide was prepared by the procedure of Huntress and Autenrieth[12] and crystallized twice from dilute alcohol and twice from benzene–pentane solution. It melted at 187–188°.

(10) H. Pines and V. N. Ipatieff, THIS JOURNAL, **61**, 1076 (1939).

(11) D. Nightingale, *Chem. Rev.*, **40**, 117 (1947).

(12) E. H. Huntress and J. S. Autenrieth, THIS JOURNAL, **63**, 3446 (1941).

Anal. Calcd. for $C_{17}H_{27}NSO_2$: C, 66.02; H, 8.74; N, 4.53. Found: C, 66.22; H, 8.71; N, 4.65.

Fraction 9, b. p. 156° at 4 mm., $n^{20}D$ 1.5580, 128 g., corresponds to 1,3,3,6-tetramethyl-1-*p*-tolylindan.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 91.31; H, 8.96.

The product crystallized out very slowly until it was seeded with (I). It melted at 37.5°.

Nitration.—One gram of the hydrocarbon $C_{20}H_{24}$ was dissolved in 5 ml. of chloroform, cooled to 0°, and to it was added 1.5 ml. of 96% sulfuric acid and 0.5 ml. of 72% nitric acid. A crystalline derivative was obtained, melting at 112–114°. After crystallization from ethanol it melted at 114–115°; it corresponded to 1,3,3,6-tetramethyl-5-nitro-1-(4-methyl-3-nitrophenyl)-indan.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.80; H, 6.21; N, 7.90. Found: C, 68.12; H, 6.02; N, 7.89.

One-half ml. of the product was treated with 5 ml. of a nitrating mixture, composed of 1 vol. 72% nitric acid and 2 vol. 96% sulfuric acid, and heated for a few minutes to 70–80°. The product solidified while still hot; it was poured over ice, filtered and the solid crystallized from a hot ethanol–chloroform mixture. White glistening crystals were obtained, which melted at 251–252°. The nitro compound corresponds to 1,3,3,6-tetramethyl-5,7-dinitro-1-(4-methyl-3,5-dinitrophenyl)-indan. Mixed melting point with a synthetically prepared tetranitro derivative showed no depression.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.20; H, 4.43; N, 12.84.

The sulfonamide crystallized from water–alcohol mixture; it melted at 227–228° and corresponded probably to 1,3,3,6-tetramethyl-1-(4-methyl-3-sulfonamido-phenyl)-5-sulfonamido-indan.

Anal. Calcd. for $C_{20}H_{26}O_4N_2S_2$: C, 56.87; H, 6.16; N, 6.63. Found: C, 57.57; H, 6.34; N, 6.34.

Oxidation.—One gram of the product was heated under reflux with a solution composed of 30 ml. of acetic acid, 30 ml. of water, 5 ml. of 96% sulfuric acid and 7 g. of chromic anhydride. The mixture was heated for six hours. The solution was cooled and diluted with water; a solid precipitated out, which was filtered and washed with water. The solid was dissolved in dilute aqueous sodium hydroxide and extracted with ether to remove any neutral material which might be present. The aqueous solution was then acidified with dilute hydrochloric acid. The organic acid which separated out melted at 294–295°; it corresponds to 1,3,3-trimethyl-1-(4-carboxyphenyl)-6-carboxyindan.

Anal. Calcd. for $C_{20}H_{20}O_4$ (mol. wt. 324): C, 74.08; H, 6.17. Found: C, 73.22; H, 6.78; neutral equivalent of the acid, 160.

Hydrogenation.—Fifteen grams of the hydrocarbon $C_{20}H_{24}$ was hydrogenated at 100° under an initial hydrogen pressure of 120 atmospheres and in the presence of 2.5 g. of a nickel–kieselguhr catalyst. From the pressure drop it was calculated that 6 moles of hydrogen were absorbed per mole of hydrocarbon.

The hydrogenated material distilled at 183° (13 mm., $n^{20}D$ 1.4982, d^{20}_4 0.9248. It corresponds to 1,3,3,6-tetramethyl-1-(4-methylcyclohexyl)-hexahydroindan (Compound II).

Anal. Calcd. for $C_{20}H_{36}$: C, 86.87; H, 13.13. Found: C, 86.70; H, 13.20.

Destructive Hydrogenation.—Twenty-seven grams of fraction 9 was submitted to destructive hydrogenation in the presence of 4 g. of a coprecipitated copper oxide–alumina catalyst (copper oxide 60% by wt.). The reaction was carried out in a 450 cc. capacity rotating autoclave at 270° and at an initial hydrogen pressure of 122 atm. measured at 28°. The time of heating was seven hours; the maximum pressure was 230 atm.; the final pressure measured at 28° was 106 atm.

The gases were collected and analyzed; they consisted of 99.4% of hydrogen. The liquid product was fractionally distilled and the following cuts were collected:

Cut 1, b. p. 108–110°, $n^{20}D$ 1.4940, 3.5 g., consisted of toluene. A dinitrotoluene was prepared melting at 70°.

Cut 3, b. p. 210–212°, $n^{20}D$ 1.5071, 6.5 g., corresponded to 1,1,3,5-tetramethylindan (Compound III).

Anal. Calcd. for $C_{13}H_{18}$: C, 89.66; H, 10.34. Found: C, 89.47; H, 10.50.

Cut 4, b. p. 158° at 4 mm., $n^{20}D$ 1.5545, 12.5 g., corresponded to recovered compound I. It melted at 37.5° and yielded a tetranitro derivative melting at 250° and a sulfonamide melting at 123–124°.

Anal. Calcd. for $C_{13}H_{19}SO_2N$: N, 5.53. Found: N, 5.47.

A larger amount of 1,1,3,5-tetramethylindan was prepared and 17 g. of the hydrocarbon was hydrogenated in the presence of 3 g. of nickel–kieselguhr catalyst at 100° and under an initial hydrogen pressure of 100 atmospheres at 25°. From the drop in hydrogen pressure it was calculated that three moles of hydrogen was absorbed per mole of hydrocarbon. The hydrogenated product distilled at 213–215°, $n^{20}D$ 1.4622. It corresponds to 1,1,3,5-tetramethylhexahydroindan (Compound IV).

Anal. Calcd. for $C_{13}H_{24}$: C, 86.25; H, 13.75. Found: C, 86.77; H, 13.40.

Synthesis of 1,1,3,6-Tetramethyl-1-*p*-tolylindan (I)

4-Methyl-4-*p*-tolyl-2-pentanone (V).—The reaction vessel consisted of a 2-liter three-neck flask containing a mercury sealed stirrer, a dropping funnel and a reflux condenser. Toluene, 108 g. (2 *M*) and 200 g. of carbon disulfide were placed in the reaction flask which was surrounded with ice. To this solution was added 160 g. (1.2 moles) of aluminum chloride; on the addition of the catalyst the solution turned a deep red color. To the contents of the flask 98 g. (1 mole) of mesityl oxide was added over a period of two and one-half hours. After the addition was completed, the stirring was continued for an additional two hours. During all this time a slow stream of hydrogen chloride was bubbled into the liquid. The content of the flask was then poured onto ice. Two layers were formed: the upper (organic) layer was separated, washed with water, followed by sodium carbonate solution and again with water. The product was then steam distilled to remove the excess of toluene and carbon disulfide; the remaining material was separated from the water, dried and distilled under reduced pressure.

The 4-methyl-4-*p*-tolyl-2-pentanone (V) formed, distilled at 160° at 37 mm., $n^{20}D$ 1.5082, d^{20}_4 0.9594; yield, 40%.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.11; H, 9.47. Found: C, 82.15; H, 9.37.

Semicarbazone, after two crystallizations from 60% ethanol, melted at 190–191°.

Anal. Calcd. for $C_{14}H_{21}ON_3$: N, 17.00. Found: N, 17.40.

Oxidation.—One half gram of the ketone was treated under reflux for three hours with a solution consisting of 3.5 g. of chromic anhydride, 15 ml. of glacial acetic acid, 15 ml. of water and 4 ml. of 96% sulfuric acid. On dilution with water, a solid separated, which was filtered, washed with water and dried. It did not melt at 290°. The solid corresponded to terephthalic acid since the corresponding dimethyl ester melted at 141° and did not show a depression in melting point when mixed with a known sample of dimethyl terephthalate.

4-Methyl-2,4-di-*p*-tolyl-2-pentanol (VI)

p-Tolylmagnesium bromide prepared from 21 g. (0.12 mole) of *p*-bromotoluene and 2.9 g. (0.12 atom) of magnesium was condensed with 19 g. (0.1 mole) of (V). The carbinol VI, 18 g., distilled at 160° (3 mm.); $n^{20}D$ 1.5520.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.11; H, 9.22. Found: C, 85.10; H, 9.17.

1,1,3,6-Tetramethyl-*p*-tolylindan (I)

Six grams of (VI) was dissolved in 15 g. of methylcyclohexane and the solution was added, with stirring,

to 17 g. of anhydrous hydrogen fluoride at 0°. The content of the copper flask was then poured onto ice. The hydrocarbon layer was separated, washed with potassium hydroxide, water, dried over calcium chloride and distilled. Three grams of (I) was obtained, boiling at 161° (7.5 mm.), $n^{20}D$ 1.5579.

The infrared and ultraviolet absorption spectra were taken.

Two-tenths gram of (I) was nitrated with 5 ml. of nitrating mixture consisting of 2 vol. 96% sulfuric acid and 1 vol. of 72% nitric acid. The nitro compound obtained was crystallized from a solution of ethanol and chloroform. It melted at 251°, and did not depress the melting point of the tetranitro derivative of the $C_{20}H_{24}$ hydrocarbon.

Dimerization of 1-Methyl-4-isopropenylbenzene

A. Dimethyl-*p*-tolyl-carbinol.—The carbinol was prepared from 256 g. (1.5 mole) of *p*-bromotoluene and 81 g. (1.4 mole) of acetone via a Grignard reaction according to the procedure of Sabatier and Marat.[13] The carbinol distilled at 73° (2.5 mm.), $n^{20}D$ 1.5168; yield 66%.

B. 1-Methyl-4-Isopropenylbenzene.—Forty-three grams of the carbinol was passed at 350° during a period of one hour over 40 cc. of activated alumina of a 10–12 mesh size. The hydrocarbon distilled at 82° (21 mm.), $n^{20}D$ 1.5350; yield was over 80%.

C. Polymerization of 1-Methyl-4-isopropenylbenzene.—Eight grams of 1-methyl-4-isopropenylbenzene dissolved in 7 g. of methylcyclohexane was added with agitation to 10 ml. of anhydrous hydrogen fluoride placed in a copper beaker. The mixture was stirred for fifteen minutes and then poured onto 15 g. of ice precooled to −40°. The hydrocarbon layer was separated, diluted with ether, washed with aqueous potassium hydroxide, dried, and distilled. Three grams of a hydrocarbon boiling at 171° (5 mm.) was obtained; $n^{20}D$ 1.5545, melting point 33°. According to ultraviolet analysis it consisted of 1,3,3,6-tetramethyl-1-*p*-tolylindan (Compound I).

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 91.03; H, 9.11.

(13) P. Sabatier and M. Murat, *Compt. rend.*, **156**, 184 (1913); *Ann. Chim.*, [9] **4**, 253 (1915).

On nitration with nitrating mixture consisting of 2 vols. of sulfuric acid and 1 vol. of nitric acid it formed a tetranitro derivative, which after two crystallizations from ethanol–chloroform solution melted at 248°, and did not depress the melting point of the tetranitro derivative prepared from a known sample of Compound I.

Acknowledgment.—We are indebted to Mr. Don Strehlau for some of the derivatives, to Mrs. Margaret Ledyard for the elementary analyses and to Dr. W. S. Gallaway of the Universal Oil Products Company for the infrared analyses.

Summary

The reaction of *p*-cymene with trimethylethylene, methylcyclohexene, dihydrolimonene, 1-octene, and cyclohexene in the presence of either sulfuric acid or hydrogen fluoride was investigated.

Hydrogen transfer occurs when *p*-cymene reacts with the first three olefins; the products resulting from such reaction consist of isopentane, methylcyclohexane, and *p*-menthane, respectively, and 1,3,3,6-tetramethyl-1-*p*-tolylindan which is formed in each case.

1,3,3,6-Tetramethyl-1-*p*-tolylindan was synthesized.

A mechanism for the hydrogen transfer reaction is proposed:

The following new compounds and their derivatives were prepared: (a) 4-methyl-4-*p*-tolyl-2-pentanone, (b) 4-methyl-2,4-di-*p*-tolyl-2-pentanol, (c) 1,3,3,6-tetramethyl-1-(4-methylcyclohexyl)-hexahydroindan, (d) 1,1,3,5-tetramethylindan, and (e) 1,1,3,5-tetramethylhexahydroindan.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL]

The Acid Hydrolysis of Egg Albumin. I. Kinetic Studies

BY HENRY B. BULL AND J. WILFRID HAHN

It becomes increasingly clear that a central problem of protein chemistry is the localization of the amino acid residues in the peptide chains, and it is possible that study of the hydrolysis of proteins might shed light on this problem. While the literature on protein hydrolysis is extensive, there are certain features of this reaction which have not been explored. The present paper reports the results of an investigation of the hydrolysis of purified hen's egg albumin at 30°, at 45° and at 60° by hydrochloric acid. The amino nitrogen, the free amino acids, the ammonia, the material insoluble in trichloroacetic acid as well as the heat coagulable material have been determined, and an interpretation of these results is suggested.

Experimental

One volume of a solution of crystalline albumin prepared from fresh chicken eggs by the method of Kekwick and Cannan[1] was added to two volumes of concentrated hydrochloric acid. The flask containing the reaction mixture was securely stoppered and placed in a water-bath at the desired temperature and rotated occasionally. A single, clear, homogeneous phase resulted in a few minutes. At intervals, 20-cc. aliquots were removed and neutralized with powdered sodium bicarbonate, and the turbid solutions resulting made up to 50 cc. with water. Ammonia, free amino acids and amino nitrogen were determined on these dilutions.

Material precipitable by trichloroacetic acid was measured on 5-cc. aliquots of the reaction mixture which were diluted to 50 cc. without neutralization. Five cc. of this dilution was treated with 10 cc. of a 4% trichloroacetic acid solution, and after fifteen minutes filtered and the total nitrogen of the filtrate determined.

The heat coagulable material was determined by adjusting a 5-cc. aliquot of the hydrolyzate to about *p*H 4.5, heating on a boiling water-bath for five minutes, diluting to 50 cc. and filtering. Total nitrogen was run on the filtrate.

(1) Kekwick and Cannan, *Biochem. J.*, **30**, 227 (1936).

On the basis of total nitrogen in egg albumin,[2] the reaction mixture contained 4.25 g. of protein per 100 cc. The hydrochloric acid during the first part of the reaction was 7.95 *N* as determined by titration with standard base.

The ammonia was obtained by a steam distillation in the Pregl micro-Kjeldahl apparatus, using magnesium oxide as the alkalizing agent.

The amino nitrogen was measured in the Van Slyke volumetric apparatus by the Kendrick–Hanke modification,[3] and the reaction time was ten minutes. An ammonia correction was determined by the method of Irving, Fontaine and Samuels[4] and this correction, which amounted to 55% of the ammonia, was applied to the amino nitrogen values.

To calculate the rate of hydrolysis of peptide bonds from the amino nitrogen, it was necessary to assume that the bonds involving proline and hydroxyproline were hydrolyzed at a rate proportional to their amounts[5] in egg albumin.

The free amino acids released were measured by the ninhydrin titrimetric method at *p*H 2.5.[6] Aspartic acid yields carbon dioxide from both its carboxyl groups, and the ninhydrin values are too large by this amount. Following Frost and Heinsen,[7] we have assumed that aspartic acid is liberated at a rate proportional to its relative concentration[8] in the protein, and the ninhydrin values corrected on this basis.

Controls were prepared by neutralizing 13.5 cc. of concentrated hydrochloric acid with sodium bicarbonate and then adding 6.67 cc. of the mother protein solution. Control values have been subtracted from each determination to give the groups actually produced by the hydrolysis.

Results

Tables I, II and III show the quantities of ammonia, amino nitrogen and free amino acids produced by acid hydrolysis at 30°, at 45° and at 60° expressed in milliequivalents per gram of egg albumin. From the average residue weight for egg albumin and on the basis of 4 peptide chains in this protein,[8] there are about 8.89 milliequivalents of peptide bonds in one gram of protein. Percentage hydrolysis was calculated using this value after the proline correction had been applied.

Table IV shows the percentage of the total nitrogen in solution after treatment with trichloroacetic acid by the technique described above. Also shown is the per cent. of the total nitrogen in solution after isoelectric heat coagulation. The agreement between these sets of data is by no means perfect. We are inclined to believe that

TABLE I

MILLIEQUIVALENTS OF AMMONIA, AMINO NITROGEN AND FREE AMINO ACIDS PER GRAM OF EGG ALBUMIN PRODUCED BY ACID HYDROLYSIS AT 30°. ALSO SHOWN ARE THE PERCENTAGES OF PEPTIDE BONDS HYDROLYZED

Time in hours	NH_3	Amino nitrogen: Corrected for NH_3	Amino nitrogen: Corrected for NH_3 and proline	Amino nitrogen: Per cent. hydrolysis	Free amino acids: Uncorrected	Free amino acids: Corrected for aspartic acid
2	0.05	..	..	..	...	...
4	.09	0.17	0.18	2.0	...	...
9	.21	0.73	0.76	8.5	0.019	0.017
22	.36	1.59	1.66	18.6	.152	.142
29.5	.50	1.86	1.94	21.8	.248	.232
48.5	.60	2.50	2.61	29.3	.357	.334
72.25	.66	3.02	3.15	35.4	.515	.482
120	.70	3.44	3.59	40.4	.935	.875
144	.71	3.88	4.04	45.4	.930	.870
195	.69	4.32	4.50	50.5	1.14	1.07
240	.72	4.42	4.62	52.0	1.36	1.27
289	.72	4.84	5.04	56.5	1.54	1.44
335	.71	4.96	5.17	58.1	1.81	1.69

TABLE II

MILLIEQUIVALENTS OF AMMONIA, AMINO NITROGEN AND FREE AMINO ACIDS PER GRAM OF EGG ALBUMIN PRODUCED BY ACID HYDROLYSIS AT 45°. ALSO SHOWN ARE THE PERCENTAGES OF PEPTIDE BONDS HYDROLYZED

Time in hours	NH_3	Amino nitrogen: Corrected for NH_3	Amino nitrogen: Corrected for NH_3 and proline	Amino nitrogen: Per cent. hydrolysis	Free amino acids: Uncorrected	Free amino acids: Corrected for aspartic acid
0.5	0.03	..	..	..	...	...
1.0	.10	0.51	0.53	6.0	0.071	0.066
1.5	.15	.57	.59	6.6	...	...
2.0	.20	.81	0.84	9.5	.038	.035
3.0	.30	1.00	1.04	11.7	.140	.131
3.1	.32	1.06	1.11	12.5	.102	.096
4.0	.37	1.14	1.19	13.4	.179	.167
6.1	.50	1.66	1.73	19.4	.236	.221
10.0	.62	1.93	2.01	22.6	.338	.316
24.0	.70	3.20	3.14	35.3	.812	.760
30.5	.70	3.76	3.92	44.0	.965	.903
48.0	.65	4.51	4.70	52.9	1.38	1.29
77.0	.68	5.13	5.35	60.0	1.88	1.76
103.0	.72	5.54	5.77	64.8	2.60	2.43
127.0	.69	5.60	5.84	65.5	2.75	2.57
145.0	.72	5.68	5.92	66.5	...	...

TABLE III

MILLIEQUIVALENTS OF AMMONIA, AMINO NITROGEN AND FREE AMINO ACIDS PER GRAM OF EGG ALBUMIN PRODUCED BY ACID HYDROLYSIS AT 60°. ALSO SHOWN ARE THE PERCENTAGES OF PEPTIDE BONDS HYDROLYZED

Time in hours	NH_3	Amino nitrogen: Corrected for NH_3	Amino nitrogen: Corrected for NH_3 and proline	Amino nitrogen: Per cent. hydrolysis	Free amino acids: Uncorrected	Free amino acids: Corrected for aspartic acid
0.30	0.12	..	..	..	0.050	0.047
.50	.17	0.85	0.88	9.9	.056	.052
.75	.29	0.95	0.99	11.1	.118	.110
1.00	.36	1.35	1.41	15.8	.087	.081
1.50	.48	1.83	1.91	21.4	.206	.193
2.00	.57	2.11	2.20	24.7	.224	.210
2.50	.59	2.30	2.39	26.8	.330	.319
3.00	.63	2.62	2.73	30.7	.387	.362
4.08	.65	2.94	3.06	34.4	.516	.483
5.00	.66	3.24	3.37	37.8	.610	.571
6.00	.68	3.53	3.68	41.4	.718	.672
7.00	.68	3.88	4.04	45.4	.855	.800

(2) Chibnall, Reese and Williams, *Biochem. J.*, **37**, 354 (1943).
(3) Kendrick and Hanke, *J. Biol. Chem.*, **117**, 161 (1937).
(4) Irving, Fontaine and Samuels, *Arch. Biochem.*, **4**, 347 (1944).
(5) Calvery, *J. Biol. Chem.*, **94**, 613 (1931).
(6) Van Slyke, MacFadyen and Hamilton, *ibid.*, **141**, 627 (1941).
(7) Frost and Heinsen, *ibid.*, **161**, 517 (1945).
(8) Chibnall, *Proc. Roy. Soc.* (*London*), **B131**, 152 (1942).

the isoelectric heat coagulation is more nearly a measure of the intact protein present in the hydrolysate than is trichloroacetic acid precipitation.

TABLE IV

PER CENT. OF THE TOTAL NITROGEN IN THE FILTRATE AFTER PRECIPITATION BY 2.67% TRICHLOROACETIC ACID (TCA) AND BY ISOELECTRIC HEAT COAGULATION (IHC)

30° Hydrolysis			45° Hydrolysis			60° Hydrolysis		
Time in hours	% Nitrogen TCA	IHC	Time in hours	% Nitrogen TCA	IHC	Time in hours	% Nitrogen TCA	IHC
2	8.27	8.64	0.5	7.46	10.10	0.25	18.70	..
4	21.70	25.50	1.0	22.65	31.65	.316	24.40	..
6	...	39.80	1.5	38.50	45.00	.50	43.7	50.0
8	...	51.70	2.0	47.50	55.40	.75	61.2	67.6
9	49.20	...	3.0	67.30	73.30	1.00	71.3	75.9
10	...	62.0	4.0	72.30	78.20	1.50	81.3	80.5
24.5	78.50	...	6.0	...	90.6	2.00	89.5	90.7
			6.1	81.40	...			

Discussion

The liberation of ammonia follows the kinetics of a first order reaction, and the rate constants for this reaction were 0.039, 0.22 and 0.79 mole per hour per mole at 30, at 45 and at 60°, respectively. These rates were proportional to 0.72, 0.72 and 0.71 millimole ammonia per gram of protein at 30, at 45 and at 60°, respectively. The values compare favorably with that reported by Chibnall.[4] The energies of activation were 22,100 calories and 17,700 calories for the temperature ranges 30–45 and 45–60°, respectively.

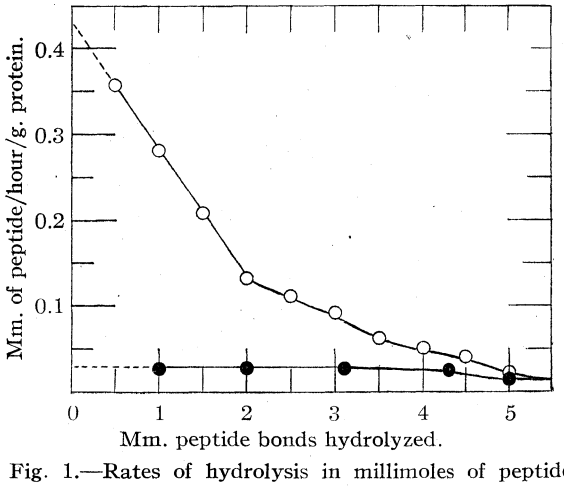


Fig. 1.—Rates of hydrolysis in millimoles of peptide bonds per hour per gram of protein. Open circles represent total peptide bonds and filled circles the liberation of free amino acid, 45° hydrolysis.

For a molecular weight of 45,000 for egg albumin, there are about 400 peptide bonds per molecule and, accordingly, there are potentially a large number of simultaneous reactions to consider. This is a complex problem, and its complete solution must await the future. It is not surprising that none of the measures of reaction velocity, with the exception of the ammonia liberation, follows with exactness any simple kinetic relation, and we do not regard speculation on the order of these reactions as profitable at the present.

The peptide bonds hydrolyzed and the amino acids liberated were plotted against the time of hydrolysis and the rates of rupture of the peptide bonds obtained from the slopes of the curves as a function of the bonds split. Shown in Fig. 1 is a plot of these rates at 45° against the extent of hydrolysis. The rates at 30° and at 60° exhibit the same qualitative behavior as is shown in Fig. 1.

From Figure 1, it appears that there is a fast reaction whose rate is 6 to 7 times greater than the slow reaction which accompanies it, and that the fast reaction is exhausted after a fraction of the peptide bonds have been hydrolyzed.

As a measure of the initial rates of reaction, we have determined the slopes of the tangents drawn from the origin for the various amount–time curves. From these rates we have calculated the ratio of the initial rate of hydrolysis of total peptide bonds and the initial rate of liberation of amino acids to the initial rate of destruction of protein as judged by isoelectric heat coagulation. We have calculated the energies of activation from these initial rates. These results are shown in Table V.

The average ratio of the initial rate of hydrolysis of peptide bonds to initial rate of destruction of protein is 56.5, and the corresponding ratio for the rate of liberation of amino acids is 4.58. When the intact protein is measured by the trichloroacetic acid precipitation, the total peptide ratio is about 70 and the free amino acid ratio is about 6.

Shown in Fig. 2 is a plot of the number of millimoles of peptide bonds hydrolyzed per gram of egg albumin against the fraction of the protein hydrolyzed. It will be noted that the experimental points lie on lines which apparently tend to converge into a single straight line during the first part of the reaction. As the reactions proceed toward completion, the curves swing upward rather sharply. Expressing the slope of the linear portion of the curve in peptide bonds hydrolyzed per gram molecular weight of egg albumin, we find

TABLE V

INITIAL RATES OF HYDROLYSIS IN MILLIMOLES PER HOUR PER GRAM OF PROTEIN, THE RATIO OF INITIAL RATES TO THE INITIAL RATE OF DESTRUCTION OF PROTEIN AND THE ENERGIES OF ACTIVATION

Temp., °C.	Free amino acids			Total peptide			Protein	
	Rate	Ratio to protein	Energy of activation	Rate	Ratio to protein	Energy of activation	Rate	Energy of activation
30	0.0066	4.55		0.074	50.7		0.00146	
45	.0294	4.23	19,100	0.43	61.1	22,500	.00695	20,000
60	.120	4.95	19,700	1.40	57.6	16,700	.0241	17,500

that 55 peptide bonds and 4.3 free amino acids are liberated for each egg albumin molecule destroyed. These values compare favorably with those given in Table V.

As can be seen in Table V the energies of activation for the hydrolysis of peptide bonds, the liberation of free amino acids and the destruction of protein are all of the same order of magnitude, and the conclusion is drawn that the destruction of the protein molecule is initiated by the hydrolysis of a single peptide bond, and the simultaneous activation of two or more peptide bonds is not necessary. It is to be noted that while the energy of activation for the liberation of amino acids is substantially constant over the temperature interval, the energy required for the activation of bonds leading to the destruction of the protein as well as the energy involved in the hydrolysis of total peptide bonds decreases significantly with increasing temperature, reflecting the existence of a complex reaction. Probably of great significance for the problem of hydrolysis of peptide bonds is the resonance energy of this bond. It can be estimated from bond distances that the peptide bond has about 45% double bond character and the activation of this bond, no doubt, blocks the resonance and weakens the bond by the extent of the resonance energy. It should be noted that the hydrolysis of a peptide bond is an exothermic reaction[9] yielding between 2,000 and 4,000 calories per mole. Whether or not the release of this energy would be sufficient to start an energy chain is not known.

In light of the above results and discussion, we suggest that the most reasonable interpretation of the acid hydrolysis of egg albumin is as follows: There exist two classes of peptide bonds in the protein as far as ease of hydrolysis is concerned. About 56 peptide bonds out of the 400 in the protein molecule can be hydrolyzed rapidly. The fragments produced by this initial split of the molecule are then further hydrolyzed, but at much slower rates. The rate at which a peptide bond is split is probably determined by the nature of the amino acid residues next to this bond.

(9) Haugaard and Roberts, THIS JOURNAL, **64**, 2664 (1942).

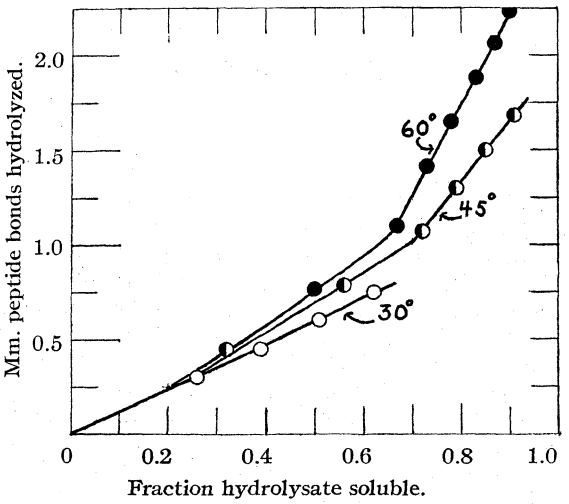


Fig. 2.—Millimoles of peptide bonds hydrolyzed per gram of egg albumin plotted against the fraction of protein not heat coagulable at the isoelectric point. Open circles 30° hydrolysis, half circles 45° hydrolysis and filled circles 60° hydrolysis.

Acknowledgment.—It is a pleasure to acknowledge the generous support afforded this research by Corn Products Refining Company.

Summary

1. The hydrolysis of egg albumin by hydrochloric acid has been studied at 30, at 45 and at 60°.

2. The amino nitrogen, the free amino acids and the ammonia liberated have been determined. The material soluble in trichloroacetic acid as well as the amount which cannot be heat coagulated at the isoelectric point have been measured.

3. The hydrolysis of a protein is not a simple kinetic process. About 56 of the peptide bonds in an egg albumin molecule are rapidly hydrolyzed, but the remaining bonds are hydrolyzed at a much lower rate.

CHICAGO 11, ILLINOIS RECEIVED DECEMBER 6, 1947

[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL]

The Acid Hydrolysis of Egg Albumin. II. Molecular Weight Distribution of Peptides

BY HENRY B. BULL AND J. WILFRID HAHN

This paper describes a new method for the estimation of the molecular weight distribution of the products resulting from the partial acid hydrolysis of proteins. The hydrolysate is spread on the surface of an ammonium sulfate solution and compressed. The peptides are forced into the substrate solution. The film is re-expanded, and the average molecular weight of the peptides remaining in the film determined by the application of the gas laws in two dimensions. By successive compressions to higher and higher pressures, it is possible to estimate the molecular weight distribution of the peptides in the hydrolysate. The hydrolysates have been described,[1] and were obtained by the action of 7.95 *N* hydrochloric acid on egg albumin at 30, at 45 and at 60°.

The Method

The general film technique has already been described.[2] The Wilhelmy slides consisted of two thin microscope cover glasses suspended from an arm of a Chain-o-Matic analytical balance and were located at one end of a well paraffined cast aluminum tray which was 65 cm. by 14 cm. One milligram of weight was equivalent to 0.0409 dyne per centimeter film pressure.

The substrate solution was a 5% ammonium sulfate solution which had been treated with activated charcoal and filtered. Glycerol which had been exhaustively extracted with petroleum ether was added to the ammonium sulfate to the extent of 2% by volume. It is not easy to obtain solution surfaces sufficiently free of surface active impurities, and care has to be exercised. Spreading was done with a Blodgett pipet whose delivery volume was 0.0850 cc. From 20 to 30 micrograms is a convenient weight of film for the size of tray used.

One minute after spreading, pressure readings were made as a function of film area up to a pressure of about one dyne per centimeter. The film was then compressed to 5 dynes per centimeter and held at this pressure for five minutes by moving the barrier in as part of the film passed into solution. The film was then re-expanded and a series of pressure readings below one dyne per centimeter was made as a function of the film area. The film was then compressed to 10 dynes per centimeter and held at this pressure for five minutes. The film was re-expanded and the low pressure measurements made. This process was repeated at 15, at 20 and at 25 dynes per centimeter pressure. It was possible to determine the complete molecular weight distribution of an hydrolysate in about an hour and a half.

When the film pressure is multiplied by the film area and this product plotted against the film pressure a straight line results, the equation of which is

$$FA_1 = \alpha_1 F + \beta_1 \qquad (1)$$

At zero film pressure, FA_1 is equal to β_1 and when A_1 is expressed in square meters per milligram, β_1 is equal to NRT which at 25° is equal to $24.6 \times 10^2/M$. The slope is equal to α_1 which is the area occupied by the gaseous film molecules.

Before we can calculate the molecular weight we must know the weight of the film. To find this weight we proceeded in the following manner.

A known weight of intact egg albumin was spread on the surface and compressed to 5 dynes per centimeter, and it was found that 1.11 milligram occupies one square meter at this pressure. An hydrolysate film was compressed to 5 dynes for five minutes. The film was then re-expanded and low pressure readings made. The area of the gaseous film was then determined with the use of equation 1. The relation between the gaseous area and the area at 5 dynes per centimeter for many different films is shown in Fig. 1. Evidently, there is a close relation between these two areas. The average ratio between the gaseous area and the 5 dyne per centimeter area is 1.065. If we assume that the area per milligram of the hydrolysate film at 5 dynes per centimeter is the same as that of the film of intact egg albumin, we can calculate the weight of the hydrolysate film by multiplying the area of the gaseous film by 1.035.

Shown in Fig. 2 is a typical plot of FA_1 against F, and demonstrates the reversibility of the pressure–area relation.

The weight of the Wilhelmy slides tends to increase with time. This increase amounted in some cases to as much as 5 mg. in the course of one and one-half hours and tends to give a non-linear relation when FA_1 is plotted against F, the apparent pressure being too small. It can be determined what weight must be added to the apparent pressures to yield a straight line when FA_1 is plotted against F, and such values have been accepted as valid provided the weight which had to be added was what was to be expected from the apparent increase of the surface tension of the clean surface during the same interval of time.

The return of some of the displaced peptides to the surface after the expansion of the film to low pressures would not invalidate this method, but would render the fractionation of the hydrolysate

(1) Bull and Hahn, THIS JOURNAL, **70**, 2128 (1948).

(2) Bull, *ibid.*, **67**, 4, 8 (1945); **68**, 745 (1946); *Adv. Prot. Chem.*, **3**, 95 (1947). See also Guastalla, *Cahiers phys.*, 2nd ser., **10**, 30 (1942).

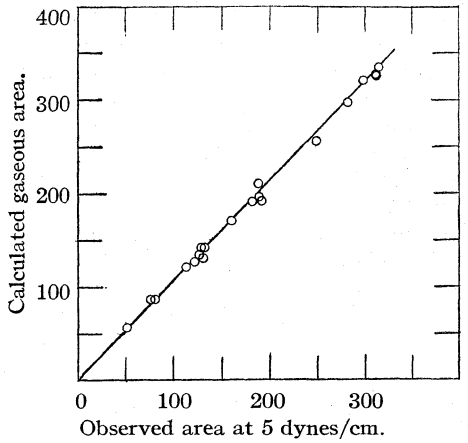


Fig. 1.—Calculated gaseous areas (α_1) in square meters plotted against the observed film area at 5 dynes per centimeter pressure.

inefficient to the extent to which such return occurs. To obtain a measure of this return to the surface the following experiment was done.

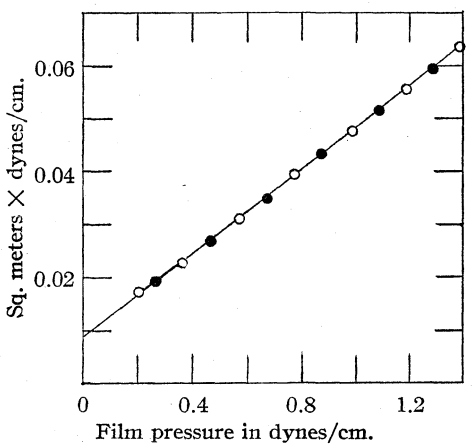


Fig. 2.—FA_1 in dynes per centimeter–square meter plotted against F in dynes per centimeter: open circles compression; filled circles, expansion.

An hydrolysate film was compressed to 25 dynes per centimeter and held at this pressure for five minutes. It was then re-expanded and after a few minutes compressed to 5 dynes per centimeter. This expansion and compression to 5 dynes per centimeter was repeated several times and the results plotted in Fig. 3.

The return of peptides to the film is probably small during a determination of the molecular weight distribution. Judging from the results shown in Fig. 3, roughly 2 to 3% of the displaced peptides would be expected to return to the film during an actual measurement of the molecular weight.

No answer can be given as to the accuracy of the present method because no other method exists for the resolution of peptides on the basis of their molecular weights, and it is not practical to synthesize a series of long chain peptides to calibrate the method. As shown previously,[2] results on the determination of the molecular weight of intact proteins were satisfactory and in accord with the results from accepted methods. As shown in Fig. 4, results from duplicate analyses of the molecular weight distribution of peptides are in reasonable agreement.

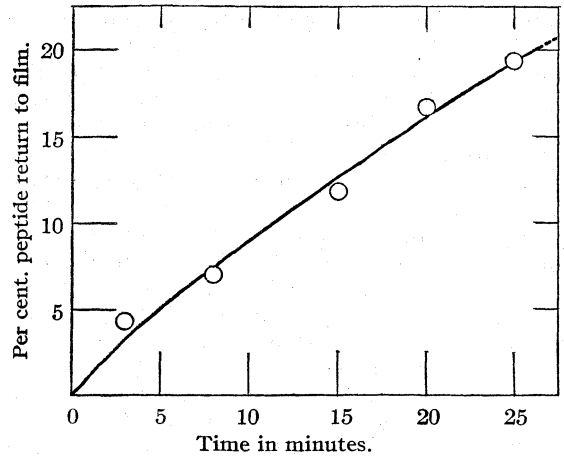


Fig. 3.—Per cent. of return of peptides to the surface as a function of time: 60° hydrolysate with 1.41 millimoles of peptide bond per gram of protein hydrolyzed.

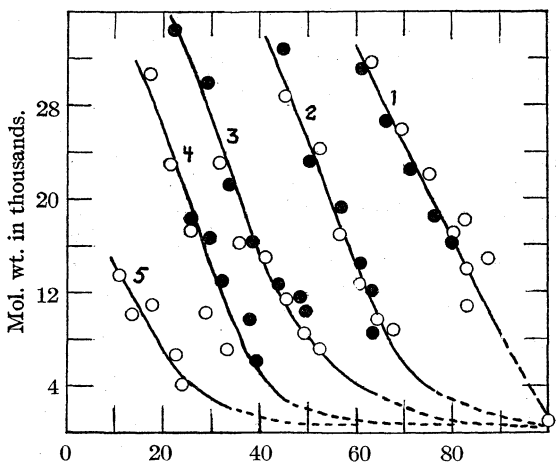


Fig. 4.—Number average molecular weights of peptides remaining in the film plotted against the per cent. of the total hydrolysate remaining in the film. The per cent. of the total peptide bonds hydrolyzed were as follows: Curve 1, 9.9; curve 2, 11.14; curve 3, 15.85; curve 4, 21.45; curve 5, 24.75. Open circles represent one series of measurements, while the filled circles are duplicates; 60° hydrolysates.

Results and Discussion

The partial hydrolysates used have been described[1] and were prepared for spreading by transferring 5 cc. of the hydrolysate resulting from the sodium bicarbonate neutralization to a 250 cc.

volumetric flask. A few drops of concentrated hydrochloric acid were added and after water was added nearly to volume, the flask was warmed to bring all of the hydrolysate into a clear solution. After cooling and making to volume the solutions were ready for spreading.

The primary data resulting from this investigation are very extensive, and it is not practical to report them in detail. It was found that the molecular weight distribution is, within limits of experimental error, the same for 30°, for 45° and for 60° hydrolysates for a given extent of hydrolysis and we are confining our report mainly to results for the 60° hydrolysates.

Shown in Fig. 4 are the number average molecular weights in thousands of the material remaining in the film after being subjected to compression, plotted as a function of the per cent. of the total amount of material in the hydrolysates. The individual curves are identified as representing material from different extents of hydrolysis at 60°. The open circles correspond to one series of measurements and the filled circles to results obtained several weeks later during a second series of measurements. While there is not perfect agreement between the two series, the agreement is reasonably satisfactory.

In order to express the results in Fig. 4 in a more understandable form, we have proceeded in the following manner:

The total number of moles of peptides remaining on the surface at any given compression have been calculated and these values plotted against the weight of the peptides in the film. The slopes of the smooth curves drawn through the points were measured with a Bausch and Lomb Tangent Meter. The reciprocal of these slopes is evidently equal to the molecular weight of the peptides being displaced from the film. These molecular weights were then plotted against the weight percentage of the peptides to give integral weight distributions which are shown in Fig. 5.

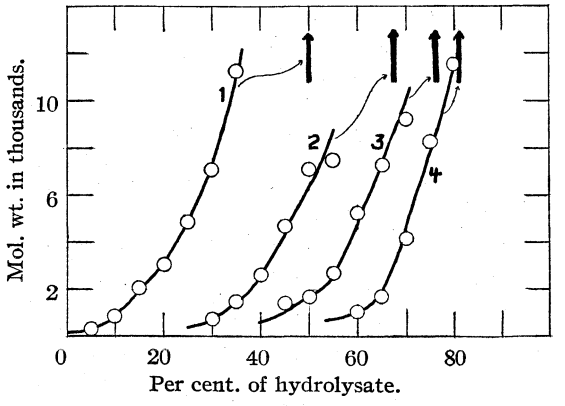


Fig. 5.—Integral molecular weight distribution curves for peptides resulting from the acid hydrolysis at 60°. The number of the curves corresponds to those shown in Fig. 4. Vertical lines at top of figure are the percentages of heat coagulable material at the isoelectric point.

It will be noted from Fig. 5 that the amount of isoelectric heat coagulable material is consistent with the molecular weight distribution of peptides. All curves in Fig. 5 are smooth, and there is no evidence for any appreciable accumulation of a peptide of a particular molecular weight.

A 30°, two hour hydrolysate was subjected to isoelectric heat coagulation. The percentage of peptide bonds hydrolyzed in the soluble peptides was 12.7. The integral distribution curve for these peptides is shown in Fig. 6.

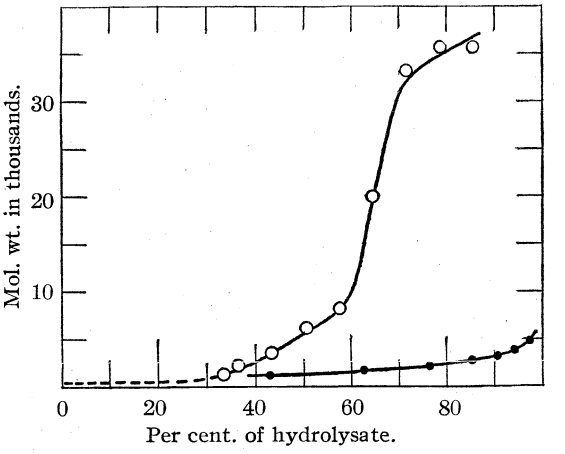


Fig. 6.—Integral molecular weight distribution curve of peptides after removal of isoelectric heat coagulable material: two hour hydrolysate at 30°. Also shown is the distribution of peptides on the basis of random hydrolysis for the same extent of hydrolysis (filled circles).

The molecular weight distribution of the pepides has been calculated for random hydrolysis with the theory of Montroll and Simha.[3] In these calculations the molecular weight of the monomer was assumed to be 111.3[4] and the number of residues to be 400. The fraction hydrolysis was 0.127. Figure 6 shows the results of these calculations, and it is clear that the hydrolysis of peptide bonds in egg albumin is far from being a random process.

Comparing the results shown in Fig. 6 with some of the conclusions drawn in the first paper of this series,[1] we can say the following: The 56 fast hydrolyzing bonds must be rather evenly distributed throughout at least part of the protein molecule, otherwise there would not be such a large fraction of low molecular weight peptides. On the other hand, there is a fairly large amount of peptides with molecular weights between 1,000 and 10,000. There is no way of knowing whether this heavier material is simply an intermediate in the fast reaction or is an end-product of this reaction. It is perhaps significant that there is little material whose molecular weight is between 10,000 and 30,000. This seems to indicate that the initial attack occurs on the ends of the peptide chains rather than in the middle.

(3) Montroll and Simha, *J. Chem. Phys.*, **8**, 721 (1940).
(4) Chibnall, *Proc. Roy. Soc.* (*London*), **B131**, 152 (1942).

In order to obtain the relation between the molecular weight of the peptides forced into the substrate solution and the pressure exerted on the film, the percentages of the hydrolyzed material remaining in the film were plotted against the pressures exerted. The corresponding molecular weights were then interpolated from Figs. 5 and 6. The logarithms of the molecular weight have been plotted against the pressures exerted and are shown in Fig. 7.

The points in Fig. 7 extrapolate at zero pressure to log molecular weight of about 3. This means that peptides whose molecular weight is about 1,000 or less pass spontaneously into the substrate solution and will not form a film.

The techniques described in this paper are being applied to the study of the molecular weight distribution of peptides resulting from the action of enzymes on proteins. These results will be reported in due time.

It is a pleasure to acknowledge the generous assistance granted this research by Corn Products Refining Company.

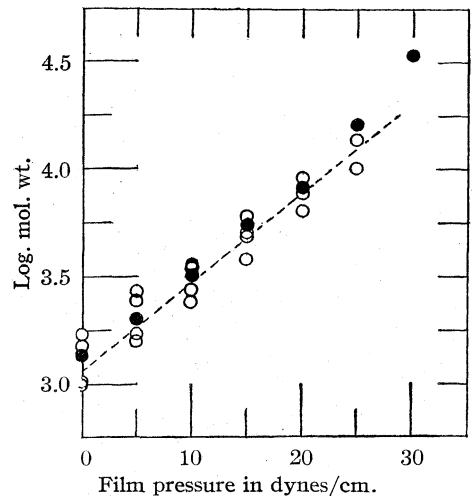


Fig. 7.—Logarithm of molecular weights of displaced peptides plotted against pressure exerted on the film. Open circles are 60° hydrolysates and filled circles two hour hydrolysate at 30° (protein free).

Summary

1. A new method has been described for the determination of the molecular weight distribution of peptides in a partial acid hydrolysate of a protein.

2. An hydrolysate is spread as a monomolecular layer on a 5% ammonium sulfate solution and is compressed to progressively increasing pressures. The logarithm of the molecular weight of the displaced peptides is proportional to the pressure exerted on the film. The molecular weight of the peptides remaining in the film after exposure to a given pressure is determined by the application of the gas laws in two dimensions.

3. The molecular weight distribution of egg albumin hydrolyzed by hydrochloric acid at several degrees of hydrolysis has been reported.

4. It is found that while the molecular weight distribution of peptides departs greatly from that expected for a random hydrolysis, there is no evidence for the accumulation of any considerable amounts of a peptide of a given molecular weight.

CHICAGO 11, ILLINOIS RECEIVED DECEMBER 6, 1947

[CONTRIBUTION FROM THE UNITED SHOE MACHINERY CORPORATION RESEARCH DIVISION]

Partition Chromatography of Amino Acids with Applied Voltage

BY GOTFRED HAUGAARD[1] AND THOMAS D. KRONER

In the one dimensional partition chromatography developed by Consden, Gordon and Martin[2] it is often very difficult to detect the bands of amino acids whose R_F values lie close together. To overcome this difficulty, two dimensional chromatography employing two solvents was developed by these workers.

In our work, we encountered overlapping of R_F values between the basic, acidic and certain neutral amino acids. We have effected a two dimensional chromatography by the passage of current through paper treated with phosphate buffer at *p*H 6.2.[3] The negatively charged acids—aspartic and glutamic—move toward the anode; the basic acids—lysine and arginine—migrate toward the cathode and the neutral amino acids are unaffected by the voltage gradient at the *p*H close to their isoelectric point.

Experimental

The papers used in the chromatograms were prepared as follows. Whatman no. 1 paper was dipped in *M*/15 phosphate buffer at *p*H 6.2 and the excess fluid was removed by pressing with a photographic roller over a glass plate. The paper strips (570 × 120 mm.) were air dried before use. We have employed aluminum, nickel and platinum as electrodes and have found little difference between them. The nickel ribbon (6.35 × 0.025 mm.) is woven into slits cut into the edges of the paper and the electrodes extend not more than one half the length of the paper. The electrodes may also be attached to the paper by stapling. The mixture of amino acids consisted of two dicarboxylic acids—aspartic and glutamic; two basic acids—lysine and arginine; and six neutral amino acids—serine, glycine, alanine, valine, leucine and proline. The concentration of the individual amino acids in the

(1) Present address: National Dairy Corporation, Oakdale, Long Island, New York.

(2) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

(3) R. R. Goodall and A. A. Levi, *Nature*, **158**, 675 (1946).

mixture was 0.1 mg. of NH_2-N/ml. and the mixture was applied from a micropipet at the center of the strip. The chromatograms were developed overnight (sixteen to eighteen hours) in a constant temperature room (23°) and phenol was the developing solvent. The potential used in most of the experiments was 100–105 v.

An example of the separation obtained with platinum electrodes and a potential of 105 v. is shown in Fig. 1. The separation of the bands is clear and sharp. It is obvious that little or no differentiation would have been possible without the applied voltage. The identity of the basic and acidic amino acids is substantiated by both the characteristic R_F value and the direction of migration in the electric field.

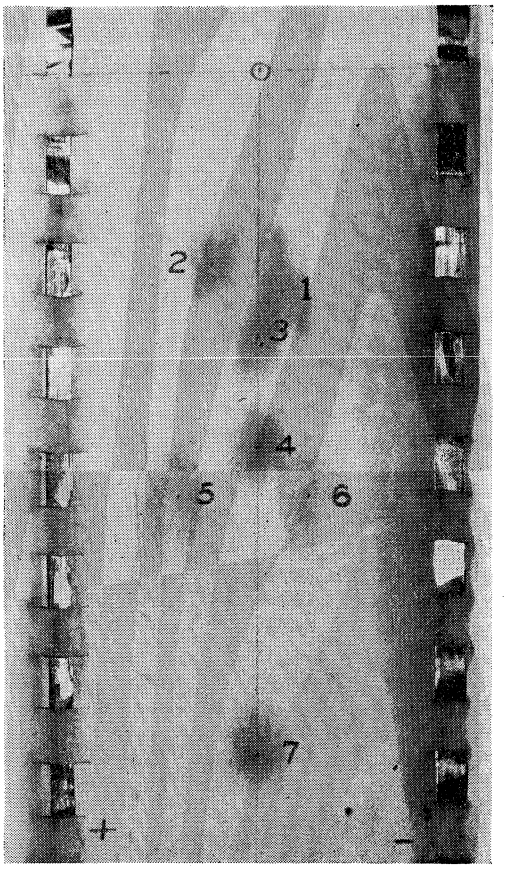


Fig. 1.—Partition chromatography of amino acids with applied voltage: 1, lysine; 2, aspartic acid; 3, serine; 4, glycine; 5, glutamic acid; 6, arginine; 7, alanine. Phenol is the developing solvent. Valine, leucine and proline with greater R_F values than alanine not shown.

In Table I, is shown statistical analysis of R_F values of 26–32 determinations on the ten amino acids. The error on the average values is not tabulated. The error in any of the determined R_F values is less than 0.01. The error in a single determination is found in the table and varies between the limits of ±0.02–0.04.

The R_F values found by us, except in the case of glutamic acid, are for the most part less than those reported by Consden, *et al.* The presence of the salts and the fixed *p*H may account for the lower R_F values.

Discussion

The optimum conditions for this method are (1) a voltage of 100; (2) a run of sixteen to eighteen hours; (3) paper buffered with *M*/15 phosphate at *p*H 6.2; (4) controlled temperature. Chromatograms have been carried out at 50 and 70 v.; the migration rates of the charged acids were a little lower but not as much as expected. The explanation of this phenomenon was found experimentally by measuring the potential gradients across the paper. The largest gradients were close to the electrodes and the potential differences at the interior of the paper were not proportional to the applied voltage. Chromatograms developed for eight hours at 100 v. failed to effect separation of the charged amino acids from the neutral acids. Tailing and spreading of the bands occurred on papers prepared with buffer at one-quarter and one-eighth strength. The optimum has been found to be 6.2.

In several runs, it was noticed that although separation had occurred some of the charged amino acids failed to give the typical color with ninhydrin. In these instances, it was shown by testing the paper with *p*H indicators that a high *p*H and a low *p*H zone extended, respectively, from the cathode and anode toward the midline. This phenomenon was associated with a final current greater than 0.3 milliampere. We believe that excessive electrolysis of the buffer resulted in this marked change in the *p*H of the paper. Careful preparation of the paper is necessary to avoid too great salt concentration.

TABLE I

R_F VALUES OF AMINO ACIDS IN PHENOL[a] ON WHATMAN NO. 1 PAPER BUFFERED WITH *M*/15 PHOSPHATE AT *p*H 6.2, AT 23°

Acid	R_F values	Error on a single measurement[b]
Serine	0.21	±0.02
Glycine	.28	± .04
Alanine	.49	± .04
Valine	.74	± .02
Leucine	.82	± .02
Proline	.86	± .02
Aspartic acid	.16	± .02
Glutamic acid	.32	± .03
Lysine	.17	± .02
Arginine	.32	± .03

[a] Hydrogen cyanide added to the tray. [b] $\sqrt{\Sigma\delta^2/(n-1)}$.

Under the conditions of this study, histidine with an isoelectric point of *p*H 7.6 would not be expected to migrate. This has been found to be true experimentally.

We have observed that tailing of certain acids such as lysine, arginine, histidine, aspartic and glutamic acid has occurred on chromatograms developed on plain paper. Dipping the Whatman no. 1 paper in phosphate buffer at *p*H 6.2 has eliminated this phenomenon, except in the instance of histidine.

Control of temperature should be maintained to prevent (1) distillation of solvent from the paper to the walls of the chamber, (2) disruption of the single phase solvent system; also because temperature has an effect on the constancy of the R_F values.

The authors express thanks to Dr. John T. Edsall for the interest he has taken in this work.

Summary

1. A study of partition chromatography with applied voltage has been presented.
2. R_F values for ten amino acids obtained under the experimental conditions are given.
3. Paper buffered with phosphate at *p*H 6.2 has been used.

BEVERLY, MASSACHUSETTS RECEIVED MARCH 16, 1948

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

The Electrical Conductance of Strontium Chloride and Strontium Bromide in Ethanol–Water Mixtures[1]

BY RICHARD LOUIS BATEMAN AND DWIGHT T. EWING

The earliest investigations of electrical conductance in mixed solvents were those of Lenz,[2] and Stephan.[3] This type of work was extended by other workers and particularly by Jones and coworkers.[4]

In general, these investigations showed that the conductance of electrolytes in mixed solvents decreased as the solvent viscosity and degree of solvation became greater but increased as the dielectric constant of the solvent and temperature became greater. A large part of these early investigations concerned the uni-univalent electrolytes with less attention given to those of higher valence types. No recorded data are given for the conductance behavior of strontium chloride and strontium bromide in ethanol–water mixtures.

The purpose of the present investigation was to determine the influence of concentration, solvent composition and temperature on the conductance behavior of strontium chloride in ethanol–water solutions and to note the influence of viscosity and dielectric constant of the solvent on the conductance of these solutions. For purposes of comparison, a limited amount of work was also done on the conductance of strontium bromide in ethanol–water solutions.

Experimental

Purification of Materials.—J. T. Baker C. P. $SrCl_2 \cdot 6H_2O$ was recrystallized from conductance water once above and once below the transition temperature (61.34°) by the method of Richards and Yngve[5] and oven-dried to constant weight.

J. T. Baker C. P. KCl designated "special crystals" (low in Ca, Mg and NH_4OH ppt.) were twice recrystallized from conductance water. The salt was then partially fused in a platinum crucible and transferred to a closed bottle while still hot.

Ethyl alcohol was purified by distilling 95% alcohol from concentrated sulfuric acid (20 ml. of acid per liter of alcohol) to remove amines. The distillate was then treated with alcoholic lead acetate[6] (3 g. of lead acetate in 5 ml. of water and then 5 g. of KOH in 25 ml. of alcohol) and distilled. Absolute alcohol was then prepared by treating each liter of distillate with fresh calcium oxide (200 g. per liter of alcohol), refluxing and distilling. In these distillations, the first and last portions of distillate were discarded. The water content was determined by density measurement and reference to standard density tables.[7] The alcohol thus obtained was 99.9% absolute and had a specific conductance of 2.0×10^{-7} mho at 25°.

Conductance water was prepared by distilling water containing a little potassium permanganate through a block tin condenser. About 50% of the distillate was allowed to condense and only the middle fraction was retained. At 25° the specific conductance of this water was $1.00\text{–}1.04 \times 10^{-6}$ mho.

Apparatus.—A Leeds and Northrup Kohlrausch slide wire bridge with extension coils, tunable head phones, Curtis coil resistance boxes, adjustable air condensers and Leeds and Northup audiooscillator were used. All parts of the bridge assembly were protected by properly grounded shields. A thermostat bath filled with water was kept constant to within 0.01° during the series of measurements. Temperature measurements were made on a thermometer (No. 23044) that had been certified by the Bureau of Standards (certificate No. 49571). Temperature fluctuations were followed by a Beckmann thermometer. The conductance cells were of the Jones and Bollinger[8] type with the filling tubes widely separated. The electrodes were not platinized.[9] The primary standard solution for cell constants was the 0.01 demal KCl solution of Jones and Bradshaw.[10] Cells having low constants were calibrated using a more dilute solution which had been compared to the standard 0.01 demal KCl in another cell.

Procedure.—The ethanol–water solvents were prepared by the weight method. The electrolytic solutions were prepared in volumetric flasks after attaining thermal equilibrium in the thermostat bath. The conductance cells were rinsed several times with the appropriate solution, brought to thermal equilibrium and the conductance determined. All final readings were taken near the center of the bridge with the air condensers adjusted for the most satisfactory null-point. The cells were selected so that the resistance was ordinarily above 1000 ohms. Duplicate determinations were made from two independently prepared solutions. The conductance of the solvent was determined immediately before the preparation of the elec-

(1) This paper represents part of a thesis submitted by Richard Louis Bateman to the Graduate Faculty of Michigan State College in partial fulfillment of the Ph.D. degree, June, 1944.

(2) R. Lenz, *Mem. de l'Acad. de St. Petersbourg*, **7**, 30 (1882).

(3) C. Stephan, *Wied. Ann.*, **17**, 673 (1882).

(4) H. C. Jones and co-workers, Carnegie Inst. Reports; No. 80 (1907), No. 180 (1913) and No. 210 (1915).

(5) Richards and Yngve, THIS JOURNAL, **40**, 91 (1918).

(6) S. Kiczales, *Ind. Eng. Chem.*, **20**, 493 (1928).

(7) "International Critical Tables," **3**, 118 (1928).

(8) Jones and Bollinger, THIS JOURNAL, **55**, 1780 (1933).

(9) J. R. Partington, *J. Chem. Soc.*, **99**, 1937 (1911).

(10) Jones and Bradshaw, THIS JOURNAL, **55**, 1780 (1933).

trolytic solution and the specific conductance of the solvent was subtracted from the specific conductance of the solution.

TABLE I

EQUIVALENT CONDUCTANCE OF STRONTIUM CHLORIDE IN ETHANOL–WATER MIXTURES AT 25°

C[b] / % Ethanol	0	Λ_c[a] 5	20	40
0.1000	101.6	85.5	53.1	33.84
.0500	107.9	90.7	56.50	36.44
.0250	113.9	95.8	59.89	39.18
.0100	120.4	102.3	64.67	43.24
.0050	124.2	105.2	66.33	45.45
.0025	127.2	108.4	68.23	46.54
.0010	129.6	...	69.38	48.53
.0000	134.5	115.0	71.7	50.8
C	60	80	90	99.89
0.1000	23.54	15.31	...	...
.0500	26.05	17.51	13.17	...
.0250	28.74	20.19	15.44	...
.0100	33.12	24.57	19.38	9.75
.0050	35.62	27.51	22.23	11.80
.0025	37.87	30.96	25.76	14.27
.0010	40.96	....	30.73	16.92
.0000	44.2	41.4	37.4	22.1

[a] Λ_c = ohm^{-1} × cm.^{2} × equivalent^{-1}. [b] C = normality.

Discussion

Figure 1 shows the influence of concentration on the equivalent conductance of strontium chloride in various ethanol–water mixtures at 25°. The absence of experimental transference data for the ions in these solutions made it unfeasible to evaluate Λ_0 with the aid of the Onsager equation.[11] Curves similar to those in Fig. 1 were drawn on a large scale and the values for Λ_0 were obtained by graphical extrapolation. As one might expect, the values of both Λ_c and Λ_0 decrease as the percentage of ethanol becomes larger.

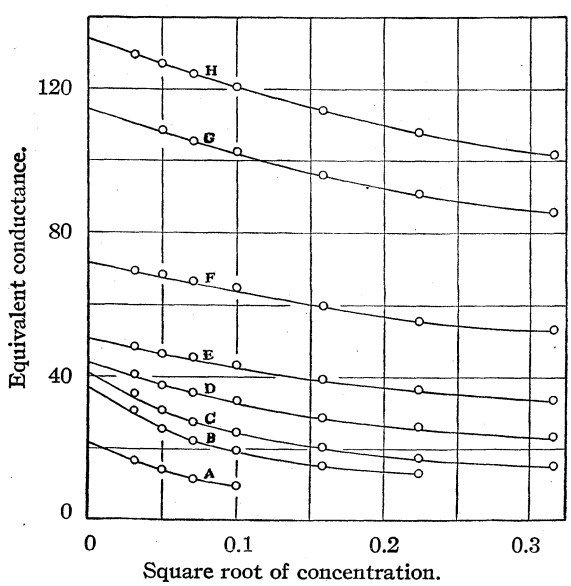


Fig. 1.—Equivalent conductance of strontium chloride in ethanol–water mixtures at 25°: A, 99.89%; B, 90%; C, 80%; D, 60%; E, 40%; F, 20%; G, 5% and H, 0% ethanol in solvent.

(11) L. Onsager, *Physik. Z.*, **27**, 388 (1926); **28**, 277 (1927).

TABLE II

EQUIVALENT CONDUCTANCE OF STRONTIUM BROMIDE IN ETHANOL–WATER MIXTURES AT 25°

C / % Ethanol	0	Λ_c 40	60
0.1000	...	36.02	26.92
.0500	110.4	38.71	29.15
.0250	...	41.13	31.74
.0100	122.9	44.31	35.14
.0050	...	45.83	37.54
.0025	130.1	47.76	39.73
.0010	134.0	49.45	42.13
.0000	137.7	51.9	45.5

TABLE III

EQUIVALENT CONDUCTANCE OF 0.01 NORMAL STRONTIUM CHLORIDE IN ETHANOL–WATER MIXTURES AT 20, 25 AND 30°

Temp., °C. / % Ethanol	0	Λ_c 40	80	99.89
20	106.7	35.81	21.10	8.59
25	120.4	43.24	24.57	9.75
30	131.6	49.28	26.40	10.76

Figure 2 shows the influence of solvent composition on the equivalent conductance of 0.001, 0.005, 0.025 and 0.100 normal solutions of strontium chloride. Increasingly larger percentages of ethanol cause progressively smaller change in the equivalent conductance up to a point of inflection. Beyond this point, the change in equivalent

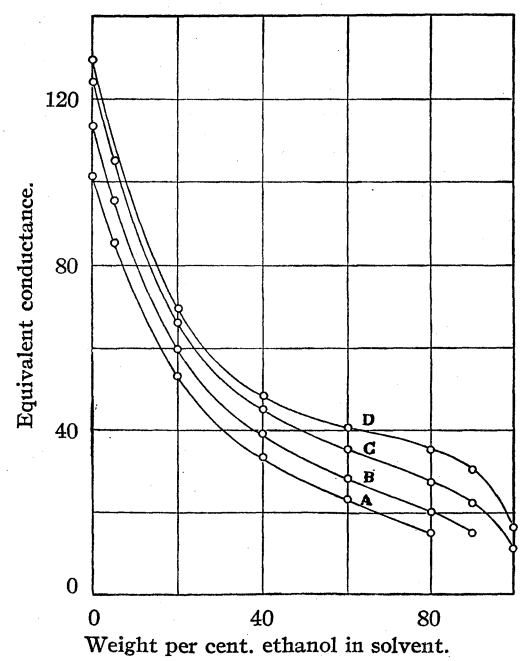


Fig. 2.—Equivalent conductance of strontium chloride in ethanol–water mixtures at 25°: A, 0.1 *N*; B, 0.025 *N*; C, 0.005 *N* and D, 0.001 *N*.

conductance becomes progressively greater as the percentage ethanol increases. An explanation for this might be: in the less alcoholic solutions the change in viscosity is the most significant factor influencing conductance while in the more alcoholic solutions the change in dielectric constant is more significant. Between these two extremes, the two solvent properties are of about equal importance in influencing the conductance. Also, for an electrolytic solution of this type, the ionic "sizes" should vary with solvent composition giving a corresponding influence on conductance. From this, it would follow that Walden's rule[12] ($\Lambda_0\eta$ = constant) should not apply very accurately. The quantity $\Lambda_0\eta/D$ has been applied to electrolytes[13] and in the present case this quantity is more nearly a constant value than $\Lambda_0\eta$. Table IV gives Λ_0, $\Lambda_0\eta$ and $\Lambda_0\eta/D$ for strontium chloride in different ethanol–water mixtures at 25° in which η is the viscosity and D is the dielectric constant of the pure solvents.

TABLE IV

LIMITING CONDUCTANCES OF STRONTIUM CHLORIDE IN ETHANOL–WATER MIXTURES AT 25°

% Ethanol in solvent	Λ_0	η^a poise	D^b	$\Lambda_0\eta$	$\Lambda_0\eta/D$
0	134.5	0.00895	78.5	1.204	0.0153
5	115.0	.01087	75.6	1.250	.0165
20	71.9	.01808	67.0	1.300	.0194
40	50.8	.02374	55.0	1.206	.0219
60	44.2	.02232	43.4	.986	.0227
80	41.4	.01738	32.8	.719	.0219
90	37.4	.01422	28.1	.532	.0189
99.89	22.1	.01104	24.2	.244	.0101

[a] "International Critical Tables," **5**, 22 (1929). [b] G. Akerlof, THIS JOURNAL, **54**, 4133 (1932).

From Table IV it may be observed that $\Lambda_0\eta/D$ is relatively constant for solutions containing between 20 and 90% ethanol in the solvent.

Figure 3 illustrates, at 25°, the dependence of Λ_0 and $\Lambda_0\eta$ on the composition of the solvent for strontium chloride solutions and gives the values for the viscosities and dielectric constants of the pure solvents.

Figure 4 shows the influence of temperature on the equivalent conductance of 0.01 normal solutions of strontium chloride in four different solvent compositions. In all cases the temperature coefficients are positive and become less as the temperature increases. From tangents to these curves at 25° the information in Table V was obtained.

TABLE V

TEMPERATURE COEFFICIENT OF CONDUCTANCE OF 0.01 NORMAL STRONTIUM CHLORIDE IN ETHANOL–WATER MIXTURES AT 25°

% Ethanol in solvent	Λ	$d\Lambda/dT$	$(d\Lambda/dT)/\Lambda$
99.89	9.75	0.20	0.0232
80	24.57	.51	.0208
40	43.24	1.47	.0340
0	120.3	2.55	.0125

(12) P. Walden, *Z. physik. Chem.*, **55**, 207, 246 (1906).

(13) Van Rysselberghe and Fristom, THIS JOURNAL, **67**, 680 (1945).

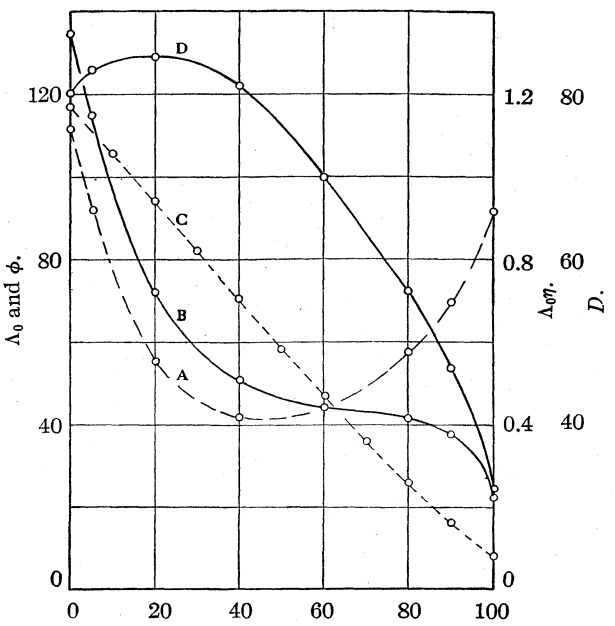


Fig. 3.—Curve A, the fluidity ϕ and curve C, the dielectric constant D of ethanol–water mixtures at 25°: Curve B, the limiting equivalent conductance Λ_0 and curve D, the conductance viscosity product $\Lambda_0\eta$ for strontium chloride at 25°.

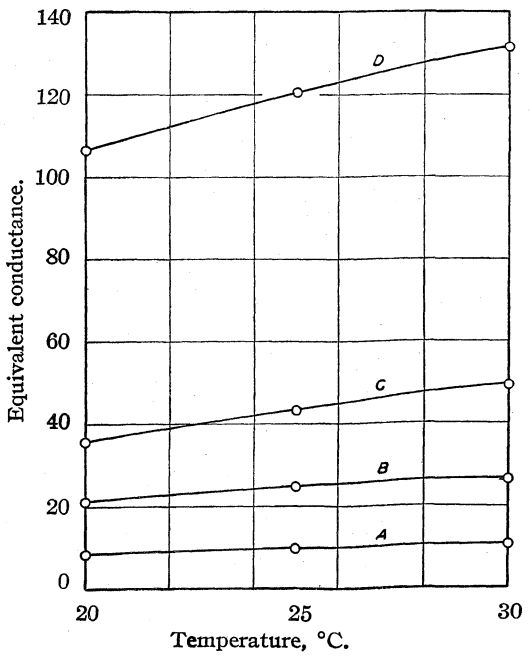


Fig. 4.—Equivalent conductance of 0.01 N strontium chloride in ethanol–water mixtures as a function of temperature: A, 99.89%; B, 80%; C, 40% and D, 0% ethanol in solvent.

For the solvents used in Fig. 4, the temperature coefficients of the dielectric constants are negative and become smaller at the higher temperatures. This would tend to cause the conductance to be less at the higher temperatures and to influence the temperature coefficient of conductance less at the higher temperatures. For these same solvents the temperature coefficients of viscosity are negative and have smaller values at higher temperatures. This would cause an increase of conductance with increasing temperature but the rate of increase should be less at higher temperatures. Even though these two solvent properties work in opposition to each other, they both favor a smaller temperature coefficient at higher temperatures.

Preliminary work on the conductances of magnesium and barium chlorides gave curves of the same general form as those for strontium chloride.

Summary

The conductances of strontium chloride and of strontium bromide in different ethanol–water mixtures have been measured at 25° and the significance of the results discussed.

The conductance of strontium chloride in different ethanol–water mixtures has been measured at 20, 25 and 30° and the temperature coefficients evaluated.

In strongly aqueous solutions the conductances are influenced mostly by the viscosity of the solvent and in the strongly alcoholic solutions mostly by the dielectric constant of the solvent.

EAST LANSING, MICHIGAN RECEIVED JANUARY 23, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Repulsive Forces in Relation to Bond Energies, Distances and Other Properties

BY KENNETH S. PITZER

While the concepts of quantum theory have given a qualitative understanding of most chemical bond phenomena, there are a number of less prominent features that remain puzzling. Many of the ideas in this paper have been held by the writer and very likely by others for some time. However, they were based on conflicting and uncertain data. The immediate reason for this paper is the recent developments in dissociation energy data which makes possible a greatly improved and considerably changed table of bond energies.

Bond Energies.—Gaydon[1] has recently published a very fine compilation of dissociation energies. Furthermore his recommended value of *ca.* 170 kcal. for the heat of sublimation of carbon (to normal ^3P atoms) has been fully confirmed by new thermodynamic measurements of Brewer and Gilles[2] in this Laboratory. The heat of vaporization values of Kelley[3] together with some revisions of these values by Brewer[4] have been employed. These new data supplement the older values of Bichowsky and Rossini[5] upon which Pauling[6] based most of his bond energies. The conventions followed in Tables I and II follow Pauling's system except that the dissociation energies of the nomal $^3\Sigma$ states rather than excited singlet states are taken for O=O, S=S, etc. The energy of dissociation of a molecule completely into atoms is taken as the sum of the energies of all bonds. Thus the C–H bond energy is not the energy change of the reaction of $CH_4 = CH_3 + H$ but rather one fourth of the energy for $CH_4 = C + 4H$. The values are for 0°K. Heat capacities from 0 to 300°K. were estimated where necessary.

In Table I there are listed values for single bonds in elements and for single bonds to hydro-

TABLE I

SINGLE BOND ENERGIES (KCAL./MOLE AT 0°K.)

Elements		Hydrides		Chlorides	
H–H	103.2	H–H	103.2	H–Cl	102.1
Li–Li	26	Li–H	58	Li–Cl	118.5
C–C	80 (85)	C–H	98.2	C–Cl	78
N–N	37	N–H	92.2	N–Cl	46 (?)
O–O	34	O–H	109.4	O–Cl	49
F–F	50 (?)	F–H	141 (?)	F–Cl	60.3
Na–Na	17.8	Na–H	47	Na–Cl	97.7
Si–Si	(45)	Si–H	76 (?)	Si–Cl	87
P–P	(53)	P–H	77	P–Cl	77
S–S	63 (?)	S–H	87 (?)	S–Cl	65 (?)
Cl–Cl	57.1	Cl–H	102.1	Cl–Cl	57.1
K–K	11.8	K–H	42.9	K–Cl	101.4
Cu–Cu		Cu–H	62	Cu–Cl	83
Ge–Ge	(39.2)	Ge–H	...	Ge–Cl	...
As–As	(39)	As–H	56	As–Cl	69
Se–Se	(50)	Se–H	67	Se–Cl	59
Br–Br	45.4 (53)	Br–H	86.7	Br–Cl	52.1
Rb–Rb	11.1	Rb–H	39	Rb–Cl	101.0
Ag–Ag	...	Ag–H	53	Ag–Cl	71
Sn–Sn	(35)	Sn–H	...	Sn–Cl	76
Sb–Sb	(42)	Sb–H	...	Sb–Cl	75
Te–Te	(49)	Te–H	59	Te–Cl	...
I–I	35.6 (51)	I–H	70.6	I–Cl	49.6
Cs–Cs	10.4	Cs–H	41	Cs–Cl	103

(1) A. G. Gaydon, "Dissociation Energies and Spectra of Diatomic Molecules," Chapman and Hall, London, 1947.

(2) L. Brewer and P. Gilles, unpublished data.

(3) K. K. Kelley, U. S. Bureau of Mines, Bulletin 383, 1935.

(4) L. Brewer, "The Thermodynamic and Physical Properties of the Elements," Declassified Atomic Energy Report CC 2058, 1945.

(5) F. R. Bichowsky and F. D. Rossini, "Thermochemistry of Chemical Substances," Reinhold Pub. Co., New York, N. Y., 1936.

(6) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

TABLE II

MULTIPLE BOND ENERGIES (KCAL./MOLE AT 0°K.)

	Single	Double	Triple
C–C	80	145	198
N–N	37	...	225.1
O–O	34	117.2	...
P–P	(53)	...	116.0
S–S	63 (?)	101 (?)	...
As–As	(39)	...	90.8
Se–Se	(50)	65	...
Sb–Sb	(42)	...	69
Te–Te	(49)	53	...
C–N	66	...	209
C–O	79	173	...
P–N	...	...	138 (?)
S–O	...	120 (?)	...
Te–O	...	62.8	...

gen and chlorine. Table II gives values for multiple bond energies and includes the corresponding single bond energy for comparison. Naturally many more values could be included but these will serve as a basis of the discussion to follow.

In some cases the single bond energies for elements must be taken from solids where there may be additional weak bonding of a van der Waals or semi-metallic nature. Such values are inclosed in parentheses.

The first value given for the C–C bond is an average of several hydrocarbons.[7] It would be 77.7 for ethane but approaches 81.0 for higher and branched paraffins. The value from diamond, 85 kcal., is given in parenthesis. The values for N–N and O–O come from hydrazine and hydrogen peroxide on the basis of the values for N–H and O–H from ammonia and steam, respectively. The details for phosphorus will be typical of many other cases. The value for P≡P is from Gaydon.[1] Since the P–P bonds in P_4 are considerably strained, red phosphorus was taken as a basis. Bichowsky and Rossini give 29.1 kcal. for the heat of vaporization to P_2. Brewer gives 42 kcal. Adopting the latter, the heat of dissociation of two gram atoms of red phosphorus to atoms is therefore 42 + 116 = 158 kcal. Since this involves three bonds per two atoms the value for P–P is 53 kcal.

Tetrahedral *vs.* p Orbital Bonding.—The very pronounced drop in bond energy from C–C to N–N must be connected in some way with the appearance of the unshared electron pair on nitrogen. Tetravalent carbon must be based on the $2s2p^3$, ^5S state which is 96.4 kcal. higher in energy[8] than the normal $2s^22p^2$, ^3P state. Thus to the ^5S state the C–C bond energy would be 128 kcal., the C–H bond energy 122.3 kcal., etc. However, according to Bacher and Goudsmidt[9] the $2s2p^4$, ^4P state of nitrogen is 260 kcal. above the normal $2s^22p^3$, ^4S state. The large increase arises because in nitrogen the 2s electron is moved to a half filled 2p orbital whereas in carbon the 2s electron was moved to a vacant 2p orbital. If the trivalent nitrogen atom were to bond with sp^3 hybrid tetrahedral orbitals it would have to be excited $^3/_4$ of the way to the $2s2p^4$ state which would then amount to 65 kcal. extra per bond per atom. On this basis the N–N bond energy becomes 167 kcal. which is well above the value for C–C. However, it would seem more likely that the nitrogen bonding orbitals are mostly p with only a small s component. This avoids the large excitation energy but gives weaker bonds.[6] The less than tetrahedral bond angles in ammonia, etc., tend to confirm this picture. Presumably the normal valence bonding of all the 5th, 6th and 7th group elements is primarily p bonding since the bond angles for PH_3, H_2S, etc. approach the 90° value characteristic of p orbitals.

If the drop in bond energy at nitrogen is caused by the change to p bonds one is confronted by the absence of a corresponding drop from Si–Si to P–P. I believe this is closely related to the weakness of multiple bonds below the first row which will be considered next.

Single and Multiple Bonds.—It has long been recognized that multiple bonds of strength equal or greater than a corresponding number of single bonds occur only with the first row elements oxygen, nitrogen, carbon and possible boron. Only carbon disulfide and a few less clean cut examples show stable multiple bonds between first and second row elements. Multiple bonds with heavier atoms are confined to molecules such as P_2, Se_2, etc., which are of higher energy per atom than single bond structures P_4,S_8 etc.

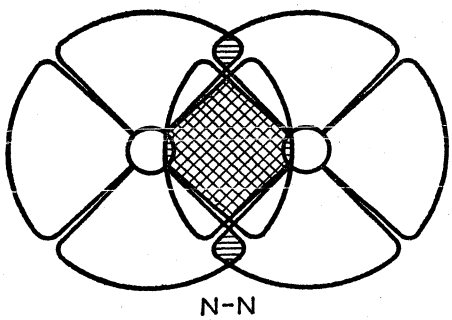
Figures 1 and 2 indicate crudely the approximate size of various orbitals in nitrogen and phosphorus. The inner shells are given Pauling's "single bond" radii for N^{+5} and P^{+5}, respectively. The outer radius is taken as 0.9 times the van der Waals radius also from Pauling.[6] The value of 0.9 was selected because it was felt the compressional forces within a molecule were rather larger than the intermolecular forces in a molecular crystal. The 2s orbital for nitrogen and the 3s for phosphorus were omitted to avoid confusion. Regions of bonding or attractive exchange overlap are diagonally cross hatched while the principal regions of repulsive exchange overlap are lined horizontally. The overlap of orthogonal orbitals such as $3p_x$ with $3p_z$ will have only a secondary effect. The atoms are shown at the bond distances experimentally observed.

It should be emphasized that orbitals do not have sharp boundaries and that Figs. 1 and 2 are therefore only crude representations. In particular the p orbitals gradually decreased in intensity from a maximum along their principal axis to zero in the plane perpendicular to that axis. They have been cut off at 44° from the axis to separate

(7) E. J. Prosen, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 403 (1945).

(8) A. G. Shenstone, *Phys. Rev.*, **72**, 411 (1947).

(9) R. F. Bacher and S. Goudsmidt, "Atomic Energy States," McGraw Hill Book Company, New York, N. Y., 1932.



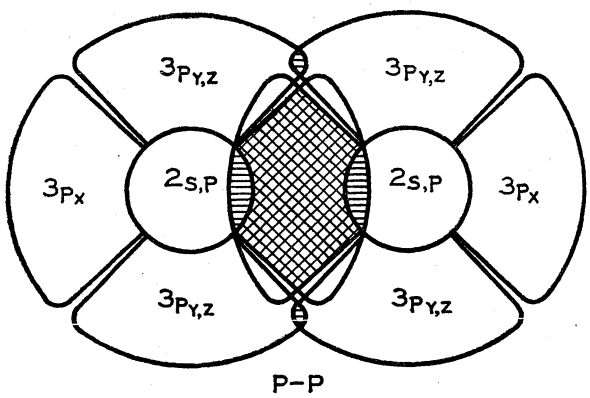
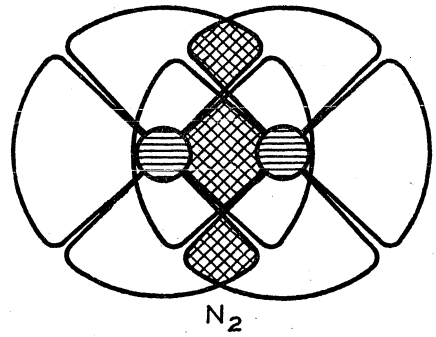


Fig. 1.—Diagrams of relative orbital sizes in N–N and P–P bonds.



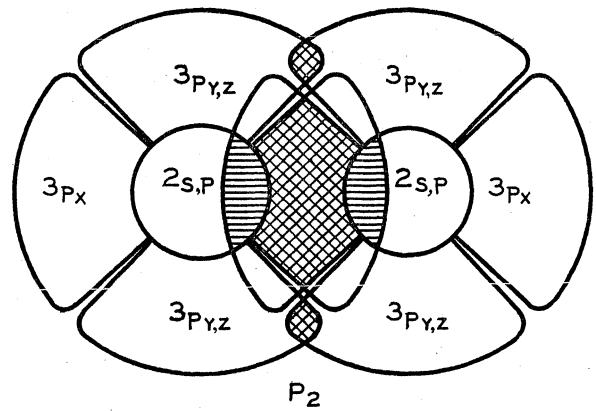


Fig. 2.—Diagrams of relative orbital sizes for N≡N and P≡P bonds.

the p orbitals on the same atom. Also since the intensity decreases both radially and angularly, the outer corners are of particularly low intensity. These corners rounded to remind one of this situation. In spite of their limitations the figures are useful in illustrating qualitative differences between nitrogen and phosphorus.

Repulsive Effects of Inner Shells.—In hydrogen the attractive force of the bonding electrons on the nuclei is balanced by the repulsive force of the two nuclei. However, in P_2 we postulate that the repulsive interactions of the $3p_x$ orbital of one atom with the inner shell of the other constitute a more important repulsive force. Let us call this merely *inner shell* repulsion. In nitrogen the inner shell contains only two electrons as compared to ten in phosphorus. Consequently it is reasonable to suppose that this inner shell repulsive effect is much smaller in nitrogen. These ideas receive support in Fig. 2 in that the N≡N bond distance is so short that the $2p_x$ orbital of one atom extends completely across and beyond the inner shell of the other while in P≡P the $3p_x$ orbital only partially overlaps the inner shell of the other atom. Since other interactions in P_2 are attractive there would appear to be no other reason why the distance should remain relatively longer than in N_2.

The increase in bond energy between the single and triple bonds comes from two principal sources. First, the interaction of the p_y and p_z orbitals changes from repulsive to attractive. Second, the bond distance decreases giving better overlap for all the bonding orbitals. If the p_x-inner shell repulsion keeps the bond distance large, both of these items are small. In the second case the reason is self-evident, and in the first it is because the p_y and p_z overlap is small at large distances. For double bonds the same argument applies but only the p_y interaction is affected.

This inner shell repulsive effect will be general for all atoms below the first row. Consequently it will explain the relative weakness of multiple bonds for all atoms outside the first row. Next let us see if it will help account for other peculiarities.

Pauling[6] suggests that p bonds should have $^3/_4$ of the energy of tetrahedral whereas we find a much smaller value for the ratio of N–N to C–C bond energy. However, Pauling's value may be interpreted as the ratio of the attractive energies of the bonding electrons alone. The net bond energy will be less by the repulsive effects of nonbonding interactions. We see in Fig. 1 that there is a considerable overlap of the $2p_z$ (and $2p_y$) orbitals which is repulsive. A shift to tetrahedral orbitals would decrease this greatly because of the increase from 90° to 109.5° in the angle between orbital axes. Thus one concludes that in the first row elements, single bonds with p orbitals are weaker than with tetrahedral orbitals because of

increased repulsive interactions. Let us call these *valence shell* repulsions.

In heavier elements than the first row, however, we have assumed that the inner shell repulsions are important. Consequently, the valence shell repulsive effect will be less important. There is another factor to be considered here. The character of bonding orbitals may be modified by linear combination with any vacant orbitals, although only those of approximately the same energy can be important. Thus while the 3d orbitals could have only a minor effect for first row elements, the orbitals of second row elements may be considerably modified. The electron density will be concentrated more along the bond axis and will not spread out so far to each side. This change means that the p_y and p_z orbitals which are forming other single bonds perpendicular to the one shown in Fig. 1 will overlap even less than indicated there. Thus the absence of a marked drop in bond energy from Si–Si to P–P is also understandable.

Bond Distances.—While the concept of covalent bond distances as sums of radii is undoubtedly but a first approximation, it has met with considerable success. Schomaker and Stevenson[10] modified this simple concept for partial ionic bonding effects and have found generally improved agreement. The major failure which remained was the series of bonds Si–O, P–O, Si–F and P–F (together with S–O in $SO_4^=$, Cl–O in ClO_4^-, etc.). These bonds are shorter than expected by about 0.10 Å. on the Schomaker and Stevenson formula and by 0.12 to 0.27 Å. on the Pauling and Huggins[11] scale.

Pauling[6] explains these effects as due to multiple bonds using 3d orbitals, but the writer has never regarded this acceptable because it is entirely *ad hoc* and without confirmation from energies and other sources. Also logical extensions of Pauling's structures lead to absurdities such as diatomic argon with the structure: $:\ddot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{A}}} = \ddot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{A}}}:$.

Now it has been postulated in this paper that the N–N and similarly the O–O and F–F distances are determined largely by the valence shell ($2p_y$, $2p_z$) repulsion while the Si–Si, P–P, and S–S distances are determined principally by the repulsive interaction of the inner shell with the $3p_x$ orbital (or the tetrahedral hybrid in silicon). The basic radii are taken as half of the single bond distance with like atoms. However, when a phosphorus atom approaches an oxygen atom, for example, neither of these repulsive effects sets in at the distance calculated from the radii because of this difference in type of predominant repulsion. This is shown clearly in Fig. 3 which depicts P–O on the same basis as Figs. 1 and 2. Thus the upper diagram shows the nuclei at 1.76 Å. as calculated by Pauling and Huggins. The $2p_x$ orbital of oxygen hardly more than touches the inner shell of phosphorus and the p_z (and p_y) orbitals have not overlapped partly because of the difference in atomic size. The $3p_x$ orbital of phosphorus overlaps the inner shell of oxygen but the latter contains only two electrons and was therefore regarded as less important.

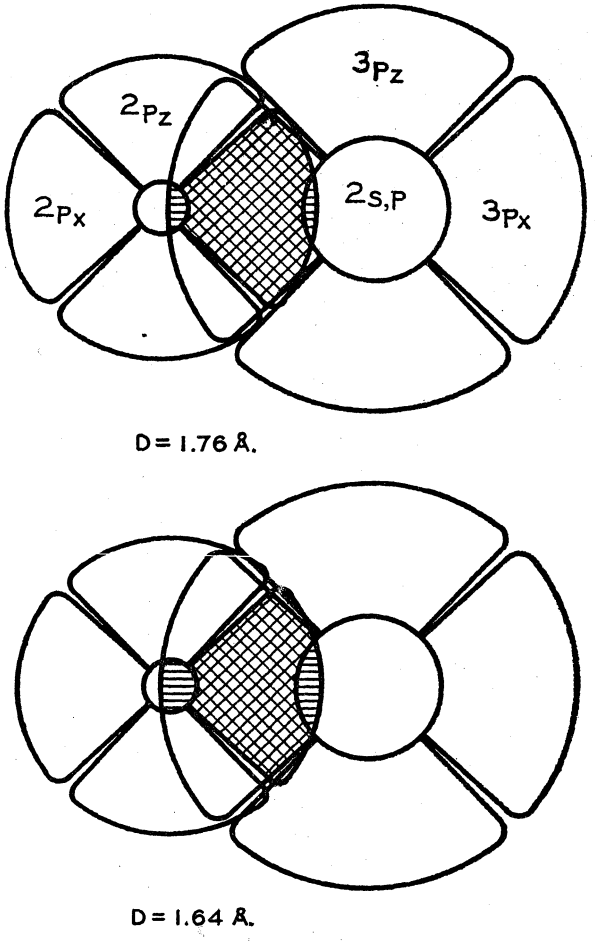


Fig. 3.—Diagrams of the P–O bond at distances indicated.

The lower diagram in Fig. 3 shows the atoms at the distance 1.64 Å. observed in the P_4O_6 gas molecule. Even there the respulsive overlap of various orbitals is moderate. Furthermore the Si–O bond energy is quite normal. On Pauling's electronegativity formula, but using recent data, one calculates 106 kcal. for a single Si–O bond as compared to the observed 103 kcal. Data are not available for the normal P–O bond energy, but the values for Si–F are 159 kcal. calculated for a single bond and 138 kcal. observed. Thus the energies give no indication of multiple bonding.

In molecules such as P_4O_{10} and $PO_4^=$ even shorter bonds arise. While double bonds involving 3d orbitals are more likely in these cases than before, even here a formal charge explanation is equally reasonable. If one maintains the octet for phosphorus in P_4O_{10} then the four oxygens which

(10) V. Schomaker and D. P. Stevenson, THIS JOURNAL, **63**, 37 (1941).

(11) L. P. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

are bonded to only one phosphorus have a net charge of -1 and the phosphorus atoms have a $+1$ charge. At the distance of about 1.6 Å. these charges give an attractive force of 9×10^{-4} dynes. The force constant for a normal P–O single bond is not known but may be expected to be about 4×10^5 dynes/cm. from comparison with other molecules. Thus the electrostatic attractive force may be expected to lower the bond distance by about 0.2 Å. which is roughly that observed.

From these considerations, it is the writer's opinion that in the oxygen and fluorine compounds with second row elements multiple bonding is not significant (in the sense of more than one pair of electrons shared between the two atoms). The short bond distances are explainable in terms of (1) the difference in type of repulsive effect predominating in P–P, etc., from that in O–O, etc., and (2) the large polar effects.

Thus although the 3d orbitals undoubtedly play a part in the detailed nature of the p or sp^3 bonds in second row elements, it appears that they are not available for additional bonds of significant strength.

Barriers to Rotation about Single Bonds.—The very simplest quantum mechanical theory of single bonds indicates no restriction of rotation of the two groups connected by the bond. Thus the experimentally determined barriers of 1 to 4 kcal. per mole must be related to some refinements of the simplest theory. In ethane, if the carbon atom orbitals are strictly sp^3 hybrids, only H–H interactions are affected by rotation and they are too small. However, if the carbon orbitals are concentrated just a little more along the C–H bond directions then these atoms are no longer axially symmetrical. The C–C bond is pulling the two carbons together against the repulsion of these C–H bond electrons. Consequently it is reasonable to assume this repulsion to be larger when the C–H bonds at one end line up with those at the other end and to be less when the C–H bonds are staggered. The stability of the staggered orientation is now well verified. Let us examine the consistency of the magnitude of the rotation restricting barriers listed in Table III with the concepts that the barrier arises from variation in the valence shell repulsion as defined above.

Whereas the axial symmetry of a carbon atom is disturbed by three hydrogens in ethane there are only two hydrogens on the nitrogen of methyl amine and one on the oxygen of methanol. Thus one might expect the barriers to decrease in the ratio 3 to 2 to 1. However, the decrease in bond angle from tetrahedral at the carbon to smaller values for nitrogen and oxygen should increase this repulsive effect. The series ethane, methylamine, methanol and the series propane, dimethylamine, dimethyl ether both show increase from carbon to nitrogen followed by decrease to oxygen in reasonable accord with these ideas.

TABLE III

POTENTIAL BARRIERS RESTRICTING INTERNAL ROTATION (KCAL./MOLE)

CH_3CH_3[12]	2.8		
CH_3NH_2[13]	3.0		
CH_3OH[13]	2.3 ± 1(?)	CH_3SH[14]	1.5
$(CH_3)_2CH_2$[16]	3.4		
$(CH_3)_2NH$[13]	3.5		
$(CH_3)_2O$[13]	3.1	$(CH_3)_2S$[15]	2.0
$(CH_3)_4C$[17]	4.3	$(CH_3)_4Si$[13]	1.3

Unfortunately, barrier values for bonds between two second row elements are now available. They should be small because the valence shell repulsion is largely replaced by the inner shell repulsion discussed above. The situation for bonds between carbon and a second row element should be intermediate and the values in Table III are clearly consistent with this concept.

Bonds to Hydrogen.—Since hydrogen has no further electrons, there should be no electronic repulsion effects of the valence shell type. Consequently the bond energies should show greater regularity. Thus the decrease in bond energy from C–H to N–H is very small compared with that from C–C to N–N or from C–Cl to N–Cl.

Conclusions.—In a single bond between two first row elements the attractive force of the bond itself is balanced principally against the repulsion of the remaining valence shell electrons. Between two second row or heavier elements the repulsion between the bonding orbital and the inner shell becomes more important. The concepts are shown to give qualitative explanation for:

1. The relative absence of stable multiple bonds except with first row elements.
2. The striking drop in bond energy from C–C to N–N.
3. The failure of bond radii to correctly predict the Si–F, P–O and related bond distances.
4. The relative magnitude of barriers to internal rotation about single bonds.

Certain predictions are made.

It does not seem likely that presently feasible quantum mechanical calculations could do more than confirm these qualitative conclusions. However, more quantitative relationships of an empirical nature might be developed.

Summary

A revised table of bond energies is calculated from recent sources.

The concept is introduced of a balance in a

(12) K. S. Pitzer, *Chem. Rev.*, **27**, 39 (1940).

(13) J. G. Aston, *Ind. Eng. Chem.*, **34**, 514 (1942); *Chem. Rev.*, **27**, 59 (1940).

(14) H. Russell, D. W. Osborne and D. M. Yost, THIS JOURNAL, **64**, 165 (1942).

(15) D. W. Osborne, R. N. Doescher and D. M. Yost, *ibid.*, **64**, 169 (1942).

(16) K. S. Pitzer, *J. Chem. Phys.*, **12**, 310 (1944).

(17) K. S. Pitzer and J. E. Kilpatrick, *Chem. Rev.*, **39**, 435 (1946).

(18) B. L. Crawford, Jr., *J. Chem. Phys.*, **8**, 744 (1940).

chemical bond between attractive and repulsive forces both of electronic nature. In first row elements the repulsive effects for single bonds arise principally in the valence shell whereas for heavier atoms the inner shells play a predominant role. The ideas are shown to account for several peculiarities in bonding behavior.

BERKELEY, CALIFORNIA RECEIVED DECEMBER 22, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Susceptibility Isotherms for Supported Copper Oxide

BY P. W. SELWOOD AND NICK S. DALLAS

The purpose of this work was to examine the structure of supported copper catalysts by use of the magnetic methods previously described.[1] The present paper gives magnetic data on a series of copper–alumina catalyst systems, together with some X-ray and catalytic activity results.

Experimental

Preparation and Analysis of Samples.—Pure γ-alumina of surface area approximately 200 sq. m./g. and magnetic susceptibility -0.2×10^{-6} at $-190°$, was impregnated with copper nitrate solution, then filtered, dried, and ignited at 390° for twenty-four hours. Twelve samples of supported copper oxide were thus made, ranging in concentration from 0.60 to 34.7% copper.

The several samples were analyzed by dissolving them in nitric acid and titrating by the standard iodide–thiosulfate method. One catalyst sample was prepared by multiple impregnation. The copper nitrate impregnating solution was adjusted so as to give a catalyst containing about 1% copper. After ignition this catalyst was reimpregnated and ignited. The process was repeated until the copper concentration reached 5.2%.

Most of the catalyst samples were examined in the reduced condition as well as oxidized. Reduction was carried out in hydrogen at 300° for twelve hours. No change was caused by raising the reduction temperature to 400°.

It is of interest to record that the oxidized catalyst systems were bluish-green in color at all lower concentrations. The reduced catalysts were all jet black.

During the course of these studies it became necessary to prepare some supported silver oxide on alumina. This was obtained by impregnating γ-alumina with dilute silver nitrate solution, followed by drying and ignition at 390°. The sample contained approximately 2% silver. This sample was reduced in hydrogen at 200°. It may be mentioned that the oxidized silver supported on γ-alumina is rapidly changed from white to brown by mere exposure to hydrogen well below room temperature.

The reduced forms of all catalysts were readily reoxidized in air at room temperature. The lower concentrations were handled in the absence of air, although the reduced copper could be stabilized to a fair degree by exposure to carbon dioxide.

Catalytic Measurements.—Comparison of catalysts containing varying proportions of copper was made by mechanically mixing all samples, except the lowest in copper, with γ-alumina so that all samples contained 3.2% copper. The catalytic measurements were not extended below that concentration. The reaction chosen was the dehydrogenation of isopropyl alcohol.

A pelleted catalyst sample containing 0.32 g. of copper in 10 g. of catalyst was placed in the reaction chamber. The catalyst was reduced in hydrogen at 400° for two hours. The temperature was then lowered and held at 225°. Redistilled isopropyl alcohol was fed over the catalyst at the rate of 32 cc. (liquid) per hour. Tests were continued for one hour, and three successive such one hour activity runs were made for each catalyst.

The gaseous product was collected and the volume measured. The liquid product was fractionated in a simple column and a rough analysis was thereby obtained for acetone, unconverted isopropyl alcohol and higher boiling products.

The several catalysts used for the activity tests are conveniently described in the following manner. Catalyst 3.2/10.3 means a sample containing 3.2% of copper but that this was obtained by mechanically mixing appropriate amounts of γ-alumina and a CuO/Al_2O_3 impregnate which contained 10.3% of copper. Four such catalysts were tested. These are thus designated as 3.2/3.2, 3.2/10.3, 3.2/13.3 and 3.2/22.9.

Results

Table I shows the magnetic susceptibility at three temperatures for all the oxidized copper catalyst samples except that prepared by multiple impregnation. Samples containing less than 3% copper are discarded as being too dilute to permit accurate estimation of the susceptibility of the copper. Figure 1 shows the susceptibility isotherms calculated from the data of Table I.

TABLE I

MAGNETIC SUSCEPTIBILITY OF CuO/Al_2O_3 CATALYST SAMPLES

Weight per cent. copper	$\chi \times 10^6$ 25°	$\chi \times 10^6$ −80°	$\chi \times 10^6$ −190°
4.0	0.5 (±0.05)	0.9	2.4
7.2	0.9	1.8	4.4
10.3	1.4	2.5	5.6
11.9	1.3	1.8	3.8
13.3	1.0	1.4	3.1
16.5	0.9	1.2	2.6
22.9	1.0	1.4	2.6
28.4	1.3	1.5	2.6
30.6	1.4	1.7	2.6
34.7	1.7	1.7	2.5

Reduction of the copper in the samples in all cases caused the magnetic susceptibility to drop substantially to zero. The susceptibility isotherms at −180° for oxidized, reduced and reoxidized copper–alumina are compared in Fig. 2.

The magnetic susceptibility of the sample prepared by multiple impregnation was 2.45×10^{-6} at −170°. The susceptibility of the copper in this catalyst, which contained 5.2% copper, was, therefore, 51×10^{-6} at −170°.

(1) This is the third paper on the susceptibility isotherm from this Laboratory. The second paper appeared in THIS JOURNAL, **69**, 2698 (1947). Descriptions of magnetic, X-ray and surface area experimental methods will be found in the earlier papers.

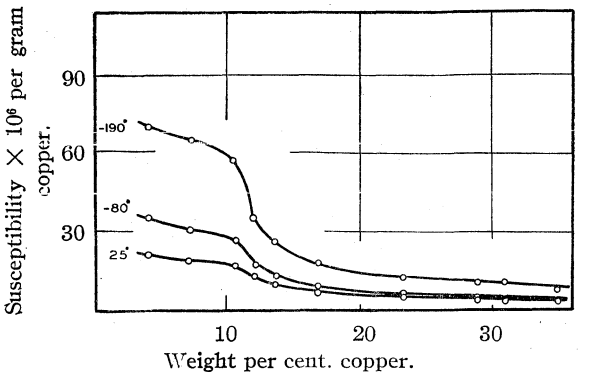


Fig. 1.—Susceptibility isotherms for supported copper oxide on γ-alumina.

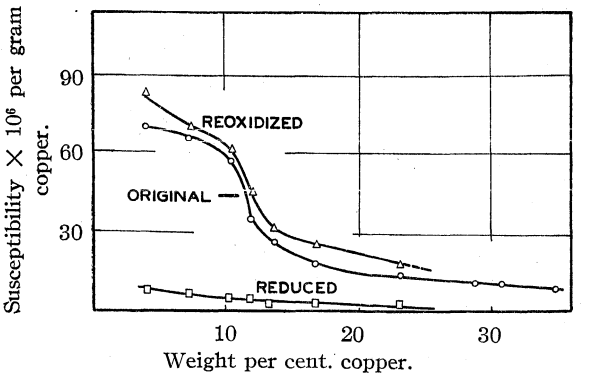


Fig. 2.—Susceptibility isotherms for copper and copper oxide on γ-alumina, all at −190°.

The single sample of supported silver on γ-alumina had a susceptibility of substantially zero both at 25° and at −170°.

The X-ray diffraction results showed clearly the principal lines of cupric oxide at 2.51, 2.30, 1.86, 1.58 and 1.50 Å. down to a concentration of 11.9% copper. But at 10.3% copper no cupric oxide lines, or any lines other than those of γ-alumina, were observed. There is, therefore, a parallelism between the disappearance of the cupric oxide lines and the region of maximum rise of susceptibility in the isotherm.

The results of the catalytic activity tests are summarized in Table II, which gives results for the second of three concordant runs in each case.

TABLE II

RELATIVE CATALYTIC ACTIVITY OF COPPER–ALUMINA CATALYSTS

Catalyst	% Acetone	% High boiling
Pure alumina	None	None
3.2/ 3.2	52	10
3.2/10.3	31	4
3.2/13.3	31	4
3.2/22.9	22	3

In addition, it should be stated that the more dispersed systems gave a relatively smaller volume of higher density gaseous product, and that these systems also lost activity much more rapidly during use than did the less dispersed systems.

Conclusions.—The susceptibility isotherm is generally characterized by a large increase of susceptibility at low concentrations. Copper shows this effect to a greater extent than any other element so far studied. The susceptibility of copper in supported cupric oxide at low concentrations is about twenty times larger than that of copper in massive (unsupported) cupric oxide.

Below about 10% copper the susceptibilities of the several samples accurately follow the Curie–Weiss law, from which it is possible to compute the Weiss constant and the magnetic moment. In this region the Weiss constant is small, but slowly rises, showing the normal effects of decreasing copper–copper distance. At the lower concentrations the magnetic moment is 1.8 Bohr magnetons. This corresponds exactly with the moment predicted from the "spin-only" formula for cupric ion. There is, therefore, no inductive effect of the support on the valence of the copper.

The most striking feature of the susceptibility isotherm for copper is the sharp rise in the neighborhood of 11% copper. The magnetic data, taken in conjunction with the X-ray results, suggest that this is the concentration region below which it is impossible to maintain extensive organization of the copper and oxide ions into unit cells. It might be said that cupric oxide crystallites do not exist below about 11% copper. Nevertheless, the copper can scarcely be considered as atomically dispersed even below 11%. This is shown by the gradual decrease of the Weiss constant and by considerations on the magnetic properties of the reduced copper.

Our general picture of the oxidized copper catalysts is, therefore, not dissimilar to that earlier obtained for the chromia–alumina system. The tendency in such supported systems is shown definitely to be toward inhomogeneity and formation of ionic assemblies, and not toward two-dimensional solid solution except at the greatest dilutions.

Turning now to the results on the reduced copper–alumina systems we are faced with a difficulty. The isotherm for the oxidized form strongly suggests that below 10% copper we are approaching infinite magnetic dilution because the susceptibility is not rising very rapidly. This is in contrast to the case for chromia–alumina.

It is well known that massive copper is slightly diamagnetic, but isolated copper atoms ought to be paramagnetic because they contain an odd number of electrons. It would be anticipated that the higher supported copper concentrations would become diamagnetic on reduction because the massive cupric oxide present is being converted to massive copper metal. But if the cupric ions were atomically dispersed at very low concentrations, then reduction should have no effect on the susceptibility.

Some very careful efforts were made to detect

this effect. But the low susceptibilities and the ubiquitous trace of ferro-magnetic impurity combined to make it difficult to examine this region. We can say, however, that certainly no more than 10% of the copper atoms can be considered as atomically dispersed.

It was hoped that the multiple impregnation catalyst would lead to higher, more readily measureable, susceptibilities and to greater dispersion, but such was not the case. It was also hoped that dispersed silver might yield a more readily observable result. The reason for the choice of silver was that the oxidized form is here diamagnetic. But certainly no large fraction of the supported reduced silver became paramagnetic.

Our conclusion from all these negative results is that the tendency for aggregation is so strong that even when the support must be, of necessity, mostly unoccupied surface, still the supported atoms tend to cling together. It will be noted that the larger size of the reduced atoms may lead to greater exchange interaction as compared with the oxidized forms, even though the ion centers do not appreciably move during the oxidation–reduction cycle.

When reduced supported copper is reoxidized the susceptibility goes as high as or higher than in the original oxidized sample. This shows that no aggregation into crystallites occurs during the oxidation–reduction cycle. In fact the slight increase of susceptibility shown in Fig. 2 may be due to three-dimensional solution of cupric ions in the alumina.

The results on catalytic activity support in a general way this picture of the active surface. The more highly dispersed copper would normally be expected to show greater activity, and such is the case. It is somewhat surprising that no change of activity occurs in the anomalous 11% concentration region. This result must mean that the mere aggregation into definite cupric oxide crystallites has no effect on the activity. There is, of course, the possibility that in the *reduced* form there is no such obvious structural change occurring in this concentration region.

Summary

Susceptibility isotherms are given for copper oxide supported on γ-alumina, for the reduced catalyst, and for related systems. The magnetic data are related to X-ray diffraction studies, and to catalytic activity results on the dehydrogenation of isopropyl alcohol.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 19, 1948

[CONTRIBUTION FROM ARGONNE NATIONAL LABORATORY AND DEPARTMENT OF PHYSICS, UNIVERSITY OF CHICAGO]

Double Fluorides of Potassium or Sodium with Uranium, Thorium or Lanthanum

BY W. H. ZACHARIASEN

This paper summarizes the results of studies of the systems $KF–UF_4$, $KF–ThF_4$, $KF–LaF_3$, $NaF–UF_4$, $NaF–ThF_4$ and $NaF–LaF_3$. The investigations were carried out within the Manhattan Project during 1945.

The systems were studied by means of the X-ray diffraction method. The systematic survey extends over the entire composition range except for a gap between 35 and 65 mole per cent. ThF_4 in the $NaF–ThF_4$ system.

1. The Chemical Preparations.—All chemical preparations were made by the writer. The systematic studies were carried out by determining the phase compositions of solidified melts by means of X-ray diffraction patterns. Thermal analysis data were not taken, however. In the systems involving potassium fluoride precipitates from solutions were also examined.

The dry method preparations were made by melting together the component fluorides in a platinum crucible. The uranium tetrafluoride was from the Harshaw Chemical Company. Dr. Ralph Livingston had prepared the thorium fluoride by treating $ThF_4 \cdot xH_2O$ with HF. The Los Alamos Laboratory supplied the lanthanum fluoride.

The wet way preparations were obtained in the following ways:

1. Solutions of potassium chloride and uranium tetrachloride, of potassium nitrate and thorium or lanthanum nitrate were precipitated with hydrofluoric acid.
2. Solutions of uranium tetrachloride, of thorium nitrate or of lanthanum nitrate were precipitated with a potassium fluoride solution.
3. Solutions of $K_3UO_2F_5$ or of uranyl nitrate and potassium fluoride were reduced with formic acid and direct sunlight whereby precipitates were formed.

2. The Identification of the Phases.—The chemical identity of the various phases was deduced through interpretation of the X-ray diffraction patterns. This unorthodox method of analysis had to be used because the chemical analysts were busy with more important work. Direct chemical analyses of a few single phase preparations were, however, made. These direct analyses were rather unsatisfactory because the alkali content was not determined and because of the customary difficulty in obtaining reliable results for the fluorine percentage.

Because the method is unknown to most chem-

ists it may be useful to discuss in some detail how the chemical formulas of the various phases were determined from the X-ray data.

The method presupposes that the lattice dimensions of the various phases can be deduced from the X-ray diffraction patterns. The observed diffraction intensities can with good approximation be attributed to the heavy atoms since the scattering powers of potassium, sodium and fluorine are small compared to those of uranium, thorium and lanthanum. A small number of degrees of freedom being involved it may accordingly be assumed that intensity considerations have led to a determination of the number and positions of the heavy atoms within the unit cell. The volume of the unit cell, V, and the number of heavy atoms within it, N_X, may thus be regarded as accurately known experimental quantities.

The volume of the unit cell for fluorides of the heavy elements under consideration can with good approximation be attributed to the fluorine atoms alone with the heavy metal atoms fitting into the interstices between the anions. The volume requirement of a fluorine atom may be set at $V_F = 18$ Å.^{3} as shown by the experimental values of Table I.

TABLE I

VOLUME REQUIREMENT OF A FLUORINE ATOM

Compound	UF_3	UF_4	U_2F_9	α-UF_5	β-UF_5	UF_6	LaF_3
V_F	18.1	19.4	16.9	19.0	17.0	19.3	18.2

The mean values for the volume requirement of a sodium or potassium atom as obtained from a number of known crystal structures are $V_K = 21$ Å.^{3} and $V_{Na} = 7$ Å.^{3}.

For the volume of the unit cell we have

$$V = N_A V_A + N_F V_F$$

where N_A and N_F are the number of alkali atoms and the number of fluorine atoms per unit cell, and where V_A is the volume requirement of an alkali atom. The numbers N_A, N_X and N_F are not independent since the valences must be balanced. Making use of this fact it becomes possible to determine the unknown quantities N_A and N_F in terms of the experimentally known quantities V, V_F, V_A and N_X. The result is

I. Systems AF–XF_4

$$N_A = \frac{V - 4N_X V_F}{V_A + V_F} \qquad N_F = \frac{V + 4N_X V_A}{V_A + V_F} \quad (2a)$$

II. Systems AF–XF_3

$$N_A = \frac{V - 3N_X V_F}{V_A + V_F} \qquad N_F = \frac{V + 3N_X V_A}{V_A + V_F} \quad (2b)$$

Since the writer succeeded in determining the lattice dimensions and the number and positions of the heavy atoms in the unit cell for all the observed phases through interpretation of the X-ray diffraction patterns, the chemical formulas of all the compounds could be determined in this novel manner. The results of this method of analysis for the KF–UF_4 and NaF–ThF_4 systems are shown in Tables II and III for purposes of illustration.

TABLE II

IDENTIFICATION OF THE PHASES IN THE KF–UF_4 SYSTEM

Phase no.	V	N_U	N_K	N_F	Deduced formula
1	951 Å.^{3}	12	$2.2 \approx 2$	$50.2 \approx 50$	KU_6F_{25}
2	497	6	$1.7 \approx 2$	$25.7 \approx 26$	KU_3F_{13}
3	697	8	$3.1 \approx 4$	$35.1 \approx 36$	KU_2F_9
4	684	6	$6.5 \approx 6$	$30.5 \approx 30$	KUF_5
5	209	$1.6 \approx 4/3$	$2.4 \approx 8/3$	$8.8 \approx 8$	α-K_2UF_6
6	139	1	$1.7 \approx 2$	$5.7 \approx 6$	β_1-K_2UF_6
7	149	1	$2.0 \approx 2$	$6.0 \approx 6$	β_2-K_2UF_6
8	781	4	$12.6 \approx 12$	$28.6 \approx 28$	α-K_3UF_7
9	1558	8	$25.2 \approx 24$	$57.2 \approx 56$	α'-K_3UF_7

TABLE III

IDENTIFICATION OF THE PHASES IN THE NaF–ThF_4 SYSTEM

Phase no.	V	N_{Th}	N_{Na}	N_F	Deduced formula
1	660 Å.^{3}	8	$3.4 \approx 4$	$35.4 \approx 36$	$NaTh_2F_9$
2	119	1	$1.9 \approx 2$	$5.9 \approx 6$	β_2-Na_2ThF_6
3	241	2	$3.9 \approx 4$	$11.9 \approx 12$	δ-Na_2ThF_6
4	2054	12	$47.6 \approx 48$	$95.6 \approx 96$	Na_4ThF_8

The results from eqs. (2) should correspond to rational stoichiometric ratios and should give values N_K and N_F which are compatible with the observed space group symmetry. As a further check one knows, of course, the gross composition of the melts from which the phases were prepared.

N_X assumes fractional values for the α-phase compounds A_2XF_6 and for the β-phase compounds AXF_4. These phases have disordered crystal structures involving A-atoms and X-atoms in structurally equivalent positions. In these instances $N_A + N_X$, rather than N_X, is experimentally determined from the intensity calculations. Thus $N_A + N_X = 4$ for α-A_2XF_6 and $N_A + N_X = 3$ for β-AXF_4.

When the A-atoms and X-atoms are regarded as structurally equivalent the formulas for α-A_2XF_6 and β-AXF_4 may be written as YF_2 where Y repre-

TABLE IV

RESULTS OF CHEMICAL ANALYSES

Compound	Theoretical	Experimental: Direct method	Experimental: X-ray method
KU_2F_9	U 69.5%	69.6%	70.7%
	F 24.9	23.4	24.8
	K 5.6	..	4.5
KTh_2F_9	Th 68.8	67.0	68.7
	F 25.4	22.0	25.4
	K 5.8	..	5.9
α-K_2UF_6	U 55.3	55.0	54.2
	F 26.5	26.5	26.5
	K 18.2	..	19.3
β_1-K_2UF_6	U 55.3	59.9	57.7
	F 26.5	24.9	26.2
	K 18.2	..	16.1
β_1-$KLaF_4$	La 54.6	52.6	54.7
	F 29.9	26.7	29.9
	K 15.5	..	15.4

sents the A-atoms as well as the X-atoms. Thus, the α-A_2XF_6 and the β-AXF_4 phases may be regarded as pseudo-difluorides, and the unit cell will contain an integral number of formula weights YF_2. The unit cell of α-A_2XF_6 contains four molecules YF_2 and that of β-AXF_4 three molecules.

The method of analysis is remarkably accurate. This is demonstrated in Table IV where the results of this method are compared with those of the orthodox, direct method of chemical analysis for some of the phases. C. Carter and B. Holt carried out the conventional analyses.

3. The Phase Composition of the Preparations.—Tables V–X show the phase compositions of the preparations made from melts as determined by analysis of the X-ray diffraction patterns. It is seen that the two lanthanum systems are very simple ones while the uranium and thorium systems are exceptionally complex.

TABLE V

PHASE COMPOSITION OF MELTS IN THE SYSTEM KF–UF_4

Mole % UF_4	Phases present: Major	Minor	Trace
89	KU_6F_{25} + UF_4		
86	KU_6F_{25}	KU_2F_9 + UF_4	
83	KU_6F_{25}	KU_2F_9	UF_4
80	KU_2F_9 + KU_6F_{25}		UF_4 + KU_3F_{13}
75	KU_2F_9 + KU_6F_{25}		KU_3F_{13} + UF_4
67	KU_2F_9	KU_6F_{25} + KU_3F_{13} + KUF_5	
60	KU_2F_9 + UF_5		
50	KUF_5		
45	KUF_5	β_1-K_3UF_6	
40	KUF_5 + β_1-K_2UF_6		
36	β_1-K_2UF_6	α-K_2UF_6	
33 (a)[a]	β_1-K_2UF_6		
(b)	β_1-K_2UF_6	α-K_2UF_6	
(c)	β_1'-K_2UF_6[b]		
(d)	β_2-K_2UF_6		
29	β_1-K_2UF_6 + α-K_3UF_7		
25 (a)	α'-K_3UF_7		
(b)	α-K_3UF_7		
22	α-K_3UF_7		
20	α-K_3UF_7		KF
17	α-K_3UF_7	KF	
14	α-K_3UF_7	KF	

[a] Symbols (a), (b), (c), (d) are used to indicate different rates of cooling, a indicating the lowest rate. [b] β_1' — A_2XF_6 is a disordered form of β_1 — A_2XF_6 involving isomorphous replacement between A-atoms and X-atoms.

TABLE VI

PHASE COMPOSITION OF MELTS IN THE KF–ThF_4 SYSTEM

Mole % ThF_4	Phases present: Major	Minor
86	KTh_6F_{25}	ThF_4 + KTh_2F_9
75	KTh_2F_9 + KTh_6F_{25}	
67	KTh_2F_9	$KThF_5$ + KTh_6F_{25}
50	$KThF_5$	
40	$KThF_5$ + β_1-K_2ThF_6	
33 (a)[a]	β_1-K_2ThF_6	
(b)	β_1-K_2ThF_6	α-K_2ThF_6
(c)	β_1'-K_2ThF_6	
29	β_1-K_2ThF_6	
25	β_1-K_2ThF_6	K_5ThF_9
20	K_5ThF_9	
17	K_5ThF_9	

TABLE VII

PHASE COMPOSITION OF MELTS IN THE KF–LaF_3 SYSTEM

Mole % LaF_3	Phases present: Major	Minor
67	LaF_3 + α-$KLaF_4$	β_1-$KLaF_4$
58	α-$KLaF_4$	LaF_3 + β_1-$KLaF_4$
50 (a)[a]	β_1-$KLaF_4$	
(b)	β_1-$KLaF_4$	α-$KLaF_4$
33	β_1-$KLaF_4$ + KF	
25	β_1-$KLaF_4$ + KF	

TABLE VIII

PHASE COMPOSITION OF MELTS IN THE NaF–UF_4 SYSTEM

Mole % UF_4	Phases present: Major	Minor
67	$NaUF_5$ + UF_4	
50	$NaUF_5$	
40	α-Na_2UF_6	
36	α-Na_2UF_6	
33 (a)[a]	γ-Na_2UF_6	
(b)	γ-Na_2UF_6	β_2-Na_2UF_6 + α-Na_2UF_6
(c)	β_2-Na_2UF_6 + α-Na_2UF_6 + γ-Na_2UF_6	
31	γ-Na_2UF_6	
29	Na_3UF_7	
27	Na_3UF_7	
25	Na_3UF_7	
20	Na_3UF_7	NaF

TABLE IX

PHASE COMPOSITION OF MELTS IN THE NaF–ThF_4 SYSTEM

Mole % ThF_4	Phases present: Major	Minor
67	$NaTh_2F_9$	
33–67	Not investigated[b]	
33 (a)[a]	δ-Na_2ThF_6	
(b)	β_2-Na_2ThF_6	
29	δ-Na_2ThF_6	Na_4ThF_8
25	Na_4ThF_8	δ-Na_2ThF_6
20	Na_4ThF_8	
14	Na_4ThF_8 + NaF	

[b] Preliminary data indicate two new phases in this range.

TABLE X

PHASE COMPOSITION OF MELTS IN NaF–LaF_3 SYSTEM

Mole % LaF_3	Phases present
67	β_2-$NaLaF_4$ + LaF_3
50	β_2-$NaLaF_4$
33	β_2-$NaLaF_4$ + NaF
25	β_2-$NaLaF_4$ + NaF

The systems involving potassium were also examined by means of samples precipitated from solutions. The precipitates from lanthanum solutions all proved to consist of anhydrous lanthanum fluoride irrespective of the potassium concentration in the solution. However, some of the potassium–uranium and potassium–thorium fluorides can be prepared in the wet way.

KU_2F_9 and KTh_2F_9 are obtained as pure and anhydrous phases by precipitation from solutions containing large excess of uranium or thorium over potassium. Anhydrous KUF_5 and $KThF_5$ are present as pure phases in the precipitates from

solutions containing potassium and uranium or thorium in equal amounts. Single phase precipitates of anhydrous α-K_2UF_6 or α-K_2ThF_6 are obtained from solutions with large excess of potassium over uranium or thorium provided the rate of precipitation is high. Solutions with high potassium concentration yield KUF_5 or $KThF_5$ at low precipitation rates. These are the only double fluorides of potassium and uranium or thorium which the writer has observed in the precipitates.

The various phases which have been found in the systems under consideration are compiled in Table XI. Phases listed in the same horizontal row of the table represent isomorphous compounds.

TABLE XI

OBSERVED PHASES

K–U	K–Th	Na–U	Na–Th	K–La	Na–La
KU_6F_{25}	KTh_6F_{25}				
KU_3F_{13}					
KU_2F_9	KTh_2F_9				
			$NaTh_2F_9$		
KUF_5	$KThF_5$	$NaUF_5$	?		
α-K_2UF_6	α-K_2ThF_6	α-Na_2UF_6	?	α-$KLaF_4$	
β_1-K_2UF_6	β_1-K_2ThF_6			β_1-$KLaF_4$	
β_2-K_2UF_6		β_2-Na_2UF_6	β_2-Na_2ThF_6		β_2-$NaLaF_4$
		γ-Na_2UF_6			
			δ-Na_2ThF_6		
α-K_3UF_7					
α'-K_3UF_7					
		Na_3UF_7			
			Na_4ThF_8		
	K_5ThF_9				

It seems that only a few of the twenty-seven phases listed in Table XI have been previously described in the literature.

As stated earlier, the writer has succeeded in determining lattice dimensions and the positions of the heavy atoms for all the phases. Complete crystal structures have been found for $NaTh_2F_9$, the α-phase compounds, the β-phase compounds, γ-Na_2UF_6 and Na_3UF_7. These crystal structure determinations will be treated in another paper to appear elsewhere.

Some of the structural constants are listed in Table XII, together with the number of molecules per unit cell, n, and the calculated densities ρ.

4. Other Isomorphous Compounds.—Compounds isomorphous with those listed in Table XI and involving other elements have been observed. These compounds were encountered in incidental preparations submitted to the writer for X-ray diffraction study.

KNp_2F_9 was observed as the only crystalline phase in a sample labeled "Np(V)-fluoride" which had been prepared by T. LaChapelle and L. B. Magnusson. Another sample prepared by the same investigators and labeled "Np(IV)-fluoride" was found to contain KNp_2F_9 as a minor and K_2SiF_6 as the major phase.

KPu_2F_9 was the only crystalline phase in a sample labeled "H-Pu(IV)-fluoride" which H. H. Anderson had prepared.

The compounds $NaPuF_5$, $KPuF_5$, and $RbPuF_5$ were prepared by H. H. Anderson and the correct

TABLE XII

CRYSTAL STRUCTURE DATA FOR DOUBLE FLUORIDES

Compound	Symmetry	Unit cell dimensions, Å.	n	ρ
KU_6F_{25}	Hexagonal $C\bar{6}/mmc$	$a_1 = 8.18 \pm 0.01$ $a_3 = 16.42 \pm 0.02$	2	6.73
KTh_6F_{25}	Hexagonal $C\bar{6}/mmc$	$a_1 = 8.32 \pm 0.01$ $a_3 = 16.78 \pm 0.02$	2	6.25
KU_3F_{13}	Orthorhombic Pmcm	$a_1 = 8.03 \pm 0.03$ $a_2 = 7.25 \pm 0.03$ $a_3 = 8.53 \pm 0.04$	2	6.64
KU_2F_9	Orthorhombic Pnam	$a_1 = 8.68 \pm 0.01$ $a_2 = 7.02 \pm 0.01$ $a_3 = 11.44 \pm 0.04$	4	6.49
KTh_2F_9	Orthorhombic Pnam	$a_1 = 8.85 \pm 0.03$ $a_2 = 7.16 \pm 0.02$ $a_3 = 11.62 \pm 0.04$	4	6.04
KNp_2F_9	Orthorhombic Pnam	$a_1 = 8.63 \pm 0.05$ $a_2 = 7.01 \pm 0.05$ $a_3 = 11.43 \pm 0.07$	4	6.54
KPu_2F_9	Orthorhombic Pnam	$a_1 = 8.56 \pm 0.04$ $a_2 = 6.95 \pm 0.04$ $a_3 = 11.33 \pm 0.06$	4	6.73
$NaTh_2F_9$	Cubic $I\bar{4}3m$	$a = 8.705 \pm 0.001$	4	6.58
$KThF_5$	Rhombohedral $R\bar{3}$	$a = 9.510 \pm 0.005$ $\alpha = 107° 17' \pm 5'$	6	5.10
$NaUF_5$	Rhombohedral $R\bar{3}$	$a = 9.08 \pm 0.01$ $\alpha = 107° 56'$	6	5.81
KUF_5	Rhombohedral $R\bar{3}$	$a = 9.387 \pm 0.002$ $\alpha = 107° 15' \pm 2'$	6	5.38
$NaPuF_5$	Rhombohedral $R\bar{3}$	$a = 8.93 \pm 0.03$ $\alpha = 107° 28' \pm 10'$	6	6.03
$KPuF_5$	Rhombohedral $R\bar{3}$	$a = 9.27 \pm 0.03$ $\alpha = 107° 2' \pm 10'$	6	5.66
$RbPuF_5$	Rhombohedral $R\bar{3}$	$a = 9.46 \pm 0.03$ $\alpha = 106° 56' \pm 10'$	6	5.88
α-K_2ThF_6	Cubic Fluorite	$a = 5.994 \pm 0.004$	4/3	4.33
α-Na_2UF_6	Cubic Fluorite	$a = 5.565 \pm 0.004$	4/3	5.08
α-K_2UF_6	Cubic Fluorite	$a = 5.934 \pm 0.001$	4/3	4.53
α-$KLaF_4$	Cubic Fluorite	$a = 5.931 \pm 0.001$	2	4.06
β_1-K_2ThF_6	Hexagonal $C\bar{6}2m$	$a_1 = 6.565 \pm 0.002$ $a_3 = 3.815 \pm 0.001$	1	4.91
β_1-K_2UF_6	Hexagonal $C\bar{6}2m$	$a_1 = 6.54 \pm 0.01$ $a_3 = 3.76 \pm 0.01$	1	5.10
β_1-$KLaF_4$	Hexagonal $C\bar{6}2m$	$a_1 = 6.526 \pm 0.002$ $a_3 = 3.791 \pm 0.001$	3/2	4.52
β_2-K_2UF_6	Hexagonal C32	$a_1 = 6.53 \pm 0.02$ $a_3 = 4.04 \pm 0.01$	1	4.77
β_2-Na_2UF_6	Hexagonal C32	$a_1 = 5.94 \pm 0.01$ $a_3 = 3.74 \pm 0.01$	1	5.74
β_2-Na_2ThF_6	Hexagonal C32	$a_1 = 5.99 \pm 0.02$ $a_3 = 3.81 \pm 0.01$	1	5.46
β_2-$NaLaF_4$	Hexagonal C32	$a_1 = 6.167 \pm 0.001$ $a_3 = 3.819 \pm 0.002$	3/2	4.68
β_2-$NaPuF_4$	Hexagonal C32	$a_1 = 6.12 \pm 0.02$ $a_3 = 3.75 \pm 0.01$	3/2	6.87
γ-Na_2UF_6	Orthorhombic Immm	$a_1 = 5.56 \pm 0.02$ $a_2 = 4.01 \pm 0.01$ $a_3 = 11.64 \pm 0.04$	2	5.06
δ-Na_2ThF_6	Hexagonal	$a_1 = 6.14 \pm 0.01$ $a_3 = 7.36 \pm 0.02$	2	5.37
α-K_3UF_7	Cubic	$a = 9.21 \pm 0.01$	4	4.12
α'-K_3UF_7	Tetragonal I4/amd	$a_1 = 9.20 \pm 0.02$ $a_3 = 18.40 \pm 0.06$	8	4.13
Na_3UF_7	Tetragonal I4/mmm	$a_1 = 5.448 \pm 0.007$ $a_3 = 10.896 \pm 0.014$	2	4.49
Na_4ThF_8	Cubic	$a = 12.706 \pm 0.002$	12	4.59
K_5ThF_9	Orthorhombic Ccmm	$a_1 = 12.87 \pm 0.04$ $a_2 = 7.90 \pm 0.02$ $a_3 = 10.83 \pm 0.03$	4	3.58

formulas deduced by him with the aid of direct chemical analyses. X-Ray diffraction patterns of these preparations showed the compounds to be isomorphous with the corresponding uranium and thorium compounds.

$NaPuF_4$ was found in a sample which was supposed to be plutonium metal. L. Baumbach had prepared this sample.

The isomorphous compounds of neptunium and plutonium are also listed in Table XII.

Miss Anne Plettinger gave valuable aid by taking most of the numerous X-ray diffraction patterns which were required. Mr. W. C. Koehler helped by measuring some of the diffraction patterns. Miss C. Carter and Mr. B. Holt contributed to the work by carrying out direct chemical analyses for some of the phases. The loan of micro-preparations of neptunium and plutonium made by Drs. T. LaChapelle and L. B. Magnusson, H. H. Anderson and L. Baumbach is gratefully acknowledged. The writer is also indebted to Dr. R. Livingston for some pure thorium tetrafluoride.

Abstract

A large number of double fluorides have been found in the systems $KF–UF_4$, $KF–ThF_4$, $KF–LaF_3$, $NaF–UF_4$, $NaF–ThF_4$ and $NaF–LaF_3$. In addition to the terminal compounds the following phases have been observed:

In the $KF–UF_4$ system: KU_6F_{25}, KU_3F_{13}, KU_2F_9, KUF_5, α-K_2UF_6, β_1-K_2UF_6, β_2-K_2UF_6, α-K_3UF_7, and α'-K_3UF_7.

In the $KF–ThF_4$ system: KTh_6F_{25}, KTh_2F_9, $KThF_5$, α-K_2ThF_6, β_1-K_2ThF_6, and K_5ThF_9.

In the $KF–LaF_3$ system: α-$KLaF_4$, β_1-$KLaF_4$.

In the $NaF–UF_4$ system: $NaUF_5$, α-Na_2UF_6, β_2-Na_2UF_6, γ-Na_2UF_6, and Na_3UF_7.

In the $NaF–ThF_4$ system: $NaTh_2F_9$, β_2-Na_2ThF_6, δ-Na_2ThF_6, and Na_4ThF_8.

In the $NaF–LaF_3$ system: β_2-$NaLaF_4$.

Lattice dimensions are given for all the phases. Some results for isomorphous neptunium and plutonium compounds are reported.

CHICAGO, ILLINOIS RECEIVED FEBRUARY 27, 1948

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Versatile Technique for X-Ray Single Crystal Structural Analysis Applied to Benzaldehyde 2,4-Dinitrophenylhydrazone and Zinc Salts of Salicylic and Benzoic Acids

BY GEORGE L. CLARK AND HUNG KAO

It is well known among crystal structure analysts that Weissenberg diffraction photographs provide distorted projections of the levels of a reciprocal lattice, from which the true reciprocal lattice, and thence the direct lattice, may be reconstructed after more or less elaborate measurement and interpretation; whereas the comparatively new precession technique devised by Buerger[1] gives X-ray diagrams which are undistorted images of the reciprocal lattice and thus easily interpreted by inspection only. Although the precession method records only a limited part of the reciprocal lattice, especially in case of n-levels and has some other disadvantages, it has some distinct advantages over Weissenberg methods in that it requires a less perfect crystal, shorter time of exposure and above all simpler interpretation. Moreover the precession method makes it possible to precess along two crystal axes without changing a crystal setting if the angle between the two axes is known; thus two reciprocal lattice photographs which will give all three linear constants and two angles can be obtained.

Inasmuch as new Weissenberg and precession cameras designed by Buerger and made by one instrument maker[2] under the same conditions of precision were available, the crystal holders for the two cameras could be interchanged. Thus it seemed possible that a combination usage of the precession and Weissenberg cameras might provide a simpler and more dependable technique than any single method. This paper is a brief report of our first experience in using the precession camera, presented in the hope that it may be helpful in other laboratories, as well as a record of crystallographic information so obtained for benzaldehyde 2,4-dinitrophenylhydrazone, zinc salicylate trihydrate, zinc benzoate and zinc hydrogen benzoate dihydrate.

Notes on the Precession Method

A few remarks concerning our own experience on this method may be useful. The first step in crystal analysis of course is to adjust a crystallographic axis to the precession axis. The techniques are discussed in detail in Buerger's monograph. An improved technique which we have used is the pre-usage of a 57.3 mm. Weissenberg camera. Since the 57.3 mm. Weissenberg camera and the precession camera have an interchangeable adjustable crystal holder, transfer from one to the other is easily accomplished without disturbing the crystal. From the zero-level Weissenberg pattern the possible zones and the angles between them can be determined by simple inspection.

(1) M. J. Buerger, "The Photography of the Reciprocal Lattice," ASXRED Monograph No. 1, 1944.

(2) Charles Supper, Newton Centre, Mass.

One of these zone axes can be located and set parallel to the X-ray beam by several trials on the precession camera. Once it is identified any of the others can be located by turning the crystal through the angle between them followed by readjustment of the crystal. (In the cases of an orthorhombic, a tetragonal crystal or a monoclinic crystal oriented on its b-axis the other axis can be located by simply turning the crystal.) By this method even in the case where the crystal does not possess any well developed faces, it is still possible to locate its axes unambiguously. Moreover the data from the 0-layer line Weissenberg film will provide the best criterion to check whether the correct zone axis is chosen for precession.

Various methods have been discussed in the monograph for the determination of d^* (reciprocal lattice spacing) values for n-level photographs. From the information obtained from a 0-layer Weissenberg film as described above, the value of d^* for one crystallographic axis can be determined easily from the precession photograph along the other axis and *vice versa*. For example, for a monoclinic crystal whose b-axis is parallel to the axis of the crystal holder and whose β-angle is known from the Weissenberg pattern with the crystal rotating along this axis, a precession photograph is made along one axis, say the a-, and then after turning the crystal through $\beta°$ another precession photograph is made along the c-axis. The former will give the d^* value for n-level precession along the latter axis and *vice versa*.

It has been found, in the case of zinc hydrogen benzoate dihydrate, that the value of d^*, derived from precession along the c-axis with Cu Kα radiation, is so small that the annular slit of the layer-line screen will permit more than one level of the reciprocal lattice to register simultaneously, if the layer-line screen is set at the usual distance from the crystal. This will yield patterns with entirely anomalous extinctions. The difficulty can be avoided by selecting the n-level such that the layer-line screen will be as far from the crystal as possible. An alternative way is, of course, to change the X-ray radiation to one with longer wave length (for example Cr Kα radiation).

The Suggested Simple Technique for Single Crystal Structural Analysis

After considerable experience a simple procedure has been adopted by utilizing both the 57.3 mm. Weissenberg camera and precession camera, especially for needle crystals, where the orientation of the crystal along the axis other than needle axis is very difficult, if not impossible, as follows:

(1) Set the crystal on its holder so that the needle axis coincides with the horizontal axis of the crystal holder. Suppose that the needle axis is the b-axis of a monoclinic crystal. Take a rotation pattern from which the approximate value of b can be determined simply by means of a Bernal chart.

(2) Take zero- and first-layer Equi-inclination Weissenberg photographs from which the angle β^* can be accurately measured and a^* and c^* uniquely determined.

(3) Remove the crystal holder from the Weissenberg camera to the precession camera and make a zero-level photograph along one of the other axes, say the a-axis, from which b^*, c^* and α^* are determined by inspection.

(4) Turn the crystal β^* or 180°-β^* and make the zero-level precession photograph along c-axis, and thus determine a^*, b^*, γ^*. Take the n-level precession photographs using the d^* value obtained from (3).

(5) Turn the crystal back to the position (3) and make n-level photographs along a-axis using the d^* found in (4).

By these operations all lattice translations and angles of the reciprocal and hence of the direct lattice can be found. The space group can be determined by examining the extinction data from these two sets of precession photographs. This is usually enough, but additional n-layer line Weissenberg photographs along the b-axis can be made, if necessary.

The Crystal Structure of Benzaldehyde- 2,4-Dinitrophenylhydrazone

This compound was chosen as a logical extension of the work in the laboratory on the X-ray diffraction and crystallography of the 2,4-dinitrophenylhydrazones of aldehydes and ketones.[3]

The benzaldehyde derivative was prepared by the method of Shriner and Fuson.[4] Orange crystals with sharp melting point 233–4° were obtained after four recrystallizations from ethyl acetate. No polymorphism was observed in crystallization from other solvents such as glacial acetic acid. Well-defined crystals were easily obtained. The density of the crystal determined by flotation in a solution of silver nitrate was 1.54. The "ideal" density calculated from X-ray data was 1.569.

X-Ray Data.—The results obtained by using the above procedure for single crystal analysis and that obtained by the Weissenberg method are summarized as follows for comparison:

		From Precession	From Weissenberg
(1) Unit cell constants	α	90°	90°
	β	92.7° ± 0.2°	92.8° ± 0.2°
number of molecules per unit cell		4	4
a (A. U.)		12.8 ± 0.1	13.1 ± 0.1
b		6.78 ± 0.01	6.79 ± 0.01
c		14.26 ± 0.02	14.20 ± 0.05
(2) Space-group		$P2_1/c$	$P2_1/c$
Extinctions (from both):		$h0l$ appears only when $l = 2n$	
		$0k0$ appears only when $k = 2n$	

(3) G. L. Clark, W. I. Kaye and T. D. Parks, *Ind. Eng. Chem., Anal. Ed.*, **18**, 310 (1946).

(4) "Identification of Organic Compounds," 2nd ed., 1940.

The Crystal Structure of Zinc Salicylate Trihydrate

Because of some interest in zinc salts of salicylic (*o*-hydroxybenzoic) and benzoic acids and their complexes with boric acid as antiseptics, a determination of structure may have added significance. Zinc salicylate trihydrate is formed by mixing equal volumes of 2-molar sodium salicylate and 1-molar zinc sulfate solutions at room temperature. A white powder rapidly separates which may be recrystallized to fine single crystals. It has been claimed that the crystals are needles, but only in the first stage of crystallization was this found to be true since the crystals lost their acicular shape during growth. The composition of the crystal as zinc salicylate trihydrate, $Zn(C_7H_5O_3)_2 \cdot 3H_2O$, is verified by its powder pattern, and by chemical analysis.

For this crystal a procedure similar to that just described was used. From the Weissenberg data the following results are obtained:

$\beta = 94°$
$a = 15.40 \pm 0.02$ A. U.
$b = 5.36 \pm 0.01$ A. U.
$c = 9.18 = 0.01$ A. U.

Extinctions: hkl appears only when $h + k = 2n$
$h0l$, $h = 2n$; $0k0$, $k = 2n$
Space group C2/m, C2, or Cm

From zero, first and second layer fine precession photographs around all three axes, the following data are obtained

$\beta = 93.8° \pm 0.2°$
$a = 15.40 \pm 0.02$ A. U.
$b = 5.37 \pm 0.01$ A. U.
$c = 9.18 \pm 0.01$ A. U.

Extinctions and space group as above.

The measured density is 1.64 from which about 2 molecules per unit cell are found. The ideal density for $n = 2$ is 1.653 g./ml.

The Crystal Structure of Zinc Benzoate

These crystals were prepared by double recrystallization from a pure commercial material, or from the product obtained by treating zinc carbonate with benzoic acid followed by slow evaporation of the solvent. Chemical analysis indicated pure anhydrous $Zn(C_6H_5COO)_2$, with a measured density of 1.54 by flotation in chloroform and carbon tetrachloride. Both equi-inclination Weissenberg and precession patterns gave concordant data as follows:

Monoclinic $\beta = 94° 26'$
$a = 10.67 \pm 0.02$ A. U.
$b = 12.94 \pm 0.02$ A. U.
$c = 19.22 \pm 0.02$ A. U.

Systematic extinctions: hkl all appear
$h0l$ appears only when $l = 2n$
$0k0$ appears only when $k = 2n$
Space group $P2_1/c$

Number of molecules per unit cell 8. The "ideal" density calculated 1.546 g./ml.

The Crystal Structure of Zinc Hydrogen Benzoate Dihydrate

The compound was prepared either by adding zinc chloride to an aqueous solution containing sodium benzoate and benzoic acid or by the reaction of benzoic acid with zinc carbonate in aqueous solution. It was also obtained, as observed in this work, by the addition of benzoic acid to zinc borate which was suspended in hot water; from such solutions benzoic acid first settled out, then long colorless needles of $ZnH_2(C_6H_5COO)_4 \cdot 2H_2O$ crystallized out (for zinc found 11.17%; calculated 11.13%). The compound is soluble in ether and alcohol and slightly soluble in benzene. The crystals have about the same density as pure chloroform at 32°, 1.47 g./ml.

The usual series of equi-inclination Weissenberg and precession patterns in 0, 1 and 2-levels were made yielding the following data:

Orthorhombic, with shortest translations

$a = 5.20 \pm 0.02$ A. U.
$b = 25.4 \pm 0.02$ A. U.
$c = 40.0 \pm 0.5$ A. U.

Compounds	Crystal habits	Crystal system	Cell constants	Space group	n	"Ideal" density
Benzaldehyde 2,4-dinitrophenylhydrazone	Orange plates	Monoclinic	a 12.8 ± 0.1 A. U. b 6.79 ± 0.01 c 14.23 ± 0.02 β 92.8° ± 0.2°	$P2_1/c$	4	1.569
Zinc salicylate trihydrate	Colorless plates	Monoclinic	a 15.4 ± 0.02 b 5.36 ± 0.01 c 9.18 ± 0.01 β 94.0° ± 0.2°	C2/m or C2 or Cm	2	1.653
Zinc benzoate	Colorless plates	Monoclinic	a 10.67 ± 0.02 b 12.94 ± 0.02 c 19.22 ± 0.02 β 94.4° ± 0.2°	$P2_1/c$	8	1.546
Zinc hydrogen benzoate dihydrate	White needles	Orthorhombic	a 5.20 ± 0.02 b 25.4 ± 0.2 c 40.0 ± 0.5	F d d	8	1.47

Systematic extinctions:

hkl appears only when all odd or all even
0kl appears only with $k = 2n$ and $l = 2n$
h0l appears only with $h = 2n$, $l = 2n$ and $h + l = 4n$
hk0 appears only with $h = 2n$, $k = 2n$ and $h + k = 4n$
Space group: F d d

The number of molecules per unit cell is 8 and the "ideal" density of the crystal is 1.478 g./ml. The compound is unusually interesting because of the very small *a* spacing in comparison with *b* and *c*, probably indicating very flat molecules lying extended in the *bc* plane, also probably with hydrogen bonding. Hence this offers an excellent opportunity for a two-dimensional Fourier analysis of electron densities which is now being carried out.

Summary

1. A new simple procedure for single crystal analysis by the combination of the equi-inclination Weissenberg and the Buerger precession methods has been investigated and its application has been illustrated with practical problems. This new procedure provides a simple solution for needle crystals the orientation of which, along the crystallographic axes other than needle axis, is extraordinarily difficult.

2. Determinations were made of crystal habits, densities, lattice constants and probable space-groups of four compounds, for which no previous X-ray and crystallographical data are available, as tabulated on the preceding page.

URBANA, ILLINOIS RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

Heat Contents at High Temperatures of Vanadium Dichloride and Vanadium Trichloride[1]

BY E. G. KING[2]

In continuation of a program of study of the thermodynamic properties of vanadium compounds, high-temperature heat contents of vanadium dichloride and vanadium trichloride were measured. No previous similar values exist for these substances, but low temperature heat capacity and entropy data have been reported by Shomate.[3]

Materials

The samples used in this work were portions of the materials prepared for previous low temperature heat capacity measurements, and the methods of preparation and the analyses were described by Shomate.[3] Before the present measurements were begun, both compounds were given a preliminary heating in vacuum, the dichloride to 850° and the trichloride to 150°.

Measurements and Results

The high temperature heat content measurements were made by the "dropping" method with previously described[4,5] apparatus. Frequent calibrations of the furnace thermocouple at the gold point were made by the method described by Southard.[4]

The samples were contained in platinum–rhodium alloy capsules. Two capsules were employed for the dichloride, containing, respectively, 8.9608 and 8.6643 g. (corrected to vacuum) of sample. These capsules were sealed by platinum welding after replacing air in the pore space by helium. One capsule, containing 7.4429 g. (corrected to vacuum) of sample was used for the trichloride. It was sealed by gold soldering, after the pore space was filled with helium. Corrections for the capsules were made by means of separate measurements of the platinum–rhodium alloy and the known heat contents of gold and platinum. These corrections amounted to 25% of the total measured heats for the dichloride and 28% for the trichloride.

The experimental results, expressed in defined calories[6] (1 cal. = 4.1833 int. joules), are in Table

TABLE I

HIGH-TEMPERATURE HEAT CONTENT OF VCl_2
(Mol. wt. = 121.86)

T, °K.	$H_T - H_{298.16}$, cal./mole	T, °K.	$H_T - H_{298.16}$, cal./mole
339.9	760	875.9	10,730
389.0	1670	971.3	12,620
393.9	1745	1029.5	13,850
471.7	3125	1072.7	14,640
570.4	4895	1172.9	16,660
673.8	6830	1272.5	18,740
773.8	8740		

HIGH-TEMPERATURE HEAT CONTENT OF VCl_3
(Mol. wt. = 157.32)

T, °K.	$H_T - H_{298.16}$, cal./mole	T, °K.	$H_T - H_{298.16}$, cal./mole
343.1	1070	704.9	9,875
400.3	2405	803.8	12,420
502.2	4775	902.5	14,870
601.9	7225		

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.
(2) Chemist, Pacific Experiment Station, Bureau of Mines.
(3) Shomate, THIS JOURNAL, **69**, 220 (1947).
(4) Southard, *ibid.*, **63**, 3142 (1941).
(5) Kelley, Naylor and Shomate, *Bur. Mines Tech. Paper*, 686, 1946, 34 pp.
(6) Mueller and Rossini, *Am. J. Phys.*, **12**, 1 (1944).

I. Molal weights accord with the 1947 International Atomic Weights.

Measurements of the dichloride could not be extended beyond 1272°K. because of swelling of the capsule from vapor pressure of the substance. Pressure of tetrachloride from the disproportionation reaction of the trichloride precluded obtaining results above 902°K. for the latter substance.

The heat content curves are shown in Fig. 1. No anomalous behavior of either substance was observed.

Smooth curve values of the heat contents and entropy increments calculated from them are in Table II. The average deviation of experimental points from the smooth curves is 0.15% for the dichloride and 0.3% for the trichloride.

TABLE II

HEAT CONTENTS AND ENTROPIES ABOVE 298.16°K.

	VCl_2		VCl_3	
T, °K.	$H_T - H_{298.16}$, cal./mole	$S_T - S_{298.16}$, cal./deg./mole	$H_T - H_{298.16}$, cal./mole	$S_T - S_{298.16}$, cal./deg./mole
400	1,840	5.30	2,360	6.80
500	3,620	9.27	4,730	12.09
600	5,450	12.61	7,180	16.55
700	7,330	15.50	9,700	20.43
800	9,250	18.07	12,270	23.85
900	11,200	20.36	14,860	26.90
1000	13,180	22.45		
1100	15,190	24.36		
1200	17,220	26.13		
1300	19,270	27.77		

Heat content equations, representing the data, were derived by the method of Shomate,[7] use being made of his values[3] of the heat capacities at 298.16°K. The average deviations from smooth values and temperature ranges of validity are given in parentheses. Corresponding molal heat capacity equations also are listed.

For VCl_2

$$H_T - H_{298.16} = 17.25T + 1.36 \times 10^{-3}T^2 + 0.71 \times 10^5T^{-1} - 5502$$

(298–1200°K.; 0.3%)

$$C_p = 17.25 + 2.72 \times 10^{-3}T - 0.71 \times 10^5T^{-2}$$

(7) Shomate, THIS JOURNAL, **66**, 928 (1944).

For VCl_3

$$H_T - H_{298.16} = 22.99T + 1.96 \times 10^{-3}T^2 + 1.68 \times 10^5T^{-1} - 7592$$

(298–900°K.; 0.2%)

$$C_p = 22.99 + 3.92 \times 10^{-3}T - 1.68 \times 10^5T^{-2}$$

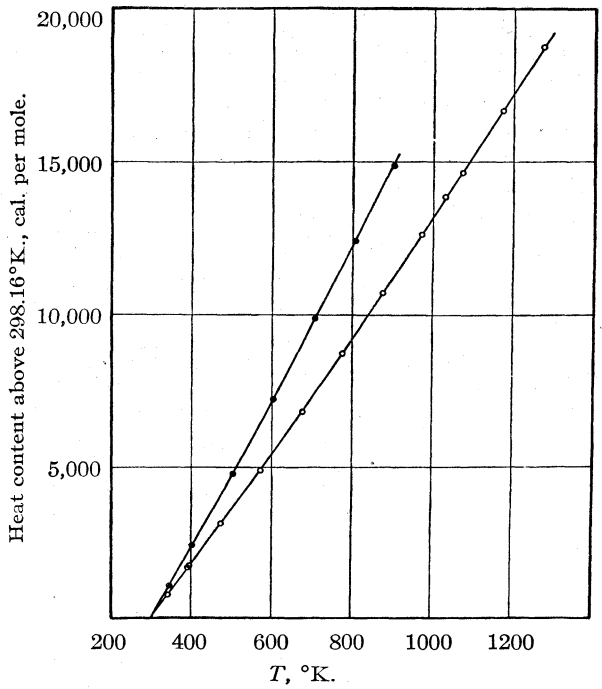


Fig. 1.—High temperature heat content of vanadium chlorides: upper curve, VCl_3; lower curve, VCl_2.

Summary

High-temperature heat contents of vanadium dichloride and vanadium trichloride were measured from 298.16°K. to 1272°K. and 902°K., respectively.

Tables of heat contents and entropy increments above 298.16°K. are assembled and heat content and heat capacity equations are derived.

BERKELEY, CALIFORNIA RECEIVED JANUARY 30, 1948

[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

A Hydrofluoric Acid Solution Calorimeter and the Determination of the Heats of Formation of Mg_2SiO_4, $MgSiO_3$, and $CaSiO_3$[1]

BY D. R. TORGESON[2] AND TH. G. SAHAMA[3]

Heats of formation of most silicates are not amenable to determination by either combustion or ordinary solution calorimetry. However, many silicates can be studied with a hydrofluoric acid solution calorimeter, operating near 75°. This paper describes a calorimeter of this type and presents values of the heats of formation of magnesium orthosilicate, magnesium metasilicate and calcium metasilicate.

Materials

The materials employed were artificial magnesium metasilicate (clinoenstatite), natural calcium metasilicate (wollastonite), a series of 6 natural solid solutions in the Mg_2SiO_4–Fe_2SiO_4 system with a wide range of magnesium: iron ratios, artificial ferrous orthosilicate (fayalite), natural quartz, artificial magnesium hydroxide, and artificial calcium oxide.

The magnesium metasilicate and ferrous orthosilicate were the materials used in previous measurements by Kelley.[4,5] The former contained 92.0% $MgSiO_3$, 5.6% Mg_2SiO_4, and 2.4% uncombined SiO_2. The latter was virtually 100% pure.

The calcium metasilicate was that described by Southard.[6] It contained about 0.6% impurities.

The quartz was the purest available grade. It was crushed, screened through 325-mesh, washed with hot hydrochloric acid for several days, water-elutriated to eliminate the coarser particles, and finally dried. Analyses indicated at least 99.9% silica content.

Magnesium hydroxide was prepared from reagent-grade magnesium oxide in a manner similar to that used by Taylor and Wells.[7] In this instance, the washed oxide was calcined at 900° and then hydrated with steam at 150 lb. per sq. in. pressure. The wet hydrate was dried in vacuum at 120°. Analysis showed 0.1% carbon dioxide content (equivalent to 0.19% $MgCO_3$) and 99.78% magnesium hydroxide.

Calcium oxide was prepared by calcining special reagent grade calcium carbonate at 1150°. Analysis of the product showed 99.98% calcium oxide.

The Mg_2SiO_4–Fe_2SiO_4 samples are described in Table I, using the classification proposed by Deer and Wager.[8] Before chemical analysis, the samples were purified by hand sorting, table classification, magnetic separation, and gravity separation with Clerici solution (aqueous solution of thallium formate and thallium malonate). Final products were examined microscopically.

Apparatus and Method

The calorimetric assembly is shown in Fig. 1. As it is expected that several researches employing this equipment will be published, a brief description is warranted.

The calorimeter, V, is a cylindrical platinum vessel, 10 cm. diam. and 12.5 cm. high, filled with hydrofluoric acid to the level indicated at Y. Chimneys, V and W, provide for admission of the stirrer, X, and for insertion of samples. A cylindrical well, K, 2.2 cm. diameter, extending from 1.3 cm. above the bottom to 2.5 cm. above the top, houses the resistance thermometer and calibrating heater coils.

The resistance thermometer, L, and heater, N, are wound on the hollow copper cylinder, M, which has closed ends. This cylinder has 0.1-mm. wall thickness except at the ends where projecting flanges were left to anchor the coils and provide thermal contact with K. The resistance thermometer consists of B. & S. No. 40, single silk-covered and enameled copper wire and has 104.7 ohms resistance at 73.7°, the sensitivity being 308 μV. per degree. (As both calibration and reaction heats are measured in terms of μv., actual conversion to degrees never is necessary.) The heater is a 100-ohm coil of B. & S. No. 34, double-silk-covered manganin wire. Paraffin was used to fill the annular space between cylinder M and the walls of K. The top of K is closed by the cork, I, to which radiation shield, J, is attached.

Lead wires, A, from the resistance thermometer and

TABLE I

Mg_2SiO_4–Fe_2SiO_4 SAMPLES

	Sample	Source	Analysis for major constituents, wt. %[9] SiO_2	FeO	MgO	Fe_2O_3	TiO_2	MnO	Microscopically estimated impurities
(A)	Forsterite	Dreis, Eifel, Germany	40.60	8.35	49.60	0.96	0.00	0.16	None
(B)	Forsterite	Ultenthal, Tyrol, Austria	40.72	9.48	49.52	0.10	.12	0.13	None
(C)	Chrysolite[10]	Marjalahti, Finland	40.24	10.92	48.08	0.68	.00	0.28	None
(D)	Hyalosiderite	Lake Leistilänjärvi, Nakkila, Finland	35.20	35.40	25.94	2.60	.45	0.60	2% titanomagnetite
(E)	Hyalosiderite[11]	Susimäki, Vampula, Finland	35.12	36.98	25.42	2.10	.10	0.53	0.75% magnetite and ilmenite
(F)	Ferrohortonolite[12]	St. Utterviks Hage, Tunaberg, Södermanland, Sweden	29.80	64.06	2.22	0.00	.00	4.38	1% magnetite

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Chemist, Pacific Experiment Station, Bureau of Mines.

(3) Professor of Geochemistry, University of Helsinki, Finland, and at present Visiting Investigator of the Carnegie Institution of Washington, associated with the staff of the Geophysical Laboratory. Acknowledgment is gratefully made of support received from the Carnegie Institution of Washington throughout the course of this work.

(4) Kelley, THIS JOURNAL, **65**, 339 (1943).

(5) Kelley, *ibid.*, **63**, 2750 (1941).

(6) Southard, *ibid.*, **63**, 3142 (1941).

(7) Taylor and Wells, *Bur. Standards J. Research*, **21**, 133 (1938).

(8) Deer and Wager, *Am. Mineralogist*, **24**, 18 (1939).

(9) Chemical analyses were made by O. v. Knorring, University of Helsinki, Finland.

(10) Described by Borgström, *Bull. Comm. Geol. Finlande*, 14 (1903).

(11) Described by Palmunen, *Fennia*, **45**, No. 9 (1925).

(12) Described by Palmgren, *Bull. Geol. Inst., Upsala*, **14**, 109 (1916).

heater coils are protected from acid vapors by the bakelite tube B, which ends in the vapor seal E containing heavy silicon grease.

The calorimeter is supported by the bakelite ringstand, O, which also supports the thin, gold-plated copper surrounding shield, F.

The outer container, G, is of heavy, gold-plated brass. It is attached to the top, D, by means of a bolted flanged joint, the seal being made by a tygon gasket. The top has three chimneys in line with the calorimeter chimneys and well. Chimneys R and C, for admission of the stirrer and the lead wire protection tube, are shown in Fig. 1. A third chimney, not in the plane of the drawing, admitted samples.

The stirrer, X, is pure platinum. Attachment to the drive mechanism is made through the teflon assembly Q-T which also houses two sets of ball bearings. The lower part of T serves as a closure for calorimeter chimney V.

The entire assembly is immersed in an oil-bath to the level indicated at U. The oil bath is thermostatically controlled at 73.7 ± 0.1°.

Readings of resistance thermometer e. m. f. and calibrating heater current are made with a White 100,000 μ v. range double potentiometer. This instrument also serves in fixing and maintaining constant the resistance thermometer current which is 900.000 ± 0.002 μ amp. Energy input times for calibrations are measured with a stopwatch, calibrated against a standard chronometer of the Astronomy Department of the University of California. The resistance of the manganin heater coil is determined at operating temperature by direct comparison with a 100-ohm standard resistance.

All samples are contained in gelatin capsules, sizes O and OO being the most convenient. These are dropped from room temperature through chimney W into the calorimeter at operating temperature. Platinum weights are enclosed with the samples to assure immediate sinking of capsule and contents.

In each heat of reaction measurement, 856.0 g. of 20.1% (by weight) hydrofluoric acid was used. Amounts of reacting materials were in stoichiometric proportion: 0.6750 g. of quartz, 1.1281 g. of magnesium metasilicate, 2.2900 g. of ferrous orthosilicate, 0.6556 g. of magnesium hydroxide, 1.3053 g. of calcium metasilicate, 0.6303 g. of calcium oxide, 1.6482 g. of sample A, 1.6510 g. of sample B, 1.6649 g. of sample C, 1.8931 g. of sample D, 1.9061 g. of sample E, and 2.2482 g. of sample F (all corrected to vacuum).

Reagent grade hydrofluoric acid was employed. This was obtained in case lots consisting of 25 one-pound plastic bottles of approximately 48% acid. The case lots were sampled for uniformity and analyzed in transparent bakelite containers by titration against standard alkali. Each 856.0 g. batch of 20.1% acid was made up separately by weight, correction being made to vacuum.

The time required for complete reaction and attainment of final steady state conditions after dropping a sample into the calorimeter ranged from ten to thirty minutes, depending upon the substance. The temperature rise varied from 120.70 μv. for magnesium hydroxide to 400.64 μv. for olivine A.

All heat-of-reaction values are adjusted to correspond with the process, Reactant (solid, 25°) → Product (73.7°). This was accomplished by measuring the temperature of the gelatin capsule and contents just before dropping into the calorimeter and making the minor correction resulting from deviation of room temperature from 25°. Although reaction with the hydrofluoric acid occurs at 73.7°, this method of adjustment leads to values of heats of formation at 25°.

Measured heats of reaction were corrected for the sensible heat and heat of solution of the gelatin capsules. For the process, gelatin (solid, 25°) → gelatin (in solution, 73.7°), six measurements gave, respectively, 22.06, 22.15, 22.80, 22.79, 22.85, and 22.63 cal. per g., the mean being 22.63 ± 0.22 cal. per g. The gelatin correction ranged from 1 to 2%, depending upon the substance. Correction, from 0.2 to 1%, also was made for the sensible heat in the platinum sinkers, using $H_{73.7} - H_{25.0} = 1.70$ cal. per g. The magnitude of the corrections for impurities will be considered later.

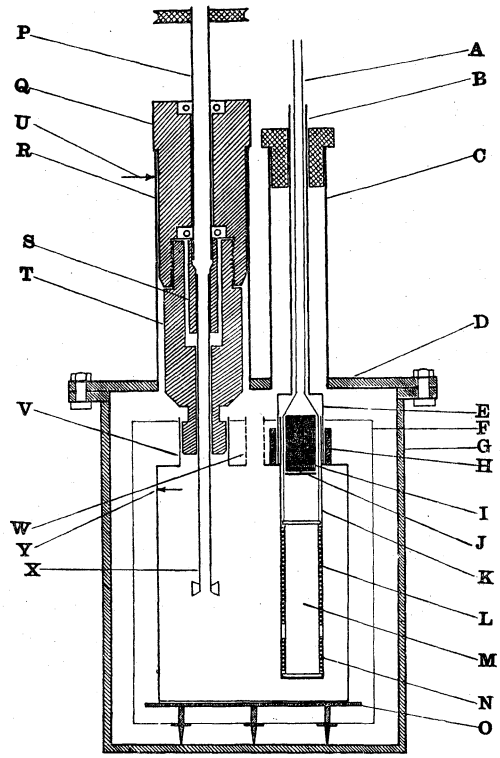


Fig. 1.—Hydrofluoric acid solution calorimeter.

An electrical calibration was made either just before or just after each heat-of-reaction measurement, in terms of the defined calorie (1 cal. = 4.1833 int. joules).[13] The maximum spread in calibration values during the course of this work was 0.2%.

Measurements and Results

Each of the heats of formation is obtained as a resultant of the measurement of the heats of several reactions for which skeleton equations are given in Tables II, III, and V. The method of ascribing uncertainties to the individual reaction heat values and their resultant follows Rossini and Deming.[14]

Heat of Formation of $MgSiO_3$.—Table II summarizes the data for obtaining the heat of formation of magnesium metasilicate from the component oxides. In this and subsequent tables various symbols are employed: c = crystals, l = liquid, p = precipitate, and sol. = in solution.

Six determinations of the heat of reaction (1) were made, the results being −29,901, −29,102, −29,069, −29,095, −29,060 and −29,111 cal. per mole. The mean is −29,090 ± 20. These results include a net correction of 35 cal. for the 0.19% magnesium carbonate impurity. By net correction is meant the difference between the actual reported value and what would have been reported if the impurity had been neglected. It

(13) Mueller and Rossini, *Am. J. Physics*, **12**, 1 (1944).

(14) Rossini and Deming, *J. Wash. Acad. Sci.*, **29**, 416 (1939).

TABLE II

HEAT OF FORMATION OF $MgSiO_3$ (CLINOENSTATITE) (CAL. PER MOLE)

Reaction	ΔH	Uncertainty
(1) $Mg(OH)_2$ (c, 25°) + 2HF (sol., 73.7°) → MgF_2 (p, 73.7°) + $2H_2O$ (sol., 73.7°)	−29,090	20
(2) SiO_2 (c, 25°) + 6HF (sol., 73.7°) → H_2SiF_6 (sol., 73.7°) + $2H_2O$ (sol., 73.7°)	−33,000	20
(3) $MgSiO_3$ (c, 25°) + 8HF (sol., 73.7°) → MgF_2 (p, 73.7°) + H_2SiF_6 (sol., 73.7°) + $3H_2O$ (sol., 73.7°)	−63,060	140
(4) MgO (c, 25°) + H_2O (l, 25°) → $Mg(OH)_2$ (c, 25°)	− 8,850	25
(5) H_2O (l, 25°) → H_2O (sol., 73.7°)	810	5
(6) MgO (c, 25°) + SiO_2 (c, 25°) → $MgSiO_3$ (c, 25°)	− 8,690	150

$\Delta H_6 = \Delta H_1 + \Delta H_2 - \Delta H_3 + \Delta H_4 - \Delta H_5$

should be noted that to make the final solution from reaction (1) equivalent in H_2SiF_6 content to those of reactions (2) and (3), the magnesium hydroxide reacted with a solution in which had already been dissolved the stoichiometrical amount of silica.

Seven determinations of the heat of reaction (2) gave −33,003, −33,033, −32,981, −32,983, −33,003, −33,008, and −33,019 cal. per mole, the mean being −33,000 ± 20. These values include a net correction of 40 cal. for adsorbed water, which was determined to be about 0.1%.

For reaction (3), seven values of the heat were measured. The results are −62,869, −63,195, −63,059, −63,299, −63,232, −62,893, and −62,899 cal. per mole. The mean is −63,060 ± 140. The net correction included for impurities, magnesium orthosilicate and uncombined silica, is 90 cal.

The heat of reaction (4), the hydration of magnesium oxide, was not determinable in the hydrofluoric acid calorimeter because of slowness of reaction of the oxide. Recourse was taken to the ordinary solvents calorimeter described by Southard[15] and Young[16] and used by Shomate and Huffman[17] in their determination of the heat of formation of magnesium oxide.

Six determinations of the heat of solution of magnesium hydroxide in 1.000 *N* hydrochloric acid were conducted under conditions virtually identical with those of Shomate and Huffman for the oxide and with equivalent stoichiometrical amounts of materials. The results were −26,948, −26,957, −26,953, −26,942, −26,948, and −26,968 cal. per mole. The mean, −26,950 ± 10, is $\Delta H_{298.16}$ for the reaction

$$Mg(OH)_2(c) + 2H^+ = Mg^{++} + 2H_2O(l)$$

(15) Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).
(16) Young, THIS JOURNAL, **67**, 257 (1945).
(17) Shomate and Huffman, *ibid.*, **65**, 1625 (1943).

Corrections included in these results are 10 cal. for the heat of dilution by the two moles of water formed in the reaction and 35 cal. net correction for the magnesium carbonate impurity. Shomate and Huffman obtained $\Delta H_{298.16} = -35{,}799 \pm 21$ cal. per mole for the reaction

$$MgO(c) + 2H^+ = Mg^{++} + H_2O(l)$$

Combination of these values leads to $\Delta H_{298.16} = -8{,}850 \pm 25$ cal. per mole for the reaction

$$Mg(OH)_2(c) = MgO(c) + H_2O(l)$$

which is reaction (4) of Table II.

Four determinations of the heat of reaction (5) were made, obtaining 816, 815, 811 and 807, with a mean of 810 ± 5 cal. per mole. Because of the low heat, these determinations were made with 8 to 12 times the stoichiometrical amount of water, to realize a higher over-all accuracy. To be specific, amounts of water ranging from 1.597 g. to 2.418 g. were dissolved in 856.0 g. of 20.1% hydrofluoric acid to which had already been added amounts of magnesium hydroxide and silica corresponding to those employed in reactions (1) and (2).

The summation, $\Delta H_6 = \Delta H_1 + \Delta H_2 - \Delta H_3 + \Delta H_4 - \Delta H_5$, gives $\Delta H_{298.16} = -8{,}690 \pm 150$ as the heat of formation of magnesium metasilicate from magnesium oxide and quartz.

Heat of Formation of Mg_2SiO_4.—Data for obtaining the heat of formation of magnesium orthosilicate are summarized in Table III.

TABLE III

HEAT OF FORMATION OF Mg_2SiO_4 (FORSTERITE) (CAL. PER MOLE)

Reaction	ΔH	Uncertainty
(7) $2Mg(OH)_2$ (c, 25°) + 4HF (sol., 73.7°) → $2MgF_2$ (p, 73.7°) + $4H_2O$ (sol., 73.7°)	−58,180	40
(8) SiO_2 (c, 25°) + 6HF (sol., 73.7°) → H_2SiF_6 (sol., 73.7°) + $2H_2O$ (sol., 73.7°)	−33,000	20
(9) Mg_2SiO_4 (c, 25°) + 10HF (sol., 73.7°) → $2MgF_2$ (p, 73.7°) + H_2SiF_6 (sol., 73.7°) + $4H_2O$ (sol., 73.7°)	−95,380	200
(10) $2MgO$ (c, 25°) + $2H_2O$ (l, 25°) → $2Mg(OH)_2$ (c, 25°)	−17,700	50
(11) $2H_2O$ (l, 25°) → $2H_2O$ (sol., 73.7°)	1,620	10
(12) $2MgO$ (c, 25°) + SiO_2 (c, 25°) = Mg_2SiO_4 (c, 25°)	−15,120	210

$\Delta H_{12} = \Delta H_7 + \Delta H_8 - \Delta H_9 + \Delta H_{10} - \Delta H_{11}$

Heats of reactions (8), (10), and (11) were discussed previously as heats of reactions (2), (4) and (5), respectively. Reaction (7) is the same as reaction (1) except that twice the amount of magnesium hydroxide is concerned. However, it was determined quantitatively that no measurable difference in molal heat of reaction resulted from

TABLE IV

HEATS OF REACTION OF Fe_2SiO_4 AND Mg_2SiO_4–Fe_2SiO_4 SOLID SOLUTIONS WITH 20.1% HYDROFLUORIC ACID

Sample	Number of detns.	Composition, mole % Mg_2SiO_4	Composition, mole % Fe_2SiO_4	Net correction for impurities	ΔH, cal./mole Meas.	Calcd.	Diff.
A	4	90.6	9.4	100	−94,250 ± 160	−94,060	−190
B	4	90.2	9.8	70	−93,590 ± 80	−94,000	410
C	5	88.2	11.8	160	−93,930 ± 140	−93,720	−210
D	4	56.0	44.0	590	−89,070 ± 100	−89,200	130
E	4	54.2	45.8	470	−88,820 ± 160	−88,940	120
F	4	5.9	94.1	750	−82,080 ± 160	−82,160	80
Fe_2SiO_4	6	0.0	100.0	0	−81,330 ± 50	−81,330	0

the use of 1.3112 g. rather than 0.6556 g. of magnesium hydroxide with 856.0 g. of hydrofluoric acid. Consequently, the heat of reaction (7) is just twice that of reaction (1).

The heat of reaction (9) was obtained by extrapolation of results for the Mg_2SiO_4–Fe_2SiO_4 solid solutions. This was necessary because a suitable sample of pure magnesium orthosilicate was not available. Table IV summarizes the heat of reaction data for the six solid solutions and for pure ferrous orthosilicate. Corrections were made for the principal impurities, the net correction being shown in column (5) and the resulting adjusted molal composition in columns (3) and (4).

The mean measured values in column (6) are represented by

$$\Delta H = -81{,}330 - 140.5\, X_{Mg}$$

in which X_{Mg} is the molal % of magnesium orthosilicate. Values calculated from the equation are in column (7). Extrapolation to 100% magnesium orthosilicate leads to $\Delta H = -95{,}380 \pm 200$ cal. per mole, which is the value adopted for the heat of reaction (9).

The summation, $\Delta H_{12} = \Delta H_7 + \Delta H_8 - \Delta H_9 + \Delta H_{10} - \Delta H_{11}$, gives $\Delta H_{298.16} = -15{,}120 \pm 210$ as the heat of formation of magnesium orthosilicate from magnesium oxide and quartz.

Heat of Formation of $CaSiO_3$.—Data for obtaining the heat of formation of calcium metasilicate are summarized in Table V.

TABLE V

HEAT OF FORMATION OF $CaSiO_3$ (WOLLASTONITE) (CAL. PER MOLE)

Reaction	ΔH	Uncertainty
(13) CaO (c, 25°) + 2HF (sol., 73.7°) → CaF_2 (p, 73.7°) + H_2O (sol., 73.7°)	−54,960	20
(14) SiO_2 (c, 25°) + 6HF (sol., 73.7°) → H_2SiF_6 (sol., 73.7°) + $2H_2O$ (sol., 73.7°)	−33,000	20
(15) $CaSiO_3$ (c, 25°) + 8HF (sol., 73.7°) → CaF_2 (p, 73.7°) + H_2SiF_6 (sol., 73.7°) + $3H_2O$ (sol., 73.7°)	−66,710	120
(16) CaO (c, 25°) + SiO_2 (c, 25°) → $CaSiO_3$ (c, 25°)	−21,250	130

$\Delta H_{16} = \Delta H_{13} + \Delta H_{14} - \Delta H_{15}$

Six determinations of the heat of reaction (13) gave −54,973, −54,974, −54,937, −54,965, −54,963, and −54,959 cal. per mole, the mean being −54,960 ± 20.

The heat of reaction (14) was discussed previously as the heat of reaction (2). Six measurements were made of the heat of reaction (15). The results are −66,711, −66,785, −66,795, −66,705, −66,605, and −66,681 cal. per mole. The mean is −66,710 ± 120. In this instance the calculated uncertainty has been doubled, an estimated allowance for neglect of impurities.

The summation, $\Delta H_{16} = \Delta H_{13} + \Delta H_{14} - \Delta H_{15}$, gives $\Delta H_{298.16} = -21{,}250 \pm 130$ as the heat of formation of calcium metasilicate from calcium oxide and quartz.

Discussion

The only previous data with which comparison can be made are for wollastonite. Bichowsky and Rossini[18] list a heat-of-formation value for 291.16°K. that corresponds to −22,800 cal. per mole for the heat of formation of wollastonite from calcium oxide and quartz. Their result is a weighted mean of values covering a range of some 10,000 cal. The two best of these values appear to be those attributed to Roth and Chall and Wagner which lead, respectively, to −19,660 and −21,460 cal. per mole heat of formation from the oxides. A more recent value of Troitzsch[19] is −21,750 cal. per mole at 293.16°K. The present value, $\Delta H_{298.16} = -21{,}250$, intermediates these results and is considered the most reliable.

Using entropy data listed by Kelley[20,21] the reported heat values lead to the following free energies of formation from the component oxides: $\Delta F^0_{298.16} = -8{,}540 \pm 160$ for magnesium metasilicate, $\Delta F^0_{298.16} = -14{,}970 \pm 230$ for magnesium orthosilicate, and $\Delta F^0 = -21{,}250 \pm 160$ for calcium metasilicate.

Summary

A hydrofluoric acid solution calorimeter, employing 20% acid and operating near 75°, is described.

(18) Bichowsky and Rossini, "Thermochemistry of the Chemical Substances," Reinhold Publishing Corporation, New York, N. Y., 1936.

(19) Landolt–Börnstein, "Physikalisch-chemische Tabellen," Julius Springer, Berlin, 3rd Supplement, vol. 3, 1936, p. 2763.

(20) Kelley, *Bureau of Mines Bulletin*, 434 (1941).

(21) Kelley, THIS JOURNAL, **65**, 339 (1943).

Heats of formation from the component oxides were obtained for magnesium metasilicate, magnesium orthosilicate, and calcium metasilicate by measuring heats of solution and reaction of the pertinent substances in hydrofluoric acid.

BERKELEY, CALIFORNIA RECEIVED JANUARY 30, 1948

CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

High-Temperature Heat Contents of $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$, and $CaO \cdot 2B_2O_3$[1]

BY E. G. KING,[2] D. R. TORGESON[2] AND O. A. COOK[3]

In two recent papers,[4,5] heats of formation and low-temperature heat-capacity and entropy data were presented for the four calcium borates, $3Ca \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$, and $CaO \cdot 2B_2O_3$. These are all the compounds in the CaO–B_2O_3 system, according to the work of Carlson.[6] The present paper reports high temperature heat content values, thus completing basic data needed for thermodynamic calculations of reactions of these compounds in both the crystalline and liquid states. The results have additional interest in that this is the first complete series of interoxidic compounds for which high temperature heat content measurements have been carried beyond the melting points so that adequate heat of fusion values are available. No previous high temperature heat content data exist for any of these substances.

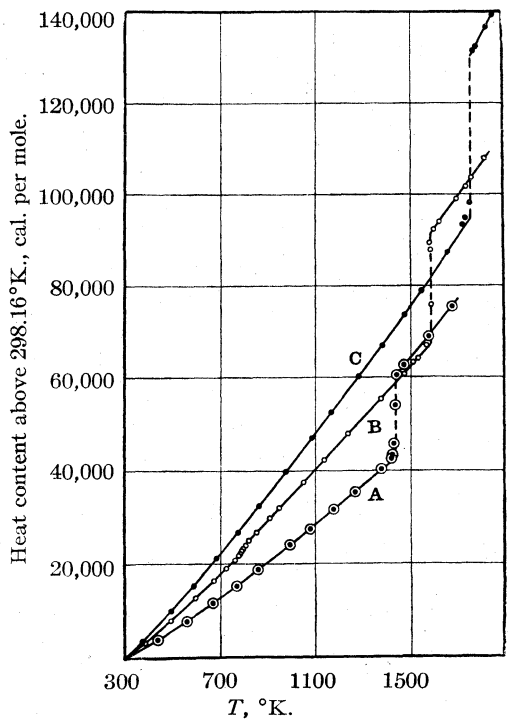


Fig. 1.—Heat contents of calcium borates: A, $CaO \cdot B_2O_3$; B, $2CaO \cdot B_2O_3$; C, $3CaO \cdot B_2O_3$.

Method and Materials

Measurements were made by the "dropping" method, using previously described apparatus.[7,8] During measurement, the samples were enclosed in platinum–rhodium alloy capsules, pure platinum being used in welding shut the capsule necks after evacuating and filling the pore space with helium. The heat contents of the empty capsules were determined by separate experiments. At the highest temperatures, small pinholes developed in the capsules, and it was necessary to weigh capsules and contents after each measurement. The total loss in weight during a complete series of measurements never exceeded 0.5% of the original sample weight. Correction was made on the assumption that boric oxide was lost by volatilization and that the equivalent amount of the borate next higher in calcium oxide had formed. As the net correction always was less than 0.2%, no appreciable error in reported results is involved.

The preparation, analysis, and X-ray diffraction examination of the borates was described by Torgeson and Shomate,[4] whose samples also were used in the present work. It should be noted that the sharpness of the observed melting points and the agreement with results of the National Bureau of Standards[6,9] substantiates the purity of the materials.

Results and Discussion

The experimental heat content values are given in Table I and Figs. 1 and 2, being expressed in defined calories (1 cal. = 4.1833 int. joules)[10] per mole (in vacuum) of borate. Molal weights accord with the 1947 International Atomic Weights. Values marked (t) and (p) show, respectively, effects of pretransition and of premelting or in-

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Chemist, Pacific Experiment Station, Bureau of Mines.

(3) Formerly chemist, Pacific Experiment Station, Bureau of Mines.

(4) Torgeson and Shomate, THIS JOURNAL, **69**, 2103 (1947).

(5) Kelley, Todd and Shomate, *ibid.*, accepted for publication.

(6) Carlson, *Bur. Standards J. Research*, **9**, 825 (1932).

(7) Southard, THIS JOURNAL, **63**, 3142 (1941).

(8) Kelley, Naylor and Shomate, *Bur. Mines Tech. Paper* **686** (1946), 34 pp.

(9) Flint and Wells, *Bur. Standards J. Research*, **17**, 727 (1936).

(10) Mueller and Rossini, *Am. J. Phys.*, **12**, 1 (1944).

complete melting. Table II gives smooth values of heat contents and entropy increments above 298.16° K. at 100° intervals and at transition and melting points.

The compound $2CaO \cdot B_2O_3$ has a transition at 804° K., with a heat absorption of 1,100 cal. per mole and an entropy change of 1.37 e. u.

With the exception of $CaO \cdot 2B_2O_3$, the compounds melted and recrystallized reversibly under the prevailing experimental conditions. The molten diborate solidified completely in the glassy state (single phase) when dropped from the furnace into the calorimeter. It could be reconverted to the crystalline state by heating for a short time in the region just below the melting point of the crystals. This behavior agrees with the ob-

TABLE I

HEAT CONTENT OF $3CaO \cdot B_2O_3$ ABOVE 298.16° K.

Base, crystals at 298.16° K. Mol. wt., 237.88

T, °K.	$H_T - H_{298.16}$, cal./mole	T, °K.	$H_T - H_{298.16}$, cal./mole
Crystals		1473	73,660
372.5	3,656	1545	78,940
491.1	10,025	1660	87,250
586.0	15,370	1725	93,280(p)
682.2	21,180	1738	94,820(p)
771.7	26,720	1757	98,450(p)
860.7	32,410	Liquid	
973.8	39,750	1771	131,310
1083.7	46,990	1784	132,210
1165.1	52,510	1829	136,500
1281.1	60,260	1856	139,150
1380	66,990		

HEAT CONTENT OF $2CaO \cdot B_2O_3$ ABOVE 298.16° K.

Base, α-crystals at 298.16° K. Mol. wt., 181.80

α-Crystals		1135.2	42,270
381.8	3,295	1137.4	42,340
491.4	7,905	1235.9	47,910
594.3	12,690	1374	55,420
670.4	16,410	1472	60,770
723.3	18,990	1510	63,370
760.2	20,820	1531	64,200
776.4	21,730(t)	1564	67,070(p)
782.2	22,130(t)	1582	89,470(p)
787.9	22,820(t)	1585	87,840(p)
794.3	23,280(t)	1587	75,910(p)
β-Crystals		Liquid	
804.6	23,990	1599	92,300
819.3	25,030	1623	93,970
850.6	26,730	1700	98,980
906.5	29,820	1740	101,630
946.9	32,030	1764	103,600
1048.6	37,460	1821	107,790

HEAT CONTENT OF $CaO \cdot B_2O_3$ ABOVE 298.16° K.

Base, crystals at 298.16° K. Mol. wt., 125.72

Crystals		1375	40,260(p)
435.8	3,944	1417	42,560(p)
558.2	7,822	1422	43,370(p)
667.3	11,630	1427	45,800(p)
765.7	15,260	1433	54,070(p)
858.3	18,800	Liquid	
990.9	24,090	1439	60,620
1076.8	27,500	1471	62,650
1176.5	31,610	1575	69,020
1265.5	35,350	1678	75,480

HEAT CONTENT OF $CaO \cdot 2B_2O_3$ (CRYSTALS) ABOVE 298.16° K.

Base, crystals at 298.16° K. Mol. wt., 195.36

Crystals		948.9	37,390
369.3	3,045	991.0	40,200
426.9	5,755	1043.5	44,010
433.6	6,155	1076.7	46,250
542.6	11,820	1091.5	47,140
605.1	15,500	1130.0	49,970
645.6	17,810	1173.2	52,870
749.2	24,310	1178.2	53,530(p)
764.8	25,220	1220.7	57,650(p)
874.1	32,330	1259.1	68,790(p)
906.2	34,570		

HEAT CONTENT OF $CaO \cdot 2B_2O_3$ (GLASS AND LIQUID) ABOVE 298.16° K.

Base, glass at 298.16° K. Mol. wt., 195.36

Glass		Liquid	
392.1	4,173	1260.7	73,620
603.2	15,290	1279.3	75,900
794.0	26,970	1296.0	77,540
850.1	31,260	1327	80,670
1005.3	44,620	1355	84,020
1101.1	49,310(m)	1406	89,730
1131.3	50,750(m)	1521	101,850
1143.6	58,920	1645	114,490
1204.7	66,020(m)	1747	124,350

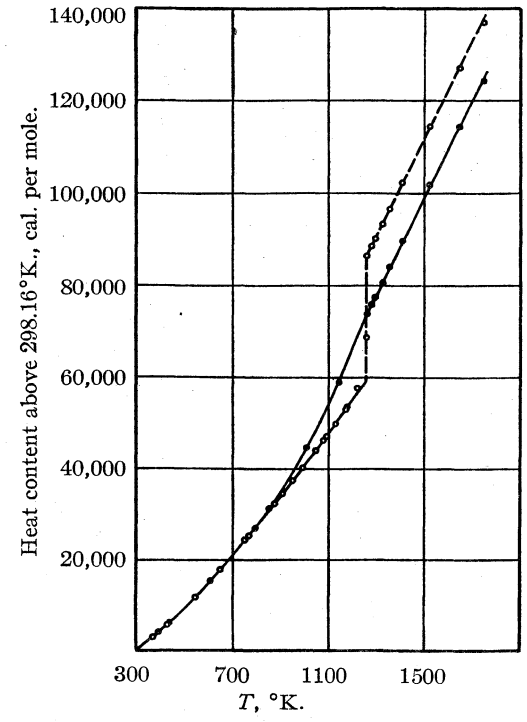


Fig. 2.—Heat content of $CaO \cdot 2B_2O_3$: open circles, crystals and liquid; black circles, glass and liquid.

TABLE II

HEAT CONTENTS (CAL./MOLE) AND ENTROPIES (CAL./DEG./MOLE) ABOVE 298.16° K.

T, °K.	$3CaO \cdot B_2O_3$(c,l) $H_T - H_{298.16}$	$3CaO \cdot B_2O_3$(c,l) $S_T - S_{298.16}$	$2CaO \cdot B_2O_3$(c,l) $H_T - H_{298.16}$	$2CaO \cdot B_2O_3$(c,l) $S_T - S_{298.16}$	$CaO \cdot B_2O_3$(c,l) $H_T - H_{298.16}$	$CaO \cdot B_2O_3$(c,l) $S_T - S_{298.16}$	$CaO \cdot 2B_2O_3$(c,l)[a] $H_T - H_{298.16}$	$CaO \cdot 2B_2O_3$(c,l)[a] $S_T - S_{298.16}$	$CaO \cdot 2B_2O_3$(gl,l)[b] $H_T - H_{298.16}$	$CaO \cdot 2B_2O_3$(gl,l)[b] $S_T - S_{298.16}$
400	5,180	14.88	4,010	11.53	2,840	8.16	4,470	12.83	4,470	12.85
500	10,520	26.79	8,310	21.11	5,950	15.09	9,500	24.03	9,500	24.05
600	16,250	37.22	12,940	29.55	9,280	21.16	15,130	34.29	15,130	34.28
700	22,220	46.42	17,830	37.08	12,820	26.61	21,170	43.59	21,180	43.59
800	28,410	54.69	22,880	43.82	16,550	31.59	27,510	52.05	27,710	52.30
804	....	...	23,080(α)	44.07	....	...	....	....	....	....
804	....	...	24,180(β)	45.44	....	...	....	....	....	....
900	34,780	62.19	29,410	51.57	20,420	36.14	34,090	59.79	35,210	61.13
1000	41,300	69.06	34,860	57.32	24,410	40.35	40,870	66.94	44,100	70.49
1100	47,950	75.40	40,330	62.54	28,480	44.22	47,820	73.56	54,390	80.29
1200	54,720	81.28	45,840	67.33	32,630	47.84	54,920	79.74	66,080	90.46
1260	....	...	....	....	....	...	59,340(c)	83.33	73,760(gl)	96.71
1260	....	...	....	....	....	...	86,400(l)	104.81	73,760(l)	96.71
1300	61,590	86.78	51,380	71.76	36,870	51.23	90,650	108.11	78,010	100.01
1400	68,540	91.93	56,930	75.87	41,210	54.44	101,280	115.99	88,640	107.89
1435	....	...	....	....	42,740(c)	55.52	....	....	....	....
1435	....	...	....	....	60,410(l)	67.83	....	....	....	....
1500	75,600	96.80	62,490	79.71	64,420	70.57	111,910	123.34	99,270	115.23
1585	....	...	67,260(β)	82.80	....	....	....	....	....	....
1585	....	...	91,350(l)	98.00	....	...	....	....	....	....
1600	82,790	101.44	92,370	98.64	70,590	74.55	122,540	130.19	109,900	122.09
1700	90,110	105.88	99,190	102.77	76,760	78.29	133,170	136.63	120,530	128.52
1760	94,550(c)	108.44	....	....			....	....	....	....
1760	130,040(l)	128.60	....	....			....	....	....	....
1800	133,800	130.71	106,010	106.68			143,800	142.72	131,160	134.62
1900	143,200	135.79	112,830	110.37						

[a] Base = crystals at 298.16° K. [b] Base = glass at 298.16° K.

servations of Carlson.[6] As a consequence, direct measurements were made of the heat content of the crystals with respect to crystals at 298.16° K. as the base, and of the heat content of glass and liquid with respect to glass at 298.16° K. as the base.

Results marked (m) in Table I were obtained under conditions that resulted in partial reconversion of glass to crystals. These values are given no weight and are not plotted in Fig. 2. Results for the glass are, of necessity, sparse in the region just below the melting point and of lower accuracy than the other values.

It was necessary to obtain the heat of fusion of crystalline $CaO \cdot 2B_2O_3$ by an indirect method. This was accomplished by use of the calorimeter described by Southard[11] and Young[12] and also used by Torgeson and Shomate[4] in their heat of formation determinations of the calcium borates. Using 1.000 *N* hydrochloric acid as solvent, 3.4836 g. of $CaO \cdot 2B_2O_3$-glass was dissolved in 1845.5 g. of acid (identical with procedure of Torgeson and Shomate) and the heat of solution was measured. Three determinations were made, yielding, respectively, −22,720, −22,730, and −22,700 cal. per mole, the mean being −22,720 ± 20 for $CaO \cdot 2B_2O_3$-glass. Torgeson and Shomate obtained −10,080 ± 10 cal. per mole as the heat of solution of $CaO \cdot 2B_2O_3$-crystals. The difference, 12,640 ± 30 cal. per mole, is the heat of transformation of crystals to glass at 298.16° K. Combination of this result and heat content values of crystals and glass from Table II yields 27,060 cal. per mole as the heat of fusion of the crystals at the melting point, 1260° K.

Melting points and heats and entropies of fusion are summarized in Table III. The melting point temperatures are in substantial agreement with determinations of the National Bureau of Standards except in the case of $2CaO \cdot B_2O_3$. The entropies of fusion are remarkably constant when considered on a mean gram-atom basis, 1.69 to 1.83 e. u.

TABLE III

FUSION DATA

Substance	Melting point, °K. This work	Melting point, °K. N. B. S.[6,9]	ΔH (fusion), cal./mole	ΔS (fusion), cal./deg./mole
$3CaO \cdot B_2O_3$	1760	1761	35,490	20.16
$2CaO \cdot B_2O_3$	1585	1571	24,090	15.20
$CaO \cdot B_2O_3$	1435	1427	17,670	12.31
$CaO \cdot 2B_2O_3$	1260	1259	27,060	21.48

Heat content equations for crystals and liquids, derived by the method outlined by Shomate,[13] are listed below. In each instance there are indicated the temperature range of validity and mean devia-

(11) Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).

(12) Young, THIS JOURNAL, **67**, 257 (1945).

(13) Shomate, *ibid.*, **66**, 928 (1944).

tion from the experimental data, excluding those marked (t) and (p) in Table I.

$3CaO \cdot B_2O_3$(c)

$H_T - H_{298.16} = 56.44T + 5.21 \times 10^{-3}T^2 + 13.02 \times 10^5T^{-1} - 21{,}658$ (298–1760° K.; 0.4%)

$3CaO \cdot B_2O_3$(l)

$H_T - H_{298.16} = 94.00T - 35{,}400$ (1760–1900° K.; 0.1%)

$2CaO \cdot B_2O_3(\alpha)$

$H_T - H_{298.16} = 43.75T + 5.75 \times 10^{-3}T^2 + 10.69 \times 10^5T^{-1} - 17{,}141$ (298–804° K.; 0.5%)

$2CaO \cdot B_2O_3(\beta)$

$H_T - H_{298.16} = 52.29T + 1.20 \times 10^{-3}T^2 - 18{,}633$ (804–1585° K.; 0.3%)

$2CaO \cdot B_2O_3$(l)

$H_T - H_{298.16} = 68.20T - 16{,}750$ (1585–1900° K.; 0.2%)

$CaO \cdot B_2O_3$(c)

$H_T - H_{298.16} = 31.02T + 4.88 \times 10^{-3}T^2 + 8.07 \times 10^5T^{-1} - 12{,}389$ (298–1435° K.; 0.3%)

$CaO \cdot B_2O_3$(l)

$H_T - H_{298.16} = 61.70T - 28{,}130$ (1435–1700° K.; 0.1%)

$CaO \cdot 2B_2O_3$(c)

$H_T - H_{298.16} = 51.34T + 9.58 \times 10^{-3}T^2 + 17.16 \times 10^5T^{-1} - 21{,}914$ (298–1260° K.; 0.4%)

$CaO \cdot 2B_2O_3$(l)

$H_T - H_{298.16} = 106.30T - 47{,}540$ (1260–1800° K.; 0.2%)

The corresponding molal heat capacity equations are:

$3CaO \cdot B_2O_3$(c): $C_p = 56.44 + 10.42 \times 10^{-3}T - 13.02 \times 10^5T^{-2}$

$3CaO \cdot BaOO_3$(l): $C_p = 94.00$

$2CaO \cdot B_2O_3(\alpha)$: $C_p = 43.75 + 11.50 \times 10^{-3}T - 10.69 \times 10^5T^{-2}$

$2CaO \cdot B_2O_3(\beta)$: $C_p = 52.29 + 2.40 \times 10^{-3}T$

$2CaO \cdot B_2O_3$(l): $C_p = 68.20$

$CaO \cdot B_2O_3$(c): $C_p = 31.02 + 9.76 \times 10^{-3}T - 8.07 \times 10^5T^{-2}$

$CaO \cdot B_2O_3$(l): $C_p = 61.70$

$CaO \cdot 2B_2O_3$(c): $C_p = 51.34 + 19.16 \times 10^{-3}T - 17.16 \times 10^5T^{-2}$

$CaO \cdot 2B_2O_3$(l): $C_p = 106.30$

Summary

High temperature heat contents of the calcium borates, $3CaO \cdot B_2O_3$, $2CaO \cdot B_2O_3$, $CaO \cdot B_2O_3$ and $CaO \cdot 2B_2O_3$, were measured from 298.16° K. to temperatures well above their melting points. Melting point temperatures and heats of fusion were determined and also the transition temperature and heat of transition in the case of $2CaO \cdot B_2O_3$.

Heat content and heat capacity equations, adequately representing the measured data, were derived for each borate in the crystalline and liquid states.

Entropy increments above 298.16° K. at 100° intervals and at phase-change points are tabulated, together with smooth values of the heat contents.

BERKELEY, CALIFORNIA RECEIVED JANUARY 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Electrophilic Attack on Halogen in a Homogeneous Medium: Reaction of Mercuric Nitrate with some Primary and Secondary Alkyl Bromides

BY O. THEODOR BENFEY*

Introduction

In the work of Dostrovsky and Hughes[1] on the series of bromides, methyl, ethyl, *n*-propyl, isobutyl, neopentyl, reactions expected to proceed by the nucleophilic substitution mechanism S_N2 gave the rate sequence

Me > Et > *n*-Pr > *iso*-Bu ≫ Neopentyl

The sharp fall from isobutyl to neopentyl is attributed to a pronounced steric effect, the remaining rate sequence being explainable on the postulation of an inductive effect of methyl groups even on the β-carbon, opposing the approach of the nucleophilic reagent. Steric hindrance is a contributory factor except for methyl.

In order to bring out the alternative ionization mechanism S_N1, the behavior of the halides was studied by these workers both in the highly ionizing solvent formic acid, and in the presence of the electrophilic reagent silver nitrate, which acts by virtue of its affinity for halogen. In these reactions the rate sequence was changed to

Me < Et > *n*-Pr > *iso*-Bu > Neopentyl

Steric hindrance was shown to be absent, and the last member reacted by a pure S_N1 mechanism. The fact that the Me–Et rate sequence is inverted speaks strongly for the idea that the ethyl halide reacts largely by the same mechanism, the inductive effect being operative in assisting the breaking of the carbon-halogen bond. This strongly suggests that the intermediate members also react by this mechanism in spite of the rate sequence Et > *n*-Pr > iso-Bu being opposite to that expected from the influence of the inductive effect. The authors' suggestion that the wrong sequence beyond ethyl is due to an appreciable incursion of mechanism S_N2 is therefore unlikely. An alternative explanation in the case of the silver ion catalyzed reaction is that the catalytic effect of solid silver halide produced during the reaction decreases along this series.

In the reaction of alkyl halides with mercuric

* Present address: Department of Chemistry, Haverford College, Haverford, Pa.

(1) Dostrovsky and Hughes, *J. Chem. Soc.*, 157 ff. (1946).

ion, the mercuric halide produced, though largely un-ionized, is appreciably soluble, and the catalytic effect of solid metal halide is thus eliminated. The reaction of mercuric nitrate with ethyl, *n*-propyl and isobutyl bromides was therefore studied. Roberts and Hammett[2] have presented strong evidence in the case of benzyl chloride that the reaction proceeds by way of a rate determining formation of a carbonium ion intermediate

$$Hg^{++} + RX \longrightarrow HgX^{+} + R^{+}$$

followed by fast reactions to form the alcohol or alkyl nitrate. The reaction rate of alkyl halides in ionizing solvents is normally accelerated by a factor of several hundred on addition of small concentrations of mercuric nitrate. The acceleration is no doubt due to the driving force derived from the energy of formation of a mercury–halogen bond. Mercuric ion and mercuric salts have a strong affinity for halogen, as shown by the small ionization of the mercuric halides,[3] and by their ability to form complex ions such as $HgCl_4^{--}$.[4] Mercuric nitrate converts neopentyl iodide, notoriously unreactive toward nucleophilic reagents,[1] into the rearranged *t*-amyl alcohol.[5]

Cyclohexyl chloride and bromide react in some reactions like typical secondary halides, while in others their rates are considerably slower.[6] Mercuric ion has a larger accelerating effect than silver ion on the reactions of alkyl halides and is consequently expected to favor even more the mechanism involving an ionic intermediate. A comparison was therefore made between the rates of reaction of cyclohexyl and isopropyl bromides with mercuric nitrate.

Experimental

Apparatus.—The thermostat at 12.50° was the one described previously.[7] That at 25.00° was of the conventional type. The temperatures were determined with thermometers calibrated by the U. S. Bureau of Standards. The thermostat temperatures were constant to ±0.02°.

Materials.—Technical **1,4-dioxane** was purified in 2- to 3-liter quantities by a modification of the method of Beste and Hammett.[8] After treatment on the steam-bath with sodium hydroxide, the filtered product was boiled with 200 cc. of water and 25 cc. of concentrated hydrochloric acid for twelve hours, in a stream of air or nitrogen to carry away the aldehyde formed. The acid was neutralized and the aqueous portion removed with sodium hydroxide pellets. The dioxane was then refluxed over sodium wire for twelve hours and distilled through a 15-plate glass-helices packed column; b. p. 100.9–101.1° (760 mm).

***n*-Pentane** and ***n*-hexane** used for extraction of alkyl halides in the fast kinetic runs were found to be free of halide and were used directly.

Eastman Kodak Co. **ethyl bromide** was distilled through a 15-plate column, b. p. 38.5–38.6°. Analysis for bromide gave 100.0%.

Eastman Kodak Co. ***n*-propyl bromide** and A. D. Mackay **isopropyl bromide** were washed with concentrated hydrochloric acid and dilute sodium hydroxide and dried over sodium sulfate. On fractional distillation *n*-propyl bromide boiled at 71.6–71.7° (761 mm.), isopropyl bromide at 59.1–59.5°.

Eastman Kodak Co. **isobutyl bromide** was shaken with water for one hour to hydrolyze any *t*-butyl bromide. It was washed with concentrated hydrochloric acid and a 10% sodium carbonate solution, dried over sodium sulfate and fractionated, b. p. 91.6–92.0° (762 mm.).

Eastman Kodak Co. **bromocyclohexane** (b. p. 61–62° (15 mm.)) was twice distilled at reduced pressure through a Vigreux column. It was colorless and free from acid.

Colorless C. P. J. T. Baker analyzed **nitric acid** was used in making up the reaction mixtures.

Primary standards for titration were Mallinckrodt ACS grade potassium acid phthalate, and ACS grade potassium chloride which was recrystallized, and dried at 130° *in vacuo* over phosphorus pentoxide.

Merck reagent grade mercuric nitrate and C. P. mercuric bromide were used directly.

Method.—The titration method for following the production of bromide is described in detail by Roberts.[9,2]

The same solvent, "70% dioxane by volume," was used throughout. It was made up by mixing seven parts of dioxane with three parts of water containing the amount of nitric acid required for an acidity of the solvent within the limits 0.281–0.286 *N*. Mercuric nitrate (0.025 *N* appr.) was added and its concentration as well as that of the nitric acid determined by titration. A known volume, usually 100 cc., was transferred into the reaction flask, and placed in the thermostat. For all runs except that of isopropyl bromide at 25°, the alkyl bromide (0.022 *N* appr.) was weighed out in a 1-cc. weighing bottle closed with a well-fitting ground glass stopper. The bottle was inserted in the reaction flask which was shaken rapidly till the bottle opened. The initial time was then taken. It was found that this method was accurate even for appreciably volatile compounds, while the alternative of taking infinity readings was invalidated, except for the very fast runs, by slow complicating reactions, probably between mercury salts and the solvent. In the case of isopropyl bromide the approximate quantity was transferred with a weight pipet, and reproducible infinity readings were obtained.

At measured intervals 10-cc. samples were pipetted out and the reaction stopped by delivering into 5 cc. of 0.1 *N* potassium chloride. The excess chloride ion was then determined. In the case of isobutyl bromide this simple sampling method could not be used because of the formation of a precipitate. The reaction was started as before, but when the reaction had proceeded for a few minutes, 10-cc. samples were transferred into a series of 25-cc. erlenmeyer flasks and were tightly closed with rubber stoppers. To stop the reaction 5 cc. of standard potassium chloride solution was added to the flask which was then allowed to stand so that the precipitate could react completely. On first addition the precipitate turns white and then slowly dissolves. The contents of the flask were washed into a larger erlenmeyer flask and titrated as before.

For the fast reactions of isopropyl and cyclohexyl bromides a pipet with an outflow time of eleven seconds was used. The pipet delivered accurately reproducible volumes. However, the reaction was not completely stopped by addition to potassium chloride solution, and the end-points were not sharp. Samples were therefore delivered into a mixture of 5 cc. of 0.1 *N* potassium chloride, 5 cc. of *n*-pentane (or *n*-hexane) and 5 cc. of water. The organic layer took up the bulk of unreacted alkyl halide, it was separated and washed several times with small amounts of water, the washings being added to the

(2) Roberts and Hammett, THIS JOURNAL, **59**, 1063 (1937).

(3) Sillén and Infeldt, *Svensk Kem. Tid.*, **58**, 52, 61 (1946); Morse, *Z. physik. Chem.*, **41**, 709 (1902).

(4) Nicolet and Stevens, THIS JOURNAL, **50**, 135 (1928).

(5) Whitmore, Wittle and Popkin, *ibid.*, **61**, 1586 (1939).

(6) (a) Tronow and Ladigina, *Ber.*, **63**, 3060 (1930); (b) Conant and Hussey, THIS JOURNAL, **47**, 476 (1925).

(7) Price and Hammett, *ibid.*, **63**, 2387 (1941).

(8) Beste and Hammett, *ibid.*, **62**, 2481 (1940).

(9) Roberts, *Ind. Eng. Chem. Anal. Ed.*, **8**, 365 (1936).

aqueous layer. The aqueous portion was titrated as before, and gave very sharp end-points.

Roberts and Hammett[2] mention that an impurity in the dioxane slowly reacts with mercuric nitrate forming mercurous salt, but that the error introduced was found to be negligible under the conditions of their kinetics.

In the work here described a fine white precipitate was observed to form slowly in mercuric nitrate solutions in 70% dioxane, when the concentration of nitric acid was 0.015 *N*. Good kinetics were observed for the fast reactions, but considerable interference took place in the slower runs. On increasing the concentration of nitric acid to 0.3 *N* no precipitate appeared except after long ageing of the dioxane before use. This concentration was therefore used throughout.

Rate Calculations

A possible reaction scheme would be

$$RBr + Hg^{++} \xrightarrow{k_1} R^+ + HgBr^+ \qquad (A)$$

$$RBr + HgBr^+ \xrightarrow{k_2} R^+ + HgBr_2 \qquad (B)$$

with an equilibrium controlling the concentrations of the two mercuric ions.

$$Hg^{++} + HgBr_2 \rightleftharpoons 2HgBr^+ \qquad (C)$$

$$K = \frac{[HgBr^+]^2}{[Hg^{++}][HgBr_2]} \qquad (1)$$

The following abbreviations are used

$x_0 = 2[Hg^{++}]_0$ = initial concentration of mercuric ion in equivalents

$x = 2[Hg^{++}] + [HgBr^+]$ = concentration of total mercuric ion in equivalents

$y_0 = [RBr]_0$ = initial concentration of alkyl halide.

$y = [RBr]$

Two methods are used for the approximate evaluation of initial rate constants[10]

Method I.—Assuming that $K = 0$, *i. e.*, that an $HgBr^+$ ion when formed immediately disproportionates into $^1/_2Hg^{++} + {}^1/_2HgBr_2$, the second order rate equation becomes

$$k_a = \frac{2}{(x_0 - y_0)\,t} \ln \frac{y_0 x}{x_0 y} \qquad (2)$$

where t is the time in minutes. The factor 2 is required because one mole of mercuric ion reacts with two moles of alkyl halide. The values of k_a will rise or fall during the reaction depending on the actual values of k_2 and K, but will extrapolate at zero reaction to the correct value k_1.

Method II.—Assuming that k_2 is negligible and that an $HgBr^+$ ion when formed does not disproportionate, a value of k may be calculated, taking one mole Hg^{++} and one mole RBr as equivalent quantities. The rate equation then becomes

$$-dx/dt = k_b [Hg^{++}][RBr] \qquad (3)$$

$$k_b = \frac{1}{(^1/_2x_0 - y_0)} \ln \frac{y_0\,(^1/_2x_0 - (y_0 - y))}{^1/_2x_0\,y} \qquad (4)$$

If $HgBr^+$ disproportionates or reacts further, the titration of total mercuric ion will indicate greater reaction than expected, and the values of k_b will rise. In the case where $^1/_2x_0 < y_0$, the values of k_b will approach infinity as $(y_0 - y)$ approaches $^1/_2x_0$. At zero reaction $k_b = k_1$.

For a full analysis of the observed data into k_1, k_2 and K, we have

$$x_0 = 2[Hg^{++}]_0 = 2[Hg^{++}] + 2[HgBr^+] + 2[HgBr_2] \qquad (5)$$

$$x_0 - x = [HgBr^+] + 2[HgBr_2] \qquad (6)$$

Substituting for $[Hg^{++}]$ and $[HgBr_2]$ in the equilibrium equation

$$K = \frac{[HgBr^+]^2}{[Hg^{++}][HgBr_2]} = \frac{4[HgBr^+]^2}{(x - [HgBr^+])(x_0 - x - [HgBr^+])} \qquad (7)$$

Solving for $[HgBr^+]$ we obtain

$$[HgBr^+]/x = \frac{-x_0/x + \sqrt{(x_0/x)^2 + 4(x_0/x - 1)\,(4/K - 1)}}{2(4/K - 1)} \qquad (8)$$

$$\therefore [Hg^{++}]/x = {}^1/_2 - \frac{-x_0/x + \sqrt{(x_0/x)^2 + 4(x_0/x - 1)(4/K - 1)}}{4(4/K - 1)} \qquad (9)$$

$$\text{Now } -dx/dt = k_1[RBr][Hg^{++}] + k_2[RBr][HgBr^+] \qquad (10)$$

$$\therefore -dx/[RBr]x dt = k_1[Hg^{++}]/x + k_2[HgBr^+]/x = N \qquad (11)$$

In the special case when $K = 4$

$$[HgBr^+]/x = 1 - x/x_0,\ [Hg^{++}]/x = {}^1/_2x/x_0 \qquad (12)$$

For any value of K, tables and graphs may be set up giving values of $[Hg^{++}]/x$ and $[HgBr^+]/x$ as a function of x/x_0.

Experimental Results and their Analysis

Initially all rate constants were calculated according to Method I, assuming $K = 0$. The resulting values of k_a invariably showed an appreciable decrease during the reaction, the final value of k_a being approximately 50% lower than the initial one for ethyl, *n*-propyl and cyclohexyl bromides, while that for isopropyl was even lower. The isobutyl case will be dealt with in the next section.

Values of k_b were calculated by method II, and were found to increase rapidly, approaching infinity as $(y_0 - y)$ approaches $^1/_2x_0$. On extrapolation of k_a and k_b to the point of zero reaction, a good estimate of the actual initial rate constant k_1 is obtained. The value, however, is very sensitive to small variations in the initial values of k_a and k_b and it is subject to the inherent uncertainties of non-linear extrapolation. It may therefore be in error by up to 5%. A plot of k_a and k_b against per cent. alkyl halide reacted is shown for *n*-propyl bromide in Fig. 1.

Isobutyl Bromide. Formation of an Olefin–Mercuric Complex.—In runs in the presence of this halide, an orange yellow precipitate appeared very soon after the beginning of the reaction.

The precipitate (I) was isolated on a large scale using 7 g. of isobutyl bromide in 200 cc. of 3*N* nitric acid. Approximately two equivalents of mercuric nitrate were required to react with the alkyl bromide. The precipitate was filtered,

(10) A similar method is described by Skrabal, "Homogenkinetik," Steinkopf, Dresden, 1941, p. 165.

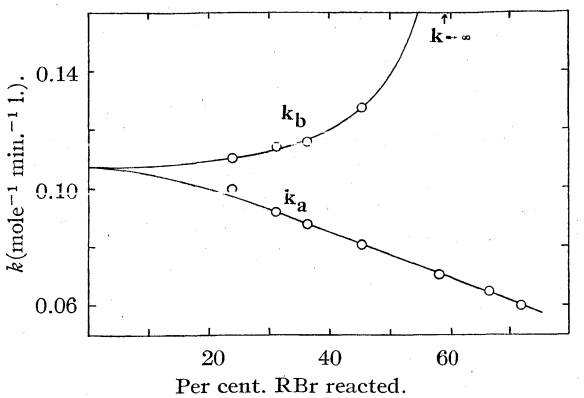


Fig. 1.—Approximate determination of k_1: [n-PrBr] = 0.02185 N, [$Hg(NO_3)_2$] = 0.02575 N, [HNO_3] = 0.281 N, 70% dioxane, 25°.

washed with hot water and dried on a porous plate and in a desiccator. It is insoluble in hot and cold water, alcohol, ether and chloroform. Analysis showed the presence of mercuric ion and the complete absence of mercurous. The compound could not be prepared from isobutanol which is one of the reaction products, nor if mercuric nitrate is replaced by mercuric bromide. Now it is to be expected that an electrophilic attack on isobutyl bromide will produce isobutene as one of its major products. Many reactions of olefins with mercuric salts are reported in the literature,[11] the simplest being an addition compound of one mole olefin to one mole mercuric salt.

A compound of similar properties has been reported by Denigès[12] as being the product of the mercuric nitrate reaction with t-butanol or isobutene. The above procedure was repeated using tertiary butanol instead of isobutyl bromide, and an orange yellow solid (II) was quickly precipitated. Both compounds had the same properties toward solvents, both evolved a gas on treatment with concentrated hydrochloric acid. On heating slowly, their color changed to orange and red, on placing suddenly in an environment at 200° both decomposed, the t-butanol compound with detonation. Contrary to Denigès no mercurous mercury was detected in the t-butanol compound, nor did it decompose in sunlight.

Since Denigès has reported the formation of the precipitate from isobutene, this gas was tested for in the original precipitate I by treating it with concentrated hydrochloric acid and passing the gas evolved into a nitric acid solution of mercuric nitrate. A yellow precipitate III was formed of similar properties to those of I and II. That their physical properties are not identical is probably due to the presence of Hg–Br linkages in I, and to differences in the amount of washing and drying.

The common intermediate from the three starting materials can only be isobutene. Rough titrations on the precipitates suggest the presence of one mercury atom to one isobutene molecule. This suggests the composition of the product from isobutyl bromide to be $C_4H_8 \cdot HgY_2$, and $C_4H_8 \cdot HgBrY$ where Y is NO_3 or OH.

The formation of a compound $C_4H_8 \cdot Hg(NO_3)_2$ under similar conditions to ours is reported by Lucas, Winstein and co-workers.[13,11b] A similar compound with cyclohexene and one of isobutene with silver ion[14] have also been shown to exist.

N-Propyl and Ethyl Bromides. The Cause of the Decrease in Values of k_a—The fall in k_a during the n-propyl bromide reaction may be due to the removal of mercuric ion by olefin to form a soluble complex.

Instantaneous rate constants k'_a were calculated from the formula

$$k'_a = \frac{2}{(x_0 - y_0)(t_2 - t_1)} \ln \frac{y_1 x_2}{x_1 y_2}$$

where (x_1,y_1,t_1), (x_2,y_2,t_2), correspond to alternate reaction samples. Their values for the reaction of n-propyl bromide in the usual conditions are given in Table I, together with the corresponding mean concentration of alkyl halide. Detailed

TABLE I

CALCULATION OF INSTANTANEOUS RATE CONSTANTS k'_a IN THE n-PROPYL BROMIDE–MERCURIC NITRATE REACTION IN 70% DIOXANE AT 25°

[$Hg(NO_3)_2$] = 0.02575 N, [n-PrBr] = 0.02185 N, [HNO_3] = 0.281 N

t_1, min.	t_2, min.	x_1[a]	x_2[a]	Mean [RBr] mol./l.	k'_a mol.$^{-1}$ min.$^{-1}$ l.
70.50	247.50	9.42	8.14	0.01821	0.0917
154.60	368.30	8.67	7.52	.01650	.0777
247.5	485.0	8.14	7.07	.01526	.0748
368.3	751.0	7.52	6.29	.01352	.0700
485.0	1384.0	7.07	5.21	.01158	.0618
751.0	2113.5	6.29	4.46	.00964	.0555
1384.0	2857.0	5.21	3.98	.00767	.0493

[a] x_1, x_2, expressed in cc. of 0.02520 N $Hg(NO_3)_2$ per 9.99 cc. sample.

analysis of the rate constants gives an initial rate k_1 = 0.105 mole^{-1}min.$^{-1}$l. (next section). A second run was carried out, using half the usual concentrations of n-propyl bromide and mercuric nitrate, and adding 0.0125 N mercuric bromide. This duplicates the conditions of the run tabulated in Table I, at the point of half reaction. If the fall in rate constants is due to olefin formation in the first case, then its absence here should yield a rate constant of a value approximately 0.10. If the fall in rate is due to the equilibrium between mercuric ion and mercuric bromide, rate constants in this run should duplicate the previous ones for the same mean alkyl bromide ion concentration.

The values of k'_a for both runs are plotted against mean alkyl halide concentration in Fig. 2. The results leave no doubt that olefin complex for-

(11) (a) Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., Reinhold Publ. Corp., New York, N. Y., 1921, p. 106; (b) Lucas, Hepner and Winstein, THIS JOURNAL, **61**, 3102 (1939).

(12) Denigès, *Ann. chim. phys.*, [7] **18**, 387 (1899).

(13) Lucas and Eberz, THIS JOURNAL, **56**, 460 (1934).

(14) Eberz, Welge, Yost and Lucas, *ibid.*, **59**, 45 (1937).

TABLE II

n-PROPYL BROMIDE–MERCURIC NITRATE REACTION IN 70% DIOXANE AT 25°

$[Hg(NO_3)_2]$ = 0.02575 *N*, [*n*-PrBr] = 0.02185 *N*, $[HNO_3]$ = 0.281 *N*; $N = -dx/[RBr]x dt$, *x* expressed in cc. 0.02520 *N* $Hg(NO_3)_2$ per 9.99 cc. sample; $K = 4$; $[Hg^{++}]/x$ and $[HgBr^+]/x$ calculated by eqn. 12. By extrapolation methods k_1 = 0.107 mol.$^{-1}$ min.$^{-1}$ l.

t_1, min.	0	247.5	368.3	485.0	751.0	1384.0	2113.5
t_2, min.	247.5	368.3	485.0	751.0	1384.0	2113.5	2857.0
x_1	10.21	8.14	7.52	7.07	6.29	5.21	4.46
x_2	8.14	7.52	7.07	6.29	5.21	4.46	3.98
[RBr] (mol./l.)	0.01922	0.01584	0.01450	0.01294	0.01059	0.00827	0.00671
N	.0474	.0414	.0364	.0339	.0280	.0257	.0228
$N_{cor.}$	.0482	.0400	.0370	.0336	.0292	.0253	.0223
$[Hg^{++}]/x$	.450	.384	.358	.327	.282	.237	.207
$[HgBr^+]/x$	.101	.233	.285	.346	.437	.527	.587
0.107 $[Hg^{++}]/x$	.0482	.0411	.0383	.0350	.0302	.0254	.0221
$k_1 = N_{cor.}/[Hg^{++}]/x$	.107	.104	.103	.103	.104	.107	.108

mation is not the cause of the fall in rate. It is likely therefore that the decrease in rate constant is due to an equilibrium between mercuric ion, mercuric monobromide ion, and mercuric dibromide.

In a run using mercuric bromide instead of mercuric nitrate, it was shown that catalysis of the reaction by mercuric bromide is negligible under the conditions of the kinetics. Mechanisms A and B alone should therefore account for the rate data.

The value of N was calculated for *n*-propyl bromide according to the left-hand side of equation 11, where $dx/dt = (x_2-x_1)/(t_2-t_1)$, with (x_1,t_1), (x_2,t_2), referring to consecutive points. The values of N were plotted against the mean x/x_0, and a smooth curve drawn through the points to give the corrected values of N. This procedure is necessary because of the small increments (x_2-x_1). The calculated and corrected values of N for *n*-propyl bromide are shown in Table II.

Using the approximate value of the initial rate constant k_1, determined by extrapolation to zero reaction of k_a and k_b, the quantity $k_1[Hg^{++}]/x$ is calculated for differing values of K. The difference $N - k_1[Hg^{++}]/x$ gives a measure of the rate of reaction *B*, *i. e.*, $k_2[HgBr^+]/x$. Hence k_2 may be obtained which must be constant during the reaction. The only constants that fitted the results were $K = 4$, $k_2 = 0$. For $K < 4$, k_2 is negative, for $K > 4$, k_2 increases during the reaction, the increase being more pronounced the greater the value of K.

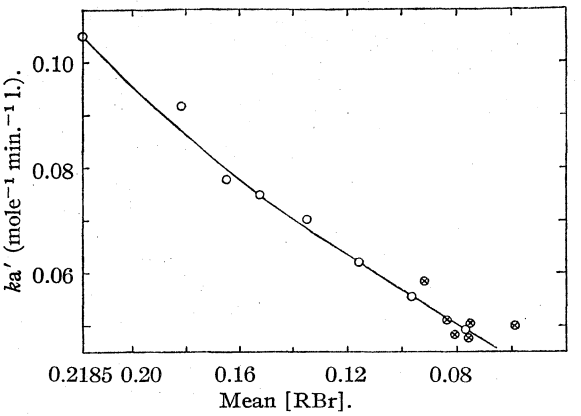


Fig. 2.—Runs to test the cause of the fall in rate: O, [*n*-PrBr] = 0.02185 *N*, $[Hg(NO_3)_2]$ = 0.02575 *N*, $[HNO_3]$ = 0.281 *N*, ⊗ [*n*-PrBr] = 0.00995 *N*, $[Hg(NO_3)_2]$ = 0.01246 *N*, $[HNO_3]$ = 0.284 *N*, $[HgBr_2]$ = 0.0125 *N*; 70% dioxane, 25°.

TABLE III

ETHYL BROMIDE–MERCURIC NITRATE REACTION IN 70% DIOXANE AT 25°

$[Hg(NO_3)_2]$ = 0.02538 *N*, [EtBr] = 0.02201 *N*, $[HNO_3]$ = 0.286 *N*; x_1, x_2 expressed in cc. 0.02518 *N* $Hg(NO_3)_2$ per 10.00 cc. sample; $K = 4$; $k_1 = N_{cor.}/[Hg^{++}]/x$ mol.$^{-1}$ min.$^{-1}$ l.

t_1, min.	t_2, min.	x_1	x_2	$N_{cor.}$	k_1, mole^{-1} min.$^{-1}$ l.
0	45.8	10.08	9.14	0.1033	0.217
45.8	92.7	9.14	8.40	.0913	.210
92.7	153.9	8.40	7.73	.0824	.206
153.9	240.9	7.73	6.99	.0746	.204
240.9	510.3	6.99	5.59	.0646	.207
510.3	1354	5.59	3.88	.0510	.217

If this analysis is correct, the ethyl bromide results should yield good rate constants if the same value of K is used. This was found to be the case k_2 again being zero. We may therefore calculate the rate constant k_1 for reaction *A* from the ratio

$$\frac{N}{[Hg^{++}]/x} = \frac{1}{[RBr][Hg^{++}]}\frac{dx}{dt} = k_1$$

Details of the calculation are given for *n*-propyl bromide in Table II. Results for ethyl bromide are shown in Table III.

Isobutyl Bromide.—Due to the formation of an olefin–mercuric salt complex, the rate coefficients k_a fell far more rapidly than in the case of other alkyl halides. An empirical equation of the form

$$k = \frac{2}{(x_0 - 3y_0)t}\ln\frac{y_0}{x_0}\frac{(x_0 - 3(y_0 - y))}{y}$$

gave constant values of k during a major part of the measured reaction. It derives from the expression $-dx/dt = ky(x_0 - 3(y_0 - y))$ and there-

fore coincides with k_1 when (y_0-y) is small. The rate constant obtained in this way had the value $k_1 = 0.0289$ mole^{-1}min.$^{-1}$l. (average deviation of mean ± 0.0002).

Now for ethyl and *n*-propyl bromide the equilibrium constant is given by $K = 4$, and the rate constant k_2 is negligible. The first condition must apply also for isobutyl bromide, since we have only changed the alkyl halide, while the second is highly probable.

Knowing K and an approximate k_1, as well as the experimentally determined dx/dt, we may calculate the value of x that is responsible for this rate of change of concentration. The difference between calculated and observed values of x gives the amount of total mercuric ion complexed for a given amount of alkyl bromide reacted. From this result the proportion of olefin in the product can be determined if we assume that the complex is a mixture of $C_4H_8 \cdot HgY_2$ and $C_4H_8 \cdot HgBrY$ (Y is NO_3 or OH) in the proportion in which Hg^{++} and $HgBr^+$ appear in solution, and that olefin when formed is immediately complexed. A very rough value of 63% olefin formation is obtained for the isobutyl reaction.

Knowing the proportion of olefin formed, we may calculate the amount of total mercuric ion in solution from the experimental titer by subtracting the amount removed by complex formation. This value is used in the rate equation. If the analysis is correct, calculation of the ratio $-dx/[RBr][Hg^{++}]\,dt$ should yield constant values of k_1. The results are given in Table IV. Since the rate fell rapidly values of Δx are small, and liable to appreciable error. The values of N did not warrant the determination of corrected values $N_{cor.}$ Rate constants were therefore calculated directly from N.

TABLE IV

ISOBUTYL BROMIDE–MERCURIC NITRATE REACTION IN 70% DIOXANE AT 25°

$[Hg(NO_3)_2] = 0.02567$ *N*, [iso-BuBr] = 0.02218 *N*, $[HNO_3] = 0.286$ *N*; x_1', x_2' = experimentally determined total concentration of mercuric ion; x = mean concentration of total mercuric ion not complexed with isobutene, assuming 63% olefin formation, and immediate complexing. x'_1, x'_2, x, expressed in cc. 0.02534 *N* $Hg(NO_3)_2$ per 10.00 cc. of sample. $x_0 - x = (1 + 2 \times 0.63)(x_0 - x') = 2.26(x_0 - x')$; $x_0 = 10.13$. $\Delta x/\Delta t$ determined for alternate reaction samples.

t_1, min.	t_2, min.	x_1'	x_2'	x	N	k_1, mole^{-1} min.$^{-1}$ l.
163.3	352.0	9.47	9.07	8.19	0.01295	0.0283
254.2	471.0	9.29	8.84	7.73	.01375	.0308
352.0	591	9.07	8.65	7.26	.01275	.0291
471	777	8.84	8.40	6.72	.01165	.0274

A slight fast reaction was observed at the start of the reaction, probably due to a small amount of *t*-butyl bromide impurity. This was corrected for in the rough determination, of k_1, it does not affect the accurate determination, as instantaneous rate constants were calculated in this case.

Isopropyl Bromide.—Steady rate constants ($k_1 = 30.5$ mole^{-1}min.$^{-1}$ l. ($K = 4$)) were obtained in the reaction of this halide at 25°, up to 55% of alkyl halide reacted, followed by a decrease. It suggests slow formation of a soluble olefin–mercury complex due to a few per cent. olefin in the product. Small proportions of olefin (3–7%) are reported as products in the hydrolysis of the halide in formic acid[15] and in dry ethyl alcohol.[16]

An analogous run at 12.5° gave results that fitted the theoretical equations if the equilibrium is given by $K = 8$ and $k_1 = 8.81$ mole^{-1}min.$^{-1}$l. There was no decrease in the constants during the reaction, suggesting that the amount of olefin in the product is sharply reduced as the temperature falls. Hughes and Ingold[16] give evidence that in the S_N1 reactions of tertiary halides an analogous situation is observed. From the rate constants obtained at the two temperatures, an activation energy for the reaction of 16.8 kilocalories per mole is obtained.

Cyclohexyl Bromide.—Numerous reactions of this halide are cited in the literature in which the predominant product is cyclohexene.[17] Lucas, Hepner and Winstein[11b] have shown that unstable complexes are formed between cyclohexene and mercuric ion, followed by the precipitation of a solid which probably has the structure of a true addition compound. In an experiment using 8 g. of mercuric nitrate, 4 g. of cyclohexene, 25 cc. of 6 *N* nitric acid and 25 cc. of dioxane, a pale yellow precipitate was formed after one day. Since the reaction of the halide in our conditions is complete in a few hours, there may be little interference by reaction between cyclohexene and mercuric ion. This was actually found to be the case. Rate constants during the reaction in the usual conditions at 25° were $k_1 = 8.16, 8.13, 8.16, 8.31, 8.72$ mole^{-1}min.$^{-1}$l. The slight rise in rate as the reaction proceeds may be due to a slight incursion of attack by $HgBr^+$. The mean of the first three points gives $k_1 = 8.15$ mole^{-1}min.$^{-1}$l.

Discussion

General.—Sillén and Infeldt[3] have recently measured the equilibrium constant at 25° for the equilibrium $Hg^{++} + HgX_2 \rightleftarrows 2HgX^+$ (X = Br or Cl), in aqueous solution with excess perchlorate ion. The values obtained were $K = 5.8 \pm 0.5$ for X = Br, $K = 1.8 \pm 0.1$ for X = Cl, where K is defined by equation 1, and its analog for the mercuric chloride case. In the measurements here recorded a value of $K = 8$ at 12.5°, and of $K = 4$ at 25°, were obtained.

The rate data given in this paper can be analyzed into good second order rate constants derived according to the system

$$RBr + Hg^{++} \longrightarrow R^+ + HgBr^+$$

if the relative concentrations of the two mercuric ions are controlled by the above equilibrium.

Roberts and Hammett[2] calculated rate con-

(15) Bateman and Hughes, *J. Chem. Soc.*, 945 (1940).

(16) Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

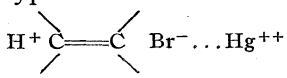
(17) Loevenich, Utsch, Moldrickx and Schaefer, *Ber.*, **62**, 3084 (1929).

stants k_a for the benzyl chloride reaction assuming $K = 0$ (Method I), and found these values to be constant or drifting upward in 60% dioxane while drifting downward in 75% and 95% dioxane. The fact that these drifts are far smaller than with alkyl bromides is explained by the far lower value of K when X = Cl. The upward drifts can only be explained if attack by $HgCl^+$ and probably by $HgCl_2$ contribute to the total reaction rate. This is possible since even the reaction of benzyl chloride in absence of mercuric nitrate is easily measurable at 50°.[8]

The accelerations caused by nitrate and perchlorate ion in all three media can be explained by their salt effect on the equilibrium. The thermodynamic equilibrium constant K_0 is related to the experimentally determined constant K by the equation $K_0 = Kf_1^2/f_2$, where f_1, f_2 are the activity coefficients of $HgCl^+$ and Hg^{++}, respectively. According to the Debye–Hückel theory for dilute solutions the activity coefficient of an ion is independent of the nature of other ions present, being related only to the ionic strength of the solution according to the equation $-\log f = Az^2\sqrt{\mu}$ where z is the charge of the ion, μ the ionic strength and A a constant for all ions in the same conditions. It follows that $K = K_0 10^{-2A\sqrt{\mu}}$. An increase in ionic strength decreases K and therefore increases the concentration of doubly charged mercuric ion whose reaction is far faster than that of $HgCl^+$. In solvents of low dielectric constant, the Debye–Hückel theory breaks down even at quite low ionic strengths, and the specificity of ions soon becomes apparent. The differing accelerations caused by nitrate and perchlorate ions are probably due to this cause.

By the postulation of the equilibrium C, the effects of added nitrate ion and perchlorate ion become understandable without the assumption that complexes of the type $HgClO_4^+$, $HgNO_3^+$ react at differing rates. It may be that these complexes do exist, but the rate calculations suggest that the only factor influencing the rate of reaction of mercuric mercury is the number of halogens with which it is combined.

The Rate Sequence Ethyl, *n*-Propyl, Isobutyl.—The rate constants for the reaction of these halides were as follows: EtBr 0.210, *n*-PrBr 0.105, iso-BuBr 0.0289 $mole^{-1}min.^{-1}l.$ These rate changes Et > *n*-Pr > iso-Bu are in the same order and of similar magnitude to those found in the reaction with silver nitrate. Heterogeneous catalysis by solid metal halide is therefore eliminated as a cause of the fall in rate along this series. Now the rate series Me < Et > *n*-Pr > iso-Bu can be explained if the determining factor in the stabilization of the transition state is the contribution of hyperconjugation due to the β-hydrogen atoms. Contribution in the transition state of resonance forms of the type



would greatly facilitate ionization on the attack of an electrophilic reagent on halogen. The effect would be far greater in the transition state than in the ground state, and it would be much more marked in a mechanism involving ionization than in one where electron transfer from a nucleophilic reagent compensates the electron demand created by the breaking of the carbon–halogen bond (S_N2).[18] Hyperconjugation effects increase with an increase in the number of available β-hydrogen atoms and therefore explain the rate sequence.

Hughes[19] objects to this explanation on the ground that in the tertiary halides, the rate of ionization increases along the series *t*-butyl, *t*-amyl, α,α-diethyl neopentyl, in spite of the progressive decrease in the number of β-hydrogen atoms. Crowding of methyl groups and hydrogen atoms however increases along this series and the decrease in these compression energies on attaining to the planar carbonium ion configuration may greatly influence the rate sequence.[20] Further progress in attributing rate changes unambiguously to specific electronic or steric influences can only be made when accurate energies and entropies of activation become available.

Cyclohexyl and Isopropyl Bromides.—The results (k_1(Cyclohexyl bromide) = 8.15, k_1(Iso-PrBr) = 30.5 $mole^{-1}min.^{-1}l.$) show that these halides have rates of the same order of magnitude in their reaction with mercuric nitrate. Evidence indicates that the rates of cyclohexyl chloride and bromide are far lower than those of the corresponding isopropyl halide toward iodide ion,[6b] pyridine and piperidine[6a] while the rates are normal toward sodium methoxide.[6a] An inspection of Fisher–Hirschfelder atomic models shows that there is considerable steric hindrance toward the approach of a nucleophilic reagent at the α-carbon atom if the bromine atom is in the radial position. A reagent whose reactivity toward carbon is much greater than that toward hydrogen (*e. g.*, iodide ion) should therefore react at a very slow rate. Methoxide ion however has a strong affinity for hydrogen and can attack the β-hydrogen atom by the bimolecular elimination mechanism E2.[16] In agreement with this, the preponderant product is cyclohexene.[17] There should be no steric hindrance in the reaction of cyclohexyl bromide with mercuric ion, and its rate as well as that of attack by methoxide ion is found to be of similar magnitude to that of isopropyl bromide.

Acknowledgments.—The author wishes to thank the University of London for the award of a postgraduate travelling studentship, and the authorities of Columbia University for extending their hospitality to him. He wishes to record his heartfelt thanks to Professor L. P.

(18) Hughes, Ingold and Taher, *J. Chem. Soc.*, 949 (1940).

(19) Hughes, *Trans. Faraday Soc.*, **37**, 624 (1941).

(20) H. C. Brown, paper presented before the Organic Division of the American Chemical Society at its New York meeting, September, 1947.

Hammett for suggesting this work and for his continual interest, help and encouragement.

Summary

The reaction of mercuric nitrate with the primary alkyl bromides, ethyl, *n*-propyl, isobutyl and the secondary bromides isopropyl and cyclohexyl has been studied in aqueous dioxane. The reaction is shown to occur by the rate determining attack of doubly charged mercuric ion on halogen, with an equilibrium determining the relative concentrations of mercuric ion, mercuric monobromide ion and mercuric dibromide. Of the three mercuric species involved in the equilibrium only the first is shown to contribute perceptibly to the rate.

A precipitate of the probable composition $C_4H_8 \cdot HgY_2$ and $C_4H_8 \cdot HgBrY$ (Y = NO_3 or OH) forms during the reaction of isobutyl bromide. On making allowance for this secondary reaction the halide fits into the general reaction scheme.

The experimentally determined rate sequence ethyl > *n*-propyl > isobutyl is explained by a hyperconjugation effect. The approximate equality of rates between isopropyl and cyclohexyl bromides is expected because of the absence of steric hindrance in this reaction.

The work of Roberts and Hammett[2] on the analogous benzyl chloride reaction falls in line with the reaction scheme here outlined.

NEW YORK, N. Y. RECEIVED FEBRUARY 10, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

Methyl Silicate from Silicon and Methanol

BY EUGENE G. ROCHOW[1a]

Knowing that hydrocarbon halides will react with elementary silicon in the presence of certain catalysts to yield the corresponding alkyl or aryl halosilanes,[1,2,3,4] it is of interest to inquire whether alcohols will react in similar fashion to form organosilanols or organosiloxanes

$$2ROH + Si \xrightarrow{\text{catalyst}} R_2Si(OH)_2 \xrightarrow{-H_2O} [R_2SiO]_x$$

It was found that of the several lower alcohols tried, only methanol reacted readily to form recognizable products. While the methanol responded to the action of the same copper catalyst used for the reaction of methyl chloride and silicon,[1] it followed an entirely different course of reaction and produced methyl silicate.

$$4CH_3OH + Si \xrightarrow[250^\circ]{Cu} Si(OCH_3)_4 + 4H$$

Some of the hydrogen resulting from the reaction appears in the effluent as molecular hydrogen, while the rest combines with the reactants to form silane linkages and reduction products of methanol:

$$H + Si \longrightarrow -\overset{|}{\underset{|}{Si}}-H$$

$$CH_3OH + 2H \longrightarrow CH_4 + H_2O$$

The reaction further is complicated by the action of the water on some of the methyl silicate to form condensed methoxysilanes, $2Si(OCH_3)_4 + H_2O \rightarrow (CH_3O)_3SiOSi(OCH_3)_3 + 2CH_3OH$, etc. A small fraction of the methyl groups later were shown to be bonded directly to silicon $\left(CH_3-\overset{|}{\underset{|}{Si}}-\right)$ in the manner of the first equation given; no individual methylmethoxysilanes were isolated, however, and the effect was noticed only upon extensive analysis of the intermediate distillation fractions and the solid polymers produced.

Anhydrous *ethanol* was found to react sluggishly with silicon at 280 to 325° in the presence of copper as a catalyst to convert about 10% of the alcohol to condensed ethyl silicates. A search for a more effective catalyst was fruitless. A small amount of material containing C_2H_5–Si bonds was found after one run, but it does not seem likely at this time that ethyl silicate or ethylethoxysilanes can conveniently be prepared from ethanol and silicon in this way.

Experimental

A glass tube 2 cm. in diameter and 50 cm. long was packed with pellets of 90% silicon[5] and 10% copper prepared by pressing the mixed powders in a die and heating the pellets in hydrogen at 1050° for two hours. The tube was sealed to a water condenser leading to a receiver, and the uncondensed products were led through traps held at −80 and −196°. A dropping funnel was connected to the other end of the tube. The tube was heated to 280°[6] and 57.2 g. of anhydrous methanol was allowed to drip in slowly from the funnel. An exothermic reaction set in at once, and the furnace current had to be reduced. A combustible gas (hydrogen) issued from the −196° trap. Thirty-eight grams of liquid was recovered from the receiver, 8.4 g. from the −80° trap, and 2.0 g. from the −196° trap. The liquid in the receiver was found upon distillation to consist of methyl silicate (b. p. 120–122°, m. p. 2°), a little unchanged methanol, some water, and small amounts of materials boiling above and below methyl silicate. The −80° condensate melted at

(1a) Present address: Harvard University, Cambridge, Mass.

(1) Rochow, THIS JOURNAL, **67**, 963 (1945).

(2) Rochow and Gilliam, *ibid.*, **67**, 1772 (1945).

(3) Hurd, *ibid.*, **67**, 1813 (1945).

(4) U. S. Patents 2,380,995 and 2,383,818.

(5) Commercial massive silicon, 98% Si, crushed to pass a 60 mesh sieve.

(6) As measured by a thermometer embedded in the silicon.

TABLE I

Sample and origin	H, %	C, %	Si, %	Probable composition
Product of CH_3OH and Si, no catalyst	12.1	37.2	−0.03	Pure CH_3OH
Fr. 3, b. p. 80–118°	8.33	31.2	21.6	$CH_3Si(OCH_3)_3$ and $Si(OCH_3)_4$
Fr. 6, b. p. 155–183°	10.4	35.6	12.0	$C_{6.94}H_{24.2}SiO_{6.14}$
Product, b. p. 121°	9.82	34.3	12.4	$Si(OCH_3)_4$
Fr. 2a, b. p. 100–110°	8.28	30.7	22.2	$(CH_3)_{0.17}H_{0.70}Si(OCH_3)_{3.1}$
Same, after hydrolysis[a]	1.59	1.89	44.5	$(CH_3)_{0.10}H_{0.25}SiO_{1.61}(OH)_{0.45}$
Same, after hydrolysis[a] + heating to 150° 18 hr.	1.39	2.10	46.6	$(CH_3)_{0.10}H_{0.25}SiO_{1.88}$

[a] In the samples so designated, methoxy groups were hydrolyzed off so that CH_3–Si and H–Si groups could be determined more accurately.

about 0° and appeared to consist of the same substances, carried over by uncondensed gas. The −196° condensate had melting and boiling points corresponding to those of methane; when a portion was vaporized through a jet it burned with a hydrocarbon flame, and when the rest was passed through a bunsen burner it burned with a blue flame and formed no white smoke. Examination of the powder left in the tube showed some particles of silicon dioxide, some copper (I) oxide, and some gummy material that appeared to be a condensed silicon ester resin.

Two similar experiments were carried out at 250 and 300° to determine the yield of methyl silicate. Eighty grams of methanol was allowed to drip into a tube of fresh copper–silicon pellets over a period of five hours, and the liquid in the receiver (59 g.) was distilled through a column of about five theoretical plates. Neglecting the amount that may have been in the intermediate fractions, 32.2 g. of methyl silicate (2° boiling range) was obtained. This represents 40.2% of the weight of methanol used, 43.6% of the total products recovered, 51.0% of the distillate, and 48.0% of the theoretical yield if all the methanol were converted to methyl silicate. With the silicon at 250°, a similar charge of methanol gave methyl silicate equivalent to 44.4% of the weight of methanol, 47.8% of the total products recovered, 53.4% of the distillate, and 53% of the theoretical conversion. A slight advantage is shown in operating at 250°.

The reaction was carried out on a larger scale in a steel tube 2.5 cm. in diameter and 240 cm. long, heated to 220° by circulating tricresyl phosphate.[7] The tube was charged with 1315 g. of powder consisting of 90% silicon and 10% copper, previously fired in hydrogen at 1000° for one hour. Several gallons of methanol were pumped into the tube over a period of ten days by injecting approximately 40 g. per hour with a proportioning pump. The 477 g. of condensate from the first 745 g. of methanol yielded 357 g. of methyl silicate, which represents about 75% of the weight of condensate and about 49% of the weight of methanol. The yield of methyl silicate decreased over the period of operation of the tube and fell to zero after about 5700 g. of methanol was injected. The total methyl silicate obtained from the run (1358 g.) represented about 250 g. of silicon. Besides silicon dioxide, copper (I) oxide, and unused silicon and copper, the used powder contained solid materials which were shown by analysis to have Si–H and Si–C bonds. No carbon was deposited.

Analysis.—Many unknown products were obtained during the distillation of the reaction mixtures, most of which could be investigated only by combustion analysis. An arrangement of a weighable silica combustion tube and absorbers was set up, similar to that previously employed for the analysis of silicone resins,[1] except that ground-in glass stoppers were fitted to the combustion tube during weighing. Liquid samples were weighed in a glass bubbler equipped with ground plugs, and were vaporized by the stream of oxygen passing into the combustion tube. Solid samples were weighed in small porcelain boats which were inserted directly into the combustion tube and in which the sample was oxidized at a minimum temperature determined by experiment. The apparatus otherwise was operated as previously described.[1]

The apparatus was tested by analyzing pure ethyl silicate: calcd.: C, 46.1; H, 9.66; Si, 13.5. Found: C, 45.1; H, 9.55; Si, 13.9. The results obtained on a few of the fractions are summarized in Table I. It is seen that some of the samples contained Si-H and Si-CH_3 groups, but that they are mixtures of liquids and complex polymeric solids rather than pure compounds. The presence of Si-H bonds could readily be demonstrated in most of the fractions boiling above and below methyl silicate by the vigorous evolution of hydrogen obtained by treating the sample with 10% aqueous sodium hydroxide. Some of these samples also developed a pressure of hydrogen upon long standing in tightly-capped soft glass bottles.

Warning.—Methyl silicate is believed to be an exceedingly dangerous substance, since small quantities of the liquid or its vapor coming in contact with the eye will cause perforating ulceration of the cornea and possible blindness.[8] The investigation reported herein was conducted before this information was available, but fortunately no ill effects were experienced. Either there must be great variation in personal susceptibility, or there is some deleterious ingredient in the methyl silicate prepared by previous methods. A study of this point would be very welcome. In the meantime, it would be well for investigators to exercise extreme care in handling methyl silicate.

Summary

Methanol vapor is shown to react with elementary silicon at elevated temperatures and in the presence of copper as a catalyst to produce methyl silicate and hydrogen. The various by-products which are observed are believed to be produced by the action of the hydrogen upon the reactants.

SCHENECTADY, N. Y. RECEIVED JANUARY 31, 1948

(7) The help of R. C. Faught in carrying out this experiment is gratefully acknowledged.

(8) *Chem. Eng. News*, **24**, 1690 (1946) (note under Industrial News).

[FROM THE ENZYME LABORATORY, DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

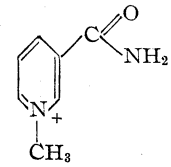
The Location of the Reactive Carbon in N^1-Methylnicotinamide

BY W. EUGENE KNOX AND WILLIAM I. GROSSMAN

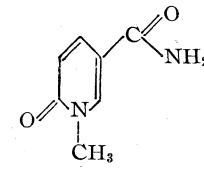
One uncertainty remaining in the structures of Coenzyme I and II as worked out by Warburg,[1] Karrer[2] and Schlenk,[3] involves the site of the reversible oxidation–reduction of the nicotinamide moiety. This uncertainty was recognized by Karrer in his first experiments using N^1-methylnicotinamide iodide as a model compound. Reduction occurs α to the ring nitrogen, but until now means have not been available to locate the reactive carbon in one of the two α-positions. From consideration of the properties of the quinine-oxidizing enzyme detailed below, the oxidation of N^1-methylnicotinamide by this enzyme to the corresponding 6-pyridone[4] enables us to locate the center of reactivity and therefore the site of oxidation–reduction in the 6-position of this quaternary nicotinamide ring. However, there is no direct evidence yet available about the arrangement obtaining in the pyridinonucleotide coenzymes themselves.

Oxidation by the quinine-oxidizing enzyme of rabbit liver is restricted to the unsaturated α-position of many pyridine, quinoline and pyrazine compounds.[5] This is referrable to the fact that only the pseudo-base forms are oxidized, as is evident from the parallelism between the rate of oxidation of various compounds and the ease of their pseudo-base formation.[6] In addition, the enzyme has been found to oxidize 1,2,2,5,5-pentamethyl - 6 - hydroxy - tetrahydropyrazine, which is itself a stable pseudo-base prepared by Dr. John G. Aston.[7] Consequently, if a compound is oxidized by the enzyme, it will be oxidized in the reactive α-position which is the site of unsaturation and of pseudo-base formation. Identification of an enzymic oxidation product will therefore locate the reactive carbon. In compounds such as pyridine, where both positions are similar, neither is "reactive" and no oxidation occurs.

The enzymic oxidation product of quinoline has previously been identified as carbostyril. We have also obtained 34 mg. of isocarbostyril, identified by mixed melting point, from enzymic oxidation of 40 mg. of isoquinoline. The reactivity in these compounds of carbon atoms 2 and 1, respectively, as shown by the enzyme reaction, thus agrees with the sites identified by other means.[8,9] Similarly, the product of the enzymic oxidation of N^1-methylnicotinamide chloride (I) has been identified as 1-methyl-3-carboxylamide-6-pyridone (II). Assay of the product in the enzyme mixture by its ultraviolet absorption at 259 and 290 mμ has shown it to be the sole product of the enzymic oxidation of N^1-methylnicotinamide chloride.[10]



I



II

This oxidation thus identifies the 6-carbon of N^1-methylnicotinamide as the reactive carbon. Because of the limits of enzyme specificity, the rate of oxidation of pure Coenzyme I by the enzyme is so slow as to preclude isolation of palpable amounts of the product for identification of the reactive carbon in this compound. However, N^1-methylnicotinamide also forms a reversibly oxidizable *o*-dihydro compound analogous in every way to the reduced coenzymes. The recent crystallization of this derivative is evidence that only one of the possible *o*-dihydro compounds is formed,[11] and it follows that this is the 1,6-dihydro derivative.

Summary

Oxidation of N^1-methylnicotinamide chloride to the corresponding 6-pyridone by the quinine-oxidizing enzyme shows that the 6-carbon is the reactive position of the quaternary nicotinamide ring.

NEW YORK, N. Y. RECEIVED NOVEMBER 7, 1947

(1) Warburg, Christian and Griese, *Biochem. Z.*, **282**, 157 (1935).

(2) Karrer, Schwartzenbach, Benz and Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(3) Schlenk, *J. Biol. Chem.*, **146**, 619 (1942).

(4) Knox and Grossman, *J. Biol. Chem.*, **166**, 391 (1946).

(5) Knox, *J. Biol. Chem.*, **163**, 699 (1946).

(6) Sidgwick, Taylor and Baker, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1937, pp. 526, 550, 556.

(7) Aston, THIS JOURNAL, **52**, 5259 (1930).

(8) Renshaw, Friedman and Gajewski, *ibid.*, **61**, 3322 (1939).

(9) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(10) Knox and Grossman, *J. Biol. Chem.*, **168**, 363 (1947).

(11) Karrer and Manz, *Helv. Chim. Acta*, **29**, 1152 (1946); Karrer and Blumen, *ibid.*, **30**, 1157 (1947).

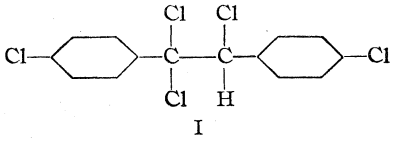
[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

The Preparation of α,α,α'-4,4'-Pentachlorobibenzyl, an Isomer of DDT

BY ELMER E. FLECK

Various attempts have been made to correlate the insecticidal action of DDT and related compounds with the presence of the *p*-chlorophenyl groups[1] or the trichloromethyl group[2] and with the ease with which hydrogen chloride is eliminated from the molecule.[3] Martin[4] has stated that, while high toxicity was not found in all the DDT analogs that are readily dehydrohalogenated, all the analogs that showed high toxicity dehydrohalogenated readily in dilute alcoholic alkali.

It was thought to be of interest to prepare an isomer of DDT which retained the *p*-chlorophenyl groups and was readily dehydrochlorinated, but in which both carbon atoms of the ethyl group were substituted with a *p*-chlorophenyl group. Such a compound has been prepared by the chlorination of *cis*-α,4,4'-trichlorostilbene to form *dl*-α,α,α',4,4'-pentachlorobibenzyl (I). This compound melted at 97–98°. When refluxed for fifteen minutes with 0.1 *N* alcoholic alkali, it readily lost hydrogen chloride to form *cis*-α,α',4,4'-tetrachlorostilbene (II). Anhydrous ferric chloride also dehydrochlorinated I, in the molten condition, to form II, just as DDT is dehydrochlorinated.[5]



I

The identity of II was established by chlorinating it to form the known compound $\alpha,\alpha,\alpha',\alpha'$,4,4'-hexachlorobibenzyl.

Insecticidal tests[6] show that I is ineffective, against house flies, pea aphids, celery leaf tiers, red spider mites, and European corn borers. These results provide evidence that insecticidal action is due to the molecule as a whole rather than to the presence of toxic groups or specific reactions.

(1) Läuger, Martin and Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

(2) Martin and Wain, *Nature*, **154**, 512 (1944).

(3) Busvine, *ibid.*, **156**, 169 (1945); Domenjoz, *Helv. Chim. Acta.*, **29**, 1317 (1946); Müller, *ibid.*, **29**, 1560 (1946); Metcalf and Gunther, THIS JOURNAL, **69**, 2579 (1947).

(4) Martin, *J. Soc. Chem. Ind.*, **65**, 405 (1946).

(5) Fleck and Haller, THIS JOURNAL, **66**, 2095 (1944).

(6) Unpublished.

Experimental

Preparation of *dl*-α,α,α',4,4'-Pentachlorobibenzyl.—Chlorine was passed through a solution of 7 g. of *cis*-α,4,4'-trichlorostilbene[7] in 75 ml. of carbon tetrachloride for two hours at room temperature. The solution was then concentrated on a steam-bath to a volume of about 15 ml. The prisms that separated, when this solution was cooled in ice, were collected and dried at room temperature in a vacuum; yield, 6.1 g. After recrystallization from alcohol the product melted at 97–98°. No yellow color was given with tetranitromethane.

Anal. Calcd. for $C_{14}H_9Cl_5$: C, 47.43; H, 2.56; Cl, 50.01. Found: C, 47.63; H, 2.92[8]; Cl, 50.32.

***cis*-α,α',4,4'-Tetrachlorostilbene.**—A solution of 0.5 g. of *dl*-α,α,α',4,4'-pentachlorobibenzyl in 50 ml. of 0.1 *N* alcoholic sodium hydroxide was refluxed for two hours. Water was then added to the hot solution until crystallization occurred. The cooled solution yielded 0.45 g. of material that melted at 83–85°. Repeated recrystallization from acetone yielded needles which melted at 166–167°.[9] With tetranitromethane a yellow color was obtained.

When this experiment was repeated quantitatively with a 100-mg. sample and a fifteen-minute reflux period, [illegible] formed indicated that 0.92 α,α,α',

The same [illegible] removal of hydrogen [illegible] α,α,α',4,4'-pentachlorobibenzyl [illegible] ferric chloride was heated in a current of air in a U-tube at 90–95° for half an hour.[5] Gas evolution was complete at the end of five minutes. Recrystallization of the product yielded needles that melted at 166–167°. Mixed melting points showed this product to be identical with that obtained by alkaline hydrolysis.

A quantitative determination showed that 0.98 mole of hydrogen chloride was eliminated by the catalyst.

$\alpha,\alpha,\alpha',\alpha',$4,4'-Hexachlorobibenzyl.—Chlorine was passed through a solution of 0.1 g. of *cis*-α,α',4,4'-tetrachlorostilbene (obtained by hydrolysis) in 5 ml. of carbon tetrachloride for two hours at room temperature. The solution was evaporated to dryness on a steam-bath, and the residue was recrystallized from chloroform. The product melted at 191–192°, and no depression of the melting point was found when this material was mixed with authentic $\alpha,\alpha,\alpha',\alpha',$4,4'-hexachlorobibenzyl.[9]

Summary

A DDT isomer, *dl*-α,α,α',4,4'-pentachlorobibenzyl, has been prepared which has two *p*-chlorophenyl groups, a hydrolyzable chlorine atom, and sensitivity to the catalytic action of anhydrous ferric chloride similar to DDT, but which has little insecticidal action.

BELTSVILLE, MARYLAND RECEIVED MARCH 10, 1948

(7) Fleck, *J. Org. Chem.*, **12**, 708 (1947).

(8) Analysis by N. Green.

(9) Kenner and Witham, *J. Chem. Soc.*, **97**, 1965 (1910).

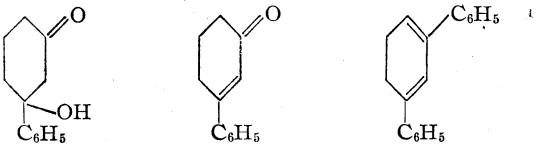
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF MARYLAND]

The Reaction of β-Cyclohexanedione (Dihydroresorcinol) and its Ethyl Enol Ether with Phenylmagnesium Bromide

BY G. FORREST WOODS AND IRWIN W. TUCKER

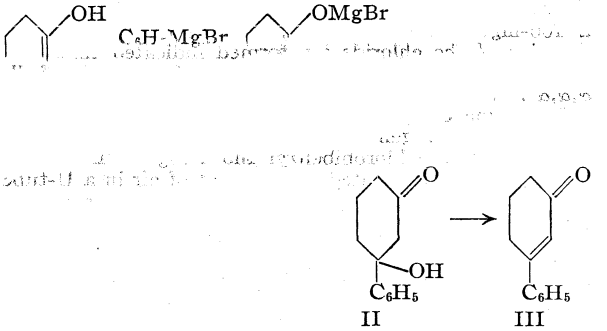
The reaction of dimedone with phenylmagnesium bromide has been previously investigated.[1] We have now studied the corresponding reaction of dihydroresorcinol (I) whose structure is very similar to that of dimedone.

Three products (II, III, and IV) and a tar were isolated after decomposing the Grignard complex.



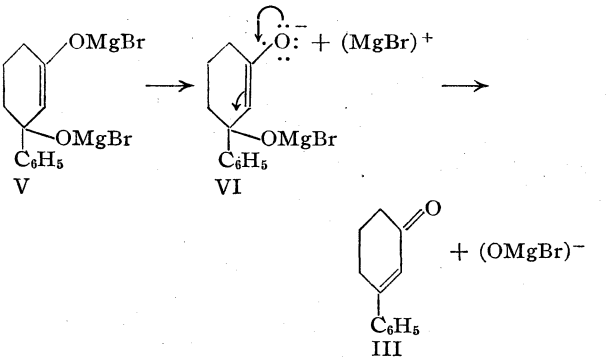
II III IV

The first two substances, II and III, are readily accounted for by the mechanism proposed by Kohler and Erickson[2] for the reaction of strongly enolic β-diketones with Grignard reagents as shown below applied to dihydroresorcinol



II III

The formation of 1,3-diphenylcyclohexadiene-1,3 (IV), however, is difficult to explain. Although this substance would obviously be the product of a double addition of phenylmagnesium bromide to dihydroresorcinol in the β-diketonic form, this concept is hardly acceptable since dihydroresorcinol is known to be strongly enolic.[3] A more reasonable mechanism is shown



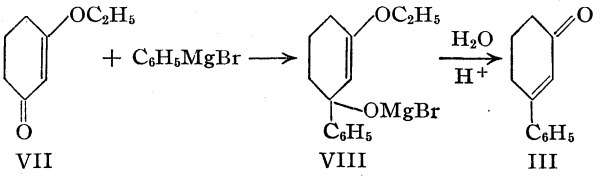
V VI III

If it is assumed that some degree of ionization exists in the magnesium enolate bond of structure (V) leading to structure (VI), then (VI) stabilizes itself by the ejection of the $(O\text{-}Mg\text{-}Br)^-$ ion, which had been activated by both the phenyl group and the ethylenic link, along with a concurrent electron shift. Thus, 3-phenyl-Δ^2-cyclohexenone (III) is generated and then reacts with phenylmagnesium bromide, the addition product subsequently losing water to give IV. In this connection it is interesting to note that the hydrocarbon (IV) was obtained in higher yield almost to the exclusion of the other products by continued refluxing of the Grignard solution after displacement of the ether with benzene. The tar formed in the reaction of dihydroresorcinol with phenylmagnesium bromide is assumed to be a polymer of 1,3-diphenylcyclohexadiene-1,3, a substance which contains both butadiene and styrene-like structures.

[illegible][1] to prove the structure of 3-phenyl-[illegible]enone and 1,3-diphenylcyclohexadi-[illegible]-1,3 by an independent mode of synthesis, and to obtain a good preparative method for these substances. The preparation of the ethyl enol ether of dihydroresorcinol and the subsequent reaction of this substance with phenylmagnesium bromide accomplished the above two points.

The white crystalline silver salt of dihydroresorcinol was obtained by mixing dihydroresorcinol and silver nitrate in water and adjusting the *p*H of the solution. The silver salt thus prepared readily reacts with ethyl iodide in refluxing benzene to yield the ethyl enol ether of dihydroresorcinol.[4] We found this method of preparation superior to the reaction of dihydroresorcinol with sodium ethylate and ethyl iodide, with diethyl sulfate and aqueous sodium hydroxide, or with absolute ethyl alcohol and sulfuric acid. This last method was the mode of preparation of the ethyl enol ether of dimedone.[5]

Dihydroresorcinol ethyl enol ether (VII) reacts with phenylmagnesium bromide to yield 3-phenyl-Δ^2-cyclohexenone (III) as shown



VII VIII III

The intermediate product (the keto alcohol from VIII) was not isolated and it was found, as had been anticipated from previous work, that the

(1) Woods, THIS JOURNAL, **69**, 2549 (1947).

(2) Kohler and Erickson, *ibid.*, **53**, 2301 (1931).

(3) (a) Blout, Eager and Silverman, *ibid.*, **68**, 566 (1946); (b) Schwarzenback and Felder, *Helv. Chim. Acta*, **27**, 1044 (1944).

(4) Merling, *Ann.*, **278**, 28 (1894).

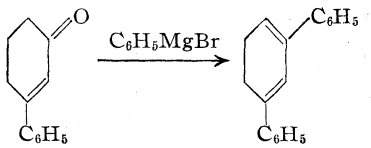
(5) Crossley and Renouf, *J. Chem. Soc.*, **93**, 640 (1908).

enol ether linkage of VIII was readily cleaved and the molecule dehydrated on treatment with dilute sulfuric acid under the conditions of steam distillation. The product, obtained in 80–85% yield, was identical with the 3-phenyl-Δ^2-cyclohexenone obtained by the reaction of dihydroresorcinol with phenylmagnesium bromide.

3-Phenyl-Δ^2-cyclohexenone (III) had previously been synthesized by Abdullaho[6] by the condensation of phenyl vinyl ketone with acetoacetic ester and the subsequent hydrolysis and decarboxylation of the condensation product. The constants of our product and its derivatives are in good agreement with his. Further, 3-phenyl-Δ^2-cyclohexenone is readily converted to *m*-phenylphenol by dehydrogenation over palladium–charcoal[7] or hydrogenated with palladium-charcoal to 3-phenylcyclohexanone.

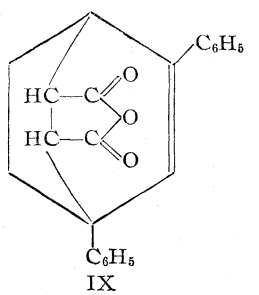
The fact that substance II, 3-phenylcyclohexane-3-ol-1-one, was readily dehydrated by refluxing in benzene in the presence of a trace of iodine to yield 3-phenyl-Δ^2-cyclohexenone establishes the structure of the former.

The structure of substance IV, 1,3-diphenylcyclohexadiene, was established by its synthesis from 3-phenyl-Δ^2-cyclohexenone (III) and phenylmagnesium bromide in good yield and superior quality



III IV

This substance was identical with the corresponding product obtained from the reaction of dihydroresorcinol with phenylmagnesium bromide. That this structure was correct was also shown by the conversion of 1,3-diphenylcyclohexadiene by dehydrogenation over palladium–charcoal to the known *m*-diphenylbenzene[8] and by the isolation of an adduct, for which the structure IX is written, from the Diels–Alder reaction of 1,3-diphenylcyclohexadiene-1,3 with maleic anhydride.



IX

Experimental

Reaction of Phenylmagnesium Bromide with Dihydroresorcinol.—An ethereal solution (1400 ml.) of phenylmagnesium bromide from 1.0 mole of bromobenzene and magnesium turnings was prepared in the pot of a Soxhlet extractor. Finely ground dihydroresorcinol[9] (28 g., 0.25 mole) was introduced into the extraction thimble and the extraction process continued until only a small residue (3 g.) remained unextracted. The Grignard complex solution, which set to a solid on cooling in an ice-bath, was hydrolyzed with dilute aqueous ammonium chloride. The ether solution, dried over anhydrous magnesium sulfate, concentrated to 300–500 ml. and chilled, gave 8 g. of solid which was recrystallized from acetone–petroleum ether (80–100°). This product was 3-phenylcyclohexan-3-ol-one (II) and melted at 155–155.5°. *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.94, 75.89; H, 7.70, 7.58.

The ethereal filtrate, after the removal of the above product, was then distilled under reduced pressure. Two substances (III and IV) were obtained after the removal of bromobenzene and biphenyl. Impure 3-phenyl-Δ^2-cyclohexenone (III) was collected which distilled over the range of 106–185° (10 mm.). The main portion of this material distilled from 165–185° (10 mm.). The yield was 15–20 g. This material, which solidified on cooling, yielded coarse white crystals upon recrystallization from petroleum ether (30–60°) which melted at 64.5–66.0°. *Anal.* Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.55, 83.64; H, 7.22, 7.17.

The second product, 1,3-diphenyl-cyclohexadiene-1,3 (IV), distilled over the range of 130–190° (0.2 mm.). The main fraction (5 g.) distilled at 176° (0.2 mm.). This substance was decolorized with norite and crystallized from petroleum ether (30–60°). Upon further recrystallization white crystalline platelets were obtained which melted at 98–99°.[10] *Anal.* Calcd. for $C_{18}H_{16}$: C, 93.10; H, 6.94. Found: C, 93.14, 92.97; H, 6.62, 6.65.

In subsequent reactions 3-phenylcyclohexan-3-ol-1-one (II) was not isolated since it was readily converted in the following operations to 3-phenyl-Δ^2-cyclohexenone (III), a desired product. The original ethereal solution from the Grignard complex was made acid with dilute sulfuric acid and subjected to steam distillation. In this manner the troublesome impurities of bromobenzene and biphenyl were readily eliminated, since 3-phenyl-Δ^2-cyclohexenone and 1,3-diphenylcyclohexadiene-1,3 are only slightly volatile with steam.

Conversion of 3-Phenylcyclohexan-3-ol-1-one to 3-Phenyl-Δ^2-cyclohexanone.—3-Phenylcyclohexan-3-ol-1-one (II) (0.6 g.) was refluxed in toluene (25 ml.) after the addition of a small crystal of iodine. The toluene was removed by distillation under reduced pressure and the residue dissolved in ether and decolorized with norite. The product was recrystallized from petroleum ether which was added after removal of most of the ether. This material melted at 64.5–66.0° and gave no depression in a mixed melting point determination with a sample of 3-phenyl-Δ^2-cyclohexenone obtained previously as above.

Preparation of Dihydroresorcinol Ethyl Ether[11] (VII).—Dihydroresorcinol[9] (50 g.) and silver nitrate (76 g.) were dissolved in 400 ml. of water. To this solution was added dropwise with stirring 1.0 *M* sodium hydroxide until the *p*H of the solution was 5.5–6.0. During this process silver oxide precipitated locally but gradually redissolved while silver dihydroresorcinate precipitated in a white crystalline form. Excessive amounts of sodium hydroxide caused a noticeable darkening of the precipitate and a subsequent lowering in yield of the ultimate product.

(6) Abdullaho, *J. Indian Chem. Soc.*, **12**, 62 (1935).

(7) Horning and Horning, THIS JOURNAL, **69**, 1359 (1947).

(8) France, Heilbron and Hey, *J. Chem. Soc.*, 1288 (1939).

(9) "Organic Syntheses," Vol. 27, John Wiley and Sons, New York, N. Y., p. 21.

(10) This product becomes contaminated readily with either the substances of polymerization or with some *m*-terphenyl (from the oxidation of the diphenylcyclohexadiene). Thus this melting point is obtained only with difficulty.

(11) The development of this method of preparation of the ethyl enol ether of dihydroresorcinol was done by Mr. Bernard Armbrecht. The details given by Merling (*Ann.*, **278**, 28 (1894)) are so brief as to amount only to an indication of procedure.

The silver salt of dihydroresorcinol was isolated by suction filtration and pressed reasonably free of water. The moist precipitate (80–85 g.) was placed in a three-neck flask to which was fitted a mechanical stirrer, a separatory funnel, and a moisture receiving tube itself connected to a reflux condenser. Benzene (300 ml.) was introduced into the three-neck flask and the mixture refluxed with stirring until all the water was removed. To the benzene solution was then added 0.5 mole of ethyl iodide and the refluxing and stirring continued for fifteen minutes. The solution, after removal of the silver iodide by suction filtration, was subjected to distillation under reduced pressure. Ethyl enol ether of dihydroresorcinol (36 g. 51%) distilled at 95–105° (1 mm.). In this preparation it was found that the yield of the ethyl enol ether was not favored by any excess of ethyl iodide while the yield was adversely affected by longer refluxing periods of ethyl iodide with the silver salt of dihydroresorcinol in benzene.

Preparation of 3-Phenyl-Δ^2-cyclohexenone (III) from Dihydroresorcinol Ethyl Ether.—Dihydroresorcinol ethyl ether (70.0 g.) dissolved in 300 ml. of ether was added slowly with stirring to a solution (600 ml.) of phenylmagnesium bromide prepared from bromobenzene and magnesium (0.75 mole). The Grignard complex was decomposed with dilute sulfuric acid. This mixture was subjected to steam distillation until all the bromobenzene and most of the biphenyl had been removed. The residue in the steam pot was extracted with ether. The ether solution was washed with dilute sodium bicarbonate and water, decolorized with norite, and dried over magnesium sulfate. After removal of most of the ether by heating on a steam-bath, the residue was dissolved in petroleum ether (30–60°). This solution deposited white to pale yellow-colored crystals (71 g., 87%) which upon recrystallization melted at 64.5–66° and which gave no depression in a mixed melting point determination with the previously obtained samples of this compound.

The remainder of this product was prepared in the usual manner and recrystallized from alcohol–water. The melting point of the product so obtained was 102–111° and only upon repeated recrystallizations from both alcohol–water and ether–petroleum ether was a product melting at 113.5–118° obtained. Abdullaho[6] reported a melting point of 117–118° for this substance. *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.98; H, 7.00. Found: C, 76.95, 77.25; H, 6.59, 6.58.

The red 2,4-dinitrophenylhydrazone of 3-phenyl-Δ^2-cyclohexenone prepared in the usual manner melted at 228–230°. *Anal.* Calcd. for $C_{18}H_{16}O_4N_4$: C, 61.36; H, 4.58. Found: C, 61.21, 61.60; H, 4.17, 4.22.

The semicarbazone of 3-phenyl-Δ^2-cyclohexenone which was prepared in the usual manner and recrystallized from alcohol melted at 227–229° with decomposition. *Anal.* Calcd. for $C_{13}H_{15}ON_3$: C, 68.10; H, 6.59. Found: C, 67.89; H, 6.23.

The *p*-nitrophenylhydrazone of 3-phenyl-Δ^2-cyclohexenone prepared in the usual manner melted at 182.5–185°. *Anal.* Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.35; H, 5.71. Found: C, 70.16, H, 5.67. Abdullaho[6] reported a melting point of 184–185° for this substance.

Reduction of 3-phenyl-Δ^2-cyclohexenone (3.0 g.) was accomplished in ethyl alcohol at atmospheric pressure and room temperature with palladium–charcoal. The hydrogenation was arrested after a 5% excess of hydrogen calculated for saturation of one ethylenic link had been adsorbed. After removal of the catalyst one half of the solution was used for the preparation in the usual manner of the semicarbazone of 3-phenylcyclohexanone which melted at 163.5–164.5° after recrystallization from alcohol–water.[12] *Anal.* Calcd. for $C_{13}H_{17}ON_3$: C, 67.51; H, 7.41. Found: C, 67.35; H, 7.03. The remaining half of the above solution was used to prepare the 2,4-dinitrophenylhydrazone of 3-phenylcyclohexanone, which was yellow and which melted at 183–186°. *Anal.* Calcd. for $C_{18}H_{18}O_4H_4$: C, 61.01; H, 5.12. Found: C, 61.14, 61.20; H, 5.18, 5.51.

(12) A melting point of 167° has been reported for this substance (Boyd, Clifford and Probert, *J. Chem. Soc.*, **117**, 1383 (1920)).

Preparation of 3-Phenylphenol from 3-Phenol-Δ^2-cyclohexenone.—The procedure for dehydrogenation and isolation of the phenol is essentially that of Horning.[7] 3-Phenyl-Δ^2-cyclohexenone (2.0 g.), palladium–charcoal catalyst[13] (0.7 g. 5% Pd), and 15 ml. of cymene were heated under reflux for approximately ninety minutes. This solution upon cooling was filtered and the filtrate extracted three times with Claisen solution (30 ml.). The Claisen solution was extracted once with benzene and then with petroleum ether (30–60°). The alkaline solution was then diluted with an equal volume of water and acidified with concentrated hydrochloric acid. The solid phenol was extracted with ether and the extract dried over magnesium sulfate. Upon evaporation of most of the ether and addition of petroleum–ether (30–60°), 1.25 g. of 3-phenylphenol crystallized on standing. This product after recrystallization from water was a white solid melting at 73.5–74.5°.[14] *Anal.* Calcd. for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.95, 84.71; H, 6.00, 6.00.

The phenylurethan of 3-phenylphenol was prepared in the usual manner and recrystallized from petroleum ether (90–100°) to which benzene was added to effect solution. The white crystalline product melted at 135–135.5°. *Anal.* Calcd. for $C_{19}H_{15}O_2N$: C, 78.87; H, 5.23. Found: C, 79.19; H, 5.54.

Preparation of 1,3-Diphenylcyclohexadiene-1,3 (IV).—To a solution of phenylmagnesium bromide prepared from 18.3 g. of bromobenzene and 2.8 g. of magnesium in 100 ml. of ether was added 10 g. of 3-phenyl-Δ^2-cyclohexenone dissolved in 100 ml. of ether. After addition of the ketone the reaction mixture was refluxed for thirty minutes, cooled in an ice-bath, and decomposed with cold 6% sulfuric acid. The ether extract was washed with aqueous sodium carbonate and with water and finally dried over anhydrous magnesium sulfate. On evaporation of the ether, 14 g. of solid residue was obtained which corresponds to a theoretical yield of 1,3-diphenylcyclohexadiene-1,3. This material, recrystallized from 95% ethanol, gave 9 g. of product (67%) melting at 96–98°. Recrystallization of this material from ethanol and decolorization with charcoal yielded colorless plates melting at 98–99°. *Anal.* Calcd. for $C_{18}H_{16}$: C, 93.10; H, 6.94. Found: C, 93.14, 92.97; H, 6.65, 6.62.

Maleic Anhydride Adduct of 1,3-Diphenylcyclohexadiene-1,3 (IX).—Maleic anhydride (1.1 g.) and 1,3-diphenylcyclohexadiene-1,3 (2.5 g.) were heated for four hours at 130–150°. The product on cooling was pulverized and warmed with 300 ml. of 10% sodium hydroxide solution. The small residue which remained undissolved was removed by filtration. The alkaline filtrate was acidified to congo red with hydrochloric acid. The precipitate was removed after cooling by filtration and redissolved in acetone and decolorized with Norite. The product (2.0 g.) crystallized upon cooling after the addition of water to the acetone solution, m. p. 149–151.5°. *Anal.* Calcd. for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 80.17, 80.22; H, 5.70, 5.60.

Preparation of *m*-Diphenylbenzene from 1,3-Diphenylhexadiene-1,3.—1,3-Diphenylcyclohexadiene-1,3 (2.0 g.) in 15 ml. of cymene was heated under reflux in the presence of 0.7 g. of 5% palladized charcoal for three hours, following which time most of the cymene was removed by distillation. The final portion of cymene was removed by using low pressure distillation. The residue was dissolved in hot ethyl alcohol and the catalyst removed by filtration. On cooling, the filtrate deposited *m*-terphenyl (1.3 g.) which was isolated by filtration, m. p. 86.5–86.8°. This product gave no depression with an authentic sample kindly furnished us by Dr. C. F. H. Allen. *Anal.* Calcd. for $C_{18}H_{14}$: C, 93.88; H, 6.12. Found: C, 94.02; H, 6.25.

Summary

1. The reaction of dihydroresorcinol with

(13) "Organic Syntheses," Vol. 26, 1946, p. 77.

(14) Jacobsen and Loch (*Ber.*, **36**, 4085 (1903)) reported 78°, and Errera and La Spada (*Gazz. chim. ital.*, **35**, II, 552) reported 75° for the melting point of this substance.

phenylmagnesium bromide has been shown to yield 3-phenylcyclohexan-3-ol-1-one, 3-phenyl-Δ^2-cyclohexenone and 1,3-diphenylcyclohexadiene-1,3. A mechanism by which the latter substance could be formed is discussed.

2. The syntheses of 3-phenyl-Δ^2-cyclohexenone from the ethyl enol ether of dihydroresorcinol and of 1,3-diphenylcyclohexadiene-1,3 from 3-phenyl-Δ^2-cyclohexenone, are reported.

3. 3-Phenylphenol and *m*-terphenyl are conveniently prepared by the catalytic dehydrogenation, using palladized charcoal, of 3-phenyl-Δ^2-cyclohexenone and 1,3-diphenylcyclohexadiene-1,3, respectively.

COLLEGE PARK, MARYLAND RECEIVED JANUARY 28, 1948

[CONTRIBUTION FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

The Partition of Acrylonitrile between Styrene and Water

BY WENDELL V. SMITH

A satisfactory discussion of the emulsion copolymerization of styrene and acrylonitrile requires a knowledge of the partition of the acrylonitrile between the water phase and the oil phase, since acrylonitrile is appreciably water soluble. Fordyce and Chapin[1] have compared the composition of the copolymer of styrene and acrylonitrile obtained in emulsion polymerization with that obtained in bulk polymerization and have found the emulsion copolymer to be consistently richer in styrene by a small amount than the bulk polymer produced from the same initial monomer composition. They have suggested that this difference may be due solely to the decrease in acrylonitrile content of the oil phase resulting from the water solubility of the acrylonitrile. The present investigation, which provides the data necessary to test this suggestion, has been carried out primarily to aid in discussing the emulsion copolymerization of these two monomers.

Under the conditions employed in emulsion polymerization, the ternary system, styrene–acrylonitrile–water, can be described sufficiently by specifying the compositions of two liquid phases, one of which may be called the aqueous phase, and the other the oil phase. A good approximation may be made by neglecting the solubility of styrene in the aqueous phase, also a fair approximation is obtained by neglecting the solubility of water in the oil phase (this is a good approximation when the oil phase is rich in styrene but becomes progressively less satisfactory as the acrylonitrile content of the oil phase increases).

Suppose that the system consists of

a volumes acrylonitrile
s volumes styrene
w volumes water

At equilibrium the oil phase will contain practically all the styrene and a_s volumes of acrylonitrile while the water phase will contain practically all the water and a_w volumes of acrylonitrile, where

$$a = a_s + a_w \qquad (1)$$

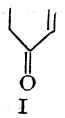
(1) Reid G. Fordyce and Earl C. Chapin, THIS JOURNAL, **69**, 581 (1947).

It is convenient to define a partition coefficient, α, by the relation

$$\alpha = \frac{a_s}{a_s + s} \cdot \frac{a_w + w}{a_w} \qquad (2)$$

Experimentally this partition coefficient may be determined by equilibrating a styrene–acrylonitrile solution of known composition with water and determining the resulting change in acrylonitrile content of the oil phase. If this change in acrylonitrile content is represented by

$$\Delta A = \frac{a}{a + s} - \frac{}{a_s}$$



I

and if the equilibrium acryloni oil phase is represented by

$$A_s = a_s/a_s + s$$

then equations 1 and 2 give

$$\alpha = A_s \left[1 + \left(\frac{w}{a + s}\right) \frac{(1 - A_s)}{\Delta A}\right] \qquad (3)$$

After having determined α it is then possible to reverse the calculation and obtain the equilibrium composition of any mixture of water and oil phase. This may be done by rearranging equation 3 to obtain the quadratic

$$A_s^2 - [R(\alpha - s/a + s) + 1]A_s + R\alpha a/a + s = 0 \qquad (4)$$

where $R = (a + s)/(a + s + w)$. The most convenient method of solving equation 4 for A_s is by successive approximation. Since the first term is small, a first approximation for A_s may be obtained by neglecting A_s^2 and estimating α from Fig. 1 and an estimated value of A_s. From this first approximation a new value of α may be obtained from Fig. 1 and the small correction due to the first term may be calculated. Then a second approximation for A_s may be calculated from equation 4. This may be continued to give any degree of approximation warranted by the experimental work.

One other problem which is treated in the experimental section is that of calculating the acrylonitrile content of a water solution by equilibrating the water solution with styrene and determining A_s, the equilibrium acrylonitrile content of the

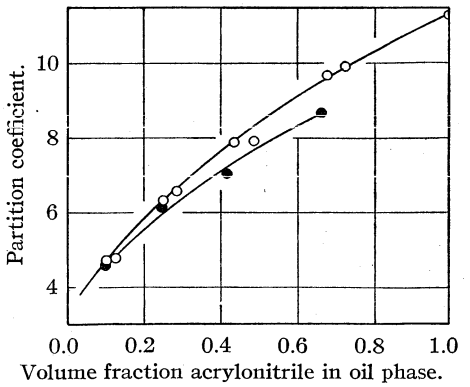


Fig. 1.—Partition coefficient of acrylonitrile between styrene–acrylonitrile solutions and water: 26°, ○; 60°, ●.

styrene solution. In this problem s, $a + w$ and A_s are measured, α is known from the relation between α and A_s, and it is desired to calculate $a/(a + w)$. This is done from equations 1 and 2 giving as a result

$$\frac{a}{a+w} = \left(\frac{s}{a+w}\right)\left(\frac{A_s}{1-A_s}\right)\left(1 - \frac{A_s}{\alpha}\right) + \frac{A_s}{\alpha} \quad (5)$$

Experimental

The compositions of all the styrene–acrylonitrile solutions used in the partition experiments were obtained from refractive index measurements. The relationship between refractive index and composition was established by making styrene–acrylonitrile solutions of known compositions, saturating them with water by adding a very slight excess of water and measuring the refractive indices with an Abbe refractometer. The results used to establish the relationship are given in Table I.

TABLE I

REFRACTIVE INDICES OF STYRENE–ACRYLONITRILE SOLUTIONS SATURATED WITH WATER

A_s	0.00	0.20	0.40	0.60	0.80	1.00
$n^{20}D$	1.5460	1.5167	1.4852	1.4536	1.4220	1.3912

The solutions were made from measured volumes of each ingredient and the above volume fractions of acrylonitrile, A_s, are based on the assumption that the volumes are additive.

The results indicate substantially a linear relationship between refractive index and volume fraction. All compositions were obtained by linear interpolation of the data in Table I.

The partition coefficients were determined by shaking styrene–acrylonitrile solutions with water and determining the refractive indices of the solutions at equilibrium. The initial compositions of the solutions and the initial volume of water and solutions were known. It was found that equilibrium was established rapidly (*i. e.*, in less than one-half hour at room temperature) as judged by constancy of the refractive index. The results are given in Table II.

The second column gives the ratio of the initial volume of aqueous to oil phase. The third and fourth columns give the volume fractions of acrylonitrile in the initial and equilibrated oil phases, respectively; they were obtained from the measured refractive indices and the data of Table I. The partition coefficients, α, in the last column were calculated from the other values using equation 3. The data obtained at 60° are considerably more uncertain than those at 26°. While the solutions and water were only allowed to remain at 60° for twenty minutes, there was evidence that polymer was present at the end. Also the boundaries in the refractometer were quite fuzzy on the samples which had been equilibrated with water at 60°; this was probably due to the formation of a cloudy suspension of water when the styrene solution was cooled down to 20° for making the refractive index measurement. Table II shows that the partition coefficient, α, is a function of the equilibrium acrylonitrile content.

TABLE II

PARTITION COEFFICIENTS OF ACRYLONITRILE BETWEEN STYRENE AND WATER

Temp., °C.	$\frac{w}{a+s}$	$\frac{a}{a+s}$	A_s	α
26	3	0.197	0.125	4.73
26	3	.379	.281	6.55
26	3	.586	.485	7.90
26	3	.788	.723	9.95
26	5	.200	.101	4.67
26	5	.400	.247	6.32
26	5	.600	.434	7.84
26	5	.800	.679	9.68
60	5	.200	.100	4.6
60	5	.400	.243	6.1
60	5	.600	.416	7.0
60	5	.800	.660	8.7

To extend the investigation to even higher acrylonitrile contents, the limiting value of the partition coefficient as the styrene approaches zero was determined from the water solubility of acrylonitrile. This was done first by making use of the above determined partition coefficients. Water was saturated with acrylonitrile by shaking with an excess and allowing it to stand in contact with the acrylonitrile overnight in a separatory funnel. The saturated water was then withdrawn and shaken with styrene, then the refractive index of the styrene layer determined. The results are given in Table III.

TABLE III

WATER SOLUBILITY OF ACRYLONITRILE FROM EQUILIBRIUM WITH STYRENE AT 25°

$\frac{w}{a+s}$	A_s	α	$\frac{a}{a+w}$
10	0.310	6.9	0.0878
5	.213	5.9	.0882

The water solubilities (volume fraction of acrylonitrile, $a/a + w$) given in the above table were calculated from equation 5, using values of α given by Fig. 1.

In order to verify this calculated water solubility and at the same time to get an independent check on our values for the partition coefficients, α, a direct determination of the solubility was made. It was found that 9.2 cc. of acrylonitrile in a total of 100 cc. of water solution gave a single homogeneous phase at 27°, while 9.4 cc. gave a very small amount of a second phase which would not dissolve. Thus, the direct determination gives the solubility as between 9.2 and 9.4%. This is in satisfactory agreement with the value calculated from the equilibration with styrene and thus serves as an independent check on the partition coefficients. Taking the water solubility to be 0.088 (volume fraction) the limiting "partition coefficient" for 0% styrene is 11.3; this neglects the effect of the solubility of water in the acrylonitrile which may give a 10% error in α.

As is to be expected, α varies with the composition of the equilibrium phases. In Fig. 1 α is plotted against the volume fraction of acrylonitrile in the hydrocarbon phase at equilibrium.

Discussion

The partition data given here make it possible to calculate the compositions of the oil phases used

by Fordyce and Chapin[1] in their study of the emulsion copolymerization of styrene and acrylonitrile. In their work the value of R was 0.367 and the temperatures were 60 and 75°. The results of this calculation are given in Table IV.

TABLE IV

ACRYLONITRILE CONTENTS OF THE OIL PHASES PRESENT DURING THE EMULSION COPOLYMERIZATION STUDIES OF FORDYCE AND CHAPIN[1]

Initial mole %	8.24	9.36	14.86	17.90	18.83	24.93
Equilibrium mole %	5.76	6.63	10.9	13.4	14.1	19.4
Initial mole %	32.92	36.32	45.68	66.25	94.64	
Equilibrium mole %	26.5	29.7	38.9	60.5	93.6	

The values given for the initial mole %'s in the table are the acrylonitrile contents of the oil phases before adding to the emulsion while the values for the equilibrium mole %'s are the acrylonitrile contents of the oil phases present in the emulsions during the polymerization. These latter values were calculated from the initial values using equation 4 and values of the partition coefficient, α, given by Fig. 1.

Having calculated the compositions of the oil phases actually present during the emulsion copolymerizations, it is now possible to compare the compositions of copolymers produced in emulsion with those produced in bulk from oil phases of identical composition. The data of Fordyce and Chapin[1] so treated are shown in Fig. 2. It is seen that this correction of the compositions of the emulsion oil phases makes the emulsion and bulk copolymerization composition curves identical within the accuracy of the data. Thus, the suggestion of Fordyce and Chapin that the consistent difference which they found was due to the water solubility of the acrylonitrile is substantiated by this investigation.

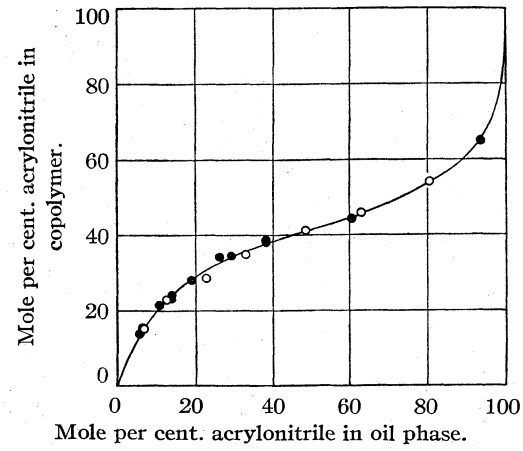


Fig. 2.—Monomer–polymer composition curve for styrene–acrylonitrile with correction for water solubility of the acrylonitrile: bulk polymerization, O; emulsion polymerization, ●.

Summary

The compositions of styrene–acrylonitrile solutions in equilibrium with water–acrylonitrile solutions have been determined. These equilibrium compositions have been used to calculate the acrylonitrile contents of the oil phases present in the emulsion copolymerization experiments of Fordyce and Chapin. It is shown that when this is done the above authors' emulsion data are identical with their bulk polymerization data in regard to composition of polymer produced from a given oil phase.

PASSAIC, NEW JERSEY RECEIVED JULY 12, 1947

[CONTRIBUTION FROM SCHOOL OF MINES AND METALLURGY, UNIVERSITY OF MISSOURI]

Some Equilibrium Relations in the System Magnesium Oxide–Sulfur Dioxide–Water (Acid Region) at Pressures below Atmospheric[1]

BY FRANK H. CONRAD AND DONAT B. BRICE

I. Introduction

This is a report of the study of the equilibrium $MgSO_3 \cdot 6H_2O$ + solution + vapor, in the system magnesium oxide–sulfur dioxide–water. It presents the pressure–composition relations at constant temperature (15 and 25°). The liquid phase of this system consists of a solution of the bisulfite of magnesium containing a small amount of the monosulfite. The vapor phase consists of SO_2 and water vapor.

These relations were desired because of the contemplated use of magnesia base cooking liquors in the "Sulfite Pulping Process" in place of calcium base liquor. Hatch[2] has pointed out that magnesia base liquor has the advantages: (a) the spent liquor may be used to recover both the magnesia and the sulfur dioxide; (b) heat is supplied to the process from the burning of the organic solids in the evaporated spent liquor; and perhaps most important; (c) the problem of disposing of the spent liquor is eliminated.

(1) This paper is based on a Dissertation presented by Donat B. Brice in May, 1947, to the Faculty of the Graduate School of the School of Mines and Metallurgy, University of Missouri, Rolla, Missouri, in candidacy for the degree of Master of Science in Chemical Engineering.

(2) R. S. Hatch, *Paper Trade J.*, **122**, No. 11, 54–56 (March 14, 1946).

II. The Experimental Part

The materials used were "C. P. Analyzed" magnesium oxide containing negligible quantities of sulfate and calcium. The sulfur dioxide and water were treated as described by Conrad and Beuschlein.[3]

The apparatus used in determining the equilibrium pressures was almost identical to that described in "reference 3." The materials for making the equilibrium mixture were prepared in the same manner with the exception of the magnesium oxide.

After equilibrium was obtained, as shown by constant pressure readings, the solid was allowed to settle and a portion of the saturated solution was withdrawn to a weighing pipet. The solution (9 to 12 g.) was drained and washed into a volumetric flask nearly full of water. The tip of the pipet was kept below the surface of the water to prevent the loss of sulfur dioxide. The flask was then filled to volume and the aliquots were withdrawn in a manner similar to the removal of water from a wash bottle. This method was used to avoid the loss of any sulfur dioxide.

Aliquots were analyzed for the total and combined sulfur dioxide by the Hohn method the essentials of which are given by Birchard.[4] The free sulfur dioxide is obtained by subtracting the combined sulfur dioxide from the total sulfur dioxide. The free sulfur dioxide is the actual free sulfur dioxide plus half of the sulfur dioxide in the bisulfite of magnesium, and is more properly called the "available sulfur dioxide" as it indicates the sulfur dioxide in excess of that required to form the monosulfite. The combined sulfur dioxide represents that required to form the monosulfite. These definitions are as set forth by the Technical Association of Pulp and Paper Institute.[5] The standard solutions used in these analyses were sodium thiosulfate and iodine of approximately 0.1 *N* and sodium hydroxide approximately 0.2 *N*. Standardizations of the iodine and thiosulfate were made by the appropriate use of sodium oxalate and potassium permanganate. Since these solutions were standardized frequently the potassium permanganate was used. The sodium hydroxide was standardized against potassium acid phthalate.

The equations for the chemical reactions during analysis and for calculation of the combined sulfur dioxide are similar to those of "reference 3," only replacing the calcium atom by magnesium.

Before making any tests on the ternary system and in order to test the reliability of the results with the particular apparatus used in these experiments, the vapor pressure of water was determined at two temperatures. The vapor pressures obtained agreed with values read from the "International Critical Tables"[6] within 0.5 mm. pressure in all cases. As a further check on both the accuracy of the pressure readings and the analytical reagents used in analysis, the solubility of sulfur dioxide in water at 25° was determined at various pressures. The equilibrium flask was charged with water and sulfur dioxide, agitated at constant temperature in a thermostat, connected to the manometer and pressure readings obtained. It was noted that after two or three minutes the pressure remained constant although tests were allowed to stand for one and one-half hours to ensure that equilibrium had been attained. These data were in good agreement with those given in the "International Critical Tables,"[7] as well as the data of reference 3. The maximum deviation of any one point was 0.1 g. of sulfur dioxide per 100 g. of water. It was concluded from these preliminary tests that the apparatus and method would give results which were sufficiently accurate for the ternary system.

(3) F. H. Conrad and W. L. Beuschlein, THIS JOURNAL, **56**, 2554 (1934).

(4) W. H. Birchard, *Paper Industry*, **8**, 793 (1926).

(5) T. A. P. P. I. Standards, "Analysis of Bisulfite Cooking Liquor," T 604 m-45, corrected, Sept., 1945.

(6) "International Critical Tables," Vol. III, McGraw-Hill Book Company, New York, N. Y., 1928, p. 212.

(7) *Ibid.*, Vol. III, p. 302.

III. Experimental Results

Results of analysis of the liquid phase at 25 and at 15° are given in tabular form in Tables I and II, respectively, and are shown in graphical form in Figs. 1 and 2.

TABLE I

ANALYSIS OF THE LIQUID PHASE OF THE SYSTEM MAGNESIUM OXIDE–SULFUR DIOXIDE–WATER EQUILIBRIUM AT 25°

Expt.	Total pressure, mm.	Grams per 100 grams of water: Total SO_2	Free SO_2	Combined SO_2
1	130.2	28.2	14.0	14.2
2	154.4	28.0	13.15	14.85
3	213.2	35.6	17.4	18.2
4	264.3	35.2	17.3	17.9
5	288.0	37.5	18.75	18.75
6	326.5	40.7	20.35	20.35
7	410.9	42.1	20.8	21.3
8	560.7	50.3	24.9	25.4
9	638.4	51.6	25.3	26.3
10	726.8	50.7	24.85	25.85
11	728.4	52.0	25.8	26.2
A[a]	728.7	50.1	24.4	25.7

[a] Experiment A made at 35°.

TABLE II

ANALYSIS OF THE LIQUID PHASE OF THE SYSTEM MAGNESIUM OXIDE–SULFUR DIOXIDE–WATER EQUILIBRIUM AT 15°

Total pressure, mm.	Grams per 100 grams of water: Total SO_2	Free SO_2	Combined SO_2
75.5	30.4	14.7	15.7
87.5	28.05	13.3	14.75
110.7	29.65	14.6	15.05
156.8	32.9	16.0	16.9
162.3	31.4	14.85	16.55
245.5	39.9	18.9	21.0
419.3	46.9	23.35	23.55
448.7	44.8	22.4	22.4
726.8	54.6	26.8	27.8
730.3	53.3	26.55	26.75

It was possible to remove only one sample of clear saturated liquid without disturbing the equilibrium in the flask. Duplicate analytical determinations made on some samples checked to within 0.6 g. of sulfur dioxide per 100 g. of water.

Saturation of the liquid phase, with respect to both gas and solid, was approached from both the supersaturated and the unsaturated conditions. In all experiments at 25° except those at atmospheric pressure the temperature at which the gas was admitted was three to five degrees below the final equilibrium temperature. Also, in order to remove any insoluble gaseous impurities admitted with the sulfur dioxide, solutions were boiled at reduced pressures. As sulfur dioxide is more soluble at low temperatures and high pressures, these experiments were approached from supersaturation with respect to the gas.

Equilibrium at 15° was approached from the unsaturated state with respect to both gas and

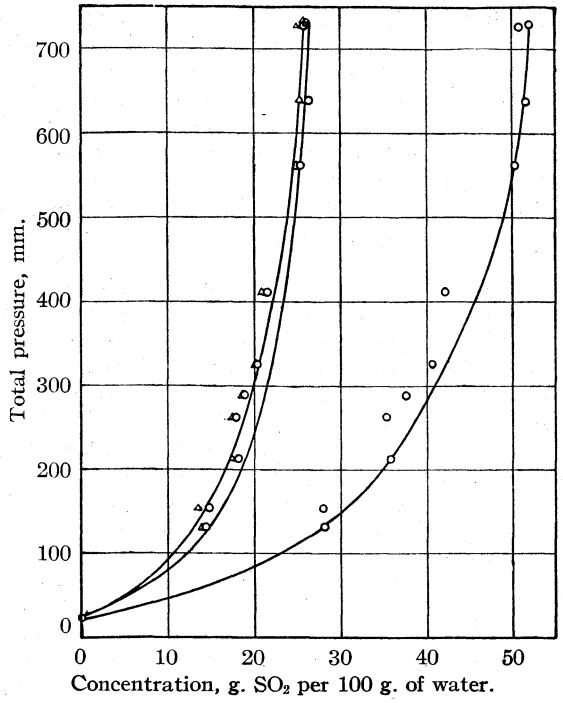


Fig. 1.—Pressure–concentration curves for liquid phase of system $MgO–SO_2–H_2O$; temperature, 25°.

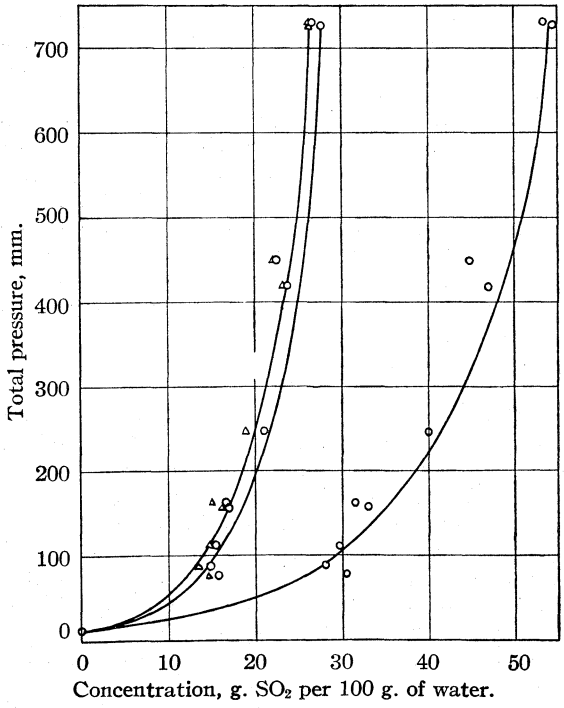


Fig. 2.—Pressure–concentration curves for liquid phase of system $MgO–SO_2–H_2O$; temperature 15°.

solid. The temperature at which the gas was admitted was five to eight degrees higher than the equilibrium temperature. The pressure was greater when the flask was placed in the thermostat than at final equilibrium. Thus these experiments were approached from the unsaturated side with respect to the gas.

In experiments 4 and 6 of Table I sulfur dioxide was added until all the solid phase was dissolved. After the solid was dissolved the solution was subjected to vacuum until solid phase reappeared. When the solid was again present the flask was placed in the thermostat and treated in the same manner as other experiments. Experiments 4 and 6 of Table I thus were approached from the supersaturated condition with respect to both gas and solid.

The curves of Figs. 1 and 2 have been constructed from data obtained. The correlation of these data by smooth curves is good.

In order to show the effect of temperature upon the concentration of sulfur dioxide, experiment "A" (Table I) was made at 35° and atmospheric pressure (in this case 728 mm.). The results of this experiment and the corresponding values at the same pressure (the 15° run was at 727 mm.), read from the curves in Figs. 1 and 2 are plotted in Fig. 3. The temperature concentration relations for the system calcium oxide–sulfur dioxide–water from "reference 3" are also plotted for comparison. It should be noted that the amount of sulfur dioxide in a solution is much greater for the magnesia system than for the calcium system at the same pressure. In the magnesia system the amount of combined sulfur dioxide was always greater than the free, in contrast to that for the calcium oxide system where it was much less. The amounts of combined and free were very nearly equal, the combined being always greater,

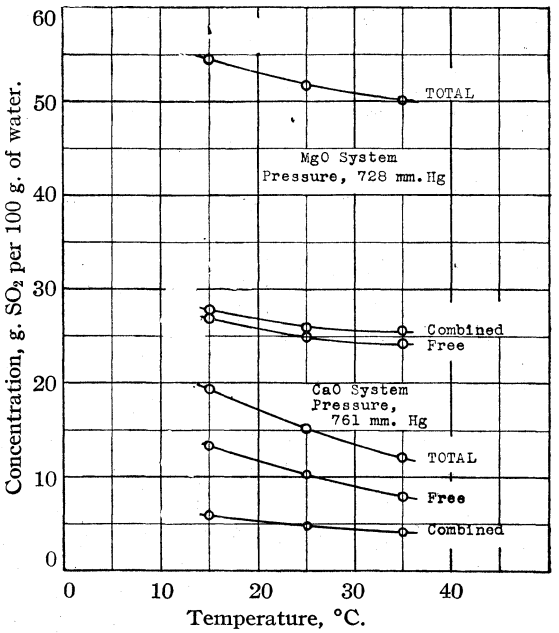


Fig. 3.—Temperature–concentration curves for liquid phase of the systems $MgO–SO_2–H_2O$ and $CaO–SO_2–H_2O$ at atmospheric pressure.

representing slightly more than 0.5 of the total. The combined was never more than 0.52 of the total.

IV. Analysis of the Solid Phase

Samples of the solid, assumed to be $MgSO_3 \cdot 6H_2O$, were removed from the equilibrium flask and analyzed. Samples for experiments 1, 2 and 3, Table III, were drained with suction and then dried to constant weight over 67% sulfuric acid in an atmosphere of carbon dioxide. Hartog[8] reports that crystals of $MgSO_3 \cdot 6H_2O$ are deposited when a solution of $Mg(HSO_3)_2$ is concentrated *in vacuo* at temperatures below 100° and then cooled. The magnesium oxide was determined by the pyrophosphate method and the sulfur dioxide by the Hohn method as previously referred to in the analysis of the liquid.

The mole ratio magnesium oxide to sulfur dioxide indicated a compound containing one mole of magnesium oxide to one of sulfur dioxide, but the amount of magnesium oxide was somewhat high in samples 1 and 2. It was thought that possibly oxidation was taking place in spite of all precautions. It was therefore decided, as other solid samples were removed from the equilibrium flask, to wash them with distilled water until free of solution and analyze a portion immediately for sulfur dioxide and magnesium oxide. Another portion of these same samples was dried as described and analyzed for the magnesium oxide content. It is thus possible to calculate from the weight of the dried sample and the magnesium oxide–sulfur dioxide ratio of the same sample, the amount of magnesium sulfite it would contain and to obtain the hydrate water by difference. Results of these analyses and calculations are shown for samples 5 to 8 (Table III).

TABLE III

COMPOSITION OF THE SOLID PHASE FOR THE SYSTEM MAGNESIUM OXIDE–SULFUR DIOXIDE–WATER

Expt.	MgO, g.	SO_2, g.	Mole ratio MgO/SO_2	Moles water / Mole $MgSO_3$
1	0.1081	0.143	1.20	..
2	.1031	.135	1.21	..
3[a]	.0860	.128	1.06	..
4[a]	.0730	.1043	1.11	..
5	.0290	.0395	1.17	6.22
6[a]	.1086	.0294	1.002	5.77
7	.0522	.0615	1.35	6.35
8[a]	.0280	.0416	1.07	5.68
9[a]	.0362	.054	1.06	..
$MgSO_3 \cdot 6H_2O$	40.32	64.06	1.000	6.00

[a] Equilibrium approached from supersaturation.

Samples of solids were obtained from solutions in which the equilibrium had been approached from both the unsaturated and the supersaturated conditions as in the liquid phase investigation. The time allowed for equilibrium to be reached in the preparation of the solid samples was identical with that used in the liquid phase work. Also constancy of pressure readings was likewise used as a criterion of equilibrium, and hence the tests should be comparable with those for the liquid phase. Examination of the results in Table III shows that solids obtained from experiments approached from the supersaturated side have close to the theoretical ratio of one to one for magnesium oxide to sulfur dioxide. The fact that this ratio is slightly greater than one may indicate a small amount of oxidation even though the samples were analyzed for sulfur dioxide without drying. Those approached from the unsaturated side deviated considerably more and the ratio varied from one run to another. It is the opinion of the authors that although equilibrium in the liquid phase was established, such that pressure–concentration curves could be constructed, there was actually some magnesium oxide occluded by the magnesium monosulfite in the solids prepared from the unsaturated side.

Sulfur dioxide was permitted to react with a suspension of magnesium oxide in water, which amounted to having a particle of magnesium oxide as the core with magnesium hydroxide covering the oxide. The sulfur dioxide reacted with the hydroxide and formed a coating of magnesium monosulfite hexahydrate around the magnesium oxide. These particles then after long standing were in equilibrium with the solution of bisulfite of magnesium. Thus, even if occluded magnesium oxide were present it would have little effect upon the liquid phase investigation.

It is realized that the removal of the solid phase from equilibrium with the liquid and gaseous phases may in some cases change the composition of the solid. Attempts were made to obtain data satisfactory for the construction of a modified Schreinemakers diagram as used by Conrad and Beuschlein[3] but the intersections were at such acute angles and so erratic as to make the method of little value.

Summary

1. The total pressure–composition relationships have been determined for the system magnesium oxide–sulfur dioxide–water in the acid region up to atmospheric pressure at 15 and 25°.

2. The total, free and combined sulfur dioxide has been determined for saturated solutions in equilibrium with solid magnesium monosulfite hexahydrate at total pressures of sulfur dioxide and water vapor from the vapor pressure of water to atmospheric pressure for the temperatures 15 and 25°.

3. The temperature–composition relationship has been determined for the total pressure of 728 mm. at temperatures of 15, 25 and 35°.

4. The analysis of the solid removed from the equilibrium is in agreement with the assumed formula of $MgSO_3 \cdot 6H_2O$.

(8) Hartog, *Compt. rend.*, **104**, 1793 (1887).

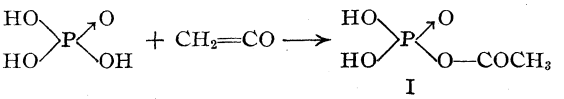
ROLLA, MISSOURI RECEIVED AUGUST 4, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

A New Synthesis of Acetyl Dihydrogen Phosphate[1]

BY RONALD BENTLEY[2]

Acetyl dihydrogen phosphate (I) was first synthesized by Lynen[3] who used the catalytic debenzylation of acetyl dibenzyl phosphate. Later, Lipmann and Tuttle[4] described its preparation from silver dihydrogen phosphate and acetyl chloride; in each case the acetyl dihydrogen phosphate was characterized as its sparingly water soluble disilver salt. It has now been found that it may be conveniently and rapidly prepared by acetylating phosphoric acid with ketene, thus confirming the previous observation of Hurd and Dull[5] that "ketene was quantitatively absorbed by phosphoric acid, presumably with the formation of acetylphosphoric acid."

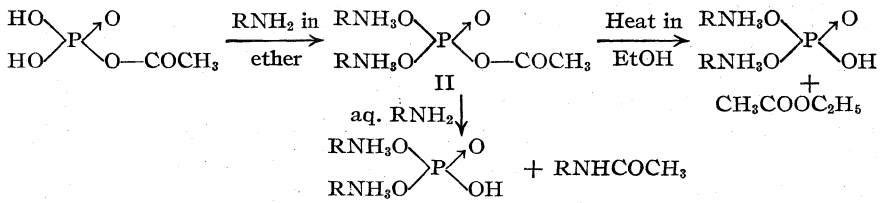


I

Solutions of the free acetyl dihydrogen phosphate were obtained by reaction of the disilver salt with hydrogen sulfide in aqueous suspension or by reaction with ethereal hydrogen chloride. The aqueous solution of the free acid was stable for some hours at 0°; on neutralization with barium hydroxide and addition of silver nitrate, the disilver salt was recovered.

Acetyl dihydrogen phosphate has been widely considered as a possible acetylating agent and also as a phosphorylating agent in physiological systems.[6] It was therefore of interest to study its reactions with various compounds. Aqueous solutions of the sodium salt were found to acetylate ammonia and aniline, but only with low yields. In neutral aqueous solutions no acetylation of γ-phenylaminobutyric acid, choline chloride, guanidine or hydroquinone was observed.

When ethereal acetyl dihydrogen phosphate was treated with aniline, bis-phenylammonium acetyl phosphate (II, R = C_6H_5) precipitated and evaporation of the ethereal mother liquor gave a small amount of acetanilide. Subsequent reaction of the bis-phenylammonium salt with aqueous aniline gave bis-phenylammonium phosphate and acetanilide. Analogous reactions were observed with ammonia.



II

Dibenzyl hydrogen phosphate reacted smoothly with ketene to yield the mixed anhydride, acetyl dibenzyl phosphate, which was converted to acetyl dihydrogen phosphate using Lynen's method. Acetyl dibenzyl phosphate could also be used as an acetylating agent. With aniline in the absence of solvent there was a vigorous reaction; acetanilide and dibenzyl hydrogen phosphate were obtained. Choline chloride dissolved in glacial acetic acid was also acetylated, in the cold, on addition of acetyl dibenzyl phosphate.

Experimental[7]

Preparation of Disilver Acetyl Phosphate.—In a typical run, sirupy phosphoric acid (85%, 10 ml.) dissolved in dry ether (150 ml.) was treated with a ketene stream for thirty minutes with ice cooling. (A ketene lamp similar to that described by Williams and Hurd[8] was used, which produced about 10 g. of ketene in that time. Ten ml. of 85% phosphoric acid required about 12.5 g. of ketene for reaction with the water and phosphoric acid present.) The ketene was led in through a sintered glass bubbler, with vigorous stirring to avoid high local concentrations. The ether solution was extracted with ice water (3 × 50 ml.; all apparatus used was previously chilled in ice) and the aqueous extract rapidly neutralized (*p*H 7.0) by dropwise addition of saturated barium hydroxide solution, with ice cooling and vigorous stirring. The precipitated barium phosphate was centrifuged off and the solution of barium acetyl phosphate was treated with excess of ice cold 10% silver nitrate solution. The pale creamy precipitate was washed with ice-water, alcohol and ether (16.7 g.). Dilution of the mother liquor with one-third volume of ethanol gave a second crop of crystals (5.0 g.).

For recrystallization the disilver salt (7.2 g.) was ground to a smooth paste with ice water, shaken with ice cold 0.25 *M* sodium chloride (150 ml.—a slight deficiency) and allowed to stand for fifteen minutes. The solution was filtered, and treated with 25% silver nitrate (3 ml.). This first precipitate was rejected, and excess 25% silver nitrate was then added. Disilver acetyl phosphate (5.5 g.) formed white prisms, not having a definite m. p.

Anal. Calcd. for $C_2H_3O_5PAg_2$: Ag, 60.9; P, 8.75. Found: Ag, 60.25; P, 8.7.

Acetyl determinations were performed by repeated steam distillation of 15 mg. samples with water (10 ml.) and concentrated sulfuric acid (2 ml.) in a Kjeldahl type apparatus: 35-ml. portions of distillate were collected until a constant blank titration was obtained. *Anal.*

(1) Presented before the Division of Biological Chemistry at the Atlantic City Meeting of the American Chemical Society, April 15, 1947.

(2) Commonwealth Fund Fellow. Present address: National Institute for Medical Research, Hampstead, London.

(3) F. Lynen *Ber.*, **73B**, 367 (1940).

(4) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1944).

(5) C. D. Hurd and M. F. Dull, THIS JOURNAL, **54**, 3427 (1932).

(6) F. Lipmann, *Advances in Enzymol.*, **6**, 242, 257 (1946).

(7) All melting points are uncorrected.

(8) J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

Calcd. for $C_2H_3O_5PAg_2$: CH_3CO, 12.2. Found: CH_3CO, 12.7. The acidity produced on warming 40–50 mg. samples with water at 70–75° for two hours was determined by titration of the filtered solution with 0.01 *N* potassium hydroxide.

$$3C_2H_3O_5PAg_2 + 5OH^- = 2Ag_3PO_4 + HPO_4^= + 3CH_3COO^- + 2H_2O$$

Calculated per cent. purity, 101.3.

Preparation of Acetyl Dihydrogen Phosphate.—(1) Aqueous solution: Disilver acetyl phosphate (1.5 g.) suspended in ice water, was treated with excess hydrogen sulfide, silver sulfide filtered off, and the filtrate freed from hydrogen sulfide by aeration at 0°. The filtrate was made up to 70 ml.: 40 ml. was immediately neutralized with barium hydroxide solution at 0°, and reprecipitated with silver nitrate (recovery, 0.7 g.). The remaining solution was kept for ninety minutes at 0°, and treated in the same way (recovery, 0.4 g.). The precipitates were recrystallized and the per cent. purity determined by hydrolysis with water as previously described: first precipitate, 104.0%; second precipitate, 100.3%.

(2) Ethereal solution: Finely powdered disilver acetyl phosphate (2.0 g.) was suspended in absolute ether (25 ml.), cooled in ice and ethereal hydrogen chloride (1.33 *N*, 8.0 ml.) added dropwise with vigorous stirring. Stirring was continued for a further ten minutes, the mixture filtered, and the silver chloride washed with a little absolute ether to yield an ethereal solution of acetyl dihydrogen phosphate.

Reaction with Aniline in Aqueous Solution.—Disilver acetyl phosphate (2.0 g.) was converted to sodium salt using 0.25 *M* sodium chloride (45 ml.). The filtered solution was treated with aniline (1.2 ml., a large excess) and acetone (5 ml.) to homogenize the solution. The solution, initially at 0°, was brought to room temperature after two hours, and allowed to stand overnight. Hydrochloric acid (1.068 *N*, 18.0 ml.) was added (*p*H 3.0), and the solution extracted with ether: the dried extract was evaporated to yield white, lath-like crystals, m. p. 114–115° (109 mg., 14% yield); no m. p. depression in admixture with authentic acetanilide.

Reaction with Aniline in Ethereal Solution.—An ethereal solution of acetyl dihydrogen phosphate (from silver salt 2.0 g.) was cooled to 0°, and treated with aniline (2.0 g.) in dry ether (15 ml.). A white precipitate of bis-phenylammonium acetyl phosphate (II, R = C_6H_5) (1.7 g.), m. p. 104–105°, soluble in sodium bicarbonate solution with effervescence. (The ethereal mother liquor was extracted with 2 *N* hydrochloric acid to remove excess aniline and yielded a little acetanilide on evaporation.)

Anal. Calcd. for $C_{14}H_{19}O_5N_2P$: CH_3CO, 13.2. Found: CH_3CO, 13.1.

On attempted recrystallization from absolute ethanol, shining plates m. p. 174–175° were obtained (unchanged on recrystallization). With bis-phenylammonium phosphate there was no depression in m. p.

Bis-phenylammonium acetyl phosphate (320 mg.) was dissolved in ice-water and aniline (1.0 ml.) and acetone (3.0 ml.) added. The mixture was placed in an ice-bath, allowed to warm up to room temperature, and kept overnight. A white crystalline precipitate formed (170 mg.), m. p. 174–175°, recrystallizing from ethanol in plates; no depression in admixture with bis-phenylammonium phosphate. The mother liquor was made acid to congo red, extracted with ether, and the dried extract evaporated; the white solid was recrystallized from chloroform-petroleum ether to form white needles (66 mg., including a second crop), m. p. 111–112°. No m. p. depression in admixture with acetanilide.

Bis-phenylammonium acetyl phosphate (200 mg.) was treated with 2 *N* ammonia (5 ml.), when an oil separated; the mixture was allowed to stand overnight, extracted with ether, and the aqueous solution evaporated to dryness *in vacuo*. The solid residue was extracted with warm chloroform, filtered, and the filtrate diluted with petroleum ether (b. p. 30–60°). White crystals separated, m. p. 81°, no depression in admixture with acetamide.

Reaction with Ammonia in Ethereal Solution.—Disilver acetyl phosphate (1 g.) was converted to the free acid in ether. The solution at 0° was treated with an excess of dry ethereal ammonia when diammonium acetyl phosphate crystallized in white plates m. p. 128–130°. It did not analyze too well.

Anal. Calcd. for $C_2H_{11}O_5N_2P$: N, 16.1; CH_3CO, 24.5. Found: N, 17.1; CH_3CO, 23.0.

The solid was allowed to stand overnight in a little aqueous ammonia, and evaporated to dryness *in vacuo:* the crystalline solid was extracted with warm ethanol, the extract being evaporated. The residue was twice recrystallized from chloroform–petroleum ether (b. p. 30–60°), to form white crystals, m. p. 82°, showing no depression with an authentic sample of acetamide.

Preparation of Acetyl Dibenzyl Phosphate.—Dibenzyl hydrogen phosphate was prepared substantially as described by Lossen and Köhler[9]; it was found preferable, however, to saponify the tribenzyl phosphate by refluxing for some hours with 10% alcoholic potassium hydroxide. Evaporation of solvent, solution of the residue in water, acidification and recrystallization from chloroform-petroleum ether gave dibenzyl hydrogen phosphate, m. p. 79.5°.

Dibenzyl hydrogen phosphate (1.0 g.) was dissolved in absolute ether containing a little chloroform, and treated with a ketene stream (about 0.5 g., an excess) at ice temperature. Solvent was removed *in vacuo* (bath temperature, 25°) to yield acetyl dibenzyl phosphate as a viscous, neutral oil, in almost the theoretical yield.

Anal. Calcd. for $C_{16}H_{17}O_5P$: CH_3CO, 13.4. Found: CH_3CO, 13.3.

The oil was dissolved in dry ether (50 ml.), palladium charcoal (500 mg.) was added and the solution hydrogenated with dry hydrogen, about 200 ml. being taken up at S. T. P. After filtration, the ether was extracted with water (2 × 15 ml.) and the solution neutralized with barium hydroxide solution at 0°. Precipitated barium phosphate was filtered off, and silver nitrate solution added. Disilver acetyl phosphate was precipitated (300 mg.); per cent. purity as determined by titration of acid produced on hydrolysis, 95.9.

Reaction of Acetyl Dibenzyl Phosphate and Aniline.—A portion of acetyl dibenzyl phosphate was treated with a slight excess of aniline, the mixture warming up considerably. After reaction, chloroform was added, and excess aniline extracted with 2 *N* hydrochloric acid. The chloroform was next extracted with saturated sodium bicarbonate solution; acidification of this extract gave a white solid, which recrystallized from chloroform–petroleum ether to form plates, m. p. 80°; no m. p. depression admixed with dibenzyl hydrogen phosphate. The chloroform solution was washed with water, dried and evaporated *in vacuo:* the residue quickly crystallized, and was recrystallized from chloroform–petroleum ether, forming white needles, m. p. 115°; mixed m. p. with acetanilide, 115°.

Reaction of Acetyl Dibenzyl Phosphate and Choline.—Dibenzyl hydrogen phosphate (1.0 g.) was converted to its acetyl derivative, the oil being held in vacuum for some time to remove any traces of ketene. Choline chloride (500 mg.) was added, and glacial acetic acid (1 ml.) to form a clear solution. After forty-eight hours, the acetic acid was evaporated *in vacuo*, the residue treated with 2 *N* hydrochloric acid (5 ml.) and an insoluble oil, extracted with ether. The filtered aqueous solution was treated with a slight excess of auric chloride solution; the yellow precipitate (0.762 g.) had m. p. 163–164°, unchanged on recrystallization from hot water. (Literature m. p. of acetylcholine aurichloride is 166°; no depression in admixture with an authentic sample.)

Summary

1. Acetyl dihydrogen phosphate may be con-

(9) W. Lossen and A. Köhler, *Ann.*, **262**, 211 (1891).

veniently prepared by the acetylation of phosphoric acid with ketene in ethereal solution, and is recovered as disilver acetyl phosphate. Similar acetylation of dibenzyl hydrogen phosphate yields acetyl dibenzyl phosphate.

2. Acetyl dihydrogen phosphate will acetylate ammonia and aniline under various conditions. No evidence of phosphorylating reactions could be obtained.

NEW YORK, N. Y. RECEIVED JANUARY 13, 1948

[CONTRIBUTION NO. 239 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

The Structure of Neoprene. I. The Molecular Weight Distribution of Neoprene Type GN

BY W. E. MOCHEL, J. B. NICHOLS AND C. J. MIGHTON

It has been recognized that synthetic high polymers in general are non-homogenous, particularly in respect to molecular weight. Therefore, the molecular weight of a particular polymer cannot be characterized accurately by a single value and there is required a knowledge of the distribution of molecular weights. Any single molecular weight value for a heterogeneous polymer must perforce be an average value and will differ appreciably with the method of averaging. Although it has been shown recently that the tensile strength of some polymers, *e. g.*, cellulose acetate, depends explicitly on the number average molecular weight regardless of the distribution of molecular weights,[1] other properties of high polymers such as plasticity,[2] are influenced markedly by the heterogeneity of molecular weights. The present investigation of the molecular weight distribution of neoprene (polychloroprene) is a part of an extensive study of the structures of these polymers.

There have appeared recently several new methods for determination of molecular weight distribution[3] but the standard method continues to be that of careful fractionation and examination of each fraction. This method also furnishes polymer samples of sufficient homogeneity that they can be used to calibrate the intrinsic viscosity–molecular weight relationship with an absolute method such as osmotic pressure. The two most common methods for fractionation of high polymers are: (1) precipitation by successive additions of a non-solvent to a solution of the polymer and (2) successive extractions of the polymer with solvent/non-solvent mixtures of increasing solvent concentration. It has been shown that neither method can give a really sharp separation of species[4] but the first method appears to be satisfactory for practical purposes if certain precautions are taken. Thus, it is advisable to use a reasonably dilute solution, precipitate at constant temperature and wash the precipitated fractions to remove low molecular weight material.

(1) A. M. Sookne and M. Harris, *Ind. Eng. Chem.*, **37**, 478 (1945); P. J. Flory, THIS JOURNAL, **67**, 2048 (1945); *Ind. Eng. Chem.*, **38**, 417 (1946).

(2) R. L. Zapp and F. P. Baldwin, *ibid.*, **38**, 948 (1946).

(3) D. R. Morey and J. W. Tamblyn, *J. Appl. Phys.*, **16**, 419 (1945); R. F. Boyer and R. D. Heidenreich, *ibid.*, **16**, 621 (1945); P. M. Doty, B. H. Zimm and H. Mark, *J. Chem. Phys.*, **13**, 159 (1945); L. H. Cragg and H. Hammerschlag, *Chem. Rev.*, **39**, 79 (1946); D. R. Morey and J. W. Tamblyn, *J. Phys. Colloid Chem.*, **51**, 721 (1947).

(4) G. Gee, *Trans. Faraday Soc.*, **38**, 276 (1942); P. J. Flory, *J. Chem. Phys.*, **12**, 425 (1944); R. L. Scott, *ibid.*, **13**, 178 (1945); D. R. Morey and J. W. Tamblyn, *J. Phys. Chem.*, **50**, 12 (1946).

Experimental

Materials.—A sample of standard, commercial Neoprene Type GN of plasticity classification[5] P3 and age two months was selected for fractionation. Neoprene Type GN is a polychloroprene polymerized in aqueous emulsion in the presence of sulfur and is stabilized with tetraethyl thiuram disulfide.[6] (Neoprene Type GN is identical with GR-M currently manufactured at Louisville by the Office of Rubber Reserve, Reconstruction Finance Corporation.) To obtain the pure polychloroprene, essentially free from soap residues, stabilizers and adjuvants used in the polymerization, 55 g. of the finely-cut neoprene was dissolved in 500 ml. of thiophene-free, dry benzene, and 500 ml. of C. P. methanol was added slowly with stirring, to precipitate the polymer. Further addition of methanol to the clear, supernatant liquid produced no cloudiness. The polymer was washed twice with 100-ml. portions of methanol and dried at room temperature under vacuum. The dry polymer weighed 50.5 g. In these operations and all subsequent handling, the polymer, its solutions and the fractions were kept under an atmosphere of nitrogen.

The benzene–methanol mixture left after precipitation of the polymer was combined with the methanol wash liquors and evaporated to dryness under vacuum. The residue, consisting of 4.6 g. of dark brown, very viscous oil, was not investigated further.

Fractionation.—The purified polychloroprene prepared as described above (50.5 g.) was dissolved in 5 l. of thiophene-free, dry benzene and to the solution was added 0.5 g. of phenyl-α-naphthylamine to inhibit degradation of the polymer. After a sample (150 ml.) of the solution of whole polymer had been removed for test, fraction A was precipitated by the slow addition of methanol, with mechanical stirring, until the solution became hazy at 25°. It was then warmed gently until it became clear, at about 26–28°. Precipitation of the first fraction required 1200 ml. of methanol. The clear, warm solution was cooled slowly to 25° and maintained overnight at constant temperature, during which time the precipitated polymer settled out as a very viscous liquid containing the high molecular weight polymer in solution. The clear, supernatant solution was siphoned off and the fraction was washed twice with a benzene–methanol mixture of the same concentration as the mixture from which the fraction had precipitated. These washings were added to the main solution and the fraction

(5) P3 corresponds to a Williams plasticity range of 116–121; see A. M. Neal and P. Ottenhoff, *Ind. Eng. Chem.*, **36**, 653 (1944), this corresponds approximately to Mooney 2.

(6) A. M. Collins, U. S. Patent 2,264,173.

was dissolved immediately in 200 ml. of thiophene-free, dry benzene. A benzene/methanol azeotrope was distilled from this solution at 30° under vacuum until about 100 ml. had been removed; then another 100 ml. of benzene was added and the distillation was continued until the refractive index of the distillate checked that of pure benzene. The remaining solution of the fraction in pure benzene was used for subsequent measurements.

The above-described procedure was followed for the preparation of the first three fractions since it had been found that evaporation of these fractions to dryness resulted in the formation of small amounts of gel.[7] Remaining fractions were coagulated with methanol after being washed and were then evaporated to dryness under vacuum at room temperature. After approximately half of the polymer had been fractionated a single washing of each fraction was considered sufficient. Eventually, when 28 g. of the neoprene had been precipitated it was necessary to concentrate the solution to about 1% solids again before proceeding with the final fractionations. This was done at 25–30° under vacuum with a slow stream of nitrogen through a fine capillary tube. Finally, when no more material could be precipitated, the remaining solution was evaporated to dryness.

An attempt to improve the homogeneity of neoprene fractions further by solution and reprecipitation gave meaningless results, presumably because of degradative changes occurring during the longer time required for the additional operations. Consequently the neoprene fractions described here were not reprecipitated. Repeated measurements on the whole polymer gave good checks on intrinsic viscosity and osmotic pressure. To diminish the effects of degradative changes, the fractions were dissolved and their molecular weights measured within a few days after preparation.

A total of 17 fractions was obtained from the purified polychloroprene. The dried fractions were dissolved in thiophene-free, dry benzene to make solutions containing 1 g. of polymer and 0.0050 g. of phenyl-α-naphthylamine per 100 ml. of solution. Solids content of each solution was accurately determined by evaporation to dryness at 70° of a 25.00-ml. aliquot (measured at 25.0°) and the remaining solution was used for the determination of number average molecular weight and intrinsic viscosity. To obtain a check on the results a rough fractionation was carried out analogously to get 6 different fractions which would approach the above in homogeneity.

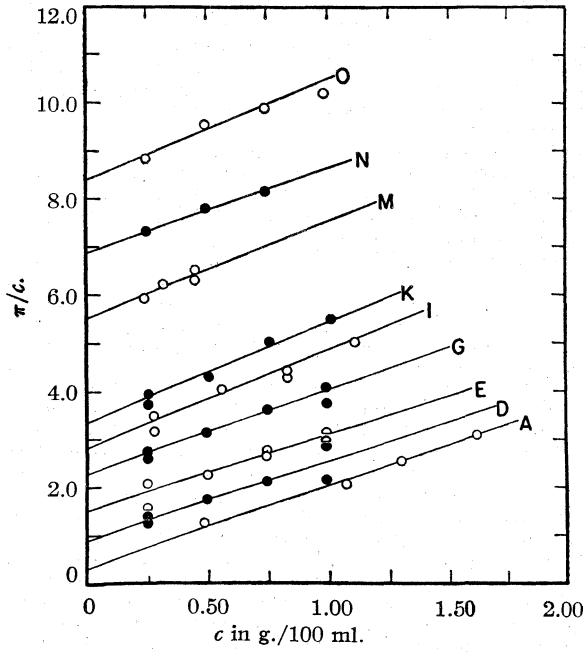


Fig. 1.—π/c *vs.* c curves for representative Neoprene Type GN fractions.

Osmotic Pressures.—The number average molecular weights in benzene solution were measured by means of static type osmometers using gel cellophane membranes (regenerated cellulose that has not been dried). The osmometers used were similar to those described by Schulz and by Wagner[8] and the membrane preparation was the same as that of Wagner.

For each sample, duplicate determinations were made at each of four different concentrations. To minimize the error due to thermometer effect, especially with the benzene solutions employed, the temperature was regulated within ±0.01°. The capillary correction for benzene was measured and since the correction for most solutions in organic solvents does not differ much from that of the pure solvent, separate measurements were not made for each individual solution. The measurements for each sample were plotted as π/c *vs.* c and extrapolated to zero concentration assuming a straight line relationship

$$\frac{\pi}{c} = \frac{RT}{M_n} + Bc$$

which appeared to fit within experimental error in the range of concentrations employed, *i. e.*, 0.25–1.50 g. per 100 ml. Representative curves are given in Fig. 1.

Intrinsic Viscosity.—Viscosities were measured in benzene solution using an Ubbelohde suspended level viscometer[9] modified by substitution of a 50-ml. reservoir for the usual 5–10 ml. bulb. Since the operation of the suspended level viscometer, unlike that of the Ostwald types, is not affected by the volume of liquid in the viscometer, it was possible to make carefully weighed additions of a 1–2% solution of polymer to solvent in the viscometer. Thus the viscosity at various concentrations could be measured without having to clean and refill the viscometer before each determination. The viscometer dimensions were such that the kinetic energy error was only 0.4% in the kinematic viscosity of benzene, having an efflux time of 116.4 seconds, and no correction was applied.

The dry, thiophene-free benzene used as solvent was measured at 25.0° in calibrated pipets and the efflux times were determined at the same temperature with a maximum fluctuation of ±0.02°. The efflux times were checked within ±0.2 second. Normally four additions of the polymer solution were made, keeping the relative viscosity between 1.15 and 1.4.

The concentration of the polymer by weight in the master solution was calculated using 1.23 as the specific gravity of polychloroprene[10] and 0.8735 as the specific gravity of benzene at 25°. The concentration of each solution measured was calculated in g. per 100 ml. and used to determine reduced viscosity, η_{sp}/c. Using a differencing technique[11] the four sets of η_{sp}/c *vs.* c values were fitted to the best straight line for the equation developed by Huggins and others[12]

$$\frac{\eta_{sp}}{c} = [\eta] + k'[\eta]^2 c \qquad (1)$$

(7) A similar observation was made in the case of natural rubber by G. F. Bloomfield and E. H. Farmer, *Trans. Inst. Rubber Ind.*, **16**, 69 (1940); G. Gee and L. R. G. Treloar, *ibid.*, **16**, 184 (1940).

(8) G. V. Schulz, *Z. physik. Chem.*, **A176**, 317 (1936); R. H. Wagner, *Ind. Eng. Chem., Anal. Ed.*, **16**, 520 (1944).

(9) L. Ubbelohde, *ibid.*, **9**, 85 (1937); G. B. Taylor, THIS JOURNAL, **69**, 635 (1947).

(10) L. A. Wood, N. Bekkedahl and F. L. Roth, *Ind. Eng. Chem.*, **34**, 1291 (1942).

(11) J. H. Awbery, *Phys. Soc. Proc.*, **41**, 384 (1929).

(12) M. L. Huggins, THIS JOURNAL, **64**, 2716 (1942); G. V. Schulz and F. Blaschke, *J. prakt. Chem.*, **158**, 130 (1941).

The intrinsic viscosity was thus obtained as the limiting reduced viscosity and simultaneously the constant k' was evaluated. The experimental results are shown graphically in Fig. 2.

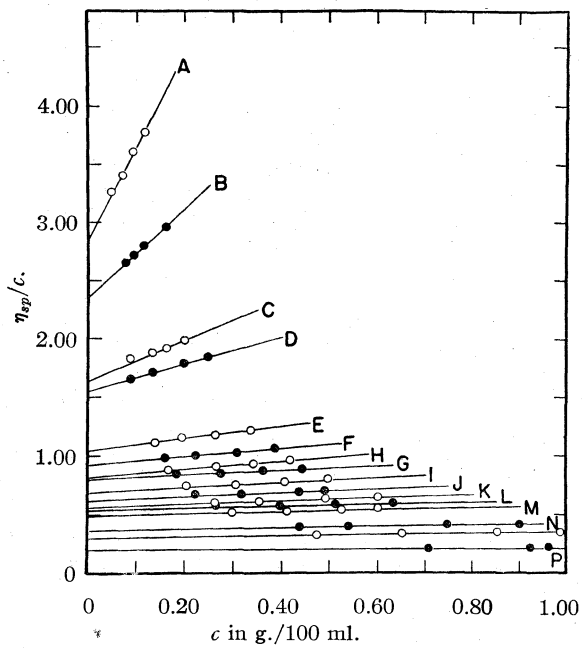


Fig. 2.—η_{sp}/c *vs.* c curves for Neoprene Type GN fractions.

Results and Discussion

The purified polychloroprene was divided into 17 fractions, the last one of which gave such erratic osmotic measurements that its molecular weight could not be calculated. The total weight of fractions isolated from the 49.0 g. of polymer fractionated (50.5 g. minus 1.5 g. for a sample of whole polymer) was 46.48 g. There was thus a loss of 2.52 g. of polymer during the fractionation. On the assumption that this loss had been uniformly distributed over all fractions, the total weight of the isolated fractions was used in calculating what per cent. of the whole each fraction constituted. The results obtained are given in Table I.

TABLE I

FRACTIONATION OF NEOPRENE TYPE GN

Fraction	Weight, g.	%[a]	$\overline{M}_n$	B[c]	[η]	k'
Whole	(49.0)	(100)	114,000	2.14	1.07	0.43
A	3.02[b]	6.5	959,000	1.71	2.88	.92
B	4.56[b]	9.8	488,000	1.68	2.38	.65
C	4.13[b]	8.9	387,000	1.36	1.65	.62
D	6.33	13.6	322,000	1.61	1.56	.48
E	4.71	10.1	190,000	1.55	1.05	.44
F	3.69	7.9	152,000	1.73	0.93	.37
G	2.56	5.5	127,000	1.70	.80	.30
H	1.92	4.1	121,000	1.90	.82	.47
I	1.65	3.6	103,000	2.05	.69	.44
J	2.27	4.9	100,000	2.29	.62	.45
K	1.65	3.6	86,400	2.05	.56	.43
L	1.75	3.8	83,000	1.80	.54	.30
M	0.70	1.5	52,000	1.95	.49	.38
N	1.78	3.8	42,000	1.76	.36	.48
O	2.64	5.7	34,500	2.10	.30	.47
P	2.10	4.5	20,500	2.31	.20	.40
Q	1.02	2.2	...	..	.04(?)	..

[a] Per cent. of the total isolated in the fractions. [b] Calculated weight; see procedure. [c] Slope term of the osmotic pressure relationship.

Note in Table I that although the number average molecular weight of the *whole* polymer was 114,000 there was present a broad range of molecular species, from 959,000 to less than 20,500 molecular weight. This range, of course would be widened by any degradation which occurred in the period of almost four weeks which elapsed between the precipitation of fraction A and isolation of the final fraction. However, the calculated number average of the molecular weights of the individual fractions was 105,000 compared with 114,000 for the original polymer indicating that degradation had not been extensive.

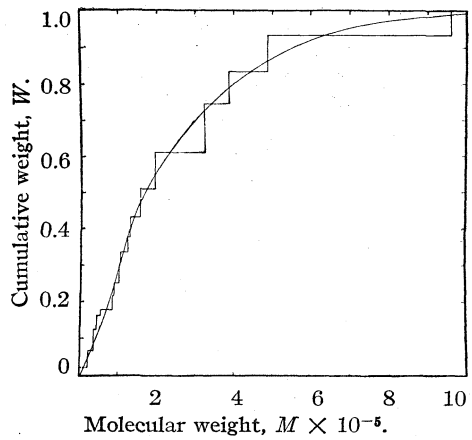


Fig. 3.—Integral molecular weight distribution for Neoprene Type GN.

In Fig. 3 is plotted the molecular weight of each fraction as a part of the whole polymer and from the smoothed curve there is calculated the differential molecular weight distribution given in Fig. 4. This illustrates very well the broad range of molecular weights and shows that the polymer species most abundant are those having molecular weights of about 100,000. The extension of the

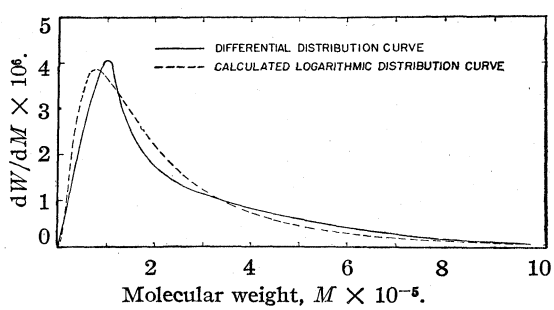


Fig. 4.—Differential molecular weight distribution for Neoprene Type GN.

neoprene distribution curve at the high molecular weight end suggests that there is present some soluble branched and/or cross-linked material, since it has been shown[13] that 10–100 p.p.m. of a cross-linking agent (diisopropenyldiphenyl) in polystyrene gave completely soluble polymers but altered the shape of the distribution curve and markedly increased the length of the high molecular weight end as the concentration of cross-linking agent was increased from 10 to 100 p.p.m.

Decreasing complexity of the fractions as the molecular weight decreases is indicated by the highly significant (probability of occurrence by chance alone is less than 1 in 100) decrease in k' of the viscosity equation (1) from 0.93 for fraction A to 0.406 as an average for fractions D to P. This constant is said to be a characteristic of any given solute–solvent system and is independent of molecular weight.[14] From studies in this laboratory it appears that k' is larger for complex molecules in a given homologous series than for simple, *i. e.*, linear ones. The greater-than-average values of k' for fractions A, B, and C indicate that approximately 25.2% of the neoprene is branched and/or cross-linked appreciably more than the major portion of the polymer. This corresponds to 5.4% of the molecules by number. The major portion of the polymer appears to be uniform in structure, at least within experimental error.

This increase of k' with polymer chain complexity is indicated also by the work of others. For example, Speiser and Whittenberger[15] showed that k' was higher (1.47) for the branched structure, amylopectin, than for the unbranched molecule, amylose ($k' = 0.58$). Also Morrison, Holmes and McIntosh[16] found that k' of solutions of polyvinyl acetate in bis-(2-chloroethyl) ether containing small amounts of ferric chloride increased as the viscosity increased and the solution gelled, indicating branching and cross-linking reactions, but in the presence of air the viscosity decreased, indicating chain scission, while k' remained constant. Furthermore, Spurlin, Martin and Tennent[17] demonstrated that k' is greatest for solutions where the solvents are poorest. Similarly, a given liquid would be a poorer solvent for cross-linked molecules than for linear molecules of the same species. The present investigation has shown that k' for polychloroprene solutions is not increased by heterogeneity of molecular species,[18] as was reported for polystyrene in toluene.[19] The whole polymer had a lower k' than several of the fractions and k' was not raised by mixing two fractions together, *e. g.*, two fractions having respective $[\eta]$ and k' values of 1.56–0.60 and 0.60–0.40, when mixed in approximately equal parts gave $[\eta] = 0.99$ and $k' = 0.43$. Unfortunately the error in k', particularly at low intrinsic viscosity, is frequently quite large, depending in calculation as it does upon the square of the intrinsic viscosity.

The same change in complexity of the fractions is suggested by the change in the slope term B of the osmotic pressure relationship[20]

$$\frac{\pi}{c} = \frac{RT}{M_2} + Bc, \text{ where } B = \frac{RTd_1}{M_1 d_2^2}(0.5 - \mu)$$

c is the solute concentration, M_1 and M_2 are the molecular weights and d_1 and d_2 the densities of the solvent and solute, respectively. The constant μ, which depends upon the entropy and heat of mixing for each solvent–solute combination, approaches the value 0.5 for poor solvents, causing B to approach zero. Thus the somewhat lower values of B for early fractions indicate poorer solutions as would be expected if there were present branched and/or cross-linked polymers, but it is recognized that the variations in B may be influenced also by the different molecular weights of the fractions.

The intrinsic viscosities of Neoprene Type GN fractions ranged from 2.88 to 0.20 as noted in Table I. The calculated weight average of the individual values was 1.18 which is not as close to the observed value, 1.07, for the whole polymer as would be desired. There is apparently an error in the value for fraction G or H since the viscosity would be expected to decrease in going from G to H. The discrepancies, however, are not large enough to nullify the general conclusions drawn in this paper.

The intrinsic viscosity is a measure of the viscosity average molecular weight, which approaches the weight average value fairly closely for most polymers, whereas the osmotic pressure determination measures the number average molecular weight. These relationships can be indicated as follows[21]

$$\text{number average: } \overline{M}_n = \frac{\Sigma NM}{\Sigma N}$$

$$\text{viscosity average: } \overline{M}_v = \left(\frac{\Sigma NM^{a+1}}{\Sigma NM}\right)^{1/a}$$

$$\text{weight average: } \overline{M}_w = \frac{\Sigma NM^2}{\Sigma NM}$$

Of course, if a polymer is homogeneous, *i. e.*, all molecules are of the same size, these averages all reduce to the same value. Consequently by assuming that the neoprene fractions were reasonably homogeneous it was possible to calibrate the

(13) I. Valyi, A. G. Janssen and H. Mark, *J. Phys. Chem.*, **49**, 461 (1945). Addition of cross-linking agent does not necessarily result in the theoretical number of cross-links; see J. W. Breitenbach, *Experientia*, **3**, 239 (1947).

(14) M. L. Huggins, *Ind. Eng. Chem.*, **35**, 980 (1943); T. Alfrey, A. Bartovics, and H. Mark, THIS JOURNAL, **65**, 2319 (1943); M. L. Huggins, *ibid.*, **66**, 1991 (1944).

(15) R. Speiser and R. T. Whittenberger, *J. Chem. Phys.*, **13**, 349 (1945).

(16) J. A. Morrison, J. M. Holmes and R. McIntosh, *Can. J. of Res.*, **24**, 179 (1946).

(17) H. M. Spurlin, A. F. Martin and H. G. Tennent, *J. Polymer Sci.*, **1**, 63 (1946).

(18) W. E. Davis, THIS JOURNAL, **69**, 1453 (1947), reports similar results for cellulose nitrate.

(19) R. S. Spencer and R. F. Boyer, *Polymer Bull.*, **1**, 129 (1945).

(20) M. L. Huggins, THIS JOURNAL, **64**, 1712 (1942); P. J. Flory, *J. Chem. Phys.*, **10**, 51 (1942).

(21) P. J. Flory, THIS JOURNAL, **65**, 380 (1943).

viscosity-molecular weight relationship against the osmotic pressure determinations. The only check on homogeneity of the neoprene fractions was obtained on a fraction from a later, similar, careful fractionation, where the osmotic molecular weights ($\overline{M}_n$) of 186,000 and 190,000 in duplicate determinations, were, within experimental error, the same as those ($\overline{M}_w$), 192,000 and 193,000, obtained by light scattering. The excellence of this agreement was probably fortuitous but the results demonstrate that the fraction was essentially homogeneous.

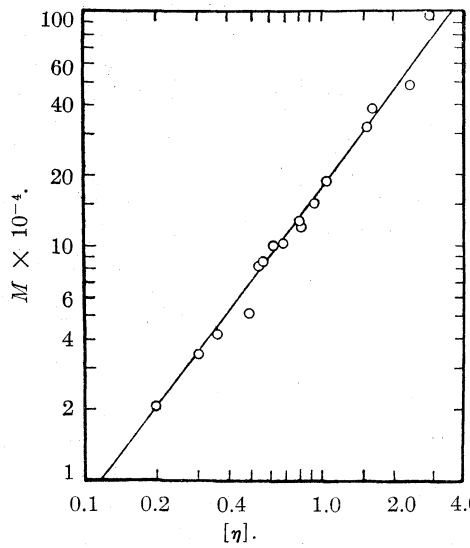


Fig. 5.—Log $\overline{M}_n$ *vs.* log $[\eta]$ for Neoprene Type GN fractions.

The values of $\overline{M}_n$ and $[\eta]$ for fractions A to P are plotted on a log–log scale in Fig. 5. The calculated best straight line is seen to account fairly well for the majority of the experimental points. The equation of this line is $\log M = 5.2466 + 1.367 \log [\eta]$ or $M = 1.76 \times 10^5 [\eta]^{1.37}$ which can be rearranged into the usual form: $[\eta] = KM^a$ where $K = 1.46 \times 10^{-4}$ and $a = 0.73$. A duplicate fractionation of only six fractions gave the equation $[\eta] = 1.26 \times 10^{-4} M^{0.75}$. This expression confirms the one above within experimental error but is less accurate because of the fewer fractions and consequent lower homogeneity of the fractions. It is of interest to note that the exponent "a" has a higher value than the 0.66 reported for GR-S[22] and the 0.67 reported for natural rubber,[23] indicating that polychloroprene chains are somewhat stiffer than those of GR-S or rubber.

Using the data of Table I the weight average and viscosity average molecular weights can be calculated by the above formulas

$$\overline{M}_w = 257{,}000$$
$$\overline{M}_v = 233{,}000$$

The ratio $\overline{M}_v/\overline{M}_w = 0.91$ indicates that the viscosity average approaches the weight average reasonably closely. From $\overline{M}_w/\overline{M}_n = 2.25$ the Lansing and Kraemer[24] non-uniformity coefficient was obtained: $\beta = 1.27$. This value shows that Neoprene Type GN is less homogeneous than sol natural rubber ($\beta = 0.7$)[25] but is more homogeneous than GR-S as indicated by $\beta = 1.60$, calculated from the data of French and Ewart.[22]

A comparison of distribution curves calculated from the non-uniformity coefficients by means of the logarithmic function of Lansing and Kraemer[24] is given in Fig. 6.[26] The neoprene molecular

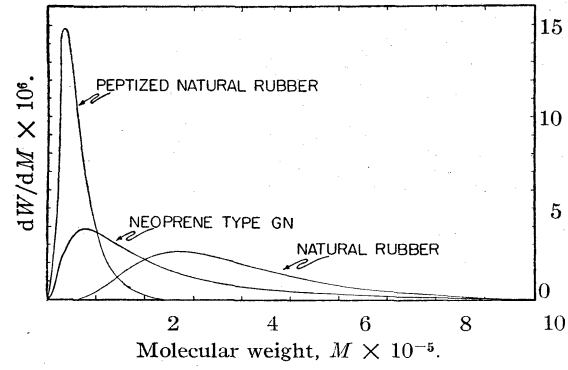


Fig. 6.—Comparison of molecular weight distribution curves for Neoprene Type GN, natural rubber sol and a peptized natural rubber.

weight distribution curve is unlike that of sol natural rubber both in shape and in the molecular weights of the most abundant species, which undoubtedly accounts for some of the differences in physical properties of these rubbers. Natural rubber sol appears to have a somewhat narrower distribution of molecular weights and a more nearly symmetrical curve with a broad maximum at M = 2–300,000. Note, however, that natural rubber peptized with phenylhydrazine[26] exhibits a distribution curve which in shape is more like that of Neoprene Type GN although it does not extend to as high molecular weight as the latter. From the data available it would appear that the distribution curve for GR-S is similar to that of Neoprene Type GN in shape but that the peak occurs at somewhat lower molecular weight.

It is to be noted that the experimental distribution curve for neoprene exhibits a positive skewness and is fairly well represented by the normal logarithmic distribution of Lansing and Kraemer

(22) D. M. French and R. H. Ewart, *Anal. Chem.*, **19**, 165 (1947).

(23) W. C. Carter, R. L. Scott and M. Magat, THIS JOURNAL, **68**, 1480 (1946).

(24) W. D. Lansing and E. O. Kraemer, *ibid.*, **57**, 1369 (1935).

(25) E. O. Kraemer and J. B. Nichols in T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford Press, 1940, p. 353. A value of $\beta = 1.0$ is reported here for an early experimental sample of polychloroprene.

(26) Similarly calculated distribution curves based on ultracentrifuge measurements made in this laboratory for GR-S sol rubber, low viscosity (peptized) rubber and an early, experimental sample of neoprene before and after peptization have been published; E. O. Kraemer and J. B. Nichols, *ibid.*, p. 423; L. B. Sebrell, *Ind. Eng. Chem.*, **35**, 736 (1943).

(see Fig. 4). Attempts to apply a two parameter distribution function[27] of the Schulz type to these data have not given particularly consistent results. The Lansing–Kraemer logarithmic distribution is considered a better representation of the data for Neoprene Type GN within the experimental errors of fractionations and molecular weight determinations.

Acknowledgment.—The authors gratefully acknowledge the helpfulness of preliminary experiments on the fractionation of neoprene carried out in this laboratory by Dr. S. L. Scott, now of the Service Department of the du Pont Company. Acknowledgments likewise are made to Dr. F. T. Wall and Dr. H. Mark for many helpful discussions during the course of this research and to Miss B. L. Price for her assistance in the osmotic pressure measurements.

Summary

Polychloroprene rubber, Neoprene Type GN, has been fractionated by partial precipitation from dilute solution in benzene and the fractions examined both osmotically and viscometrically in benzene solutions.

The molecular weight distribution curve for Neoprene Type GN based on osmotic pressure measurements shows a pronounced maximum at 100,000 but has a long extension to molecular weights of over one million, indicating the presence of branched or cross-linked material which is still soluble. The uniformity is somewhat less than that of sol natural rubber, while in shape the neoprene distribution curve resembles more closely that of a peptized natural rubber than fresh sol rubber.

Observed variations in the slopes of the π/c *vs.* c and the η_{sp}/c *vs.* c curves also indicate the presence in solution of complex, branched and/or cross-linked molecules.

Calibration of the intrinsic viscosity-molecular weight relationship by osmotic pressure measurements gave good agreement with the equation $[\eta] = KM^a$, where $K = 1.46 \times 10^{-4}$ and $a = 0.73$.

WILMINGTON, DELAWARE RECEIVED FEBRUARY 12, 1948

(27) G. V. Schulz, *Z. physik. Chem.*, **B43**, 25 (1939); R. F. Boyer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 342 (1946); I. Jullander, *J. Polymer Sci.*, **2**, 329 (1947).

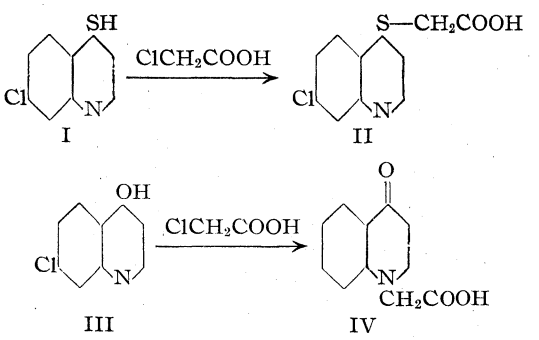
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Basic Esters and Amides of 4-Quinolylmercaptoacetic Acid Derivatives

BY ALEXANDER R. SURREY

The present investigation was undertaken to synthesize 4-quinolyloxy-, 4-quinolylamino- and 4-quinolylmercaptoacetic acid derivatives to make them available for pharmacological study.

It was observed that, in alcohol solution, 4,7-dichloroquinoline[1] reacts with thiourea to yield a thiouronium salt which on treatment with sodium carbonate gives 7-chloro-4-quinolinethiol (I) and a small amount of 7,7′-dichloro-4,4′-diquinolylsulfide. The thiol (I) reacts with chloroacetic acid



to give (7-chloro-4-quinolyl)-mercaptoacetic acid (II). The fact that compound II was also obtained by the reaction of 4,7-dichloroquinoline with mercaptoacetic acid indicates that the structure of II must be correct.

The behavior of the thiol, I, with chloroacetic acid is strikingly different from that of the corresponding 4-hydroxyquinoline, III. The reaction of III with chloroacetic acid yields only the 4-keto-1(4)-quinolineacetic acid IV. Similarly, when ethyl chloroacetate was allowed to react with 4-amino-7-chloroquinoline, ethyl 7-chloro-4-imino-1(4)-quinolineacetate (V) was obtained. The formation of IV and V is not unexpected when one considers the known behavior of similar compounds on treatment with alkyl iodide.[2] Hydrolysis of V with 5% sodium hydroxide solution gives the quinolone IV. Both V and the ethyl ester prepared from IV are high melting solids, insoluble in the usual organic solvents. A comparison of the ultraviolet absorption spectra of IV with the mercaptoacetic acid, II, is shown in Fig. 1.[3]

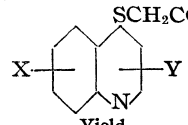
Inasmuch as the 4-amino- and 4-hydroxyquinolines did not give the desired intermediates, the present work was confined mainly to the 4-quinolylmercaptoacetic acid derivatives. The acids (Table I) were prepared from the corresponding 4-chloroquinoline by treatment with mercaptoacetic acid. The basic esters were prepared by ester interchange. Accordingly, the appropriate methyl ester (Table I) was refluxed in Skellysolve

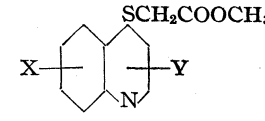
(1) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(2) F. W. Bergstrom, *Chem. Rev.*, **35**, 133, 135, 177 (1944).

(3) The absorption spectra were determined in these laboratories under the direction of Dr. G. W. Ewing, present address Union College, Schenectady, N. Y.

TABLE I





X	Y	Yield, %	M. p., °C.	Nitrogen, % Calcd.	Found	M. p., °C.	Nitrogen, % Calcd.	Found
7-Cl	H	90	228–229	253.5[a]	254.1	99.5–100.5	5.23	5.13
5-Cl	H	67	221–222	5.52	5.49	102.5–103.5	5.23	5.02
6-OCH_3	H	50	236–237	5.62	5.65	82.5–83.5	5.31	5.35
H	H	63	233–234	6.39	6.28	192–193[b]	5.19	5.27
7-Cl	2-CH_3[c]	50	229–230	S, 11.96	12.08	105–106	4.97	4.97
7-Cl	3-CH_3[d]	63	186–188	5.23	5.18	77–78	4.97	4.97
5-Cl	3-CH_3[d]	61	189–190	5.23	5.12			
8-OCH_3	3-CH_3[e]	28	178–180	5.31	5.12	81.5–82	5.05	5.04
6-OCH_3	3-CH_3[f]	76	189–191	5.31	5.29	57–58	5.05	5.05
H	3-CH_3[f]	89	179–181	6.01	5.98	62–63	5.67	5.65
8-CH_3	3-CH_3[e]	78	170–172	5.67	5.67	55–56	5.36	5.34
8-OC_2H_5	3-CH_3[e]	52	198–199	5.05	4.97	81–82	4.81	4.88
6-Br	3-CH_3[f]	56	197–199	4.49	4.35	76–77	4.30	4.28
7-Cl	3-Br	58	202–204	4.21	4.03	78–79	5.05	5.05

[a] Neutral equivalent. [b] Hydrochloride. [c] For the corresponding 4-chloro compound see Steck, Hallock, Holland and Fletcher, THIS JOURNAL, **70**, 1012 (1948). [d] For the corresponding 4-chloro compound see Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946). [e] Page 132. [f] Page 129.

E with an aminoalcohol or a primary tertiary amine, removing the methanol continuously as it formed to yield the basic ester (Table II) or basic amide (Table III). In one instance, the basic ester, diethylaminoethyl-(5-chloro-4-quinolyl)-mercaptoacetate, was prepared by heating the corresponding acid with 1-chloro-2-diethylaminoethane.[4]

Experimental[5]

7-Chloro-4-keto-1(4)-quinolineacetic Acid.—A mixture of 11 g. of 7-chloro-4-hydroxyquinoline, 5.8 g. of chloroacetic acid and 5.4 g. of sodium hydroxide in 32 cc. of water, was heated to dryness in a beaker over a free flame. The solid residue was dissolved in water, filtered hot with charcoal and the filtrate acidified with acetic acid. The separated solid was purified by dissolving in bicarbonate solution, filtering from any insoluble material, and acidifying the filtrate with acetic acid. The yield was 7 g. of a product that melted at 268–269°.

Anal. Calcd. for $C_{11}H_8ClNO_3$: neut. equiv., 237.6. Found: neut. equiv., 237.7.

The ethyl ester was prepared by refluxing 2 g. of the acid in 50 cc. of absolute ethanol containing 2.5 cc. of concentrated sulfuric acid for three hours. It was recrystallized from a large volume of ethanol, m. p. 194–195°.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: N, 5.27. Found: N, 5.46.

Ethyl 7-Chloro-4-imino-1(4)-quinolineacetate.[6]—A mixture of 5.4 g. of 4-amino-7-chloroquinoline and 4 g. of ethyl chloroacetate in 11 cc. of pyridine was heated on the steam-bath for five minutes, cooled and diluted with water. The product which separated was recrystallized from 100 cc. of ethanol; yield, 3 g., m. p. 265–266° (immersed at 240°).

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: N, 10.58. Found: N, 10.37.

Hydrolysis with 5% sodium hydroxide solution gave 7-chloro-4-keto-1 (4)-quinolineacetic acid.

(4) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(5) All melting points are uncorrected.

(6) Prepared in this laboratory by Mr. Henry F. Hammer, present address Rensselaer Polytechnic Institute, Troy, New York.

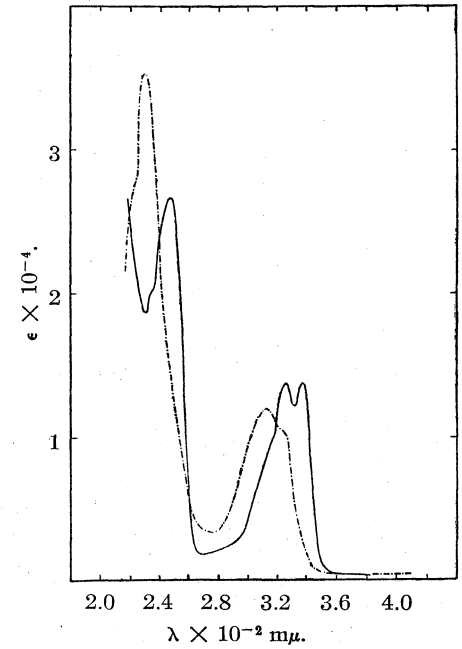


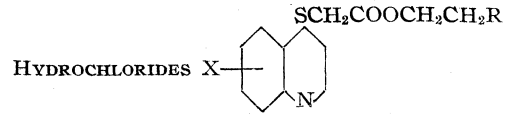
Fig. 1.—Ultraviolet absorption curves: —, compound IV; ·—·, compound II.

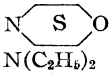
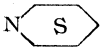
7-Chloro-4-quinolinethiol (I).—Thiourea (7.6 g.) was added to a warm solution of 19.8 g. of 4,7-dichloroquinoline in 200 cc. of absolute alcohol. After shaking for a few minutes the entire contents of the flask solidified. The white solid was filtered off, dissolved in water and the solution made alkaline with sodium carbonate. The yellow-orange solid which separated was filtered off and dissolved in dilute sodium hydroxide solution. A small amount of insoluble material was obtained which was recrystallized from pyridine, m. p. 166–167°. It analyzed for 7,7′-dichloro-4,4′-diquinolylsulfide.

Anal. Calcd. for $C_{18}H_{10}Cl_2N_2S$: S, 8.96. Found: S, 8.90.

The alkaline solution was acidified with acetic acid to

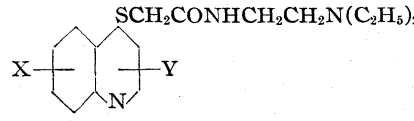
TABLE II



X	R	Recryst. solvent	Yield, %	M. p., °C.	Analyses, % Nitrogen Calcd.	Nitrogen Found	Chlorine[a] Calcd.	Chlorine[a] Found
H	$N(C_2H_5)_2$	Isopropanol	71	154–155	7.16[b]	6.97	18.16	18.18
5-Cl	$N(CH_3)_2$	Methanol–ethyl acetate	37	180–181	7.76	7.80	9.83	9.60
5-Cl	$N(C_2H_5)_2$	Ethanol	84	199–201	7.20	7.14	9.14	8.88
5-Cl		Ethanol	50	179–180	6.40[b]	6.69	16.23	15.90
5-Cl		Methanol–acetone	42	214–215	6.37[b]	6.40	16.15	15.81
6-OCH_3	$N(C_2H_5)_2$	Isopropanol	55	154–155	7.28	7.20	9.23	9.19
7-Cl	$N(CH_3)_2$	Ethanol	36	170–172	7.76	7.50	9.83	9.72
7-Cl	$N(C_2H_5)_2$	Ethanol	60	145–146	7.20	7.19	9.14	8.85
7-Cl		Ethanol	70	165–166	6.98	6.72	8.85	8.80
7-Cl		Methanol–ethyl acetate	21	199–201	6.37[b]	6.37	16.15	15.84

[a] Ionic chlorine. [b] Dihydrochloride.

TABLE III



X	Y	M. p., °C.	Nitrogen, %[a] Calcd.	Nitrogen, %[a] Found	M. p., °C.	Hydrochlorides Analyses, % Sulfur Calcd.	Sulfur Found	Chlorine[b] Calcd.	Chlorine[b] Found
7-Cl	H	98–99	11.95	12.24	130–131	N, 11.03	10.83	9.15	9.24
5-Cl	H	87–88	7.97	7.95	131–133.5	8.25	8.09	9.15	9.16
6-OCH_3	H	54–55	8.06	8.02	159–160	8.34	8.40	9.26	9.43
H	H	61–62	8.83	8.77	114–115	9.05	9.06	10.04	10.00
7-Cl	2-CH_3	108.5–109.5	7.66	7.65	127–128	7.96	7.85	N, 10.43	10.24
7-Cl	3-CH_3				162–163	7.96	7.77	8.83	8.59
8-OCH_3	3-CH_3	102.5–103.5	7.76	7.65	138–139	8.05	8.20	8.93	8.75
6-OCH_3	3-CH_3	78–79	7.76	7.72	137–138	8.05	8.09	8.93	8.68
H	3-CH_3				130–131	8.71	8.65	9.66	9.56
8-CH_3	3-CH_3	85–87	8.12	8.06	114–116	8.41	8.32	N, 11.01	10.82
8-OC_2H_5	3-CH_3	94–95	7.47	7.41	130–131	7.78	7.78	8.63	8.54
6-Br	3-CH_3				166–168	7.17	7.06	7.95	7.88
7-Cl	3-Br	130–131	9.75	9.72	165–168	6.85	6.92	N, 8.99	8.83

[a] Titration of basic nitrogen by the Toennies and Callan method (*J. Biol. Chem.*, **125**, 259 (1938)). [b] Ionic chlorine.

give the yellow thiol which was recrystallized from acetic acid; yield, 12.5 g., m. p. 196–197°.

Anal. Calcd. for C_9H_5ClNS: N, 7.16. Found: N, 6.96.

7-Chloro-4-quinolylmercaptoacetic Acid. Procedure A.—A mixture of 7-chloro-4-quinolinethiol, chloroacetic acid and sodium hydroxide was treated in the same manner as for the 4-hydroxy compound above. The yield was almost quantitative. The acid was purified by solution in 10% sodium carbonate solution followed by precipitation with acetic acid.

Procedure B.—A pyridine solution of 19.8 g. of 4,7-dichloroquinoline and 11 g. of thioglycolic acid was refluxed for three hours, sodium hydroxide added and the pyridine removed by steam distillation. The alkaline solution was treated with acetic acid, the separated solid was heated on the steam-bath with ethanol, and further purified as above; yield 8.5 g. A mixed melting point determination with the acid prepared above showed no depression. Similarly, the methyl esters prepared from both acids were identical.

Procedure C.—The following method was used for the acids described in Table I. Three hundred grams of 4,7-dichloroquinoline, 147 g. of thioglycolic acid and 256 cc. of 35% sodium hydroxide solution in 1.7 liters of absolute ethanol was refluxed with stirring for one hour. The sodium salt of the acid which separated was filtered off, dissolved in water and purified as above. Where the sodium salt failed to separate, refluxing was continued for eight to sixteen hours, the alcohol removed by distillation and the residue dissolved in water and purified as above.

Methyl 7-Chloro-4-quinolylmercaptoacetate.—The methyl esters described in Table I were prepared by refluxing the acids in methanol containing concd. sulfuric acid. The above ester was also prepared from the acid chloride. Five grams of 7-chloro-4-quinolylmercaptoacetic acid and 3.4 g. of phosphorus pentachloride in 100 cc. of dry benzene was refluxed with stirring for one hour. After distilling off the solvent, the residue was refluxed for one hour with methanol. The residue, after removing most of the methanol, was dissolved in water and the solution treated with sodium carbonate solution. The methyl

ester which separated was filtered off and recrystallized from Skellysolve C; yield 2.5 g., m. p. 98–100°.

The **ethyl ester**, after recrystallization from Skellysolve B, melted at 60–61°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.82.

The **amide** was prepared from the methyl ester with alcoholic ammonia at room temperature. After recrystallization from acetic acid and then ethanol it melted at 213–214°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: N, 11.09. Found: N, 11.04.

α-(7-Chloro-4-quinolyl)-mercaptopropionic Acid.—The acid was prepared from ethyl α-bromopropionate and 7-chloroquinolinethiol (I) by refluxing in dilute sodium hydroxide solution; yield 83%. After recrystallization from ethanol, the acid melted at 202–204°.

Anal. Calcd. for $C_{12}H_{10}ClNO_2S$: N, 5.23; neut. equiv., 267.5. Found: N, 4.95; neut. equiv., 265.1.

The **methyl ester hydrochloride** was recrystallized from isopropanol, m. p. 167–168°.

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_2S$: N, 4.40; Cl^-, 11.17. Found: N, 4.14; Cl^-, 10.84.

β-(7-Chloro-4-quinolyl)-mercaptopropionic Acid.—Prepared from β-chloropropionic acid and I; yield 52%, m. p. 212–214°.

Anal. Calcd. for $C_{12}H_{10}ClNO_2S$: N, 5.23; neut. equiv., 267.5. Found: N, 5.24; neut. equiv., 261.5.

The **methyl ester** after recrystallization from Skellysolve B, melted at 84.5–86°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.69.

Ethyl (5-Chloro-4-quinolyl)-mercaptoacetate.—Prepared from the corresponding acid, m. p., 40–41°, from Skellysolve A.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: N, 4.97. Found: N, 4.97.

The **amide,** recrystallized from ethanol, melted at 226–228°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: N, 11.09. Found: N, 11.06.

β-Diethylaminoethyl α-(7-Chloro-4-quinolyl)-mercaptopropionate Dihydrochloride.—The procedure described below is the general method used for the preparation of the basic esters described in Table II.

A mixture of one mole of methyl α-(7-chloro-4-quinolyl)-mercaptopropionate and four moles of diethylaminoethanol in Skellysolve E was refluxed with a water separator for about six to twelve hours or until no more methanol separated. The rate of reflux was maintained at such a rate that practically no Skellysolve E was collected along with the methanol. In most cases the theoretical amount of methanol was collected.

The Skellysolve was distilled under reduced pressure and the crude residue was dissolved in ether and washed thoroughly with water. After removing the ether by distillation the residue (60–95% yields) was dissolved in ten volumes of acetone, filtered with charcoal, and to the filtrate was added a slight excess of alcoholic hydrogen chloride. If necessary ether was added to precipitate the hydrochloride. The product was recrystallized from ethanol, yield 45%, m. p. 199–201°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot 2HCl$: N, 6.37; Cl^-, 16.16. Found: N, 6.05; Cl^-, 15.92.

β-Diethylaminoethyl β-(7-chloro-4-quinolyl)-mercaptopropionate recrystallized from a mixture of isopropanol and acetone, m. p. 175–176.5°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot 2HCl$: N, 6.37; Cl^-, 16.16. Found: N, 6.20; Cl^-, 15.94.

γ-Diethylaminopropyl 7-chloro-4-quinolylmercaptoacetate recrystallized from isopropanol, yield 60%, m. p. 157.5–158.5°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S \cdot HCl$: N, 6.95; Cl^-, 8.81. Found: N, 6.87; Cl^-, 8.78.

β-Diethylaminoethyl (5-Chloro-4-quinolyl)-mercaptoacetate Hydrochloride.—To a hot suspension of 12.7 g. of 5-chloro-4-quinolylmercaptoacetic acid in 60 ml. of dry isopropanol was added 6.8 g. of 2-chloro-1-diethylaminoethane. After stirring for fifteen minutes a clear solution was obtained. After twenty minutes the contents of the flask solidified, crude yield, 16.5 g., m. p. 177–188°. The product was purified by several recrystallizations from ethanol.

N-2-Diethylaminoethyl 4-Quinolylacetamides (Table III).—The general procedure for the preparation of the basic amides is essentially the same as for the basic esters described above. The appropriate methyl ester (0.1 mole) was refluxed with 0.2 mole of N,N-diethylethylenediamine in 200 cc. of Skellysolve E for about eight hours or until no more methanol was collected. In most instances, a solid product was obtained after removal of the solvent under reduced pressure. These amides could be recrystallized from one of the Skellysolve fractions. The hydrochlorides were prepared in the usual manner.

Acknowledgment.—The author wishes to acknowledge the technical assistance of Miss Marcia Rukwid. The analyses reported were performed by the analytical staff of this Institute.

Summary

The reaction of 7-chloro-4-hydroxyquinoline or 4-amino-7-chloroquinoline with chloroacetic acid or ethyl chloroacetate results in the formation of 1-quinolineacetic acid derivatives. Under similar conditions, 7-chloro-4-quinolinethiol yields the corresponding 4-quinolylmercaptoacetic acid.

The preparation of several 4-quinolylmercaptoacetic and propionic acid derivatives is reported.

RENSSELAER, NEW YORK RECEIVED FEBRUARY 3, 1948

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Allyl Ethers of Carbohydrates. VI. Polymerization of Allyl Ethers

BY A. N. WRIGLEY AND E. YANOVSKY

The second paper of this series[2] presented data on the gelation time for a number of allyl ethers of polyhydroxy compounds. A rather guarded opinion was expressed regarding the relation between the number of allyl groups in the molecule and the gelation time of the ether, but more direct evidence on this subject was desirable. Experiments with mannitol of different degrees of allylation show clearly the difference in the rate of polymerization of these compounds. Another point of interest is the relation between the configuration and the polymerization rate of isomeric compounds. In the article cited, the gelation time of two such compounds—hexaallylmannitol (220 minutes) and hexaallylsorbitol (240 minutes)—seemed to be identical within experimental error. Similar results were obtained for another pair of isomeric compounds, allyl tetraallyl-α-D-glucoside (274 minutes) and allyl tetraallyl-α-D-galactoside (283 minutes).[3] It seemed desirable, however, to verify this point with a larger number of compounds. Accordingly, besides some of those previously reported, a number of new compounds were made, such as allylated derivatives of erythritol, xylitol, arabitol, dulcitol, talitol and iditol,[4] and their gelation time and the rate of oxygen absorption were measured. And finally some theoretical considerations regarding the polymerization of allyl ethers are presented.

To study the gelation of allyl-D-mannitol of different degrees of allylation, hexaallyl-D-mannitol was prepared as described previously.[2] Approximately tetraallyl-D-mannitol was prepared essentially by the same method but with less concentrated alkali, and 3,4-diallyl-D-mannitol was made by allylating 1,2:5,6-diisopropylidene-D-mannitol, and removing the isopropylidene groups by hydrolysis with dilute hydrochloric acid. Diallylmannitol is a crystalline compound.[5] The gelation time for the three compounds was determined at 120° (above the melting point of diallylmannitol), with oxygen bubbling through at the rate of 7.5 liters per hour. The gelation time was 95 minutes for hexaallylmannitol, 165 minutes for the tetraallyl compound, and 425 minutes for the disubstituted mannitol. This clearly shows that increase in the degree of allylation (for the same compound) reduces the time of gelation.

The rate of oxygen absorption and the gelation time of various completely allylated sugar alcohols at 80° are given in Table I. All the figures in the table represent an average of two or more well agreeing results. It will be observed that with the increase of the chain from 3 to 6 carbons the gelation time decreased from 974 minutes for allyl glycerol to 900 for erythritol, to 602 for pentitols, and to 502 for the hexitols.

TABLE I

GELATION TIME AND OXYGEN ABSORPTION OF ALLYL ETHERS AT 80°

Compound	Gelation time	Oxygen absorption (micrograms per gram per minute)
Triallylglycerol	974	158
Tetraallylerythritol	900	83
Pentaallylxylitol	504	92
Pentaallyl-D-arabitol	700	91
Hexaallyl-D-mannitol	466	77
Hexaallyl-D-sorbitol	474	74
Hexaallyldulcitol	565	77
Hexaallyl-D-talitol	...	85
Hexaallyl-L-iditol	...	81

On the other hand, the rate of oxygen absorption decreased gradually (with the exception of erythritol) from 158 micrograms per gram per minute for glycerol to 92 for pentitols and 79 for hexitols. It is not clear at present why allylxylitol gels faster than allylarabitol or why allyldulcitol gels more slowly than either allylsorbitol or allylmannitol.

In a previous paper[2] Nichols and Yanovsky proposed a scheme based on the hydroperoxide theory of Criegee, Pilz and Flygare and of Farmer and Sundralingam to explain the oxidative polymerization of allyl ethers. It explained satisfactorily the presence of peroxide, epoxide[6] and acrolein during oxidation of allyl ethers. In addition to these products, water appears during the process of gelation. Thus in one experiment 200 g. of hexallylmannitol was heated at 80°, while oxygen was passed through the liquid. The outgoing oxygen was led through two traps immersed in solid carbon dioxide–chloroform–carbon tetrachloride mixture. About 4.4 g. of liquid was collected

(1) One of the laboratories of the Bureau of Agriculture and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Nichols and Yanovsky, THIS JOURNAL, **67**, 46 (1945).

(3) Talley, Vale and Yanovsky, *ibid.*, **67**, 2037 (1945).

(4) Our thanks are due to Prof. C. S. Hudson and Dr. R. M. Hann of the National Institute of Health for samples of talitol, iditol, xylitol and arabitol, and to Prof. M. L. Wolfrom of Ohio State University for a sample of xylitol.

(5) Incidental to the preparation of diallylmannitol, some monoallyl-D-mannitol was obtained, which from the method of preparation was judged to be 3-allyl-D-mannitol. Malaprade's reaction (*Bull. soc. chim.*, [4] **43**, 683 (1928); [5] **4**, 906 (1937)), was used to confirm the position of the substituent. A water solution of 0.5556 g. of the monoallylmannitol was treated with 20 ml. of 0.4070 *M* aqueous sodium metaperiodate and diluted to 50 ml. After three hours, 5 ml. and 20 ml. aliquots were titrated for periodate and formic acid, respectively. For each mole of monoallylmannitol, 3.24 moles of periodate were consumed and 1.12 moles of formic acid formed. Somewhat higher results than expected theoretically are due to a reaction between the periodate and the allyl group.

(6) Nichols, Wrigley and Yanvosky, THIS JOURNAL, **68**, 2020 (1946).

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR ALLYL ETHERS

Compound	Yield, % of theoretical	Boiling point °C.	Mm.	Formula	$n^{20}D$	d^{20}_4	Molecular refraction Calcd.	Found	Allyl, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Tetraallylerythritol	57	102–104	0.01	$C_{16}H_{26}O_4$	1.4590	0.9555	80.79	80.79	58.2	58.2	68.1	68.1	9.3	9.1
Pentaallylxylitol	65	125–127	.01	$C_{20}H_{32}O_5$	1.4667	.9728	100.44	100.48	58.3	57.7	68.2	68.2	9.2	9.2
Pentaallyl-D-arabitol[a]	65	129–131	.01	$C_{20}H_{32}O_5$	1.4662	.9756	100.44	100.10	58.3	58.3	68.2	68.1	9.2	9.1
Hexaallyldulcitol	60	128–130	.01	$C_{24}H_{38}O_6$	1.4715	.9892	120.09	119.50	58.3	57.8	68.2	68.3	9.1	9.2
Hexaallyl-D-talitol	48	113–115	.01	$C_{24}H_{38}O_6$	1.4695	.9810	120.09	120.06	58.3	58.1	68.2	68.4	9.1	8.9
Hexaallyl-L-iditol[b]	55	130–133	.01	$C_{24}H_{38}O_6$	1.4705	.9831	120.09	120.03	58.3	58.0	68.2	68.4	9.1	9.1

[a] $[\alpha]^{25}D$ of an 8% solution in absolute alcohol, −3.5°. [b] $[\alpha]^{25}D$ of an 8% solution on absolute alcohol, +3.0°.

in the traps. The analysis showed that the liquid had about 60% acrolein and about 30% water. Clover[7] found that hydroperoxides of ethers can break down, with the formation of an ester and water. In the case of ethyl benzyl ether hydroperoxide, the principal decomposition product was ethyl benzoate. It is evident that if a similar reaction takes place in allyl ethers, it will proceed according to the equation

$$R{-}O{-}\underset{\displaystyle OOH}{\underset{|}{CH}}{-}CH{=}CH_2 \longrightarrow H_2O + CH_2{=}CH{-}COOR$$

In other words, formation of acrylic ester might be expected.

This hypothesis was put to a test. Allylmannitol (113 g.) was heated at 80° while oxygen was passed through the liquid. The process was stopped at about three-quarters of the way to gelation. Determination of ester equivalent gave the figure 764, corresponding to 9.3% acrylate, or about 0.5 acrylate group per mole of the original allylmannitol. An attempt to identify the acrylic acid as its *p*-bromophenacyl ester was unsuccessful, perhaps because most or all of the acrylate was in a polymerized state. Acrylic ester, if present, probably takes part in the polymerization of allyl ethers.

Experimental

Preparation of 3,4-Diallyl-D-mannitol.—1,2:5,6-Diisopropylidene-D-mannitol was prepared according to directions of Baer.[8] The crude product (m. p., 116–117° as compared with 122° for the recrystallized material) was used for the preparation of 3,4-diallyl-1,2:5,6-diisopropylidene-D-mannitol.

To a well-stirred mixture of 122 g. of diisopropylidene mannitol in 150 ml. of dioxane and 452 g. of allyl bromide heated at 80–85°, 298 g. of 50% sodium hydroxide solution gradually was added during thirty minutes. The heating and stirring was continued for six hours. The organic layer was dried with anhydrous sodium sulfate, and its volatile constituents were removed by distillation at atmospheric pressure. The residue was distilled *in vacuo*, and the fraction distilled at 110–118° at about 1 mm. was collected. The yield was 132 g. of crude diallyl-diisopropylidene-mannitol.

Anal. Calcd. for $C_{18}H_{30}O_6$: allyl, 24.0; isopropylidene, 24.6. Found: allyl, 27.6; isopropylidene,[9] 26.1.

Without further purification this substance was used for the preparation of diallylmannitol. One part of diallyl-diisopropylidene-mannitol was hydrolyzed in eight parts of 50% alcohol containing 0.2% hydrochloric acid at 70°.[10] After eight hours the hydrochloric acid was removed with silver oxide. The precipitate was filtered off and the filtrate evaporated to dryness, yielding 104 g. of crude diallylmannitol from 129 g. of crude diallyl-diisopropylidene-mannitol. The product was purified by dissolving one part in five parts of hot methyl alcohol. Eighteen parts of hot benzene and some decolorizing carbon were added. After removing most of the methyl alcohol by azeotropic distillation, the solution was filtered and allowed to crystallize. After two recrystallizations a constant melting point, 111–112° (cor.), was reached. Diallylmannitol is soluble in water, methyl and ethyl alcohol, pyridine and glacial acetic acid but insoluble in benzene, toluene, ether and hexane. $[\alpha]^{25}D$ for a 4% solution was +42.3° in absolute alcohol and +44.7° in water.

Anal. Calcd. for $C_{12}H_{22}O_6$: hydroxyl, 25.9; allyl, 31.3; C, 54.9; H, 8.45. Found: hydroxyl, 26.4; allyl, 30.1; C, 54.8; H, 8.55.

Preparation of Monoallyl-D-mannitol.—Sixty grams of crude diallylmannitol was dissolved in 100 ml. of hot methyl alcohol, and the solution was clarified with decolorizing carbon. To the boiling solution 800 ml. of hot benzene was gradually added. Boiling was continued for a while after the entire amount of benzene was added. When the total volume was about 800 ml., the solution was allowed to crystallize. The next day 13.5 g. of crystals was filtered off. On further evaporation the solution yielded crystals of diallylmannitol. The 13.5 g. of crystals was dissolved in 80 ml. of boiling methyl alcohol to which 900 ml. of boiling benzene was added. On cooling, 6.5 g. of crystals was obtained, which on one recrystallization gave a constant melting point, 119–120° (cor.); $[\alpha]^{25}D$ for a 4% solution in water was +15.8°. On further evaporation of the filtrate, 4.5 g. of diallylmannitol was obtained.

Anal. Calcd. for $C_9H_{18}O_6$: hydroxyl, 38.3; allyl, 18.5; C, 48.6; H, 8.16. Found: hydroxyl, 37.1; allyl, 18.1; C, 48.4; H, 7.94.

Preparation of Tetraallyl-D-mannitol.—Allylmannitol with approximately four allyl groups was prepared by adding gradually (half an hour) 448 g. of allyl bromide to a stirred and heated (75°) mixture of 56 g. of mannitol and 740 g. of 20% sodium hydroxide solution. The mixture was then stirred and heated for three hours more, after which it was worked up in the usual manner. It yielded 38% of the theoretical value of a product boiling at 159–162° (1 mm.). Analytical results, 46.4% allyl and 11.2% hydroxyl, indicate the presence of 3.8 allyl groups.

Allylation of Polyhydric Alcohols.—Completely allylated sugar alcohols not described previously were prepared by the two-step method described in an earlier paper.[2] In some cases (talitol, for example, where only a small quantity of substance was available) a larger excess of allyl bromide was used to increase the volume of liquid for better stirring and handling. The physical properties and analytical results for these compounds are given in Table II.

(7) Clover, THIS JOURNAL, **46**, 419 (1924).

(8) Baer, *ibid.*, **67**, 338 (1945).

(9) Elsner, *Ber* **16**, 2364 (1928).

(10) Irvine and Paterson, *J. Chem. Soc.*, **105**, 898 (1914).

Determination of Water.—The water in the acrolein–water mixture was determined with acetylpyridinium chloride reagent.[11]

Determination of Acrolein.—The acrolein was determined by the sulfite method.[12]

Determination of Ester Equivalent.—The ester equivalent was determined—by C. O. Willits and M. S. Gaspar of this Laboratory—by refluxing partially polymerized allyl ether with 0.2 *N* alcoholic sodium hydroxide, for one hour, continuing the refluxing for another hour after an equal amount of water had been added, and titrating the excess alkali electrometrically with 0.1 *N* acid.

Determination of Allyl Groups.—For completely substituted compounds the mercuric acetate modification of the Wijs method[13] gave the most accurate results.

Acknowledgment.—The assistance of Mrs. M. F. Durchsprung in making Barcroft–Warburg and allyl group determinations, and of Miss M. J. Welsh in making carbon and hydrogen analyses is acknowledged.

(11) Smith and Bryant, THIS JOURNAL, **57**, 841 (1935); also R. L. Shriner, "Quantitative Analysis of Organic Compounds," 1944, p. 40.

(12) Adams and Adkins, THIS JOURNAL, **47**, 1358 (1925); also, R. L. Shriner, ref. 11, p. 46.

(13) Hoffman and Green, *Oil and Soap*, **16**, 236 (1939); also, Boyd and Roach, *Analytical Chemistry*, **19**, 158 (1947).

Summary

Completely substituted allyl ethers of erythritol, xylitol, arabitol, dulcitol, talitol and iditol were prepared. With the increase of the chain from three to six carbons, the gelation time decreased, from 974 minutes for allylglycerol to 900 for erythritol, to 602 for pentitols, and 502 for hexitols. On the other hand, the rate of oxygen absorption decreased with the increase of the length of carbon chain. The relation between the configuration and the time of gelation of isomeric allyl ethers is not quite clear. The possibility of the formation of acrylic ester during the oxidative polymerization of allyl ethers is suggested.

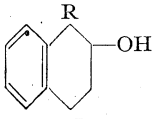
PHILADELPHIA 18, PA. RECEIVED FEBRUARY 24, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

1-Alkyl-1,2,3,4-tetrahydro-2-naphthols

BY B. C. McKUSICK[1a]

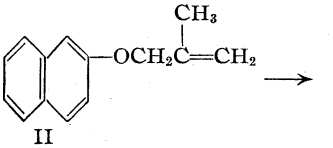
Following the finding that 1,2,3,4-tetrahydro-2-naphthol is an outstanding mosquito-repellent, several of its esters and four of its 1-alkyl homologs (I) were prepared as part of a project sponsored by the Office of Scientific Research and Development (1b) for the synthesis of new insect-repellents. The tetrahydronaphthols were prepared by hydrogenation of the corresponding 1-alkyl-2-naphthols over copper chromite.[2,3,4] The reductions were not perfectly cleancut; decahydro-2-naphthols and probably 5,6,7,8-tetrahydro-2-naphthols were by-products.



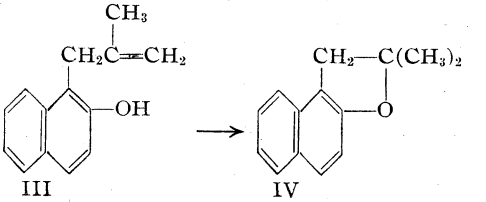
I

The 2-naphthols were synthesized by standard methods, such as reduction of 1-allyl-2-naphthol or 1-acyl-2-naphthols obtained, respectively, by the Claisen or Fries rearrangement. When an attempt was made to hydrogenate 1-*n*-butyro-2-naphthol to 1-*n*-butyl-2-naphthol over copper chromite at 130°, a major reaction was carbon–carbon hydrogenolysis to 2-naphthol and *n*-butanol. In contrast, 1-aceto-2-naphthol is reduced to 1-ethyl-2-naphthol under the same conditions.[2] Clemmensen reduction gave 1-*n*-butyl-2-naphthol in satisfactory yield.

Although allyl-2-naphthyl ether underwent a Claisen rearrangement in the normal manner, the product obtained on heating β-methylallyl-2-naphthyl ether (II) was not the expected 1-(β-methylallyl)-2-naphthol (III), but a neutral substance believed to be the isomeric dihydronaphthofuran (IV). It has been observed previously[5] that 2-(β-methylallyl)-phenols cyclize to dihydrobenzofurans much more readily than do 2-allylphenols.



II



III IV

Esters were prepared from 1,2,3,4-tetrahydro-2-naphthol and its 1-methyl homolog by treating them with acid anhydrides.

(1a) Present address: Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(1b) Contract NDCrc-136 with Harvard University, under the direction of Paul D. Bartlett as official investigator.

(2) Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

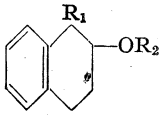
(3) Adkins and Reid, *ibid.*, **63**, 741 (1941).

(4) A paper which includes details on the hydrogenation of 2-naphthol is being prepared by Dauben, McKusick and Mueller.

(5) Bartz, Miller and Adams, THIS JOURNAL, **57**, 371 (1935); Tarbell in Adams, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc, New York, N. Y., 1944, p. 16.

TABLE I

1-ALKYL-1,2,3,4-TETRAHYDRO-2-NAPHTHOLS AND THEIR ESTERS



R_1	R_2	Boiling point °C.	mm.	$n^{25}D$	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H[a]	CH_3CO	138	11	1.5269	93	$C_{12}H_{14}O_2$	...	..	...	..
H[b]	C_2H_5CO	148	12	1.5185	95	$C_{13}H_{16}O_2$	76.7	76.4	7.9	7.9
H	n-C_3H_7CO	133–134	3	1.5129	93	$C_{14}H_{18}O_2$	77.0	77.1	8.3	8.4
CH_3	H	105–107	0.2	1.5570	58	$C_{11}H_{14}O$	81.4	80.8	8.7	8.8
CH_3	CH_3CO	147–150	14	1.5234	85	$C_{13}H_{16}O_2$	76.4	76.9	7.9	8.2
C_2H_5	H	125–130	3	1.556[c]	59	$C_{12}H_{16}O$	81.8	81.1	9.2	9.5
n-C_3H_7	H	102–107	0.3	1.540	89	$C_{13}H_{18}O$	82.1	81.7	9.5	10.0
n-C_4H_9	H	114–119	0.3	1.534	61	$C_{14}H_{20}O$	82.3	82.1	9.9	10.3

[a] Bamberger and Lodter, *Ber.*, **23**, 197 (1890). [b] Pickard and Kenyon, *J. Chem. Soc.*, **101**, 1427 (1912), prepared the *l*-ester. [c] Did not crystallize; Musser and Adkins[2] report m. p. 88–89°.

Experimental

1-Alkyl-2-naphthols.—1-Methyl-2-naphthol was obtained in 65% yield by heating 1,1-methylene-bis-(2-naphthol) with sodium methoxide[6]; it was isolated by distillation rather than extraction with hot water. 1-Ethyl-2-naphthol[7] was prepared from 1-aceto-2-naphthol by high-pressure hydrogenation over copper chromite at 130°.[2] 1-*n*-Propyl-2-naphthol,[8] m. p. 55–57° (recrystallized from hexane), was obtained in 91% yield by low-pressure hydrogenation of 1-allyl-2-naphthol[9] in 95% ethanol at 25° in the presence of Adams platinum oxide catalyst. 1-*n*-Butyl-2-naphthol, m. p. 82–83°, was prepared by the Clemmensen reduction of 1-*n*-butyro-2-naphthol.[8]

1-Alkyl-1,2,3,4-tetrahydro-2-naphthols.—These were obtained by hydrogenation of the corresponding 2-naphthols in the presence of copper chromite catalyst at 200° under hydrogen pressures of 3000–5000 lb./sq. in.[2,3,4] The hydrogenations were generally complete in two to five hours. They were equally successful with or without a solvent; usually none was used, but an equal volume of absolute ethanol was sometimes added. The weight of catalyst was 5–15% of the weight of naphthol. For the best results it was desirable to distil the naphthols over 2% by weight of Raney nickel before hydrogenation. Alternatively, poisons could be removed from a naphthol by shaking it at 200° with copper chromite and hydrogen under high pressure; one had then but to add a fresh batch of catalyst to the mixture and hydrogenate in the usual way.

To work up a reaction mixture,[4] it was diluted with an equal volume of benzene, the catalyst was removed by filtration, and the filtrate was extracted several times with 10% sodium hydroxide solution (no final washing with water), dried with magnesium sulfate, and distilled through a short Vigreux column.

In the case of 1-methyl-2-naphthol as with 2-naphthol,[4] there was no tendency for the reduction to go beyond the tetrahydro stage. The higher homologs slowly took up hydrogen after the calculated quantity had been absorbed and it was apparent from the fact that the fore-runs had lower indices of refraction than the main cuts that some decahydronaphthol had been formed. Contrary to experience in the preparation of 1,2,3,4-tetrahydro-2-naphthol,[4] the after-runs and residues from the distillations usually contained some unchanged starting material.

Some of the final products may well have contained several per cent. of impurities. In the first place, in contrast to the situation in the preparation of 1,2,3,4-tetrahydro-2-naphthol,[4] it was difficult to extract unchanged starting material or isomeric 5,6,7,8-tetrahydro-2-naphthol with alkali, the difficulty increasing with molecular weight. Secondly, purification by distillation was hindered by the closeness in boiling points of a product and its possible impurities, *i.e.*, the decahydronaphthol (boiling point lower), the naphthol (boiling point higher), and most troublesome of all, the isomeric 5,6,7,8-tetrahydro-2-naphthol (boiling point about the same). The presence of 5,6,7,8-tetrahydro-2-naphthols was not actually demonstrated in the present reductions but their presence is probable from the fact that 6–10% of one is formed during the hydrogenation of 2-naphthol under the same conditions.[4]

The tetrahydronaphthols together with their properties are listed in Table I.

1,2,3,4-Tetrahydro-2-naphthyl Esters.—The acetate, propionate and butyrate of 1,2,3,4-tetrahydro-2-naphthol[4] and the acetate of 1-methyl-1,2,3,4-tetrahydro-2-naphthol were prepared by heating the alcohols with a 20% excess of the proper anhydride for several hours on a steam-bath and distilling the reaction mixtures under reduced pressure. The properties of the esters are listed in Table I.

1,2-Dihydro-2,2-dimethylnaphtho[2,1-b]furan (IV).—β-Methylallyl chloride (139 g.) was added to a well-stirred mixture of 200 g. of 2-naphthol, 79 g. of 95% sodium methoxide, 3 g. of potassium iodide and 1 liter of methanol in an ice-bath. The mixture stood at room temperature for several days, was diluted with water, and the oil which precipitated was taken up in ether. The extract was washed successively with 10% sodium hydroxide solution and water, dried and distilled. The crude β-methylallyl 2-naphthyl ether (II), 142 g. of material distilling at 90–137° (0.3 mm.), was heated at 200° under nitrogen for six hours and distilled. The product was collected at 96–99° (0.3 mm.), $n^{25}D$ 1.6024, weight 100 g. (36% yield based on 2-naphthol). It was insoluble in Claisen[10] alkali, did not reduce dilute potassium permanganate in acetone, and only very slowly decolorized bromine in carbon tetrachloride. No hydrogen was absorbed when an alcohol solution was shaken with hydrogen at 25° and a pressure of 3 atm. in the presence of Adams platinum oxide catalyst. *Anal.* Calcd. for $C_{14}H_{14}O$: C, 84.8; H, 7.1; Found: C, 84.4; H, 7.6.

Hydrogenolysis of 1-*n*-Butyro-2-naphthol.—A mixture of 35.8 g. of 1-*n*-butyro-2-naphthol[8] and 4 g. of copper chromite catalyst was heated at 130° under an initial hydrogen pressure of 4000 lb./sq. in. Approximately

(6) Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 682 (1942).

(7) Fries and Engle, *Ann.*, **439**, 232 (1924).

(8) Gulati, Seth and Venkataraman, *J. prakt. Chem.*, **137**, 47 (1933).

(9) Hurd and Schmerling, THIS JOURNAL, **59**, 107 (1937); Adams and Rindfusz, *ibid.*, **41**, 648 (1919); Claisen, *Ber.*, **45**, 3157 (1912).

(10) Claisen, *Ann.*, **418**, 96 (1919).

two molar equivalents of hydrogen was absorbed in twenty minutes, after which no more was absorbed. The reaction mixture was taken up in acetone, filtered and distilled. Redistillation of the fore-run gave 3.4 g. of *n*-butanol (27% yield), identified by odor, boiling point (116.5–117.5°) and refractive index ($n^{25}D$ 1.3970). The amount obtained was less than the actual yield due to accidental loss of part of the fore-run. The main distillate, a solid weighing 24 g., was collected at 117–146° (1.0 mm.). It proved to be a mixture of 2-naphthol and 1-*n*-butyl-2-naphthol, with over half of it by weight the former. Fairly pure samples of each, melting at 120–121° and 77–80°, respectively, were isolated by fractional crystallization from hexane, but complete separation by this means was not practical.

Summary

Four 1-alkyl-1,2,3,4-tetrahydro-2-naphthols have been prepared by hydrogenation of the corresponding 1-alkyl-2-naphthols over copper chromite.

Instead of undergoing the Claisen rearrangement, β-methylallyl 2-naphthyl ether rearranges to what is believed to be a dihydronaphthofuran. Hydrogenation of 1-*n*-butyro-2-naphthol gives *n*-butanol and 2-naphthol besides the expected 1-*n*-butyl-2-naphthol.

WILMINGTON, DELAWARE RECEIVED FEBRUARY 27, 1948

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Arylcycloalkylamines. I. 2-Phenylcyclopropylamine

BY ALFRED BURGER AND WILLIAM L. YOST[1]

Both 1-phenyl-2-aminopropane and 1-amino-2-phenylpropane exhibit such striking effects on the central nervous system that structural variations of these drugs have received wide attention. It appeared of interest to investigate what changes in the pharmacological action of these drugs would result from the incorporation in a ring of the two-carbon chain separating the aryl from the amino group. The cyclopropyl ring was chosen as the first example because of the known analgesic and anesthetic properties of cyclopropane, cyclopropyl methyl ether (Cyprome), cyclopropyl ethyl ether (Cypreth), cyclopropylcarbinol, and related compounds.[2] It has been suggested[3] that "alicyclic residues might confer desirable pharmacological properties if introduced into compounds containing auxapharm groups. . . ." The auxapharm group in the compounds under consideration in this article is the phenethyl group.

The synthesis of the geometrically isomeric 2-phenylcyclopropylamines is reported here. The starting material was ethyl 2-phenylcyclopropanecarboxylate which had first been obtained by Buchner and Geronimus[4] from the condensation of styrene with ethyl diazoacetate. These authors heated the reagents in a sealed tube and had to cope with the high pressures of nitrogen from the reaction. These conditions were improved in the present work by slowly dropping a stoichiometric mixture of the diazo ester and styrene into an excess of styrene at 125°. Fractionation of the reaction mixture yielded from 75 to 85% of ethyl 2-phenylcyclopropanecarboxylate as a colorless oil of b. p. 103–105° (0.5–0.7 mm.).

Buchner and Geronimus hydrolyzed their ester to an acid of m. p. 105° to which they assigned the structure of *trans*-2-phenylcyclopropanecarboxylic acid. They arrived at this conclusion by nitrating their acid, reducing the nuclear nitro group, and oxidizing the resulting aminophenylcyclopropanecarboxylic acid with permanganate to *trans*-cyclopropanedicarboxylic acid. When we saponified our ester, a mixture of two isomeric carboxylic acids was always obtained which could be separated by fractional crystallization from water. The less soluble material, which we designate as 2-phenylcyclopropanecarboxylic acid A, crystallized as slender needles, m. p. 93°, and represented 74% of the total mixture.

Benzene extraction of the mother liquors of this acid yielded about 13% of a material melting at 106–107° for which we propose the name of 2-phenylcyclopropanecarboxylic acid B. Its identity with that described by the earlier investigators was corroborated by conversion of its chloride to the amide of m. p. 187–188° [190–191°(cor.)]. The amide reported in the literature[4] melts at 187–188°.

The relation of the two acids was established when it was found that the acid chloride of either product may be hydrolyzed to the A-acid, or ammonolyzed to the same amide of m. p. 190–191°. This indicates that the B-acid is probably inverted by thionyl chloride to the same acid chloride as that obtained from the A-acid, but the less likely possibility must be considered that a B-acid chloride first formed is inverted to derivatives of the A-series by hydrolysis or ammonolysis. These observations coupled with the predominant formation of the A-acid in their preparation from styrene, permit the conclusion that the acid of m. p. 93° is the more stable of a pair of geometrical isomers. It should be noted that the amide described by Buchner and Geronimus is a derivative of the lower-melting isomer they never isolated.

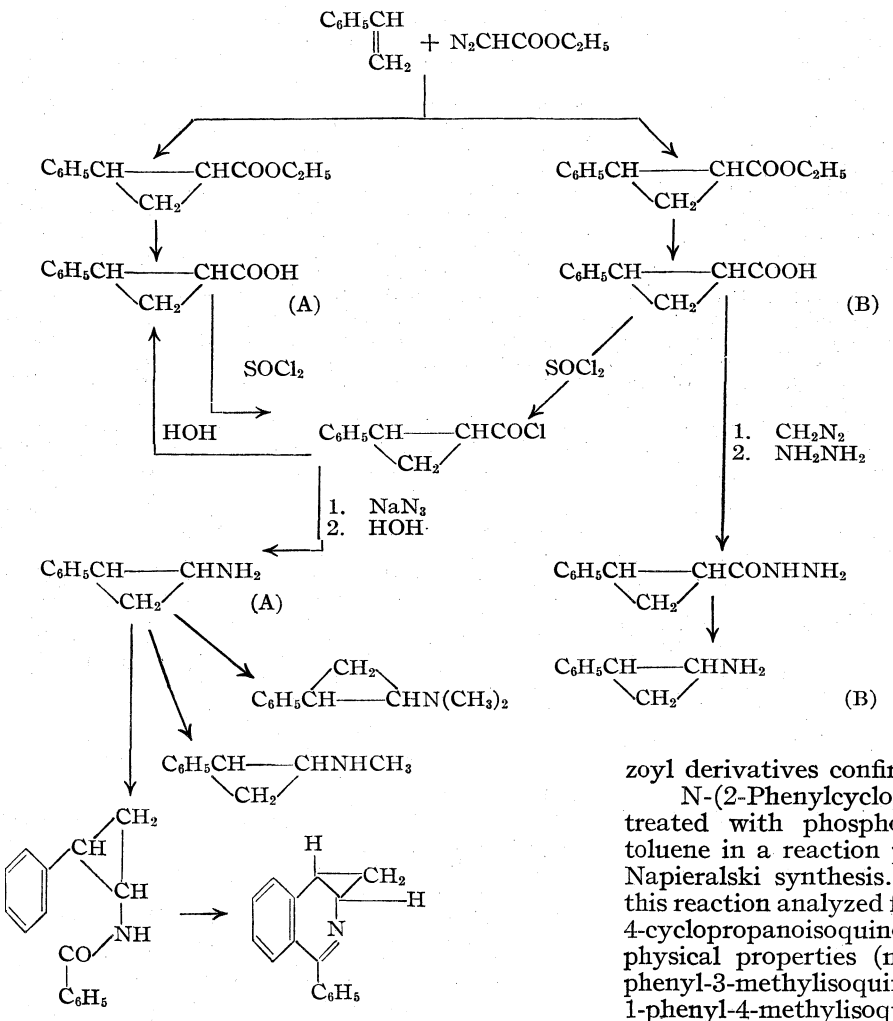
We considered the possibility that the addition of ethyl diazoacetate to styrene might have led to esters containing the ethylenic bond. This is, however, unlikely because the presence of the cy-

(1) Smith, Kline and French Laboratories Fellow.

(2) Adriani, "The Chemistry of Anesthesia," Charles C. Thomas, Publisher, Springfield, Ill., 1946, pp. 130, 174.

(3) Braker, Pribyl and Lott, THIS JOURNAL, **69**, 866 (1947).

(4) Buchner and Geronimus, *Ber.*, **36**, 3782 (1903).



clopropane ring system had already been established[4] for the acid melting at 106–107°, and the acid A can be obtained from it by means of reagents which are known not to open the cyclopropane ring.

The absolute configuration of the isomeric 2-phenylcyclopropanecarboxylic acids has not been established with certainty. The greater stability of the A-isomer casts some doubt on the previous assignment of the *trans* configuration to the B-isomer. The isomerization of the higher- to the lower-melting isomer by thionyl chloride is in accord with the general ease of conversion of *cis* to *trans* isomers by acids, acid halides, etc.

2-Phenylcyclopropane carboxamide A withstood Hofmann degradation under a number of experimental variations, and no amine could be obtained in this manner. Likewise, the A-acid (m. p. 93°) did not respond to the Schmidt reaction. However, it was found possible to subject its chloride to the Curtius degradation with sodium azide in boiling toluene; the isocyanate formed by this procedure was hydrolyzed readily to an oily 2-phenylcyclopropylamine which was characterized as the hydrochloride and benzoyl derivative. The yield of amine was 83%.

Since acid B furnishes the same chloride as its stereoisomer, it could obviously not be degraded to the amine of its own configuration by the same procedure. It was possible, however, to convert the methyl ester of acid B to a crystalline hydrazide which differed from the hydrazide of acid A prepared for comparison. Diazotization of the B-hydrazide, thermal rearrangement of the azide, and hydrolysis of the isocyanate led to a new 2-phenylcyclopropylamine, different from that obtained by Curtius degradation of acid A. The properties of the hydrochloride and benzoyl derivatives confirmed this difference.

N-(2-Phenylcyclopropyl)-benzamide A was treated with phosphorus pentoxide in boiling toluene in a reaction patterned on the Bischler–Napieralski synthesis. The base obtained from this reaction analyzed for 1-phenyl-3,4-dihydro-3,-4-cyclopropanoisoquinoline. It differed in its physical properties (m. p. 109.5–110°) from 1-phenyl-3-methylisoquinoline (m. p. 89–90°)[5] and 1-phenyl-4-methylisoquinoline [liquid, b. p. 210° (20 mm.)][6] which might have conceivably been formed by rearrangement.

Methyl-(2-phenylcyclopropyl)-amine was prepared from 2-phenylcyclopropylamine A by the Decker method,[7] and dimethyl-(2-phenylcyclopropyl)-amine by methylation of the primary amine with formaldehyde and formic acid.

The pharmacological action of the amines described in this article will be reported by Dr. E. J. Fellows of Temple University Medical School.

Acknowledgment.—We are grateful to Smith, Kline and French Laboratories for a generous grant which made this investigation possible.

Experimental[8]

Ethyl 2-Phenylcyclopropanecarboxylate.—This ester was prepared by a modification of the directions of Buchner and Geronimus.[4] A solution containing 167 g. (1.61 moles) of stabilized styrene and 183 g. (1.61 moles) of

(5) Wolfes and Dobrowsky, German Patent 456,709 (1930); *Chem. Abstr.*, **27**, 310 (1933).

(6) Boedecker and Heymons, German Patent 674,400 (1939); *Chem. Abstr.*, **33**, 5004 (1939).

(7) Decker and Becker, *Ann.*, **395**, 366 (1913).

(8) All melting points are corrected. The microanalyses were performed by Clark Microanalytical Laboratories, Urbana, Illinois.

ethyl diazoacetate was cooled to 0° and dropped into 83.5 g. (0.803 mole) of styrene with stirring, in a dry nitrogen atmosphere, at 125–135°. The rate of addition was so adjusted that the exothermic reaction held the temperature without heating. After eight hours, the gas evolution stopped, and the pale reddish mixture was distilled. A low-boiling fraction consisting largely of unchanged styrene (41% of the total amount used) was separated, and the ester was collected. It boiled at 103–105° (0.5–0.7 mm.), 105–110° (1–2 mm.), or 131° (10 mm.). The yield was 208 g. (68% based on ethyl diazoacetate, 77% based on unrecovered styrene).

2-Phenylcyclopropanecarboxylic Acid A.—A solution of 207.8 g. of the ester and 64.5 g. of sodium hydroxide in 80 cc. of water and 600 cc. of ethanol was refluxed for nine hours, the alcohol was removed by distillation, and the residue was dissolved in water. The carboxylic acid was liberated with 200 cc. of concentrated hydrochloric acid. It precipitated as an oil which solidified soon, or directly as crystals which were filtered and washed with water. The amber solid was recrystallized from boiling water in which it is soluble to about 1%.

The cooled solution deposited 131.6 g. (74.5%) of colorless felted needles which melted, after further recrystallization, at 93°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22; mol. weight, 162.2. Found: C, 74.24; H, 6.35; mol. weight, 161.8.

2-Phenylcyclopropanecarboxylic Acid B.—When the aqueous mother liquors from the recrystallization of the A-acid were concentrated and extracted with benzene, addition of low-boiling petroleum ether to the extract caused precipitation of compact crystals. The material weighed 12–13% of the calculated amount and melted, after recrystallization from boiling water, or benzene-petroleum ether, at 106–107°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22; mol. wt., 162.2. Found: C, 74.27; H, 6.09; mol. wt., 161.7.

2-Phenylcyclopropanecarbonyl Chloride.—A solution of 4.62 g. (0.0285 mole) of 2-phenylcyclopropanecarboxylic acid A or B in 15 cc. of dry benzene was refluxed with 4 cc. (*ca.* 0.057 mole) of thionyl chloride for five hours, the volatile liquids were removed, and the residue once more distilled with benzene. Fractionation of the residue yielded 4.82 g. (93.6%) of a colorless oil boiling at 108–110° (2–2.1 mm.).

Hydrolysis of the acid chloride with cold water always furnished a quantitative yield of the pure A-acid, m. p. 93°.

2-Phenylcyclopropanecarbonamide A.—When the acid chloride just described was mixed with ice-cold 20% ammonium hydroxide, the amide formed in a yield of 81%. Recrystallized from boiling water, the pale brown platelets melted at 190–191°.

The mixture melting point of the amides obtained independently from the A- or B-acid *via* their common chloride showed no depression.

2-Phenylcyclopropanecarboxylic Acid Hydrazide A.—A solution of 0.9 g. of methyl 2-phenylcyclopropanecarboxylate A ($n^{27.5}D$ 1.5263, prepared from the acid with diazomethane in almost quantitative yield) and 15 cc. of 100% hydrazine hydrate in 2 cc. of absolute ethanol was refluxed gently for five hours, and most of the liquid removed under reduced pressure. The residue was dried in a vacuum desiccator over phosphorus pentoxide, and recrystallized from absolute ethanol with the aid of some dry ether. The yield of colorless crystals was 0.75 g. (84%), m. p. 127.5–129.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O$: N, 15.90. Found: N, 15.97, 16.15.

2-Phenylcyclopropylamine A.—A three-necked flask was equipped with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser, and the condenser was connected, through a drying tube, with an azotometer arranged to collect nitrogen over water. A mixture of 15 g. of *technical* sodium azide[9] and 50 cc. of dry toluene was stirred and warmed and a solution of 10 g. of 2-phenylcyclopropanecarbonyl chloride in 50 cc. of dry toluene was added slowly. Evolution of nitrogen began almost immediately and was essentially complete when the solvent began to boil. After forty minutes 96 to 98% of nitrogen had collected in the azotometer.

Inorganic salts were filtered and washed well with dry benzene, and the solvents were removed under reduced pressure. The residual isocyanate was a clear red oil of characteristic odor. It was cooled to 10°, and treated cautiously with 100 cc. of 35% hydrochloric acid in small portions with shaking. After most of the evolution of carbon dioxide had subsided the mixture was refluxed for thirteen hours, the cooled solution was diluted with 75 cc. of water and extracted with three 50-cc. portions of ether. The acid solution was evaporated under reduced pressure with occasional additions of toluene to reduce foaming.

The almost dry residue was cooled to 0°, and made strongly alkaline with a 50% potassium hydroxide solution. The amine was extracted into several portions of ether, dried over potassium hydroxide, the solvent was removed, and the base fractionated. The colorless mobile oil boiled at 69–71° (0.5 mm.), 74–81° (1.7 mm.), and weighed 6.15 g. (83%).

Conversion to the hydrochloride proceeded best in ethyl acetate–ether solution. Over-neutralization had to be avoided because of the formation of yellow decomposition products. The crude salt, obtained in a yield of 95%, was recrystallized by dissolving it in the least amount of cold methanol, and precipitating with absolute ethyl acetate and ether. The colorless needles thus obtained sintered at 151.5°, m. p. 153.5–156.5° (dec.).

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 63.55; H, 7.53; N, 8.13; Cl, 21.05.

The **benzoyl derivative** was prepared by a Schotten-Baumann reaction. The colorless crystals were recrystallized from absolute methanol, m. p. 122–123.5°.

Anal. Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 6.03.

2-Phenylcyclopropanecarboxylic Acid Hydrazide B.—Methyl 2-phenylcyclopropanecarboxylate B was prepared from the acid with diazomethane in a yield of 92%. The oily ester showed $n^{29}D$ 1.5215. The hydrazide was obtained from the ester in the same manner as the A-isomer. The yield was 83.8%. The colorless crystals, collected from alcohol–ether, melted at 111–112°. The **hydrochloride** melted at 188–191°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: N, 13.16. Found: N, 13.17.

The **isopropylidene derivative**, prepared from the hydrazide and acetone, melted at 166–166.5°.

Anal. Calcd. for $C_{13}H_{16}N_2O$: N, 12.95. Found: N, 13.18.

2-Phenylcyclopropylamine B.—To a stirred solution of 7.5 g. of the B-hydrazide in 70 cc. of water and 20 cc. of 35% hydrochloric acid, a solution of 3.6 g. of sodium nitrite in 10 cc. of ice water was added at −3° to +5°. A yellow oil precipitated from the mixture. After another ninety minutes at 0 to 5°, the mixture was extracted with four 30-cc. portions of ether, the combined extracts were dried over sodium sulfate, and the ether was removed at 20°. The light red residue was dissolved in toluene and decomposed by heating until the evolution of nitrogen ceased. The solvent was stripped under reduced pressure, the dark isocyanate hydrolyzed by refluxing with 25 cc. of 35% hydrochloric acid for five and one-half hours, and the acid was distilled *in vacuo*. The residue was made strongly alkaline with 40% potassium hydroxide solution at 0°, the liberated amine extracted into ether, and dried over potassium hydroxide. After removal of the ether, the colorless oil boiled at 79–80° (1.5–1.6 mm.). The yield was 2.5 g. (44%).

(9) From Fairmount Chemical Co., Newark, N. J.

The **hydrochloride** crystallized from ethyl acetate and ether. The colorless crystals melted at 164–166° (dec.).

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.71; H, 7.13. Found: C, 63.62, 63.89; H, 7.13, 7.36.

A mixture melting point with the stereoisomeric hydrochloride (m. p. 153.5–156.5°) was 94–104° (dec.).

The **benzoyl derivative** crystallized from dilute ethanol, m. p. 119–120°.

Anal. Calcd. for $C_{16}H_{15}NO$: N, 5.90. Found: N, 6.07.

A mixture melting point with the A-benzoyl derivative (m. p. 122–123.5°) showed a 20–30° depression.

(2-Phenylcyclopropyl)-dimethylamine.—Following general directions[10] for the methylation of primary amines, 10.2 g. of a 40% aqueous formaldehyde solution was added to a cooled solution of 5 g. of 2-phenylcyclopropylamine A in 13.2 g. of 90% formic acid, and the mixture was refluxed overnight. The cooled reaction mixture was treated with 5.5 cc. of concentrated hydrochloric acid, the solution was evaporated under reduced pressure, the residue was made alkaline with a 50% potassium hydroxide solution, and the amine extracted into ether. After drying over potassium hydroxide and distillation of the ether, the colorless amine boiled at 70–70.5° (1.3–1.5 mm.).

The **hydrochloride** was prepared in dry ether solution and weighed 2.0 g. (27%). After recrystallization from ethyl acetate–ether, the colorless crystals showed m. p. 187–189° (dec.).

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16. Found: C, 66.85, 66.93; H, 8.20, 8.22.

(2-Phenylcyclopropyl)-methylamine.—A solution of 5 g. of 2-phenylcyclopropylamine A and 4.3 g. of benzaldehyde in 10 cc. of absolute ethanol was refluxed for three hours, the solvent was stripped under reduced pressure, and the benzal derivative distilled once. The colorless oil boiled at 170–172° (2 mm.). It was not purified further. The yield was 6 g. (70%).

A mixture of 6 g. of (2-phenylcyclopropyl)-benzalamine and 7.7 g. of methyl iodide was heated in a sealed tube at 95° for seven hours. The dark red viscous reaction product was boiled with 75 cc. of 95% ethanol for four hours, the solvent was removed under reduced pressure, the base was liberated with 40% potassium hydroxide solution and extracted with ether. The extract was dried over potassium hydroxide, the ether evaporated, and the amine distilled. The colorless mobile distillate, obtained in a yield of 25%, boiled at 88–90° (1.5 mm.).

The colorless **hydrochloride** crystallized from ethanol–ether, m. p. 99–124.5°. Repeated recrystallizations did not narrow this melting point range.

Anal. Calcd. for $C_{10}H_{14}ClN$: N, 7.63. Found: N, 7.53.

1-Phenyl-3,4-dihydro-3,4-cyclopropanoisoquinoline.—A solution of 5 g. of N-(2-phenylcyclopropyl)-benzamide A in 100 cc. of dry toluene was refluxed with 5 g. of phosphorus pentoxide for twenty minutes. Another 5 g. of phosphorus pentoxide was added, and boiling was continued for forty minutes. The mixture was cooled, the toluene decanted, and the residue was decomposed with ice and slow warming until the ice was melted. The resulting solution was cleared, washed with ether, and made strongly alkaline with a 40% potassium hydroxide solution. The reaction product was extracted with four 75-cc. portions of benzene, and the solvent was evaporated. The oily residue solidified to pale brown prisms which were recrystallized from absolute ethanol. The yield was 21%, m. p. 109.5–110.5°.

Anal. Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.97. Found: C, 88.17; H, 5.75.

The hydrochloride was hygroscopic. The **dilituarate** consisted of yellow prisms which were recrystallized from water and melted at 137–140° with darkening, and decomposed at 156–161°.

Anal. Calcd. for $C_{20}H_{16}N_4O_5$: N, 14.28. Found: N, 14.04.

Summary

Condensation of styrene with ethyl diazoacetate yields two stereoisomeric 2-phenylcyclopropanecarboxylic acids. The higher-melting member of this pair rearranges to the lower-melting one by way of their common chloride. Both acids have been degraded to the corresponding stereoisomeric 2-phenylcyclopropylamines by different modifications of the Curtius reaction. Secondary and tertiary amines in this series have been prepared, and the benzoyl derivative of the more readily accessible 2-phenylcyclopropylamine has been cyclized to a compound which probably is 1-phenyl-3,4-dihydro-3,4-cyclopropanoisoquinoline.

CHARLOTTESVILLE, VA. RECEIVED JANUARY 26, 1948

(10) Clarke, Gillespie and Weishaus, THIS JOURNAL, **55**, 4571 (1933).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Methyl 2,6-Anhydro-α-D-altroside and Other New Derivatives of Methyl α-D-Altroside[1]

BY DAVID A. ROSENFELD, NELSON K. RICHTMYER AND C. S. HUDSON

In continuation of earlier researches in this Laboratory on methyl α-D-altroside,[2] we now wish to describe a number of new crystalline derivatives of this glycoside. Our primary objective was the study of 6-desoxy-D-altrose (D-altromethylose), the corresponding L-form having been obtained previously as a sirup by Freudenberg and Raschig.[3] From methyl α-D-altroside, following the general procedure described by Haskins, Hann and Hudson,[4] we were successful in preparing, in crystalline form, methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside (I), methyl 2,3,4-tribenzoyl-6-iodo-6-desoxy-α-D-altroside (II), methyl 6-iodo-6-desoxy-α-D-altroside, and methyl 2,3,4-tribenzoyl-6-desoxy-α-D-altroside (III). However, our attempts to transform this last-named compound to the desired methyl 6-desoxy-α-D-altroside and to 6-desoxy-D-altrose have so far yielded only sirups. Gut and Prins[5] have also described these two com-

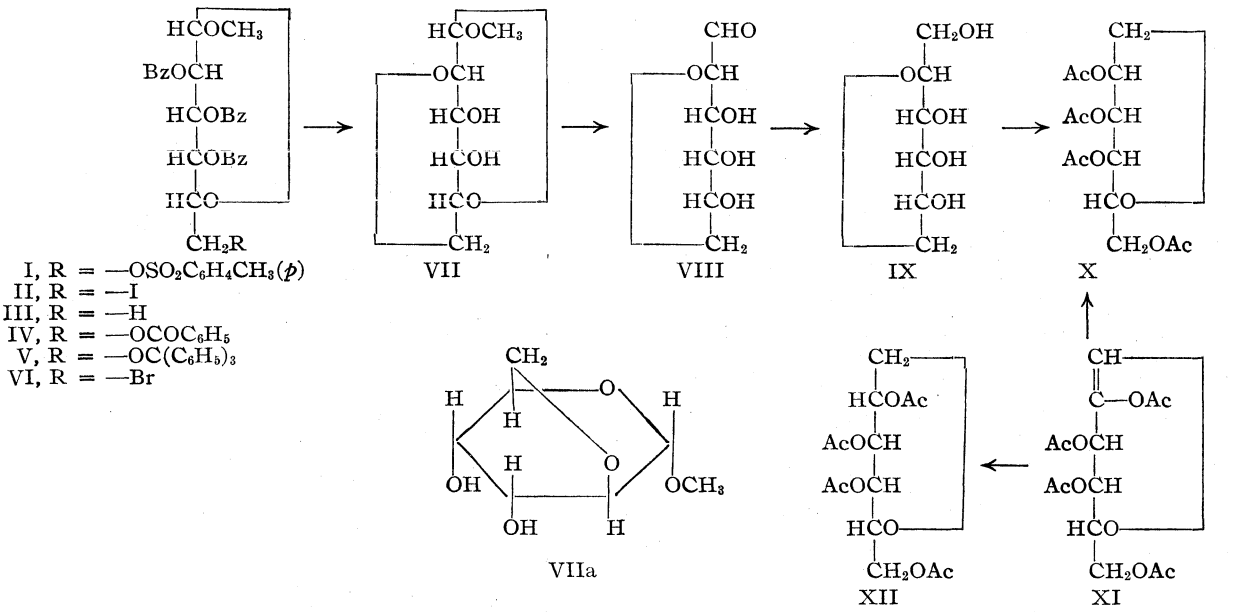
(1) Presented in part before the Division of Sugar Chemistry and Technology at the Atlantic City meeting of the American Chemical Society, April 14, 1947.

(2) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

(3) K. Freudenberg and K. Raschig, *Ber.*, **62**, 373 (1929).

(4) W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **68**, 628 (1946).

(5) M. Gut and D. A. Prins, *Helv. Chim. Acta*, **29**, 1555 (1946).



pounds recently as sirups, as well as the triacetyl derivatives analogous to our crystalline tribenzoates. A sirupy D-altromethylose has been reported also by Iwadare.[6]

The reaction of methyl α-D-altroside with benzoyl chloride in pyridine readily yields the expected tetrabenzoyl derivative (IV). The reaction with one equivalent of triphenylchloromethane in pyridine, followed by benzoylation, produces methyl 2,3,4-tribenzoyl-6-trityl-α-D-altroside (V); the corresponding triacetyl derivative has also been crystallized. By removal of the triphenylmethyl residue from V, and subsequent tosylation of the free hydroxyl group, we have converted this trityl compound to the tosyl derivative (I). A second correlation has been achieved by the action of phosphorus pentabromide upon V, whereby the trityl ether group was replaced by a bromine atom, and the resulting methyl 2,3,4-tribenzoyl-6-bromo-6-desoxy-α-D-altroside (VI) was then reduced with hydrogen and Raney nickel to methyl 2,3,4-tribenzoyl-6-desoxy-α-D-altroside (III).

Haskins, Hann and Hudson[4] have shown that methyl 2,3,4-tribenzoyl-6-tosyl-α-D-mannoside is converted readily by an excess of warm sodium hydroxide to methyl 3,6-anhydro-α-D-mannoside. Under identical conditions, methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside (I) likewise undergoes debenzoylation and loss of the tosyl group to form an anhydride, which melts at 98° and has $[\alpha]^{20}D$ + 44.6° in water. In the sugars which are known to form a 3,6-anhydroglycopyranoside from a 6-substituted glycopyranoside, namely, D-glucose, D-mannose and D-galactose,[7] the hydroxyl group on carbon 3 is on the same side of the sugar ring as the side chain carbon 6, that is, on the left in the usual Fischer projection formula; in the D-altroside only the hydroxyl on carbon 2 can be written on the left. A 2,6-anhydro ring might thus be anticipated rather than a 3,6-anhydro ring, and the new compound was indeed proved to be methyl 2,6-anhydro-α-D-altropyranoside (VII and VIIa). The simplest method of distinguishing between a 2,6-ring and a 3,6-ring, assuming the original 1,5-ring to be intact, was to apply the method of periodate oxidation. A 3,6-anhydride would not be expected to react with sodium metaperiodate; our 2,6-anhydro compound, having two adjacent hydroxyl groups, consumed rapidly one equivalent of oxidant, and liberated neither formic acid nor formaldehyde.

Further proof of the structure of methyl 2,6-anhydro-α-D-altropyranoside (VII) was secured by a series of reactions which ruptured the 1,5-ring and left the 2,6-ring intact. The glycosidic methyl group was first removed by mild acid hydrolysis, and the resulting 2,6-anhydro-D-altrose (VIII) was reduced with hydrogen and Raney nickel to an anhydrohexitol (IX) which might be named 2,6-anhydro-D-altritol, but is preferably called 1,5-anhydro-D-talitol. While neither VIII nor IX has yet been obtained in crystalline form, the latter yielded a tetraacetyl derivative (X) which separated as prisms melting at 107°, and with $[\alpha]^{20}D$ −16.2° in chloroform. These data are in good agreement with those of the prismatic crystals of melting point 108° and $[\alpha]^{22}D$ −15.3° described by Freudenberg and Rogers.[8] Their compound, prepared by the catalytic hydrogenation of 2,3,4,-6-tetraacetyl-2-hydroxy-D-galactal (XI), could be either 2,3,4,6-tetraacetyl-1,5-anhydro-D-talitol

(6) K. Iwadare, *Bull. Chem. Soc. Japan*, **17**, 296 (1942); *C. A.*, **41**, 4457g (1947).

(7) See S. Peat's review of the chemistry of anhydro sugars in "Advances in Carbohydrate Chemistry," Vol. 2, Academic Press Inc., Publishers, New York, N. Y., 1946, pp. 37–77.

(8) W. Freudenberg and E. F. Rogers, THIS JOURNAL, **59**, 1604 (1937).

(X) or 2,3,4,6-tetraacetyl-1,5-anhydro-D-galactitol (XII), because the addition of hydrogen to the ethylenic linkage could give rise to either or both of these isomers. Our work identifies their compound as the D-talitol derivative (X) because only that one is possible if we start with a D-altrose derivative. The recent synthesis in this Laboratory of 2,3,4,6-tetraacetyl-1,5-anhydro-D-galactitol (XII),[9] which is quite different from the compound first described by Freudenberg and Rogers, and now by us, completes the series of compounds and correlates all three researches.

We have prepared the methyl 2,6-anhydro-α-D-altroside (VII) by the action of alkali not only upon the 6-tosyl derivative (I) but also upon the 6-bromo derivative (VI) and the 6-iodo derivative (II). Although the formation of methyl 3,6-anhydroglycosides from 6-bromo compounds has been reported previously,[10] we believe that this is the first time that a cyclic anhydride of a glycoside has been obtained from a 6-iodo compound. However, the reaction was accompanied by the formation of a highly colored solution with attendant low yield of the anhydro compound, and the reaction cannot be recommended for preparative purposes.

It will be interesting to learn whether the compound reported by Steiger and Reichstein[11] to be an isopropylidene derivative of a methyl anhydro-D-altroside, of melting point 132° and $[\alpha]^{18}D$ −43.0°, is the 3,4-isopropylidene derivative of methyl 2,6-anhydro-β(or α)-D-altroside.

Although methyl 2,6-anhydro-α-D-altropyranoside does not show the extreme sensitivity to acids that is shown by the 3,6-anhydro derivatives of methyl α-D-galactopyranoside[12] and methyl α-D-glucopyranoside,[13] and appears to be completely stable under ordinary conditions in the laboratory, it is hydrolyzed readily by *N* hydrochloric acid at 20°. We were unable to compare the rate of hydrolysis of methyl 2,6-anhydro-α-D-altropyranoside with that of methyl α-D-altropyranoside because D-altrose, the hydrolysis product of the latter, readily forms 1,6-anhydro-D-altrose (= D-altrosan<1,5>β<1,6>) in acid solution. However, sucrose is hydrolyzed about twenty-two times faster, and methyl α-D-glucopyranoside only about one-ninetieth as fast as methyl 2,6-anhydro-α-D-altroside under comparable conditions.

Experimental Part

Methyl α-D-altroside was prepared from methyl α-D-glucoside essentially as described in a preceding publication,[2] except that ethylene dichloride was used as a solvent whenever possible instead of the more expensive chloroform. The **methyl 2,3-ditosyl-4,6-benzylidene-α-D-glucoside**[14] which was used in our earlier study crystallized as needles melting at 147–148°. A new modification has since been obtained in large, chunky prisms which melt at 154–155°. The two forms have identical rotations, $[\alpha]^{20}D$ +11.8° in chloroform (*c*, 6). In contrast to the behavior of the two modifications of the corresponding derivative of methyl β-D-glucoside reported by Littmann and Hess,[14] either form of our compound can be obtained as desired by inoculating an ethylene dichloride solution of either form with the appropriate seed crystal.

Anal. Calcd. for $C_{28}H_{30}O_{10}S_2$: C, 56.93; H, 5.12. Found (155° form): C, 57.04; H, 5.28.

In the transformation of each 100 g. of ditosyl compound to the methyl 2,3-anhydro-4,6-benzylidene-α-D-alloside it was necessary to use 1500 ml. of ethylene dichloride and 450 ml. of methyl alcohol (including 0.85 mole of sodium methoxide) to maintain a homogeneous solution.

In our most recent preparations of methyl α-D-altroside we have found it unnecessary to isolate the methyl 2,3-ditosyl-4,6-benzylidene-α-D-glucoside, and considerable time may be saved by using a modified procedure. Thus, 100 g. of well-dried, crude methyl 4,6-benzylidene-α-D-glucoside was dissolved in 600 ml. of a "practical" grade of pyridine (dried over sticks of potassium hydroxide, and filtered) and 250 g. of *p*-toluenesulfonyl chloride was added. The reaction mixture, after three days at room temperature, was decomposed with ice and water, and the product extracted with ethylene dichloride. Pyridine was removed from this extract by washing with cold dilute sulfuric acid, and after further washing with water, aqueous sodium bicarbonate, and water, and drying with granular calcium chloride, the volume was adjusted to 1500 ml. The solution was cooled in the refrigerator and to it was added a cold solution of 450 ml. of methyl alcohol containing 1.4 moles of sodium methoxide (twice the theoretical amount required to effect detosylation and anhydride formation on the assumption that the starting material was all in the form of the ditosyl compound). The mixture was kept in the refrigerator for three days, with occasional shaking at first to prevent the separation of the liquid into two layers, and then allowed to stand at room temperature for two additional days. The solution was diluted with water, and the ethylene dichloride layer and extracts washed with water, dried over granular calcium chloride, and concentrated *in vacuo*. The crystalline anhydroalloside, filtered and washed with the aid of ether, weighed 70 g., representing 75% of the theoretical amount based on the 100 g. of methyl 4,6-benzylidene-α-D-glucoside.

The alkaline hydrolysis of the anhydroalloside to methyl 4,6-benzylidene-α-D-altroside and the subsequent mild acid hydrolysis to methyl α-D-altroside were then carried out as previously described.[2]

Methyl 2,3,4,6-Tetrabenzoyl-α-D-altroside (IV).—A solution of 5 g. of methyl α-D-altroside in 75 ml. of pyridine was cooled in an ice-bath, and to it was added 15 ml. of benzoyl chloride. After standing for twenty-four hours at room temperature, the mixture was poured into one liter of ice and water, and the precipitated gum was washed thoroughly by stirring with fresh portions of water several times during the course of the next few days. Crystals were first observed after the gum had stood under water in the refrigerator for about two months. The crystalline product weighed 7 g. and was recrystallized five times from ethyl alcohol as large, brilliant prisms; the m. p. was 94–96°, and $[\alpha]^{20}D$ +32.6° in chloroform (*c*, 4).

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95. Found: C, 68.97; H, 4.94.

(9) H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 310 (1948).

(10) *E. g.*, that of the β-D-glucoside by E. Fischer and K. Zach [*Ber.*, **45**, 456 (1912)], that of the α-D-galactoside by F. Valentin [*Coll. Czechoslov. Chem. Commun.*, **4**, 371 (1932)], and that of the α-D-mannoside by F. Valentin [*ibid.*, **6**, 354 (1934)].

(11) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **19**, 1011 (1936).

(12) W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 620 (1940).

(13) W. N. Haworth, L. N. Owen and F. Smith, *ibid.*, 88 (1941).

(14) H. Ohle and K. Spencker, *Ber.*, **61**, 2392 (1928); D. S. Mathers and G. J. Robertson, *J. Chem. Soc.*, 696 (1933); O. Littmann and K. Hess, *Ber.*, **67**, 524 (1934); H. Ohle and F. Just, *ibid.*, **68**, 601 footnote 5 (1935).

Methyl 2,3,4-Triacetyl-6-trityl-α-D-altroside.[15]—A mixture of 6.75 g. of methyl α-D-altroside and 13 g. of triphenylchloromethane in 50 ml. of pyridine was heated for three hours on the steam-bath, cooled, 25 ml. of acetic anhydride added, and the mixture allowed to stand for three days at room temperature. At the end of that time the flask contained a considerable number of large, colorless crystals which were removed by filtration, washed with pyridine, and recrystallized from a mixture of chloroform and pentane as prisms melting at 175°. The action of hot aqueous sodium hydroxide upon the compound liberated pyridine, which was recognized by its odor, and triphenylcarbinol, which was identified by its melting point and by a mixed melting point with an authentic specimen. These properties, together with analyses of the substance, indicate that it is the double compound of pyridine hydrochloride with triphenylcarbinol (probably present as an impurity in the triphenylchloromethane), melting at 174°, which was described by Helferich and Sieber.[16]

Anal. Calcd. for $C_{24}H_{22}ClNO$: C, 76.68; H, 5.90; Cl, 9.43; N, 3.73. Found: C, 76.69; H, 6.05; Cl, 9.57; N, 4.01.

The filtrate from the double compound was diluted with ice water and the precipitated solid extracted with chloroform. The chloroform solution was washed with 20% aqueous copper sulfate or cold, dilute sulfuric acid to remove the pyridine, then with water, aqueous bicarbonate, and water, dried with granular calcium chloride, and concentrated to a sirup which crystallized readily. The product weighed 9 g. It was recrystallized three times from chloroform by the addition of ether and isopentane, and then twice from alcohol. The elongated prisms melted at 165–166° after sintering a few degrees lower, and showed $[\alpha]^{20}D$ +44.8° in chloroform (*c*, 2).

Anal. Calcd. for $C_{32}H_{34}O_9$: C, 68.31; H, 6.09. Found: C, 68.55; H, 6.17.

Methyl 2,3,4-Tribenzoyl-6-trityl-α-D-altroside (V).—Ten grams of methyl α-D-altroside in 100 ml. of pyridine was heated for three hours with 15.8 g. of triphenylchloromethane, then cooled, and 27.4 ml. of benzoyl chloride added. After two days the mixture was decomposed by pouring into ice water. The next day the precipitated gum was extracted with chloroform, and the solution washed successively with water, cold dilute sulfuric acid, water, aqueous sodium bicarbonate, and water. This solution was dried with Drierite, filtered, and concentrated *in vacuo* to a sirup. The first crystalline material was obtained by fractional extraction of this sirup with ethyl alcohol; the radiating clusters of small needles melted about 96–98°, and were not very soluble in alcohol. When these crystals were found to be readily recrystallizable from ether, the several alcohol solutions and residue were combined and concentrated again to a sirup which was dissolved in ether and crystallized with the aid of isopentane. The product separated in large prisms, and weighed 29 g. The melting point of 83–85° with evolution of gas indicated solvent of crystallization; the material lost weight slowly at room temperature, and finally reached a constant weight, when heated at 70°, with a loss corresponding to one molecule of ether of crystallization.

Anal. Calcd. for $C_{47}H_{40}O_9 \cdot (C_2H_5)_2O$: ether, 9.01. Found: ether, 8.86.

Finally, the compound was purified by recrystallizing it from chloroform by the addition of absolute alcohol, from which it separated in small plates. After five recrystallizations the melting point was 139–140°, and the rotation, $[\alpha]^{20}D$, was +15.2° in chloroform (*c*, 4).

Anal. Calcd. for $C_{47}H_{40}O_9$: C, 75.38; H, 5.38. Found: C, 75.43; H, 5.49.

Methyl 2,3,4-Tribenzoyl-6-tosyl-α-D-altroside (I). (a) From Methyl α-D-Altroside.—A solution of 10 g. of methyl α-D-altroside in 150 ml. of pyridine was cooled in an ice-bath and stirred vigorously while a cold solution of 11 g. of *p*-toluenesulfonyl chloride (1.1 molecular equivalents) in 20 ml. of pyridine was added dropwise. The mixture was left for six hours at 20°, then 20 ml. (3.3 molecular equivalents) of benzoyl chloride was added and the mixture kept at 20° for an additional eighteen hours. Decomposition was effected by pouring the mixture into 2 liters of ice and water. The aqueous layer was decanted, and the gummy residue was triturated with water, twice with 200 ml. of 2% aqueous sodium bicarbonate solution, then three times with water, and drained as well as possible. The heavy gum was extracted twice with boiling ethyl alcohol, two 200-ml. portions usually being sufficient to dissolve the material. The solutions deposited about 7 g. (21%) of product melting at 144–146°; small additional amounts were obtained by reworking the mother liquors. A number of variations on this procedure failed to improve the yield, and no methyl 2,3,4,6-tetrabenzoyl-α-D-altroside could be isolated from the non-crystalline residues. The methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside was purified by several recrystallizations from alcohol; it formed acicular prisms which melted at 149–150° and showed $[\alpha]^{20}D$ +30.3° in chloroform (*c*, 3).

Anal. Calcd. for $C_{35}H_{32}O_{11}S$: C, 63.63; H, 4.88. Found: C, 63.77; H, 4.74.

(b) From Methyl 2,3,4-Tribenzoyl-6-trityl-α-D-altroside (V).—In order to correlate the 6-trityl derivatives with the 6-tosyl derivatives, the following experiment was performed. Five grams of the methyl 2,3,4-tribenzoyl-6-trityl-α-D-altroside was dissolved in 100 ml. of warm glacial acetic acid, the solution was cooled to room temperature, and 3 ml. of glacial acetic acid saturated with gaseous hydrobromic acid was added. After thirty minutes the mixture was poured into one liter of ice water, and extracted with chloroform; the chloroform solution was washed with aqueous bicarbonate and water, dried with Drierite, and concentrated *in vacuo* to a sirup. Upon the addition of methyl alcohol the sirup yielded 0.64 g. of triphenylcarbinol. The mother liquor was concentrated to a dry sirup, taken up in pyridine, and 5 g. of *p*-toluenesulfonyl chloride added. After three days at room temperature the reaction mixture was decomposed with ice and water, and the product extracted with chloroform, which was then washed, dried, and concentrated to a sirup in the usual manner. The product was crystallized with the aid of ether and pentane to yield 1.6 g. of the desired methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside; after two recrystallizations from ethyl alcohol the acicular prisms melted at 149–150° and showed $[\alpha]^{20}D$ +29.9° in chloroform (*c*, 2) in good agreement with the values reported in the preceding paragraph. A mixture of the two samples showed no depression in melting point.

Methyl 2,3,4-Tribenzoyl-6-iodo-6-desoxy-α-D-altroside (II).—A solution containing 5 g. of methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside and 5 g. of sodium iodide in 40 ml. of acetonylacetone was heated at 70° for eighteen hours. The precipitated sodium *p*-toluenesulfonate, filtered from the solution after cooling, weighed 1.4 g. (theory, 1.5 g.). The filtrate, upon dilution with water, deposited 4.8 g. of product which was recrystallized several times from acetone by the slow addition of water. The acicular prisms of the purified substance melted at 143–145°, and showed $[\alpha]^{20}D$ +2.5° in chloroform (*c*, 4).

Anal. Calcd. for $C_{28}H_{25}IO_8$: C, 54.56; H, 4.09. Found: C, 54.98; H, 4.27.

Methyl 6-Iodo-6-desoxy-α-D-altroside.—Debenzoylation of the preceding compound catalytically with barium methoxide, followed by removal of the barium ions by

(15) First prepared by Mr. Frank G. Young in this Laboratory during the summer of 1940.

(16) B. Helferich and H. Sieber, *Ber.*, **59**, 600 (1926). A double compound presumed to consist of pyridine and triphenylchloromethane, melting at 173–174°, has been described by C. A. Kraus and R. Rosen [THIS JOURNAL, **47**, 2744 (1925)]; the analyses, reported only for chlorine, are not sufficient to enable one to decide whether their compound was also identical with that of Helferich and Sieber.

precipitation with the equivalent amount of sulfuric acid, yielded almost the theoretical amount of methyl 6-iodo-6-desoxy-α-D-altroside. The product, recrystallized four times from chloroform by the addition of ether or isopentane, formed clusters of rectangular prisms melting at 105–106°. The $[\alpha]^{20}D$ value was +91.4° in chloroform (*c*, 1) and +79.3° in water (*c*, 1).

Anal. Calcd. for $C_7H_{13}IO_5$: C, 27.65; H, 4.31. Found: C, 27.76; H, 4.58.

Methyl 2,3,4-Tribenzoyl-6-bromo-6-desoxy-α-D-altroside (VI).—To a solution of 22.9 g. of methyl 2,3,4-tribenzoyl-6-trityl-α-D-altroside in 200 ml. of dry, alcohol-free chloroform was added a mixture of 12.2 g. of phosphorus tribromide and 7.2 g. of bromine in 200 ml. of chloroform, corresponding to a 50% excess of the amount of phosphorus pentabromide required for the reaction. After three hours the reaction mixture was decomposed with ice water, and the chloroform layer separated and washed successively with water, aqueous bicarbonate, water, aqueous thiosulfate, and water, dried with Drierite, and concentrated *in vacuo* to a sirup. The product crystallized readily upon the addition of methyl alcohol in a yield of 13.2 g. (76%); from the mother liquor, concentrated to a sirup and taken up in ether, was obtained 6.8 g. (85%) of triphenylcarbinol which had been formed by hydrolysis of the other cleavage product, triphenylbromomethane.

The methyl 2,3,4-tribenzoyl-6-bromo-6-desoxy-α-D-altroside was freed from a small amount of levorotatory material by six recrystallizations from hot methyl alcohol; the rotation $[\alpha]^{20}D$ ±0.0° in chloroform (*c*, 8; *l*, 4) was unchanged by eight additional recrystallizations from a mixture of chloroform and pentane. The product separated as prisms melting at 146–147°.

Anal. Calcd. for $C_{28}H_{25}BrO_8$: C, 59.06; H, 4.43. Found: C, 59.11; H, 4.46.

Methyl 2,3,4-Tribenzoyl-6-desoxy-α-D-altroside (III).—Five grams of powdered methyl 2,3,4-tribenzoyl-6-iodo-6-desoxy-α-D-altroside and 1 ml. of Raney nickel catalyst were suspended in 200 ml. of methyl alcohol containing 1.7 ml. of diethylamine, and the mixture was shaken with hydrogen at atmospheric pressure. The absorption of one equivalent of gas was complete in about fifty minutes. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The crystalline residue was stirred with several portions of water to remove the diethylamine hydroiodide, and the residue was recrystallized from methyl alcohol in a yield of 2.7 g. After three additional recrystallizations the small, chunky prisms melted at 134–135° and showed $[\alpha]^{20}D$ −15.5° in chloroform (*c*, 3).

Anal. Calcd. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34; OCH_3, 6.33. Found: C, 68.69; H, 5.18; OCH_3, 6.32.

In the same manner, 5.0 g. of slightly impure methyl 2,3,4-tribenzoyl-6-bromo-6-desoxy-α-D-altroside yielded 3.0 g. of reduction product. After two recrystallizations from methyl alcohol the small, chunky prisms melted at 133–134°, and a mixture with the compound prepared from the iodo derivative melted at 133–135°; the specific rotation, however, was −19.6° in chloroform, and after twenty-five recrystallizations the substance still contained a small amount of more levorotatory impurity as shown by the value $[\alpha]^{20}D$ −17.3°.

Methyl 2,6-Anhydro-α-D-altropyranoside (VII). (a) From Methyl 2,3,4-Tribenzoyl-6-tosyl-α-D-altroside (I).—A mixture of 10 g. of methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside, 150 ml. of methyl cellosolve, and 67 ml. of 1 *N* sodium hydroxide (4.4 molecular equivalents) was heated on the steam-bath for one hour. The solution was cooled, neutralized with carbon dioxide, and concentrated *in vacuo* to dryness; a 50-ml. portion of ethyl acetate was added, and the mixture concentrated again to dryness. The product was removed from the mixture of solid sodium salts by extracting three times with 100-ml. portions of boiling anhydrous ethyl acetate. The extract, upon concentration *in vacuo*, left a sirup which crystallized after standing a few days. The average yield from a number of such experiments was 1.7 g. The methyl 2,6-anhydro-α-D-altroside was recrystallized first from acetone by the cautious addition of ether, and then from ethyl acetate, as large elongated prisms, melting, when pure, at 97–98°, and with $[\alpha]^{20}D$ +44.6° in water (*c*, 2).

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87; OCH_3, 17.61. Found: C, 47.74; H, 6.97; OCH_3, 17.55.

(b) From Methyl 2,3,4-Tribenzoyl-6-bromo-6-desoxy-α-D-altroside (VI).—The catalytic debenzoylation of methyl 2,3,4-tribenzoyl-6-bromo-6-desoxy-α-D-altroside with sodium methoxide, unlike that of the analogous iodo compound, failed to yield a crystalline product. Accordingly, 50 ml. of an aqueous solution of such a preparation, containing about 2.6 g. of methyl 6-bromo-6-desoxy-α-D-altroside ($[\alpha]^{20}D$ about +80° in water), was heated for two hours on the steam-bath with 2.5 g. of sodium hydroxide. The light-brown solution was neutralized with carbon dioxide, decolorized with activated carbon, and concentrated *in vacuo* to dryness. The product was extracted with hot ethyl acetate, and 1.6 g. of methyl 2,6-anhydro-α-D-altroside was obtained; it was identified, after several recrystallizations, by its melting point, mixed melting point, and rotation.

(c) From Methyl 6-Iodo-6-desoxy-α-D-altroside.—A solution containing 2.2 g. of methyl 6-iodo-6-desoxy-α-D-altroside and 2.2 g. of sodium hydroxide in 35 ml. of water was heated on the steam-bath for two hours. The dark, reddish-brown solution was neutralized with carbon dioxide, treated with carbon, concentrated to dryness, and extracted with ethyl acetate as above. Evaporation of the ethyl acetate left 0.85 g. of a yellowish-red sirup which did not crystallize when inoculated with the expected 2,6-anhydro compound. The sirup was therefore acetylated with acetic anhydride and pyridine at room temperature. The product was isolated in the usual manner, yielding 1.5 g. of a sirup which crystallized when inoculated with the known diacetate of the 2,6-anhydro compound (see below). One recrystallization from chloroform by the addition of pentane produced 1.0 g. of yellowish prisms; the colored impurity was removed by a fractional recrystallization, and the diacetate was obtained as the characteristic colorless elongated prisms, identical in melting point and rotation with those described in the following paragraph.

Methyl 2,6-Anhydro-3,4-diacetyl-α-D-altroside.—Acetylation of the purest 2,6-anhydroaltroside (prepared from methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside) with acetic anhydride and pyridine in the usual manner furnished the diacetate in practically quantitative yield. The product was recrystallized twice from chloroform by the addition of pentane, separating as elongated prisms of m. p. 100–101° and $[\alpha]^{20}D$ +32.5° in chloroform (*c*, 2). These values were unchanged by two additional recrystallizations.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.76; H, 6.20; OCH_3, 11.92. Found: C, 50.96; H, 6.53; OCH_3, 11.80.

Oxidation of Methyl 2,6-Anhydro-α-D-altroside with Sodium Metaperiodate.—To a solution of 0.5292 g. of the anhydro compound in 75 ml. of water was added 15 ml. of 0.4445 *M* sodium periodate solution, and the mixture diluted exactly to 100 ml. with water. The first rotation was observed twenty minutes after adding the reagent and was unchanged after four days; the value $[\alpha]^{20}D$ +113.5° was calculated for the expected oxidation product, the dialdehyde $C_7H_{10}O_5$. The first determination of the amount of reagent consumed showed that the reaction was complete at the end of forty-five minutes, and the value of 1.03 molecular equivalents of periodate had changed only to 1.07 molecular equivalents after four days. Neither formic acid nor formaldehyde could be detected in the reaction mixture.

Hydrolysis of Methyl 2,6-Anhydro-α-D-altroside with Hydrochloric Acid.—In 0.1 *N* hydrochloric acid at 20° there was no appreciable hydrolysis of the anhydroaltroside in nineteen hours; when the solution was heated in a

boiling water-bath, hydrolysis appeared to be complete within one hour. For a 2% solution of the anhydroaltroside in 0.01 *N* hydrochloric acid at 98°, the unimolecular velocity coefficient, calculated in minutes and decimal logarithms, was 0.0062; the time required for 50% hydrolysis was forty-nine minutes. Methyl α-D-glucoside in 0.1 *N* hydrochloric acid, other conditions being the same, yielded a unimolecular velocity coefficient of 0.00068; on the assumption that the rate is proportional to the acidity, this indicates that methyl 2,6-anhydro-α-D-altroside is hydrolyzed about ninety times as rapidly as methyl α-D-glucoside.

The hydrolysis of methyl 2,6-anhydro-α-D-altroside by 1 *N* hydrochloric acid at 20° was readily observed with the saccharimeter. A 4% solution required 2712 minutes for 50% hydrolysis, and the velocity coefficient was calculated to be 0.000111. An equimolecular solution of sucrose (7.8%) under the same conditions had a velocity coefficient of 0.00244 and the time required for 50% hydrolysis was 121 minutes. Hence, sucrose is hydrolyzed about 22 times as rapidly as an equimolecular solution of the anhydroaltroside.

The solutions obtained by the hydrolysis of the anhydroaltroside had a rotation, calculated as a 2,6-anhydro-D-altrose, of $[\alpha]^{20}D$ −21°. A few drops of solution restored the color to Schiff reagent within a few seconds; crystalline D-altrose restored the color slowly, and D-glucose not at all. In a separate experiment, using *N* sulfuric acid followed by neutralization with solid barium carbonate, we have been unable to obtain a crystalline 2,6-anhydroaltrose.

Hydrogenation of 2,6-Anhydro-D-altrose and the Isolation of Tetraacetyl-1,5-anhydro-D-talitol (X).—The solution obtained by the hydrolysis of several portions of methyl 2,6-anhydro-α-D-altroside (total weight 4.0 g.) with dilute hydrochloric acid were combined, neutralized to litmus with dilute sodium hydroxide, and concentrated *in vacuo* to 50 ml. The solution was transferred to the glass liner of a steel bomb, and hydrogenated, in the presence of 3 g. of Raney nickel, for six hours at 100° under a pressure of 1500 lb. per square inch. The solution no longer reduced Fehling solution. It was concentrated *in vacuo* to a dry sirup, and acetylated with 50 ml. of acetic anhydride and 50 ml. of pyridine. The acetylated product was isolated in the usual manner, and crystallized spontaneously from its concentrated ether solution. The yield was 5.5 g., or 73%. The tetraacetyl-1,5-anhydro-D-talitol thus obtained was recrystallized twice from ether, then twice from chloroform by the addition of pentane. The elongated prisms melted at 106–107°, and showed $[\alpha]^{20}D$ −16.2° in chloroform (*c*, 5); Freudenberg and Rogers[8] reported prisms of m. p. 108° and $[\alpha]^{22}D$ −15.31° in chloroform (*c*, 2).

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.62; H, 6.13.

The Specific Rotation of 1,5-Anhydro-D-talitol (IX).—The deacetylation of 2.4566 g. of tetraacetyl-1,5-anhydro-D-talitol by 0.5 ml. of 3% sodium methoxide in 50 ml. of methyl alcohol, followed by careful concentration of the solution in a desiccator over granular calcium chloride, yielded a sirup which in separate experiments we have been unable to crystallize. This sirup was dissolved and transferred quantitatively to a 25-ml. volumetric flask, and its rotation determined in a 4-dm. tube. Our value $[\alpha]^{20}D$ −11.4° in water (*c*, 4.85) is somewhat higher than the $[\alpha]^{23}D$ −7.34° reported by Freudenberg and Rogers for their sirup which was prepared in a different manner.

Acknowledgment.—The authors wish to thank Dr. Arthur T. Ness, Mr. Charles A. Kinser, Mrs. Betty G. Mount and Mrs. Margaret M. Ledyard of this Institute for carrying out the microchemical analyses.

Summary

Ten new crystalline derivatives of methyl α-D-altroside have been described. One of these, prepared by the action of alkali on the 6-tosyl, 6-bromo, or 6-iodo derivative, is methyl 2,6-anhydro-α-D-altropyranoside; this is a new type of anhydroglycoside, in contrast to the 3,6-anhydroglycosides of D-glucose, D-mannose, and D-galactose.

The acid hydrolysis of methyl 2,6-anhydro-α-D-altroside, followed by catalytic hydrogenation of the 2,6-anhydro-D-altrose, yields 1,5-anhydro-D-talitol; the crystalline tetraacetate of this substance has been identified with the product obtained previously by W. Freudenberg and K. F. Rogers by the catalytic hydrogenation of 2,3,4,6-tetraacetyl-2-hydroxy-D-galactal.

BETHESDA, MARYLAND RECEIVED FEBRUARY 11, 1948

[CONTRIBUTION FROM THE OREGON FOREST PRODUCTS LABORATORY AND THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

The Constituents of Sierra Juniper Wood (*Juniperus occidentalis*, Hooker)

BY E. F. KURTH AND HOMER B. LACKEY*

Sierra Juniper is native to altitudes ranging from 3,000 to 11,000 feet in California, Oregon, Washington, and Western Idaho. It is a low, broadheaded tree, 20 to 65 feet high, with thick trunk and stout horizontal branches. The larger trees may reach a circumference of nine feet and an age of 2,000 years. The heartwood is pale reddish-brown and the sapwood is nearly white.

It appears that no previous investigation has been made of the extractive from this species. Because large numbers of the trees are found in proposed reclamation areas, it became advisable to ascertain the constituents of the extractives from the wood.

* A part of the research reported in this paper was submitted in partial fulfillment of the requirements for degree of Master of Science in Chemistry, Oregon State College, June, 1948.

Experimental

The material for the investigation was collected from trees felled for the purpose in the vicinity of Bend, Oregon, and included cross sections from the top and bottom of logs, stumpwood and rootwood. After the bark was removed, representative specimens of sapwood, heartwood, whole wood, stumpwood and rootwood were shredded separately in a Greundler Peerless Grinder. At the time of shredding, the moisture content of the wood was roughly 40 to 50%. For quantitative yield of extractive, samples of the shredded wood were room-dried to under 10% moisture content and then further ground in a Wiley mill to pass a 40-mesh standard U. S. sieve.

The results of extractions with ethyl ether in Pyrex glass Soxhlet extractors, and calculated on the oven-dry weight of wood, are shown in Table I. Further extraction of the ether extracted wood with acetone gave roughly an additional 1% of reddish-brown phlobaphene.

TABLE I

YIELD OF EXTRACT WITH ETHYL ETHER

Material	Per cent.
Top log	4.21
Butt log	3.36
Stumpwood	2.96
Rootwood	4.01
Sapwood	3.52
Heartwood	6.50

For the purpose of obtaining sufficient quantities of extractive to determine its chemical composition, the freshly shredded moist wood was extracted with acetone in a large metal Soxhlet-type extractor. This extractor held about 10 pounds of wood and the solvent was contained in a 45-liter, round bottom Pyrex-glass flask, which was externally steam-heated.

The acetone extracts from the wood samples were concentrated by distillation at reduced pressure in a water-bath. After the acetone had been removed, the dark colored sirupy extracts were steam distilled to remove volatile oil.

Composition of the Volatile Oil.—The aqueous condensates from the distillation with steam of the extracts from cross sections from the bole of the tree contained a crust of colorless crystals. After drying on a porous plate the crystals melted at 78° and when recrystallized from hot methanol, melted at 87°. They formed a urethan, m. p. 106–107° with phenyl isocyanate. These are the properties of cedrol, $C_{15}H_{26}O$, a tertiary alcohol occurring in few other conifers. The yield was 0.9 to 1.25% of the weight of the wood.

The volatile oils from the stumpwood and rootwood were nearly colorless liquids from which crystals did not separate. They were removed from the aqueous layer by shaking out with petroleum ether in a separatory funnel.

Thirty-five grams of the oil from the rootwood extract was distilled at a pressure of 9 mm. from a 60-ml. round-bottomed flask heated in an oil-bath. Twenty-eight grams of a clear colorless oil distilled between 130 to 170°. A dark brown residue, presumably decomposition and polymerization products, remained. The oil was fractionally distilled at 41 mm. into two distinct fractions. The first fraction, a clear colorless oil amounting to 49.3% of the original rootwood oil, was identified as cedrene, $C_{15}H_{24}$. It had the following properties: b. p., 131–133° (18 mm.), 264° (759.8 mm.); sp. gr. 0.9322 $^{20}/_{20}$; sp. rotation, $[\alpha]^{20}D$ in chloroform −58° 5′; refractive index, 1.5008^{20}°. A dilute solution in 95% ethanol gave an immediate reddish color which changed to red-violet upon the addition of a solution of one-tenth g. of vanillin dissolved in 100 ml. of concentrated hydrochloric acid.

The second fraction was the white crystalline solid cedrol, $C_{15}H_{26}O$. It distilled between 155 to 165° at 41 mm., melted at 86°, and had a specific rotation, $[\alpha]^{20}D$ +8° 29′. The urethan from phenyl isocyanate melted at 106–107°. The cedrol crystals when dissolved in absolute ethanol and dehydrated with concentrated phosphoric acid gave cedrene, which gave the typical color with the vanillin–hydrochloric acid reagent.

Separation of Phlobaphene.—The thick, dark-colored residues from the separation of the volatile oil were placed in a separatory funnel and shaken with successive portions of ethyl ether. The insoluble material was then refluxed for an hour with more ether, whereupon a reddish-brown residue was obtained that dried to an amorphous powder.

This material gave a green-black coloration with dilute solutions of iron salts, precipitated gelatin from solution, and upon methylation with dimethyl sulfate in alkaline solution followed by oxidation with potassium permanganate gave veratric acid, m. p. 177°, methyl ester m. p. 55–57°. The dried product was only slightly soluble in water. This indicated that a catechol phlobaphene is present in Sierra juniper wood. The yield was roughly 1% of the weight of the whole wood.

Separation of Petroleum Ether Solubles.—The ether solutions from the separation of the phlobaphene were washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The dark colored resinous material was then extracted with petroleum ether. This solvent extracted a reddish yellow product and gave a dark colored resinous precipitate.

The petroleum ether solutions were next shaken in a separatory funnel with successive portions of 5% potassium carbonate solution to separate acidic substances from neutral materials. Complete separation of the sapwood extract, as judged by the color of the aqueous layer, was comparatively sharp after shaking with four portions of potassium carbonate solution. The coloring matter was more difficult to remove with the other wood extracts, which required up to 9 extractions with fresh portions of potassium carbonate solution. The petroleum ether solutions were then washed with water and dried over anhydrous sodium sulfate overnight. The ether was removed under reduced pressure and the residues weighed. The amounts of neutrals and acids found, as well as those of other components, are given in Table II. The method of separation is summarized in Fig. 1.

TABLE II

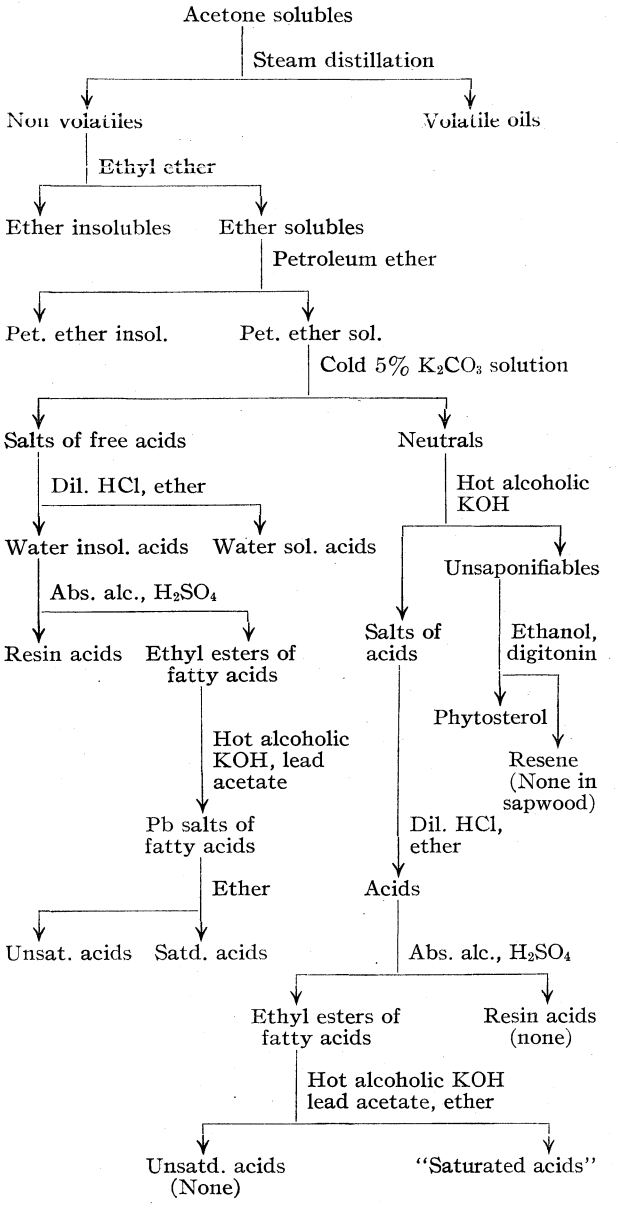
COMPOSITION OF PETROLEUM ETHER EXTRACT FROM SIERRA JUNIPER (YIELD FROM SAPWOOD 2.53%; FROM WHOLE WOOD 3.01%)

	Per cent. of total pet. ether extract	
	Sapwood	Whole wood
Free acids	27.9	43.6
Fatty acids	21.6	26.4
Resin acids	6.3	17.3
Combined acids	27.1	6.9
Fatty acids	27.1	6.9
Resin acids	0.0	0.0
Total acids	55.0	50.5
Saturated fatty acids	30.9	14.6
Unsaturated fatty acids	17.7	16.0
Resin acids	6.3	17.3
Unsaponifiables	45.0	49.5
Volatile oils		1.0
Phytosterol	45.0	5.0
Resene		43.5
Water solubles	None	Trace

Esterification of the dry acidic fractions with ethanol and sulfuric acid gave a separation into fatty acids and resin acids. The resin acid fraction from all of the wood extracts was dark colored and non-crystallizable from a variety of solvents. The neutral equivalent varied from 297 to 337, whereas that for abietic acid is 302.4.

The fatty acid fractions were further separated into presumably saturated and unsaturated acids by the difference in solubilities of their lead salts in ether. The unsaturated fatty acids thus obtained were red colored liquids, which gave iodine numbers by the Hanus method ranging from 56.7 to 68.1 and neutralization equivalents ranging from 338 to 346. This indicated that acids with more than 18 carbon atoms were present. Oxidation with cold alkaline potassium permanganate resulted in the isolation of dihydroxystearic acid, m. p. 129.5°, which indicated that oleic acid was present in the mixture.

Fig. 1.—Separation of the juniper wood extract



The saturated fatty fraction was soluble in warm methanol and crystallized from this solvent on standing. After several recrystallizations, white waxy solids were obtained, which melted at 72.5–73°. Decomposition took place at temperatures above 100°, which demonstrated a relative low stability to heat. The crystals were soluble in warm dilute sodium hydroxide, but were insoluble in 5% sodium bicarbonate solution. Neutralization values of 677 to 684 were obtained. Other investigators have obtained similar acids from Jack pine and Swedish Tall oil[1,2,3] and considered them lactonic acids.

After refluxing the crystals for one-half hour with an excess of alcoholic potassium hydroxide, acidifying the solution, extracting with ether, drying and recrystallizing, the neutral equivalent was lowered to between 396 to 422. This indicates that the material could be the dibasic lactonic acid of the same melting point described by Sandquist.[3]

The neutral fractions were saponified with 7% alcoholic potassium hydroxide by the modified Kerr–Sarber method of Jamieson[4] and separated into unsaponifiable matter and acids. No resin acids or ether soluble lead salts were found present in the acid fraction. The only acid isolated had the same properties as that described in the preceding paragraphs.

Unsaponifiables.—A one per cent. solution of the unsaponifiables in absolute ethanol was heated and to it was added an equal volume of a 1% solution of digitonin in 95% ethanol. After standing in a refrigerator for forty-eight hours, white crystals of phytosterol digitonide separated. The yield of digitonide was quantitative from the sapwood unsaponifiable matter inasmuch as no residue was found in the filtrate. The unsaponifiable from the whole wood contained only approximately 10% of sterols. The bulk of the unsaponifiable matter from this extract was not precipitated by digitonin.

The phytosterol was recovered from the unsaponifiable matter by crystallization from hot dilute alcohol. The light colored crystals, which separated, were decolorized with charcoal, and recrystallized successively from hot dilute ethanol and acetone. The properties are shown in Table III. From the experimental data in this table, the product appears to be a mixture of *alpha* and *beta* sitosterol.

TABLE III

PROPERTIES OF THE PHYTOSTEROL

	Sierra juniper wood	α-Sitosterol[4]	β-Sitosterol[4]
Melting point, °C.	134–136.5	135–136	139–140
Melting point of acetate, °C.	125.5–128		127–128
Specific rotation $[\alpha]^{20}D$ in $CHCl_3$	−21.25	−13.45	−36.11

The filtrate from the precipitation of the phytosterol digitonide from the whole wood unsaponifiables was concentrated and diluted with water, whereupon a resene was precipitated. This was recrystallized successively from hot dilute ethanol, methanol and acetone and had a melting point of 76–78.5°. It was slightly soluble in hot water and very soluble in petroleum or ethyl ether, benzene and chloroform. The compound was optically inactive. Molecular weight, as found by the Rast camphor method, together with carbon and hydrogen analyses indicated the empirical formula to be $C_{18}H_{31}O$.

Calcd. for $C_{18}H_{31}O$: C, 82.10; H, 11.86; molecular weight, 263.4. Found: C, 81.72; H, 12.10; molecular weight 262.0.

An acetate was formed by refluxing the resene for one-half hour with acetic anhydride and anhydrous sodium acetate. It had a melting point of 102–104°. Formation of the acetate established the resene as an alcohol.

Petroleum Ether Insoluble Fraction.—Investigation of this fraction gave many variable results. It appeared to be in various stages of oxidation and polymerization. In addition to being soluble in ethyl ether it was soluble in ethyl acetate, partly soluble in hot methanol and hot benzene. The product from the top log cross section, amounting to 46.2% of the ethyl ether extract, upon saponification with sodium hydroxide gave an insoluble sodium salt. The material soluble in sodium hydroxide was a mixture of resin and fatty acids. Decomposition of the insoluble sodium salt with dilute acid precipitated a light brown granular solid with a neutral equivalent of 791.

The product from a cross section of a butt log with some dry rot at the core gave on redissolving in ethyl ether and upon slow evaporation of the solvent, light fluffy crystals.

(1) H. Hibbert and J. B. Phillips, *Can. J. Research*, **4**, 1 (1931).
(2) T. Hasselstroem, *Paper Trade J.*, **83**, No. 2, 66 (1926).
(3) H. Sandquist, *Z. Angew. Chem.*, **35**, 531 (1922).
(4) Jamieson, George S., "Vegetable Fats and Oils," A. C. S. Monograph No. 58, 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1943.

These were recrystallized from hot benzene and then had the following properties: insoluble in water, petroleum ether and carbon tetrachloride; slightly soluble in ethyl ether, benzene, and ethyl acetate; and soluble in alcohol, acetone, and sodium bicarbonate solution; m. p. 229°, neutral equivalent 153, molecular weight 294, C 60.8%, and H 7.42%. This indicated an empirical formula of $C_{15}H_{22}O_6$. Methoxl groups were absent.

The compound formed a mono methyl ester with methanol in the presence of concentrated sulfuric acid that had the following properties: m. p. 136–137°, neutral equivalent 290, saponification equivalent 164. The ester was soluble in sodium bicarbonate solution and after saponification the original compound was recovered. These properties indicated a dibasic acid.

The compound was obtained in only small yield from one specimen of Sierra juniper wood containing dry rot.

Inasmuch as it was not isolated from sound wood it is questionable whether it is a normal constituent of wood with no decay.

Summary

1. The ethyl ether soluble content of Sierra juniper wood was found to range between 2.96 to 6.5%. Approximately an additional one per cent. of material is soluble in acetone which is chiefly a catechol phlobaphene. A part of the ethyl ether extractive is soluble in petroleum ether. This amounted to 2.53% on the weight of sapwood and 3.01% on the weight of the whole wood from a cross section of the trunk. A detailed analysis of the petroleum ether solubles is tabulated.

2. The constituents of the petroleum ether extract were resin acids, oleic acid and high molecular weight lactonic acids, a mixture of alpha and beta sitosterol and a hydroxy resene, $C_{18}H_{31}O$. The resin acids occurred only in the free state.

3. The volatile oil from the trunk of the tree ranged from 0.9 to 1.25% and was apparently entirely cedrol. That from the rootwood was a mixture of cedrene and cedrol.

CORVALLIS, OREGON RECEIVED MARCH 16, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

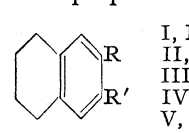
The Jacobsen Reaction. IX.[1] 6,7-Dialkyltetralins

BY LEE IRVIN SMITH AND CHIEN-PEN LO[2]

The only tetraalkylbenzenes so far studied with reference to their behavior under the conditions of the Jacobsen rearrangement are those in which the alkyl groups are methyl and ethyl. Tetraalkylbenzenes of known structure, having alkyl groups above ethyl, and with straight or branched chains, are practically unknown, and the variety and number of such compounds necessary for an extended study of the Jacobsen reaction make the preparation of the starting materials and reference compounds a very formidable task. In the previous paper[1] it was shown that a cyclic chain attached at two ortho-positions to a benzene ring could take the place of two alkyl groups in a tetraalkylbenzene, and it was shown that 6,7-diethyltetralin (a 1,2,4,5-tetraalkylbenzene) underwent the Jacobsen reaction in the normal fashion to produce 5,6-diethyltetralin (a 1,2,3,4-tetraalkylbenzene). Indeed, Schroeter and Gotzky[3] had already shown that two cyclic chains, involving the 1,2,4,5-positions of a benzene ring could replace four alkyl groups, for these authors observed that octahydroanthracene, subjected to the conditions of the Jacobsen reaction, underwent rearrangement to octahydrophrenanthrene, a 1,2,3,4-tetrasubstituted benzene. 6,7-Dialkyltetralins are quite readily prepared in some variety; moreover, these substances, as well as their rearrangement products, are readily dehydrogenated to the corresponding naphthalenes, so that the problems of identification can be solved without much difficulty.

Arnold and Barnes[1] have recently proposed a theory for the mechanism of the Jacobsen reaction. According to this theory, the migrating alkyl group is detached from the sulfonic acid molecule as a cation; this cation then replaces the more hindered sulfonic acid group of the (di)-sulfonic acid, leading to the rearranged sulfonic acid. As a necessary consequence of this theory, migration of a *n*-propyl group in a polyalkylbenzene would involve simultaneous isomerization of the group to iso-propyl, since the latter is the more stable of the two propyl cations under the conditions of the rearrangement.

With the objectives of testing this corollary of the suggested mechanism, and of extending the data on the Jacobsen reaction to groups other than methyl and ethyl, five (four of them new compounds) 6,7-dialkyltetralins have been prepared and subjected to the conditions of the Jacobsen rearrangement. Each tetralin was dehydrogenated to the corresponding naphthalene and the latter identified—hence, incidental to this work, a number of new 2,3- and 1,2-dialkylnaphthalenes have been prepared and characterized.



I, R = R′ = CH_3
II, R = CH_3, R′ = *n*-C_3H_7
III, R = CH_3, R′ = iso-C_3H_7
IV, R = C_2H_5, R′ = iso-C_3H_7
V, R = R′ = *n*-C_3H_7

When 6,7-dimethyltetralin (I) was subjected to the conditions of the Jacobsen reaction, it was converted into 5,6-dimethyltetralin, in analogy

(1) No. VIII, Arnold and Barens, THIS JOURNAL, **66**, 960 (1944).

(2) Abstracted from a thesis by Chien-Pen Lo, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, September, 1947.

(3) Schroeter and Gotzky, *Ber.*, **60**, 2035 (1927).

with the previously studied conversion of 6,7-diethyltetralin into the 5,6-isomer.[1] However, when the two alkyl groups are identical, the rearrangement of 6,7-dialkyltetralins to the 5,6-compounds gives no clue as to whether an alkyl group, or the cyclic chain has migrated, for in either case the product would be the same 5,6-dialkyltetralin. Hence it became necessary to study some 6,7-dialkyltetralins in which the substituents were different; for this purpose tetralins II, III, and IV were prepared and characterized; compound V, with two *n*-propyl groups, was also included for comparison.

6-*n*-Propyl-7-methyltetralin II, under the conditions of the Jacobsen rearrangement, was converted into a liquid hydrocarbon which yielded benzene-1,2,3,4-tetracarboxylic acid upon oxidation and 1-*n*-propyl-2-methylnaphthalene upon dehydrogenation. The liquid product was therefore 5-*n*-propyl-6-methyltetralin. There are, *a priori*, four routes for a rearrangement: (a) the propyl group may migrate from the 6- to the 8- (=5) position; (b) the methyl group may migrate to the 5- (=8) position; (c) the tetramethylene ring may open and then close in the *o*-position to the methyl group; and (d) the ring may open and then close in the *o*-position to the propyl group. The product resulting from (a) would, in accordance with the theory of Arnold and Barnes, be 5-isopropyl-6-methyltetralin, and not the *n*-propyl isomer; from (b) and (c) there would result 5-methyl-6-*n*-propyltetralin; route (d) is the only one which would lead to the product actually obtained, namely, 5-*n*-propyl-6-methyltetralin. Hence, the rearrangement proceeded *via* route (d) unless the very improbable assumption is made that a *n*-propyl cation does not rearrange to isopropyl but is stable in the presence of a great excess of sulfuric acid.

6-Isopropyl-7-methyltetralin III, under the conditions of the Jacobsen rearrangement, was converted into 6-methyltetralin, identified by dehydrogenation to 2-methylnaphthalene. In this rearrangement, the *iso*-propyl group became detached and did not re-enter the molecule, a behavior of isopropyl groups for which there is much precedent.[4]

6-Isopropyl-7-ethyltetralin IV, and 6,7-di-*n*-propyltetralin V, when subjected to the conditions of the Jacobsen rearrangement, gave only small amounts of oily products which could not be identified. The bulk of the material was destroyed or else converted into sulfonic acids which were hydrolyzed to hydrocarbons with difficulty—a fact which excluded sulfonic acids of 1,2,3,4-tetraalkylbenzenes.

The results of these experiments, together with those of Arnold and Barnes, show that 6,7-dialkyltetralins undergo the Jacobsen rearrangement to 5,6-dialkyltetralins when one or both of the alkyl groups are methyl or ethyl, or when one group is methyl and the other is *n*-propyl. In the last case, however, it is the tetramethylene ring which migrates rather than either alkyl group. When one of the alkyl groups is methyl and the other is isopropyl, the isopropyl group is lost and the product is a 6-monoalkyltetralin. Moreover, there are certain 6,7-dialkyltetralins which give as products only small amounts of complex mixtures —a behavior paralleling that of 5,6,7,8-tetrahydrobenz(f)-indan and of *s*-hydrindacene, studied by Arnold and Barnes.[1]

(4) For example, see Newton, THIS JOURNAL, **65**, 2439 (1943).

Experimental Part[5]

The Jacobsen Reactions.—The general procedure was as follows: a mixture of the 6,7-dialkyltetralin (18 g.) and sulfuric acid was stirred and slowly heated. The color became red, then dark. Complete solution usually occurred at a temperature of about 80°. The mixture was kept at 95° for fifteen minutes, and then allowed to cool to room temperature and stand overnight. The mixture was diluted somewhat with water, and was then distilled with superheated steam (temperature of the reaction mixture, 150°). The distillate was extracted with ether, the extract was washed with aqueous sodium hydroxide, the solvent was evaporated and the residual material was distilled.

6,7-Dimethyltetralin (18 g.) yielded a light yellow oil (5 g.) which, on redistillation, gave colorless 5,6-dimethyltetralin (4.3 g.) boiling at 110–115° (7 mm.) and having $n^{20}D$ 1.5530. This material (8 drops) was heated with aqueous nitric acid (3 cc. 1:2) to 199–200° for three and one-half hours. The solution was evaporated to dryness, the residue was dissolved in ether, and to this solution was added an ethereal solution of diazomethane (from 2 g. of nitrosomethylurea). The ether was evaporated and the residue, crystallized twice from methanol, melted at 130–131° alone or when mixed with an authentic specimen of tetramethyl benzene-1,2,3,4-tetracarboxylate. Dehydrogenation of the 5,6-dimethyltetralin (1 cc.) led to 1,2-dimethylnaphthalene, identified as the picrate, m. p. and mixed m. p., 129–130°.

6-*n*-Propyl-7-methyltetralin (18 g.) yielded 5-*n*-propyl-6-methyltetralin (4.8 g., 25%), b. p. 140–145° (13.5 mm.). The product was converted to tetramethyl benzene-1,2,3,4-tetracarboxylate, m. p. and mixed m. p. 130–131°, as described above, and was dehydrogenated to 1-*n*-propyl-2-methylnaphthalene, identified as the picrate, m. p. and mixed m. p. 118–119°.

6-Isopropyl-7-methyltetralin (18 g.) yielded a yellow oil (7 g.), separated into three fractions by distillation: I, b. p., 95–105° (4.5 mm.) (2.1 g.), II, b. p. 122–130° (4.5 mm.) (3.0 g.), III, residue (0.8 g.). Fraction II gave no benzene tetracarboxylic acid upon oxidation, and was identified as 6-methyltetralin by dehydrogenation to 2-methylnaphthalene, m. p. and mixed m. p. of the picrate 115–117°.

6-Isopropyl-7-ethyltetralin (8 g.) (oleum, 10% sulfur trioxide, 40 cc. used instead of sulfuric acid) yielded an oil (1.2 g.) which gave no benzene tetracarboxylic acid on oxidation and which gave no picrate after dehydrogenation.

6,7-Di-*n*-propyltetralin (18 g.) gave less than 1 cc. of yellow oil from which no identifiable material could be isolated.

1-Tetralone was prepared from tetralin in 36% yield by the procedure of Thompson.[6] The product boiled at 125–126° (8 mm.), and gave a semicarbazone which, after crystallization from aqueous ethanol, melted at 215–217°.[7]

1-Methyl-1-tetralol.—To an ethereal solution of methylmagnesium iodide (prepared from magnesium 1.7 g.,

(5) Microanalyses by Sherman Sundet, Roger Amidon, Jay S. Buckley.

(6) Thompson, *Org. Syntheses*, **20**, 94 (1940).

(7) Kipping and Hill, *J. Chem. Soc.*, **75**, 148 (1899), reported the m. p. as 217°.

methyl iodide 5.5 cc. and ether 30 cc.) was added a solution of 1-tetralone (6.7 g.) in ether (10 cc.). The mixture was refluxed, and then decomposed by addition of iced ammonium chloride solution. The mixture was extracted with ether, the extract was washed with ammonium chloride solution, and the solvent was removed. The residue (7 g., 94%) solidified and then melted at 77–79°. After recrystallization from petroleum ether, the substance melted at 86–87°.[8]

1-Methylnaphthalene.—A mixture of 1-methyl-1-tetralol (3 g.) and a palladium–charcoal catalyst (0.3 g., 10%) was heated at 230–270° for three hours. The product was dissolved in ether, the catalyst was removed, and the solution was washed with aqueous sodium hydroxide (5%). Removal of the ether left 2.5 g. (95%) of residual oil which boiled at 94–96° (5 mm.), and had $n^{20}D$ 1.6037.[9]

Picrate.—The above oil (0.5 cc.) was added to methanolic picric acid and the solution was cooled. The yellow needles were removed and recrystallized from methanol. The product then melted at 141–142°.[10] *Anal.* Calcd. for $C_{17}H_{13}O_7N_3$: C, 54.99; H, 3.53. Found: C, 54.54; H, 3.56.

6-Propionyltetralin.[11]—Propionic anhydride (43.4 g.) was slowly (one hour) added to a cooled (0°) and stirred mixture of tetralin (6.6 g.), nitrobenzene (200 cc.) and aluminum chloride (150 g.). The mixture was gradually (two and one-half hours) allowed to attain room temperature and then was poured over ice and hydrochloric acid (100 cc.) and extracted with benzene. The extract was washed with water, aqueous sodium carbonate (10%) and water and dried over calcium chloride. Benzene, tetralin and nitrobenzene were removed by distillation under reduced pressure, and the residue was distilled. The product weighed 43 g. (68%), boiled at 160–163° (11 mm.) and had $n^{29}D$ 1.5508.

The semicarbazone, after crystallization from ethanol, melted at 209°.[12] *Anal.* Calcd. for $C_{14}H_{19}ON_3$: C, 69.11; H, 7.87. Found: C, 69.33; H, 8.06.

6-*n*-Propyltetralin.—A mixture of amalgamated zinc (360 g., 20 mesh), water (360 cc.), acetic acid (480 cc.), hydrochloric acid (720 cc.) and 6-propionyltetralin (61 g.) was refluxed for seventy-six hours, more hydrochloric acid (total 900 cc.) being added from time to time. The cooled mixture was extracted with ether, the extract was washed with water, aqueous sodium hydroxide (10%), and water, the solvent was removed, and the residue was distilled. The product, a colorless liquid, weighed 53 g. (92%), boiled at 123–125° (10 mm.) and had $n^{29}D$ 1.5253. *Anal.* Calcd. for $C_{13}H_{18}$: C, 89.60; H, 10.41. Found: C, 89.29; H, 10.47.

Trinitro-6-*n*-propyltetralin.—The tetralin (1 g.) was slowly dropped into a cold (0°) mixture of sulfuric acid (5 cc.) and fuming nitric acid (5 cc.). The mixture was allowed to stand for ten minutes and was then poured over ice and extracted with ether. The extract was washed with water, dilute sodium hydroxide, water, and was dried. The solvent was removed and the residue was crystallized twice from methanol. The colorless prisms (0.5 g.) melted at 97–98° and became first yellow, then red, when allowed to stand in the light. No attempt was made to determine the position of the nitro groups. *Anal.* Calcd. for $C_{13}H_{15}O_6N_3$: C, 50.5; H, 4.85. Found: C, 50.7; H, 5.12.

6-*n*-Propyltetralin Sulfonamide.—Chlorosulfonic acid (5 cc.) was added dropwise to a cold solution of the tetralin (1 g.) in chloroform (5 cc.). The mixture was allowed to attain room temperature and was poured over ice. The organic layer was removed, washed with water, and evaporated. The residual sulfonyl chloride was an oil which was converted directly to the sulfonamide by boiling it with ammonium hydroxide (5 cc.) for five minutes. The solid was dissolved in aqueous sodium hydroxide (5%), the solution was filtered, and the filtrate was acidified. The solid, after crystallization from ethanol, melted at 117–119°. No attempt was made to determine the position of the sulfonamide group. *Anal.* Calcd. for $C_{13}H_{19}O_2NS$: C, 61.5; H, 7.5. Found: C, 61.8; H, 8.1.

β-(4-*n*-Propyl)-benzoylpropionic Acid.—Aluminum chloride (75 g.) was added, in small portions, to a cooled (0°) mixture of succinic anhydride (25 g.), nitrobenzene (250 cc.) and *n*-propylbenzene (33 g.).[13] The mixture was stirred for two hours and then poured over iced hydrochloric acid and steam-distilled. The oily residue, which solidified on cooling, was dissolved in aqueous sodium carbonate (10%), the solution was warmed with charcoal, filtered, and the filtrate was acidified. The solid was removed and crystallized from methanol. It weighed 35 g. (63%) and melted at 108–115°. After two recrystallizations from benzene, the substance melted at 120–121°. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.97; H, 7.60.

The *p*-phenylphenacyl ester, recrystallized twice from ethanol, melted at 85–86°. *Anal.* Calcd. for $C_{27}H_{26}O_4$: C, 78.3; H, 6.28. Found: C, 78.7; H, 6.51.

The semicarbazone, after crystallization from dilute ethanol, melted at 171–172°. *Anal.* Calcd. for $C_{14}H_{19}O_3N_3$: C, 60.6; H, 6.91. Found: C, 60.1; H, 7.15.

3-(4-*n*-Propyl)-phenylpyridazinone-6, prepared from the acid by the procedure of Gabriel and Colman,[14] and crystallized from dilute ethanol, melted at 103.5–104.5°. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.2; H, 7.46. Found: C, 72.6; H, 7.62.

γ-(4-*n*-Propyl)-phenylbutyric Acid.—The above keto acid (55 g.) was refluxed with amalgamated zinc (100 g.), hydrochloric acid (175 cc.) and water (75 cc.) for twenty-four hours, during which time three 50-cc. portions of hydrochloric acid were added. The top layer solidified when the mixture was cooled; the solid was removed and crystallized from petroleum ether (b. p. 30–60°), when it weighed 36.5 g. (71%) and melted at 65–66°. *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.93; H, 9.01.

The *p*-phenylphenacyl ester, crystallized from ethanol, melted at 105–106°. *Anal.* Calcd. for $C_{27}H_{28}O_3$: C, 80.97; H, 7.05. Found: C, 81.23; H, 7.19.

7-*n*-Propyl-1-tetralone.—Sulfuric acid (150 cc., 80%) and γ-(4-*n*-propyl)-phenylbutyric acid (30 g.) were heated on the steam bath for one hour. The cooled solution was poured over ice and extracted with ether. The ether extract was washed with aqueous sodium hydroxide (5%), dried, and the solvent was removed. The residue, on distillation, gave 19.5 g. (71%) of a colorless liquid which boiled at 150–155° (8 mm.) and had $n^{29}D$ 1.5455. *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.51; H, 8.70.

The semicarbazone, crystallized twice from ethanol, melted at 197–198°. *Anal.* Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81. Found: C, 68.70; H, 7.86.

6-*n*-Propyltetralin.—The above 7-*n*-propyltetralone (14.5 g.) reduced by the method of Clemmensen as previously described, gave the hydrocarbon (6.6 g., 49%) boiling at 105–109° (5 mm.). Converted to the sulfonamide, as described above, the product melted at 117.5–118.5° alone or when mixed with the sulfonamide prepared from the tetralin resulting from reduction of 6-propionyltetralin.

2-*n*-Propylnaphthalene Picrate.—6-*n*-Propyltetralin (1 cc.) and a palladium–charcoal catalyst (10%, 0.1 g.)[15] were heated at 200–240° under a current of carbon dioxide for three hours. The product was taken up in ethanol,

(8) von Auwers, *Ann.*, **415**, 169 (1918), reported the m. p. as 88–89°.

(9) Anderson and Short, *J. Chem. Soc.*, 485 (1933), reported the b. p. as 100–105° (5 mm.).

(10) Lesser, *Ann.*, **402**, 10 (1913), and Meyer and Fricke, *Ber.*, **47**, 2770 (1914), reported the m. p. as 141–142°.

(11) Barnes, Ph.D. Thesis, University of Minnesota, 1943.

(12) Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930), reported 224–225°, but gave no analysis.

(13) Gilman and Catlin, "Org. Syntheses," Coll. Vol. I, 471 (1941).

(14) Gabriel and Colman, *Ber.*, **32**, 399 (1899).

(15) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

the catalyst was removed and ethanolic picric acid (15 cc.) was added to the filtrate. The cooled solution deposited yellow needles which, after crystallization from ethanol, melted at 91°.[16]

6-Acetyltetralin.—This was prepared by the procedure of Barnes[11] essentially as described for the propionyl derivative, but substituting acetic anhydride for propionic anhydride. The product, obtained in 60% yield, was a yellow oil which boiled at 151–156° (10 mm.) and had $n^{29}D$ 1.5593.

The semicarbazone, recrystallized from ethanol, melted at 233–234°.[17]

6-Tetralyldimethylcarbinol.—A solution of 6-acetyltetralin (43.5 g.) in ether (20 cc.) was slowly (forty-five minutes) added to a Grignard reagent prepared from magnesium (6 g.), methyl iodide (36 g.) and ether (120 cc.). After addition was complete, the mixture was refluxed for thirty minutes, then cooled and poured carefully over iced ammonium chloride. The ether layer was removed and the aqueous layer was extracted with ether. The combined organic solutions were washed with ammonium chloride solution and dried over sodium sulfate. The solvent was removed and the residue was distilled. The product (39.3 g., 83%) boiled at 138–141° (5 mm.), and had $n^{20}D$ 1.5497. *Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.1; H, 9.53. Found: C, 82.5; H, 9.23. Although water (1.8 cc., calcd. 2.7 cc.) was eliminated from the carbinol (29 g.) when it was heated to 150–160° with fused potassium acid sulfate (25 g.), the product (12.5 g.) was a mixture (b. p. 133–160° (10 mm.)) from which no pure material could be isolated. When heated with hydriodic acid and red phosphorus, the carbinol was converted into a thick oil which did not distill at 200° (5 mm.).

6-Isopropyltetralin.—The above carbinol (24 g.) was dissolved in ethanol (24 cc.) and the solution was refluxed with Raney nickel catalyst (1 g.) for an hour. The catalyst was removed, the filtrate was diluted with ethanol to 60 cc. and reduced over copper chromite catalyst (6 g.)[18] in a bomb at a temperature of 225° and initial hydrogen pressure of 1670 lb. The reduction was complete in one hour. The reaction product, processed in the usual way, yielded 19 g. (86%) of a colorless liquid which boiled at 120–123° (12 mm.), and had $n^{29}D$ 1.5246. *Anal.* Calcd. for $C_{13}H_{18}$: C, 89.6; H, 10.41. Found: C, 89.9; H, 10.58.

Trinitro-6-isopropyltetralin.—The trinitro compound, prepared as described above for the *n*-propyl isomer, melted at 141–142°. It also became yellow, then red, in the light. *Anal.* Calcd. for $C_{13}H_{15}O_6N_3$: C, 50.5; H, 4.85. Found: C, 50.9; H, 5.27.

6-Isopropylsulfonamide.—The hydrocarbon was converted into the sulfonamide by the procedure described above for the *n*-propyl isomer. The product, after crystallization twice from dilute methanol, melted at 157–158°. The position of the sulfonamide group was not determined. *Anal.* Calcd. for $C_{13}H_{19}O_2NS$: C, 61.5; H, 7.51. Found: C, 61.6; H, 7.95.

6-Isopropyltetralin was also prepared by direct alkylation of tetralin (396 g.) with isopropyl bromide (123 g.) at 60° in the presence of aluminum chloride (20 g.). The product was processed in the usual way. The fraction boiling at 123–125° (15 mm.) weighed 43 g. (24%), had $n^{29}D$ 1.5429, and gave the same sulfonamide, m. p. 158°, described above. When tetralin (500 cc.) and isopropyl acetate (52 g.) reacted in the presence of aluminum chloride (80 g.), a product resulted from which, on distillation, a fraction (30 g., 34%) was isolated having $n^{29}D$ 1.5250 and boiling at 113–115° (8–9 mm.). This likewise gave the sulfonamide, m. p. 157°. The middle fraction (25 g.), b. p. 149–152° (8–9 mm.), solidified on cooling and, after two crystallizations from ethanol, melted at 73–74°. It was identified as octahydroanthracene by the m. p. and analysis.[19] *Anal.* Calcd. for $C_{14}H_{18}$: C, 90.33; H, 9.68. Found: C, 90.45; H, 9.68. The mother liquor from this solid was a colorless oil boiling at 150–155° (10 mm.). and having $n^{29}D$ 1.5579. It was identified as 6-acetyltetralin by the m. p. and mixed m. p. (232–235°) of the semicarbazone. The high boiling fraction was a yellow oil, b. p. 215–220° (9 mm.) having the composition $C_{20}H_{24}$. Analysis and b. p. indicated that this was α-phenyl-δ-2-tetralylbutane.[20] *Anal.* Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 90.99; H, 9.11.

β-(4-Isopropyl)-benzoylpropionic acid (64.8 g., 59%) was prepared from succinic anhydride (50 g.) and isopropylbenzene (66 g.) by action of aluminum chloride (150 g.) in nitrobenzene (500 cc.) essentially according to Barnett and Sanders.[21] The product, crystallized twice from benzene, melted at 141°. The *p*-phenylphenacyl ester, crystallized from ethanol, melted at 101.5–102.5°. *Anal.* Calcd. for $C_{27}H_{26}O_4$: C, 78.26; H, 6.28. Found: C, 78.42; H, 6.42. The semicarbazone, crystallized from ethanol, melted at 182–182.5° (dec.). *Anal.* Calcd. for $C_{14}H_{19}O_3N_3$: C, 60.63; H, 6.91. Found: C, 60.48; H, 7.08. 3-(4-Isopropyl)-phenylpyridazinone, prepared by action of hydrazine and alkali upon the keto acid, and crystallized from ethanol, melted at 166–167°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 72.19; H, 7.46. Found: C, 72.18; H, 7.16.

γ-4-(Isopropyl)-phenylbutyric acid (37 g., 72%) was prepared from the above keto acid (55 g.) by Clemmensen reduction, according to the procedure of Barnett and Sanders.[22] The product boiled at 180–185° (11 mm.) and solidified on standing. Recrystallized from petroleum ether (b. p. 30–60°) it formed colorless prisms melting at 48–50°. The *p*-phenylphenacyl ester, after crystallization from ethanol, melted at 91–92.5°. *Anal.* Calcd. for $C_{27}H_{28}O_3$: C, 80.97; H, 7.05. Found: C, 81.22; H, 7.25.

7-Isopropyl-1-tetralone (16.5 g., 72%) was obtained by action of sulfuric acid (80%, 125 cc.) upon the above phenylbutyric acid.[23] The product boiled at 153–155° (12 mm.) and melted at 36°. The semicarbazone, after crystallization from ethanol, melted at 199–200°. *Anal.* Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81. Found: C, 68.65; H, 7.97.

This tetralone (14.5 g.) was refluxed with amalgamated zinc (100 g.), water (75 cc.) and hydrochloric acid (175 cc.) for ten hours, during which two 50-cc. portions of hydrochloric acid were added. There resulted 9.7 g. (72%) of 6-isopropyltetralin, which boiled at 123–125° (9 mm.) and had $n^{29}D$ 1.5245. The sulfonamide melted at 158–159° and was identical with the one described above.

2-Isopropylnaphthalene.—The tetralin (17.4 g.) and sulfur (6.4 g.) were heated at 200° (temperature of the metal-bath) for one hour, and then at 265–270° for thirty minutes. The reaction mixture was distilled; the distillate weighed 12 g. (70%), boiled at 126–129° (10 mm.) and had $n^{20}D$ 1.5730. The picrate, obtained by dissolving the hydrocarbon in methanolic picric acid and cooling the solution, melted at 93–94°.[24]

6-Methyltetralin was prepared by catalytic reduction of 2-methylnaphthalene, according to the procedure of Fieser and Jones,[25] although it was found that the starting material had to be pre-treated with Raney nickel catalyst before a smooth reduction occurred. The product, obtained in 94% yield, boiled at 220–222° (736 mm.), 100–103° (12 mm.), and had $n^{20}D$ 1.5358.

(16) Haworth, Letsky and Mavin, *J. Chem. Soc.*, 1784 (1932), gave the m. p. as 89–90°.

(17) Hesse, *Ber.*, **53**, 1645 (1920), reported 234–235°; Barbot (ref. 12) reported 257–258°.

(18) Catalyst 37 KAF, Connor, Folkers and Adkins, THIS JOURNAL, **54**, 1140 (1932).

(19) Schroeter, *Ber.*, **57**, 1990 (1924), reported the m. p. as 73–74°.

(20) Schroeter, Ref. 19, reported the b. p. of this substance as 236–237° (13 mm.).

(21) Barnett and Sanders, *J. Chem. Soc.*, 435 (1933), who give the m. p. as 142°.

(22) Ref. 21. The m. p. is here given at 50°.

(23) Barnett and Sanders, ref. 21. The m. p. is here given as 36°.

(24) Haworth, Letsky and Mavin, Ref. 16, reported the m. p. as 93–95°.

(25) Fieser and Jones, THIS JOURNAL, **60**, 1940 (1938).

6-Acyl-7-alkyltetralins.—These were prepared from the alkyltetralins, by action of the corresponding acid anhydride in the presence of aluminum chloride, with nitrobenzene as the solvent. A representative procedure is given.

6-Acetyl-7-methyltetralin.—Acetic anhydride (50 cc.) was added slowly (forty minutes) to a cooled (0°) and stirred mixture of 6-methyltetralin (62 g.), nitrobenzene (350 cc.), and aluminum chloride (143 g.). The mixture was stirred at room temperature for two hours and then was decomposed by pouring it into iced hydrochloric acid. The mixture was extracted with benzene and the extract was washed successively with hydrochloric acid, aqueous sodium hydroxide (10%), and water. The solvents were removed by distillation under reduced pressure and the residue was distilled. There resulted 62 g. (77%) of a yellow oil which boiled at 155–159° (10 mm.) and had $n^{20}D$ 1.5511. *Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.04; H, 8.78. The 2,4-dinitrophenylhydrazone, crystallized once from acetone and twice from a mixture of ethyl acetate and methanol, melted at 172–173°. *Anal.* Calcd. for $C_{19}H_{20}O_4N_4$: C, 61.92; H, 5.47. Found: C, 62.09; H, 5.67.

6-Propionyl-7-methyltetralin: yield 76%, b. p. 162–166° (11 mm.), $n^{20}D$ 1.5479. *Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.72; H, 8.84. The 2,4-dinitrophenylhydrazone, crystallized twice from ethyl acetate, melted at 153–154°. *Anal.* Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81; H, 5.80. Found: C, 63.07; H, 5.78.

6-Acetyl-7-*n*-propyltetralin: yield 72%, b. p. 150–155° (5 mm.); $n^{20}D$ 1.5445. *Anal.* Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.94; H, 9.20. The 2,4-dinitrophenylhydrazone, crystallized twice from ethyl acetate–methanol, melted at 133–134°. *Anal.* Calcd. for $C_{21}H_{24}O_4N_4$: C, 63.69; H, 6.25. Found: C, 63.81; H, 6.31.

6-Propionyl-7-*n*-propyltetralin: yield 78%, b. p. 182–186° (16 mm.), $n^{20}D$ 1.5350. *Anal.* Calcd. for $C_{16}H_{22}O$: C, 84.42; H, 9.63. Found: C, 83.84; H, 9.95. The 2,4-dinitrophenylhydrazone crystallized twice from ethyl acetate–methanol, melted at 123–124°. *Anal.* Calcd. for $C_{22}H_{26}O_4N_4$: C, 64.37; H, 6.38. Found: C, 64.63; H, 6.51.

6-Acetyl-7-isopropyltetralin: yield 66%; b. p., 147–150° (4 mm.), $n^{20}D$ 1.5460. *Anal.* Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.73; H, 9.45. The 2,4-dinitrophenylhydrazone, crystallized twice from ethyl acetate–methanol, melted at 166–167°. *Anal.* Calcd. for $C_{21}H_{24}O_4N_4$: C, 63.69; H, 6.25. Found: C, 63.84; H, 6.31. It was planned to convert 6-acetyl-7-isopropyltetralin into 6,7-diisopropyltetralin, *via* the dimethyl carbinol which would result by addition of methylmagnesium iodide to the acetyl compound. However, the only product isolated as a result of this reaction was unchanged 6-acetyl-7-isopropyltetralin (20 g. from 30 g. used), b. p., 138–141° (2 mm.), $n^{20}D$ 1.5408, m. p. and mixed m. p. of the semicarbazone, 166–167°. No further study of this reaction was made; it is likely that the reaction involved almost entirely enolization of the ketone, but this was not investigated.

6-Propionyl-7-isopropyltetralin: yield 57%, b. p. 170–175° (14.5 mm.), $n^{20}D$ 1.5382. *Anal.* Calcd. for $C_{16}H_{22}O$: C, 83.42; H, 9.63. Found: C, 83.53; H, 9.69. The 2,4-dinitrophenylhydrazone, crystallized twice from ethyl acetate–methanol, melted at 141–142°. *Anal.* Calcd. for $C_{22}H_{26}O_4N_4$: C, 64.37; H, 6.38. Found: C, 64.85; H, 6.57.

6,7-Dialkyltetralins.—These were, except where noted otherwise, prepared from the corresponding 6-acyl-7-alkyltetralins, by the Clemmensen method. The procedure, in general, followed those already given above for similar reductions.

6,7-Dimethyltetralin (57 g., 89%) was prepared by reduction of 2,3-dimethylnaphthalene (62 g.) in ethanol in the presence of Raney nickel catalyst.[26] The product boiled at 112–115° (9.5 mm.)[27] and had $n^{20}D$ 1.5360.

6,7-Dimethyltetralin-5-sulfonamide.—Chlorosulfonic acid (2.8 cc.) was dropped into a cold (0°) solution of the tetralin (1 cc.) in chloroform (5 cc.). The mixture was allowed to stand at room temperature for twenty minutes, then was poured over ice and extracted with chloroform. The extract was washed with water, dried, the solvent was removed, and the residual oil was boiled with ammonium hydroxide. The mixture was diluted with water, and the solid was removed and crystallized several times from some dilute ethanol. It then melted at 135–136°.[28] *Anal.* Calcd. for $C_{12}H_{17}O_2NS$: C, 60.22; H, 7.16. Found: C, 60.48; H, 7.27. 6-Ethyl-7-methyltetralin, from 6-acetyl-7-methyltetralin: yield 81%, b. p. 121–124° (10 mm.), $n^{20}D$ 1.5272. *Anal.* Calcd. for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.34; H, 10.71.

6-(7-Methyltetralyl)-dimethylcarbinol.—A solution of 6-acetyl-7-methyltetralin (37.6 g.) in ether (20 cc.) was slowly added to a Grignard reagent prepared from magnesium (4.8 g.), methyl iodide (13 cc.) and ether (40 cc.). The mixture was refluxed for thirty minutes, then cooled, poured into iced ammonium chloride solution and extracted with ether. The extract was washed with aqueous ammonium chloride and water, the solvent was removed and the residue was distilled. The carbinol (32 g., 78%) formed a light yellow oil which boiled at 135–136° (3 mm.) and had $n^{20}D$ 1.5435. *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.3; H, 9.87. Found: C, 83.0; H, 9.50.

6-Isopropyl-7-methyltetralin.—The above carbinol (32 g.) in ethanol (32 cc.) was refluxed with Raney nickel catalyst for one hour. The catalyst was removed and the filtrate was diluted to 70 cc. by addition of ethanol. This solution, together with copper chromite catalyst (9 g.) was heated to 220–225° for two hours in a bomb under an initial hydrogen pressure of 1820 lb. The catalyst was removed by centrifugation, the solvent was removed by distillation under reduced pressure, and the residue was distilled. The product, a colorless liquid, boiled at 113–116° (6 mm.) and had $n^{20}D$ 1.5250. *Anal.* Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.46; H, 10.84. The hydrocarbon (8 drops) and nitric acid (3 cc., 1:2) were heated at 190–200° for sixteen hours. The solution was evaporated to dryness and the residue was taken up in ether. Ethereal diazomethane (from 2 g. of nitrosomethylurea) was added, the solution was evaporated, and the residue was crystallized twice from methanol. The product melted at 141–142° alone or when mixed with an authentic specimen of tetramethyl pyromellitate.

6-*n*-Propyl-7-methyltetralin, from 6-propionyl-7-methyltetralin: yield 84%, b. p., 130–135° (11 mm.), $n^{20}D$ 1.5250. *Anal.* Calcd. for $C_{14}H_{20}$: C, 89.30; H, 10.71. Found: C, 88.87; H, 10.62. Oxidation of the hydrocarbon, as described above, gave tetramethyl pyromellitate, m. p. and mixed m. p. 141–142°.

6-*n*-Propyl-7-ethyltetralin, from 6-acetyl-7-*n*-propyltetralin: yield 78%, b. p. 114–117° (2.5 mm.), $n^{20}D$ 1.5228. *Anal.* Calcd. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.66; H, 10.95.

6,7-Di-*n*-propyltetralin, from 6-propionyl-7-*n*-propyltetralin: yield 80%, b. p. 157–162° (12 mm.), $n^{20}D$ 1.5234. Oxidation of the hydrocarbon, as described above, gave tetramethyl pyromellitate, m. p., and mixed m. p., 141–142°. *Anal.* Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.95, 88.61; H, 11.51, 11.15.

6-Isopropyl-7-ethyltetralin, from 6-acetyl-7-isopropyltetralin: yield 61%, b. p. 127–130° (5 mm.), $n^{20}D$ 1.5200. *Anal.* Calcd. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.50; H, 11.02.

6-Isopropyl-7-*n*-propyltetralin, from 6-propionyl-7-isopropyltetralin: yield 53%, b. p. 157–160° (15 mm.), $n^{20}D$ 1.5238. *Anal.* Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.59; H, 11.04.

2,3-Dialkylnaphthalenes.—These were prepared by dehydrogenation of the corresponding 6,7-dialkyltetralins by heating them to 220–250° in a current of carbon dioxide and in the presence of a palladium-charcoal (10%)

(26) Craig, Ph.D. Thesis, University of Minnesota, 1947.

(27) Coulson, *J. Chem. Soc.*, 1305 (1938), reported the b. p. as 244–246°.

(28) Coulson, ref. 27, reported the m. p. as 135°.

catalyst for approximately three hours. The catalyst was used in an amount roughly 10% of that of the dialkyltetralin taken. The reaction product was taken up in ether, the catalyst was removed, and the naphthalene was distilled. The picrates were prepared by dissolving the hydrocarbon in methanolic picric acid and cooling the solution. They were recrystallized from ethanol or methanol.

2-Ethyl-3-methylnaphthalene, from 6-ethyl-7-methyltetralin: yield 85%, b. p. 109–112° (3 mm.), $n^{20}D$ 1.5658. *Anal.* Calcd. for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.17; H, 8.67. Picrate, yellow needles, m. p., 129–130°. *Anal.* Calcd. for $C_{19}H_{17}O_7N_3$: C, 57.14; H, 4.29. Found: C, 57.45; H, 4.57.

2-Isopropyl-3-methylnaphthalene, from 6-isopropyl-7-methyltetralin: yield 99%, b. p. 130–132° (7 mm.), $n^{20}D$ 1.5599. *Anal.* Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.54; H, 8.83. Picrate, yellow needles, m. p., 133–136°. *Anal.* Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63. Found: C, 58.17; H, 4.66.

2-*n*-Propyl-3-methylnaphthalene, from 6-*n*-propyl-7-methyltetralin: yield 70%, b. p. 121–123° (3 mm.), $n^{20}D$ 1.5647. *Anal.* Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.20; H, 8.95. Picrate, yellow needles, m. p., 110–112°. *Anal.* Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63. Found: C, 57.85; H, 4.87.

2-*n*-Propyl-3-ethylnaphthalene from 6-*n*-propyl-7-ethyltetralin: yield 81%, b. p. 131–134° (4 mm.), $n^{20}D$ 1.5752. *Anal.* Calcd. for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.47; H, 9.02. Picrate, yellow needles, m. p., 92–93°. *Anal.* Calcd. for $C_{21}H_{21}O_7N_3$: C, 59.01; H, 4.95. Found: C, 59.15; H, 5.09.

2,3-Di-*n*-propylnaphthalene from 6,7-di-*n*-propyltetralin: The tetralin (17.2 g.) and sulfur (4.8 g.) were heated at 200–205° for one hour and then at 270–275° for one hour. The product was distilled, then allowed to stand over sodium for several hours, and redistilled. It weighed 13 g. (77%), boiled at 155–158° (8.5 mm.), and had $n^{20}D$ 1.5601. *Anal.* Calcd. for $C_{16}H_{20}$: C, 90.50; H, 9.50. Found: C, 90.33; H, 9.56. Picrate, yellow needles, m. p., 83–84°. *Anal.* Calcd. for $C_{22}H_{23}O_7N_3$: C, 59.86; H, 5.25. Found: C, 59.70; H, 5.38.

2-Isopropyl-3-ethylnaphthalene, from 6-isopropyl-7-ethyltetralin: yield 95%, b. p., 132–135° (5 mm.), $n^{20}D$ 1.5742. *Anal.* Calcd. for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.58; H, 9.11. Picrate, yellow needles, m. p., 117–119°. *Anal.* Calcd. for $C_{21}H_{21}O_7N_3$: C, 59.01; H, 4.95. Found: C, 58.66; H, 5.06.

2-Isopropyl-3-*n*-propylnaphthalene, from 6-isopropyl-7-*n*-propyltetralin: yield 95%, b. p., 135–138° (5 mm.), $n^{20}D$ 1.5604. *Anal.* Calcd. for $C_{16}H_{20}$: C, 90.50; H, 9.49. Found: C, 90.27; H, 9.90. This naphthalene failed to form a picrate when treated with methanolic picric acid.

2-Methoxalyl-1-tetralone, m. p., 64–65°, was prepared from 1-tetralone in 59% yield by the procedure of Bachmann and Thomas,[29] who reported it to melt at 65.5–66.5°.

2-Carbomethoxy-1-tetralone was prepared from the methoxalyl compound in 91% yield, according to Bachmann and Thomas.[29]

2-Methyl-2-carbomethoxy-1-tetralone, m. p., 58–59.5°, was prepared in 80% yield by alkylation of the carbomethoxytetralone with methyl iodide, following Bachmann and Thomas[29] who reported the m. p. as 56.5–57.5°.

2-Methyl-1-tetralone, b. p. 138–140° (15 mm.),[30] was obtained in 91% yield by alkaline hydrolysis of 2-methyl-2-carbomethoxy-1-tetralone according to the general procedure of Kloetzel.[31] The semicarbazone, crystallized from ethanol, melted at 201–202°.[32]

2-Methyl-1-*n*-propyltetralol.—A solution of *n*-propylmagnesium bromide (prepared from magnesium 1.1 g., *n*-propyl bromide 4.5 cc., and ether 30 cc.) was cooled and stirred while a solution of 2-methyl-1-tetralone (5 g.) in ether (20 cc.) was slowly added. The mixture was refluxed for one and one-half hours, then poured into ammonium chloride solution and extracted with ether. The extract was washed successively with aqueous ammonium chloride and water, the solvent was removed, and the residue was distilled. The product, 4.8 g. (75%) was a colorless liquid boiling at 146–150° (14–15 mm.), which solidified on cooling. Twice crystallized from petroleum ether (b. p. 30–60°), the substance melted at 82–83°. *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.4; H, 9.8. Found: C, 83.1; H, 9.7.

2-Methyl-1-*n*-propylnaphthalene.—The above tetralol (3 g.) was heated to 230–270° for three hours with palladium–charcoal catalyst (0.3 g., 10%). The mixture was taken up in ether, the catalyst was removed, and the solvent was evaporated. There resulted 2.4 g. of oil which boiled at 102–105° (5 mm.), and had $n^{20}D$ 1.5961. *Anal.* Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.08; H, 8.97.

Picrate.—The naphthalene (0.5 cc.) was dissolved in methanolic picric acid (6 cc.), the solution was cooled and the yellow crystals were removed and crystallized from methanol. The picrate then melted at 118–119°. *Anal.* Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63. Found: C, 57.98; H, 4.49.

2-Methyl-1-isopropyl-1-tetralol.—A solution of isopropylmagnesium bromide (prepared from magnesium 1.5 g., isopropyl bromide 6 cc., and ether 30 cc.) was cooled and to it was added a solution of 2-methyl-1-tetralone (6.4 g.) in ether (20 cc.). The reaction mixture was then processed as described for the *n*-propyl isomer. The product (5.4 g.) boiled at 126–129° (14 mm.), and had $n^{20}D$ 1.5562. *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.4; H, 9.8. Found: C, 84.0; H, 8.4. This tetralol (4 g.) was not dehydrated when it was refluxed with acetic acid (40 cc.) for one hour; there was recovered 3 g. of unchanged material, b. p. 127–131° (14 mm.), having $n^{20}D$ 1.5568.

2-Methyl-1-isopropylnaphthalene.—The above tetralol (3 g.) was dehydrated and dehydrogenated in one operation by heating it to 230–270° for three hours with palladium–charcoal catalyst (0.3 g., 10%). Isolated as described above for the *n*-propyl isomer, the product (1.8 g.) boiled at 92–95° (4 mm.), and had $n^{20}D$ 1.5992. *Anal.* Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.02; H, 8.62.

Picrate, prepared as described above and crystallized from methanol, formed needles melting at 142–143°. *Anal.* Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63. Found: C, 58.15; H, 4.85.

The methods used for synthesis of the 2-methyl-1-propylnaphthalenes failed when applied to the synthesis of the 1-methyl-2-propyl isomers. Thus, 2-carbomethoxy-1-tetralone could not be alkylated with *n*-propyl bromide, by the procedure of Bachmann and Thomas[29]; the only product that could be isolated was recovered 2-carbomethoxy-1-tetralone (75%). Nor was the direct alkylation of 1-tetralone successful. Action of methyl iodide upon the sodium derivative of the tetralone in liquid ammonia failed to produce any methyltetralone; action of isopropyl bromide upon the sodium derivative of the tetralone, formed in benzene by action of freshly prepared sodamide likewise failed; nor was the action of potassium *t*-butoxide in butanol effective in bringing about any reaction between 1-tetralone and isopropyl bromide.

Summary

1. Five 6,7-dialkyltetralins have been subjected to the conditions of the Jacobsen rearrangement. 6,7-Dimethyltetralin rearranged to 5,6-dimethyltetralin; 6-methyl-7-*n*-propyltetralin rearranged to 6-methyl-5-*n*-propyltetralin, the struc-

(29) Bachmann and Thomas, THIS JOURNAL, **63**, 598 (1941).

(30) Tishler, Fieser and Wendler, *ibid.*, **62**, 2866 (1940), reported the b. p. as 136–137° (16 mm.).

(31) Kloetzel, *ibid.*, **62**, 1708 (1940).

(32) Krollpfeiffer and Schaefer, *Ber.*, **56**, 631 (1923), give 199–201°; Mayer and Stamm, *Ber.*, **56**, 1424 (1923), give 200–201°; Kloetzel, Ref. 31, gives 203–205°; and Tishler, Fieser and Wendler, Ref. 30, give 205–206°.

ture of the *n*-propyl group remaining unaltered. 6-Isopropyl-7-methyltetralin gave 6-methyltetralin, the isopropyl group being eliminated. 6-Isopropyl-7-ethyltetralin and 6,7-di-*n*-propyltetralin were largely decomposed to products obtained in small yields only, and which could not be identified.

2. The theoretical aspects of these results have been discussed with reference to the theory of Arnold and Barnes on the mechanism of the Jacobsen rearrangement.

3. Satisfactory laboratory methods for preparation of the two 6-propyltetralins, *n*- and *iso*-, have been developed, and it has been shown that the structure of the *n*-propyl group remains unaltered when *n*-propylbenzene undergoes a Friedel–Crafts reaction with succinic anhydride.

4. Seven new 6,7-dialkyltetralins have been synthesized, in which one or both of the alkyl groups is methyl, ethyl, *n*-propyl or isopropyl.

5. The corresponding 2,3-dialkylnaphthalenes (and their picrates) have been prepared by dehydrogenation of the 6,7-dialkyltetralins. Syntheses of 1-isopropyl-2-methylnaphthalene and of 1-methylnaphthalene have been developed.

6. Several new intermediate ketones (acyl tetralins) and carbinols have been synthesized and characterized.

MINNEAPOLIS 14, MINNESOTA
RECEIVED FEBRUARY 21, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

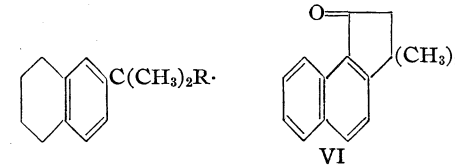
The Reaction between Tetralin and β,β-Dimethylacrylic Acid

BY LEE IRVIN SMITH AND CHIEN-PEN LO[1]

The reaction between benzene or an alkylbenzene and β,β-dimethylacrylic acid in the presence of aluminum chloride leads to a β-aryl-isovaleric acid.[2] However, when a polyalkylbenzene is used in this reaction, one or more of the following abnormal transformations may occur: (a) the condensation may occur at a position other than the one involved when the acid chloride (ordinary Friedel–Crafts reaction) is used, as is the case with 1,2,3-trimethylbenzene[3]; (b) one of the alkyl groups may rearrange to another position on the benzene nucleus, as is the case with 1,2,4-trimethylbenzene[3]; (c) one of the alkyl groups may be eliminated during the reaction, as is the case with 1,3,5-trimethylbenzene.[4]

In order to explore the limits of this reaction, tetralin has been condensed with β,β-dimethylacrylic acid in the presence of aluminum chloride. Only one acid (70% yield) was isolated; this was identified as β-(6-tetralyl)-isovaleric acid, I, by comparison with a specimen synthesized by an independent method. Thus tetralin, unlike other polyalkylbenzenes, behaves normally in this condensation.

6-(Tetralyl)-dimethylcarbinol, II,[5] was converted by action of hydrochloric acid into the chloride III, which (without isolation) was used to alkylate diethyl malonate. The substituted malonic ester IV (also without isolation) was hydrolyzed to the malonic acid V, and V, on decarboxylation, gave the isovaleric acid I, identical with the product obtained from β,β-dimethylacrylic acid and tetralin.



VI

I, R = —CH_2COOH
II, R = OH
III, R = Cl
IV, R = —$CH(COOC_2H_5)_2$
V, R = —$CH(COOH)_2$

Cyclization of the acid I, by action of sulfuric acid, in view of the work of Cauquil and Barrera[6] on the closely related β-(6-tetralyl)-butyric acid, should lead to a mixture of two tetrahydrobenzhydrindones, linear and angular. However, cyclization of β-(2-naphthyl)-propionic acids generally leads to only one benzindanone, the angular.[7] The acid I was therefore converted into the methyl ester and the latter was smoothly dehydrogenated to methyl β-(2-naphthyl)-isovalerate by action of palladium–charcoal catalyst—a result substantiating the findings of Newman and Zahm[8] that a carbomethoxy group is not affected by the hydrogen evolved during dehydrogenation. The methyl ester was hydrolyzed to β-(2-naphthyl)-isovaleric acid, and the acid, subjected to the action of sulfuric acid was dehydrated to a single benzhydrindone assigned structure VI.

Experimental[9]

β-(6-Tetralyl)-isovaleric Acid (I).—To a stirred and cooled (−10°) solution of β,β-dimethylacrylic acid (7.5 g.) in tetralin (37.5 g.), powdered aluminum chloride (13.3 g.) was added (fifteen minutes) in small portions. The mixture was thereafter stirred at −10° for one hour, at room temperature for two hours, and poured into iced hydrochloric acid. The acid fraction of the product, a

(1) Abstracted from a thesis by Chien-Pen Lo, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

(2) (a) Eijkman, *Chem. Weekblad*, **5**, 655 (1908); (b) Hoffman, THIS JOURNAL, **51**, 2542 (1929).

(3) Smith and Prichard, THIS JOURNAL, **62**, 771 (1940).

(4) Smith and Spillane, *ibid.*, **65**, 202 (1943).

(5) Smith and Lo, *ibid.*, **70**, 2209 (1948).

(6) Cauquil and Barrera, *Compt. rend.*, **223**, 679 (1946).

(7) Johnson, "Org. Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 125.

(8) Newman and Zahm, THIS JOURNAL, **65**, 1097 (1943).

(9) Microanalyses by R. Amidon and S. Sundet.

yellow oil, was dissolved in dilute acetic acid and the solution was set aside in a refrigerator. The yellow solid, twice recrystallized from petroleum ether (b. p., 30–60°), weighed 9 g. (68%) and melted at 88°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.81; H, 9.02. Found: C, 77.55; H, 8.68.

β-(6-Tetralyl)-β-methyl-α-carboxypropionic Acid (V).—A solution of 6-tetralyldimethylcarbinol[6] (II) (19 g.) in petroleum ether (20 cc., b. p., 40–75°) was saturated with dry hydrogen chloride at 0°, allowed to stand at room temperature for thirty minutes, then washed several times with water and dried over sodium sulfate. This solution of the crude chloro compound was added to an ethereal suspension of sodiomalonic ester (from ethyl malonate 16.5 g., sodium 2.3 g., ether 100 cc.) and the mixture was refluxed for several hours. Water was added carefully, and the organic layer was removed and washed successively with water, dilute hydrochloric acid, and water, and dried. The solvents were removed and the residual red oil was hydrolyzed by refluxing it for six hours with a solution of potassium hydroxide (22.5 g.) in methanol (70 cc.). The mixture was diluted with water and thoroughly extracted with ether. The aqueous layer was warmed to remove dissolved ether, and was acidified with dilute sulfuric acid. Some solid separated; the whole was extracted with ether and the ether solution was extracted with aqueous sodium carbonate (10%). Ether was removed from the aqueous extract, which was then acidified and set aside in a refrigerator. The product deposited as an oil which later solidified; after crystallization from ethanol, it weighed 4 g. and melted at 154–155° with effervescence.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.66; H, 7.62.

β-(6-Tetralyl)-isovaleric Acid (I).—The above malonic acid (2 g.) was heated at 180° until effervescence ceased (about thirty minutes). The residue was recrystallized from petroleum ether (b. p. 30–60°), when it melted at 88–89°, alone or when mixed with I prepared from dimethylacrylic acid.

Methyl β-(6-Tetralyl)-isovalerate.—The acid I (7 g.) was refluxed in methanol (30 cc.) with sulfuric acid (1 cc.) for two hours. The methyl ester (5.2 g., 70%), isolated in the usual way, boiled at 161–164° (11 mm.) and had $n^{20}D$ 1.5250. *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.01; H, 9.00. Found: C, 78.02; H, 8.75.

Methyl β-(2-Naphthyl)-isovalerate.—The above ester (4 g.) was heated in a stream of carbon dioxide with palladium–charcoal catalyst (0.1 g.) at 220–260° for three hours and then at 300° for thirty minutes. The product was dissolved in ethanol, the solution was filtered from the catalyst, and solvent was removed, and the residue was distilled. The distillate (2.8 g., 71%) boiled at 174–177° (10 mm.), and had $n^{20}D$ 1.5700. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.03; H, 7.20.

β-(2-Naphthyl)-isovaleric Acid.—The above methyl ester (2.6 g.) was hydrolyzed by refluxing it with aqueous sodium hydroxide (20 cc., 20%) for one hour. The acid was obtained as a colorless solid (2.4 g., 98%) which, after crystallization from petroleum ether (b. p. 30–60°) melted at 86–87°. The mixed m. p. with I (m. p. 88°) was 79–81°. *Anal.* Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.93; H, 7.36.

3,3-Dimethylbenz(e)indanone-1 (VI).—A solution of the above acid (1 g.) in sulfuric acid (8 cc.) was allowed to stand at room temperature for five hours. It was then poured over ice, the semi-solid precipitate was removed by ether extraction and crystallized twice from aqueous ethanol, when it melted at 65.5–67°.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.04; H, 6.81.

Summary

1. The reaction between tetralin and β,β-dimethylacrylic acid in the presence of aluminum chloride has been shown to yield predominantly (70%) a single acid, identified as β-(6-tetralyl)-isovaleric acid by an independent synthesis. No other product was isolated.

2. This acid has been converted (3 steps) into β-(2-naphthyl)-isovaleric acid, and the latter has been cyclized to a benzhydrindone.

3. Tetralin, unlike other polyalkylbenzenes, behaves normally in this condensation.

MINNEAPOLIS 14, MINNESOTA
RECEIVED FEBRUARY 21, 1948

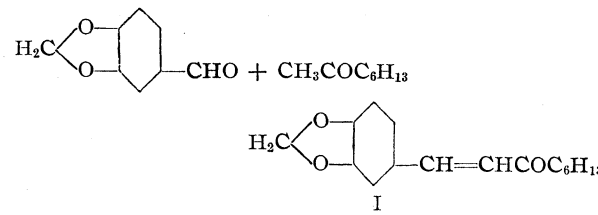
[A JOINT CONTRIBUTION FROM THE INSECTICIDE FELLOWSHIP, MELLON INSTITUTE, AND THE RESEARCH LABORATORY, DODGE & OLCOTT, INC.]

Methylenedioxyphenyl Cyclohexenones

BY OSCAR F. HEDENBURG AND HERMAN WACHS

In the search for new synthetic insecticidal materials which were to take the place of pyrethrins, 3-alkyl-5-(3,4-methylenedioxyphenyl)-2-cyclohexene-1-ones were prepared. These compounds are of very definite value where they are used as such, but they are of particular interest because of their ability to synergize the action of pyrethrins to an extraordinary degree.[1,2] They also share with pyrethrins the property of being practically nontoxic to warm-blooded animals.

The alkyl 3,4-methylenedioxystyryl ketones, precursors of the cyclohexenones, were prepared by the condensation of piperonal with methyl ketones in the presence of alkali. For example, methyl hexyl ketone gives hexyl 3,4-methylenedioxystyryl ketone I. This crystalline product is effective as an insecticide against flies, but is of little practical use because of its limited solubility in the usual vehicles, kerosene and Freon. Reduction of the ethylenic bond of I gave a liquid, soluble in kerosene and Freon but with little insecticidal activity.

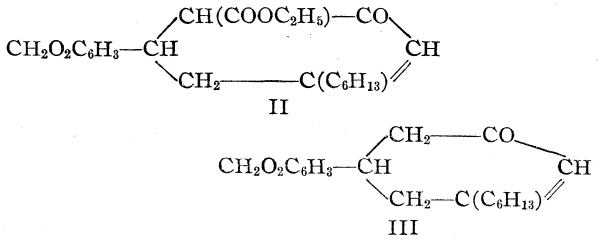


I

The condensation of hexyl 3,4-methylenedioxy-

(1) Hedenburg, pending patent applications.
(2) Wachs, *Science*, **105**, 530 (1947).

styryl ketone with ethyl acetoacetate[3,4] gave a 50% yield of crystalline 3-hexyl-5-(3,4-methylenedioxyphenyl)-2-cyclohexen-1-one (III). Saponification of the mother liquor gave more of the cyclohexenone, presumably formed from the initial cyclized addition product II. Saponification equivalents of the crude reaction product indicated approximately 30% of II. The crude reaction mixture is being used for insecticidal purposes, under the name of "Piperonyl Cyclonene."



II

III

The condensation of ethyl acetoacetate with the isobutyl styryl ketone gave approximately the same proportion of ketone and ester but only 15% of the ketone could be obtained in crystalline form. The amyl compound failed to give any solid product.

Catalytic hydrogenation of III gave the cyclohexanone, which was ineffective as an insecticide. It is therefore apparent, at least in this series of substances, that the conjugated system, =CH—CO—, is essential for insecticidal activity.

Experimental

Hexyl 3,4-Methylenedioxystyryl Ketone, I.—To a stirred mixture of 38.4 g. (0.3 mole) of methyl hexyl ketone, 48 g. of methanol and 7.5 g. of 20% sodium hydroxide was added 45 g. (0.3 mole) of piperonal over a period of thirty minutes, keeping the temperature between 20 and 25°. Stirring was continued until crystallization began and the mixture was then allowed to stand overnight. The usual manipulations gave 68 g. of solid product which can be either recrystallized from methanol or distilled *in vacuo*. The ketone boils from 175–185° at 1 mm. and gives light yellow crystals melting at 61°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; CO, 10.73. Found: C, 73.61; H, 7.63; CO, 10.84.

Amyl 3,4-Methylenedioxystyryl Ketone.—The amyl ketone, prepared by the above method, boils from 171–181° at 1.3 mm. and melts at 73°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; CO, 11.37. Found: C, 73.41; H, 7.48; CO, 11.34.

Isobutyl 3,4-Methylenedioxystyryl Ketone.—The isobutyl ketone boils from 166–173° at 2 mm. and melts at 66.5°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; CO, 12.05. Found: C, 72.51; H, 7.14; CO, 11.88.

Piperonylmethyl Hexyl Ketone.—An alcohol solution of I was hydrogenated at room temperature and under 20 lb. pressure, using palladium–charcoal catalyst, until one mole of hydrogen was absorbed. The liquid product boils at 204° at 4.5 mm., has a specific gravity of 1.0539 at 25° and a refractive index of 1.5109 at 20°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46; CO, 10.69. Found: C, 73.39; H, 8.23; CO, 10.31.

3-Hexyl-5-(3,4-Methylenedioxyphenyl)-2-cyclohexen-1-one, III.—To a stirred solution of 24.1 g. of sodium in 600 cc. of absolute alcohol was added 260 g. of I and then, over a period of fifteen minutes, 143 g. of ethyl acetoacetate. During the addition the bath temperature was 21.5° while the temperature of the solution rose to 24°. Stirring was continued for one hour while the bath temperature was raised to 33°. One hundred cc. of benzene was then added to dissolve the remaining solid, after which the solution was allowed to stand in the bath overnight.

The solution was poured into 100 g. of concentrated hydrochloric acid in 1200 cc. of water, 350 cc. of benzene was added, the mixture was thoroughly agitated, the bottom layer separated and extracted with 50 cc. of benzene. The combined benzene solution was washed with salt water, neutralized with sodium bicarbonate, shaken with Celite, filtered, and the benzene was finally removed *in vacuo*. The product, weighing 320 g., was a thick, reddish oil of specific gravity 1.136 at 25° and with a saponification value of 60. After standing for five weeks, the solid which had crystallized from the oil was isolated by centrifugation. About 160 g. of white crystals was obtained melting at 59° after recrystallization from alcohol.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.8; H, 8.0. Found: C, 75.9; H, 8.1.

Saponification of the above mother liquor with 0.5 *N* potassium hydroxide gave more of the cyclohexenone, identified by mixed melting point.

3-Hexyl-5-(3,4-methylenedioxyphenyl)-cyclohexanone.—An alcohol solution of the cyclohexenone readily absorbed one mole of hydrogen at room temperature and atmospheric pressure, using palladium–charcoal catalyst. The cyclohexanone is a liquid which could not be crystallized at −20°. It has a specific gravity of 1.0754 at 25° and a refractive index of 1.528 at 20°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66; CO, 9.26. Found: C, 75.21; H, 8.69; CO, 9.15.

3-Isobutyl-5-(3,4-methylenedioxyphenyl)-2-cyclohexen-1-one.—Prepared by the procedure used for the hexyl compound, there was obtained a pale orange product, which melted at 70.5° after recrystallization from alcohol.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.9; H, 7.4; CO, 10.28. Found: C, 74.9; H, 7.2; CO, 10.35.

The oxime of the isobutyl cyclohexenone melts at 106.5°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.08; H, 7.37; N, 4.87. Found: C, 69.84; H, 7.29; N, 4.80.

Summary

Alkyl 3,4-methylenedioxystyryl ketones, as well as their condensation products with ethyl acetoacetate, were prepared and found to be useful as non-toxic insecticides and as synergists for pyrethrins.

Hydrogenation of the methylenedioxystyryl ketones and of the cyclohexenones destroys the insecticidal activity.

(3) Michael, *J. prakt. Chem.*, **35**, 351 (1887).

(4) Knoevenagel, *Ber.*, **37**, 4464 (1904).

PITTSBURGH, PENNSYLVANIA
BAYONNE, NEW JERSEY

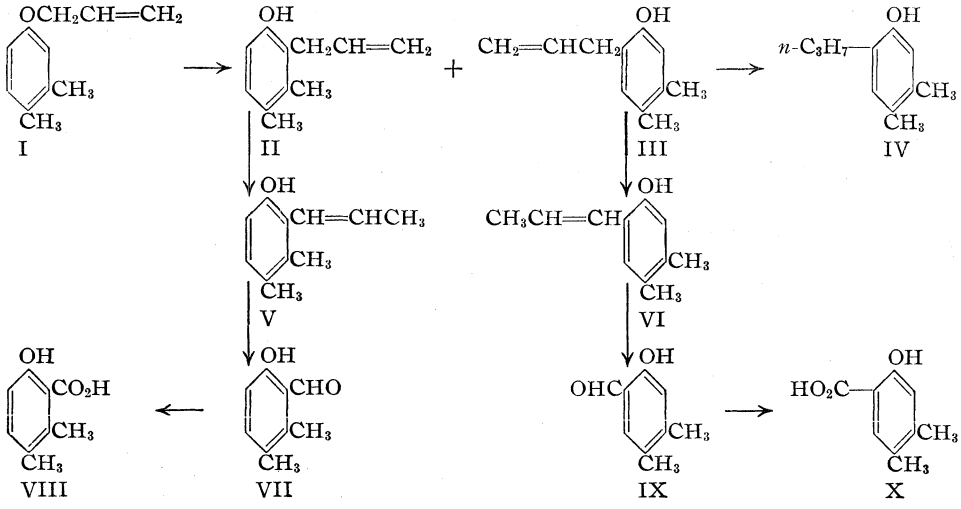
RECEIVED MARCH 17, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Claisen Rearrangement of Allyl 3,4-Dimethylphenyl Ether[1]

BY C. S. MARVEL AND N. A. HIGGINS[2]

In connection with an investigation of inhibitors we had need for a sample of 3,4-dimethyl-6-propylphenol (IV) and prepared it by the Claisen rearrangement of allyl 3,4-dimethylphenyl ether (I) followed by hydrogenation



We found that the rearrangement of the allyl ether (I) gave rise to a mixture of phenols (II and III) as might be expected from the report of Claisen and Eisleb[3] on the behavior of allyl 3-methylphenyl ether. Reduction of this mixture gave a mixture of the two propyl phenols from which a single isomer separated as a crystalline solid, m. p. 59°, in 52% yield.

Since it appears that no one has carefully examined the isomers that may be formed in an allyl rearrangement of this type,[4] we have established the structure of the two isomers and determined their ratio in our rearrangement mixture.

The mixed phenols (II and III) were isomerized with alkali to give the mixed propenyl phenols (V and VI), which were then ozonized to give the mixed aldehydes (VII and IX). These aldehydes are known compounds[5] and have different crystalline forms so the mixture obtained by ozonization could be separated mechanically into the two pure aldehydes. The identities of these aldehydes were confirmed by oxidation to the known acids (VIII and X).[5]

By the quantities of the two aldehydes obtained, it was established that in the original rearrangement 70 ± 5% of the 6 isomer (III) and 30 ± 5% of the 2 isomer (II) was produced. Hence the pure *n*-propylphenol which was obtained by hydrogenation must have been the desired 3,4-dimethyl-6-*n*-propylphenol (IV).

Experimental

Allyl 3,4-Dimethylphenyl Ether.—To 175 ml. of absolute alcohol in a 500-ml., three-necked flask, fitted with stirrer, dropping funnel, and condenser were added 11.5 g. (0.5 mole) of sodium chips. When solution was effected, 61.0 g. (0.5 mole) of 4-hydroxy-1,2-dimethylbenzene was added and the flask heated in an oil-bath to 85–90°. The mixture was stirred, and 41.8 g. (0.55 mole) of distilled allyl chloride was added slowly. The reaction mixture was heated for fifteen hours, stirring being discontinued after seven hours. The cooled reaction mixture was poured into 1 liter of water in a separatory funnel and the layers separated. The aqueous layer was extracted with two 100-ml. portions of petroleum ether (b. p. 35–45°) and the extract was combined with the previous organic layer. This solution was washed with 10% sodium hydroxide solution to remove unreacted starting material, dried over anhydrous magnesium sulfate, and distilled in a modified Claisen flask. The allyl 3,4-dimethylphenyl ether, 66.1 g., b. p. 75–79° (3 mm.), $n^{20}D$ 1.5200, d^{20}_4 0.9543, was obtained in 82% yield.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.45; H, 8.70; MR, 49.87. Found: C, 81.40; H, 8.70; MR, 51.28.

Mixed 2- and 6-Allyl-3,4-dimethylphenols.—Allyl 3,4-dimethylphenyl ether, 66.1 g. (0.41 mole), was rearranged by heating with one-half its weight of freshly distilled diethylaniline in a 245° bath for one-half hour. The boiling point of the mixture rose gradually during this time from 218 to 231°. The cooled mixture was dissolved in petroleum ether (b. p. 35–45°) and the diethylaniline removed by several washes with dilute sulfuric acid. The product was then removed as the potassium salt by extraction with aqueous-alcoholic potassium hydroxide (35 g. of potassium hydroxide, 25 g. of water, 90 g. of methanol) in four equal portions. The alkaline solution was washed with petroleum ether, acidified, and extracted exhaustively with petroleum ether. The petroleum ether solution was dried over anhydrous magnesium sulfate and distilled in a modified Claisen flask. The mixed 2- and 6-allyl-3,4-dimethylphenols distilled at 82–85°

(1) This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Present address: Rayon Department, E. I. du Pont de Nemours and Company, Buffalo, New York.

(3) Claisen and Eisleb, *Ann.*, **401**, 21 (1913).

(4) Tarbell, "The Claisen Rearrangement" ("Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944).

(5) Clayton, *J. Chem. Soc.*, **97**, 1404 (1910).

(1 mm.), $n^{20}D$ 1.5434, d^{20}_4 0.9671. The yield was 46.8 g. or 71% of the theoretical amount.

Mixed 3,4-Dimethyl-2-propylphenol and 3,4-Dimethyl-6-propylphenol.—Hydrogenation of 46.8 g. of the mixed 2- and 6-allyl-3,4-dimethylphenols in ethanol solution at 25° with a Raney nickel catalyst proceeded smoothly and the theoretical amount of hydrogen was absorbed in twenty minutes. The catalyst was removed by filtration and the mixture distilled in a modified Claisen flask to yield 30.6 g. (65%) of mixed 3,4-dimethyl-2-propylphenol and 3,4-dimethyl-6-propylphenol, b. p. 77–77.5° (<1 mm.).

3,4-Dimethyl-6-propylphenol.—The mixture of 3,4-dimethyl-2-propylphenol and 3,4-dimethyl-6-propylphenol was a very viscous oil. When this material had stood for two weeks, crystals began to form; crystal growth proceeded, but the whole of the material did not crystallize. The crystals were removed by filtration through a sintered glass filter; thus 16.0 g. (52%) of the material was obtained as a white crystalline solid. This was recrystallized four times from petroleum ether (b. p. 35–45°) to a constant melting point of 59°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.45; H, 9.75. Found: C, 80.49; H, 9.83.

Mixed 3,4-Dimethyl-2-propenylphenol and 3,4-Dimethyl-6-propenylphenol.—To a 500-ml. round-bottomed flask containing 152 g. of *n*-amyl alcohol was added 105 g. of potassium hydroxide flakes. The mixture was refluxed for a short time, the clear supernatant liquid decanted, and to it was added 40 g. (0.247 mole) of the rearrangement product from allyl 3,4-dimethylphenyl ether (2- and 6-allyl-3,4-dimethylphenols). The solution was heated at the boiling point for twenty-four hours, the amyl alcohol removed by steam distillation, and the remaining solution acidified with phosphoric acid. The acidified solution was extracted with four 100-ml. portions of ether and the ether solution dried over anhydrous magnesium sulfate and distilled without fractionation. A yield of 24.6 g. (61.6%) of mixed 3,4-dimethyl-2-propenylphenol and 3,4-dimethyl-6-propenylphenol was obtained.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.45; H, 8.70. Found: C, 81.90; H, 8.59.

4,5- and 5,6-Dimethylsalicylaldehydes.—A solution of 8.4 g. (0.052 mole) of mixed 3,4-dimethyl-2-propenylphenol and 3,4-dimethyl-6-propenylphenol in 400 ml. of chloroform was ozonized for six hours at 0° with approximately 4% ozone. The chloroform solution of the ozonide was treated with 120 ml. of water, and the chloroform was distilled from the mixture under reduced pressure. After the chloroform had been completely removed, the flask was heated vigorously and the contents distilled. A yield of 4.95 g. (63.8%) of aldehyde was obtained from the steam-distillate by ether extraction, while 1.4 g. of material remained in the pot.

The aldehyde thus obtained was converted to the bisulfite addition product by shaking vigorously with nearly saturated sodium bisulfite solution at about 40°. The white crystalline addition product was removed by suction filtration, washed repeatedly with ether, and finally decomposed with 150 ml. of warm 3% hydrochloric acid. The purified aldehyde was recovered by ether extraction, drying of the extract, and removal of the solvent by distillation. The solid, light-yellow aldehyde thus obtained was recrystallized from petroleum ether (b. p. 35–45°), the solution being allowed to cool very slowly so that large crystals formed. Two types of crystals were formed, long spike-like needles of 5,6-dimethylsalicylaldehyde and lustrous plates of the 4,5-isomer; a quantity of the material was separated into its component crystals mechanically. Thus it was determined that 70 ± 5% of the material crystallized as plates and 30 ± 5% as needles. The two crops of crystals were separately recrystallized first from dilute alcohol and then from petroleum ether (b. p. 35–45°). The plates of 4,5-dimethylsalicylaldehyde melted at 69° and the needles of 5,6-dimethylsalicylaldehyde at 70°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 72.00; H, 6.72. Found: Plates—C, 72.04; H, 6.65; Needles—C, 72.10; H, 6.60.

Clayton[5] who prepared a similar mixture of aldehydes from a Reimer–Tiemann reaction on 3,4-dimethylphenol found that 4,5-dimethylsalicylaldehyde crystallized in plates, m. p. 71°, and the 5,6-isomer in needles, m. p. 72°.

4,5-Dimethylsalicylic Acid.—About 0.1 g. of 4,5-dimethylsalicylaldehyde was sprinkled into 0.6 g. of fused sodium–potassium hydroxide (50–50 containing a little water) at 210° in a nickel crucible. As soon as gas evolution had ceased the mixture was cooled, dissolved in water, filtered, and acidified. The 4,5-dimethylsalicylic acid which precipitated was collected on a filter, dried, and recrystallized from aqueous methanol. The purified product melted at 197.6°. The literature[5] reports a melting point of 198–199°.

5,6-Dimethylsalicylic Acid.—This material was prepared from 5,6-dimethylsalicylaldehyde exactly as described above for 4,5-dimethylsalicylic acid. The 5,6-dimethylsalicylic acid melted at 140°. Clayton[5] describes this acid as melting at 142–143°.

Summary

The rearrangement of allyl 3,4-dimethylphenyl ether gives 70 ± 5% of 6-allyl-3,4-dimethylphenol and 30 ± 5% of 2-allyl-3,4-dimethylphenol.

Reduction of this mixture of allyl phenols gives a 50% yield of crystalline 3,4-dimethyl-6-*n*-propylphenol.

URBANA, ILLINOIS RECEIVED FEBRUARY 26, 1948

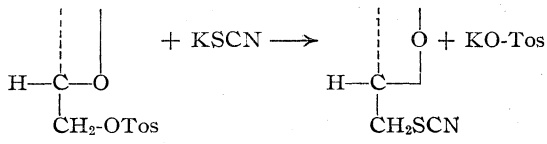
[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

The Thiocyanation of Polysaccharide Tosyl Esters

BY J. F. CARSON AND W. DAYTON MACLAY

The replacement of tosyloxy groups in the primary position of carbohydrates by iodine[2] as a method of distinguishing primary from secondary hydroxyl groups has had a wide application. In polysaccharide chemistry, the reaction has been applied quantitatively to cellulose,[3] partially substituted ethyl cellulose[4] and cellulose acetate,[4,5] and to arabogalactan[6] from larch wood. It has now been found that polysaccharide tosyl esters undergo an analogous reaction with alkali thiocyanates to yield thiocyano derivatives. The replacement of tosyloxy in a number of polysaccharide tosyl esters by thiocyanate has been investigated, and the reaction has been found to have approximately the same degree of specificity for primary tosyloxy groups as the familiar iodination reaction.

Müller and Wilhelms[7] found that tetra-acetyl-6-tosyl β-glucose and triacetyl-6-tosyl α-methylglucoside when heated with potassium thiocyanate in acetone at 130° formed the corresponding 6-thiocyanates according to the equation



The 6-thiocyanates were observed to be very stable in contrast to the previously known 1-thiocyanates and showed no tendency to rearrange to the isothiocyanates even at elevated temperatures. A tosyl or mesyl group in the 3 position was found to be unreactive to thiocyanate. The apparent specificity of thiocyanate substitution for primary tosyloxy groups in glucose derivatives cannot be extended to non-carbohydrate materials, since tosyl esters of secondary alcohols have been observed to react with thiocyanates under mild conditions. Cholesterol *p*-toluenesulfonate[8] and ethyl α-tosylpropionate[9] both react with potassium thiocyanate in acetone or alcohol solution to yield the corresponding thiocyano derivatives.

In the present work, potato starch, cellulose, guar mannogalactan, and corn-cob and lima-bean pod hemicelluloses have been tosylated and the esters reacted with sodium thiocyanate in acetonyl acetone at 110–112°. The tosyl esters were also iodinated by heating at 110–112° with sodium iodide in acetonyl acetone, and the primary hydroxyl content as determined by iodine substitution was compared with values obtained by thiocyanation. The results are compiled in Table I.

Discussion of Results

A potato starch tosyl ester, when treated with sodium thiocyanate for varying periods of time, yielded tosyl thiocyano derivatives containing approximately 0.94 equivalent of thiocyanate per anhydroglucose repeating unit. Iodination of the same tosylate likewise yielded iodo compounds containing 0.93 to 0.95 equivalent of iodine per repeating unit.[10]

Thiocyanation and iodination of the cellulose tosyl esters gave more variable results than starch, but approximately one thiocyano group was introduced per anhydroglucose unit. Thiocyanation of a tosyl ester of wood pulp cellulose yielded derivatives containing 0.95 to 1.03 equivalents per repeating unit. Iodination of the same ester for seven hours produced a derivative with 0.98 equivalent of iodine per unit. Thiocyanation of a tosyl ester of regenerated cellulose (Cellophane) yielded derivatives with thiocyanate contents varying from 0.90 to 1.09.

Two different tosyl esters of guar mannogalactan, the water-soluble polysaccharide of guar endosperm (*Cyamopsis tetragonoloba* Taub) when thiocyanated for different periods of time yielded derivatives with thiocyanate contents varying from 0.44 to 0.52 equivalent per anhydrohexose unit. Iodination gave slightly higher replacement values from 0.50 to 0.56 equivalent per anhydrohexose unit. If the two reactions are assumed to be specific for primary hydroxyl in this polysaccharide, approximately half of the primary alcohol groups must be blocked by linkages of the 1,6 type.[11] This observation is at variance with the report of Moe, Miller and Iwen[12] who postulated 1,4 link-

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(3) Honeyman, *J. Chem. Soc.*, 168 (1947).

(4) Cramer and Purves, THIS JOURNAL, **61**, 3458 (1939); Mahoney and Purves, *ibid.*, **64**, 9, 15, 1539 (1942).

(5) Malm, Tanghe and Laird (abstract of paper delivered at Division of Cellulose Chemistry, American Chemical Society, New York, Sept., 1947).

(6) Low and White, THIS JOURNAL, **65**, 2430 (1943).

(7) Müller and Wilhelms, *Ber.*, **74B**, 698 (1941).

(8) Müller and Batyka, *ibid.*, **74B**, 705 (1941).

(9) Gerrard, Kenyon and Phillips, *J. Chem. Soc.*, 153 (1937).

(10) The theoretical thiocyanate or iodine content should be slightly less than unity because of the presence of a small number of 1,6 linkages in the amylopectin component of potato starch.

(11) Swanson (abstract of paper delivered at Division of Sugar Chemistry, American Chemical Society, New York, Sept., 1947) has obtained by hydrolysis of methylated guar polysaccharide 2,3,4,6-tetramethylgalactose and unidentified trimethyl and dimethyl sugars. From the quantities isolated, the author suggests that the polysaccharide consists of a main chain of anhydromannose units with a side unit of galactose attached to every other mannose unit.

(12) Moe, Miller and Iwen, THIS JOURNAL, **69**, 2621 (1947).

TABLE I

THIOCYANATION OF POLYSACCHARIDE TOSYL ESTERS

Tosyl ester			Thiocyanation					Iodination				
Polysaccharide	% S[a]	Number of tosyl groups per repeating unit	Reaction time, hr.	% N[b]	Equivalents of SCN per repeating unit[c]	% S Found[a]	% S Calcd.	Time, hr.	% I[d]	Equivalents of I per repeating unit[e]	% S Found[a]	% S Calcd.
White potato starch	13.19	1.82	3	3.72	0.91	16.89	17.2	3.5	30.0	0.95		
			4	3.76	.91	16.98	17.2	7	29.2	.93	6.97	7.16
			6	3.91	.94	17.11	17.4	9	29.7	.94		
			9	3.89	.94	17.09	17.3					
			12	3.96	.95	17.03	17.4					
Cellulose (wood pulp)	13.05	1.77	7	4.06	0.95	16.80	17.3	3.5	29.6	0.92		
			9	4.41	1.01			5	30.2	.94	6.3	6.79
			11	4.52	1.03	17.4	17.8	7	31.6	.98	6.3	6.51
Cellulose (cellophane)	13.38	1.90	7	3.55	0.90	16.9	17.2					
			8	4.23	1.02	17.6	18.0					
			9	4.61	1.09	18.2	18.4					
Guar (mannogalactan)	13.50	1.95	4	1.56	0.46	14.95	15.2	6	15.6	0.54	10.04	10.3
			8	1.72	0.50	15.20	15.4	8	16.1	.56	9.90	10.2
	13.78	2.07	6	1.44	.44	15.15	15.4	3	13.8	0.50		
			9	1.61	.49	15.20	15.5	6	13.7	0.50		
			10	1.73	.52	15.41	15.7	9	15.2	0.55		
			12	1.49	.46	14.83	15.4	12	14.8	0.53		
Lima bean pod hemicellulose	7.67	0.534	6	1.05	.15	8.19	8.32	6	8.58	0.15	5.42	5.73
			7.5	1.01	.15	8.17	8.29					
			9.5	1.06	.16	8.20	8.32					
			12	0.86	.13	8.12	8.20					
	13.03	1.53	5	.81	.20	13.83	13.9	4	10.0	0.29	11.1	11.06
			7	.84	.21	13.89	13.9	6	11.5	.33	10.7	10.73
			8	.82	.21	14.03	13.9					
			9	.98	.24	14.02	14.1					
			11	.92	.23	14.14	14.0					
Corn-cob xylan	13.96	1.81	7	.62	.18			5	5.65	0.18	12.3	12.8
			8.5	.78	.22	14.71	14.8					
			9	.74	.21							
			10	.75	.21	14.80	14.8					

[a] Sulfur was determined gravimetrically by the Parr bomb method. [b] Nitrogen was determined by the Kjeldahl method. [c] The number of equivalents of thiocyanate (m) per repeating unit was calculated from nitrogen analyses by the formula

$$m = \frac{u + 154.18n}{113.11 + (1401/N)}$$

where n = number of tosyl groups per repeating unit in original ester; N = % nitrogen; and u = average repeating unit, *i. e.*, 162.1 for a hexosan. For the corncob and lima bean pod hemicelluloses, the calculated values of u were, respectively, 137 and 141, on the assumption that the material unaccounted for as xylan, uronic anhydride, and methoxyl is hexosan. The theoretical percentage of sulfur was calculated by the formula:

$$\% \text{ S} = \frac{3206n}{u + 154.18n - 113.11n}$$

Calculation of thiocyanate content from sulfur analyses would have yielded slightly lower values in each case. [d] Iodine was estimated by the method of Clark, "Semimicro Quantitative Analysis," Academic Press, New York, N. Y., 1943, p. 62. [e] The number of equivalents of iodine per repeating unit was calculated from iodine analyses assuming no loss of tosyl ester except by replacement.

ages from the observation that guar mannogalactan consumes one mole of periodate.[13]

Thiocyanation and iodination of a corn-cob hemicellulose tosylate gave unexpectedly high values for thiocyanate and iodine substitution. Analysis of the hemicellulose indicated that approximately 96% could be determined as xylan[14] and methoxy uronide. Lignin content was not greater than 1%. Since the anhydroxylose units

(13) Investigations in this Laboratory of the periodate oxidation of mannogalactan are also in disagreement with the report of Moe, *et al.*[12] It has been observed that in the oxidation of guar polysaccharide, formic acid is always produced (0.3 to 0.4 mole per equivalent of polysaccharide) and that consumption of paraperiodic acid (buffered at *p*H 5) or of sodium metaperiodate at temperatures from 5° to 25° was greater than one mole, the rate curve having such a shape that it was difficult to determine the exact consumption of oxidant.

(14) Bennett (*J. Agr. Res.*, **75**, [1] 43 (1947)), in investigations of an unfractionated sample of corn cob hemicellulose, reported the presence of a trace of L-arabinose in the acid hydrolysate. Our hemicellulose fraction was found to be free of arabinose to the extent that no test could be obtained with diphenylhydrazine or benzylphenylhydrazine.

of the xylans are considered to be in the pyranose form,[15] the actual replacement by iodine or thiocyanate should not be greater than 0.04 equivalent per average repeating unit. A tosyl ester containing 1.81 tosyl groups per average repeating unit yielded thiocyanates containing 0.18 to 0.22 equivalent of thiocyanate per repeating unit and iodination gave a replacement of 0.18 equivalent.

The lima bean pod hemicellulose fraction had analyses indicating that 82% of the polysaccharide could be accounted for as xylan, uronic anhydride and methoxyl. Arabinose could not be detected. On the assumption that the material unaccounted for by these analyses is hexosan, the maximum degree of replacement should be approximately 0.18 equivalent per average repeating unit (weighted average of xylan, methoxy uronide and hexosan). Thiocyanation and iodination of a tosylate with a low ester content (0.53 equivalent of tosyl per unit) seemed to confirm this supposition. Both reactions proceeded to the extent of 0.15 equivalent per unit. However, iodination of a tosyl ester having a higher tosyl content (1.53 equivalents per unit) gave higher values which would indicate a primary hydroxyl content of 0.29 to 0.33. Thiocyanate substitution was also significantly higher than before, 0.20 to 0.24 equivalent per repeating unit.

When these reactions are applied to polysaccharides, two conditions are presupposed: (1) that substantially all of the primary alcohol groups are tosylated and (2) that the replacement occurs only at the primary position. Complete tosylation of the polysaccharide would automatically satisfy the first condition, but this often leads to dark-colored degraded products containing some nitrogen and chlorine. Purves and co-workers[16] have measured the relative rates of tosylation in the unsubstituted positions of cellulose acetate and ethyl cellulose and found them to be in the ratios, respectively, of 2.2:0.11:23 and 2.3:0.07:15 for the 2,3 and 6 hydroxyls. Other polysaccharides may not have such a favorable ratio for attaining complete esterification of the primary alcohol groups. On the other hand, lima bean pod hemicellulose tosylate appeared to undergo iodination and the corncob hemicellulose tosylate apparently underwent both iodination and thiocyanation in secondary positions. Malm, *et al.*,[5] have reported that in the tosylation and subsequent iodination of cellulose acetate or regenerated cellulose, the amount of iodine introduced increased when the time of reaction in either the tosylation or the iodination step was extended. These discrepancies would be particularly significant in assigning structures to polysaccharides with a low primary hydroxyl content and would restrict the utility of the reactions to very crude approximations of primary hydroxyl content.

Acknowledgment.—The authors wish to thank L. M. White and A. Bevenue for the determinations of nitrogen and sulfur.

Experimental

Polysaccharides

Potato Starch.—A commercial sample was used without purification.

Cellulose samples used were Dupont Cellophane and Brown Co. "Solka Floc," a purified wood pulp in a finely divided form. The latter had a xylan content of 2.5%.

Lima Bean Pod Hemicellulose.—The pods from lima beans of normal canning maturity were extracted successively with benzene–ethanol (2:1), boiling water and boiling 0.5% ammonium oxalate. The material was delignified by the sodium chlorite procedure of Wise, *et al.*,[17] and the holocellulose extracted successively with boiling water, 2% sodium carbonate, and 5% potassium hydroxide at room temperature for one hour under nitrogen. The hemicellulose isolated from the potassium hydroxide extraction was re-dissolved in alkali and precipitated with copper sulfate according to the directions of Angell and Norris.[18]

Anal. Uronic anhydride, 9.0%; xylan, 72%; methoxyl, 1.4%; and $[\alpha]^{20}D$ −45.3 (*c*, 1.28 in 2% potassium hydroxide).[19]

Corn-cob Hemicellulose.—This material was prepared in the same manner as the lima bean pod hemicellulose. *Anal.* Uronic anhydride, 6.2%; xylan, 89.3%; methoxyl, 0.7%; and $[\alpha]^{20}D$ −98.2 (*c*, 0.917 in 2% potassium hydroxide).[19]

Guar Mannogalactan.—The water-soluble fraction was isolated from guar flour (*Cyamopsis tetragonoloba* Taub) obtained from General Mills, Inc. An aqueous dispersion of the flour was first digested with trypsin to remove proteins, then centrifuged, and the extract was clarified by filtration. The polysaccharide was isolated as a white fibrous precipitate when the filtrate (after concentration *in vacuo* to a 0.4% solution) was poured into two and one-half volumes of ethanol. It was purified by washing with 70% ethanol–1% hydrochloric acid, neutral 70% ethanol, 95% ethanol and acetone. *Anal.* Nitrogen, 0.07%; anhydromannose, 59%[20]; anhydrogalactose, 32%; uronic anhydride, 3.5%; pentosan <1%; and $[\alpha]^{20}D$ +61° (*c*, 0.57 in water).[19]

Tosylation

Potato starch, guar mannogalactan, and the hemicelluloses were pretreated by pasting with boiling water, coagulating with pyridine, and removing the water by washing with pyridine to obtain the polysaccharide in a reactive form. The wood-pulp and the Cellophane were steeped in 25 to 30 parts of 5% sodium hydroxide for one hour at 20°, and were then washed with water until free of alkali and the water was replaced by pyridine.

Esterification was performed in a mixture of pyridine and *p*-toluenesulfonyl chloride, the latter in an excess of four to five times the calculated quantity. Tosylation was allowed to proceed at 20–23° (after initial cooling of the reaction mixture) for periods of time varying from two days to three weeks. The esters were isolated and purified in the usual manner. Under these conditions, starch and guar polysaccharide could be tosylated to a degree of 1.7 to 2.0 tosyl groups per repeating unit in forty-eight

(15) Hampton, Haworth and Hirst, *J. Chem. Soc.*, 1739 (1929); Haworth and Percival, *ibid.*, 2850 (1931); Haworth, Hirst and Oliver, *ibid.*, 1917 (1934); Bywater, Haworth, Hirst and Peat, *ibid.*, 1983 (1937).

(16) Mahoney and Purves, THIS JOURNAL, **64**, 9 (1942); Gardner and Purves, *ibid.*, **64**, 1539 (1942).

(17) Wise, Murphy and D'Addieco, *Paper Trade Journal*, **122** [2], 35 (1946).

(18) Angell and Norris, *Biochem. J.*, **30**, 2155 (1936).

(19) Specific rotations were determined by measuring the rotations in 2 dm. tubes with the D line of sodium at 20°.

(20) Mannose was estimated by a modification of Bertrand's method, and galactose was estimated by the differential fermentation procedure of Wise and Appling (*Ind. Eng. Chem., Anal. Ed.*, **16**, 28 (1944)).

hours on a shaking machine. Cellulose samples required from four to five days at 20° with shaking for the same degree of esterification; the hemicelluloses reacted very slowly, a high degree of tosylation requiring from two to three weeks. The esters had nitrogen contents of 0.05% or less.

Thiocyanation and Iodination

Replacement of tosyloxy by thiocyanate was effected by heating a mixture of 2 g. of tosyl ester, 200 ml. of freshly distilled acetonyl acetone, and 6 g. of sodium thiocyanate (dried *in vacuo* at 100°) under anhydrous conditions at 110–112° for periods of time as indicated in Table I. Low values for nitrogen were usually obtained unless the reaction mixture was heated for at least five hours.

The starch and mannogalactan tosylates were almost completely soluble in the hot reaction medium, the cellulose tosylates were partly soluble and the hemicellulose esters swelled without appreciable solution. The thiocyanotosylates were recovered in quantitative yields by pouring into four volumes of ice water. The esters were washed repeatedly with distilled water, 95% ethanol, and finally with ether. For analyses, they were dried *in vacuo* at 70° over phosphorus pentoxide. The thiocyano derivatives when dried were powdery materials, white to a light grey in color. Their solubility behavior was very similar to that of the corresponding iodo compounds.

Iodination was performed under conditions comparable to the thiocyanation procedure. Five grams of sodium iodide was used for each gram of tosyl ester and 100 ml. of acetonyl acetone. No apparent difference was noted in iodination at 100 and 110°, although thiocyanation at the lower temperature was, in some cases, slightly slower than at 110°.

Summary

The replacement of tosyloxy in the primary position by thiocyanate has been found to be applicable to several polysaccharide tosyl esters. When applied to potato starch, cellulose, and guar mannogalactan, the reaction had approximately the same degree of specificity for replacement of the tosyloxy group in the primary position as the iodination reaction.

Both thiocyanation and iodination of the tosylate of the water-soluble polysaccharide of guar indicate that approximately half of the primary hydroxyl groups are involved in linkages.

Thiocyanation and iodination of a corn-cob hemicellulose tosyl ester and iodination of a lima bean pod hemicellulose tosylate yielded substitution to a greater extent than was expected, from the structure of these materials, indicating that possibly some secondary tosyloxy groups were replaced.

ALBANY, CALIFORNIA RECEIVED FEBRUARY 24, 1948

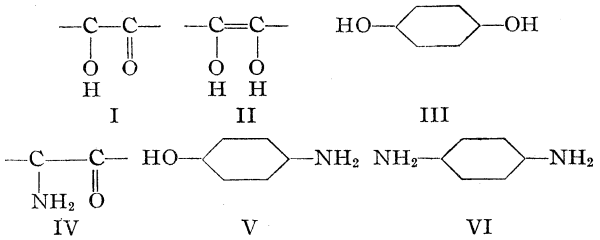
[COMMUNICATION NO. 1167 FROM THE KODAK RESEARCH LABORATORIES]

Oxidation Processes. XXI.[1] The Autoxidation of the *p*-Phenylenediamines

BY JAMES E. LUVALLE, DUDLEY B. GLASS AND ARNOLD WEISSBERGER

Introduction

Previous papers of this series discussed the autoxidation of α-ketols, I,[2] enediols, II,[3] hydroquinones, III,[4] and α-aminoketones, IV.[5] The present paper deals with the autoxidation of *p*-phenylenediamines, VI, and, briefly, of *p*-aminophenols, V.



I II III

IV V VI

Like the dihydroxy compounds, these substances react with molecular oxygen, and the reaction proceeds in two univalent steps.[6] From the results of earlier papers of this series,[3,4,5] the rate of the over-all reactions can be expected to depend upon the rate of formation of the semiquinone, upon its concentration in the various equilibria involved, and upon its reactivity with oxygen.

$$R + O_2 \longrightarrow T + H_2O_2 \qquad (1)$$

The intensely colored intermediate products of *p*-phenylenediamines, *Wurster's salts*, exist as free radicals, semiquinones, in dilute solution,[6] and as dimers or higher polymers in higher concentration.[6c] These semiquinones are much more stable than the corresponding fully oxidized quinonediimines,[6b,7] and quinoneimines[7] which are readily hydrolyzed to the corresponding quinones. Moreover, the higher N-methylated diamines undergo a demethylation reaction when oxidized. Thus, N,N′-tetramethyl-*p*-phenylenediimine loses a methyl group with formation of N,N′-trimethyl-*p*-phenylenediamine and formaldehyde,[6,7] and N,N′-tetramethyl-, N,N′-trimethyl-, and N-dimethyl-*p*-phenylenediamine couple in oxidizing solutions with a *p*-substituted phenol to give an identical indoaniline dye.[8] The latter reaction shows that the trimethyl-*p*-phenylenedi-

(1) XX. LuValle and Weissberger, THIS JOURNAL, **69**, 1821 (1947).

(2) (a) Weissberger, Mainz and Strasser, *Ber.*, **62**, 1942 (1929); (b) Weissberger and Bach, *J. Chem. Soc.*, 226 (1935).

(3) Weissberger and LuValle, THIS JOURNAL, **66**, 700 (1944).

(4) (a) James and Weissberger, *ibid.*, **60**, 98 (1938); (b) James, Snell and Weissberger, *ibid.*, **60**, 2084 (1938); (c) LuValle and Weissberger, Part XIX, *ibid.*, **69**, 1576 (1947).

(5) James and Weissberger, *ibid.*, **59**, 2040 (1937).

(6) (a) Michaelis and Hill, *ibid.*, **55**, 1487 (1933); (b) Michaelis, Schubert and Granick, *ibid.*, **61**, 1981 (1939); (c) Michaelis and Granick, *ibid.*, **65**, 1747 (1943).

(7) (a) Willstätter and Meyer, *Ber.*, **37**, 1494 (1904); (b) Willstätter and Pfannenstiel, *ibid.*, **37**, 4605 (1904); (c) Willstätter and Kubli, *ibid.*, **42**, 4135 (1909).

(8) W. R. Ruby, of these Laboratories, private communication.

amine also undergoes demethylation upon oxidation in a rapid reaction.

The concentration of *Wurster's salts*, the semiquinones, in the equilibrium

$$R + T \rightleftharpoons 2S \qquad (2)$$

increases with increasing methylation of the amino group.[6b] The *rate of reaction* of the semiquinones with molecular oxygen may also be expected to vary within wide limits, depending on kind and number of substituents.

In a first approximation we consider resonance as the main stabilizing factor for the semiquinones.[6] The principal structures of the semiquinones of *p-phenylenediamine* are given in Fig. 1a. The cationic semiquinone, SH_2^+, has three pairs of equivalent structures, the neutral molecule, SH, has no equivalent structures, and the anionic semiquinone, S^-, has again three equivalent structures. For this reason, SH_2^+ and S^- should be stable and exist in appreciable concentrations in their respective *p*H ranges, at variance with SH, which is expected to be unstable. When two R groups are on one hydrogen, the negative semiquinone ion will not be stabilized by structures shown in Fig. 1a.

The ionic species for the N-alkylated-*p*-phenylenediamines are given in Fig. 2a. The semiquinones of *monalkyl-p-phenylenediamine* and *s-dialkyl-p-phenylenediamine* resemble *p*-phenylenediamine. The anionic semiquinone of *as-N-dialkyl-p-phenylenediamine* lacks structures a′, b, b′, c and c′ and is therefore probably about as unstable as the neutral semiquinone. *Trialkyl-p-phenylenediamines* do not form an anionic semiquinone, and *tetramethyl-p-phenylenediamine* even lacks a neutral semiquinone.

The principal resonance forms of the semiquinones of the *p*-aminophenols are given in Fig. 1b. None of the semiquinones has equivalent resonance states. The neutral semiquinone, SH, is probably represented by group (b) because the hydroxyl group will lose a proton more readily than the amino group. The structures of group (a) under SH are tautomers of the structures of group (b).

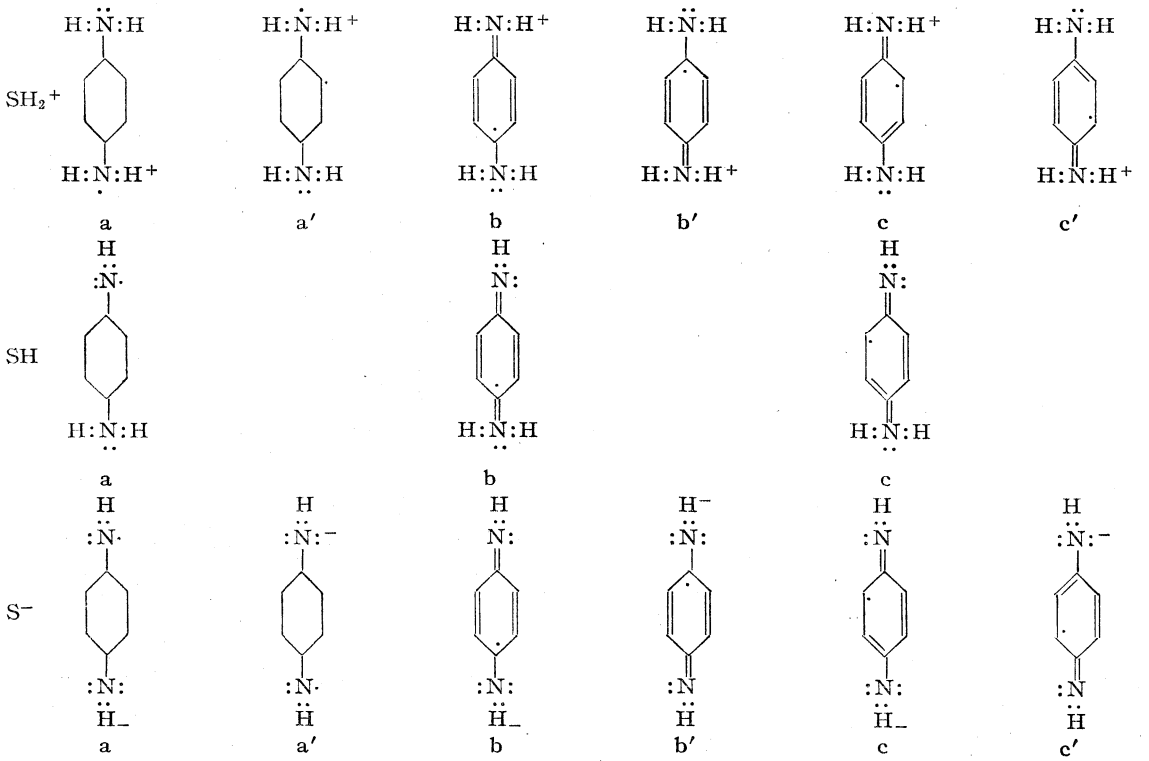
The ionic species for the semiquinones of the three types of *p*-aminophenols are given in Fig. 2b. The dimethyl semiquinone exists only as SH_2^+ and SH. The remainder may exist as cation, neutral molecule, or anion depending on the *p*H.

Michaelis and Schubert[9] have investigated the dependence of the *concentration of certain semiquinones* upon *p*H. If the oxidized form, T, is stable, the semiquinone concentration has a maximum when half of the initial quantity of diamine is oxidized, *i. e.*, when R = T. At this point

$$(S/a)_{max.} = \sqrt{K_s}/(2 + \sqrt{K_s}) \qquad (3)$$

where a is the concentration of R + T + S[9] and

A



(9) (a) Michaelis and Schubert, *Chem. Rev.*, **22**, 437 (1938); (b) Michaelis, *Annals N. Y. Acad. Sci.*, **40**, 39 (1940); (c) Schubert, *ibid.*, **40**, 111 (1940).

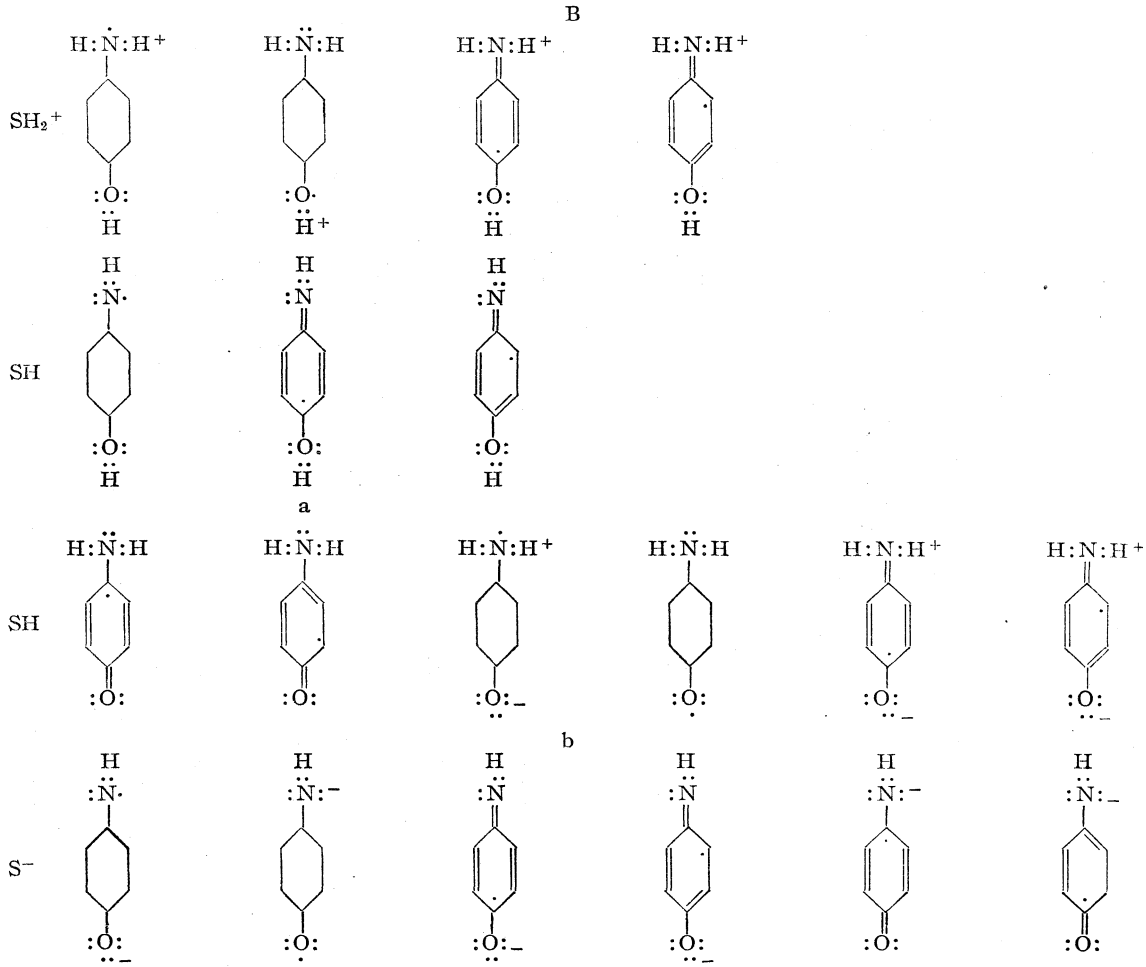
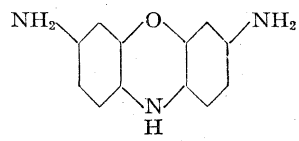


Fig. 1.—(A) Principal structures of the *p*-phenylenediamine semiquinones. (Note that the anionic semiquinone would only occur for the N-dialkyl-substituted diamine.) (B) Principal structures of the *p*-aminophenol semiquinones. (Note that for the neutral semiquinone, structures b are much more likely than structures a. Structures a are tautomeric with structures b.)

K_s is the semiquinone formation constant of equation (2).

Semiquinone formation constants for oxonine over the *p*H range −6 to +12 are plotted in Fig. 3 from the data of Table II of Michaelis and Granick.[10] The ionic states of R, S and T are those assigned by these authors. The figure shows that



the concentrations of the several *ionic species of S* go through two minima and one maximum between *p*H 2 and 12.

If the rate of a reaction is determined by the over-all semiquinone concentration, then the rate at 50% completion will vary with *p*H as $(S/a)_{max.}$ However, according to Figs. 1 and 2, SH_2^+, SH and S^- cannot be expected to have the same reactivity. Differences in the reactivity of the ionic species will therefore be superimposed upon the changes in semiquinone concentration with *p*H. It follows that quite complicated rate–*p*H curves can be expected for substances such as the *p*-phenylenediamines.

(10) Michaelis and Granick, THIS JOURNAL, **63**, 1636 (1941).

Experimental

Technique, Materials, Calculations

The techniques and apparatus were the same as in previous investigations of this series.[2,3,4,5] Measurements of *p*H were made with a Beckman Model G *p*H meter. The temperature of the thermostat was 19.97 ± 0.02°. Buffers were C. P. or reagent grade chemicals and used at a concentration of 0.200 *M*. Doubly distilled water was used in all experiments, and absolute alcohol in making the aqueous alcoholic solutions.

All experiments reported in this paper were run in solutions 0.005 *M* in potassium thiocyanate and potassium cyanide, respectively. Under these conditions, metallic-ion catalysis was negligible, and the data were reproducible. In the absence of these substances, the experiments were very erratic. In some experiments, in absence of potassium cyanide and potassium thiocyanate, cupric ion was added. This eliminated the induction period and increased the total uptake by approximately 50%.

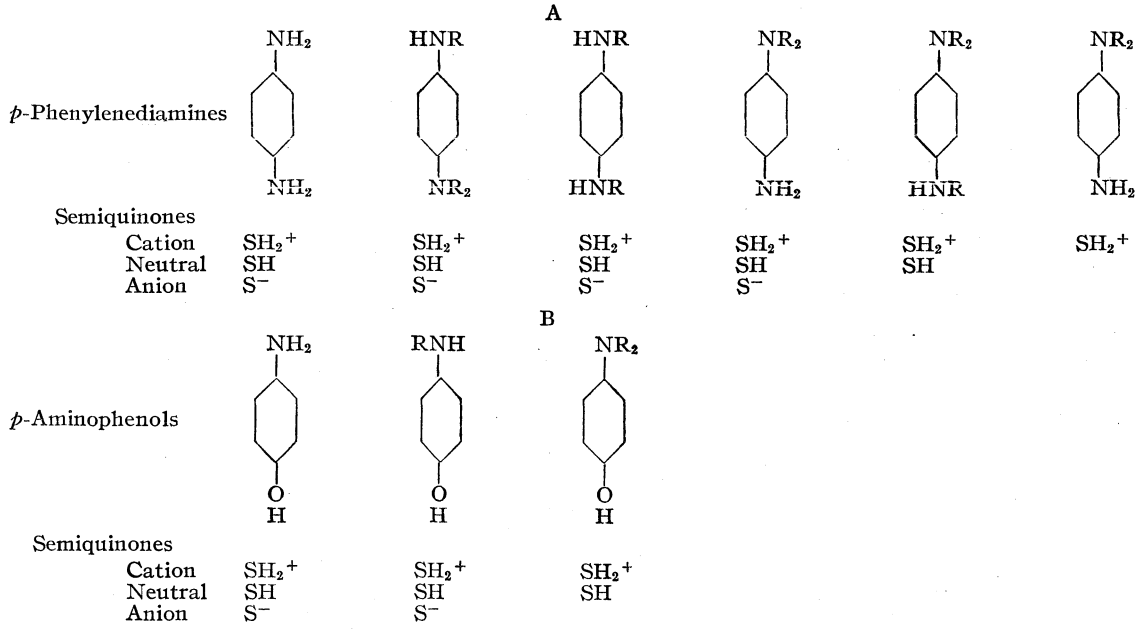


Fig. 2.—(A) Ionic species of the *p*-phenylenediamines; R represents any alkyl group, usually CH_3 or C_2H_5. (B) Ionic species of the *p*-aminophenols.

The final products of the reaction of diaminodurene were identified as duroquinone by mixed melting point, ammonia by smell, and hydrogen peroxide.[2a] The overall consumption of oxygen indicates a similar course of the oxidation of the other compounds reported in this paper. However, the hydrogen peroxide presumably reacts with the quinonoid products.

Organic Preparations

Eastman Kodak Co. Grade chemicals were used as starting materials for the preparation of all compounds. When working with the free bases, they were kept under an atmosphere of hydrogen or nitrogen to reduce oxidation by the air. All of the products were dried in a vacuum desiccator over sulfuric acid. High-grade filter paper (*e. g.*, Whatman no. 12) was used for all filtrations.

***p*-Phenylenediamine Dihydrochloride.**—Fifty-four grams of *p*-phenylenediamine was dissolved in a solution of 200 ml. of water and 90 ml. of concentrated hydrochloric acid. The resulting solution was treated with Filtrol and filtered while still hot. The dihydrochloride was precipitated by the addition of 100 ml. of concentrated hydrochloric acid. The product was removed by filtration, dissolved in 200 ml. of hot water, and precipitated with 100 ml. of concentrated hydrochloric acid. The precipitate was removed by filtration, washed with alcohol, and dried.

N-Methyl-*p*-phenylenediamine Dihydrochloride.—The salt was recrystallized twice from three volumes of methanol which contained a few drops of concentrated hydrochloric acid.

N,N′-Dimethyl-*p*-phenylenediamine Dioxalate.—The salt was recrystallized twice from 60% aqueous alcohol. In the first recrystallization the hot solution was treated with Darco and filtered; in the second recrystallization, the hot solution was filtered without the Darco treatment.

N,N-Dimethyl-*p*-phenylenediamine Hydrochloride.—N,N-Dimethyl-*p*-phenylenediamine was distilled under reduced pressure. The fraction that boiled at 134–135° at 12 mm. (68 g.) was collected and converted to the hydrochloride by dissolving in 200 ml. of methanol and 43 ml. of concentrated hydrochloric acid. The solution was allowed to stand at 0° until crystallization was complete. The precipitate was removed by filtration and recrystallized from methanol.

N,N,N′-Trimethyl-*p*-phenylenediamine Dihydrochloride.—This material was prepared satisfactorily in fairly large batches from N,N-dimethyl-*p*-phenylenediamine by a modification of the method used by Michaelis, Schubert and Granick.[6b]

A mixture of 170 g. of N,N-dimethyl-*p*-phenylenediamine hydrochloride, 190 g. of *p*-toluenesulfonyl chloride, and 400 ml. of pyridine was heated on the steam-bath for two hours. At the end of this time, the reaction mixture was poured into 2 liters of water and stirred until crystallization occurred. The precipitate was removed by filtration, washed with water, and recrystallized from 95% alcohol. There resulted 190 g. of 4′-dimethylamino-*p*-tolylsulfonanilide which melted at 125–126°.

A solution of 11.5 g. of sodium in 500 ml. of absolute alcohol was added to 145 g. of 4′-dimethylamino-*p*-tolylsulfonanilide in 1 liter of absolute alcohol. After 75 g. of methyl iodide had been added, the mixture was boiled under reflux for twenty hours. At the end of this time, 800 ml. of 5% alkali was added and the alcohol was removed by distillation under reduced pressure. The residue was diluted with 1.5 liters of warm water and the mixture was stirred for thirty minutes. The precipitate was removed by filtration, washed with water, and recrystallized twice from 95% alcohol. The resulting 4′-dimethylamino-N-methyl-*p*-tolylsulfonanilide (80 g.) melted at 101–101.5°. *Anal.* Calcd. for $C_{16}H_{20}N_2O_2S$: N, 9.20. Found: N, 9.20.

The 4′-dimethylamino-N-methyl-*p*-tolylsulfonanilide (41 g.) was hydrolyzed by heating on the steam-bath for four hours with 40 ml. of acetic acid and 80 ml. of concentrated sulfuric acid. The reaction mixture was dissolved in 800 ml. of water and made alkaline with 275 ml. of 40% sodium hydroxide. The diamine[11] was extracted with ether, the ethereal solution was dried over sodium hydroxide pellets, and the ether was evaporated. The residue was dissolved in 375 ml. of acetone and the salt was precipitated by the addition of 20 ml. of concentrated hydrochloric acid. The precipitate was removed by filtration, washed with acetone, and dissolved in 100 ml. of warm methanol containing 1 ml. of concentrated

(11) Care should be taken to prevent the diamine from coming in contact with the skin. It has a strong irritating and numbing action.

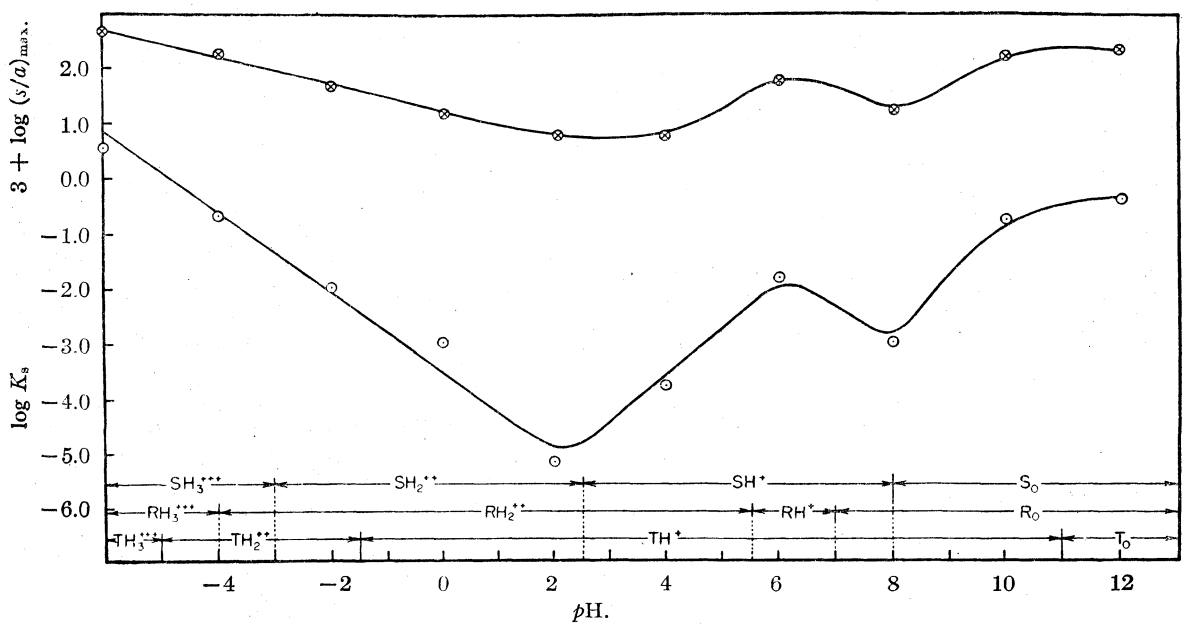


Fig. 3.—Oxonine: -⊙-⊙-, log K_s–*p*H; -⊗-⊗-, 3 + log $(S/a)_{max.}$–*p*H, S_0 and SH_3^{+++} are quite stable; SH^+ and SH_2^{++} exist only at low concentrations. Data are from Table II of Michaelis and Granick (THIS JOURNAL, **63**, 1636 (1941)).

hydrochloric acid. This solution was diluted slowly with 250 ml. of acetone. The product was removed by filtration, washed with acetone, and dried; yield, 19 g.

N,N,N′,N′-Tetramethyl-*p*-phenylenediamine Dihydrochloride.—The salt was recrystallized twice from 85% aqueous alcohol which contained a small amount of concentrated hydrochloric acid.

Octamethyl-*p*-phenylenediamine was prepared from diaminodurene and methyl iodide.[6d] The hydrochloride was recrystallized from 1,2-ethanol acetone.

N,N-Diethyl-*p*-phenylenediamine Hydrochloride.—The free base was distilled under reduced pressure. The fraction that boiled at 115–116° at 5 mm. (131 g.) was dissolved in 200 ml. of absolute alcohol, and 68 ml. of concentrated hydrochloric acid was added. The salt which crystallized was removed by filtration, washed with alcohol containing a little hydrochloric acid, and dried.

N,N-Di-*n*-propyl-*p*-phenylenediamine Sulfate.—A solution of 177 g. of N,N-di-*n*-propylaniline in a mixture of 1 liter of water and 250 ml. of concentrated hydrochloric acid was cooled to 0° and 70 g. of sodium nitrite in 200 ml. of water was added during a period of five minutes. The solution was stirred at 0–1° for thirty minutes and then made alkaline with 200 ml. of concentrated ammonium hydroxide. The crystals were removed by filtration, washed with water, and recrystallized twice from 95% alcohol. There resulted 85 g. of N,N-di-*n*-propyl-4-nitrosoaniline which melted at 43–44°. *Anal.* Calcd. for $C_{12}H_{18}N_2O$: N, 13.58. Found: N, 13.70.

N,N-Di-*n*-propyl-4-nitrosoaniline (20.6 g.) was placed in the Parr reduction apparatus with 100 ml. of absolute alcohol and 5 g. of Raney nickel, and reduced at a temperature of 60° and a hydrogen pressure of 3 atmospheres. The reaction mixture was filtered and a solution of 5.6 ml. of concentrated sulfuric acid in 25 ml. of absolute alcohol was added. The precipitate was removed by filtration, washed with alcohol, and recrystallized from 125 ml. of absolute alcohol. The product weighed 20 g. *Anal.* Calcd. for $C_{12}H_{20}N_2 \cdot H_2SO_4$: N, 9.65. Found: N, 9.35.

4-Amino-N,N-dimethyl-*o*-toluidine Dihydrochloride.—N,N-Dimethyl-4-(*p*-nitrophenylazo)-*o*-toluidine was prepared by the method of Fieser and Thompson[12] and recrystallized from acetic acid. The melting point of this material was 121–122°. The azo compound (28.4 g.) was placed in the Parr reduction apparatus with 100 ml. of absolute alcohol and 5 g. of Raney nickel, and reduced at a temperature of 50° and a hydrogen pressure of 3 atmospheres. The catalyst was removed by filtration and the alcohol was distilled under reduced pressure. Acetic anhydride (50 ml.) was added and the mixture was heated on the steam-bath for one hour. The reaction mixture was diluted with 300 ml. of water, neutralized with sodium carbonate, and acidified with 50 ml. of concentrated hydrochloric acid. The mixture was stirred for ten minutes and the precipitate was removed by filtration. The filtrate was made alkaline with 40% sodium hydroxide solution and the product extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and the ether was evaporated. The residue (15.6 g.) was dissolved in 100 ml. of 15% hydrochloric acid and the solution was boiled under reflux for one hour. This solution was concentrated to a thick syrup under reduced pressure and the residue was crystallized from 60 ml. of absolute alcohol. The product was removed by filtration, washed with absolute alcohol, and recrystallized from absolute alcohol containing a little concentrated hydrochloric acid. There resulted 12 g. of product. *Anal.* Calcd. for $C_9H_{14}N_2 \cdot 2HCl$: N, 12.55. Found: N, 12.66.

4-Amino-N,N-diethyl-*m*-toluidine Hydrochloride.—The salt was recrystallized twice from 95% alcohol which contained 2% concentrated hydrochloric acid.

Diaminodurene Dihydrochloride.—Dinitrodurene (21 g.) was placed in the Parr reduction apparatus with 100 ml. of absolute alcohol and 3 g. of Raney nickel, and reduced at a temperature of 60° and a hydrogen pressure of 3 atmospheres. The catalyst was removed by filtration and 50 ml. of concentrated hydrochloric acid was added, all at once, with vigorous stirring. The precipitate was removed by filtration and dissolved in boiling water. This solution was treated with Darco, filtered, and diluted with 25 ml. of concentrated hydrochloric acid. The precipitate was removed by filtration and recrystallized as before but without the Darco treatment. There resulted 15 g. of diaminodurene dihydrochloride. *Anal.* Calcd. for $C_{10}H_{16}N_2 \cdot 2HCl$: N, 11.81. Found: N, 11.98.

1-(*p*-Aminophenyl)-pyrrolidine Hemisulfate Dihydrate.—A mixture of 13.4 g. of *p*-nitrochlorobenzene and 12.1 g. of pyrrolidine was heated at 95–100° in a sealed tube

(12) Fieser and Thompson, THIS JOURNAL, **61**, 376 (1939).

for six hours. The reaction mixture was stirred with 100 ml. of water and the product was removed by filtration, washed with water, and recrystallized twice from acetic acid. There resulted 10 g. of 1-(*p*-nitrophenyl)-pyrrolidine that melted at 167–168°. *Anal.* Calcd. for $C_{10}H_{12}N_2O_2$: N, 14.58. Found: N, 14.62.

The 1-(*p*-nitrophenyl)-pyrrolidine (10 g.) was placed in 100 ml. of absolute alcohol and reduced to the diamine by the method used to reduce dinitrodurene. The catalyst was removed by filtration and a solution of 2.8 ml. of concentrated sulfuric acid in 10 ml. of water was added to the filtrate. After dilution with 50 ml. of alcohol, the precipitate was removed by filtration, washed with alcohol, and recrystallized from 100 ml. of 75% aqueous alcohol. There resulted 9 g. of product. *Anal.* Calcd. for $C_{10}H_{14}N_2 \cdot 0.5H_2SO_4 \cdot 2H_2O$: N, 11.33. Found: N, 11.65.

1-(4-Amino-*m*-tolyl)-pyrrolidine Hemisulfate.—A mixture of 22.4 g. of 2-nitro-5-iodotoluene and 12 g. of pyrrolidine was heated at 95–100° in a sealed tube for one hour and the reaction mixture was stirred with 100 ml. of water. The precipitate was removed by filtration and recrystallized twice from acetic acid. There resulted 8 g. of 1-(4-nitro-*m*-tolyl)-pyrrolidine that melted at 86–88°. This nitro compound was reduced by the method used for dinitrodurene. The catalyst was removed and a solution of 1.2 ml. of concentrated sulfuric acid in 15 ml. of absolute alcohol was added. The precipitate was removed by filtration, washed with alcohol, and recrystallized twice from 80% aqueous alcohol. There resulted 5 g. of product. *Anal.* Calcd. for $C_{11}H_{16}N_2 \cdot 0.5H_2SO_4$: N, 12.43. Found: N, 12.29.

1-(*p*-Aminophenyl)-piperidine Hemisulfate.—A mixture of 79 g. of *p*-nitrochlorobenzene and 100 ml. of piperidine was heated at 95° for four hours in a flask attached to an air condenser. At the end of this time, the reaction mixture was diluted with 200 ml. of water and stirred thoroughly. The precipitate was removed by filtration, washed with water, and recrystallized twice from 200 ml. of 95% alcohol. There resulted 70 g. of 1-(*p*-nitrophenyl)-piperidine that melted at 103–103.5°. *Anal.* Calcd. for $C_{11}H_{14}N_2O_2$: N, 13.58. Found: N, 13.69.

The 1-(*p*-nitrophenyl)-piperidine (20.6 g.) was reduced by the method used for dinitrodurene. The catalyst was removed and a solution of 2.8 ml. of concentrated sulfuric acid in 150 ml. of alcohol was added to the filtrate. The precipitate was removed and recrystallized twice from 300 ml. of 75% aqueous alcohol. There resulted 10 g. of 1-(*p*-aminophenyl)-piperidine hemisulfate. *Anal.* Calcd. for $C_{11}H_{16}N_2 \cdot 0.5H_2SO_4$: N, 12.43. Found: N, 12.34.

1-(4-Amino-*m*-tolyl)-piperidine Sulfate.—A mixture of 26.3 g. of 2-nitro-5-iodotoluene and 20 ml. of piperidine was heated in an oil-bath at 110° for four hours. The oily reaction mixture was washed with water and crystallized from 50 ml. of methanol. The crystals were stirred with 80 ml. of 15% hydrochloric acid, the insoluble material was filtered off (unreacted 2-nitro-5-iodotoluene), and the filtrate was poured into water containing an excess ammonium hydroxide. The precipitate was removed by filtration, washed with water, and recrystallized from 50 ml. of methanol. There resulted 12.5 g. of 1-(4-nitro-*m*-tolyl)-piperidine that melted at 53–54°. This nitro compound was reduced by the method used for dinitrodurene. The catalyst was removed and a solution of 3.2 ml. of concentrated sulfuric acid in 5 ml. of water was added. The precipitate was removed by filtration, washed with alcohol, and recrystallized twice from 75 ml. of 75% aqueous alcohol. There resulted 14 g. of 1-(4-amino-*m*-tolyl)-piperidine sulfate. *Anal.* Calcd. for $C_{12}H_{18}N_2 \cdot H_2SO_4$: N, 9.72. Found: N, 9.69.

1-(*p*-Aminophenyl)-morpholine Hemisulfate Hydrate.—A mixture of 80 g. of *p*-nitrochlorobenzene and 100 g. of morpholine was heated at 115–120° for three and one-half hours. The reaction mixture was ground in a mortar with 300 ml. of warm water. The solid was removed by filtration, washed with water, and the product recrystallized twice from 150 ml. of acetic acid. There resulted 85 g. of 1-(*p*-nitrophenyl)-morpholine that melted at 150–151°. A portion of this nitro compound (20.8 g.) was mixed with 200 ml. of absolute alcohol and reduced by the method used for dinitrodurene. The catalyst was removed and a solution of 2.8 ml. of concentrated sulfuric acid in 40 ml. of water was added. The mixture was heated to a boil, filtered, and allowed to cool. The product was removed and recrystallized from 75% aqueous alcohol. There resulted 15 g. of 1-(*p*-aminophenyl)-morpholine hemisulfate hydrate. *Anal.* Calcd. for $C_{10}H_{14}N_2O \cdot 0.5H_2SO_4 \cdot H_2O$: N, 11.42. Found: N, 11.43.

1-(4-Amino-*m*-tolyl)-morpholine Sulfate.—A mixture of 80 g. of 2-nitro-5-iodotoluene and 61 g. of morpholine was heated at 95–100° for four hours. The reaction mixture was ground in a mortar with 500 ml. of water and the solid was separated. The solid was added to 800 ml. of 15% hydrochloric acid. The mixture was stirred and heated at 70–80° for twenty minutes. After cooling, the mixture was filtered and the filtrate made alkaline with concentrated ammonium hydroxide. The precipitate was removed by filtration and recrystallized twice from acetic acid. There resulted 33 g. of 1-(4-nitro-*m*-tolyl)-morpholine that melted at 142–143°. The nitro compound (22.2 g.) was mixed with 200 ml. of absolute alcohol and reduced by the method used for dinitrodurene. The catalyst was removed and a solution of 5.6 ml. of concentrated sulfuric acid in 100 ml. of water was added. The mixture was warmed until solution took place and then was allowed to cool. The product was separated and recrystallized from 75% aqueous alcohol. There resulted 20 g. of 1-(4-amino-*m*-tolyl)-morpholine sulfate. *Anal.* Calcd. for $C_{11}H_{16}N_2O \cdot H_2SO_4$: N, 9.65. Found: N, 9.67.

***p*-Aminophenol Hydrochloride.**—A boiling solution of 100 g. of the salt in 150 ml. of water containing 1 ml. of concentrated hydrochloric acid was treated with Darco, filtered, and allowed to cool. The precipitate was removed by filtration and recrystallized from water.

***p*-Methylaminophenol Hemisulfate.**—The salt was recrystallized twice from water which contained 0.1% sulfuric acid.

***p*-Dimethylaminophenol Hemisulfate.**—The salt was dissolved in boiling 75% aqueous alcohol, treated with Darco, filtered, and cooled. The solid was separated and recrystallized from 75% aqueous alcohol.

Calculations and Results

All calculations of $\log(V'_i - V_i)$–time curves were made by Guggenheim's method,[13] as outlined in a previous paper.[4c] The oxygen uptake–time curves represent several types: (1) first-order reactions, denoted by (1st), (2) autocatalytic reactions, denoted by (α), and (3) reactions which are initially autocatalytic, reach saturation and then follow the first-order law, denoted by (β).

The mean values for the reaction-rate constants, k, of (1) and (3) are taken in the first-order part of the reactions. This part always includes the point at which the reaction is 50% complete. For comparison, the k values of the autocatalytic reactions (2) were therefore taken at 50% completion of the reactions. Figure 4 shows Guggenheim curves of 1st, α-, and β-type reactions of various *p*-phenylenediamines. The β-curves may remain first-order up to the end or drop off near the end of the reaction.

In addition, there are several curves which can be dissected and allotted to consecutive reactions. In the autoxidation of *N,N'-dimethyl-*

(13) Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

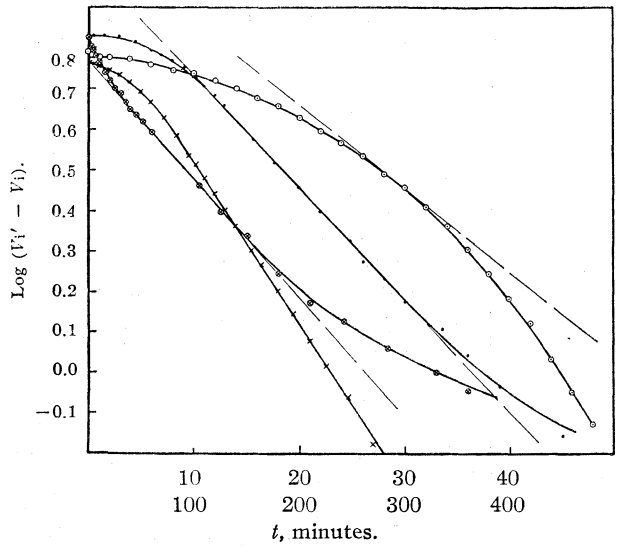


Fig. 4.—Types of Guggenheim curves: -⊙-⊙-, diaminodurene, α-curve, upper time scale; -⊗-⊗- N-dimethyl-*p*-phenylenediamine in presence of 6.00×10^{-4} *M* benzoquinone at *p*H 7.57. Composite curve with rapid initial reaction, lower time scale; -×-×- N-dimethyl-*p*-phenylenediamine at *p*H 7.88, β-curve, lower time scale; -●-●- N-dimethyl-*p*-phenylenediamine at *p*H 7.56, β-curve, lower time scale.

p-phenylenediamine at *p*H 11.33, a rapid autocatalytic reaction is followed by a slower first-order reaction. The uptake–time curves are given in Fig. 5. The upper curve shows the total uptake–time curve, and the lower curve gives the uptake of the first six milliliters of oxygen on an expanded time scale. The theoretical uptake for the oxidation of the diamine to the diimine according to equation (1) is 6.0 ml. Hence, the autoxidation of the diamine takes place in the autocatalytic reaction, and the following first-order reaction represents the autoxidation of some secondary product of the diimine, presumably the quinone.

The uptake–time curves for the autoxidation of *N,N'-tetramethyl-p-phenylenediamine* at *p*H 6.65 and *p*H 13.20 are given in Fig. 6. There is a definite break in each curve after approximately three milliliters of oxygen have been absorbed, and the Guggenheim curve for the total reaction (Fig. 7) shows two distinct sections with a transition period. The theoretical uptake for the autoxidation of the diamine to the semiquinone is 3.0 ml., and the inspection of the reaction mixture shows that Wurster's Blue accumulates to a high concentration. The rate constant for the first three milliliters of oxygen uptake belongs, therefore, to the autoxidation of the diamine to the semiquinone, while the latter portion of the uptake represents the autoxidation of the semiquinone to the diimine. Inasmuch as the latter portion of the uptake exceeds three milliliters, the diimine again undergoes secondary reactions.

The tabulated rate data for *p*-phenylenediamine and some of its alkyl derivatives, and for the *p*-aminophenols, may be obtained in the form of an American Documentation Institute Document.[14]

The rates are all in such a region that, from the point of view of accuracy of measurement, the data are of equal significance. However, the measurement on tetramethyl-*p*-phenylenediamine at *p*H 13.2, though it is also in an easily observed region of rate, may be less reliable because of the possibility of demethylation and the possibility of higher solubility of oxygen at very high *p*H.

Discussion

Type of Curve and Mechanism.—An α-curve, exemplified by dihydroxydurene,[4a,15] is again found on the autoxidation of diaminodurene. The recoverable product from the autoxidation of diaminodurene is duroquinone. In some experiments, however, the autoxidation was completed about a half hour before the precipitation of the duroquinone, which probably is formed by hydrolysis of the duroquinonediimine. Thus, diaminodurene autoxidizes by the mechanism of Classes I-A-3[15] or I-C.[15] With the exception of diaminodurene, all of the *p*-phenylenediamines autoxidize by a mechanism giving a β-type curve. Only occasionally, at low *p*H or high *p*H, will a compound give an α-type curve. The β-curves

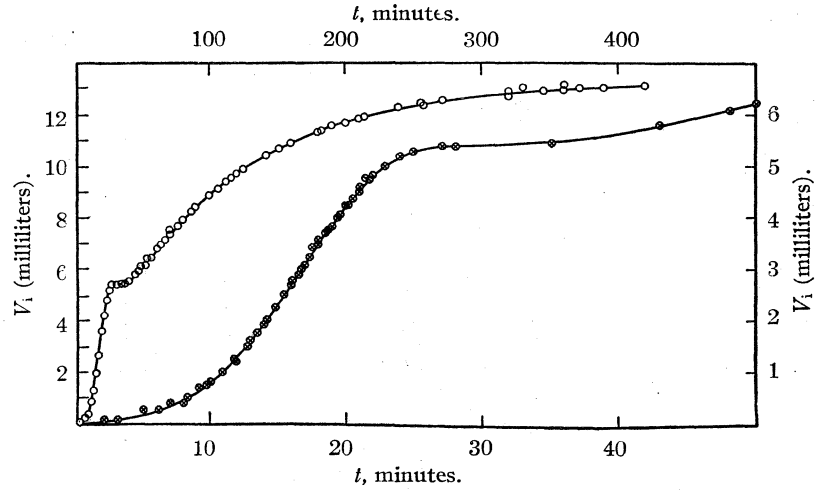


Fig. 5.—Uptake–time curves for N,N'-dimethyl-*p*-phenylenediamine at *p*H 11.33: -⊗-⊗-, first six milliliters, bottom abscissa, right-hand ordinate; -O-O-, total uptake, top, abscissa, left-hand ordinate.

(14) Request Document 2498 and send $0.70 for photoprints or $0.50 for microfilm to the American Documentation Institute, 1719 N Street, N. W., Washington, D. C.

(15) LuValle and Weissberger, THIS JOURNAL, **69**, 1567 (1947).

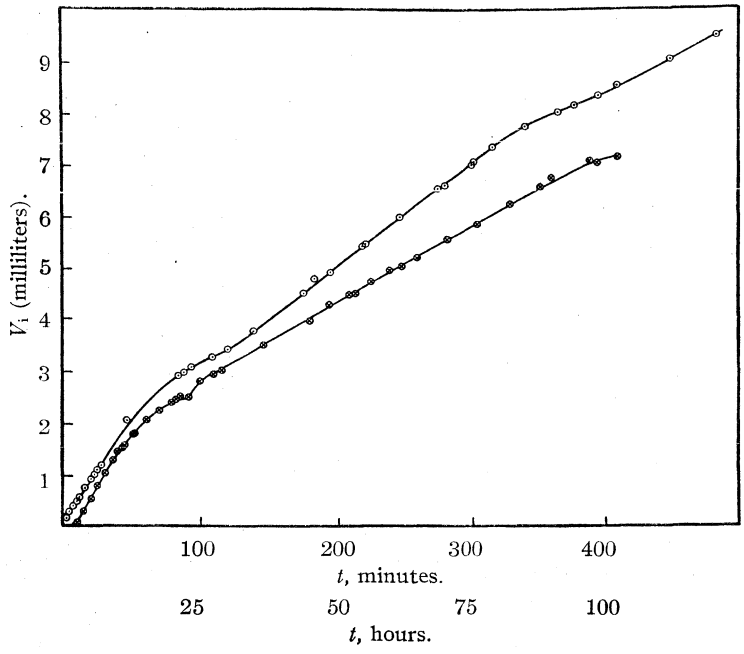


Fig. 6.—Uptake–time curves for N,N′-tetramethyl-*p*-phenylenediamine: -⊙-⊙-, *p*H 6.65, upper time scale; -⊗-⊗-, *p*H 13.20, lower time scale.

correspond to the mechanism of Class II-A-3 which was assigned to the *p*-phenylenediamines in an earlier paper of this series.[15] Kinetically, it is difficult to distinguish Class II-A-3 from Class I-E.[15] The rate of autoxidation for the latter mechanism is determined by the rate of *formation* of the semiquinone, but, for the former mechanism, the rate of *autoxidation* of the semiquinone enters into the rate equation. Class II-A-3 is differentiated from Class I-E by the appearance of intensely colored fairly stable semiquinones during the course of the reaction. These latter were observed with all of the *p*-phenylenediamines investigated in the present study.

If the rate of autoxidation of the semiquinone is high compared with the rate of formation of the semiquinone, the latter is rate-determining, and the concentration of semiquinone is low. Insofar as the rate of autoxidation of the semiquinone drops, it becomes more and more rate-determining, and the concentration of the semiquinone increases until eventually the mechanism becomes that found with tetramethyl-*p*-phenylenediamine.

Addition of quinone to a diamine in the proper concentration before autoxidation eliminates the induction period and causes a (β) reaction to become first-order throughout its course. The necessary concentration of quinone varies with the diamine between one-twentieth of the concentration of the diamine and less. The rate constant is identical with that derived from the autoxidation of the diamine alone. If less than the critical concentration of quinone is added, the induction period is not completely eliminated. If more than this critical concentration of quinone is added, a very rapid initial uptake of 10–20% of the total oxygen consumption during thirty to sixty seconds is followed by the normal first-order reaction. The elimination of the induction period appears to be caused by the poised equilibrium

$$R + Q \rightleftarrows S_{diamine} + S_{quinone}$$

Effect of Solvents.—Experiments with diaminodurene and *p*-diethyl-*o*-toluidine show that the rate in 20% ethanol solutions is lower than in water. Since the semiquinones are more stable in alcoholic solution than in water,[6b] the lower rate may be due to the increased stability of the semiquinone.

Rate Dependency upon the Concentrations of Substrate and Oxygen.—Experiments with N-dimethyl-*p*-phenylenediamine, N,N′-trimethyl-*p*-phenylenediamine, and diaminodurene show that the rate is first-order with respect to the *initial concentration* of the *diamine*. The rate

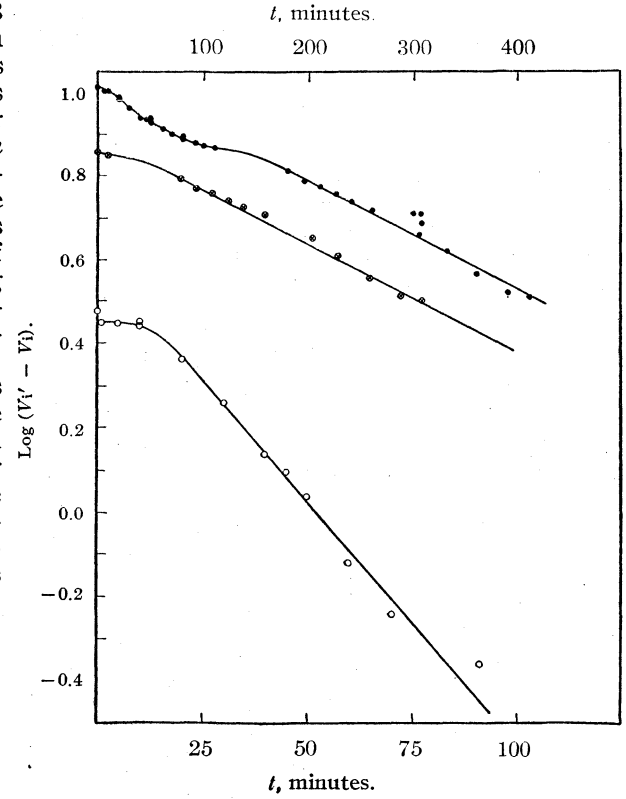


Fig. 7.—Guggenheim curves for N,N′-tetramethyl-*p*-phenylenediamine at *p*H 6.65: -●-●-, total uptake, top abscissa; -O-O-, first three milliliters of uptake, bottom abscissa; -⊗-⊗-, latter seven milliliters of uptake, top abscissa.

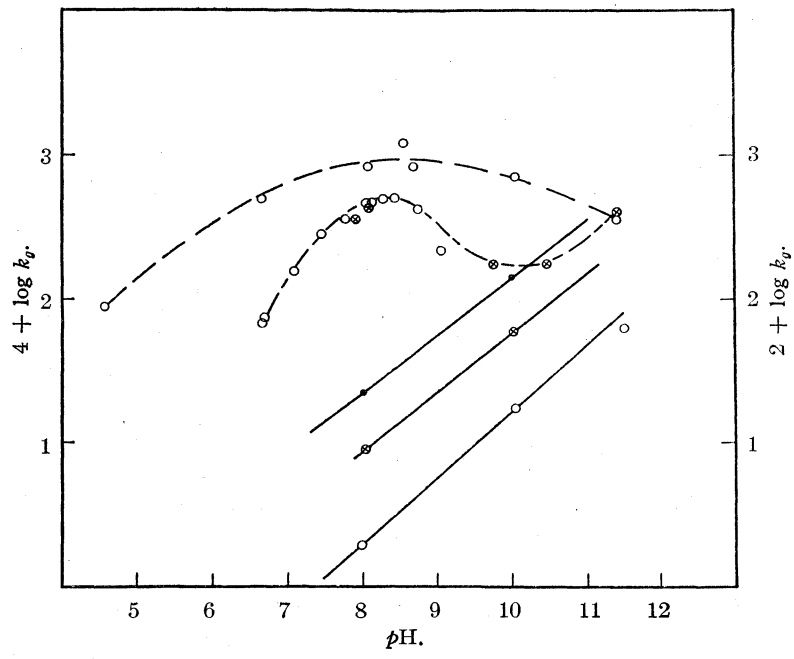


Fig. 8.—Straight lines refer to right-hand ordinate, 2 + log k_g: -O-O-, *p*-aminophenol; -●-●-, *p*-methylaminophenol; -⊗-⊗-, *p*-dimethylaminophenol. Curves refer to left-hand ordinate, 4 + log k_g: ———, *p*-diethylamino-*o*-toluidine; O, in presence of 2.00 × 10^{-4} *M* benzoquinone; ⊗, in absence of benzoquinone; -⊖- -⊖-, diaminodurene.

laws observed give no reason to assume a more complicated dependency for any of the other compounds in the range of concentration investigated.

A few experiments with N,N′-trimethyl-*p*-phenylenediamine indicate that the *rate dependency with respect to oxygen varies* with the *p*H. At *p*H 7.8 and 11.3, the rate is about of order 0.8 with respect to oxygen, while at *p*H 9.8 the rate appears to be first-order with respect to oxygen. These data indicate that the mechanism of Class I-E[15] may also occur with the *p*-phenylenediamines. The effect of added quantities of the diimines was not investigated because of the instability of these compounds in aqueous solution.[7]

Dependency of Rate on *p*H.—The data for *p*-aminophenol and the N-methylated *p*-aminophenols (Fig. 8) are not sufficient to warrant a detailed discussion. However, from the points measured it appears that the change of the rate of autoxidation of *p*-aminophenol itself with *p*H is not far from linear in the range investigated. It is known that the salts of *p*-aminophenol are stable, while the free base reacts with oxygen, and the anion of the base might be expected to have an even higher autoxidation rate in line with the results on desylamine and on dihydroxy compounds. The low slope (about 0.4) of the curves may suggest that the reactivity of the anions is not very much higher than that of the neutral molecules.

The rate–*p*H relation of *p*-phenylenediamine and of the N-alkylated *p*-phenylenediamines shown in Fig. 9 is rather complicated. For N-tetramethyl-*p*-phenylenediamine, the figure gives

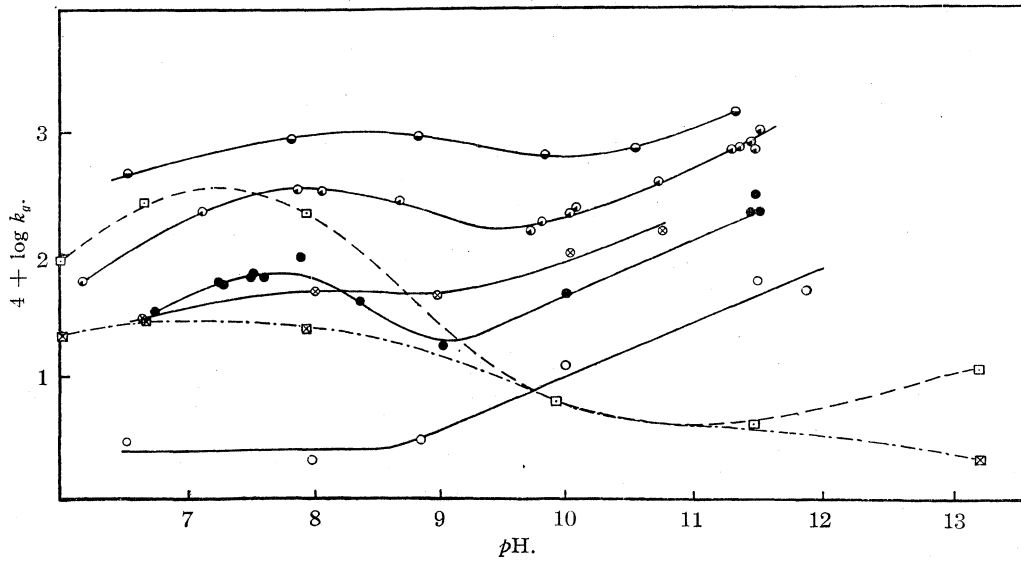


Fig. 9.—*p*-Phenylenediamines, 4 + log k_g − *p*H: -O-O-, *p*-phenylenediamine; -⊗-⊗-, N-methy -*p*-phenylenediamine; -●-●-, N-dimethyl-*p*-phenylenediamine; -◒-◒-, N,N′-dimethyl-*p*-phenylenediamine; N-methyl, N′-dimethyl-*p*-phenylenediamine; -⊡-⊡-, N,N′-tetramethyl-*p*-phenylenediamine, semiquinone formation; -·⊠-·⊠-·, N,N′-tetramethyl-*p*-phenylenediamine, semiquinone autoxidation.

the data for the oxidation to the semiquinone and for the oxidation of the semiquinone. The salts of these compounds with strong acids are known to be stable, while the free bases are oxidized by air. Accordingly, all curves may be extrapolated to reaction rates close to zero at very low *p*H. Our measurements begin between *p*H 6 and 7, in most cases in a distinctly ascending part of the rate-*p*H curve. However, between *p*H 7 and 9, maxima are reached, and the rates begin to drop. The drop of the curves is not steady but leads to minima at *p*H about 10 and from there on the rates increase again sharply. For *p*-phenylenediamine itself and N-methyl-*p*-phenylenediamine, the maximum and minimum are very flat, almost fused into a region of inflection.

The increase in k in the lower *p*H region can be ascribed to a predominance of the liberation of the free base, *i. e.*, to a formation of R from RH^+. The drop from the maximum to the minimum may be ascribed either to a decrease in the total concentration of the semiquinone or to a shift in the ionic equilibrium of the semiquinone in favor of less reactive ionic species, or to both. A definitive discussion is not possible with the present information, but some suggestions are offered in the following:

Table I gives the number of equivalent structures of the semiquinones of *p*-phenylenediamine and of its N-alkyl derivatives. The lack of any entry indicates that the compound in question does not exist. We learn from the table that of all semiquinones listed, SH_2^+ can be expected to be the predominant ionic species of the semiquinones at low and medium *p*H. It is noteworthy in this connection that the more or less steep drop in rate constant, k, with increasing *p*H is common to all *p*-phenylenediamine compounds investigated. Michaelis has stated that SH_2^+ in equilibrium with other ionic species of the semiquinones of *p*-phenylenediamines has a maximum concentration at about *p*H 4, and from this its concentration drops with increasing *p*H. We are therefore inclined to believe that the drop in the rate of autoxidation of the *p*-phenylenediamine compounds between *p*H 7 and 10 is due to a decrease in concentration of the semiquinone species, SH_2^+.

TABLE I

NUMBER OF EQUIVALENT STRUCTURES FOR THE SEMIQUINONE SPECIES OF *p*-PHENYLENEDIAMINE AND ITS N-ALKYL DERIVATIVES

No. of N-Alkyl groups	SH_2^+	SH	S^-
0	3	0	3
1	3	0	3
2 sym.	3	0	3
2 asym.	2	0	0
3	3	0	
4	3		

The steep rise in k above a *p*H of about 10 remains to be explained. Two alternative suggestions are offered. The increase may be due to an increased concentration of SH, provided that SH is more reactive than SH_2^+; the latter can be safely assumed because of the instability of SH to be expected from Table I and Fig. 2. The other reason for the increase of k with *p*H above 10 would be an increase in the concentration of S^-; this explanation cannot be completely excluded. However, the uniformly steep gradient of k *versus* *p*H at a *p*H higher than 10 for *p*-phenylenediamine, methyl-*p*-phenylenediamine, the dimethyl-*p*-phenylenediamines and trimethyl-*p*-phenylenediamine, as contrasted with the retarded and questionable (see Fig. 9) flat increase in k of tetramethyl-*p*-phenylenediamine, favors the former explanation; Fig. 2 and Table I show that SH can be formed by all the compounds listed except by tetramethyl-*p*-phenylenediamine, while S^- would also not be formed by the trimethyl compound. Inasmuch as the first acid ionization constant for the *p*-phenylenediamines occurs at extremely high pK values, the increase in rate above $p\mathrm{H}_{min.}$ cannot be attributed to the formation of R^-. As the slopes above $p\mathrm{H}_{min.}$ are the same for all the N-alkyl-*p*-phenylenediamines except the N-tetramethyl compound, Table II, it appears that the increase in rate may be attributed to the increase in the concentration of SH.

TABLE II

COMPARISON OF SLOPES OF k_g–*p*H CURVES

Compound	Slope of k_g–*p*H curve above $p\mathrm{H}_{min.}$	$p\mathrm{H}_{min.}$
p-Phenylenediamine	0.44	8.5 (inflection)
N-Methyl-*p*-phenylenediamine	.41	8.5 (inflection)
N,N′-Dimethyl-*p*-phenylenediamine	.32	10
N-Dimethyl-*p*-phenylenediamine	.43	9.1
N,N′-Trimethyl-*p*-phenylenediamine	.44	9.5
N,N′-Tetramethyl-*p*-phenylenediamine	.27(?)	11–12(?)
p-Diethylamino-*o*-toluidine hydrochloride	.38	10.1
p-Aminophenol	.46 straight line	
N-Methyl-*p*-aminophenol	.40 probable straight line	
N-Dimethyl-*p*-aminophenol	.39 probable straight line	

Figure 8 shows that the *addition of benzoquinone* to a concentration of 2×10^{-4} M merely changes the reaction from β to first-order but does not affect the *p*H dependency.

Effect of Substituent on Rate.—N-Methylation increases the rate of autoxidation of *p-aminophenol;* the rate of the dimethyl compound was between that of the monomethyl derivative and the parent substance. Figure 9 affords a comparison of the effect of N-methylation upon the rate of autoxidation of *p*-phenylene-

diamine. The dimethyl derivative autoxidizes most readily at all *p*H values investigated; next ranks the trimethyl derivative, and the rates of the asymmetrical dimethyl and the monomethyl compounds lie between the higher methylated products and the parent substance. N-Tetramethyl-*p*-phenylenediamine autoxidizes relatively fast at low *p*H but more slowly than the parent substance at high *p*H values.

A comparison of rates for different substances which have not been studied over a considerable *p*H range requires caution because it is not known whether at an arbitrarily chosen *p*H value one substance may not be close to its maximum autoxidation rate while any other substance is measured in a relatively slow part of the rate–*p*H curve. However, a comparison at *p*H 8 of closely related compounds should furnish some information because at this *p*H the *k*–*p*H curve for most substances is either close to a maximum or flat. The comparison at *p*H 8 and 11.5 is given in Table III. It is obvious that asymmetrical dialkylation has an effect of about the same order of magnitude, irrespective of whether methyl, ethyl, or propyl groups are introduced. However, it may be significant that the diethyl compound has the highest rate of autoxidation.

TABLE III

EFFECT OF SUBSTITUENTS UPON THE RATE OF AUTOXIDATION (RELATIVE RATES)

Compound	$\frac{k_g\ (p\text{H } 11.5)}{k_g\ (p\text{H } 8)}$
p-Phenylenediamine	29
N-Methyl-*p*-phenylenediamine	3
N-Dimethyl-*p*-phenylenediamine	3.2
N,N′-Dimethyl-*p*-phenylenediamine	1.6
N,N′-Trimethyl-*p*-phenylenediamine	2.3
N,N′-Tetramethyl-*p*-phenylenediamine	0.018
N-Diethyl-*p*-phenylenediamine	5.4
N-Di-*n*-propyl-*p*-phenylenediamine	....
Diaminodurene	0.44
N-Diethylamino-*o*-toluidine	0.93
4-Amino-N,N′-dimethyl-*m*-toluidine	10
N-(4-Aminophenyl)-piperidine	11
N-(4-Aminophenyl)-morpholine	....
N-(4-Aminophenyl)-pyrrolidine	22
N-(4′-Amino-3′-methylphenyl)-piperidine	0.61
N-(4′-Amino-3′-methylphenyl)-morpholine	4
N-(4′-Amino-3′-methylphenyl)-pyrrolidine	11
Octomethyl-*p*-phenylenediamine	No measurable rate

The effect of ring alkylation is illustrated by a comparison of N-diethyl-*p*-phenylenediamine with N-diethylamino-*o*-toluidine and of N,N′-dimethyl-*p*-phenylenediamine with 4-amino-N,N′-dimethyl-*m*-toluidine. The introduction of a methyl group into the ring in the *meta*-position to the diethylamino group causes a considerable increase in the reaction rate. This can be expected in view of the electron-releasing effect of the methyl group upon the neighboring amino group. However, if the methyl group is present in the *ortho*-position to the dimethylamino group of N-dimethyl-*p*-phenylenediamine, the reaction rate is cut down considerably. Presumably, a steric interference of the ring methyl group with the N-methyl groups makes less probable a configuration necessary for the formation of the semiquinone.

Diaminodurene exhibits a reaction rate close to that of N,N′-dimethyl-*p*-phenylenediamine. Figure 8 gives the rate–*p*H dependency for diaminodurene. In the *p*H range investigated it shows a broad flat maximum, but no minimum, *i. e.*, no rise in oxidation rate at *p*H higher than 10.

If the two alkyl groups in N-dialkyl-*p*-phenylenediamine are fused to form a ring, compounds result, some of which are listed in Table III.

The *piperidine* derivatives autoxidize considerably more slowly than N-diethyl-*p*-phenylenediamine and N-diethylamino-*o*-toluidine, respectively. Substitution of a *morpholone* ring for the piperidine ring further diminishes the autoxidation rate. However, a remarkable effect is obtained when the six-membered ring of piperidine is shrunk to the five-membered ring of *pyrrolidine*. Table III shows that the resulting pyrrolidine derivatives autoxidize at surprisingly high rates, particularly at *p*H 11. It is difficult to explain this effect. However, we are inclined to believe that the strain upon the C–N–C angle in the five-membered ring favors the π nature of the remaining nitrogen bonds and thus the formation of the semiquinone.

Summary

The autoxidation of *p*-phenylenediamine and of several of its derivatives has been investigated over a wide *p*H range.

ROCHESTER 4, N. Y. RECEIVED OCTOBER 21, 1947

[COMMUNICATION NO. 1183 FROM THE KODAK RESEARCH LABORATORIES]

Oxidation Processes. XXII. Some Biological Implications in Autoxidation Mechanisms

BY JAMES E. LUVALLE

Autoxidation, *i. e.*, oxidation by molecular oxygen, supplies much of the energy needed for synthetic processes by biological systems. Frequently the idea is expressed that enzymes react by chain mechanisms, and in the case of reactions with oxygen, *via* organic peroxide formation. Both suggestions are usually based upon the data for the autoxidation of organic systems involving unsaturated hydrocarbons. The postulates of chain reactions and organic peroxide formation are not necessary, however, to explain enzymatic action, and an alternate mechanism involving semiquinone formation is set forth here which gives a better explanation of the observed facts.

Two mechanisms have been shown to occur in the oxidation of organic systems by molecular oxygen. Hydrocarbon (saturated and unsaturated) systems have been shown to autoxidize by a chain mechanism involving free radicals and the formation of organic peroxides (hydroperoxides) as the bivalently oxidized product.[1] The intermediate free radical, R·, is assumed to be stabilized to some extent by resonance. All the hydrocarbons which have been shown to undergo this chain autoxidation are characterized by the extreme instability of the bivalently oxidized molecule, R″ (the primes denote that two electrons have been removed); the addition of an electron donor stabilizes it; hence, the radical O_2^- combines with R″ to form RO_2^-.

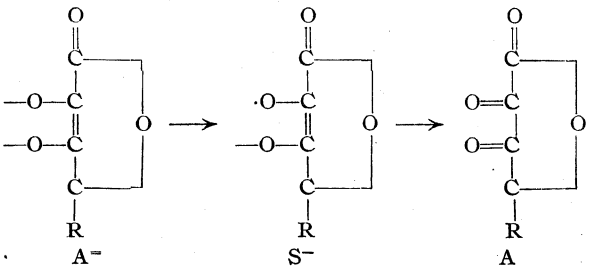
$$R\cdot + :O\overset{\cdot\cdot}{\underset{\cdot\cdot}{=}}O: \longrightarrow R-\ddot{O}-\ddot{O}:$$

which then reacts

$$R-\ddot{O}-\ddot{O}: + RH \longrightarrow R-\ddot{O}-\ddot{O}-H + R\cdot$$

to form the hydroperoxide and another radical, R·. Aldehydes also autoxidize by a chain mechanism involving peroxide formation.

A second mechanism, named the semiquinone mechanism, has been established for the autoxidation of enediols, eneamines and their vinylogs like hydroquinone and *p*-phenylenediamine.[2] The semiquinones (free radicals) are much more stable than the free radicals formed in the chain mechanism. The bivalently oxidized product is stabilized by a rearrangement of bonds to form a quinonoidal structure. The compound undergoing autoxidation is frequently characterized by the stability of the neutral molecule and the extreme reactivity of one or more of its ions.[3] Thus, in *l*-ascorbic acid, the divalent ion is much more reactive than the monovalent ion or the neutral molecule.



This molecule shows the typical bond rearrangement which takes place in the semiquinone mechanism.

In metallic ion catalysis of either mechanism and in inhibition of the semiquinone mechanism, the catalyst or inhibitor apparently forms a complex with the substrate and this complex reacts with oxygen.[1a,1e,2a,3c]

In the peroxide mechanism, the free radical is stabilized to some extent by resonance, and the bivalently oxidized product is stabilized only by addition of an electron donor to form the peroxide radical. In the semiquinone mechanism, the free radical is stabilized quite strongly by resonance, the bivalently oxidized product is stabilized by a rearrangement of bonds, and the ion (or ions) is (are) frequently more reactive than the parent substance.

Many enzymatic mechanisms involve oxidation by oxygen. Waters[4] has recently discussed autoxidation in biological systems. He suggests chain mechanisms to explain the data and he also points out the objections to chain mechanisms. Hinshelwood[5] has proposed a group of enzymes spatially arranged, with free radical groupings at given spots (active centers) on their surfaces. These radicals are assumed to have a temporal existence. Michaelis[6] has suggested that both electron donor and acceptor are bound in adjacent sites on the enzyme surface and that they remain there until reaction takes place.

Virtually every coenzyme discussed by Waters[4]

(1) Only a few of the pertinent authors and references are cited: (a) Farmer, *Trans. Faraday Soc.*, **42**, 228 (1946); (b) Bolland and Gee, *ibid.*, **236**, 244 (1946); (c) George, *ibid.*, 210 (1946); (d) Robertson and Waters, *ibid.*, 201 (1946); (e) George, Rideal and Robertson, *Proc. Roy. Soc.* (*London*), **A185**, 288 (1946); (f) Zuidema, *Chem. Rev.*, **38**, 197 (1946); (g) Bolland and Ten Have, *Trans. Faraday Soc.*, **43**, 201 (1947).

(2) References to earlier papers are contained in the papers cited: (a) LuValle and Weissberger, THIS JOURNAL, **69**, 1567, 1576, 1821 (1947); (b) LuValle and Weissberger, *ibid.*, **70**, 2223 (1948).

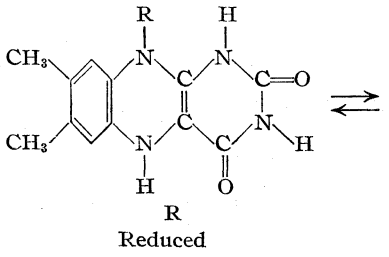
(3) (a) James and Weissberger, *ibid.*, **60**, 98, 2084 (1938); (b) Weissberger, LuValle and Thomas, *ibid.*, **65**, 1934 (1943); (c) Weissberger and LuValle, *ibid.*, **66**, 700 (1944).

(4) Waters, "The Chemistry of Free Radicals," Oxford Press, 1946, Chap. XII.

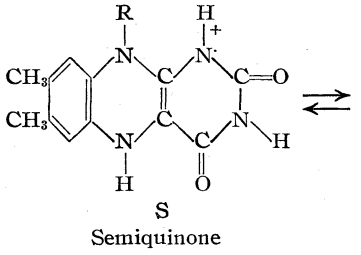
(5) Hinshelwood, "The Chemical Kinetics of the Bacterial Cell," Oxford Press, 1946, Chap. I.

(6) Michaelis, *Ann. N. Y. Acad. Sciences*, **11**, 37 (1940).

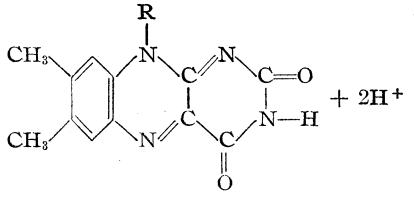
that reacts with oxygen can stabilize itself in the oxidized state by a bond rearrangement, *i. e.*, there is no necessity of proposing the formation of organic peroxides. For example, riboflavin nucleotides are the prosthetic groups of the flavo (yellow) enzymes. Let R represent the ribose group, the phosphate linkage, and the adenine group.



R
Reduced



S
Semiquinone



T
Oxidized

On oxidation, the bonds rearrange similarly to the rearrangement for the semiquinone mechanism. It is probable that even the oxidases that reduce oxygen to water do not form organic peroxides. Formation of enzyme peroxide probably leads to inactivation of the enzyme. Ionization preceding or following the oxidation adequately explains the hydrogen balance without introducing the idea of atomic hydrogen exchange (Wieland's dehydrogenation theory). Certainly in aqueous solution at the *p*H of normal cell activity there is an adequate supply of hydrogen ions to give instantaneous exchange.

LuValle and Goddard[7] have suggested that electron donor and electron acceptor are bound in a complex and that reaction takes place by the semiquinone mechanism. Either the donor or acceptor may combine with the enzyme, followed by a univalent oxidation–reduction, and this enzyme–semiquinone complex will then react with the other reactant to form the final products. By this mechanism the semiquinones are never free in the solution; they only exist bound to the enzyme. It is shown that the semiquinone mechanism can explain the observed kinetics for many respiratory enzymes. This mechanism does not involve bound peroxide formation or exchange of hydrogen atoms. Chain mechanisms are not necessary to explain the observed data.

Summary

The chain peroxide mechanism of autoxidation is briefly compared with the semiquinone mechanism. It is pointed out that the coenzymes involved in biological oxidation–reductions are much more likely to undergo reaction with oxygen *via* the semiquinone mechanism than by the chain, bound peroxide mechanism.

(7) LuValle and Goddard, in publication, "Quarterly Review of Biology."

ROCHESTER 4, N. Y. RECEIVED FEBRUARY 26, 1948

CONTRIBUTION FROM THE RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Preparation of 1-C^{14}-Propene-1 and the Mechanism of Permanganate Oxidation of Propene[1]

BY B. A. FRIES[2] AND M. CALVIN

The preparation of 1-C^{14}-propene-1 was undertaken in order to have available propene labelled in a terminal position and, incidentally, to study the stability of the double bond to migration when preparing propene under a variety of conditions. During the course of this investigation, a reliable procedure for the degradative analysis of the propene had to be developed. This analytical problem led to a study of the oxidative degradation of propene with permanganate.

A number of methods were available for the preparation of propene. Several of these methods were tried with C^{14} labelled materials, while others were discarded when preliminary tests with nonradioactive materials indicated either very poor yields or impure products. The first three of the following methods were actually employed for radioactive propene synthesis: (1) dehydration of *n*-propanol with metaphosphoric acid, (2) dehydration of *n*-propanol over heated alumina, (3) pyrolysis of *n*-propyltrimethylammonium hy-

(1) This paper is based on work performed under Contract Number W-7405-eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory of the University of California, Berkeley, California.

(2) While on leave California Research Corporation, Richmond, California.

droxide, (4) pyrolysis of methyl *n*-propyl xanthate, and (5) dehydrobromination of *n*-propyl bromide with alcoholic potassium hydroxide. Extensive rearrangement of the double bond was found to occur when preparing propene by dehydration with metaphosphoric acid and with heated aluminum oxide. However, the pyrolysis of the quaternary ammonium base gave little, if any, rearrangement and the product consisted principally of 1-C^{14}-propene-1 ($CH_3—CH=\overset{*}{C}H_2$), whereas in the other cases, mixtures of 1-C^{14}-propene-1 and 3-C^{14}-propene-1 ($\overset{*}{C}H_3—CH=CH_2$) were obtained.

Degradation Procedure. Permanganate Oxidation of Propene.—A number of procedures were available for the analysis of the labelled propene, including oxidative degradation with permanganate or dichromate, ozonolysis and glycol formation with hydrogen peroxide, acetyl peroxide or Prévost reagent, and subsequent oxidation and splitting of the glycol with periodate. Ozonolysis of propene gives rise to a mixture of formaldehyde and acetaldehyde, which are not too easily separated. Preliminary glycol formation and periodate oxidation also yields these same two aldehydes and in addition involves more manipulation. Acid permanganate oxidation should produce acetic and carbonic acids if propylene glycol is an intermediate. This appeared to be a satisfactory procedure, particularly since Evans[3] reported that propylene glycol was converted quantitatively to acetic acid and carbon dioxide with neutral permanganate at 50°, although in the presence of alkali, oxalic acid was formed. Hence, examination of the acetic and carbonic acids for C^{14} should indicate the extent of labelling of the two terminal carbon atoms of the propene. However, rearrangement of the double bond might also occur during the analysis, but this could not be determined until some radioactive propene had been prepared. Although permanganate oxidation was chosen for the degradative analysis, in one instance ozonolysis was employed to confirm the results of the permanganate method.

The following procedure was first tested with non-radioactive propene. Approximately three millimoles of propene was introduced into an evacuated 3-necked flask of about 385 ml. volume. Fifty ml. of water or buffer solution was added through a dropping funnel. An induction stirrer[4] was used to agitate the aqueous phase. An amount of 0.4 *N* potassium permanganate calculated to be just sufficient to oxidize propene to propylene glycol was added over a period of forty-five minutes. This was followed by the addition of 110% of the amount of 2 *N* potassium permanganate required for the oxidation of propylene glycol to acetic and carbonic acids. This addition required forty-five minutes, after which the solution was stirred fifteen minutes more. A sulfuric acid-acidified solution of ferrous sulfate was added to reduce all manganese to the manganous state and simultaneously liberate carbon dioxide. The flask was connected to a sodium hydroxide absorber and swept with nitrogen gas to collect this carbon dioxide fraction. The solution remaining was steam distilled to recover acetic acid. This latter was titrated with sodium hydroxide and evaporated to dryness as sodium acetate. The weight of the salt obtained and its subsequent combustion to carbon dioxide when compared with the titration value indicated that the salt was the acetate. This procedure was studied at several values of *p*H and at two temperatures. The results are shown in Table I.

TABLE I

OXIDATION OF PROPENE WITH POTASSIUM PERMANGANATE AT SEVERAL VALUES OF *p*H

Starting solution	0.04 *N* NaOH	0.02 *N* NaOH	0.1 *M* $PO_4^{=}$ *p*H 7.4	Distilled water	0.1 *M* $PO_4^{=}$ *p*H 6.0	0.1 *M* $PO_4^{=}$ *p*H 4.0
Temp., °C.	35	35	35	35	25	25
Moles CO_2/ moles C_3H_6	1.54	1.31	1.28	1.11	0.94	0.94
Moles acetic acid/ moles C_3H_6	0.18	0.38	0.46	0.57	0.73	0.70
Acetic acid/CO_2	0.11	0.29	0.36	0.51	0.78	0.75

It can be seen that in weak acid solution about 70% of the theoretical amount of acetic acid and 90% of the theoretical amount of carbonic acid may be recovered. This calculation was based on the splitting of propene at the double bond to yield equimolar amounts of acetic and carbonic acids. There was no significant change in yield of these two fractions on decreasing the *p*H from 6 to 4 and stronger acid was avoided to reduce the possibility of a shift of the double bond in propene during the analysis. In the subsequent use of this procedure with the various samples of radioactive propene, the reaction was carried out at *p*H 4 and at room temperature. Inasmuch as the total carbon recovery in the carbon dioxide and acetic acid fractions was quite low (70–80%) an attempt was made to locate the missing carbon. The solution remaining after steam distillation of the acetic acid was made 6 *N* in sulfuric acid and 0.5 *M* in chromic oxide, heated to boiling and swept with oxygen for one hour. Considerable carbon and C^{14} activity was found in this fraction. The inclusion of this additional carbon boosted the total carbon recovery to 85–95%.

There were several indications that this oxidizable residue was oxalic acid. First, oxalic acid may be found during alkaline permanganate oxidation of propylene glycol.[3] Second, oxalic acid is oxidized very slowly at 25° and *p*H 4 by potassium permanganate or manganese dioxide and therefore, the oxalic acid would be stable, if present. Third, the nature of the analytical procedure eliminated the possibility of a one carbon compound, since these compounds (methyl alco-

(3) W. L. Evans, THIS JOURNAL, **45**, 171 (1923).

(4) W. G. Dauben, J. C. Reid and P. E. Yankwich, *Anal. Chem.*, **19**, 828 (1947).

hol, formaldehyde, formic acid), if not completely oxidized by the permanganate, would be volatilized during the steam distillation. In addition, subsequent specific activity determinations of this fraction (see Discussion) eliminated the possibility of a three carbon compound and corresponded well with a two-carbon substance. Hence, this residue was either oxalic, glycolic or glyoxylic acid. The last two of these may be intermediates in the formation of oxalic acid. Ethylene glycol also satisfies the chemical properties set for the residue, but it is difficult to see why this glycol should remain unoxidized while propylene glycol, a probable intermediate in the above oxidation, is apparently completely reacted.

In one experiment with radioactive propene, the isolation of oxalic acid was attempted. After the addition of the last permanganate, all manganese was removed as manganese dioxide by centrifugation. Inactive sodium oxalate was added as a carrier and the oxalate was ultimately precipitated as calcium oxalate after separation from phosphate by employing the scheme of Swift.[5] The completeness of recovery of oxalate could not be accurately determined, but appeared to be nearly quantitative. However, since the calcium salts of glycolic and glyoxylic acid are relatively insoluble, they might have been carried down with the calcium oxalate if present. The calcium oxalate was titrated with permanganate in the usual manner, and the carbon dioxide was collected and analyzed for C^{14} activity. The titration agreed within 3% with the formula calcium oxalate for the calcium precipitate; however, since the amount of carrier was about four times the amount of oxalate expected, the presence of other insoluble calcium salts might have been masked. The amount of C^{14} found as oxalate was about 70% of the amount found by direct chromic oxide oxidation of the residue in another experiment using radioactive propene from the same preparation.

Ozonolysis Method.—A highly refined procedure was not developed but the following scheme gave a satisfactory check with the result of the acid permanganate oxidation. About three millimoles of propene was transferred to the ozonolysis vessel, 15 ml. of ethyl chloride was added and the vessel immersed in a Dry Ice–acetone-bath. A current of oxygen containing 2–3% ozone was bubbled through the solution until the solution turned blue (indicating excess ozone). The vessel and contents were warmed to 0°, 10 ml. of water added and shaken with the ethyl chloride. The ethyl chloride was removed by evaporation under house vacuum. The aqueous solution, which now contained formaldehyde and acetaldehyde, was made alkaline with sodium hydroxide. Excess potassium permanganate was added and the solution heated to 50°. The formaldehyde was oxidized to carbon dioxide while the acetaldehyde was oxidized to acetic acid. From this point on, the analysis was carried out in the same manner as the permanganate procedure. In this ozonization some propene probably was swept out of the solution by the current of oxygen, while some of the aldehydes were lost during the evaporation of ethyl chloride. In addition some ethyl chloride remained in the aqueous phase and was oxidized to acetic acid. Although the total carbon recovery was high and C^{14} recovery was low, the distribution of C^{14} should not be affected.

Preparation of 1-C^{14}-*n*-Propanol ($CH_3—CH_2—\overset{*}{C}H_2OH$).—The principal intermediate in the synthesis of propene was *n*-propanol. The starting point of this synthesis was barium carbonate containing C^{14}. Ethylmagnesium bromide was carbonated with the $C^{14}O_2$ obtained from 21 millimoles of barium carbonate containing approximately 800 microcuries of C^{14}. A vacuum line technique (4) was employed. Solid sodium propionate was recovered in 95% yield. A very high specific activity product was not required in this experiment and a large dilution of C^{14} activity could be tolerated. Consequently, the reduction of the acid to alcohol was carried out on the *n*-propyl ester. The use of this ester eliminated the subsequent separation of two alcohols following the hydrogenation. The esterification was carried out on a 40 millimole scale by adding inactive sodium propionate to 1.62 g. (16.8 millimoles) of the radioactive salt. The esterification was driven to completion by azeotropic distillation. The solid salt was refluxed for several hours with a mixture of 9.0 ml. of *n*-propyl alcohol, 10.0 ml. of benzene and 1.1 ml. of concentrated sulfuric acid. Water was removed as the ternary azeotrope (68.5°) with *n*-propyl alcohol and benzene. A 16-inch, 6-mm. i. d., vacuum-jacketed, unpacked column was used for the distillation. When the temperature of the distillate reached 74°, the flask was cooled and 1.0 g. of calcium carbonate was added to destroy excess sulfuric acid. The distillation was continued, the remaining benzene being removed as the binary azeotrope (77.1°) with *n*-propyl alcohol. The distillation was stopped when the temperature reached 92°. The ester–alcohol solution remaining was removed from the calcium sulfate–calcium carbonate residue by vacuum transfer. This solution, about 8 ml. was pipetted into a high pressure hydrogenation bomb (Aminco, 43 ml. size) containing 2.0 g. of copper chromite catalyst (Adkins). The bomb was charged with 2500 p. s. i. of hydrogen, heated to 250° and maintained there for nine hours. The contents of the bomb were transferred on the vacuum line into a flask containing calcium oxide where the alcohol was dried. The alcohol was again transferred on the vacuum line into a small distilling flask and fractionally distilled using the column described above. The fraction boiling from 96–97° was recovered. The fraction boiling below 96° (about 2 ml.) was returned to the distilling flask with 2.5 ml. of *n*-propyl alcohol and the mixture redistilled. This was repeated again with 2.0 ml. of *n*-propyl alcohol. The 96–97° fractions were combined with the first fraction collected. In this manner 10.3 ml. of 1-C^{14}-*n*-propyl alcohol was obtained. The individual steps in the above procedure were tested first with inactive materials. These tests gave yields of 90–95% for the carbonation of ethylmagnesium bromide and 95% for the esterification and hydrogenation when measured by saponification. In the radioactive synthesis, the carbonation yield was 95%. The chemical yields of the other steps were not checked because the amount of alcohol which remained with the ester after azeotropic distillation was not known. About 80% of the starting C^{14} was recovered in the final product, which contained 4.58×10^6 c./min./ml. or about 50 μc/ml.

Preparation of 1-C^{14}-*n*-Propyl Bromide.—Propyl bromide was prepared from *n*-propanol by the phosphorus and bromide method,[6] but additional phosphorus and bromine were added. The yield of propyl bromide was 76% based on propanol. A low C^{14} activity sample of propanol was prepared by dilution of the high activity material for use in this preparation.

Dehydration of *n*-Propanol with Metaphosphoric Acid.—A 2-ml. sample of propanol containing 6350 c./m. C^{14} per millimole of alcohol (prepared by dilution of the high activity product) was dehydrated to propene by dropwise addition of the alcohol to 3 ml. of metaphosphoric acid at 250° according to the method of Newth.[7] Water and

(5) E. H. Swift, "A System of Chemical Analysis," Prentice–Hall, Inc., New York, 1904, p. 469, *et seq.*

(6) A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 37.

(7) G. S. Newth, *J. Chem. Soc.*, **79**, 915 (1901).

alcohol were condensed in a trap at −20° while the propene was passed through Drierite, then condensed in a Dry Ice trap. Considerable alcohol distilled out of the flask without reacting and the yield of propene was 40% based on the starting propanol. The gas sample was analyzed by mass spectrometer.[7a] The analysis of the gas showed 80% propene, 9% butenes, 9% butanes and pentanes and 1% pentenes and hexenes. The propanol was analyzed by mass spectrometer and found to be 99.5% pure; the impurity may have been butyl alcohol.

Dehydration of *n*-Propanol over Heated Aluminum Oxide.—A 2-ml. portion of the above dilute propanol was dehydrated by dropwise addition over a period of thirty minutes into a vertically mounted quartz furnace tube containing aluminum oxide at 390°. The aluminum oxide was 12–24 mesh Alorco Alumina (Aluminum Company of America, Grade F-1) packed in a bed 23 cm. long and 0.7 cm. in diameter. Traps were arranged as in the previous experiment. Continuous nitrogen sweeping was maintained to reduce the residence time in the catalyst. The contact time was approximately 5 seconds. A second sample of alcohol was dehydrated over laboratory prepared aluminum oxide obtained by precipitation of aluminum hydroxide from reagent grade aluminum nitrate. The catalyst temperature was 415° while the contact time was only 2 seconds. The analysis of the first of these gas samples was 97% propene and 3% butenes, while the second gas sample contained 95% propene, 3.5% butenes, 0.5% propane and 0.5% *n*-butane. The yield of propene was about 95% in both cases.

Pyrolysis of *n*-Propyltrimethylammonium Hydroxide.—The quaternary ammonium bromide was prepared by the addition of 5 ml. of *n*-propyl bromide (containing 8300 c./m. C^{14}/millimole) to excess $(CH_3)_3N$ in alcohol and refluxing for several hours. The solvent was evaporated, the bromide dissolved in water and excess freshly prepared silver oxide was added to convert the bromide to hydroxide. After filtering silver bromide and excess silver oxide the aqueous solution was boiled to dryness in a system containing a cold water condenser, a 1 *N* hydrochloric acid wash bottle to remove $(CH_3)_3N$, a tube of Drierite and a liquid nitrogen trap to condense propene. The system was swept with nitrogen during the heating. The yield of propene was approximately 90%. Analysis of the gas showed 99% propene, 0.5% butenes and 0.5% ethylene.

Pyrolysis of Methyl *n*-Propyl Xanthate.—The procedure of Schurmann and Boord[8] was employed for preparing the xanthate ester, however, the final ester was not purified by vacuum distillation as carried out by these authors. The decomposition of the ester took place very slowly and after boiling for twenty-four hours, only half the ester was decomposed. The slow decomposition of primary xanthates was observed by Whitmore and Simpson.[9] The system was swept with a slow current of nitrogen and the gases were passed through a 1 *N* sodium hydroxide wash bottle to remove COS and CH_3SH, then through a drying tube and finally into a liquid nitrogen trap. The yield of propene was about 25% and the gas composition was 56% propene, 38% butenes, 1.4% ethene, 14% COS while the remainder of the gas consisted of several sulfides and mercaptans. This method of propene preparation, besides giving a gas difficult to free of sulfur compounds also contained an extraordinarily large amount of butene. The use of this method was not attempted with radioactive propanol.

Dehydrobromination of *n*-Propyl Bromide with Alcoholic Potassium Hydroxide.—Propene was prepared by refluxing the bromide with excess potassium hydroxide dissolved in absolute ethanol in a system similar to those described above. The yield of propene was about 10%, the bulk of the product being ethyl propyl ether. Nef[10] reported a yield of 20% propene. Analysis of the gas sample showed 75% propene, 16% butenes, 3% isobutane, 3% ethyl propyl ether and traces of ethane, propane and propyl bromide. The use of this method was not attempted with radioactive propyl bromide.

Radioactivity Determination.—The procedures developed by Dauben, Reid and Yankwich[4] were employed for sample preparation and counting.

Results and Discussion

In Table II a summary of the results of the permanganate degradations of the various samples of propene is presented. Since the mechanism of permanganate oxidation of propene, the reliability of this oxidation as an analytical procedure, and the nature of the labelling of the propene could not be determined independently, it was necessary to examine the data from these three points of view. The fact that different specific activities were found in the various fractions from propene prepared by different methods proved that rearrangement of the double bond to the equilibrium mixture did not occur during the analysis. Inspection of experiments 1, 2, and 3 showed that extensive migration of the double bond occurred during the preparation by these methods and, in fact, the propene produced in experiments 1 and 3 consisted of equilibrium mixtures of 1-C^{14}-propene-1 and 3-C^{14}-propene-1. However, the propene derived from the quaternary ammonium base (experiment 4) showed little, if any, rearrangement of the double bond and the product consisted, almost entirely, of 1-C^{14}-propene-1.

The mechanism which has been assumed for the oxidative splitting of olefins with permanganate consists of rupture of the molecule at the site of the double bond with the production of acetic and carbonic acids in the case of propene. If the acetic acid was to be used as a measure of labelling of the methyl group of propene, it was necessary to demonstrate that all the C^{14} activity was present in the methyl group of the acetic acid. Therefore in the pyrolysis of a sample of barium acetate to acetone and barium carbonate, the latter should contain no C^{14}. A sample of acetate from experiment 2, when pyrolyzed, showed that 5% of the C^{14} present was present in the carboxyl group. The pyrolysis of a sample of synthetic methyl-labelled acetate[11] yielded 1.5–2% of the total activity in the barium carbonate which would correspond to 3–4% of the activity apparently present in the carboxyl group. Hence, the above result may be taken to mean that little, if any, carboxyl activity was present and that the carboxyl group of the acetate was derived solely from the central carbon atom of the propene. Therefore, in every case shown in Table II, the specific activity of the methyl carbon of acetic acid may be obtained by doubling the specific activity shown for acetic acid. If acetic acid is obtained only from splitting of propene at the double bond, then

(7a) All gas samples were analyzed by mass spectrometer by Dr. N. Bauer, through the courtesy of California Research Corporation, Richmond, California.

(8) I. Schurmann and C. E. Boord, THIS JOURNAL, **55**, 4930 (1933).

(9) F. C. Whitmore and C. T. Simpson, *ibid.*, **55**, 3809 (1933).

(10) J. U. Nef, *Ann.*, **309**, 126 (1899).

(11) S. Aronoff, V. Haas, B. A. Fries, to be published.

TABLE II

ACID PERMANGANATE ANALYSES OF PROPENE SAMPLES

Preparative procedure	Expt. 1 Dehydration with metaphosphoric acid			Expt. 2 Dehydration with Alorco aluminum oxide			Expt. 3 Dehydration with laboratory-prepared aluminum oxide			Expt. 4 Pyrolysis of *n*-propyltrimethyl-ammonium hydroxide		
Specific activity of C^{14} in starting material (c./m./millimole of C_3H_6)	6350			6350			6350			8300		
Fraction analyzed	Carbon dioxide	Acetic acid	Oxalic acid	Carbon dioxide	Acetic acid	Oxalic acid	Carbon dioxide	Acetic acid	Oxalic acid	Carbon dioxide	Acetic acid	Oxalic acid
Specific activity of C^{14} in fraction (c./m./millimole C)	2790	1610	1560	3980	1100	2130	2840	1530	2020	7600	130	3810
% of total C^{14} recovered in fraction[a]	41	42	5.0	59	24	5.9	38	39	6.2	91	2.2	5.7
Moles/mole C_3H_6	0.94	0.83	0.10	0.94	0.70	0.09	0.85	0.81	0.10	1.0	0.71	0.07
Total C^{14} recovery		88			89			83			99	
Total C recovery		94			84			89			85	

[a] In this calculation only the olefin content of the gas sample used in the potassium permanganate analyses was taken into account. The presence of labelled butene and other olefins derived from the original labelled propanol introduces some error in the calculation of yields as well as in the specific activity of the various fractions. This error cannot be corrected, since neither the number of C^{14} labelled atoms per molecule nor the isomers were known.

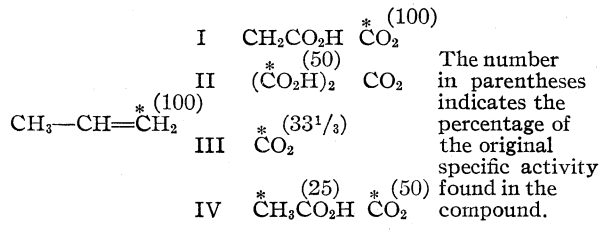
a case in which there was no activity in the acetate fraction would prove that all the C^{14} was in the methylene carbon of the propene. This was the case in experiment 4 where only 3% of the C^{14} activity was present in the acetate. This particular propene sample was checked by the ozonization analysis previously described and no activity could be found in the acetate. Therefore, the propene produced in experiment 4 consisted of the isomer 1-C^{14}-propene-1 to the extent of 97–100%. This result also demonstrated that acetic acid can arise only from the CH_3—CH= portion of the molecule. Accordingly, acetate was the most reliable indicator of the activity of the CH_3— position in propene and this was true even though acetic acid was not recovered in 100% yield.

The specific activity of the carbon dioxide fraction always was found to be lower than that calculated on the basis of the specific activity of the acetate. Thus, in experiment 1, the specific activity of the starting propanol was 6350 c./m. per millimole. Since all the C^{14} was located in the 1-position in the propanol, the specific activity of this particular carbon atom was also 6350 c./m. per millimole of carbon. The specific activity of the methylene carbon of the propene produced in experiment 1 was, therefore, $6350 - (2 \times 1610) = 3130$ c./m. per millimole C, but the specific activity found in the carbon dioxide fraction was only 2790 c./m. In experiment 2 the results were similarly 4150 c./m. *versus* 3980 c./m.; in experiment 4, 8040 c./m. *versus* 7600 c./m. These data indicated that the carbon dioxide–carbon was not derived exclusively from the methylene carbon, but probably from the methyl and central carbon atoms as well to a small extent.

Examination of the oxalic acid fraction revealed that the oxalate contained the methylene carbon atom of propene. The possibility of one carbon compounds being present in this residue has been considered already and has been eliminated on the basis of oxidation and volatility. The possibility that relatively large amounts of some three carbon compounds might be present may be eliminated on the basis of the specific activity of the fractions. If this oxidizable residue were entirely a three carbon compound, the specific activity in the active position would be three times the value shown in Table II. In experiment 4, the specific activity reported, when multiplied by three would give a result much higher than the original specific activity present in the starting material. On the other hand, if the substance were a two carbon compound, the specific activity in the labelled position corresponded closely to that known to be present in the methylene carbon. These results demonstrated that some propene was split at the CH_3—CH bond, perhaps to the extent of 15–20%. The —CH=CH_2 group was oxidized to oxalic acid, while the CH_3-group was split off as a one carbon compound, presumably oxidized to carbon dioxide, although some may not have been oxidized beyond methanol or formaldehyde. These last two compounds would not be recovered in the analytical procedure and this may account for the incomplete recovery of C^{14} and total carbon. The specific activity of C^{14} in the carbon dioxide fraction (representing the =CH_2 group) was therefore low due to the carbon dioxide which arose from the methyl group and probably from the central carbon atom as well.

In the alkaline oxidation of propylene glycol,[3] the yield of carbon dioxide was over one mole per mole of glycol, while acetate was lower and oxalate higher than that obtained from the acid oxidation. This led to the performance of an alkaline oxidation on propene from experiment 4. The oxidation was carried out in the same manner as those previously described except that the medium was 0.04 *N* in sodium hydroxide. The number of moles of carbon dioxide, acetic acid, and oxalic acid obtained per mole of propene were 1.64, 0.33, and 0.16, respectively. The specific activities of these three fractions were, respectively, 3410, 560, and 4370 c./m. per millimole of carbon. The yield of carbon dioxide was very high and its spe-

cific activity was very low, indicating that a considerable portion of it had come from carbon atoms other than the methylene group of the propene. Quantitative estimates, based upon relative yields and specific activities, indicated that nearly half of the propene had been completely oxidized to carbon dioxide, the remainder going partly ($^1/_3$) to acetic acid and carbon dioxide and partly ($^1/_6$) to oxalic acid and carbon dioxide. Still another route of oxidation was required to account for the small amount of activity found in the acetate fraction. This could be accounted for by some symmetrical intermediate (retaining the methyl group) such as isopropyl alcohol or acetone. There are three, and probably four, paths through which propene may be oxidized by permanganate. In the acid oxidation, path I predominates ($^5/_6$) with paths II and III contributing minor and approximately equal parts. Somewhat similar conclu-



sions were deduced for the alkaline permanganate oxidation of propionic acid by Nahinsky and Ruben.[12]

On the basis of the acetic acid specific activity, the propene prepared with metaphosphoric acid was a 50–50 equilibrium mixture of the two forms of labelled propene, the propene prepared from commercial aluminum oxide was 65% 1-C^{14}-propene-1 and 35% 3-C^{14}-propene-1, the propene prepared from the laboratory alumina was approximately a 50–50 equilibrium mixture; while the propene derived from the quaternary ammonium hydroxide was 97% 1-C^{14}-propene-1 and 3% 3-C^{14}-propene-1.

Isomerization during olefin preparation by dehydration reactions has been reported frequently,[13–16] while many cases have been reported where little or no isomerization occurred.[17–20] Asinger[13] found general isomerization of the double bond all along the carbon chain when dodecanol was dehydrated over alumina at 370–380° or with metaphosphoric acid. Isomerization was observed with alumina at temperatures as low as 250° where the dehydration reaction was incomplete. Pines[17] obtained only butene-1 when dehydrating *n*-butanol over alumina although Matignon, Moureau, and Dode[14] reported 15% butene-2 when using pure alumina and 90% with impure alumina. Pines believed the isomerization reported by Matignon occurred during analysis. Appleby, Dobratz and Kapranos[18] and Komarewsky, Uhlick and Murray[19] employing spectroscopic examination found no isomerization during the dehydration of primary hexanol, heptanol and octanol over alumina. Ewell and Hardy[21] studied the isomerization of pentenes over alumina and showed that the reaction required several hours to come to equilibrium. In the present study dehydration of *n*-propanol with alumina or phosphoric acid resulted in complete equilibration of the two isomeric forms. The ease of isomerization may be due to the symmetrical structure of propene.

Pyrolysis of *n*-propyltrimethylammonium hydroxide gave essentially pure 1-C^{14}-propene-1 in 90% yield. A side reaction of this pyrolysis results in the formation of methanol and a mixed tertiary amine. von Braun[22] found 5–10% methanol while Hanhart and Ingold[23] and Ingold and Vass[24] obtained 16–19% methanol on pyrolysis of the above quaternary base. The yield of propene in the present experiment falls between these two sets of results. This procedure appears to be a good, general, preparative method since the yields of olefins although falling off with higher olefins, does not drop below 70% even in the case of octene.[24]

Acknowledgment.—Our thanks are due to Mrs. Martha Kirk for her technical assistance in this work and particularly for the performance of many isotopic analyses.

Summary

1-C^{14}-propene-1 has been prepared. The migration of the double bond under a variety of experimental conditions in the preparation of propene has been investigated. The mechanism of the permanganate oxidation of the labelled propene has been examined. It has been found to proceed by several paths the relative importance of which depends upon the experimental conditions, especially the *p*H.

BERKELEY, 4, CALIF. RECEIVED FEBRUARY 25, 1948

(12) P. Nahinsky and S. Ruben, THIS JOURNAL, **63**, 2275 (1941).
(13) F. Asinger, *Ber.*, **75B**, 1247 (1942).
(14) C. Matignon, H. Moureau and M. Dode, *Compt. rend.*, **196**, 973 (1933).
(15) G. Egloff, J. C. Morell, C. L. Thomas and H. S. Bloch, THIS JOURNAL, **61**, 3571 (1939).
(16) G. T. Morgan and W. J. Hickingbottom, *J. Chem. Soc., Trans.*, **73**, 97 (1923).
(17) H. Pines, THIS JOURNAL, **55**, 3892 (1933).
(18) W. G. Appleby, C. J. Dobratz and S. W. Kapranos, *ibid.*, **66**, 1938 (1944).
(19) V. I. Komarewsky, S. C. Uhlick and M. J. Murray, *ibid.*, **67**, 557 (1945).
(20) A. L. Henne and A. F. Matuszak, *ibid.*, **66**, 1649 (1944).
(21) R. H. Ewell and P. E. Hardy, *ibid.*, **63**, 3460 (1941).
(22) J. von Braun, *Ann.*, **382**, 1 (1911).
(23) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927).
(24) C. K. Ingold and C. C. N. Vass, *ibid.*, 3125 (1928).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Polarography in Liquid Ammonia. I. The Alkali Metals

BY H. A. LAITINEN AND C. J. NYMAN

Up to the present time, no research has been carried out on polarographic measurements in liquid ammonia, although the dropping mercury electrode has been used in this solvent. Murtazaev[1] has measured electrocapillary curves of salts in liquid ammonia and has shown that chloride, bromide and iodide ions are adsorbed at the mercury–solution interface, causing shifts in the electrocapillary maximum similar to those observed in aqueous solution. Pleskov and Monosson[2] have measured the potential of the electrocapillary maximum in 0.1 normal ammonium nitrate solution at −35° and found it to be 0.386 v. more positive than the potential of a lead electrode in 0.1 normal lead nitrate solution. Dropping amalgam electrodes were used by Pleskov[3] and by Pleskov and Monosson,[4] in their determination of the standard electrode potentials of the alkali metals in liquid ammonia. Since it was known that the dropping mercury electrode would function in liquid ammonia, a polarographic study of the reduction of the alkali metal ions was undertaken.

Experimental

The electrolysis cell shown in Fig. 1a was used for all the experiments in this investigation unless otherwise specified. A platinum wire was sealed through the bottom of the cell so that the mercury pool could be used as the non-polarizable electrode. A conventional H-type cell, as shown in Fig. 1b, was used when it was desired to have the anode and cathode compartments separated; a sintered glass disc prevented mixing of the solutions in the two sides of the cell. When using this cell, two connections to the drying system (Fig. 2) were necessary.

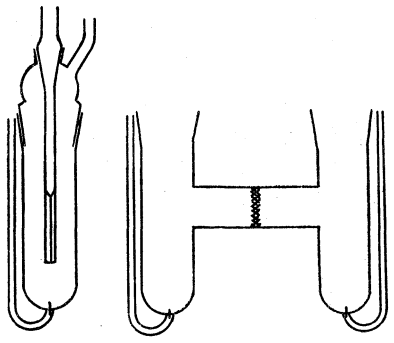


Fig. 1.—Electrolysis cells.

Using the apparatus shown in Fig. 2, the following procedure was carried out in the preparation of air-free anhydrous liquid ammonia solutions. The cell was connected to the drying system as shown at A after a weighed sample had been introduced into it. Ampules B and B′ each contained a small piece of sodium metal, approximately 1 g., in order to dry the ammonia. The system was evacuated through tube C, and after ampule B was cooled with a Dry Ice and acetone-bath, gaseous ammonia was allowed to enter the system through tube D. When 35 to 40 cc. had condensed, the ammonia was distilled from ampule B to B′, and then into the electrolysis cell until the desired volume was obtained. Stopcock E was then closed, and the bath surrounding the cell was brought to −36° by the addition of warm acetone. The solution was allowed to stand for one hour to be certain that the indifferent electrolyte had reached solubility equilibrium. Occasional stirring was achieved by opening stopcock E and evaporating ammonia into ampule B′, which was cooled with a Dry Ice and acetone-bath. In this evaporation, small bubbles formed which stirred the solution, but which did not cause any splattering on the walls of the cell.

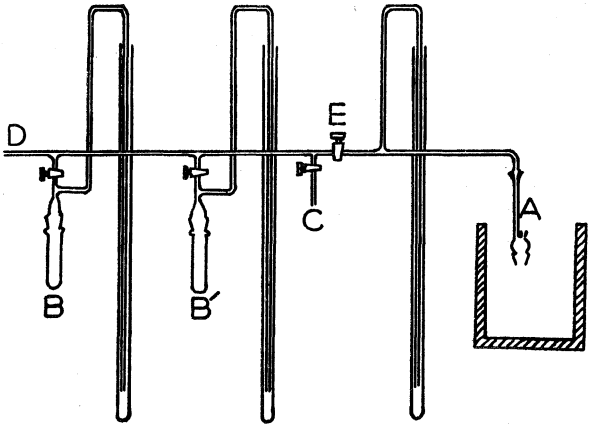


Fig. 2.—Drying system for the preparation of anhydrous liquid ammonia solutions.

The thermostat consisted of a one-gallon Dewar flask filled with acetone, a copper cooling coil, a cone drive stirrer and a toluene expansion udder for controlling the temperature. The toluene expanded against a mercury filled U-tube outside the bath forcing the mercury into a capillary. Electrical contact was made through the bottom of the U-tube and through the capillary. A leveling device for controlling the amount of mercury was sealed into the bottom of the U-tube. As the temperature rose and contact was made through the mercury in the U-tube, a mercury relay switch was actuated starting the pump which circulated cold acetone through the cooling coil. This thermostat held the temperature at a constant value of $-36.0 \pm 0.2°$.

Dropping mercury electrode 1 had the following characteristics in a saturated solution of tetrabutylammonium iodide in liquid ammonia at −36°. At a pressure of 20 cm., the drop time was 6.4 seconds (open circuit), and the value of m was 0.844 mg./sec. Under similar conditions, electrode 2 had an m of 1.184 mg./sec., and a drop time of 5.1 seconds (open circuit). As a comparison, electrode 1 had the following characteristics in air-saturated water at 25°. At a pressure of 20 cm., the drop time was 7.1 seconds (open circuit), and the value of m was 1.14 mg./sec.

The polarograph used was a Sargent Model XX. The calibration of this instrument was checked by inserting

(1) A. Murtazaev, *Acta Physicochim. U. R. S. S.*, **12**, 225 (1940).
(2) V. A. Pleskov and A. M. Monosson, **2**, 621 (1935).
(3) V. A. Pleskov, **6**, 1 (1937); **21**, 235 (1946).
(4) V. A. Pleskov and A. M. Monosson, *ibid.*, **2**, 615 (1935).

a known resistance in place of the electrolysis cell and measuring accurately the applied potential. With these data, the current flowing through the circuit could be calculated and compared with that indicated by the recorder. All applied potential values were checked by means of a student type potentiometer.

The ammonia used in these investigations was obtained from the Matheson Company and was dried as previously described before use. The alkali metal salts were C. P. materials of commerce and were dried at 110° before use. The tetrabutylammonium iodide was prepared by a slight modification of the method used by Cox, Kraus and Fuoss,[5] as previously described by Laitinen and Wawzonek.[6] That this material was free of alkali metal ions was indicated by the fact that the residual current curve showed no wave at potentials corresponding to their reduction.

Data and Discussion

The expression

$$E_{d.e.} = E_{1/2} - \frac{RT}{nF} \ln i/(i_d - i)$$

is the equation of the current–voltage curve obtained for the reduction of a metal ion at the dropping mercury electrode when the metal is soluble in mercury.[7] $E_{d.e.}$ is the potential of the dropping mercury electrode; $E_{1/2}$ is the half-wave potential; i_d is the diffusion current; and i is the current which flows at a potential $E_{d.e.}$. A plot of $E_{d.e.}$ *versus* $\log i/(i_d - i)$ should be a straight line with a slope of $-2.303RT/nF$, if the reduction process is reversible. The half-wave potentials of the alkali metal ions were obtained from a plot of this type by determining the potential at which $\log i/(i_d - i)$ was zero. Typical polarograms are shown in Fig. 3 and Fig. 4.

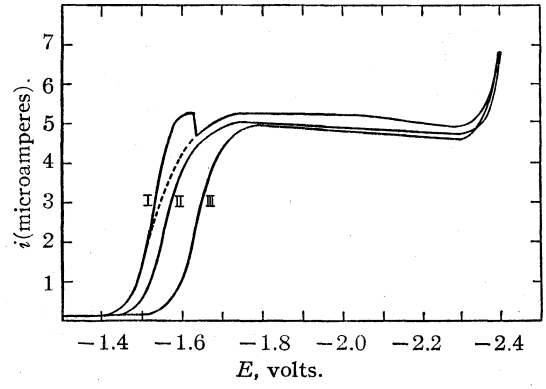


Fig. 3.—Polarograms of sodium, potassium and rubidium iodides in saturated tetrabutylammonium iodide: curve I, 9.8×10^{-4} *M* RbI; curve II, 1.00×10^{-3} *M* KI; curve III, 1.04×10^{-3} *M* NaI.

It is possible to evaluate the half-wave potentials theoretically either by an equation derived by Lingane[8] or by one derived by von Stackelberg.[9]

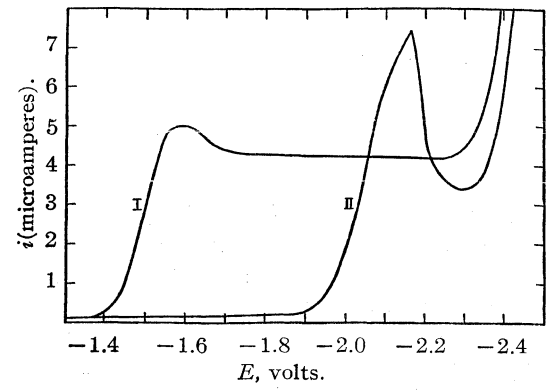


Fig. 4.—Polarograms of cesium and lithium chlorides in saturated tetrabutylammonium iodide: curve I, 8.1×10^{-4} *M* CsCl; curve II, 1.01×10^{-3} *M* LiCl.

The latter is more convenient in the case of the alkali metals, as the standard electrode potentials of the metals are not necessary. The half-wave potential as measured polarographically is equal to the potential of an amalgam electrode in the cell

$$M(Hg)_x\ (C_a) \mid M^+\ (C_s) \mid \text{Ref. elect.}$$

when the concentration of metal ion in the solution is equal to the concentration of metal in the amalgam. For the dropping mercury electrode to have the same potential as the amalgam electrode in the above cell, the diffusion coefficients of the ion in solution and the metal in the amalgam must be equal. The potential E of the amalgam electrode in the above cell is given by the equation

$$E = E_{1/2} - \frac{RT}{nF} \ln \frac{C_a}{C_s}$$

where C_a is the concentration of metal in the amalgam and C_s is the concentration of metal ion in the solution. The data necessary for calculation of the half-wave potentials are available, since Pleskov and Monosson[3,4] have made such measurements in the evaluation of the standard electrode potentials of the alkali metals in liquid ammonia. A lead electrode in 0.1 normal solution of lead nitrate was used by these authors as a reference electrode. In the experimental determination of the half-wave potentials, a mercury pool in a saturated solution of tetrabutylammonium iodide was used as the reference electrode. In order to relate the two reference electrodes, the following cell was prepared. The dropping mercury electrode and a quiet mercury pool were placed in one compartment of the cell shown in Fig. 1b. The solution in this compartment was 0.001 molar with sodium iodide and saturated with tetrabutylammonium iodide. The other compartment contained a lead electrode in 0.1 normal lead nitrate solution. Since the half-wave potential of sodium ion must be a constant, it was determined against each electrode, and the difference between the two values must be equal to the difference of potential between the two reference electrodes. The mercury

(5) N. L. Cox, C. A. Kraus and R. M. Fuoss, *Trans. Faraday Soc.*, **31**, 749 (1935).

(6) H. A. Laitinen and S. Wawzonek, THIS JOURNAL, **64**, 1765 (1942).

(7) J. Heyrovsky and D. Ilkovic, *Coll. Czech. Chem. Commun.*, **7**, 198 (1935).

(8) J. J. Lingane, THIS JOURNAL, **61**, 2099 (1939).

(9) M. von Stackelberg, *Z. Elektrochem.*, **45**, 466 (1939).

pool was found to be 0.318 v. more positive than the lead electrode.

Table I contains the values of the half-wave potentials calculated from the data of Pleskov and Monosson, as well as the values observed with the dropping mercury electrode in 0.001 molar metal iodide solution with a saturated solution of tetrabutylammonium iodide as indifferent electrolyte. The observed values have been corrected for the iR drop through the solution. The slopes of the plots of $E_{d.e.}$ *versus* $\log i/(i_d - i)$ are also recorded.

TABLE I

$E_{1/2}$ IN LIQUID AMMONIA AT $-36°$ *versus* Pb | $Pb(NO_3)_2$ (0.1 *N*)

Ion	E, v.	C_a, m./l.	C_s, m./l.	$E_{1/2}$ (calcd.), v.	$E_{1/2}$ (obs.), v.	Slope of $E_{d.e.}$ *vs.* $\log i/(i_d - i)$
Li^+	−1.658	0.351	0.1	−1.632	−1.67	−0.058
Na^+	−1.337	.564	.1	−1.302	−1.31	− .057
K^+	−1.287	.770	.1	−1.245	−1.24	− .056
Rb^+	−1.229	.367	.1	−1.202	−1.21	− .061
Cs^+	−1.078	.192	.01	−1.018	−1.15	− .065

In the case of lithium, a large maximum (see Fig. 4) approximately equal to the diffusion current was observed, and smaller maxima were observed with rubidium and cesium ions. All of these maxima decreased when the concentration of the reducible ion was lowered to 2×10^{-4} molar, and they practically disappeared in the case of rubidium and cesium ions. Attempts to eliminate the lithium maximum by the use of gelatin did not succeed, and the problem was not investigated further.

It is seen that there is a reasonable agreement between the observed and calculated values of the half-wave potentials, and that the slope of $E_{d.e.}$ *vs.* $\log i/(i_d - i)$ plot approaches the reversible value −0.047, but in no case was a reversible slope obtained.

The half-wave potentials of the alkali metal ions become more positive as the atomic number increases. There are two reasons why this inverse order of reduction might be expected. The solvation energy of the smaller ions is greater than for the larger ions, and, therefore, more energy must be supplied to the smaller ions to reduce them. The free energy of amalgamation of the metals, as indicated by the difference of potential between the metal and its amalgam, shows a tendency to increase as the atomic number increases. These two factors are working in the same direction, and, therefore, an inverse order of the ease of reduction is a logical one.

The diffusion currents of the alkali metal ions, as measured in liquid ammonia at −36°, are recorded in Table II. A saturated solution of tetrabutylammonium iodide served as the supporting electrolyte. As a comparison, theoretical values were calculated by means of the Ilkovic equation[10,11]

$$i_d = 605nCD^{1/2}m^{2/3}t^{1/6}$$

which relates the diffusion current i_d (microamperes) of an ion to n, the number of faradays of electricity required per mole of electrode reaction, to its concentration C (millimoles per liter), to its ionic diffusion coefficient D ($cm.^2$/sec.), and to the capillary characteristics m (mg./sec.) and t (sec.). The ionic diffusion coefficient D can be evaluated by means of the expression[12,13]

$$D = RT\lambda^0/zF^2$$

where R is 8.317 volt-coulombs per degree, T is the absolute temperature, λ^0 is the equivalent conductance of the ion at infinite dilution (ohm^{-1}-$cm.^2$-equiv.$^{-1}$), z is the charge of the ion, and F is 96,500 coulombs. The remaining terms in the Ilkovic equation are experimental quantities which are easily obtained.

TABLE II

DIFFUSION CURRENTS OF THE ALKALI METAL IONS IN LIQUID AMMONIA AT −36°

Ion	λ_0, ohm^{-1}-$cm.^2$ equiv.$^{-1}$	$D \times 10^5$, $cm.^2$/sec.$^{-1}$	$m^{2/3}t^{1/6}$, mg.$^{2/3}$-sec.$^{-1/2}$	C, mm./l.	i_d (calcd.), microamperes	i_d (obs.), microamperes	% Diff.
Li^+	122	2.59	0.893	1.01	2.78	3.11	12
Na^+	135	2.86	1.256	1.04	4.23	4.84	14
K^+	174	3.69	1.262	1.00	4.64	4.71	2
Rb^+	179	3.80	1.262	0.98	4.62	5.06	10
Cs^+	180	3.82	1.273	0.81	3.83	4.21	10

Table II contains the data necessary for and the results of such calculations. The values for the equivalent ionic conductance at infinite dilution were obtained by interpolation between the data of Pleskov and Monosson[14] at −40° and data which they recalculated for −33.5° from the work of Franklin and Kraus.[15] Since no values were available for rubidium and cesium at −33.5°, the same correction which was applied to potassium was used to correct the values for these ions from −40 to −36°.

The diffusion currents calculated from the Ilkovic equation are lower than the observed values. The discrepancy can largely be attributed to the failure to obtain complete suppression of the migration current. The concentration of indifferent electrolyte was 0.0057 molar ±5% and, therefore, the ratio of indifferent electrolyte to reducible ion was about 6 to 1. Assuming as a first approximation the mobilities of all ions to be equal, the migration current would represent 7% of the total current.

Another cause for the observation of abnormally high diffusion currents lies in the failure of Ilkovic equation at excessively rapid drop rates. At the potentials at which the diffusion currents of the alkali metal ions were measured, the drop time was 1.0 to 2.2 seconds. Lingane and Lover-

(10) D. Ilkovic, *Coll. Czech. Chem. Commun.*, **6**, 498 (1934).

(11) D. MacGillavry and E. K. Rideal, *Rec. trav. chim.*, **56**, 1013 (1937).

(12) W. Nernst, *Z. physik. Chem.*, **2**, 613 (1888).

(13) I. M. Kolthoff and J. J. Lingane, THIS JOURNAL, **61**, 825 (1939).

(14) V. A. Pleskov and A. Monosson, *Z. physik. Chem.*, **156**, 176 (1931).

(15) E. C. Franklin and C. A. Kraus, *Am. Chem. J.*, **23**, 277 (1900); THIS JOURNAL, **27**, 191 (1905).

idge[16] and Buckley and Taylor[17] have observed abnormally high values of the quantity $i_d/Cm^{2/3}t^{1/6}$ at drop times less than three seconds unless a suppressor, such as gelatin, was present.

The use of some other supporting electrolyte with a higher solubility was not attempted because of the difficulty involved in finding one which was not reduced at very negative potentials and which could also be freed easily from traces of the alkali metal ions. In all probability, better agreement between the observed and calculated values of the diffusion current would be obtained if higher ratios of non-reducible to reducible ion were to be used.

(16) J. J. Lingane and B. A. Loveridge, THIS JOURNAL, **66**, 1425 (1944).

(17) F. Buckley and J. K. Taylor, *J. Research Nat. Bur. Standards*, **34**, 97 (1945).

Summary

The half-wave potentials of the alkali metal ions in liquid ammonia were found to agree with those calculated theoretically, and the reduction process appeared to be reversible.

The diffusion currents of the alkali metal ions were measured and compared with those calculated from the Ilkovic equation.

URBANA, ILLINOIS RECEIVED MARCH 4, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

Mechanical Properties of Substances of High Molecular Weight. IV. Rigidities of Gelatin Gels; Dependence on Concentration, Temperature and Molecular Weight[1]

BY JOHN D. FERRY

Earlier measurements[2] have shown that the rigidity of a gelatin gel is approximately proportional to the square of the concentration, and it is well-known that the rigidity decreases with increasing temperature[3] or with degradation.[4] Previous work has, however, been confined to samples of unknown molecular weight. The series of degraded gelatins described by Scatchard, Oncley, Williams and Brown[5] has now afforded the opportunity of studying samples of known average molecular weight and molecular size distribution. The method of propagation of transverse vibrations[6] permits absolute measurements of rigidity to be made conveniently at concentrations lower than those usually employed by previous investigators. This paper reports rigidity measurements by the transverse vibration method on certain of the gelatin samples studied by Scatchard, Oncley, Williams and Brown, together with several other gelatins from different sources.

Materials and Method

The following gelatin samples were employed: four of the series of degraded ossein gelatins,[5] originally furnished through the kindness of Dr. D. Tourtellotte of the Knox Gelatin Company; one sample each of ossein (A-O), porkskin (A-P), and calfskin (A-C) gelatin, furnished by the Atlantic Gelatin Company; and one calfskin gelatin (EK-120), purchased from the Eastman Kodak Company. Table I lists the values of number-average molecular weight, M_n, derived from osmotic pressure and viscosity measurements.[7] Values of α, the fraction of bonds broken in the parent molecule, and M_w, the weight-average molecular weight, as calculated from the statistics of degradation,[5] are also included for the degraded series. They are omitted for the other samples because it is not certain that the details of the statistical treatment are applicable to those.

TABLE I

MOLECULAR WEIGHTS OF GELATIN SAMPLES

Sample	α	$M_n \times 10^{-3}$	$M_w \times 10^{-3}$
Degraded Series (Ossein)			
L1–00	0.00125	45	74
L1–80	.00235	29	53
L1–180	.00345	22	41
P7–180	.00470	17	33
Additional Samples			
A-P		47	
A-C		47	
A-O		39	
EK–120		37	

The degraded samples were furnished as sterile stock solutions, at a concentration of about 60 g./l., in 0.15 *M* sodium chloride at *p*H 7; the others, furnished in solid form, were dissolved in 37° and adjusted to the same *p*H and salt concentration, unless otherwise specified. Stock solutions were kept at 0°, except for occasional brief warming to 37° to withdraw samples, with sterile precautions. From studies of the rate of degradation,[5,7] no perceptible change in molecular weight would be expected for several years under these conditions. The measurements described here were completed in less than two years. Recent unpublished measurements on similar samples indicate that there is no change after five years.

The stock solutions, after warming at 37° for one hour, were diluted with 0.15 *M* sodium chloride (unless otherwise specified) to the desired concentrations and transferred to rectangular glass cells provided with clamps[8] to hold the

(1) Part of this work was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. Presented in part at meetings of the Society of Rheology, New York, N. Y., Oct. 30, 1943, and Nov. 17, 1944.

(2) A. Leick, *Ann. Physik*, **14**, 139 (1904); S. E. Sheppard and S. S. Sweet, THIS JOURNAL, **43**, 545 (1921).

(3) M. L. Sheely, *Ind. Eng. Chem., Anal. Ed.*, **2**, 348 (1930); J. C. Derksen, Thesis, Amsterdam, 1935.

(4) E. T. Oakes and C. E. Davis, *J. Ind. Eng. Chem.*, **14**, 708 (1922).

(5) G. Scatchard, J. L. Oncley, J. W. Williams and A. Brown, THIS JOURNAL, **66**, 1980 (1944).

(6) J. D. Ferry, *Rev. Sci. Instruments*, **12**, 79 (1941); THIS JOURNAL, **64**, 1323 (1942).

(7) Unpublished measurements by Drs. G. Scatchard and A. Brown, Massachusetts Institute of Technology.

(8) Designed by Dr. S. H. Armstrong, Jr.

vibrator plates in place until rigidity had developed. The solutions were usually covered with paraffin oil to prevent evaporation. The velocity of propagation of transverse waves, V, was measured as previously described.[6] The modulus of rigidity is given by $G = V^2\rho$, where ρ is the density. The latter value was calculated from the density of the salt solution and an assumed value of 0.70 for the partial specific volume of gelatin. Damping was not measured. For each gel at each temperature, measurements of V were made at four or five different frequencies, covering a range of about twofold; these values usually agreed within 1–2% of the mean for the strongest gels and within 5% for the weakest. The rigidity was calculated from the mean value in each case. Measurements on three separate series of gels prepared from the same stock solution showed agreement to about the same extent (represented in Fig. 2). Since one year had elapsed between the first and the third series, this agreement confirms absence of degradation in storage.

There was no evidence of dispersion of the rigidity; the frequency ranges employed varied from about 1250–2500 cycles for the strongest gels to about 320–630 cycles for the weakest. Absence of dispersion indicates that the rigidity thus measured dynamically can be taken as identical with that which would be measured by the static methods used by previous investigators[2]; it is certainly of the same order of magnitude. A direct comparison of dynamic and static rigidities will be reported subsequently.[9]

Results

Changes of Rigidity with Time at Constant Temperature.—When a solution was quickly cooled from 37 to 15° and held at the latter temperature, gelation occurred within half an hour, with development of a measurable rigidity. The rigidity increased rapidly at first and continued to rise slowly for many hours without attaining a constant value. However, when a solution was first chilled at 0° for a day or more, and then quickly warmed to and held at 15°, the rigidity fell rapidly from its value characteristic of the lower temperature and reached an essentially constant value, usually within five hours. These changes are illustrated in Fig. 1 for sample EK-120 at a concentration of 25.7 g./l. and *p*H 5.4 (no salt). Similar measurements on several other samples at various concentrations showed the same behavior; when a chosen temperature was approached from above, the rigidity failed to attain a constant value in as long a period as fifty hours, but when it was approached from below, the rigidity became constant within five hours. These observations agree with earlier studies of the optical rotation,[10] specific volume,[11] and light scattering[12] of gelatin gels, in which equilibrium was always more rapidly attained after precooling.

Accordingly, the following procedure was adopted for all subsequent experiments: each solution, after introduction into the cell, was quickly cooled and kept at 0° for about twenty-four hours; the rigidity of the gel at 0° was measured; the temperature was raised a few degrees and kept constant (±0.1°) for five to twelve hours, and the rigidity was again measured; and this process was repeated until the gel melted. Since the initial measurement does not involve approach from a lower temperature, it cannot be compared with the others; and even at 10° the rigidity values are slightly higher when the chilling at 0° is prolonged for several weeks instead of limited to twenty-four hours. However, above 10° the results appear to be independent of the time of chilling. All the values are quite closely reproducible when the above procedure is followed.

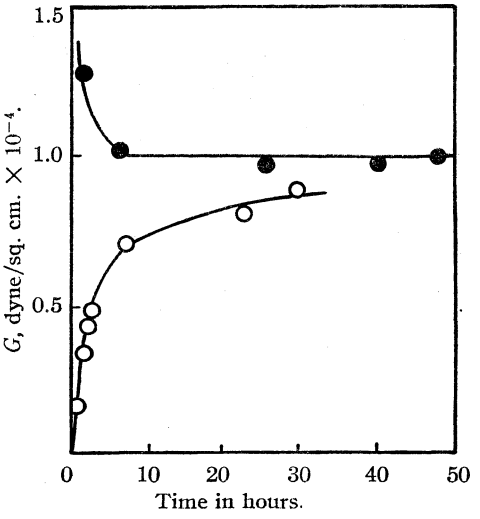


Fig. 1.—Change of rigidity with time at 15°, sample EK-120, concentration 27.4 g./l., *p*H 5.4: ●, after warming from 0°; ○, after cooling from 37°.

Dependence of Rigidity on Concentration.—The rigidities of gels of sample L1-00 are plotted against the square of the concentration in Fig. 2 for several temperatures. Close proportionality is observed up to a concentration of about 60 g./l.; the values of G/c^2 in (dyne/sq. cm.)(g./l.)$^{-2}$ are 44 at 0°, 23 at 15°, and 12 at 21.8°. For a sample of similar molecular weight, A-O, over a much higher concentration range (up to 160 g./l.), there is slight downward curvature (Fig. 3); while for a sample of lower molecular weight, Ll-80, in the more dilute range there is slight upward curvature (Fig. 4).

Dependence of Rigidity on Temperature.—Values of G/c^2 for sample L1-00 are plotted against temperature in Fig. 5. The rigidity falls rapidly with increasing temperature, and vanishes at about 30°. It follows from Fig. 2, of course, that the curves for several different concentrations coincide. Nevertheless, these curves presumably diverge just below the melting point (where the rigidity disappears), because the latter is a function of concentration. For a gelatin with this molecular weight, the melting point, determined[13] after chilling for twenty-four hours at 0°, varies from 28.2° at a concentration of 20 g./l. to 30.6°

(9) J. E. Eldridge and J. D. Ferry, unpublished experiments at the University of Wisconsin.

(10) C. R. Smith, THIS JOURNAL, **41**, 135 (1919).

(11) E. Heymann, *Trans. Faraday Soc.*, **32**, 1, 462 (1936).

(12) W. Heller and E. Vassy, *Compt. rend.*, **207**, 157, 991 (1938).

(13) R. S. Gordon, Jr., and J. D. Ferry, *Federation Proc.*, **5**, 136 (1946).

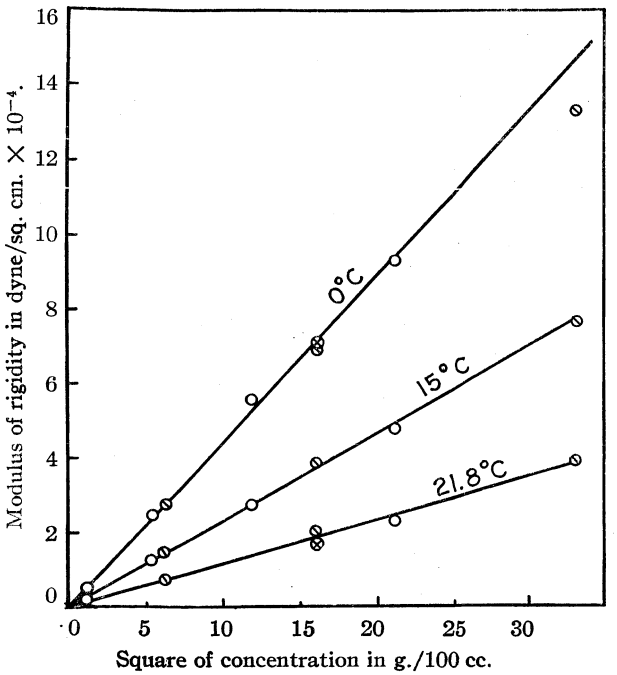


Fig. 2.—Rigidities of sample L1–00, plotted against square of concentration at different temperatures; age of stock solution: O, six months; ⊘, seven months; ⊗, eighteen months.

at 55 g./l. The rigidities of gels in the immediate vicinities of their melting points will be reported subsequently.[9]

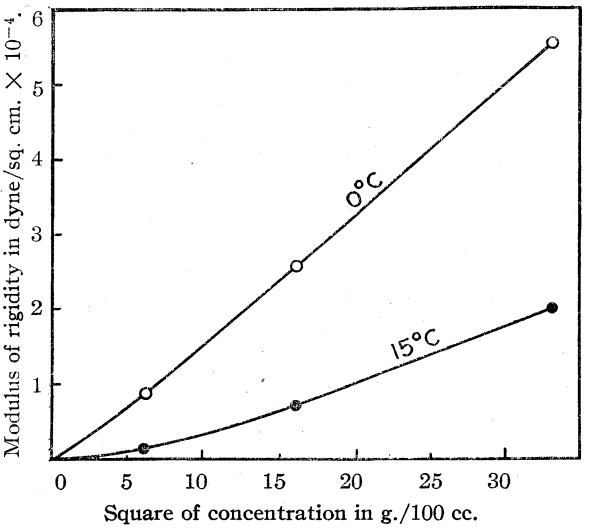


Fig. 4.—Rigidities of sample L1–80, plotted against square of concentration at different temperatures.

Since the values at 0° do not represent equilibrium approached from a lower temperature, and

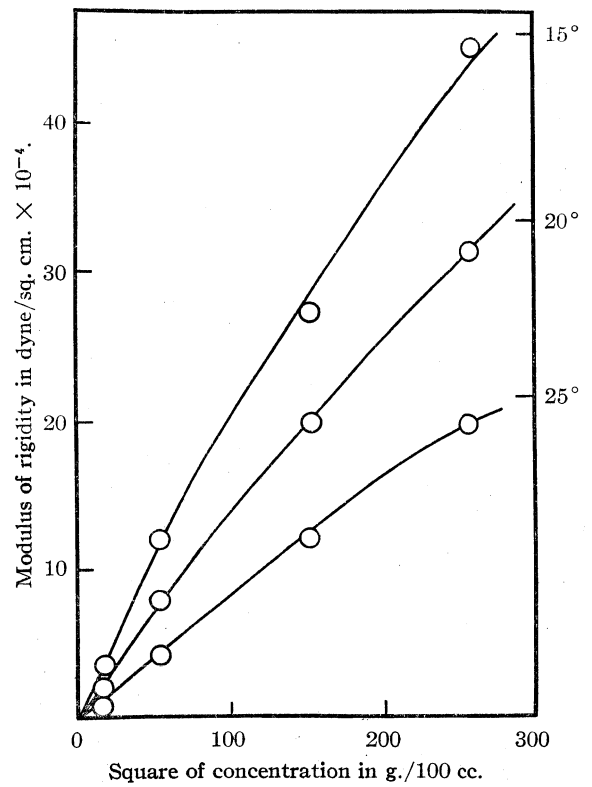


Fig. 3.—Rigidities of sample A-O, plotted against square of concentration at different temperatures.

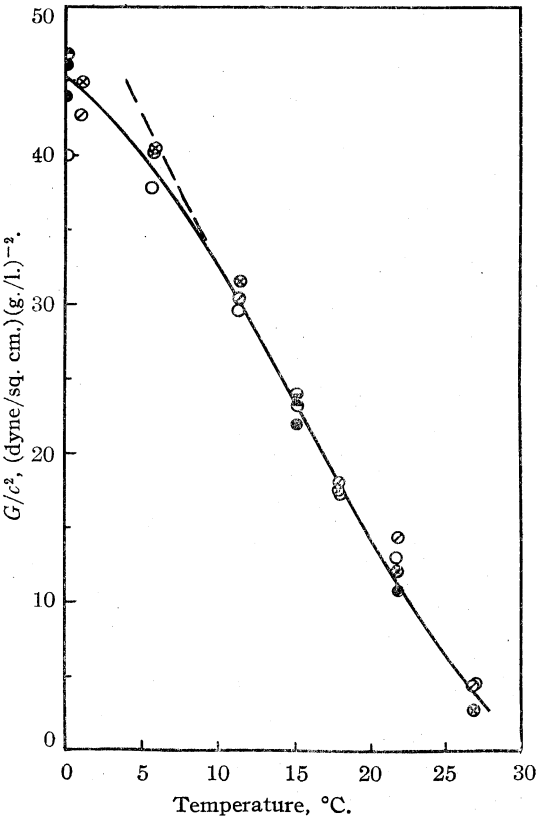


Fig. 5.—G/c^2 plotted against temperature, for sample L1–00; concentrations in g./l.: Ō, 57.5; ●, 46; ⊘, 40; ◓, 34.5; ⊗, 25; ◒, 23.

are undoubtedly too low, it is possible that the inflection point in Fig. 5 is an artifact and the curve representing fully developed rigidity should more nearly follow the dashed line.

Rigidities for different gelatin samples, all at a concentration of 40 g./l., are plotted against the temperature in Fig. 6. The marked decrease in rigidity with increasing temperature is seen in each case; the curves form a coherent family except for that of sample A-C. Below 10° the curves are broken because, as pointed out above, they probably do not represent equilibrium values.

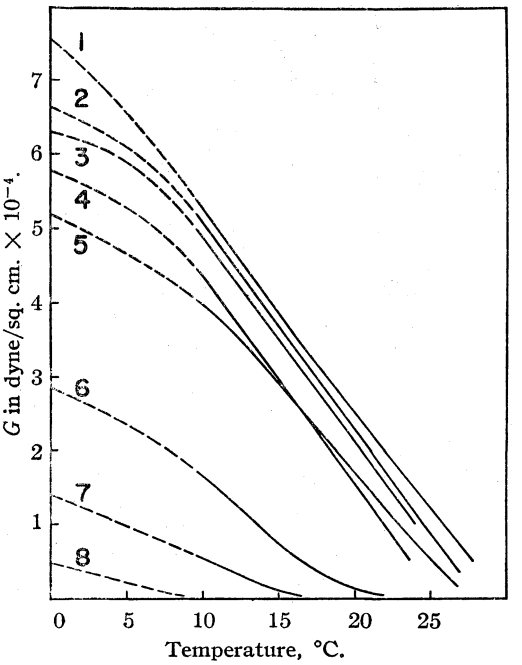


Fig. 6.—Rigidity plotted against temperature, at a concentration of 40 g./l.: 1, L1–00; 2, A-P; 3, A-O; 4, EK-120; 5, A-C; 6, L1–80; 7, L1–180; 8, P7–180.

Dependence of Rigidity on Molecular Weight.—Values interpolated from Fig. 6 at 5° and 15° are given in Table II, and are plotted against the number-average molecular weight in Fig. 7. The

TABLE II

RIGIDITIES OF VARIOUS SAMPLES AT GEL CONCENTRATIONS OF 40 G./L.

Sample	$M_n \times 10^{-3}$	$G \times 10^{-4}$, 5°	$G \times 10^{-4}$, 15°
Degraded Series			
L1-00	45	6.6	3.9
L1-80	29	2.35	0.7
L1-180	22	1.0	0.1
P7-180	17	0.2	0
Additional Samples			
A-P	47	6.2	3.7
A-C	47	4.7	2.9
A-O	39	5.8	3.55
EK-120	37	5.6	3.0

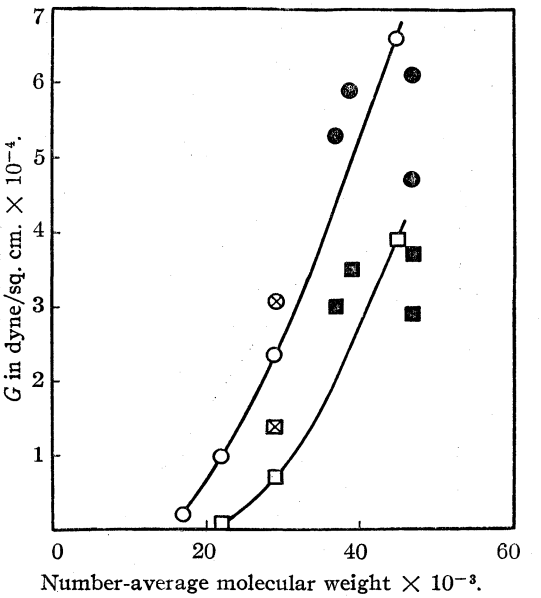


Fig. 7.—Rigidity plotted against number-average molecular weight, at 5° (circles) and 15° (squares): open points, degraded series; crossed points, mixture; solid points, additional samples.

points for the degraded series fall on a smooth curve. The scatter of the other points indicates that gelatins from various sources have roughly similar rigidities when compared on the basis of number-average molecular weight, but that the exact value of the rigidity is influenced by the details of preparative procedure. These data suggest further that the rigidity may depend more on the details of preparation than on the nature of the tissue source (ossein, porkskin or calfskin).[14]

Rigidities of a Mixture of Samples.—Two samples of widely different average molecular weight, L1-00 and L1-180, were combined in equal proportions by weight, yielding a mixture with $M_n = 29{,}500$ and $M_w = 57{,}500$, The rigidities of the mixture are compared with those of the original samples, all at a concentration of 57.5 g./l., in Fig. 8. (The points for L1-180 represent measurements at 40 g./l., corrected by the factor $(57.5/40)^2$.) The rigidity of the mixture does not correspond to the arithmetic mean of values for the individual samples, $(G_1 + G_2)/2$; instead, it

(14) A few measurements were made on several fractionated calfskin gelatin samples, sent by Dr. S. E. Sheppard of the Eastman Kodak Company to Professor Scatchard, in which the distribution of molecular weights was presumably far sharper than in the degraded series described here. The temperature dependence of rigidity for the fractionated samples was very similar to that shown Figs. 5 and 6, but the dependence on number-average molecular weight was quite different from that shown in Fig. 7. For M_n ranging approximately from 80,000 to 120,000, as estimated by Mr. R. H. Wagner in Dr. Sheppard's laboratory, the rigidity was almost independent of molecular weight and slightly less than that of our sample L1-00 at comparable concentration and temperature. This behavior was in agreement with unpublished measurements of the rigidity of these samples obtained by Dr. R. C. Houck in Dr. Sheppard's laboratory. The relation of these results to the measurements reported in this paper is not clear.

agrees closely with values calculated as $[(\sqrt{G_1} + \sqrt{G_2})/2]^2$, given by the dashed curve. Thus the square roots of the rigidities, rather than the rigidities themselves, are additive.

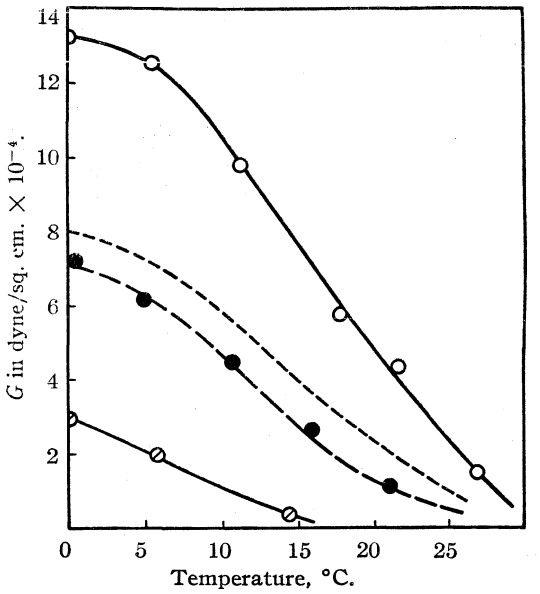


Fig. 8.—Comparison of rigidities of a mixed sample and of its components, at a concentration of 57.5 g./l.: ○, L1-00 (G_1); ⊘, L1-180 (G_2); ●, mixture of equal parts by weight. ---, $(G_1 + G_2)/2$ (calculated); ———, $[(\sqrt{G_1} + \sqrt{G_2})/2]^2$ (calculated).

Rigidities of the mixture at 5 and 15°, corrected to a concentration of 40 g./l., are included in the plot against M_n in Fig. 7; they do not fall on the curve for the individual degraded samples. However, when M_w is taken as the independent variable, points for the mixtures fall on the curves for the individual samples. Moreover, the square root of the rigidity is found to be a linear function of the weight average molecular weight (Fig. 9). It can easily be shown from the definition[5] of M_w that additivity of $\sqrt{G}$ for different samples on a weight concentration basis, as shown in Fig. 8, is a necessary consequence of the linear relation exhibited in Fig. 9.

Points interpolated at other temperatures and plotted as in Fig. 9 also give straight lines of equal slope, and their intercepts follow an exponential function of the reciprocal absolute temperature. These relations can be combined in the empirical equation

$$\sqrt{G} = 0.00484(M_w - 1.20 \times 10^{10} e^{-7330/RT}) \quad (1)$$

which expresses the rigidities of every gel of the degraded series at a concentration of 40 g./l. from 5° to the melting point; the fit is within experimental error except near the melting point for the most degraded samples.

Discussion

The highly elongated shape of the largest gelatin molecules in these mixtures[4,15] makes plausible the concept of gelation as network formation by cross-linking through secondary forces of attraction.[16] Some of the bonds may be represented by regions of local crystallinity, as postulated by Herrmann and Gerngross[17] (although their X-ray evidence was based on gels far more concentrated than those described here); others may be formed by lateral association of chain segments in pairs. The stability and low internal viscosity of gelatin gels suggest that there are specific loci of attraction widely spaced along the molecules,[18] corresponding either to sequences of easily crystallizable amino acids in the polypeptide chain (a series of glycine residues, for example), or to combinations of certain side chains resulting in strong attraction. Between these loci the attractive forces must be relatively slight; otherwise highly unstable gels such as those encountered in denatured proteins or inorganic colloids would be expected.

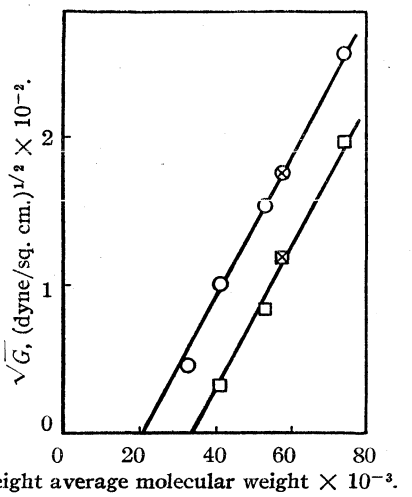


Fig. 9.—$\sqrt{G}$ plotted against weight-average molecular weight, at 5° (circles) and 15° (squares). Open points are degraded series; crossed points, mixture.

In such a network, the number of useful junctions which contribute to the rigidity is smaller than the total number of bonds or cross-links because of (a) bonds in the "sol fraction" which is not attached to the network, (b) possible cyclic structures, and (c) a number of bonds equal to the number of molecules initially present (half the number of loose ends) which will not contribute to the network.[19] Decrease in rigidity due to decreasing concentration, increasing temperature, or decreasing molecular weight may involve a decrease in the total number of bonds per cc. (n_t), an increase in the number of useless bonds per cc. (n_a), or both.

The fact that the rigidity is proportional to the

(15) E. O. Kraemer, *J. Phys. Chem.*, **45**, 660 (1941).
(16) P. J. Flory, *ibid.*, **46**, 132 (1942).
(17) K. Herrmann, O. Gerngross and W. Abitz, *Z. physik. Chem.*, **B10**, 371 (1930).
(18) J. D. Ferry, *Adv. Protein Chemistry*, Vol. IV, in press.
(19) P. J. Flory, *Chem. Rev.*, **35**, 51 (1944).

square of the concentration except near the melting point or when M_w is small indicates that, with the latter exceptions, the ratio of useless to total bonds is independent of concentration. Either $G \propto (n_t - n_a)$, as would be expected for rubberlike elasticity, and $n_t \propto c^2$, following a binary association; or $G \propto (n_t - n_a)^2$, which might correspond to a stiff strutted structure, and $n_t \propto c$, a peculiar type of association recently postulated by Doty for polyvinyl chloride solutions.[20] At present it is not possible to distinguish between these two alternatives.

Decrease in rigidity with increasing temperature must be due primarily to decrease in n_t. At the same time, the change is probably enhanced, at least near the melting point, by an increase in n_a, since the contributions to n_a from loose ends remain constant and those in the sol fraction should increase.

The decrease in rigidity with decreasing average molecular weight is clearly not due solely to the increase in loose ends, since in this case the total number of bonds should be constant and either G or $\sqrt{G}$ should be a linear function[19] of $1/M_n$. The total number of bonds evidently varies with average molecular weight, and with molecular weight distribution. Further work will be needed to explain the form of the empirical relationship given in equation (1).

(20) P. Doty, H. Wagner and S. Singer, *J. Phys. Colloid Chem.*, **51**, 32 (1947).

Summary

1. The rigidity of a gelatin gel at a given temperature reaches a constant value more rapidly if the temperature is approached from below than from above.

2. For a sample of slight degradation (M_n = 45,000), the rigidity was closely proportional to the square of the concentration up to 60 g./l. At higher concentrations, it increased somewhat less rapidly; for a sample of higher degradation, somewhat more rapidly, than with the square of the concentration.

3. For all samples and at all concentrations, the rigidity decreased gradually with increasing temperature from 0° to the melting point.

4. The rigidity decreased markedly with increasing degradation, or decreasing average molecular weight.

5. An empirical equation for the dependence of rigidity on temperature and weight average molecular weight is given.

BOSTON, MASS. RECEIVED SEPTEMBER 30, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, PURDUE UNIVERSITY AGRICULTURAL EXPERIMENT STATION]

Chemical Composition and Properties of Guar Polysaccharides[1,2]

BY EILEEN HEYNE AND ROY L. WHISTLER

Endosperm of the guar seed consists principally of a galactomannan polysaccharide. It is thus analogous to the endosperm of locust beans which are widely used in commerce, and to galactomannans from other sources. Guar, a drouth-resistant legume of the genus *Cyamopsis*, is native to India where it is used for food and feed. The endosperm can be employed industrially in many ways, such as a size for paper and textiles, a dispersing agent, and a thickener. These uses have resulted in the recent growing of the guar plant in commercial quantities in the United States. As yet, however, little information is available with regard to the fundamental composition and structure of the endosperm polysaccharides. This report covers a preliminary investigation of the general composition and properties of the guar endosperm and particularly of the water soluble component which constitutes the major portion of the endosperm.

Experimental

Material.—Guar flour, produced by grinding the endosperm of the decorticated guar seed, was obtained through the kindness of General Mills, Inc. The grayish-white flour contained 0.60% nitrogen, 0.06% phosphorus, 1.06% ash and 1.5% ethanol solubles from twenty-four hours of Soxhlet extraction.

Analytical Methods.—Galactose anhydride content was determined by the following procedure: One gram of polysaccharide material ground to pass a 60-mesh sieve was dissolved in 150 ml. of 5% nitric acid by heating the mixture to 100°. After hydrolysis for three and one-half hours at this temperature, the solution was concentrated on a steam-bath to a volume of 25 ml. and 5.6 ml. of concentrated nitric acid was added to make a solution concentration of 25%. The solution was then oxidized according to the methods proposed by Tollens,[3] Van der Haar,[4] and Wise and Peterson.[5] The weight of the solution was reduced to 20 g. by heating on a steam-bath. Because of the high galactose content of the preparations, it was not found necessary to add the 500 mg. of pure mucic acid recommended by earlier works. The crystallization of mucic acid was allowed to proceed for forty-eight hours at a temperature of 0° ± 0.1° obtained with a large constant temperature bath. The solubility of mucic acid at 0° is 0.0175 g. per 100 ml. The amount of galactose anhydride equivalent to mucic acid was found by multiplying the weight of mucic acid obtained in this procedure by the factor 1.33. This factor was computed from data obtained on the analysis of a mixture of galactose and mannose combined in such proportions as to give the same yield of mucic acid as the guar samples.

(1) Journal Paper No. 319 of the Purdue University Agricultural Experiment Station.

(2) Paper presented before the Division of Sugar Chemistry and Technology at the 111th meeting of the American Chemical Society, Atlantic City, 1947.

(3) B. Tollens, *Ann.*, **227**, 223 (1885); **232**, 187 (1886).

(4) A. W. Van der Haar, *Biochem. Z.*, **81**, 263 (1917).

(5) L. E. Wise and F. C. Peterson, *Ind. Eng. Chem.*, **22**, 362 (1930).

Mannose anhydride content was determined through isolation of mannose phenylhydrazone by Nowotnowna's[6] modification of Schorger's[7] and Tollens'[8] procedure.

Both mannose and galactose are of the D-series as evidenced by the optical rotations of their derivatives. Mannose phenylhydrazone from guar showed the same optical mutarotation as the derivative of D-mannose[9] changing from $[\alpha]^{25}D$ +21 (1 hour) → −3 (33 hours) → +35 (216 hours) (*c*, 1 in pyridine). Melting point and mixed melting point with D-mannose phenylhydrazone were 182.5°. The benzimidazole of galactose prepared from guar hydrolyzate after D-mannose had been removed as the phenylhydrazone agreed with the known rotation of D-galactose benzimidazole[10] $[\alpha]^{25}D$ +43.3 (*c*, 0.5 in 5% citric acid).

Pentosans were determined by isolation of the furfural-phloroglucinol complex.[11]

Viscosities were determined at approximately 0.2% concentrations in 1 *N* sodium hydroxide solution at 25°. Solution of the sample was obtained by shaking it overnight in an atmosphere of nitrogen. Viscosity measurements were made twenty hours after the addition of alkali.

Water Fractionation.—An 0.8% aqueous suspension of guar flour was prepared by sprinkling 4-g. portions of the flour into 500-ml. portions of distilled water stirred in a Waring Blendor and by repeating this procedure until 8 liters were obtained. The viscous dispersion was autoclaved at 15 pounds pressure for three hours (*p*H 5.8) and immediately centrifuged in a supercentrifuge (40,000 r. p. m.) to remove the insoluble component. Longer periods of autoclaving did not appreciably change the ratio of soluble to insoluble fractions. The insoluble component was gradually added to ethanol stirred in a Waring Blendor, filtered, and stirred three further times with fresh portions of ethanol in the Blendor. After the final washing and filtration, the brown flocculent precipitate was dried over calcium chloride in a vacuum desiccator. The residue represented approximately 7.8% of guar flour.

The soluble component was recovered by adding an equal volume of ethanol with rapid stirring to the centrifugate; preferably the ethanol was added to small portions of solution stirred in a Waring Blendor. Precipitated material was filtered and washed four successive times with fresh portions of ethanol in the Blendor. The white fibrous precipitate was dried as described above and represented approximately 86.5% of the guar flour. A small amount of carbohydrate was not recovered by this method of treatment. The isolated material contained 0.15% nitrogen, 0.3% or less pentosan, 35.6% D-galactose anhydride and 63.1% D-mannose anhydride. The absence of glucose was indicated by the fact that after nitric acid oxidation of the hydrolyzate and separation of mucic acid, it was not possible to crystallize potassium acid saccharate from the mother liquor. Neither was it possible to isolate glucose as the benzimidazole from the sugar hydrolyzate. Intrinsic viscosity in 1 *N* sodium hydroxide was 5.57; $[\alpha]^{25}D$ +54.5 (*c*, 1 in 1 *N* sodium hydroxide). No uronic acid was detected by the quantitative method of Whistler, Martin and Harris.[12]

Ethanol Fractionation.—Subfractionation of the water soluble component was accomplished by gradual addition of ethanol to the aqueous centrifugate recovered from the separation of insoluble component. Ethanol was added drop by drop from a separatory funnel to 11 l. of the strongly stirred centrifugate. At the first appearance of precipitate the addition of ethanol was stopped and the mixture was supercentrifuged. The solution was allowed to stand for twenty-four hours to allow any additional precipitate to form. If a precipitate formed, the solution was allowed to stand an additional twenty-four hours. If no precipitate occurred, the solution was stirred and further addition of ethanol was made. In this manner a number of fractions were obtained as shown in Fig. 1.

The first precipitate occurred at an alcohol concentration of 20% by volume and the last at 40%. When the alcohol concentration reached 31%, an additional increase of 2% concentration brought about a slow but continuous precipitation which continued for three days. This precipitate which accumulated from 31 to 33% alcohol concentration represented 58% of the total soluble component. Approximately 93% of the soluble component was precipitated by ethanol. Precipitated fractions were washed through four fresh portions of ethanol and dried as described above.

After separation of the above individual fractions, the solution was concentrated under reduced pressure to 1.5 l. and 0.4 l. of ethanol was added. This procedure precipitated fraction number 15. The centrifugate from the precipitation was concentrated under reduced pressure to 280 ml. and 3 l. of ethanol was added to produce fraction number 16. On concentration of the final centrifugate to dryness on the steam bath, fraction 17 was obtained.

Preparation of Guaran.—Material of uniform chemical composition was separated from the water soluble component by discarding the first 10% of material which precipitated up to an ethanol concentration of 25% and then collecting all material which precipitated up to an ethanol concentration of 40% by volume. While only the first 3–5% of ethanol precipitated material appeared to be different from the central fraction, the first 10% which precipitated was discarded simply as a precaution against possible contamination of the central fraction. This material separating between ethanol concentrations of 25–40% and called guaran contained 34.5% D-galactose anhydride, 63.4% D-mannose anhydride and 0.1% nitrogen. The rotation was $[\alpha]^{25}D$ +53 (*c*, 1 in 1 *N* sodium hydroxide). Guaran is not oxidized by Fehling solution. Addition of small amounts of Fehling solution to aqueous solutions of guaran causes the precipitation of a polysaccharide–copper complex.

Acid Hydrolysis of Guaran.—A 1% water solution of guaran was prepared by dispersing 5.50 g. of guaran of known moisture content in 500 ml. of distilled water and by heating this dispersion in an oil-bath at 100° until solution was accomplished. Twenty-five per cent. by weight sulfuric acid was added to make a 1% acid solution. Hydrolysis was carried out at 100°. Rotation measurements were made on 15-ml. aliquots which were removed from the reaction flask and cooled to 25°. The specific rotation changed from an initial value of about +59 to a final value of +37.

Enzymatic Hydrolysis of Guaran.—A 1% water solution prepared as above was treated with a commercial diastase in the proportion of 0.1 g. of diastase for each 100 ml. of solution. Viscosity measurements taken in an Ostwald–Cannon–Fenske tube indicated a decrease to about one-third the initial value in a period of eighteen hours.

Esterification of Guaran.—Freshly precipitated guaran was freed of ethanol by stirring with glacial acetic acid for fifteen minutes and by filtering off the excess reagents. To the pretreated guaran was added 33 parts pyridine and 33 parts acetic anhydride. The mixture was heated in an oil-bath with stirring for four to five hours at 105°. The acetate was then precipitated by pouring the solution into excess ethanol stirred in a Waring Blendor. The precipitate was filtered and washed in the Blendor four successive times with fresh portions of ethanol. The final product was air dried. It was a white, very fibrous material closely resembling amylose triacetate in appearance.

(6) A. Nowotnowna, *Biochem. J.*, **30**, 2177 (1936).

(7) A. W. Schorger, *Ind. Eng. Chem.*, **9**, 748 (1917).

(8) B. Tollens, *Ber.*, **23**, 2990 (1890).

(9) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **53**, 4358 (1931).

(10) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 300 (1940).

(11) N. C. Pervier and R. A. Gortner, *Ind. Eng. Chem.*, **15**, 1167 (1923); B. Tollens and E. Krober, *J. Landw.*, **48**, 355 (1900); **49**, 7 (1901); see also Browne and Zerban, "Sugar Analysis," 3rd ed., p. 904.

(12) R. L. Whistler, A. R. Martin and M. Harris, *Bur. Standards J. Research*, **24**, 13 (1940).

Acetyl content, 44.8%; theory, 44.78%; $[\alpha]^{25}D$ 34° (*c*, 1 in chloroform), m. p. 224–226°.

The acetate could be cast into a film by standard methods.[13] The films were lustrous, clear, strong, and flexible. When placed in water at 95–100°, films containing 20% dibutyl phthalate plasticizer could be elongated 550%. The stretched films were birefringent in polarized light but showed no detectable crystallinity on examination with X-rays. When broken under stress, the elongated films developed many longitudinal cracks.

A 2% solution of guaran triacetate dissolved in chloroform was fractionally precipitated by dropwise addition of ethanol with rapid stirring. Seven fractions were obtained each of which possessed a constant rotation of $[\alpha]^{25}D$ 34° (*c*, 1 in chloroform).

Results and Discussion

Guar flour consists principally of carbohydrate material. There is present only 1.5% fatty material or other substances extractable by ethanol. The low nitrogen value indicates the presence of but 3.5–4.0% protein. Only very small amounts of phosphorus-containing compounds are present. From this principally carbohydrate material it is, therefore, not surprising that a water soluble polysaccharide can be easily separated in 86–7% yield. The polysaccharide contains 35.6% D-galactose anhydride and 63.1% D-mannose anhydride. No ketoses[14,15] or uronic acids have been detected in the polysaccharide material. The absence of uronic acids differentiates the polysaccharide from the great majority of plant gums and mucilages.

Information with regard to the homogeneity of the soluble component is obtained by ethanol fractionation of its aqueous solution and comparison of the various fractions. The per cent. of the material received in each fraction is shown in Fig. 1, and the amount precipitated at different concentrations of ethanol is shown in Fig. 2. Comparison of the various fractions as to mannose anhydride content, specific optical rotation, and intrinsic viscosity are shown in Figs. 3, 4 and 5, respectively. These graphs indicate that the first 2.5% of the soluble component to be precipitated is of slightly different composition and lower viscosity than the main portion of the soluble component whose fractions are similar. The lower mannose anhydride content (40.2%) of the first material precipitated may relate it to the water insoluble component which has a mannose anhydride content of 39.1%. It is possible that some of the insoluble component is solubilized by the autoclave treatment. The graphs also indicate that there is present in the soluble component about 3% of very low molecular weight material which judged by its low mannose anhydride content and negative rotation is quite different from the main polysaccharide fractions.

Collectively, the graphs suggest that the water soluble component of guar endosperm consists principally (90–95%) of a polysaccharide which precipitates in a narrow range of ethanol concentration. Further evidence for the homogeneity of the polysaccharide material is the observation that when its acetate in chloroform solution is fractionated into seven parts by gradual ethanol addition, all fractions are found to possess identical optical rotations. Since the polysaccharide contains 34.5% D-galactose anhydride and 63.4% D-mannose anhydride, it may properly be termed a galactomannan. For convenience in designation, this particular polysaccharide fraction in this and future papers is given the name "guaran."

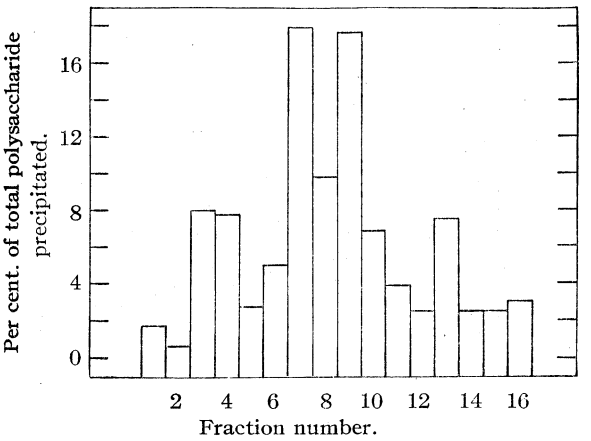


Fig. 1.—Per cent. of guar in each fraction.

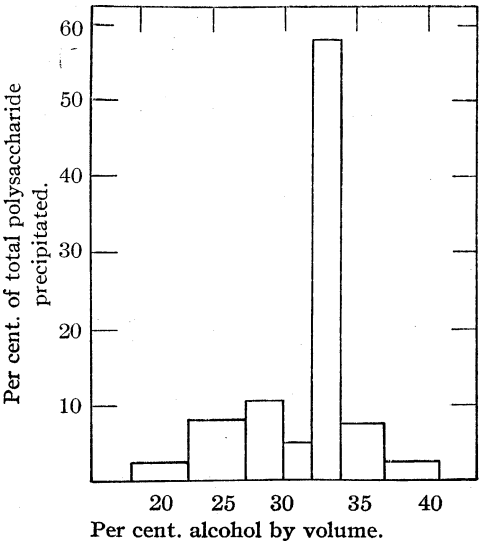


Fig. 2.—Per cent. polysaccharide precipitated at various alcohol concentrations.

On heating guaran in acid solution it undergoes hydrolysis and the specific optical rotation changes from a value of about +59 to +37. This change from a positive to a less positive value is indicative of the predominance of α-D-glycosidic links and is in agreement with the view of Lew and Gortner[16] who suggest the presence of alpha linkages in the galactomannan of carob bean endosperm. A further indication of the predominance of alpha link-

(13) R. L. Whistler and G. E. Hilbert, *Ind. Eng. Chem.*, **36**, 796 (1944).

(14) B. Th. Seliwanoff, *Ann. Chim. Applicata*, **21**, 535 (1931).

(15) R. Ofner, *Chem. Ztg.*, **53**, 682 (1929).

(16) B. W. Lew and R. A. Gortner, *Arch. Biochem.*, **1**, 325 (1943).

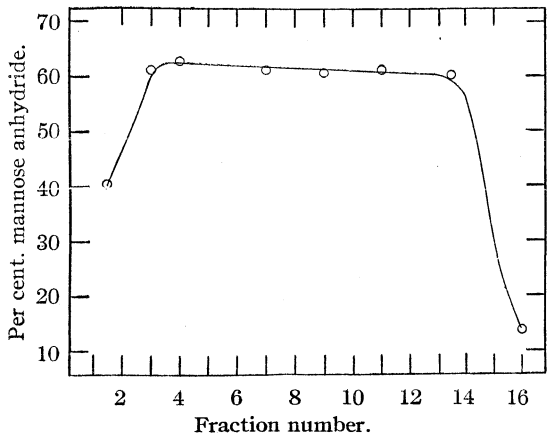


Fig. 3.—Per cent. mannose anhydride in guar fractions.

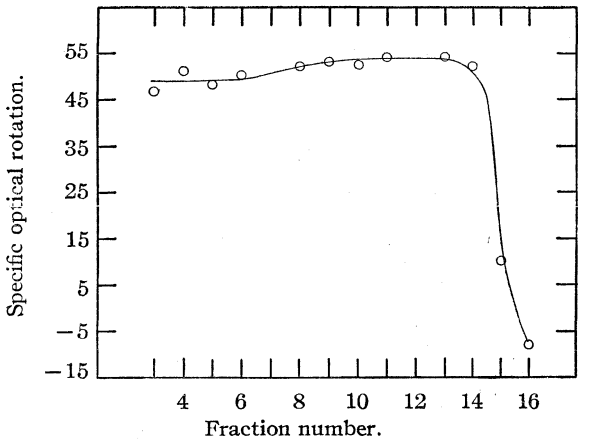


Fig. 4.—Specific optical rotation of guar fractions.

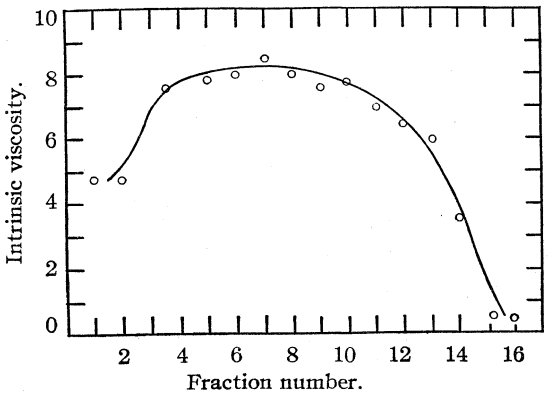


Fig. 5.—Intrinsic viscosity of guar fractions.

ages in guaran is the fact that its solutions are hydrolyzed by diastase, the viscosity decreasing to a value about one-third or less of the original.

Films produced by casting guaran acetates are clear, lustrous, strong, and pliable. Films plasticized with 20% dibutyl phthalate may be easily stretched in water at 100° to elongations of about 550%. During the stretching the film properties change from isotropic to anisotropic. The elongated films when broken under stress tend to shatter in lines parallel to the direction of elongation. Furthermore, a pronounced birefringence is developed during the process of elongation. These occurrences are all indications of the presence of anisodimensional and perhaps linear molecules which are orientated when the film is subjected to plastic flow. However, while the presence of linear molecules is indicated, X-ray analysis of the elongated films failed to give evidence of crystallinity. Films of uniform linear molecules would be expected to produce a fiber pattern or evidence some degree of crystallinity. Failure to obtain this effect may be accounted for by assuming that the guaran chains consist of D-galactose and D-mannose units arranged in random order or that the principal chain may possess branches of very short length. Therefore, although the chains become ordered when the films undergo plastic flow, an orderly three dimensional arrangement of sugar units is not brought about.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. J. Yearian for the X-ray work and to Mrs. Ann Kimmell and Mrs. Helen Gleason for their assistance in part of the analytical determinations.

Summary

Guar flour can be readily separated into a water soluble (86–87%) and a water insoluble component. The water soluble component contains only small amounts of nitrogen and phosphorus impurities.

By gradual addition of ethanol to an aqueous solution of the water soluble component, it is separated into 17 fractions. Analyses of the fractions indicate that the third to the twelfth fractions are identical as to composition and represent a galactomannan polysaccharide which contains 34.5% D-galactose anhydride and 63.4% D-mannose anhydride. This polysaccharide is given the name "guaran."

Presence of α-D-glycosidic linkages in guaran is indicated by its rapid acid hydrolysis with accompanying decrease in specific rotation and by its hydrolysis under the action of diastase.

Guaran may be esterified easily to the triacetate which may be cast into a strong, flexible film. On stretching to 550% the film becomes strongly birefringent but yields only an amorphous X-ray pattern. It is assumed that the guaran molecules are linear or highly anisodimensional but have either a random distribution of D-galactose and D-mannose units in the molecular chains or that the chains have very short branches.

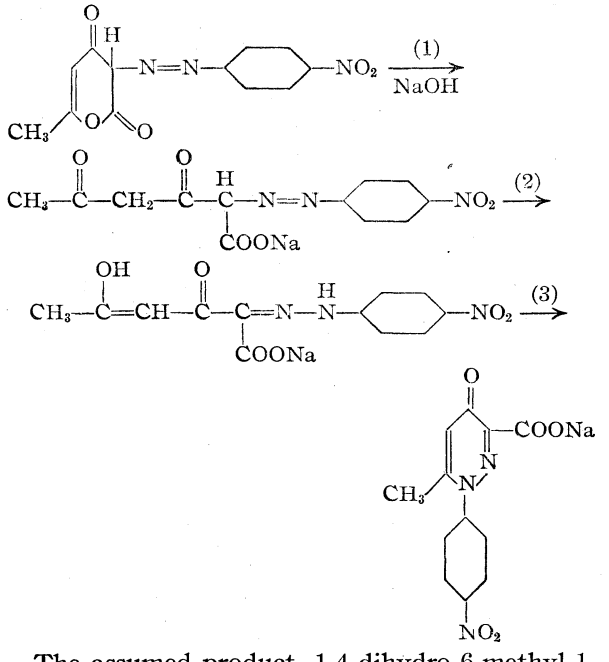
LAFAYETTE, INDIANA RECEIVED NOVEMBER 5, 1947

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORY OF GENERAL ANILINE AND FILM CORPORATION]

A New Synthesis of 4-Pyridazones

BY JACK F. MORGAN

During an investigation of azo dyes derived from substituted 1,2-pyran-2,4(3)-diones, it was observed that many of these dyes gradually fade in color when heated in dilute alkaline solutions. For example, when an aqueous alcohol solution of 6-methyl-3-*p*-nitrophenylazo-1,2-pyran-2,4(3)-dione was refluxed for one to two hours with an equi-molar amount of sodium hydroxide, a good yield of a very pale yellow carboxylic acid resulted. This acid had the same empirical formula as the original dye as shown by analysis and neutralization equivalent. Obviously, some sort of rearrangement of the original molecule had taken place. The apparent course of the reaction is shown below.



The assumed product, 1,4-dihydro-6-methyl-1-(*p*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic acid, is in agreement with the experimental product in regard to empirical formula, neutralization equivalent, expected color and expected melting point. In addition, the steps outlined above represent a logical sequence of events when considered in the light of known facts regarding the chemical behavior of similar compounds.

Step 1.—The 1,2-pyran-2,4(3)-dione ring is quite stable toward acid hydrolysis but is cleaved at the oxygen bridge in hot alkaline solutions.

Step 2.—Azo compounds derived from aliphatic active methylene compounds like acetoacetic ester are in tautomeric equilibrium with the corresponding hydrazones.[1]

(1) Frank C. Whitmore, "Organic Chemistry," D. Van Nostrand Co., New York, N. Y., p. 755.

Step 3.—Aryl hydrazones of this general type are known to undergo ring closure to form pyridazones.[2]

The conversion of the azo compound to the pyridazone may be carried out about equally well in either aqueous–alcohol or water alone. The alkali used may be sodium hydroxide, sodium carbonate or sodium bicarbonate. The reaction proceeds satisfactorily when excessive amounts of sodium bicarbonate are used though too much sodium hydroxide may have a harmful effect on yields.

The main advantage of the method of synthesis under discussion is that it leads to products not available by other reactions. Thus all the pyridazones prepared by this method were new and no other method was available for their preparation. This pyridazone synthesis seems to be fairly general in application though an exhaustive study was not made to determine its limitations. The reaction did fail when applied to 3-(2,5-dichlorophenylazo)-4-hydroxycoumarin.

The azo compounds required as starting materials were easily prepared from 1,2-pyran-2,4(3)-diones and the appropriate diazo compounds in either alkaline or slightly acid solution. The corresponding pyridazones are most conveniently prepared without isolation or purification of the azo intermediates.

General methods for the preparation of the 1,2-pyran-2,4(3)-diones used in this work are adequately described in the literature.[3,4,5,6] One of these compounds, 6-ethyl-1,2-pyran-2,4(3)-dione (m. p. 107–108°) had not previously been described in the literature. This product was prepared in 70% yield from 6-ethyl-3-propionyl-1,2-pyran-2,4(3)-dione[4,5] by the method of Collie.[3]

Experimental

The general procedure for preparing 4-pyridazones is illustrated by the following example which includes the preparation of the azo intermediate.

1,4-Dihydro-6-methyl-1-(*o*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic Acid.—*o*-Nitroaniline (11 g., 0.08 mole) was dissolved in a hot solution of concentrated hydrochloric acid (40 ml.) and water (50 ml.), poured onto ice and diazotized in the usual manner by rapid addition of a slight excess of sodium nitrite solution. This solution (250 ml.) was then added to a stirred solution of 6-methyl-1,2-pyran-2,4(3)-dione (10.8 g., 0.085 mole) and sodium carbonate (35 g.) in water (550 ml.). The coupling reaction was complete within fifteen minutes. The resultant slurry was stirred and heated at the reflux temperature for two and one-half hours. The hot clear solution was neutralized (*p*H 6–7) with acetic acid, treated with charcoal and filtered. The filtrate was then acidified (*p*H 2) with hydrochloric acid and cooled in ice. The

(2) A. Sonn, *Ann.*, **518**, 290 (1935).
(3) J. N. Collie, *J. Chem. Soc.*, **59**, 609 (1891).
(4) von Pechmann and Neger, *Ann.*, **273**, 201 (1893).
(5) Deshapande, *J. Indian Chem. Soc.*, **9**, 303–307 (1932).
(6) Panly and Lockemann, *Ber.*, **48**, 31 (1915).

TABLE I

1,4-DIHYDRO-4-OXO-3-PYRIDAZINECARBOXYLIC ACIDS

Substituent in 1-Position	6-Position	Yield,[a] %	M. p.,[b] °C., %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Nitrophenyl	Methyl	72	224[a]	52.37	3.30	15.27	52.36	3.24	15.14
3-Nitrophenyl	Methyl	87	224	52.37	3.30	15.27	52.97	3.69	15.46
4-Nitrophenyl	Methyl	92	247	52.37	3.30	15.27	51.96	3.52	15.15
2,5-Dichlorophenyl	Methyl	78	209	48.18	2.70	9.37	48.22	2.76	9.29
4-Chlorophenyl	Ethyl	87[c]	160			10.05			10.18
4-Chlorophenyl	Ethyl	85	158			10.05			10.11
3-Nitrophenyl	Phenyl	82	206			12.50			12.25
2-Chlorophenyl	Phenyl	63	218			8.62			8.48

[a] Crude product. [b] Recrystallized from alcohol or acetic acid. Melting points are uncorrected. [c] Prepared in 50% alcohol solution.

pale yellow crystals were removed by filtration, washed with water and dried to obtain 15.8 g. (72%) of 1,4-dihydro-6-methyl-1-(*o*-nitrophenyl)-4-oxo-3-pyridazinecarboxylic acid melting at 224° (uncor.).

Summary

A new synthesis of 4-pyridazones has been described. Alkaline hydrolysis of 6-alkyl-3-arylazo-1,2-pyran-2,4(3)-diones results in cleavage of the pyran-2,4(3)-dione nucleus followed by rearrangement to 1,4-dihydro-6-alkyl-1-aryl-4-oxo-3-pyridazinecarboxylic acids.

EASTON, PENNSYLVANIA RECEIVED FEBRUARY 19, 1948

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE]

Succinic Acid Derivatives of 4-Nitro-4′-aminodiphenylsulfone and of 4,4′-Diaminodiphenylsulfone

BY HUGO BAUER

Recent studies in experimental tuberculosis carried on in this institute[1] have demonstrated that potentiation is obtained in combined therapy with streptomycin and certain derivatives of 4,4′-diaminodiphenylsulfone. The presence of one free amino group appears to be essential for good action. It seemed desirable to test the chemotherapeutic properties of *n*-acylamide and ester derivatives. Compounds of this type were obtained by the preparation of succinic acid derivatives of diaminodiphenylsulfone. Furthermore, derivatives of succinic acid have been found to be active in tuberculosis.[2]

The action of succinic acid or succinic anhydride upon 4,4′-diaminodiphenylsulfone has been reported to lead to the formation of a disubstituted product.[3] An attempt was made to obtain the monosubstituted product by heating equivalent amounts of diaminodiphenylsulfone with succinic acid. From the reaction mixture 4-amino-4′-succinimidodiphenylsulfone (II) could be isolated in poor yield (12–13% of the calcd.).

Better results were obtained by starting with 4-nitro-4′-aminodiphenylsulfone. At a temperature of about 220°, it combines easily with succinic anhydride, yielding 4-nitro-4′-succinimidodiphenylsulfone (I). The products obtained from I by hydrolysis, esterification, ammonolysis and reduction are shown in Table I. The nitro group was reduced with hydrogen at atmospheric pressure in presence of Raney nickel catalyst, with excellent yields.

Compound II was tested[1c] alone and in combination with streptomycin in experimental tuberculosis in guinea pigs. The chemotherapeutic effectiveness was in the same range as that found for promin, but inferior to that of 4-amino-4′-*n*-propylaminodiphenylsulfone.[1b,c] Compound VII showed approximately the same activity in experimental tuberculosis as compound II.[4]

Compounds II, IV, VII and IX, also were active when tested in experimental pneumococcus infection in mice.[5]

Experimental

4-Nitro-4′-succinimidodiphenylsulfone (I).—A mixture of 27 g. of 4-nitro-4′-aminodiphenylsulfone and of 12 g. of succinic anhydride was heated in an oil-bath at 220° for thirty minutes. A clear orange melt resulted which crystallized upon cooling. The crude product melted at 230–232°. From hot glacial acetic acid cream-colored needles (29.5 g.) of m. p. 240–241° were obtained (calcd. 35 g.). The substance is soluble in hot acetone, hot glacial acetic acid, sparingly in hot dioxane.

4-Amino-4′-succinimidodiphenylsulfone (II).—Either 4,4′-diaminodiphenylsulfone or compound (I) was used

(1) M. I. Smith, *et al.*, (a) *Pub. Health Repts.*, **60**, 1129 (1945); (b) *Am. Rev. Tuberc.*, **55**, 366 (1947); (c) *Proc. Soc. Exptl. Biol. and Med.*, **64**, 261 (1947).

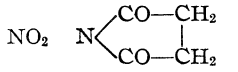
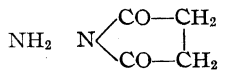
(2) V. C. Barry and P. A. McNalley, *Nature*, **156**, 48 (1945).

(3) W. H. Gray and B. C. Platt, *J. Chem. Soc.*, 42 (1942); M. S. Kharasch and O. Reinmuth, U. S. Patent 2,268,754, Jan. 6, 1942; H. Heymann and L. F. Fieser, THIS JOURNAL, **67**, 1979 (1945).

(4) Unpublished data; personal communication by W. T. McClosky of this Laboratory.

(5) Unpublished data; personal communication by J. M. Junge of this Laboratory.

TABLE I

No.	R	R′	Yield % of calcd.	M. p., uncor., °C.	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
I[b]	NO_2		86	240–241	53.33	53.46	3.36	3.61	7.78	7.54	8.90	8.94
II	NH_2		12.2 83	227–228	58.17	58.26	4.27	4.31	8.48	8.40	9.71	9.81
III[c]	NO_2	$NHCOCH_2CH_2CO_2H$	96.5	205 d.	50.79	50.93	3.73	4.01	7.40	7.20	8.47	8.53
IV[e]	NH_2	$NHCOCH_2CH_2CO_2H$	65	185–186	55.16	55.06	4.63	4.79	8.04	7.92	9.20	9.08
V[c]	NO_2	$NHCOCH_2CH_2CO_2C_2H_5$	95	223–224					6.89	6.67	7.89	7.79
VI[c]	NO_2	$NHCOCH_2CH_2CO_2CH_3$	80	225–226							8.17	8.10
VII	NH_2	$NHCOCH_2CH_2CO_2C_2H_5$	90	178	57.43	57.49	5.36	5.54	7.44	7.17	8.52	8.42
VIII	NO_2	$NHCOCH_2CH_2CONH_2$	95	242	50.92	50.31	4.01	4.35	11.14	10.83	8.50	8.48
IX	NH_2	$NHCOCH_2CH_2CONH_2$	90	140	53.92	53.90	5.09	5.12	11.79	11.26	9.00	8.84
X[b]	NO_2	$NHCOCH_2CH_2CONHC_6H_5$	62	225–226	58.27	58.24	4.22	4.40	9.27	9.01	7.07	6.91
XI	NH_2	$NHCOCH_2CH_2CONHC_6H_5$	85	257							7.68	7.58
XII[b]	NO_2	$NHCOCH_2CH_2CONHC_6H_{11}$	86	275–276							6.98	6.98
XIII	NH_2	$NHCOCH_2CH_2CONHC_6H_{11}$	94	241							7.46	7.37

[a] I am indebted to Mr. C. A. Kinser for the determination of carbon and hydrogen and (in part) of nitrogen. [b] Cream crystals. [c] Pale yellow crystals. [d] See ref. 6. [e] $+{}^1/_2H_2O$: m. p. 140–143°, H_2O calcd. 2.52, found 2.55; $+C_2H_5OH$: m. p. 185–186°, C_2H_5OH, calcd. 11.66, found 11.63; $+HCl + 2H_2O$: m. p. 202–204°, Cl calcd. 8.42, found 8.25.

as starting material. The first procedure was rather unsatisfactory and was abandoned in favor of the second.

1. A mixture of finely powdered 4,4′-diaminodiphenylsulfone (50 g.) and succinic acid (24 g.) was heated in an oil-bath at 200–210° for two to three hours, until the evaporation of water ceased and a homogeneous liquid was formed. After cooling, the cake was powdered. The reaction product consisted of a mixture of mono- and disubstituted derivatives, besides unreacted diaminodiphenylsulfone. Eight batches were combined and extracted with three liters of warm acetone. II was isolated by fractional crystallization from acetone and acetone-alcohol mixture. The fractions of m. p. 200–230° were combined (about 85 g.) and recrystallized from acetone, thus giving about 65 g. of material of m. p. 220–223°. The melting point was raised to 226–227° by repeated recrystallization.

Using succinic anhydride instead of succinic acid offered no advantage in preparing the compound.

2. Compound I (5 g.) was suspended in 100 cc. of 95% alcohol and shaken with Raney nickel catalyst in a hydrogen atmosphere at atmospheric pressure and room temperature. The calculated amount of hydrogen was taken up in seven to eight hours. (The time should be considerably shortened with application of higher pressures.) The reaction product was brought in solution by heating with the addition of acetone. From the filtered and concentrated solution, 3.8 g. of beautiful needles of m. p. 226–227° were obtained (83% of the calcd.). After recrystallization from acetone, the m. p. was 227–228°.

4-Nitro-4′-β-carboxypropionylaminodiphenylsulfone (III): Hydrolysis of I.—Compound I (7.2 g., $^1/_{50}$ mole) was heated to boiling with 100 cc. of 95% alcohol. With vigorous shaking, 5 cc. of 5 *N* sodium hydroxide solution (calcd. 4.0 cc.) was added until an almost complete solution was formed. The orange solution including a small amount of insoluble material, was cooled with running water, whereupon the sodium salt crystallized as a white crystalline powder. The sodium salt was isolated, dissolved in water, the solution was filtered and acidified with 2 *N* hydrochloric acid. A colorless, voluminous precipitate of the free acid separated which, after filtering and drying, weighed 7.3 g. and melted at 200–202°.

From alcohol clusters of fine, pale yellow needles of m. p. 205° were obtained.[6] The compound is soluble in sodium hydrogen carbonate solution. When heated with an excess of sodium hydroxide, it is split with formation of 4-nitro-4′-aminodiphenylsulfone.

4-Amino-4′-β-carboxypropionylaminodiphenylsulfone (IV).—Compound III was reduced with Raney nickel catalyst and hydrogen in alcoholic suspension. From alcohol colorless crystals, containing alcohol of crystallization, of m. p. 185–186° were obtained. The alcohol can be removed by heating at 110°. From hot water the compound crystallizes with 0.5 mole of water, showing m. p. 140–143°. It is soluble in ammonia; from this solution it is precipitated by dilute hydrochloric acid and dissolved by an excess of acid, when freshly precipitated. After short standing the base crystallizes again. The hydrochloride was obtained by addition of an excess of concentrated hydrochloric acid. It contained two moles of water and melted at 202–204°. For analysis the water was removed by heating *in vacuo* at 100° for two hours.

A yellow water-insoluble diazo compound was formed by diazotization of the suspension of IV in 2 *N* hydrochloric acid, which coupled with β-naphthol with a deep red color.

Compound IV was also obtained by hydrolysis of II with about 40% yield, when heated with 4 *N* hydrochloric acid for five minutes. Succinic acid was partially split off.

4-Nitro-4′-β-carboethoxypropionylaminodiphenylsulfone (V): 1. Alcoholysis of I.—Compound I (5 g.) was heated in a sealed tube with absolute alcohol and ten drops of concentrated hydrochloric acid at 200° for six hours. Small yellow crystals formed. The product was boiled with alcohol, the insoluble residue weighed 2.8 g. It was recrystallized from hot pyridine with addition of alcohol. Pale yellow crystals (2.3 g.) were obtained, m. p. 222–223°.

2. Esterification of III.—Compound III (10 g.) was suspended in 150 cc. of absolute ethyl alcohol and, without cooling, dry hydrochloric acid gas was passed through until the mixture was saturated. After cooling, the reaction mixture was poured in ice water and filtered. The crystalline product was suspended in water containing a little ammonia, filtered and dried; yield 10.7 g., m. p. 223°. When recrystallized as before it melted at 223–224°.

4-Nitro-4′-β-carbomethoxypropionylaminodiphenylsulfone (VI) was prepared according to the procedure V 2.

4-Amino-4′-β-carboethoxypropionylaminodiphenylsulfone (VII).—The procedure II 2 was used.

4-Nitro-4′-β-carbamylpropionylaminodiphenylsulfone (VIII): Ammonolysis of I.—Ammonolysis of I with al-

(6) Previously prepared by Q. Mingoia and F. Berti, *Arquiv. biol. (Sao Paolo)*, **27**, 55 (1943); *C. A.*, **39**, 2057 (1945); a m. p. of 194° is reported.

coholic ammonia gave the succinamide derivative, with admixture of the ethyl ester V.

Compound I (14.4 g.), finely powdered, was allowed to stand in saturated alcoholic ammonia for six days, with occasional shaking. The appearance changed while the heavy crystalline powder became more voluminous. When all heavy material had disappeared, the product was filtered off and washed with alcohol. It melted at 228–232°. After recrystallization from a mixture of pyridine and acetone it melted at 240°. The admixture of the ester was detected only after reduction (see below).

A pure preparation was obtained by ammonolysis with concentrated aqueous ammonium hydroxide. Compound I was warmed with 28% ammonium hydroxide in a stoppered bottle at 60° for two days. The product was washed with water and crystallized from pyridine. To remove pyridine of crystallization, the crystals were suspended in warm alcohol; the volume of the material increased considerably. After washing with alcohol and drying, the m. p. was 242°.

The compound was not soluble in alcohol or acetone, sparingly soluble in dioxane or glacial acetic acid, soluble in hot pyridine.

4-Amino-4′-β-carbamylpropionylaminodiphenylsulfone (IX).—Compound VIII, obtained by alcoholic ammonolysis, was reduced with Raney nickel catalyst and hydrogen in alcoholic suspension. The crude reduction product melted at 135°. Most of it was soluble in hot water. When recrystallized from hot water, containing a little ammonia, colorless fine needles were obtained of m. p. 140°. The solubility in water at 26° was 0.4%. The water-insoluble material was identified with VII by melting point and analysis.

4-Nitro-4′-β-phenylcarbamylpropionylaminodiphenylsulfone (X).—Compound I (13.5 g.) was refluxed with aniline for fourteen hours. After dilution with alcohol, 10.5 g. of material m. p. 205–210° was isolated. From hot acetone (charcoal) cream crystals of m. p. 225–226° were obtained. It is sparingly soluble in hot alcohol.

4-Amino-4′-β-phenylcarbamylpropionylaminodiphenylsulfone (XI) was prepared from X using the procedure II 2.

4-Nitro-4′-β-cyclohexylcarbamylpropionylaminodiphenylsulfone (XII).—Compound I (7.2 g.) was refluxed with cyclohexylamine for five hours. The yield was 8.7 g., the m. p. 276°. Recrystallized from glacial acetic acid, the cream needles melted at 275–276°. The compound was not soluble in alcohol or acetone, soluble in hot pyridine and hot glacial acetic acid.

4-Amino-4′-β-cyclohexylcarbamylpropionylaminodiphenylsulfone (XIII) was prepared from XII using the procedure II 2.

Summary

The preparation of succinic acid derivatives of 4-nitro-4′-aminodiphenylsulfone and of 4,4′-diaminodiphenylsulfone has been described. 4-Amino-4′-succinimidodiphenylsulfone (II) and 4′-amino-4′-β-carboethoxypropionylaminodiphenylsulfone (VII) were tested in experimental pneumonia and tuberculosis and found to be active. 4-Amino-4′-β-carboxypropionylaminodiphenylsulfone (IV) and 4-amino-4′-β-carbamylpropionylaminodiphenylsulfone (IX) were also active in experimental pneumococcus infections in mice.

RECEIVED[7] MARCH 29, 1948

(7) Original manuscript received October 30, 1947.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STATE UNIVERSITY OF IOWA

Kinetic Analysis of Irreversible Consecutive Reactions

BY JEN-YUAN CHIEN

The kinetics of consecutive reactions have been of considerable interest since even simple chemical change may go through a number of intermediate steps. When the rate constants of each step are comparable in magnitude, the integration of the kinetic equations presents considerable difficulties. Especially when reactions of high order in the intermediate steps are involved, the resulting system of non-linear differential equations can only be solved by successive approximations. Hill[1] has recently outlined a general scheme of such methods, but the amount of labor required would be tremendous because of the fact that the rate constants themselves are the unknown parameters sought. In this paper, certain types of two step irreversible consecutive reactions are considered, where the solution in closed form has been found. These solutions serve as an extension to the summary of formulas compiled by Moelwyn-Hughes.[2]

(1) T. L. Hill, THIS JOURNAL, **64**, 465 (1942).

(2) E. A. Moelwyn-Hughes, "Physical Chemistry," Cambridge University Press, Appendix 9, 1940, pp. 633–641.

Integration of the Kinetic Equations

I. Uni-unimolecular Reaction.—The general solution for a unimolecular reaction chain of any number of steps has been found.[3] For the particular case of a two-step reaction

$$\mathrm{A} \xrightarrow{k_1} \mathrm{B} \xrightarrow{k_2} \mathrm{C} \qquad (\mathrm{I})$$

starting with a_0 mole of A, the solution may be expressed in terms of a dimensionless variable τ and a dimensionless parameter κ in the following form, where A, B and C are concentrations of A, B and C, respectively, at t.

$$\left.\begin{aligned} A &= a_0\tau \\ B &= a_0\left(\frac{\tau^\kappa - \tau}{1-\kappa}\right) \\ C &= a_0 - A - B \end{aligned}\right\} \quad (1)$$

where

$$\tau = e^{-k_1 t} \text{ and } \kappa = k_2/k_1$$

II. Uni-bimolecular reaction.—Two separate cases are to be considered, one with a single

(3) H. Bateman, *Proc. Camb. Phil. Soc.*, **15**, 423 (1910).

starting material and the other with two starting materials.

$$\begin{array}{lcccc} \text{(a)} & \mathrm{A} & \xrightarrow{k_1} & \mathrm{B} & \\ & & & 2\mathrm{B} & \xrightarrow{k_2} \mathrm{C} \\ t = 0: & a_0 & & 0 & 0 \\ t \quad : & x_1 & & x_2 & x_3 \end{array} \qquad \text{(IIa)}$$

These kinetic equations describe the processes:

$$\begin{cases} \mathrm{d}x_1/\mathrm{d}t = -k_1x_1 & \text{(2i)} \\ \mathrm{d}x_2/\mathrm{d}t = k_1x_1 - k_2x_2^2 & \text{(2ii)} \\ \mathrm{d}x_3/\mathrm{d}t = {}^1/_2k_2x_2^2 & \text{(2iii)} \end{cases}$$

Integration of (2i) gives

$$x_1 = a_0e^{-k_1t} \qquad (3)$$

and then the Riccati equation (2ii) becomes

$$\mathrm{d}x_2/\mathrm{d}t = a_0k_1e^{-k_1t} - k_2x_2^2 \qquad (4)$$

On using the transformation

$$x_2(t) = \frac{1}{k_2u(t)}\frac{\mathrm{d}u(t)}{\mathrm{d}t} \qquad (5)$$

which transforms the non-linear first order equation (4) in x_2 into a linear second order equation in $u(t)$

$$\mathrm{d}^2u/\mathrm{d}t^2 - a_0k_1k_2e^{-k_1t}\,u = 0$$

A further change of the independent variable t to $\tau = e^{-k_1t}$ yields an equation of the Bessel type[4]

$$\frac{\mathrm{d}}{\mathrm{d}\tau}\left(\tau\frac{\mathrm{d}u}{\mathrm{d}\tau}\right) - \kappa u = 0,\ \kappa = a_0k_2/k_1 \qquad (6)$$

The solution of (6) is

$$u = \alpha J_0(2i\sqrt{\kappa\tau}) + \beta' iH_0^{(1)}(2i\sqrt{\kappa\tau})$$

where α,β' are arbitrary constants, $i = \sqrt{-1}$, and J_0, $H_0^{(1)}$ are Bessel functions of the first and third kind of order zero respectively. Then, by the recurrence relations of Bessel functions[5]

$$\frac{\mathrm{d}J_0(2i\sqrt{\kappa\tau})}{\mathrm{d}\tau} = -\sqrt{\frac{\kappa}{\tau}}\,iJ_1(2i\sqrt{\kappa\tau})$$

$$i\frac{\mathrm{d}H_0^{(1)}(2i\sqrt{\kappa\tau})}{\mathrm{d}\tau} = \sqrt{\frac{\kappa}{\tau}}\,H_1^{(1)}(2i\sqrt{\kappa\tau})$$

and hence the solution[6] for x_2 is, by (5)

$$x_2 = a_0\sqrt{\frac{\tau}{\kappa}}\,\frac{iJ_1(2i\sqrt{\kappa\tau}) - \beta H_1^{(1)}(2i\sqrt{\kappa\tau})}{J_0(2i\sqrt{\kappa\tau}) + \beta iH_0^{(1)}(2i\sqrt{\kappa\tau})} \qquad \text{(7i)}$$

where the arbitrary constant β is determined by the initial condition $x_2(0) = 0$, which gives

$$\beta = \frac{iJ_1(2i\sqrt{\kappa})}{H_1^{(1)}(2i\sqrt{\kappa})} \qquad \text{(7ii)}$$

For $x_3(t)$, use is made of (2ii) and (2iii), *i. e.*

$$x_3 = \frac{k_1}{2}\int_0^t x_1\mathrm{d}t - \frac{x_2}{2} = \frac{a_0}{2}(1-\tau) - \frac{x_2}{2}$$

The complete solution of the problem is summarized as

$$\left.\begin{aligned} A &= a_0\tau \\ B &= a_0\sqrt{\frac{\tau}{\kappa}}\,\frac{iJ_1(2i\sqrt{\kappa\tau}) - \beta H_1^{(1)}(2i\sqrt{\kappa\tau})}{J_0(2i\sqrt{\kappa\tau}) + \beta iH_0^{(1)}(2i\sqrt{\kappa\tau})} \\ C &= {}^1/_2(a_1 - A - B) \end{aligned}\right\} \qquad (8)$$

where

$$\tau = e^{-k_1t},\ \kappa = a_0k_2/k_1,\ \beta = iJ_1(2i\sqrt{\kappa})/H_1^{(1)}(2i\sqrt{\kappa})$$

$$\begin{array}{lcccc} \text{(b)} & \mathrm{A} & \xrightarrow{k_1} & \mathrm{B} & \\ & & & \mathrm{B}+\mathrm{D} & \xrightarrow{k_2} \mathrm{C} \\ t = 0: & a_0 & & 0 \quad d_0 & 0 \\ t \quad : & a_0 - x & & x - y \quad d_0 - y & y \end{array} \qquad \text{(IIb)}$$

The kinetic equations are

$$\begin{cases} \mathrm{d}(a_0 - x)/\mathrm{d}t = -k_1(a_0 - x) & \text{(9i)} \\ \mathrm{d}y/\mathrm{d}t = k_2(x - y)(d_0 - y) & \text{(9ii)} \end{cases}$$

Integration of (9i) gives

$$x = a_0(1 - e^{-k_1t})$$

then (9ii) becomes

$$\mathrm{d}y/\mathrm{d}t = k_2(a_0 - a_0e^{-k_1t} - y)(d_0 - y)$$

This is also a Riccati equation which in general cannot be solved. However, it is known that if one particular solution y_1 is found, the equation can be reduced to linear form by the transformation $y = y_1 \pm 1/v$. Following Bruins[7] $y_1 = d_0$ is obviously a solution, and

$$y = d_0 - 1/v(t)$$

leads to an equation for $v(t)$

$$\frac{\mathrm{d}v}{\mathrm{d}t} - a_0k_2(\lambda_0 - e^{-k_1t})\,v = k_2$$

where $\lambda_0 = (a_0 - d_0)/a_0$ The solution of this linear differential equation in v is

$$v = \tau^{-\lambda_0\kappa}\,e^{\kappa\tau}\left[-\frac{\kappa^{(1-\lambda_0\kappa)}}{a_0}\,\Gamma(\lambda_0\kappa,\kappa\tau) + \gamma\right] \qquad \text{(10i)}$$

where

$$\tau = e^{-k_1t},\quad \kappa = a_0k_2/k_1$$

and

$$\Gamma(n,x) = \int_0^x \xi^{n-1}\,e^{-\xi}\,\mathrm{d}\xi \qquad \text{(10ii)}$$

is the incomplete Γ-function.[8] Evaluation of the arbitrary constant γ by the initial condition gives

$$y = d_0\left[1 - \frac{\tau^{\lambda_0\kappa}\,e^{-\kappa\tau}}{e^{-\kappa} - (1-\lambda_0)\kappa^{(1-\lambda_0\kappa)}\{\Gamma(\lambda_0\kappa,\kappa\tau) - \Gamma(\lambda_0\kappa,\kappa)\}}\right] \qquad (11)$$

Hence

$$\left.\begin{aligned} A &= a_0\tau \\ D &= d_0\frac{\tau^{\lambda_0\kappa}\,e^{-\kappa\tau}}{e^{-\kappa} - (1-\lambda_0)\kappa^{(1-\lambda_0\kappa)}\{\Gamma(\lambda_0\kappa,\kappa\tau) - \Gamma(\lambda_0\kappa,\kappa)\}} \\ C &= d_0 - D \\ B &= a_0 - A - C \end{aligned}\right\} \qquad (12)$$

where

$$\tau = e^{-k_1t},\ \kappa = a_0k_2/k_1,\ \lambda_0 = (a_0 - d_0)/d_0$$

(4) *Cf.* T. v. Kármán and M. A. Biot, "Mathematical Methods in Engineering," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter II, p. 66.

(5) *Cf.* G. N. Watson, "A Treatise on the Theory of Bessel Functions," Cambridge University Press, Second Edition, 1944, pp. 45, 74.

(6) Tables of $J_0(ix)$, $-iJ_1(ix)$, $iH_0^{(1)}(ix)$ and $-H_1^{(1)}(ix)$ are given in E. Jahnke and F. Emde, "Tables of Functions," Dover Publications, New York, N. Y., 1943, pp. 224–229, 236–243.

(7) E. M. Bruins, *Rec. trav. chim.*, **59**, 739 (1940).

(8) Values of $I(x,n) = \Gamma(n,x)/\Gamma(n)$ have been tabulated by K. Pearson, "Tables of the Incomplete Γ-function," His Majesty's Stationery Office, London, 1922.

For the particular case when $a_0 = d_0$, it is necessary to return to (10i) and in this case

$$v = e^{\kappa\tau}\left[\frac{\kappa}{a_0}\{-Ei(-\kappa\tau) + Ei(-\alpha)\} + \gamma'\right]$$

where

$$-Ei(-x) = \int_x^\infty \frac{e^{-\xi}}{\xi}\,d\xi$$

is the exponential integral,[9] and α is some positive number.[10] Evaluation of γ' by the initial condition gives

$$D = a_0\frac{e^{-\kappa\tau}}{e^{-\kappa} + \kappa\{-Ei(-\kappa\tau) + Ei(-\kappa)\}} \qquad (12')$$

III. Bi-unimolecular Reaction.—One of the two possible cases of consecutive bi-unimolecular reactions is

$$\begin{array}{lccc} & 2A \xrightarrow{k_1} & B \xrightarrow{k_2} & C \\ t = 0: & a_0 & 0 & 0 \\ t\ \ : & a_0 - 2x & x - y & y \end{array} \qquad (III)$$

The kinetic equations are

$$\begin{cases} \dfrac{d(a_0 - 2x)}{dt} = -k_1(a_0 - 2x)^2 & (13i) \\ dy/dt = k_2(x - y) & (13ii) \end{cases}$$

Integration of (13i) gives

$$a_0 - 2x = a_0/(1 + a_0k_1t) \qquad (14)$$

Then (13ii) becomes

$$\frac{dy}{dt} + k_2y = \frac{a_0^2}{2}\frac{k_1k_2}{1 + a_0k_1t}\,t \qquad (15)$$

This linear equation has the solution

$$y = e^{-k_2t}\left[\frac{a_0^2}{2}k_1k_2\int^t \frac{te^{k_2t}}{1 + a_0k_1t}\,dt + \gamma\right]$$

The indefinite integral in the above expression for y can be evaluated by a change of variable. Let

$$\tau = 1 + a_0k_1t, \text{ and } \kappa = k_2/a_0k_1$$

then

$$\frac{a_0^2}{2}k_1k_2\int^t \frac{te^{k_2t}}{1 + a_0k_1t}\,dt = \frac{a_0}{2}\kappa e^{-\kappa}\left[\int^\tau e^{\kappa\tau}\,d\tau - \int^\tau \frac{e^{\kappa\tau}}{\tau}\,d\tau\right]$$
$$= \frac{a_0}{2}\left[e^{\kappa(\tau-1)} - \kappa e^{-\kappa}\,Ei(\kappa\tau) + \text{const.}\right]$$

where the exponential integral[11]

$$Ei(x) = \int_{-\infty}^x \frac{e^\xi}{\xi}\,d\xi$$

And therefore

$$y = \frac{a_0}{2}\left[1 - \kappa e^{-\kappa\tau}\,Ei(\kappa\tau) + \gamma'e\kappa(1 - \tau)\right]$$

Evaluation of the constant γ' by the initial condition $y(0) = 0$ gives

$$y = \frac{a_0}{2}\left[1 - e^{-\kappa(\tau-1)} - \kappa e^{-\kappa\tau}\{Ei(\kappa\tau) - Ei(\kappa)\}\right] \qquad (16)$$

Thus the complete solution[12] is

$$\left.\begin{aligned} A &= a_0/\tau \\ B &= \frac{a_0}{2}\left[e^{-\kappa(\tau-1)} + J\right] - \frac{A}{2} \\ C &= \frac{a_0}{2}\left[1 - e^{-\kappa(\tau-1)} - J\right] \end{aligned}\right\} \qquad (17)$$

where

$$\tau = 1 + a_0k_1t,\ \kappa = k_2/a_0k_1$$

and

$$J = \kappa e^{-\kappa\tau}\{Ei(\kappa\tau) - Ei(\kappa)\}$$

IV. Bi-bimolecular Reaction.—Two particular cases of reactions of this type where solutions to the kinetic equations have been found are

$$\begin{array}{lccc} \text{(a)} & 2A \xrightarrow{k_1} & B & \\ & & 2B \xrightarrow{k_2} & C \\ t = 0: & a_0 & 0 & 0 \\ t\ \ : & x_1 & x_2 & x_3 \end{array} \qquad (IVa)$$

The kinetic equations are

$$\begin{cases} dx_1/dt = -k_1x_1^2 & (18i) \\ \dfrac{dx_2}{dt} = \dfrac{k_1}{2}x_1^2 - k_2x_2^2 & (18ii) \\ \dfrac{dx_3}{dt} = \dfrac{k_2}{2}x_2^2 & (18iii) \end{cases}$$

Integration of (18i) gives

$$x_1 = \frac{a_0}{1 + a_0k_1t} \qquad (19)$$

Then

$$\frac{dx_2}{dt} = \frac{k_1}{2}\frac{a_0^2}{(1 + a_0k_1t)^2} - k_2x_2^2 \qquad (20)$$

This is also a Riccati equation[13] and inspection shows that

$$X_2 = \frac{\alpha a_0}{1 + a_0k_1t}$$

is a particular solution, where α is a constant so chosen as to satisfy the equation. Thus

$$\alpha = \frac{1}{2\kappa}(1 + \sqrt{1 + 2\kappa}),\quad \kappa = k_2/k_1$$

Let the general solution be

$$x_2 = X_2 + 1/v(t)$$

then the equation for v will be

$$dv/dt - 2k_2X_2v = k_2 \qquad (21)$$

The solution to this equation is

$$v = \tau^{\mu+1}\left[-\frac{\kappa}{a_0\mu}\tau^{-\mu} + \gamma\right]$$

where $\tau = 1 + a_0k_1t$ and $\mu = 2\alpha\kappa - 1 = \sqrt{1 + 2\kappa}$.

(9) "Tables of Sine Cosine and Exponential Integrals," Federal Works Agency, New York, 1940; or E. Jahnke and F. Emde, "Tables of Functions," *loc. cit.*, pp. 6–9.

(10) Here the indefinite integral is changed to a definite integral with a lower limit α by changing the additive constant γ' to avoid the difficulty of infinite Ei(0).

(11) In Jahnke and Emde, *loc. cit.*, this function is tabulated under the notation $\overline{\text{Ei}}(x)$.

(12) The solution of this type of reaction has been previously reported by A. A. Balandin and L. S. Leebenson, *Comp. rend. URSS.*, **39**, 22 (1943), but apparently they gave a wrong sign on J for both B and C.

(13) The equation (20) can also be solved by the following transformation

$$x_2 = \frac{1}{k_2u}\frac{du}{dt},\quad 1 + a_0k_1t = e^s$$

which leads to a second order linear equation in u with constant coefficients:

$$\frac{d^2u}{ds^2} - \frac{du}{ds} - \kappa u = 0,\quad \kappa = k_2/k_1$$

Determination of the arbitrary constant γ from the initial condition $x_2(0) = 0$ leads to

$$v = -\frac{\kappa\tau}{a_0\mu}\left[1 + \frac{\mu - 1}{\mu + 1}\tau^{\mu}\right] \tag{22}$$

Therefore

$$x_2 = \frac{a_0}{2}\frac{1}{\kappa\tau}\left[\mu + 1 - \frac{2\mu}{1 + \frac{\mu - 1}{\mu + 1}\tau^{\mu}}\right] \tag{23}$$

Integration of (18iii) by using (18ii) gives

$$x_3 = \frac{a_0}{4}\left(1 - \frac{1}{\tau}\right) - \frac{x_2}{2}$$

Thus the complete solution[14] is

$$\left.\begin{aligned} A &= a_0/\tau \\ B &= \frac{a_0}{2}\frac{1}{\kappa\tau}\left[\mu + 1 - \frac{2\mu}{1 + \frac{\mu - 1}{\mu + 1}\tau^{\mu}}\right] \\ C &= \frac{1}{2}\left[\frac{a_0}{2} - \frac{A}{2} - B\right] \end{aligned}\right\} \tag{24}$$

where

$$\tau = 1 + a_0k_1t, \quad \kappa = k_2/k_1, \quad \mu = \sqrt{1 + 2\kappa}$$

(b) $2\mathbf{A} \xrightarrow{k_1} \mathbf{B} + \mathbf{D} \xrightarrow{k_2} \mathbf{C}$ (IVb)

	A		B	D	C
$t = 0$:	a_0		0	d_0	0
t :	$a_0 - 2x$		$x - y$	$d_0 - y$	y

The kinetic equations are

$$\begin{cases} \mathrm{d}(a_0 - 2x)/\mathrm{d}t = -k_1(a_0 - 2x) & \text{(25i)} \\ \mathrm{d}y/\mathrm{d}t = k_2(x - y)(d_0 - y) & \text{(25ii)} \end{cases}$$

Integrating (25i) gives

$$a_0 - 2x = \frac{a_0}{1 + a_0k_1t}$$

Then (25ii) becomes

$$\frac{\mathrm{d}y}{\mathrm{d}t} = k_2\left(\frac{1}{2}\frac{a_0^2k_1t}{1 + a_0k_1t} - y\right)(d_0 - y) \tag{26}$$

As in the case IIb, $y_1 = d_0$ is obviously a solution of this Riccati equation, so

$$y = d_0 - 1/v(t)$$

leads to a linear equation in v

$$\frac{\mathrm{d}v}{\mathrm{d}t} - k_2\left(\frac{1}{2}\frac{a_0^2k_1t}{1 + a_0k_1t} - d_0\right)v = k_2$$

The solution for v is

$$v = e^{\lambda_0\kappa\tau}\tau^{-\kappa}\left[\frac{2\kappa}{a_0}\int^{\tau} e^{-\lambda_0\kappa\tau}\tau^{\kappa}\,\mathrm{d}\tau + \gamma\right]$$

or

$$v = e^{\lambda_0\kappa\tau}\tau^{-\kappa}\left[\frac{2}{a_0\lambda_0}(\lambda_0\kappa)^{-\kappa}\,\Gamma(\kappa + 1, \lambda_0\kappa\tau) + \gamma'\right] \tag{27}$$

where

$$\tau = 1 + a_0k_1t, \quad \kappa = k_2/2k_1, \quad \lambda_0 = (a_0 - 2d_0)/a_0$$

and $\Gamma(n,x)$ is the incomplete Γ-function defined previously by (10ii). By the initial condition $y(0) = 0$, the constant γ' is evaluated and then

$$y = d_0\left[1 - \frac{\tau^{\kappa}e^{-\tau}}{1 - \left(\frac{1 - \lambda_0}{\lambda_0}\right)(\lambda_0\kappa)^{\kappa}e^{\lambda_0\kappa}\{\Gamma(\kappa + 1, \lambda_0\kappa\tau) - \Gamma(\kappa + 1, \lambda_0\kappa)\}}\right] \tag{28}$$

Therefore the complete solution is

$$\left.\begin{aligned} A &= a_0/\tau \\ D &= d_0\frac{\tau^{\kappa}e^{-\tau}}{1 - \left(\frac{1 - \lambda_0}{\lambda}\right)(\lambda_0\kappa)^{\kappa}e^{\lambda_0\kappa}\{\Gamma(\kappa + 1, \lambda_0\kappa\tau) - \Gamma(\kappa + 1, \lambda_0\kappa)\}} \\ C &= d_0 - D \\ B &= {}^1/_2(a_0 - A) - C \end{aligned}\right\} \tag{29}$$

where

$$\tau = 1 + a_0k_1t, \quad \kappa = k_2/2k_1, \quad \lambda_0 = (a_0 - 2d_0)/a_0$$

For the special case when $\lambda_0 = 0$, *i. e.*, $a_0 = 2d_0$, equation (28) becomes indeterminate, but the solution is easily obtained from (27) where the integral gives an algebraic function of τ, and the particularly simple result

$$D = \frac{a_0}{2}\frac{(\kappa + 1)\tau^{\kappa}}{1 + \kappa\tau^{\kappa+1}} \tag{29'}$$

is obtained.

Discussion

All the solutions obtained for the two step irreversible consecutive reactions considered above have been expressed in terms of a dimensionless variable τ and some dimensionless parameters defined for each type of reaction in question. The general behavior of these solutions is shown in Figs. 1 and 2 for hypothetical reactions with $\kappa = 0.5$. For the reaction type IIb and IVb, equal initial concentrations for A and D are assumed. In these plots, $1/1 + a_0k_1t$ is chosen as abscissa. This particular choice appears to be most suitable to show the different characters of the reaction mechanism. It is obvious that if the first step is bimolecular, the decay curve for A will be linear. A unimolecular step will result in a change of the direction of curvature in the formation curve of both B and C, while no inflection point will be found on the curve if the steps involved are bimolecular. Therefore, such a plot will give directly an insight into the reaction mechanism. A linear time scale is also attached on the top of each curve.

Experimentally the aim is always the evaluation of the rate constants of each step and thus an assignment of possible reaction mechanism. In view of the difficulties involved in a simultaneous evaluation of the two rate constants, it appears desirable to follow the decay of the initial compound **A**. This will give the rate constant k_1 immediately. The evaluation of κ can then be made, by comparing the experimental formation curve of either the product C or the intermediate B, or the decay curve of the other starting compound D, to

(14) The solution of this problem has been considered by J. Hirniak, *Acta Physico-chimica URSS*, **14**, 613 (1941). He arrived at essentially the same result as (24) but through an entirely different and lengthy derivation. However, his b differs from μ of this paper, which should be identical, because he overlooked the fact that four molecules not two of **A** are consumed to give one molecule of **C**.

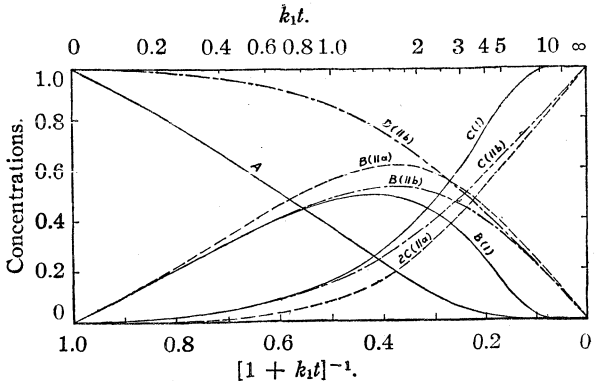


Fig. 1.—Uni-uni- and uni-bi-molecular reactions, $a_0 = 1$, $k = 0.5$.

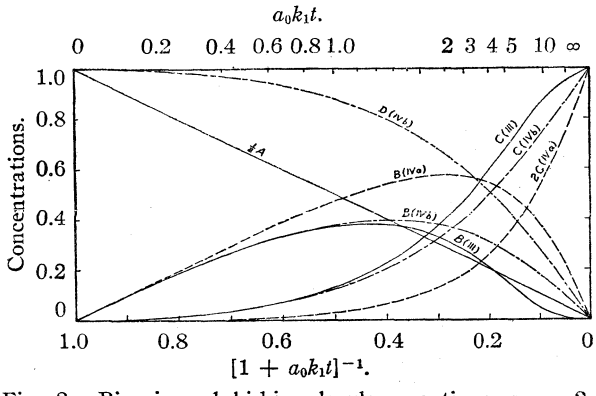


Fig. 2.—Bi-uni- and bi-bi-molecular reactions, $a_0 = 2$, $k = 0.5$.

a set of computed curves. It might be mentioned here that for the special case of reaction type I, Swain[15] has devised a graphical method of evaluating k_1 and k_2 from a single experimental curve of $(a_0 - A + C)$.

Experimental studies on the kinetics of consecutive reactions have been handicapped by their complexity. The present analysis shows definitely that a separate determination of the kinetic behavior of the initial step leads to an essential simplication of the problem. With the value of a_0 chosen as 1 or 2, depending on the reaction mechanism of the first step of the reaction, the graphs shown in Figs. 1 and 2, with different values of κ can be constructed and can then be used to analyze all experimental data in any given case. This procedure amounts to plotting all experimental values of concentrations relative to the concentration of the initial compound A and on a time scale of $(1 + a_0k_1t)^{-1}$. A similar procedure has been used for the study of concurrent consecutive reactions.[16]

It is interesting to note here that for the reaction type III, the formation curve of C as computed from equation (17) could well be represented by an empirical unimolecular equation with an apparent induction period. For example, for $a_0 = 2$ and $\kappa = 0.5$, the theoretical curve and an empirical equation like

$$C' = 1 - e^{-0.253(\tau - 1.50)} \qquad (30)$$

agree very well from 15 to 90% completion of the reaction as shown in Table I. This case corresponds to an apparent unimolecular rate constant of approximately half the true value of k_2. As κ decreases the agreement will be better, and finally when $a_0k_1 \longrightarrow \infty$

$$\lim_{a_0k_1 \to \infty} J = k_2e^{-k_2t} \lim_{a_0k_1 \to \infty} \frac{\int_{k_2/a_0k_1}^{k_2t} \frac{e^\xi}{\xi} d\xi}{a_0k_1} =$$

$$k_2e^{-k_2t} \lim_{a_0k_1 \to \infty} \frac{e^{k_2/a_0k_1}}{a_0k_1} = 0$$

Therefore

$$C \xrightarrow[a_0k_1 \to \infty]{} \frac{a_0}{2}(1 - e^{-k_2t})$$

which is the unimolecular formation of C from B as would be expected.

TABLE I

COMPARISON OF EQUATIONS (17) AND (30) FOR $a_0 = 2$ AND $\kappa = 0.5$

τ	C	C'	Δ%
1.0	0		
1.4	0.029		
1.8	.092	0.073	−21
2.2	.166	.162	−3.0
2.6	.242	.243	+0.4
3.0	.314	.316	+0.6
3.5	.398	.398	±0.0
4.0	.473	.468	−1.1
5.0	.593	.588	−0.8
6.0	.682	.680	−0.3
8.0	.794	.807	+1.6
10.0	.855	.884	+3.4
20.0	.943	.991	+5.1

In conclusion, it is hoped that the solutions of irreversible consecutive reactions here presented will be useful for the study of many organic reactions. Some of the results appear to be particularly simple to apply. The only limitation will lie in the reversibility of the reactions. For such cases the kinetic equations have not been integrated at the present moment.

Acknowledgment.—The author is indebted to Professor R. E. Langer of the Mathematics Department, University of Wisconsin, for valuable suggestions and to Professor G. Glockler for a discussion of the topic involved.

Summary

1. Solutions in closed form for some two step irreversible consecutive reactions are presented, with the results expressed in terms of a dimension-

(15) C. G. Swain, THIS JOURNAL, **66**, 1696 (1944).

(16) C. Potter and R. R. McLaughlin, *Can. J. Research*, **B25**, 405 (1947).

less variable and dimensionless parameters. Uni-bi-, bi-uni- and bi-bi-molecular reactions are the cases considered.

2. Experimental evaluation of the rate constants is discussed. A separate determination of the rate of decay of the initial substance is desirable for the interpretation of the mechanism and the evaluation of rate constants.

3. Practical applications of the results are limited only by the possible reversibility of the reaction steps involved.

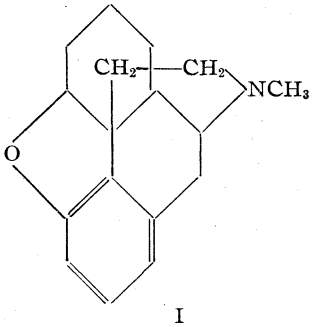
IOWA CITY, IOWA RECEIVED DECEMBER 9, 1947

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

The Synthesis of Ring Systems Related to Morphine. I. 9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene

BY MARSHALL GATES AND WILLIAM F. NEWHALL

A synthesis of the ring system (I) present in morphine and its close relatives has not yet been achieved although a number of interesting at-

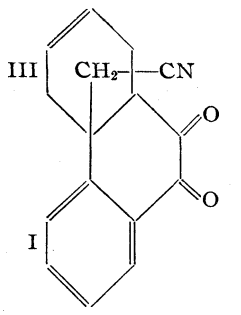


I

tempts have been reported.[1] We have been engaged for some time in an attempt to synthesize derivatives of such a ring system which might be compared with certain degradation products of the morphine alkaloids. Such a synthesis would offer a rigorous solution to the question of the point of attachment of the ethanamine side chain of morphine. The appearance in recent months of several publications[1a,c,d] bearing on this general problem has prompted us to offer our results for publication.

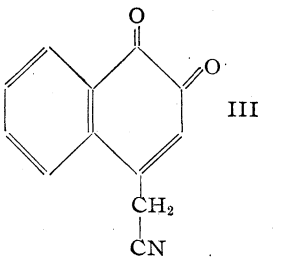
We have developed a convenient synthesis for 9,10 - dioxo - 13 - cyanomethyl - 5,8,9,10,13,14-hexahydrophenanthrene (II) which appears to be flexible enough to allow the introduction of substituents into rings I and III by suitable choice of starting materials.

The starting point for the preparation of this substance is the 4-(carbethoxycyanomethyl)-1,2-naphthoquinone of Sachs and Craveri,[2] which is available from ammonium 1,2-naphthoquinone-4-sulfonate by an improved procedure in 91% yield. This material is reduced, hydrolyzed and decarboxylated in one step giving 4-cyanomethyl-1,2-



II

naphthohydroquinone in 91% yield. Dichromate oxidation of this hydroquinone in glacial acetic acid affords 4-cyanomethyl-1,2-naphthoquinone (III)[3] in 83% yield.



The quinone III condenses readily with butadiene in acetic acid to give the diketone II. Excellent quality adduct is readily obtained in 56% yield.[4] Its formulation as II appears to be required by the fact that its azine IV, easily prepared by condensation with *o*-phenylenediamine, yields 1,2,3,4-dibenzophenazine (9,10-phenanthrenequinone azine) (V) on distillation with zinc dust.

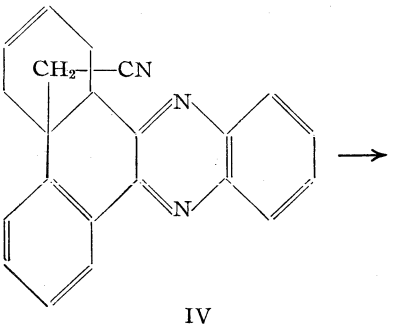
Experiments are in progress on the reduction of II by a variety of methods. We hope to effect a

(1) See, for example, (a) Holmes' recent [THIS JOURNAL, **69**, 2000 (1947)] extension of (b) Fieser and Holmes' [*ibid.*, **60**, 2548 (1938)] work; also the recent papers of (c) Horning, *ibid.*, **69**, 2929 (1947); (d) Newman, *ibid.*, **69**, 942 (1947), (e) Grewe, *Ber.*, **76**, 1072, 1076 (1943); (f) Ghosh and Robinson, *J. Chem. Soc.*, 506 (1944); (g) Ganguly, *Science and Culture*, **7**, 319 (1941); (h) Koelsch, THIS JOURNAL, **67**, 569 (1945), and others.

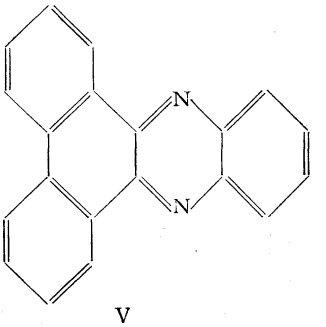
(2) Sachs and Craveri, *Ber.*, **38**, 3685 (1905).

(3) The position of the cyanomethyl group in this substance has been conclusively demonstrated by Miss Elizabeth R. Carmichael, working in this laboratory on another problem, by hydrolyzing and decarboxylating the azine of this substance to 4-methyl-1,2-naphthophenazine [Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939)] which was compared with an authentic sample kindly furnished us by Professor Louis F. Fieser of Harvard University.

(4) Compare the work of Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939), in which 2,3-dimethylbutadiene was shown to add slowly to 4-benzyl- and 4-dicarbethoxymethyl-1,2-naphthoquinones.



IV



V

ring closure to the 9 position through the nitrogen atom.

We are also investigating the condensation of III with other dienes, such as chloroprene, 2-ethoxybutadiene, piperylene, isoprene and others, and are in process of preparing derivatives of II and III carrying hydroxyl and alkoxyl groups in the 3 and 4 positions of II (5 and 6 positions of III).

We wish gratefully to acknowledge the help of a Frederick Gardner Cottrell Special Grant-in-aid from the Research Corporation with which a part of the expenses of this work have been defrayed.

Experimental Part[5]

4-Carbethoxycyanomethyl-1,2-naphthoquinone was prepared from ammonium 1,2-naphthoquinone-4-sulfonate[6] by a modification of the method of Sachs and Craveri.[2] A solution of 20 g. of ethyl cyanoacetate in 300 cc. of methanol was added with vigorous stirring to a solution of 30 g. of ammonium 1,2-naphthoquinone-4-sulfonate in 500 cc. of water. Thirty cc. of 25% sodium hydroxide was then added, and the resulting deep purple solution, on acidification to congo red with 12 *N* hydrochloric acid, yielded 28.8 g. (91%) of bright yellow material, m. p. 129.9–130.4°.

4-Cyanomethyl-1,2-naphthohydroquinone.—A solution of 20 g. of 4-carbethoxycyanomethyl-1,2-naphthoquinone in the minimum quantity of methanol was reduced by excess sodium hydrosulfite solution. After the color had been completely discharged, 30 cc. of 25% sodium hydroxide solution was added, and the mixture was refluxed until a test portion turned clear red with no purple on exposure to air. This required about seventy minutes. While still warm the mixture was acidified to congo red, and on cooling 13.4 g. (91%) of 4-cyanomethyl-1,2-naphthohydroquinone crystallized as colorless or pink needles, m. p. 220–227° with much decomposition. For analysis, a small sample was crystallized several times from dilute alcohol containing stannous chloride and a little hydrochloric acid and dried at 110° and 10^{-4} mm. Its melting point is not a reliable criterion of purity.

(5) All melting points are corrected.

(6) "Organic Syntheses," **21**, 91 (1941).

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.64; N, 6.63.

The hydroquinone is easily soluble in methanol, moderately soluble in cold acetic acid, and sparingly soluble in cold benzene. It dissolves in concentrated sulfuric acid with the production of a deep blue color changing to blue-green, then to amber-green, finally to a clear amber-yellow.

4-Cyanomethyl-1,2-naphthoquinone (III) was prepared by oxidation of the above hydroquinone as follows: A warm suspension of 13.4 g. of 4-cyanomethyl-1,2-naphthohydroquinone in 200 cc. of glacial acetic acid was treated with a solution of 6 g. of sodium dichromate in aqueous acetic acid. On cooling, the quinone separated as yellow needles (10.9 g., 83%), m. p. 190–194°, with decomposition. A small sample was recrystallized several times from alcohol and dried at 110° and 10^{-4} mm. for analysis, m. p. 191–194° with decomposition.

Anal. Calcd. for $C_{12}H_7O_2N$: C, 73.08; H, 3.58. Found: C, 73.22; H, 3.69.

The quinone is moderately soluble in methanol, sparingly soluble even in hot benzene, and moderately soluble in glacial acetic acid. Its solution in concentrated sulfuric acid is orange-yellow.

9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (II).—A suspension of 3.0 g. of 4-cyanomethyl-1,2-naphthoquinone in 40 cc. of glacial acetic acid and 20 cc. of butadiene was heated for twenty-two hours in a pressure bottle suspended in an oil-bath maintained at 80–85°. After cooling and opening, the excess butadiene was removed and the acetic acid decanted from the well-formed light tan prisms of adduct, m. p. 176–180°, which had separated. Crystallization from methanol with the aid of norite afforded 2.1 g. (56%) of colorless prisms, m. p. 181–182°. A small amount of additional material could be obtained from the filtrate. For analysis, a small sample was crystallized several times from methanol and dried at 110° and 10^{-4} mm., m. p. 185.6–186.6°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.21. Found: C, 76.40; H, 5.22.

The diketone II dissolves in concentrated sulfuric acid to give a pale yellow solution, and is soluble in aqueous alkali with the production of a yellow color. It is sparingly soluble in cold methanol and in cold acetic acid.

The azine of 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene was prepared by refluxing 100 mg. of the adduct described above with an equivalent amount of *o*-phenylenediamine in benzene containing a few drops of acetic acid. The solvent was removed and the residue in ether was extracted several times with dilute acid, twice with carbonate, dried and concentrated. The colorless solid residue (129 mg., m. p. 169–171.5°) was crystallized several times from methanol and dried at 110° and 10^{-4} mm. for analysis, 60 mg., m. p. 173.3–173.8°.

Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.70; H, 5.30; N, 12.99. Found: C, 81.78; H, 5.63; N, 13.09.

The azine is sparingly soluble in cold benzene, moderately soluble in methanol.

Zinc Dust Distillation of the Azine of 9,10-Dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene.—The azine of III (60 mg.), intimately mixed with zinc dust was heated at 350° (salt-bath) at atmospheric pressure for one hour in a microsublimation apparatus. During this time a sublimate of bright yellow crystals (21 mg., m. p. 193–206°) appeared on the cold finger. Several recrystallizations from alcohol yielded 4 mg. of pale yellow needles, m. p. 223.4–223.9°, whose mixed m. p. with 9,10-phenanthrenequinone azine of m. p. 223.9–224.4° was 223.4–224.9°.

Summary

A convenient preparation of 9,10-dioxo-13-

cyanomethyl - 5,8,9,10,13,14 - hexahydrophenanthrene as an intermediate and model compound for the synthesis of substances containing the morphine ring system has been developed.

BRYN MAWR, PENNSYLVANIA
RECEIVED FEBRUARY 24, 1948

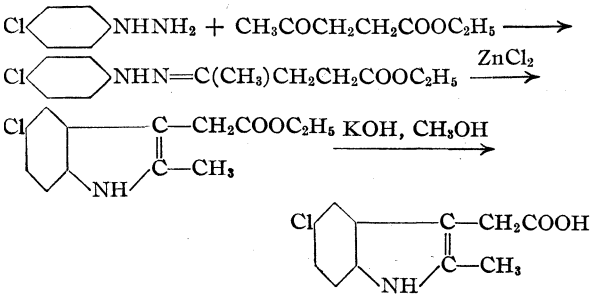
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Amino Acid Conversion Products. IV. Some Substituted 3-Indoleacetic Acids and Some Substituted Phenylhydrazones of β-Formylpropionic Acid[1]

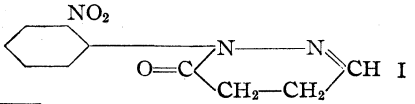
BY FRANK J. STEVENS[2] AND SIDNEY W. FOX

The natural plant growth hormone, 3-indoleacetic acid[3] (*heteroauxin*), and the substituted phenoxyacetic acids[4] have received much attention as stimulants of plant growth. A search of the literature does not reveal many syntheses of indoleacetic acid derivatives for phytological studies. The indoleacetic acid derivatives containing the types of substitution which have been useful in the phenoxyacetic acid series, are of especial interest. The present paper deals with the preparation of a number of such substances.

For the compounds reported here, the reactions involved are typified by the sequence below. In this example, the chlorophenylhydrazone of levulinic ester was converted *via* Fischer's ring closure[5] to the substituted indoleacetic acid



In attempts to cyclize β-formylpropionic acid phenylhydrazones, there was obtained in some cases an anhydride of the type reported as a by-product by Fischer in his experiments on cyclization of the phenylhydrazone of levulinic acid.[6] In the present study, ring closure of this type was obtained with the phenylhydrazone and *o*-nitrophenylhydrazone of β-formylpropionic acid. The product in the case of the nitrophenylhydrazone was 4,5-dihydro-2-(*o*-nitrophenyl)-3(2)-pyridazone, represented by I.



Of the compounds prepared in the present series, the 2-methyl-5-chloro derivative was more active in preliminary Pea Tests[7] than the 2-methyl-5-chloro and 2-methyl-7-chloro or 2-methyl-5,7-dichloro derivatives of 3-indoleacetic acid.

The indoleacetic acids reported all are substituted in the 2-position. For the corresponding unsubstituted indoleacetic acids obtained from β-formylpropionic acid, only the phenylhydrazones are recorded here. Ring closure has not been effected as readily with these latter compounds as with the derivatives of levulinic acid. The synthesis of indoleacetic acid itself, however, has been accomplished, and work is continuing on this series.

Experimental

All m.p.'s were corrected.

All nitrogen analyses were made by the micro Dumas method.

Levulinic Acid *o*-Nitrophenylhydrazone.—A hot solution of 7.65 g. (0.05 mole) of *o*-nitrophenylhydrazine[8] in 150 cc. of 20% acetic acid was added to 5.8 g. (0.05 mole) of levulinic acid (stores) in 200 cc. of hot water. The red-orange oil which precipitated crystallized upon cooling; yield 10.2 g. (81%). The solid was recrystallized from ethanol with the addition of water; m. p. 149–150°. Two more such recrystallizations raised the m. p. to 150–150.5°.

Anal. Calcd. for $C_{11}H_{13}O_4N_3$: N, 16.7. Found: N, 16.9, 16.3.

Ethyl Levulinate *o*-Nitrophenylhydrazone.—Dry hydrogen chloride was bubbled rapidly into a solution of 1.00 g. (0.0040 mole) of levulinic acid *o*-nitrophenylhydrazone in 60 cc. of absolute ethanol, and the solution was refluxed for two hours. The preparation was diluted with 200 cc. of water and extracted with four 50-cc. portions of ether. The combined ether extracts were washed with sodium bicarbonate solution and water. After drying with Drierite the ether was distilled off and the residue was recrystallized from ethanol; yield 0.88 g. (80%), m. p. 57.5–58.5°. Recrystallization from ethanol with the addition of water gave orange crystals of m. p. 58.5–59°. A mixed m. p. with the ester prepared from ethyl levulinate[9] and *o*-nitrophenylhydrazine showed no depression.

Anal. Calcd. for $C_{13}H_{27}O_4N_3$: N, 15.1. Found: N, 14.9.

2-Methyl-7-nitro-3-indoleacetic Acid.—To 20.0 cc. of a saturated solution of zinc chloride in concentrated hydrochloric acid solution, 2.0 g. (0.0071 mole) of the ester hydrazone was added and the mixture was refluxed

---

(1) From the thesis submitted by Frank J. Stevens to the Graduate School of Iowa State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Department of Chemistry, Alabama Polytechnic Institute, Auburn, Ala.

(3) Thimann, *Ann. Rev. Biochem.*, **4**, 545 (1935).

(4) Zimmerman and Hitchcock, *Contrib. Boyce Thompson Inst.*, **12**, 321 (1941–1942).

(5) Fischer, *Ber.*, **19**, 1563 (1886).

(6) Fischer, *Ann.*, **236**, 147 (1886).

(7) Went and Thimann, "Phytohormones," Macmillan Company, New York, N. Y., 1937.

(8) Müller, Montigel and Reichstein, *Helv. Chim. Acta*, **20**, 1472 (1937).

(9) Grote, Kehrer and Tollens, *Ann.*, **206**, 221 (1881).

for one hour. The resultant solution was extracted with four 50-cc. portions of ether, and the combined extract was dried. The ether was distilled off and the residue refluxed with 25 cc. of 2% ethanolic sodium hydroxide for one hour. Twenty-five cc. of water was added and the alcohol was removed by distillation. The alkaline solution was then extracted with 100 cc. of ether, and the extract was discarded. The solution was made acid with dilute hydrochloric acid solution, and extracted with three 50-cc. portions of ether. The combined ether extracts were dried and the ether removed by distillation; yield 0.47 g. (28%), the material decomposed about 245°. Recrystallization from acetic acid with the addition of water gave a material that melted 265° (dec.). The substance was soluble in ethanol, acetic acid, and sodium bicarbonate solution, but insoluble in water.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: N, 12.0. Found: N, 11.9, 11.8.

Other treatments which were unsuccessfully tested for ring closure were: heating with zinc chloride alone, and in boiling xylene, and heating with aluminum chloride in hexane.

Ethyl Levulinate *o*-Chlorophenylhydrazone.—A hot solution of 17.9 g. (0.10 mole) of *o*-chlorophenylhydrazine hydrochloride,[10] 8.5 g. (0.104 mole) of sodium acetate, and 25 g. of acetic acid in 200 cc. of water was slowly added to 14.4 g. (0.10 mole) of ethyl levulinate in 300 cc. of hot water. The light yellow oil, which immediately precipitated, solidified after cooling. The precipitate was filtered and washed with water; yield 25.5 g. (95%). Recrystallization from ethanol with the addition of water gave a white crystalline precipitate of m. p. 58.5–59.5°. The material was unstable, however, and soon turned to a dark oil. Kögl and Kostermans[11] reported that levulinic acid *p*-tolylhydrazone behaved similarly. The chlorophenylhydrazone was not analyzed.

2-Methyl-7-chloro-3-indoleacetic Acid.—A mixture of 3.0 g. (0.012 mole) of freshly prepared *o*-chlorophenylhydrazone and 15 g. of zinc chloride was heated at 100° for one hour, and the melt was dissolved in 50 cc. of 1 *N* hydrochloric acid solution. The brown oil which separated was extracted with two 100-cc. portions of ether. The ether extract was dried with Drierite and evaporated. The residual brown oil was refluxed for forty minutes with 25 cc. of 10% methanolic potassium hydroxide.

After addition of 50-cc. of water, the methanol was removed under reduced pressure by distillation. The aqueous solution was extracted once with ether, and acidified with hydrochloric acid solution, whereupon a brown oil precipitated. This was taken up in ether and shaken with half-saturated sodium bicarbonate solution. The bicarbonate layer was separated and acidified. The brown oil which resulted was extracted from its aqueous suspension with four 50-cc. portions of ether. The combined ether extracts were dried with Drierite and the ether was distilled off under reduced pressure. The residue was dissolved in acetic acid, decolorized with Norit and concentrated in a vacuum desiccator over sodium hydroxide. The solid obtained was 0.8 g. (30%) with a m. p. of 157–159°. The material was recrystallized thrice from benzene, and once from benzene with addition of hexane after decolorization. There resulted white slender needles of m. p. 164–164.5°.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.06; H, 4.51; N, 6.26; neut. equiv., 223.5. Found: C, 59.45; H, 4.47; N, 6.12, 6.36; neut. equiv. (phenolphthalein), 226, 225. A 7.5-g. portion of ester hydrazone, treated as above, yielded 2.7 g. (43%) of crude product.

The products gave a test with Ehrlich reagent which was negative in the cold but positive upon warming.

Ethyl Levulinate *p*-Chlorophenylhydrazone.—This compound was prepared in 63% yield in the same way as the *o*-chlorophenylhydrazone by use of the *p*-chlorophenylhydrazine.[8] The unstable product, when freshly prepared, had a m. p. of 104–106°. An earlier preparation of this compound[12] recorded a m. p. of 112–113°.

2-Methyl-5-chloro-3-indoleacetic Acid.—Six grams (0.022 mole) of crude ester was mixed thoroughly with 36 g. of zinc chloride and heated in an oil-bath at 125–135° for one hour. The solidified melt was distributed between 80 cc. of 1 *N* hydrochloric acid and 100 cc. of ether. The acid layer was further extracted with ether until a negative test with Ehrlich reagent was obtained (three 100-cc. portions of ether). The combined ether extracts were evaporated, after drying, and the residue was refluxed for twenty minutes with a solution of 3.0 g. of potassium hydroxide in 25 cc. of methanol.

The solvent was diluted with 50 cc. of water, and the alcohol removed under vacuum. The solution was extracted with 100 cc. of ether and the extract was discarded. The solution was then acidified with hydrochloric acid and the oily liquid was extracted with ether until the indole test was negative. The substance was shaken from the ether into 100 cc. of half-saturated sodium bicarbonate solution, which was separated and carefully acidified. The oily precipitate was extracted with four 100-cc. portions of ether. The extract was dried and the ether was distilled off from a residue of 2.2 g. (45%) of m. p. 183–186° (dec.). Recrystallization from benzene with addition of hexane gave 1.8 g. of m. p. 190° (dec.). Another recrystallization did not raise the m. p.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.06; H, 4.51; N, 6.26; neut. equiv., 223.5. Found: C, 58.94; H, 4.34; N, 6.36, 6.37; neut. equiv., 221, 224.

The acid was soluble in alcohol, ether and benzene, insoluble in water and hexane.

Ethyl Levulinate 2,4-Dichlorophenylhydrazone.—A hot solution of 9.3 g. (0.044 mole) of 2,4-dichlorophenylhydrazine hydrochloride,[13] 30 g. of acetic acid and 4.5 g. of sodium acetate in 100 cc. of water was added to a solution of 7.5 g. (0.052 mole) of ethyl levulinate in 200 cc. of water. The light brown oil which separated crystallized on cooling. The crystals were collected, washed with ethanol, and dried in a vacuum desiccator. The yield was 12.2 g. (91%), m. p. 74–76° (dec.). This hydrazone, also, decomposed in the air.

2-Methyl-5,7-dichloro-3-indoleacetic Acid.—Ten grams (0.033 mole) of ester hydrazone was heated with 50 g. of anhydrous zinc chloride at 165–170° for one hour. The solidified melt was distributed between 100 cc. of ether and 100 cc. of 1 *N* hydrochloric acid. The acid solution was extracted with three 100-cc. portions of ether. The combined ether extracts were dried and the ether was evaporated. The residue was refluxed with 5 g. of potassium hydroxide dissolved in 50 cc. of methanol for twenty minutes. None of the extracts gave a positive indole test.

After addition of 50 cc. of water, the methanol was removed under reduced pressure. The basic solution was extracted with ether, and the extract discarded. The solution was then acidified with dilute hydrochloric acid and the oil which separated was extracted with three 100-cc. portions of ether. The combined extracts were shaken with 100 cc. of half-saturated sodium bicarbonate solution, the latter separated, carefully acidified, and extracted with three 100-cc. portions of ether. After drying, the extract was concentrated to 3.2 g. (38%) of solid of m. p. 215° (dec.). Recrystallization from benzene by addition of hexane raised the m. p. to 220–221° (dec.).

Anal. Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.16; H, 3.52; N, 5.43; neut. equiv., 258. Found: C, 50.81; H, 3.33; N, 5.42, 5.36; neut. equiv., 262, 260.

Substituted Phenylhydrazones of β-Formylpropionic Acid.—The phenylhydrazones of β-formylpropionic acid were prepared from the acid[14] with the phenylhydrazines

(10) Hewitt, *J. Chem. Soc.*, **59**, 209 (1891).

(11) Kögl and Kostermans, *Z. physiol. Chem.*, **235**, 215 (1935).

(12) Sah, Lei and Shen, *Sci. Repts. Natl. Tsing Hua Univ.*, [A] **2**, 7 (1933); *C. A.*, **27**, 4222 (1933).

(13) Chattaway and Pearse, *J. Chem. Soc.*, **107**, 33 (1915).

(14) Langheld, *Ber.*, **42**, 2371 (1909).

described above, in about 60% yield. The m. p.'s and N contents of those not found in the literature are presented in Table I.

TABLE I

PHENYLHYDRAZONES OF β-FORMYLPROPIONIC ACID

Substituents of phenylhydrazine	M. p., °C. cor., dec.	Nitrogen, % Calcd.	Found
2-Nitro	155–156	17.7	17.4 17.4
2-Chloro	180–185.5	12.4	12.3 12.2
2,4-Dichloro	181–182	10.7	10.4 10.6

4,5-Dihydro-2-(*o*-nitrophenyl)-3(2)-pyridazone.—One gram (0.0042 mole) of the *o*-nitrophenylhydrazone of β-formylpropionic acid was dissolved in concentrated sulfuric acid. After twenty-four hours at room temperature, the solution was poured into a large amount of water. The aqueous solution was extracted with ether, and the ether extract dried with Drierite. The ether was allowed to evaporate and the residue crystallized from hot benzene. There was obtained 0.5 g. (54%) of crystals of m. p. 99–102°. Several recrystallizations from ethanol with addition of water raised the m. p. to 101.5–102°. The compound was not soluble in 5% hydrochloric acid solution, nor immediately soluble in cold 5% sodium hydroxide solution. It dissolved slowly in cold, rapidly in hot, sodium hydroxide solution to give a deep red-brown solution. The color of the solution changed to yellow upon acidification. Analysis indicated this compound to be the pyridazone.

Anal. Calcd. for $C_{10}H_9O_3N_3$: N, 19.2. Found: N, 19.4, 19.2.

Acknowledgments.—Dr. S. W. Loo, now of the Botany Department of the University of Peking, was very helpful in the testing of the compounds. We are indebted to General Mills for a generous supply of technical grade glutamic acid.

Summary

The preparation of a series of substituted 2-methyl-3-indoleacetic acids and of a series of substituted phenylhydrazones of β-formylpropionic acid has been described.

AMES, IOWA RECEIVED[15] APRIL 8, 1948

(15) Original manuscript received July 10, 1947.

[CONTRIBUTION FROM PHILLIPS PETROLEUM COMPANY, RESEARCH DEPARTMENT]

Relative Rates of Propylation of Monoalkylbenzenes

BY FRANCIS E. CONDON

Repeated observations by many workers that monoalkylation of benzene is accompanied by considerable polyalkylation have indicated that aromatic alkylation, like halogenation[1] and nitration,[2] is faster for an alkylbenzene than for benzene.[3] As indicated by Francis and Reid,[4] the rate of alkylation of a monoalkylbenzene relative to that of benzene can be evaluated from the composition of the reaction mixture. Although they favored the view that the rates are equal, some of their calculations showed that, under some conditions, benzene appeared to be twice as readily ethylated as ethylbenzene.[5] They pointed out, however, that this may not represent the true relative reactivities of benzene and ethylbenzene because the reaction mixture was not homogeneous and because of the possibility of simultaneous dealkylation of polyethylbenzenes.

In the work reported herein, the rates of propylation of toluene, ethylbenzene, cumene and *t*-butylbenzene relative to the rate of propylation of benzene were determined, in competition-type experiments, in homogeneous reaction mixtures and under conditions which were shown to be ineffective for dealkylation of the polyisopropylbenzenes produced. In one series of runs, boron fluoride etherate, which is completely miscible with these hydrocarbons, was used as a catalyst. In other runs, aluminum chloride was the catalyst and nitromethane was the solvent.[6]

(1) de la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).

(2) Ingold, Lapworth, Rothstein and Ward, *ibid.*, 1959 (1931).

(3) See, for example, Fieser and Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, 1945, p. 535; Price, in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, 1946, p. 5.

(4) Francis and Reid, *Ind. Eng. Chem.*, **38**, 1194 (1946).

(5) Coincidentally, relative rates calculated from the data of Slanina, Sowa and Nieuwland, THIS JOURNAL, **57**, 1547 (1935), indicate that benzene is apparently about twice as readily propylated as cumene.

I. Experimental Part

Materials.—Commercial C. P. benzene and toluene were distilled, discarding the first and last ten per cents., approximately.

Ethylbenzene, *p*-cymene (both Eastman Kodak Co. White Label) and *t*-butylbenzene (from hydrogen fluoride alkylation of benzene with isobutylene) were distilled in a Podbielniak Hypercal column with Heligrid packing[7]; only middle fractions of constant boiling point were used.

Nitromethane from the Commercial Solvents Corporation was distilled from an ordinary Claisen flask and the first and last ten per cents., approximately, were discarded.

Boron fluoride etherate was obtained from Eastman Kodak Company. The formula $BF_3 \cdot (C_2H_5)_2O$ was assumed.

Reagent quality anhydrous aluminum chloride was used.

The propylene was a high-purity product of Phillips Petroleum Company.

Alkylation Procedure.—Alkylation was carried out in a 500-cc. flask provided with a mercury-sealed Hershberg stirrer,[8] an inlet tube for propylene, a thermometer, and a reflux condenser, the top of which communicated through a Drierite-filled drying tube with a water-bubbler that indicated any escape of propylene. The flask was charged with a mixture of 100–150 g. of aromatic hydrocarbons and boron fluoride etherate or nitromethane and aluminum chloride. The stirrer was started and the

(6) Schmerling, paper presented before the Petroleum Division, ACS Meeting, New York, September, 1947.

(7) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **13**, 639 (1941).

(8) Hershberg, *ibid.*, **8**, 313 (1936).

temperature of the mixture was adjusted to 40° by a water-bath. Propylene, dried with Drierite, was introduced above the surface of the mixture only as rapidly as it was absorbed. After two and one-half to five hours in the boron fluoride runs, or one-half to three hours in the aluminum chloride runs, the addition of propylene was stopped, and the catalyst was washed out with water and with sodium hydroxide solution. Enough of the latter was used to remove all nitromethane. After a final wash with water, the mixture was dried with calcium chloride. Tests showed that this rather extensive treatment did not alter the composition of mixtures of aromatic hydrocarbons; and recoveries after fractional distillation quite generally reached 96–97 mole per cent. of the aromatics charged.

Analytical Procedure.—The products were analyzed by fractional distillation in a Podbielniak Hypercal column. Cut points were selected on the basis of analyses of mixtures of known composition. A high-boiling residue, generally less than 10% of the material distilled, was not completely analyzed, but its molecular weight was determined cryoscopically in benzene or, in many cases, was estimated from its probable composition as a mixture of polyalkylbenzenes, so that the composition of the total mixture could be computed in mole fractions.

Calculations.—The relative rate of propylation (benzene = 1) was calculated for toluene, ethylbenzene and *t*-butylbenzene by the well-known formula[2]

$$k'/k = \log (c'/c_0')/\log (c/c_0)$$

derived from the rate equations for irreversible propylation

$$dc/dt = -k(C_3H_6)c \text{ and } dc'/dt = -k'(C_3H_6)c'$$

in which c_0 and c, and c_0' and c', are initial and final mole fractions of benzene, and of alkylbenzene, respectively, in the hydrocarbon part of the reaction mixture. The relative rate of propylation of cumene was evaluated from the formula

$$\log (c + c' - (k'/k)c') = (k'/k) \log c$$

which was derived (for a reaction mixture initially containing no cumene) from the rate equations

$$dc/dt = -k(C_3H_6)c \text{ and } dc'/dt = k(C_3H_6)c - k'(C_3H_6)c'$$

and which is equivalent to the formula derived by Francis and Reid.[4]

Tests for Dealkylation.—Three experiments were made to determine if dealkylation of polyisopropylbenzenes occurred during propylation of benzene, inasmuch as such dealkylation would lead to too low a relative rate of propylation of cumene.

Experiment 1.—A homogeneous mixture of benzene (508 g., 76.0 mole per cent.), polyisopropylbenzenes (mol. wt. = 200; mainly triisopropylbenzenes obtained by vacuum distillation of accumulated residues boiling above 215° from benzene–propylene alkylations) (125.5 g., 7.3 mole per cent.), nitromethane (83.0 g., 15.7 mole per cent.), and aluminum chloride (10.8 g., 1.0 mole per cent.) was stirred at 40° for several hours and samples were withdrawn at intervals for analysis. The results were

Time, minutes	0	33	95	181	323	555
Composition, wt. %						
Benzene	79.6	79.6	79.8	80.2	79.7	79.2
Diisopropylbenzenes	1.5	2.1	2.0	1.6	1.9	2.2
Residue	18.9	18.3	18.2	18.2	18.4	18.6

No cumene was found in any of the samples, nor did the composition of the mixture apparently change.

Experiment 2.—A homogeneous mixture of benzene (304.6 g., 59.9 mole per cent.), polyisopropylbenzenes (76.2 g., 5.8 mole per cent.), nitromethane (111.0 g., 27.9 mole per cent.), and aluminum chloride (55.7 g., 6.4 mole per cent.) was treated as in Expt. 1. The results of analysis of samples were

Time, minutes		0	33	136
Composition, wt. %	Benzene	80.0	77.9	76.3
	Cumene	..	2.4	5.1
	Diisopropylbenzenes	..	0.9	3.2
	Residue	20.0	18.8	15.4

Depropylation took place under these conditions. The conditions of this experiment were, however, more conducive to depropylation than the conditions used in the propylation experiments. The concentrations of both the polyisopropylbenzenes and the catalyst were higher than in the propylation runs.

Experiment 3.—A homogeneous mixture of benzene (61.3 mole per cent.), *p*-cymene (21.7 mole per cent.), nitromethane (15.8 mole per cent.), and aluminum chloride (1.2 mole per cent.) was stirred at 65° and propylene was passed into it for two hours. The catalyst was washed out with water and the nitromethane with sodium hydroxide solution, and the alkylate was dried and analyzed by fractional distillation. No toluene was found, indicating that depropylation of the cymene did not take place; furthermore, the recovered cymene was pure *p*-cymene, with no *o*- and no *m*-cymene, indicating that no depropylation of the isopropylcymenes produced in the reaction took place.

In addition, it is noteworthy that no xylenes were found among the products of propylation of toluene-containing mixtures, indicating that no demethylation took place during propylation; and no diethylbenzenes were found among the products of propylation of ethylbenzene-containing mixtures, indicating that no deëthylation took place.

II. Results

The results from 51 competition experiments are summarized in Table I. In the first row are averages of two runs each in which the reaction mix-

TABLE I

RELATIVE RATES OF PROPYLATION AT 40° (BENZENE = 1)

Catalyst	Toluene	Ethylbenzene	Cumene	*t*-Butylbenzene
Boron fluoride	2.09 ± 0.10	1.73 ± 0.06	....	1.23 ± 0.06
Aluminum chloride	2.10 ± 0.15	1.81 ± 0.14	1.69 ± 0.05	1.40 ± 0.16

tures contained 27 mole per cent. boron fluoride and 27 mole per cent. diethyl ether. In the second row are averages of from 7 runs in the case of *t*-butylbenzene to 19 runs in the case of cumene, for aluminum chloride concentrations of 1.0 to 7.7 mole per cent. and nitromethane concentrations of 12.7 to 42 mole per cent. No dependence of the rate ratios on either of these concentrations could be found in runs in which one was varied while the other was held constant, although the results for any one compound were quite scattered, as is indicated by the rather large average deviation from the mean. This scattering is attributable to limitations in the analytical method (fractional distillation). The fact that the relative rates were independent of the aluminum chloride concentration, within experimental error, whereas the rate of depropylation was demonstrated to be dependent on the aluminum chloride concentration (see Experimental Part), indicates that not enough depropylation was taking place in those runs in which the conditions were most favorable for it (high aluminum chloride concentration and long contact time) to influence detectably the apparent relative rates. (Noteworthy here are results of some preliminary attempts to measure relative rates of alkylation with isobutylene. It appeared that *t*-butylbenzene was three to six times as readily butylated as benzene when the aluminum chloride concentration was about 4 mole per cent. but 12–14 times as readily when the catalyst concentration was only 1.3 mole per cent. The lower apparent relative rate is attributable to a greater amount of dealkylation, which would be easier for a *t*-butyl than for an isopropyl group, in the presence of the greater catalyst concentration.)

III. Discussion

The relative rates of propylation of the alkylbenzenes listed in Table I are in the same order as their relative rates of chlorination and bromination.[1] In order to account for this order of reactivity, both steric hindrance in the ortho position, increasing with the size of the alkyl group, and a no-bond resonance involving the α-hydrogen atoms of the alkyl group have been suggested.[9]

(9) See Berliner and Bondhus, THIS JOURNAL, **68**, 2355 (1946), for a review and additional references.

The most important factor in propylation appears to be steric hindrance in the ortho positions. The propylation of toluene gives 31% *o*-, 25% *m*-, and 44% *p*-cymene,[10] and the propylation of cumene gives 7% *o*-, 43% *m*-, and 50% *p*-diisopropylbenzene[11]; and, relative to one position in benzene, the rate of propylation of toluene is $6 \times 2.10 = 12.6$, and that of cumene is $6 \times 1.69 = 10.1$; so that the relative rate of propylation of toluene in an ortho position is $12.6 \times 0.31/2 = 1.95$, and the relative rate of propylation of cumene in an ortho position is $10.1 \times 0.07/2 = 0.35$; similarly, the relative rates of propylation of toluene and cumene in a meta position are $12.6 \times 0.25/2 = 1.6$ and $10.1 \times 0.43/2 = 2.2$, respectively, and in the para position, $12.6 \times 0.44 = 5.5$ and $10.1 \times 0.50 = 5.1$, respectively.[12] That is, the rates of propylation in the meta and para positions are approximately the same for toluene and cumene, whereas the rate of propylation in an ortho position of cumene is only about one-sixth the rate of propylation in an ortho position of toluene, and the difference, which is attributable to steric hindrance, is sufficient to account for all the difference in reactivities of toluene and cumene.

Acknowledgment.—Phillips Petroleum Company made possible the publication of this work.

Summary

The relative rates of propylation of benzene, toluene, ethylbenzene, cumene and *t*-butylbenzene are 1, 2.1, 1.8, 1.7 and 1.4, respectively. Steric hindrance in the ortho positions, increasing with the size of the alkyl group, appears to be the principal cause of the differences in rates of propylation of the alkylbenzenes.

BARTLESVILLE, OKLAHOMA RECEIVED FEBRUARY 2, 1948

(10) Simons and Hart, *ibid.*, **69**, 979 (1947). Averages were taken of all the values reported.

(11) Melpolder, Woodbridge and Headington, *ibid.*, **70**, 935 (1948).

(12) It is supposed that the isomeric dialkylbenzenes are formed principally by direct alkylation at the various available positions, and not to any great extent by isomerization nor by dealkylation of trialkylbenzenes as suggested by Price and Ciskowski, *ibid.*, **60**, 2499 (1938).

[CONTRIBUTION NO. 241 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

Interchange Reactions of Orthothioformates and Mercaptoles

BY W. E. MOCHEL, C. L. AGRE[1] AND W. E. HANFORD[2]

Interchange reactions of carboxylic esters and alcohols have been known for some years,[3] and the related interchanges in the cases of ortho esters[4] and of ketals[5] have been reported. Work in this Laboratory has now shown that oxygen-for-sulfur interchanges in orthiothioformates and mercaptoles[6] can be readily carried out, furnishing a convenient means of preparation of orthoformates and ketals.[7] Thus, in the presence of a catalyst such as zinc chloride the following reactions take place.

$$HC(SC_2H_5)_3 + 3ROH \longrightarrow HC(OR)_3 + 3C_2H_5SH \quad (1)$$

$$(CH_3)_2C(SC_2H_5)_2 + 2ROH \longrightarrow (CH_3)_2C(OR)_2 + 2C_2H_5SH \quad (2)$$

Since the orthothioformates and mercaptoles are easily prepared in nearly quantitative yields, the corresponding orthoformates and ketals frequently can be prepared more easily by the above reactions than by more conventional means. These interchanges were found to be equilibrium reactions and can be shifted to give high yields of the desired ortho esters or ketals by removal of the low-boiling thiol. Evidence for the reverse of reaction (1) above exists in the reported preparation of an orthothioformate from ethanedithiol and ethyl orthoformate,[8] with the liberation of ethanol, but the equilibrium nature of the reaction was not demonstrated. These reactions are normally very slow, but they may be greatly accelerated by Friedel–Crafts type catalysts. While strong acids, such as sulfuric or *p*-toluenesulfonic, at elevated temperatures were found to decompose the oxygen ortho esters in some cases,[9] forming normal esters and the corresponding ethers, such catalysts were satisfactory for the preparation of ketals. However, the ketals should not be worked up in the presence of acid since they may be converted to unsaturated ethers.[10]

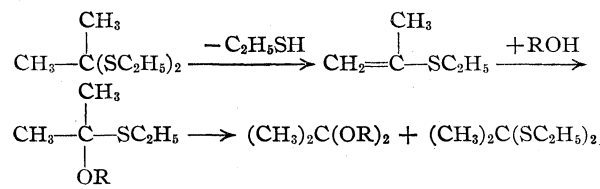
The mechanism of these reactions has not been established. However, from the type of catalyst involved it would appear that the mechanism is ionic in nature and may be identical with that for the acid-catalyzed formation of ketals from ketones and orthoformates. Post has proposed a mechanism for the latter reaction[11] and, by analogy, the following stepwise addition mechanism may be postulated for the reaction of an alcohol with ethyl orthothioformate.

$$HC(SC_2H_5)_3 + H^+ \rightleftharpoons HC(SC_2H_5)_2S(H^+)C_2H_5 \rightleftharpoons$$

$$C_2H_5SH + HC^+(SC_2H_5)_2 \xrightleftharpoons{ROH} HC(SC_2H_5)_2OR + H^+$$

$$HC(SC_2H_5)_2OR \rightleftharpoons HC(SC_2H_5)(OR)_2 \rightleftharpoons HC(OR)_3$$

In support of the proposed stepwise addition mechanism in the mercaptole interchange is the the isolation of a high-boiling, sulfur-containing compound believed to be the monothioketal. In the mercaptole reaction, however, there is the possibility of formation of an unsaturated sulfide by the elimination of one mole of thiol,[12] followed by the addition of alcohol to give a monothioketal[13] which could disproportionate to yield the ketal and mercaptole.[14] However, no sulfur compounds boiling in the range of the expected unsaturated sulfides were found in the reaction mixtures.



Experimental

Ethyl Orthoformate.—A mixture of 98 g. (0.5 mole) of ethyl orthothioformate[15] and 92 g. (2.0 moles) of absolute ethanol was refluxed with 2 g. of fused zinc chloride for ten hours while 90% of the theoretical amount of ethanethiol was slowly removed by distillation at 35–37° through a 20-inch Fenske ring-packed column with adjustable take-off head. The remaining material was distilled and, after removal of the excess ethanol, 49 g. (66% yield) of ethyl orthoformate was collected at 144–146°, $n^{24}D$ 1.3917.

Butyl Orthoformate.—A mixture of 39.2 g. (0.2 mole) of ethyl orthothioformate and 59 g. (0.8 mole) of *n*-butanol was refluxed with 1 g. of fused zinc chloride for six hours during which time 91% of the theoretical thiol was liberated and removed by distillation. The reaction mixture was cooled and washed with water to remove the catalyst. The product was dried with anhydrous sodium sulfate and distilled to yield 12 g. (46%) of butyl orthoformate distilling at 240–244°, $n^{23}D$ 1.4198.

From a mixture of 58.8 g. (0.3 mole) of ethyl orthothioformate and 89 g. (1.2 moles) of *n*-butanol refluxed

(1) Present address: St. Olaf College, Northfield, Minnesota.

(2) Present address: The M. W. Kellogg Company, New York, N. Y.

(3) Fehlandt and Adkins, THIS JOURNAL, **57**, 193 (1935); Hatch and Adkins, *ibid.*, **59**, 1694 (1937).

(4) (a) Hunter, *J. Chem. Soc.*, **125**, 1389 (1924); (b) Post and Erickson, THIS JOURNAL, **55**, 3851 (1933); (c) Helferich and Reimann, *Ber.*, **80**, 163 (1947).

(5) Post, THIS JOURNAL, **55**, 4176 (1933).

(6) Hanford and Mochel, U. S. Patent 2,229,651 (1941); Mochel, U. S. Patent 2,229,665 (1941).

(7) Interchange reactions of thiol esters with alcohols and, less readily, with thiols, were also demonstrated during the course of this research.

(8) Hurtley and Smiles, *J. Chem. Soc.*, 2263 (1926).

(9) *Cf.* Staudinger and Rathsam, *Helv. Chim. Acta*, **5**, 645 (1922).

(10) Killian, Hennion and Nieuwland, THIS JOURNAL, **57**, 544 (1935).

(11) Post, *J. Org. Chem.*, **5**, 244 (1940).

(12) Sporzynski, *Arch. Chem. Farm.*, **3**, 59 (1936).

(13) Norris, Verbanc and Hennion, THIS JOURNAL, **60**, 1159 (1938).

(14) Wenzel and Reid, *ibid.*, **59**, 1090 (1937).

(15) Prepared in nearly quantitative yield from ethyl formate and ethanethiol by the method of Holmberg, *Ber.*, **40**, 1740 (1907).

with 1 ml. of concentrated sulfuric acid for thirty minutes and then distilled there was obtained nearly the theoretical yield of ethanethiol at 35–40°. Fractionation of the residue directly gave 30 g. (98% yield) of *n*-butyl formate, b. p. 107–110°, $n^{25}D$ 1.4896, and 36 g. (93%) of *n*-butyl ether, b. p. 140–141°, $n^{25}D$ 1.4005.

2,2-Dimethoxybutane.—A mixture of 178 g. (1 mole) of 2,2-di-(ethylmercapto)-butane,[16] 128 g. (4 moles) of methanol and 3 g. of hydrogen chloride was heated under a 20-inch Fenske ring-packed column with adjustable take-off head, and ethanethiol was removed as formed. After fourteen hours, 119 g. of distillate had been removed at 35–40°. By iodine titration this was shown to contain 85% of ethanethiol, indicating that 82% of the theoretical ethanethiol had been removed. The residue was made very slightly alkaline with sodium methoxide and distilled. At 40–65° there was collected 98 g. of methanol and methanol/ketal binary. The column was then put under 100 mm. pressure and a fraction taken off at 50–51° (100 mm.). This consisted of 58 g. (49% yield) of 2,2-dimethoxybutane,[17] $n^{31}D$ 1.3878. An additional 5 g. was obtained by pouring the methanol fraction into a large volume of water, separating and distilling the organic layer. Assuming a stepwise exchange with a complete first step, the yield of ketal isolated was 83% of theoretical as indicated by thiol obtained. A high boiling fraction, 93–102° (100 m.), was obtained by further distillation. This contained sulfur and liberated more thiol on treatment with methanol and acid; it presumably was the 2-methoxy-2-(ethylmercapto)-butane but it was not purified and analyzed.

(16) Mann and Purdie, *J. Chem. Soc.*, 1549 (1935).

(17) Killian, Hennion and Nieuwland, THIS JOURNAL, **56**, 1384 (1934).

In another experiment using *p*-toluenesulfonic acid as catalyst and a 500% excess of methanol, a 91% yield of a 2,2-dimethoxybutane/methanol constant boiling mixture containing 25% of the ketal was obtained at 65°. The pure ketal was isolated by drowning the mixture in water, separating and distilling the organic layer.

Following the standard procedure for the preparation of mercaptoles, 2,2-di-(cyclohexylmercapto)-butane was prepared in 57% yield; b. p. 175–176° (3 mm.), $n^{23}D$ 1.5305.

Anal. Calcd. for $C_{16}H_{30}S_2$: S, 22.37. Found: S, 21.92.

In a 1-liter flask was placed 160 g. (0.55 mole) of 2,2-di-(cyclohexylmercapto)-butane, 110 ml. of methanol (500% excess) and 8.1 g. of dry *p*-toluenesulfonic acid. This mixture was heated under a small column and distillate slowly collected at 64°. After two and one-half hours an additional 700 ml. of methanol was added. At the end of five and one-half hours the temperature had reached 70° and the distillate amounted to 210 g. Redistillation of this distillate yielded 204 g. of a 2,2-dimethoxybutane/methanol mixture boiling at 65°, $n^{23}D$ 1.3330. This binary contained 10% of the ketal, or 31% of the theoretical yield.

Summary

It has been found that alcohols react with orthothioformates or mercaptoles in the presence of acidic catalysts to yield the corresponding orthoformates or ketals, or their decomposition products.

WILMINGTON 98, DELAWARE RECEIVED FEBRUARY 26, 1948

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Exchange Reaction between Methane and Deuteromethanes on Silica–Alumina Cracking Catalysts

BY G. PARRAVANO, E. F. HAMMEL[1] AND HUGH S. TAYLOR

The following research originated in a discussion at the Gibson Island Conference on Catalysis, June 1941, in which one of us (H. S. T.) suggested that the cracking of petroleum hydrocarbons on silica–alumina catalysts should be initiated by the breaking of, at least, one C–H bond in the hydrocarbon molecule. Otherwise, it was not possible for the carbon core of a hydrocarbon chain to come within the radius of chemical interaction with the catalyst surface. The plausibility of such a view is at once evident by inspection of a molecular model of a hydrocarbon molecule, as constructed with the Fisher–Hirschfelder atom models. At the same time, the suggestion was viewed by some with skepticisim, since it was believed that the idea could not be put to experimental test.

A study of the exchange reaction between hydrocarbons and deuterohydrocarbons in contact with silica–alumina catalysts permits, however, a direct and convincing test of the idea, and under quite stringent conditions.

It is generally agreed, from the known stability of the methane molecule, that if exchange can be demonstrated between methane and deuteromethanes at temperatures below those at which catalytic cracking of higher hydrocarbons is carried out, there can be no reasonable doubt that, in the cracking reaction, the C–H bonds must be readily and freely broken as postulated. The preliminary exploration of this reaction was carried out by Mr. E. F. Hammel in 1941. The quantitative examination of the process is recorded in the following paragraphs.

(1) Present address: P. O. Box 1663, Santa Fe, New Mexico.

Experimental Details

Materials.—Methane from a commercial tank was used, without purification. A mass spectrographic analysis showed a purity of ~96%. Deuteromethanes were prepared by means of the reaction between heavy water and aluminum carbide. The deuterium oxide employed came from our supply of heavy water. The deuterium oxide distilled over C. P. aluminum carbide, and the temperature was raised to 70°. At this temperature the reaction proceeds very smoothly. It was found that, at room temperature, no reaction takes place, in agreement with Urey and Price.[2] The gas collected showed with the mass spectrometer the following composition: CD_4 40%, CD_3H 5.7%, CH_2D 1%, CH_3D 0.3%, CH_4 53%.[3]

(2) H. C. Urey and D. Price, *J. Chem. Phys.*, **2**, 300 (1934).

(3) This gas composition is abnormal. It can only have been produced by successive interactions of H_2O and of D_2O with the carbide. Since the heavy water used was of high purity we can only conclude that the carbide sample used held tenaciously by adsorption the light water and that this reacted first before the heavy water came in contact with the catalyst.

Ethylene and hydrogen were supplied from commercial tanks, without any further purification.

The silica–alumina cracking catalyst, C-825-C, was a high-quality commercial silica–alumina catalyst kindly furnished by the M. W. Kellogg Company.

Analytical Procedure.—The progress of the reaction was followed by measurements of the intensity peaks for each mass. The mass spectrometer used was of the 60° Nier type.

Experimental Procedure.—Known amounts of the deuteromethane mixture were diluted with an equal amount of methane. The following composition resulted for the reacting mixture: CD_4 20.2%, CD_3H 2.8%, CD_2H_2 0.5%, CH_3D 0.15%, CH_4 76.2%. The mixture of reacting gases was introduced into a horizontal cylindrical Pyrex vessel of 100 cc. volume which contained a layer of catalyst. Equal amounts of gas were withdrawn from time to time and transferred to the analytical vessel.

All the runs were carried out at a pressure of 150 mm.

Experimental Results.—The data obtained at 345° are summarized in Table I, in which the change in concentration for masses 19 and 20 is expressed in relative values of the mass spectrometer intensity peaks. These data serve to show that the exchange takes place at that temperature. At 384° the exchange takes place much faster. By plotting the logarithms of the concentrations of masses 20 and 19 as a function of the time at the two temperatures 345 and 384° straight lines result from which the value for the activation energy, E, has been calculated to be 13 kcal.

Since the exchange reaction is indicative of dehydrogenation activity with the silica–alumina catalyst a special test was made of its hydrogenating activity. On the same catalyst it was found that the hydrogenation of the ethylenic double bond occurs very rapidly at 345°, using an equimolecular mixture of ethylene and hydrogen.

TABLE I

RATES OF EXCHANGE FOR CD_4 AND CHD_3

Temp. 345°; pressure 150 mm.; catalyst 0.450 g.

Hours								
0	6	24	48	72	96	120	168	192
Ratio Mass 20/Mass 19								
6.25	3.75	1.39	0.65	0.51	0.48	0.47	0.48	0.51

General Discussion

From the study of the interaction of methane and deuteromethanes on silica–alumina catalyst it is concluded that exchange of C–H bonds occurs freely in a methane molecule in contact with cracking catalysts. K. Morikawa, W. S. Benedict and H. S. Taylor[4] demonstrated that the same exchange also occurs between CH_4 and CD_4 on a nickel catalyst at temperatures as low as 138° with an activation energy of 19 kcal. The fact that the exchange of C–H bonds of a hydrocarbon molecule occurs at temperatures far below the cracking temperatures appears to be convincing evidence that the first step of a cracking process is a dehydrogenation of the hydrocarbon molecule. The dehydrogenated molecule can be better held and strongly attached to the catalyst surface by catalyst-carbon linkages. The second step, which occurs at higher temperature, is the C–C bond scission, and the consequent formation of lighter hydrocarbon fragments, which then evaporate from the catalyst as saturated or unsaturated molecules dependent on the hydrogen concentration on the surface. A direct test of these two steps in the cracking of hydrocarbons was also obtained by K. Morikawa, W. S. Benedict and H. S. Taylor[5] in the case of nickel catalyst, from kinetic measurements. They showed that in the case of ethane and propane the two reactions of exchange and C–C bond scission occur at different rates in separable temperature ranges, with different dependence on the pressure of hydrogen.

In the case of cracking catalysts it can therefore also be concluded that the activated adsorption of hydrocarbons is a dissociative adsorption. On the same catalyst the ethylenic double bond is easily hydrogenated.

Acknowledgment.—One of us (G. P.) wishes to express his appreciation for fellowship aid in the prosecution of this work from a postwar Italo-American Committee for Italian Scholars and for the opportunities thereby provided in the U. S. A.

Summary

1. The exchange reaction between methane and deuteromethanes on silica–alumina cracking catalysts occurs measurably at temperatures of 345° and higher.

2. The activation energy between 345 and 384° is 13 kcal.

3. A mechanism for the cracking process of hydrocarbons is postulated. This mechanism involves two steps: scission of C–H bonds, and then scission of C–C bonds.

4. Ethylene hydrogenation takes place on the same catalyst in the same temperature range.

PRINCETON, NEW JERSEY RECEIVED JANUARY 19, 1948

(4) Morikawa, Benedict and Taylor, THIS JOURNAL, **58**, 1445 (1936).

(5) Taylor, *et al.*, *ibid*, **58**, 1795 (1936).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Structure and Activity of the Chromium–Aluminum Oxide Catalyst System

BY ROBERT P. EISCHENS[1] AND P. W. SELWOOD

This paper describes the continuation of structure studies on the chromium–aluminum oxide catalyst system.[2] The change of surface area, as a function of chromium concentration, has been determined. Activity tests have been run, using the cyclization of *n*-heptane as the test reaction, and the results have been correlated with magnetic data previously reported.[3]

Experimental

Surface areas were obtained on the undiluted catalysts by low temperature nitrogen adsorption and the BET equation.

The activity tests were run on a series of catalysts which had been prepared by impregnating γ-alumina with chromic acid solution, followed by reducing with hydrogen.[3] The catalysts varied in concentration from 1.9% to 34.5% chromium after reduction. All catalysts with a chromium concentration of more than 2% were diluted down to 2% with γ-alumina before pelleting. The pellets were 4 mm. long and 5 mm. in diameter. The pelleted catalysts were heated at 500° for twenty hours as a pretreatment, and to burn off the stearic acid used as an aid in pelleting.

The catalytic apparatus was built according to specifications furnished by Dr. H. Pines of this Laboratory. The reactor block was made of aluminum-bronze and was heated electrically. Temperature control was obtained by means of the differential expansion of the block and a porcelain rod. A small bellows type pump was used.

The reactor was made of 20-mm. Pyrex tubing. It was 80 cm. long and had ground glass connections at both ends. The reactor top has two inlets, one for feed and one for the regeneration gas. A thermowell extended from the reactor top down into the catalyst bed. The lower 20 cm. of the reactor was filled with porcelain rings. The space above the catalyst bed was packed with Berl saddles.

The *n*-heptane, obtained from the Westvaco Chlorine Products Company, had a boiling point of 98.44°, a freezing point of −90.66°, a density of 0.68382 g. per ml. and a refractive index of 1.38779, 20°/D.

All tests were run at 490°. The temperature control was accurate to within two degrees. The space velocity was 50 cc. of liquid *n*-heptane per gram of chromium per hour. Since 25 g. of catalyst was used and the chromium concentration was 2%, this space velocity corresponds to a feed rate of 25 cc. per hour. The test duration was one hour.

The catalyst was regenerated and carbon determined by burning with air for ten hours at 490°. After the regeneration, hydrogen was passed through the reactor for one hour before each test was started.

The products were condensed in a water condenser and collected in a bulb cooled with ice-water. The noncondensable gases were collected over water in a calibrated bottle. The density of the gas was determined by comparing its weight with that of an equal volume of air under the same conditions.

The liquid product was analyzed for toluene by means of the refractive indices. It was assumed that everything in the product, except the toluene, had the same refractive index as *n*-heptane. A calibration curve for the analysis was obtained from a series of mixtures of toluene and pure *n*-heptane.

The results reported are the average of several runs. In each test the runs were repeated until three values were obtained in which the maximum difference was 2% toluene. This required at least four and usually five different runs because the activity of the first run in each series tended to be very low.

(1) Sinclair Refining Company Fellow in Chemistry.

(2) Eischens and Selwood, THIS JOURNAL, **69**, 2698 (1947).

(3) Eischens and Selwood, *ibid.*, **69**, 1590 (1947).

Results

The susceptibility isotherm for an impregnation type series is given in Fig. 1. This isotherm has been presented in a previous paper.

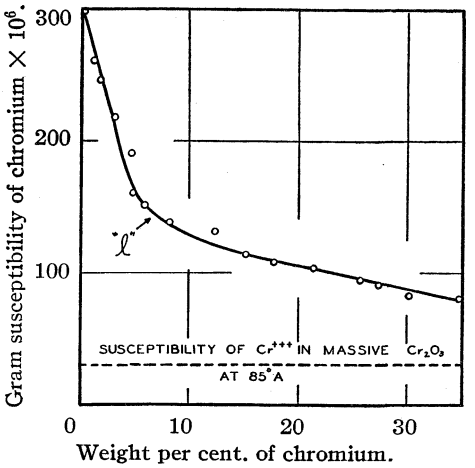


Fig. 1.—Susceptibility isotherm at 85° A. for chromia impregnated on alumina. The susceptibility of chromium in pure chromia at 85° A. is also shown.

The surface areas of catalysts of two impregnation series were measured. In one the carrier was γ-alumina; in the other it was *boehmite*. Figure 2 shows the results of these measurements.

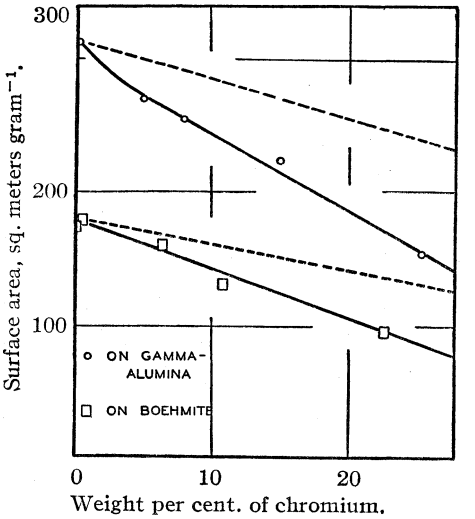


Fig. 2.—Effect of chromium concentration on surface area.

It is seen that the surface area falls off in practically a straight line for both series.

It has been shown that a point "1" of the isotherm only about one-ninth of the alumina surface could be covered by chromia and that the average chromium atom is in a crystallite about three atom layers thick.[3]

There are two possible pictures of the surface of the catalyst which could explain the fact that only a small part of the total surface is covered at the "1" point. In the first, the alumina surface is only covered in spots. Each of the spots is a crystal nucleus of chromium oxide. There are large areas of exposed alumina between the spots. A second possible representation of the surface would have a large part of the "nitrogen" area in regions inaccessible to the chromium. In this case the crystal nuclei might be touching.

The basic difference of these two extreme views lies in the manner in which they explain why only a small fraction of the alumina is covered. The first view assumes that there is enough attraction or lattice stability in the chromia nuclei so that the chromia will go together into piles rather than spread out evenly over the alumina surface. In the second case, the fraction of area covered represents all of the surface which the chromia is able to reach. The rest of the area is concealed in "caves" and "pores" and there is no exposed alumina.

If the chromia is gathered in piles on the alumina and the latter has large areas exposed, one would expect only a gradual decrease in the total area of the catalyst, as the chromium concentration is increased. At the "1" point only a small fraction of the alumina area would be covered and this decrease would be partially compensated by the area contributed by the chromia. If the entire available area were covered, it is probable that the chromia layer would cover and plug up some of the pores, making them inaccessible to the gas. In this case the area, as measured by the nitrogen, would decrease more rapidly before the "1" point than it would at higher concentrations. One would then expect a curve of area *versus* chromium concentration to have the same general shape as the susceptibility isotherm.

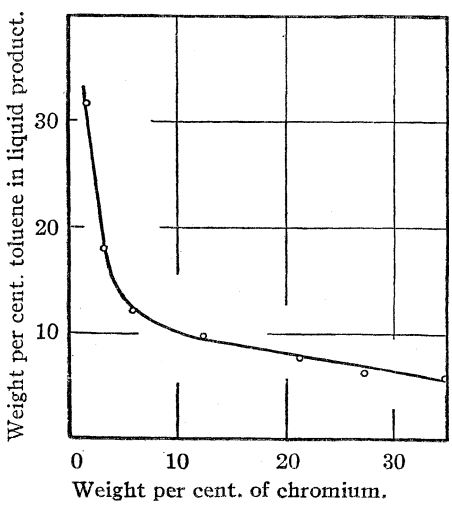


Fig. 3.—Catalytic activity as a function of chromium concentration.

The data presented in Fig. 2 shows that there is no sharp decrease in area in the low concentration region. It is, therefore, indicated that the view of the surface, as being covered with small piles of chromia, is the more nearly correct.

Since the surface area data are reported as square meters per gram of catalyst, one would expect a gradual dropping off of the area as the concentration of chromium is increased because the chromia contributes to the weight of the sample and probably has a much lower area than an equal weight of alumina.

If the assumption is made that the total area of the catalyst is due only to the alumina, one can calculate the apparent area per gram of alumina by dividing the observed area by the weight fraction of alumina. The results of these calculations are plotted by the dotted lines in Fig. 2. It is seen that, even with the above assumption, the apparent area per gram of alumina decreases as the chromium concentration is increased. This would indicate that more and more of the alumina area is covered as the concentration increases. Thus, there must be a spreading of the chromia clusters. The fact that these calculations are based on the probably invalid assumption that all of the area is due to the alumina does not invalidate the conclusion. The assumption is, in reality, the most severe test of the conclusion. If the chromia also contributes to the area, the alumina area drops off at a faster rate than indicated by the dotted line.

The results of the activity tests, reported as per cent. toluene in the liquid product, are given in Fig. 3. Pure alumina has no activity in this reaction. Since the magnetic data have been reported as susceptibility per gram of chromium, it was desirable to present the activity results so that a direct comparison could be made. To facilitate this, the same amount of chromium was used in each test. This also made it possible to have a constant space velocity without changing the pumping rate for the various samples.

On the average about 90% of the feed is recovered as liquid product. The carbon laydown accounts for a little less than 2%. Although the volume of gas formed appears to be roughly proportional to the amount of toluene in the liquid product, the weight per cent. of gas is not consistent. This is probably accounted for by the fact that small variations in the amount of cracking would not affect the volume of the gas nearly as much as they would affect the density. The cracking product gases have a much greater density than the hydrogen given off in the dehydrocyclization.

The supplementary data are given in Table I.

TABLE I

CATALYTIC ACTIVITY OF Cr_2O_3/Al_2O_3

Wt. % chromium[a]	Liters of gas[b]	Wt. % gas	Wt. % carbon[d]	Wt. % liq. prod.[d]	Wt. % toluene[c,d]
1.9/1.9	6.0	5.3	1.9	91	31.3
2.0/3.2	4.2	4.7	1.8	91	18.1
2.0/5.7	3.0	3.7	1.6	88	11.7
2.0/12.2	2.3	4.2	1.8	91	9.6
2.0/21.1	2.1	3.5	1.6	91	7.6
2.0/27.2	2.1	3.9	1.7	90	6.3
2.0/34.5	2.2	3.2	1.5	89	5.8

[a] The designation 2.0/5.7 means that the catalyst contained 2.0% Cr but that this was made by mechanically diluting a 5.7% Cr impregnate with an appropriate amount of γ-alumina. [b] 25°, 750 mm. pressure. [c] In liquid product. [d] The difference between 100 and the sum of columns 3, 4 and 5 is experimental error.

A comparison of Figs. 1 and 3 shows that there is apparently a close relationship between the activity of the chromia–alumina catalyst and the magnetic susceptibility of the chromium in the catalyst. It is important to remember that thus far this relationship has been shown to hold for a series of catalysts, the method of preparation of which is identical and which differ only in the concentrations of chromium. The only other catalysts tested were those for which the impregnation was carried out at different temperatures, as previously reported. In this case there also appeared to be a relationship between susceptibility and activity. However, these results were not extensive enough to warrant definite conclusions.

In order to discuss the relationship between the susceptibility and activity it is desirable to briefly review the work that has been done in this study of the chromium–aluminum oxide catalyst system.

First, it has been shown that the susceptibility per gram of the chromium in the catalyst varies with the concentration according to the susceptibility-composition isotherm. There is a sharp break in this isotherm at the "1" point. At concentrations below this point the slope of the curve is much greater than at higher concentrations. At this point there are important changes in the factors which determine the Weiss constant, Δ, in the Curie–Weiss law, $\chi = C/(T + \Delta)$. The Weiss constant is a measure of the interaction between electrons in adjacent atoms. The factors which determine the Curie constant (C) are also important in that the apparent valence of the chromium depends on the values of C. The shape of the isotherm has been interpreted on the basis of changes in the coördination number of chromium atoms with respect to other chromium atoms in the corundum structure. This interpretation leads to the belief that the chromia layer is three atom layers deep at the "1" point and that only a small fraction of the total alumina area is covered with chromia.

The weight of the evidence which has been gathered from many sources, such as the isotherm, Weiss constant measurements, and the effects of temperature of impregnation, heat treatment, and co-precipitation, points to the one basic fact, that the susceptibility in this system is a direct measure of the dispersion of the chromium. X-Ray studies verify these conclusions. It is commonly accepted that dispersion is an important factor, but of course not the only one, in the activity of catalysts, because it determines how much of the active element is exposed and available to the reactants. Thus, the conclusion may be drawn that the close relationship found between activity and susceptibility is due to the fact that they are both closely related to the underlying phenomenon of dispersion.

Acknowledgment.—It is a pleasure to acknowledge the support of the Sinclair Refining Company in connection with this work.

Summary

Surface area measurements have been made which, when taken together with magnetic data, support the view that at the "1" point of the susceptibility isotherm, the chromia is scattered over the surface of the alumina in small piles approximately three atom layers deep. Activity tests of a series of chromium–aluminum oxide catalysts, used in the cyclization reaction, show that there is a close relationship between the magnetic susceptibility and the activity of the chromium in the catalyst.

EVANSTON, ILLINOIS RECEIVED JANUARY 22, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

Donor-Acceptor Bonding. IV. Ammonia-Boron Trifluoride[1]

BY A. W. LAUBENGAYER AND G. F. CONDIKE[2]

Monoammonia-boron trifluoride, $H_3N:BF_3$, is the classical example of a molecular addition compound involving donor–acceptor bonding. Its formation was first observed by Gay-Lussac[3] and the system was further investigated by Davy,[4] who reported obtaining not only the mon-ammonate, but also di- and tri-ammonates, the last two described as colorless liquids. The properties of monoammonia-boron trifluoride were studied by Mixter[5] and by Kraus and Brown,[6] and Balz and Zinser[7] reported vapor pressure data for the complex. The information in the literature is often contradictory and very incomplete.

Accordingly, the present investigation has been undertaken as a comprehensive study of the ammonia–boron trifluoride system. The properties of monoammonia-boron trifluoride, the only addition compound found to exist between ammonia and boron trifluoride, have been studied in detail and the consequences of donor–acceptor bonding in this sytem are discussed.

Experimental

Determination of Mole Combining Ratio.—Known amounts of ammonia and boron trifluoride were brought together in an evacuated glass apparatus in mole ratios varying from 0.4:1 to 3:1 and allowed to come to equilibrium at 25°. The combining ratio of the two gases was calculated from the residual pressure of the system by assuming that the uncombined gas, present in excess, obeys the ideal gas laws. Table I lists the results, which clearly show that only the compound monoammonia–boron trifluoride, $H_3N:BF_3$, was formed. It accumulated as a white solid when the gases were mixed and at no time was any transparent liquid produced.

TABLE I

Moles NH_3 added per mole BF_3	Residual pressure, mm.	Moles NH_3 combining per mole BF_3
0.399	71.6	0.994
1.000	1.4	0.996
1.440	49.6	1.020
1.990	112.2	1.004
2.530	174.6	1.030
2.950	225.6	1.015
		Average 1.009

Preparation and Analysis.—Ammonia-boron trifluoride was prepared in quantity by mixing anhydrous ammonia and boron trifluoride in a one-liter three-necked flask. An outlet tube was provided for excess gases, and the flask was cooled with ice water. The vessel was first swept out with ammonia and then a slow flow of this gas was maintained. Boron trifluoride was admitted at such a rate that approximately equimolar quantities of the reactants were provided. Since any uncombined boron trifluoride fumed immediately in contact with moist air, it served as its own indicator at the outlet tube. The addition compound accumulated in the reaction flask as a white powder.

To establish the composition of the product, ammonia was liberated by boiling the compound with an excess of a concentrated solution of sodium hydroxide, and was then absorbed and titrated in the usual manner. Boron was determined as boric acid by dissolving a weighed sample of the product in a slight excess of dilute sodium hydroxide and titrating the solution by the mannitol method, in which paranitrophenol was used as the first and phenolphthalein as the second indicator.

Anal. Calcd. for $H_3N:BF_3$: NH_3, 20.05; B, 12.75. Found: NH_3, 20.05, 19.90, 19.85; B, 12.80, 12.72, 12.65.

Melting Point and Density.—The melting point of ammonia-boron trifluoride was found to be 163 ± 1°, the determination being made rapidly on a Dennis–Shelton melting point bar[8] in order to avoid serious thermal decomposition. The density was determined pycnometrically to be 1.864^{25}_4 using benzene as the immersion reference liquid.

Solubility, Polarity and Molecular Weight in Solution.—The solubilities of the compound in several solvents other than water were tested microscopically by observing the progress of evaporation of the solvent from a well-stirred mixture of a drop of the solvent and a small amount of the solid compound. In solvents of low dipole moment (0.00 to 1.12 debye units), such as benzene, carbon disulfide, carbon tetrachloride and diethyl ether, the compound appeared to be insoluble; slight solubility in cyclohexanol (1:5) and somewhat greater solubility in methanol (1.68) and in ethyl alcohol (1.70) were observed. These results indicate that the compound itself probably has a considerable dipole moment.

In water the solubility, quantitatively determined, proved to be 36.0 g. per 100 g. of solvent at 25°. The aqueous solution is remarkably stable at this temperature. Thus the powder X-ray diffraction pattern was unchanged by recrystallizing a sample of the compound from water. Furthermore, the molecular weights, determined cryoscopically in three aqueous solutions containing, respectively, 15.77, 8.15 and 6.04 g. of the compound per 1000 g. of water were 81.0, 83.9 and 82.4. Since the molecular weight calculated for the compound $H_3N:BF_3$ is 84.8, the latter is evidently not appreciably hydrolyzed, dissociated nor associated in aqueous solution at about 0°.

Crystallographic and X-Ray Examination.—A microscopic examination of ammonia-boron trifluoride recrystallized from water was made. The compound crystallizes in rhomb-shaped plates which exhibit symmetrical extinction. The crystals are in the orthorhombic system, a combination of prism faces (110) and basal pinacoids (001) being common. The prism–prism interfacial angles are 57°30′ ± 15′ and 121°30′ ± 15′. $2V = 90° \pm 3°$; $2E$ 146° ± 2°; OA Plane = 100. The direction of vibration of α is parallel to the b crystallographic axis, β to the a axis, and γ to the c axis. Refractive indices (white light): $\alpha = 1.335$, $\beta = 1.34$–1.35, $\gamma = 1.36$. It was dif-

(1) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the Atlantic City meeting, April, 1947.

(2) Present address: Fitchburg State Teachers' College, Fitchburg, Mass.

(3) Gay-Lussac, *Mémoires de la Societe d'Arcueil*, **2**, 211 (1809).

(4) Davy, *Phil. Trans.*, **30**, 365 (1812).

(5) Mixter, *Am. Chem. J.*, **2**, 153 (1881).

(6) Kraus and Brown, THIS JOURNAL, **51**, 2690 (1929).

(7) Balz and Zinser, *Z. anorg. allgem. Chem.*, **221**, 236 (1935).

(8) Dennis and Shelton, THIS JOURNAL, **52**, 3128 (1930).

ficult to decide on the optic sign, since $2V$ is so close to 90°.

The prominent lines of the powder X-ray diffraction pattern obtained for the crystals are listed in Table II.

TABLE II

POWDER X-RAY DIFFRACTION PATTERN FOR $H_3N:BF_3$

d	Intensity
4.22	Strong
3.88	Strong
3.60	Medium
3.00	Medium
2.55	Medium
2.19	Weak

Calorimetric Determination of Heat of Formation.—A Bunsen ice calorimeter was used[9] to measure the total heat effect produced at 0° by dissolving 100 cc. of gaseous boron trifluoride in diethyl ether and then introducing 100 cc. of ammonia gas into the solution. The reactions indicated by the equations took place

$$BF_3(g) + (C_2H_5)_2O(l) = (C_2H_5)_2O{:}BF_3(sol) + \Delta H$$
$$(C_2H_5)_2O{:}BF_3(sol) + NH_3(g) = (C_2H_5)_2O(l) + H_3N{:}BF_3(s) + \Delta H_2$$

The sum of these reactions is

$$BF_3(g) + NH_3(g) = H_3N{:}BF_3(s) + \Delta H_3$$

The value 41.3 kcal. per mole was obtained for ΔH_3, the heat of formation of solid ammonia–boron trifluoride from the gases at 0°.

Thermal Decomposition.—Rapid heating of ammonia-boron trifluoride results in an initial fusion of the solid; then decomposition occurs and the melt resolidifies and partially sublimes. One of the products of the thermal decomposition was shown to be ammonium fluoborate by a study of the optical properties and the powder X-ray diffraction patterns of the crystals obtained by recrystallizing the soluble part of the product from water. The other product, insoluble in water, was identified as boron nitride, BN, by X-ray diffraction and by the fact that it yielded boric acid and ammonia upon hydrolysis by boiling water.

Quantitative measurements demonstrated that the thermal decomposition, which becomes appreciable at 125° and proceeds rapidly at 150°, is represented by the equation

$$4H_3N{:}BF_3 = 3NH_4BF_4 + BN$$

These results suggest that the values reported by Balz and Zinser[7] as equilibrium vapor pressures of the ammonia complex, actually are those of ammonium fluoborate. This interpretation was confirmed by making equilibrium vapor pressure measurements on the two systems. The straight line obtained by plotting the values of log p against $1/T$ for ammonium fluoborate was found to be identical with the curves obtained by us and those obtained by Balz and Zinser by heating ammonia–boron trifluoride. It is to be noted that boron nitride has a vapor pressure of only 9.4 mm. at 1240°,[10] and that its contribution to the total pressure of the system in the temperature range studied is negligible.

Saturation Vapor Pressure and Heat of Sublimation of NH_4BF_4.—From the vapor pressure–temperature data obtained, the characteristic equation for NH_4BF_4 was calculated to be $\log_{10}p$ (mm.) $= -2469/T + 6.82$. The heat of sublimation of NH_4BF_4 is 11.3 kcal.

Discussion

The experimental results obtained in this investigation are in line with the general theory dealing with donor-acceptor bonding previously outlined.[9,11,12] The nitrogen atom in ammonia can donate its unshared pair of electrons to establish a shared electron pair bond to the boron atom in boron trifluoride and a one:one molecular addition complex is formed. It is conceivable that $H_3N:BF_3$, under conditions other than those we have used, might combine with more ammonia.

$$H_3N{:}BF_3 + NH_3 = [(NH_3)_2BF_2]^+F^-$$

However, such an ionic di-ammonate presumably would not be a liquid, as reported by Davy.[4]

The remarkable resistance to hydrolysis observed for $H_3N:BF_3$ would seem to be a result of the fact that, in forming the addition compound, both nitrogen and boron go from a coördination number of 3 to 4. This increase in the numbers of neighboring atoms strongly bonded to the central atoms appears to protect them from hydrolysis.

The configuration of $H_3N:BF_3$ may be expected to involve essentially tetrahedral bonding for both the nitrogen and boron atoms to give an ethane-like molecule. Professor Hoard of this Laboratory is now undertaking the X-ray determination of the crystal structure of the complex. It seems likely that hydrogen bonding will be pronounced in the solid.

The high polarity of $H_3N:BF_3$ and the resultant low solubility in non-polar solvents and high solubility in polar solvents is to be expected from its structure. The formation of a donor-acceptor bond between the nitrogen and boron atoms involves a considerable displacement of charge. In addition, when the complex is formed the fluorine atoms probably move from positions coplanar with boron to tetrahedral positions. The three B–F bond dipoles no longer counterbalance each other but make a considerable contribution to the polarity of the complex.

Summary

1. Only one compound, ammonia–boron trifluoride, $H_3N:BF_3$, has been found to exist between ammonia and boron trifluoride at 25°. It has been prepared in quantity and its properties have been studied.

2. Cryoscopic measurements indicate that in

(9) Laubengayer and Finlay, THIS JOURNAL, **65**, 884 (1943).

(10) Slade and Higson, *J. Chem. Soc.*, **115**, 215 (1929).

(11) Bauer, Finlay and Laubengayer, THIS JOURNAL, **65**, 889 (1943).

(12) Laubengayer and Sears, *ibid.*, **67**, 164 (1945).

water solution $H_3N:BF_3$ exists as a monomeric molecular species, and that it is not appreciably dissociated.

3. Optical studies have been made on crystals of ammonia–boron trifluoride, and its powder X-ray diffraction pattern has been established.

4. The heat of formation of solid ammonia–boron trifluoride from the gases at 0° has been determined calorimetrically as 41.3 kcal.

5. It has been shown that the compound undergoes irreversible thermal decomposition at temperatures above 125° according to the equation: $4H_3N:BF_3 \xrightarrow{125^\circ} 3NH_4BF_4 + BN$.

6. Vapor pressure measurements obtained when ammonia–boron trifluoride is heated give values shown to be those of ammonium fluoborate, the only decomposition product volatile in the temperature range studied. The P.T. equation for NH_4BF_4 is $\log_{10} p(\text{mm.}) = -2469/T + 6.82$. The molar heat of sublimation of NH_4BF_4 is 11.3 kcal.

ITHACA, NEW YORK RECEIVED NOVEMBER 1, 1947

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF TORONTO]

Thermodynamics of Sodium Chloride in 50 Mole Per Cent. Aqueous Methanol from E. m. f. Measurements on Cells with Transference

BY J. P. BUTLER AND A. R. GORDON

While concentration cells with transference have been used extensively in the study of electrolytes in aqueous solution[1,2] and have yielded some of the most precise thermodynamic data now available for such solutions, lack of transference numbers has so far prevented their use with solvents other than water. One interesting exception is provided by the work of Harned and Dreby[3] who employed cells with and without transference to yield indirectly transference numbers for hydrochloric acid in dioxane–water mixtures. Recent measurements in this laboratory[4] have now made possible the use of this method for sodium chloride in 50 mole per cent. methanol–water solution. Apart from testing the precision of the measurements with a solvent other than water, the primary purpose of this research was to determine whether the thermodynamic mean ionic diameter was significant when comparing ionic transport processes in two different solvents.

The cells, the preparation of the electrodes, and the general experimental technique have been previously described.[2] In all cases, the observed e. m. f. has been corrected for bias potential as described by Hornibrook, Janz and Gordon. One rather surprising result was that the bias potentials for stable pairs of electrodes were of the same order as those found in aqueous solution, *viz.*, 0.03 mv. or less. Even more surprising was the fact that the bias potential for a given pair was not only independent (within a microvolt or so) of the salt concentration in the mixed solvent, but had also the same value within similar limits after the electrodes had stood for half an hour in a solution with pure methanol or pure water as solvent. This suggests that lightly plated, electrolytically anodized Ag/AgCl electrodes are considerably sturdier than is generally assumed, provided a galvanometer of high currect sensitivity is used.

The solutions were prepared as described by Schiff and Gordon.[5] In computing the volume concentration C from the mass concentration, the density measurements of Shemilt, Davies and Gordon[4] were employed; these give for the range of interest here

$$C/m = 0.88123(1 - 0.0134m) \qquad (1)$$

where m is the molality.

The results are summarized in Table I under the heading E_{obs}. Only average values for round concentrations are given in the table; the method by which these were obtained from the results of individual runs, carried out at concentrations differing slightly from those recorded, will be described below.

TABLE I

m_1 = 0.05 MOLAL; 25°

m_2	$E_{obs.}$, mv.	$E_{calc.}$, mv.	m_2	$E_{obs.}$, mv.	$E_{calc.}$, mv.
0.003	+58.075	+58.075	0.04	+4.386	+4.391
.005	+47.145	+47.145	.06	−3.575	−3.564
.01	+32.565	+32.560	.07	−6.556	−6.560
.02	+18.293	+18.300	.08	−9.149	−9.147
.03	+10.114	+10.112			

The e. m. f. of a cell of the type Ag,AgCl/NaCl(m_1)//NaCl(m_2)/AgCl,Ag is of course given by the familiar expression

$$E = kt^0_+ \Delta \log ym + \Delta F(t_+) \qquad (2)$$

Here, k = 118.28 mv., t^0_+ is the limiting transference number for the cation (0.4437), Δ stands for function (m_1) − function (m_2), and $F(t_+)$ is given by

$$F(t_+) = k \int_0^m (t_+ - t^0_+)\, d \log \gamma m \qquad (3)$$

Eq. 2 can be solved by the usual method of suc-

(1) Brown and MacInnes, THIS JOURNAL, **57**, 1356 (1935); Shedlovsky and MacInnes, *ibid.*, **58**, 1970 (1936); **59**, 503 (1937).

(2) Hornibrook, Janz and Gordon, *ibid.*, **64**, 513 (1942); Janz and Gordon, *ibid.*, **65**, 218 (1943); MacWilliam and Gordon, *ibid.*, **65**, 484 (1943); McLeod and Gordon, *ibid.*, **68**, 58 (1946).

(3) Harned and Dreby, *ibid.*, **61**, 3113 (1939).

(4) Shemilt, Davies and Gordon, *J. Chem. Phys.*, **16**, 340 (1948).

(5) Schiff and Gordon, *ibid.*, **16**, 336 (1948).

cessive approximations, employing the transference data of Shemilt, Davies and Gordon,[4] to yield a consistent set of $\Delta \log \gamma = \log \gamma_1 - \log \gamma_2$.

On theoretical grounds, the activity coefficient should be given by

$$\log \gamma^* = -\alpha\sqrt{C}/(1 + \beta\sqrt{C}) + 0.4343\{j^3(X_3/2 - 2Y_3) + j^5(X_5/2 - 4Y_5)\} - \log (1 + 0.05m) \quad (4)$$

where,[6] for a solvent of dielectric constant[7] 49.84, $\alpha = 1.0072$, $\beta = 0.4125a$, $j = 11.24/a$, and a is the mean ionic diameter in ångströms. The leading term is the usual Debye–Hückel expression, the second contains the "extended terms" of the theory, which have been tabulated as functions of $\beta\sqrt{C}$ by Gronwall, LaMer and Sandved,[8] and the last takes account (with 50 mole per cent. aqueous methanol as solvent) of the change in concentration scale of the electrolyte from mole fraction to molality. If Equation 4 is valid for the concentration range involved, and if the correct value of a has been selected, $\Delta \log \gamma/\gamma^*$ should be uniformly zero. If, on the other hand, Eq. 4 is valid for the lower concentrations but not for those as great as $m_1 = 0.05$, and if once again the correct value of a has been chosen, $\Delta \log \gamma/\gamma^*$ should be a constant for the lower values of m_2, this constant being identically the difference between $\log \gamma$ and $\log \gamma^*$ at 0.05 molal.

Figure 1 shows the result of such an extrapolation with $a = 4.45$ Å.; this corresponds to $\beta = 1.836$ and $j = 2.526$. The quantity plotted is $\Delta \log \gamma/\gamma^*$ for each of the experiments, the abscissas being m_2, expressed in moles per kg. solvent. The value selected for a was chosen after a series of trials with a values ranging from 4 to 5 Å. It is at once evident from the figure that Eq. 4 with $a = 4.45$ adequately represents the activity coefficients up to about 0.025 molal. The figure also gives an idea of the precision and reproducibility of the measurements, the radius of circles corresponding to 5 microvolts in the e. m. f. The maximum deviation of any of the points from the smooth curve corresponds to 0.025 mv., and in only three cases is the discrepancy greater than 0.01 mv. The precision thus is comparable with the best that has been attained in this type of measurement with aqueous solutions.

The plot also serves as a convenient and precise means of obtaining the "observed" value of the e. m. f. for the round concentrations entered in Table I; from the mean of the observed values of $\Delta \log \gamma/\gamma^*$ for the individual runs and the known value of $\Delta \log \gamma^*$ for the round concentrations, an observed value of $\Delta \log \gamma$ and consequently of the e. m. f. may be obtained at once. From the continuous curve of the figure, the values of $\log \gamma$ entered in Table II were obtained; obviously, the

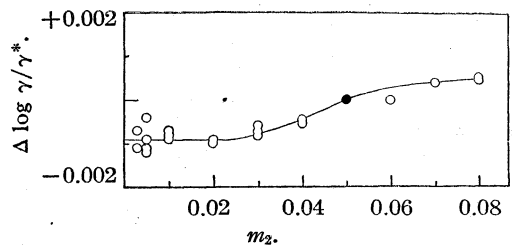


Fig. 1.

first four entries are also identically $\log \gamma^*$. Table II also gives the values of $F(t_+)$ corresponding to the tabulated values of the activity coefficients.[9] The self-consistency of the two tables is shown by the column headed $E_{\text{calcd.}}$ in Table I, which gives the e. m. f. computed from Eq. 2 by interpolation in Table II. While the precision and reproducibility of the measurements leaves little to be desired, it must nevertheless be remembered that the transference data on which the calculation of the activity coefficients is based, are at best accurate to a part in four thousand; this would correspond for the first entry in Table I to an uncertainty of 0.0003 in $\log \gamma$. We believe, however, that the results recorded here show that cells with transference can yield thermodynamic data of high precision with solvents other than water.

TABLE II

$m^{1/2}$	$1 + \log \gamma$	$F(t_+)$, mv.	$m^{1/2}$	$1 + \log \gamma$	$F(t_+)$, mv.
0.04	0.9639	−0.150	0.20	0.8552	−0.492
.08	.9318	.272	.24	.8343	.549
.12	.9034	.362	.28	.8157	.607
.16	.8782	.434	.32	(.7987)	(− .661)

Two other points deserve mention. The mean ionic diameter found here is the same as that reported by Brown and MacInnes[1] for sodium chloride in aqueous solution.[10] Thus, if a mean ionic diameter determined thermodynamically is significant in transport processes, the ratio of the limiting ion conductances in the mixture to those in water should (on the simple hydrodynamic picture) be close to the reciprocal of the ratio of the viscosities. Actually, as Schiff and Gordon[5] have shown, the limiting conductances in the mixture for sodium and chloride ions are 13% and 28% less than would be predicted from viscosity alone.

(6) The values of k and of the universal constants are those suggested by Manov, Bates, Hamer and Acree, THIS JOURNAL, **65**, 1765 (1943).

(7) Albright and Gasting, **68**, 1061 (1964).

(8) Gronwall, LaMer and Sandved, *Physik. Z.*, **29**, 358 (1928).

(9) For convenience in interpolating, the values of $F(t_+)$ in the table are carried to a greater number of significant figures than is entirely justified by the precision of the transference data.

(10) The smaller value (4.12 Å.) reported by Janz and Gordon[2] results from their use of the empirical Hückel extension to the original Debye–Hückel equation involving the introduction of a term linear in the concentration. It is well known that while this form is applicable over a wider concentration range than is the Debye–Hückel equation itself, its use removes any precise significance from the value of β used in the extrapolation; actually, the activity coefficients reported by Brown and MacInnes and by Janz and Gordon are in excellent agreement in spite of the different analytic forms used to represent the data in the two cases. It is the mean ionic diameter obtained when the linear term is not employed that should be compared with that derived from Eq. 4. In this connection see Brown and MacInnes[1] and Hornibrook, Janz and Gordon.[3]

If ion solvation in the mixture is primarily by water rather than methanol molecules, and if the Debye–LaMer diameter is a true measure of the diameter of the solvated ions, this would account for the surprising agreement between the values of a in the two cases. It would still leave unexplained, however, the decreased ion conductances in the mixture as compared with those predicted by the Walden rule, unless some additional factor, significant only in the transport process, is postulated, *e. g.*, hydrogen bonding between the water molecules in the hydrated sheath about the ions and the "free" methanol molecules of the solvent.

Secondly, it should be observed that the a value found here is considerably less than the critical Bjerrum[11] distance, given for 1:1 electrolytes by $e^2/2DkT = 5.6$ Å. for a solvent of dielectric constant 50 at 25°. Thus on the Bjerrum picture there should be considerable ion-pair formation, yet the form of the ion conductance *vs.* concentration curves[5] for this salt shows that association must be slight.

A consideration of the data presented here and of the ion conductances suggests (to us at any rate) that the use of a mixed solvent complicates the problem considerably, and that measurements in a one-component non-aqueous solvent may yield data which are more easily interpreted.

(11) Bjerrum, *Kgl. Danske Vidensk. Selskab.*, **7**, No. 9 (1926).

Summary

1. The e. m. f. of the cell with transference Ag,AgCl/NaCl(m_1)//NaCl(m_2)/AgCl,Ag, with 50 mole per cent. aqueous methanol as solvent, has been measured at 25° for sodium chloride concentrations from 0.003 to 0.08 M.

2. The precision and reproducibility of the results are comparable with those obtained with this type of cell for aqueous solutions. The bias potential between stable pairs of electrodes is 0.03 mv. or less, and is independent within one or two microvolts of the electrolyte concentration, just as is the case when water is solvent.

3. The activity coefficients, computed from the e. m. f. data and the known transference numbers, were extrapolated by means of the Gronwall, LaMer and Sandved extension to the Debye–Hückel equation, which represents the coefficients up to 0.025 M when the value selected for the mean ionic diameter is 4.45 Å. For higher concentrations, the observed values lie below those predicted by the equation.

4. The value found for the ionic diameter is in fortuitously exact agreement with that for this salt in water, and is definitely less than the critical Bjerrum distance for this solvent. The significance of the mean ionic diameter in its relation to the ion conductances for the salt in water and in methanol–water solution is discussed.

TORONTO, CANADA RECEIVED MARCH 13, 1948

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY]

Mixed Adsorption of Radon and Argon on Silica Gel

BY BENJAMIN P. BURTT[1] AND J. D. KURBATOV

Mixed adsorption studies using radon in various gases at 1 atm. have been made by Siebert[2] at −80°, by Francis[3] with silica gels of various states of hydration, by Becker and Stehberger[4] and, using charcoal, by Nikitin and Joffe.[5]

The present work lies in the general field of mixed gas adsorption. The adsorbent was silica gel and all the experiments were conducted at 25 ± 3°. Adsorption isotherms of radon in air, in carbon dioxide and in argon at near atmospheric pressure were obtained. Approximately 1×10^{-16} g. atom of radon at partial pressures around 1×10^{-10} mm. was used.

Adsorption isotherms for air, argon and carbon dioxide were determined under the same experimental conditions as for radon. A brief study was also made of the mixed adsorption of carbon dioxide and air using conventional pressure–volume methods with subsequent analysis of the gas. A more thorough study was made of the mixed adsorption of argon and carbon dioxide applying both methods of conventional analysis and radioactive tracer technique. The adsorption of argon from air was investigated using radioactive argon as a tracer.

(1) At present in the Department of Chemistry, Syracuse University, Syracuse, New York.

(2) W. Siebert, *Z. physik. Chem.*, **A180**, 169 (1937).

(3) M. Francis, *Kolloid-Z.*, **59**, 292 (1932).

(4) A. Becker and K. H. Stehberger, *Ann. Physik*, [5] **1**, 529 (1929).

(5) B. A. Nikitin and E. M. Joffe, *Bull. acad. sci. U. R. S. S., Classe sci chim.*, 1944, 210–215 (English Summary).

Description of the Apparatus and Procedure

The apparatus shown in Fig. 1 was constructed for mixed adsorption studies using radioactive gases. It was also suitable for the measurement of the simple adsorption of gases by pressure–volume methods.

The mixture of radioactive gas and the gas accompanying it is stored in buret S. Chosen volumes of the mixture can be transferred to the evacuated system as well as to the ionization chamber for analysis. The ionization chamber was connected to a Wulf bifilar electrometer. The gas is confined during adsorption in the system, A and E (total volume 26 cc.). About 0.8 g. of silica gel is placed in the removable adsorption flask E. With-

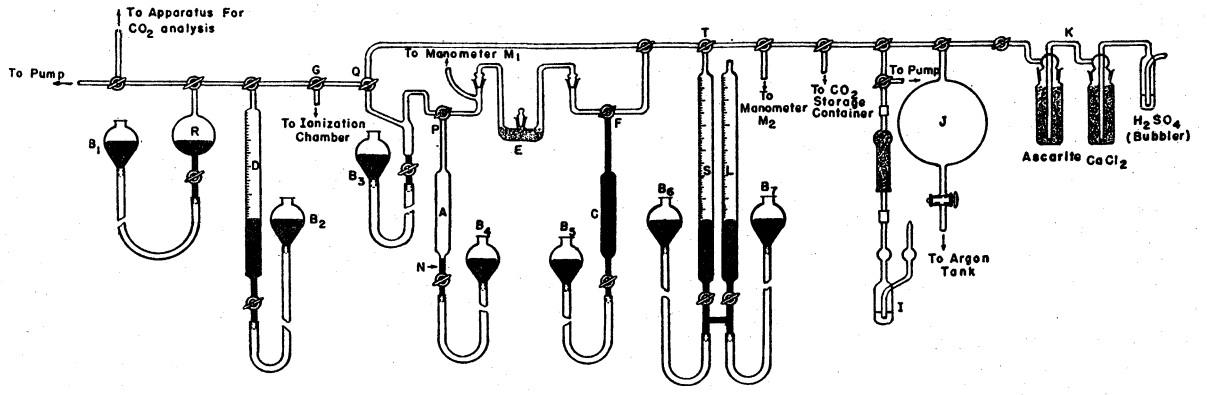


Fig. 1.—Apparatus for adsorption of gases.

out disturbing the equilibrium established, the sample of gas in pipet A is isolated from the system and removed to the ionization chamber for analysis.

To measure simple adsorption, a known quantity of gas was added to the evacuated system; after equilibrium had been established the quantity remaining in the gas phase was determined from the final pressure, volume and temperature.

In the experiments on the mixed adsorption of carbon dioxide with air, and with argon, the amount of carbon dioxide at equilibrium was determined by removing the gas in pipet A into a gas buret for absorption in potassium hydroxide.

Experimental Results

The Adsorption of Air, Argon and Carbon Dioxide on Silica Gel at 25°.—The adsorption isotherms of air, argon and carbon dioxide are plotted in Fig. 2. It was found in agreement with previous work, that carbon dioxide is adsorbed to a greater extent than air or argon. Air is adsorbed only slightly more than argon.

The data for the three isotherms were fitted by the method of least squares to the Freundlich equation

$$y = kx^{1/n} \qquad (1)$$

where y is the number of gram moles adsorbed per gram of gel and x is the number of gram moles per cc. in the gas phase. The data also conform to the Langmuir equation

$$y = y_m b'x/(1 + b'x) \qquad (2)$$

In these equations x and y have the same meanings as in the Freundlich equation, y_m is the number of gram moles of gas adsorbed per gram of silica gel when the surface is covered with a unimolecular layer and b' is the adsorption coefficient.

An estimate of the heat of adsorption of a gas can be made from the value of the adsorption coefficient b'. Laidler, Glasstone and Eyring[6] derived an expression for b' in terms of the heat of adsorption per molecule E. With some approximations the value of E can be calculated from b'.

For carbon dioxide b' and y_m are obtained by plotting equation (2) in the form

$$\frac{1}{y} = \frac{1}{y_m b'x} + \frac{1}{y_m} \qquad (3)$$

The isotherms of argon, air, and radon were experimentally linear and b' could not be obtained in this way. However, an approximate value of b' is calculated for these gases from the adsorption isotherms and estimated surface area of the adsorbent as follows. Brunauer and Emmett[7] found the area of silica gels with 6 to 9% water to be about 600 sq. m. per gram. The silica gels in this work averaged 6.27% water and the surface area is assumed to be of the same order of magnitude. The values of y_m are estimated using the above surface area for silica gel. These values of y_m are then used to calculate the adsorption coefficients b' from the adsorption isotherms. By this method the heat of adsorption of radon in air or argon is evaluated to be of the order of 9000 calories per mole (a 50% error in estimating the surface area would produce an error of about 350 cal./mole). It may be seen that this method gives values of the correct order of magnitude. The calculated value for argon is 5,500 calories per mole

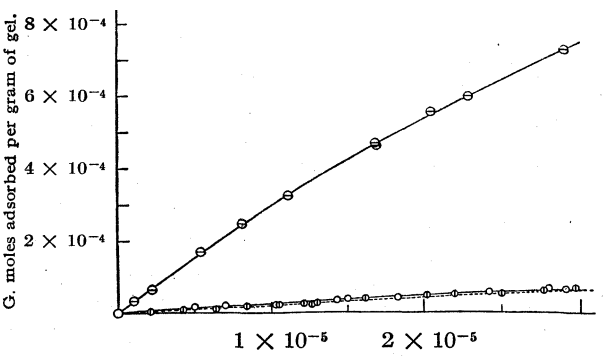


Fig. 2.—Adsorption isotherms of air, argon and carbon dioxide on silica gel, temp. 25°, wt. gel. = 0.8216 g.: -⊖-⊖-⊖- CO_2, -⊙-⊙-⊙-⊙- A, -O-O-O- air.

(6) K. J. Laidler, S. Glasstone and H. Eyring, *J. Chem. Phys.*, **8**, 659 (1940).

(7) S. Brunauer and P. H. Emmett, THIS JOURNAL, **59** 2682 (1937).

while data in the literature range from 2,500 to 3,600.[8,9,10,11,12] The value for carbon dioxide calculated from a plot of equation (3) is 7,700 calories per mole. The value calculated using the estimated surface area is 7300 calories per mole, whereas values from 6,900 to 7,900 are reported by other investigators.[8,10,13] The calculated value for air is 5,500 calories per mole and the values in the literature for oxygen and nitrogen are from 3,000 to 5,500 calories per mole.[10,13,14,15]

In addition to the per cent. adsorbed, a distribution coefficient α (the quantity of gas adsorbed per gram of adsorbent divided by the quantity of gas per cc. of space) is calculated. Slight unavoidable variations in the weight of the gel and the volume of the system from one experiment to the next do not affect α, whereas they may affect the per cent. adsorbed.

The results of the calculation are given in Table I for each gas at the same concentration in the gas phase (corresponding to a pressure of 557 mm.).

TABLE I

Gas	G. mole per cc. of space $\times 10^5$	G. mole adsorbed per gram gel $\times 10^5$	α	% of total gas adsorbed
Argon	3	6.52	2.1	6.5
Air	3	6.89	2.3	6.8
Carbon dioxide	3	78.20	26.1	45.4

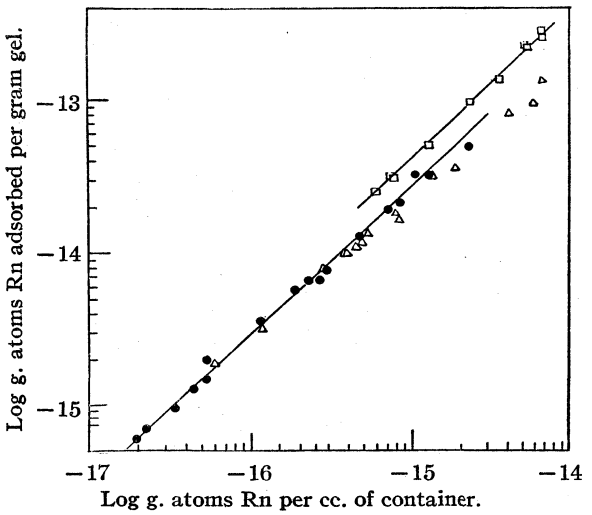


Fig. 3.—Mixed adsorption of radon on silica gel with air, carbon dioxide and argon: ●, Rn + Air at 740 mm.; △, Rn + CO_2 at 704 mm.; □, Rn + Argon at 697 mm. temp. 25°; av. wt. gel., 0.75 g.

(8) F. Dewar, *Proc. Roy. Soc.* (*London*), **A74**, 122 (1904).

(9) E. Hückel, "Adsorption and Kapillarkondensation," Leipzig, 1928, p. 22.

(10) W. Kalberer and C. Shuster, *Z. physik. Chem.*, **A141**, 270 (1939).

(11) F. G. Keyes and M. J. Marshall, THIS JOURNAL, **49**, 156 (1927).

(12) A. Lendle, *Z. physik. Chem.*, **A172**, 77 (1935).

(13) W. Kalberer and H. Mark, *Z. physik. Chem.*, **A139**, 151 (1928).

(14) S. F. Gregg, *J. Chem. Soc.*, 1494 (1927).

(15) A. Mangus, *Z. physik. Chem.*, **A142**, 401 (1929).

Mixed Adsorption Studies with Radon—Radon and Air.—The adsorption isotherm for radon in air at near atmospheric pressure is given in Fig. 3. The log–log plot is linear and of approximately unit slope. Decreasing the pressure of the accompanying air to 120 mm. produces no measurable change in the adsorption of radon. The value of the distribution coefficient α of radon obtained from the plot is 28.5. Approximately 50% of the total radon is adsorbed, the variations being due to slight differences in the weight of gel and the volume of the system.

The results of this work are in agreement with the Langmuir theory of mixed adsorption. The equations derived by Markham and Benton[16] predict that a decrease in air pressure produces no appreciable change in the adsorption of radon under these experimental conditions. No change in the adsorption of radon is observed with a decrease in air pressure.

Radon and Carbon Dioxide.—Figure 3 shows the adsorption of radon from carbon dioxide and from air at near atmospheric pressure to be the same at concentrations of radon below 3×10^{-16} g. atom/cc. At higher concentrations of radon its adsorption is less from mixtures with carbon dioxide than from mixtures with air at one atmosphere total pressure.

Studies were made of the adsorption of radon from radon-air-carbon dioxide mixtures when the total pressure of the gases was approximately one atmosphere. The adsorption of radon in mixtures containing as much as 25% carbon dioxide was not measurably different from the adsorption of radon in air alone.

The Langmuir equations predict a straight line of unit slope for the log–log plot as long as the concentration of radon is very small compared to that of carbon dioxide. In this experimentation the slope of the isotherm was slightly less than unity even though the concentration of radon was negligible. This could be partially explained by postulating that the surface of the gel is heterogenous and the adsorption of radon takes place primarily on the points of greatest unsaturation. Upon increasing the concentration of radon in the gas phase above 3×10^{-16} g. atom/cc., the active points on the gel become more nearly saturated and further increases in the partial pressure of radon do not result in a proportional increase in the amount adsorbed per gram of silica gel.

Radon and Argon.—The adsorption isotherm of radon from radon–argon mixtures at near atmospheric pressure is also given in Fig. 3. The log–log plot is experimentally linear, of approximately unit slope and lies considerably above the corresponding isotherm of radon in air.

At the same partial pressure of radon in the gas phase approximately 50% more radon is adsorbed in the presence of argon than in the presence of

(16) E. C. Markham and A. F. Benton, THIS JOURNAL, **53**, 497 (1931).

air. Decreasing the pressure of argon decreases the adsorption of radon. From Table II it can be seen that α, the distribution coefficient for radon in argon, decreases simultaneously with the pressure of the argon.

TABLE II

MIXED ADSORPTION OF RADON AND ARGON

G. atoms Rn to system $\times 10^6$	Pressure argon, mm.	α, Radon
35.1	704	42.8
133	701	42.7
360	690	42.4
74.6	684	39.5
133	345	38.6
52.7	280	37.1
384	114	35.6
42.6	105	34.9

These observations indicate that the adsorption of radon is enhanced by the presence of argon.

The Langmuir theory predicts that the plot of the amount adsorbed per gram of gel against the amount per cc. in the gas phase should be linear. In this respect the data agreed with the theory of mixtures. The Langmuir theory also predicts that for the argon–radon mixtures approximately 1% more radon should be adsorbed than from a mixture with air.

A comparison of the adsorption of radon in air, in argon and in carbon dioxide is made in Table III showing the amount of radon adsorbed per gram of silica gel corresponding to a given partial pressure of radon in the gas phase in each of the three accompanying gases.

TABLE III

COMPARISON OF THE ADSORPTION OF RADON ON SILICA GEL IN THE PRESENCE OF CARBON DIOXIDE, AIR AND ARGON

Temperature 25°; average weight of gel 0.75

Accompanying gas, at mm.	Concentration of radon in gas phase, g. atoms/cc. $\times 10^{16}$	G. atoms of radon adsorbed/gram of gel $\times 10^{16}$
CO_2 at 704	7.00	165.0
Air at 735	7.00	194.0
Argon at 684	7.00	300.0
CO_2 at 704	4.00	100.0
Air at 735	4.00	114.0
Argon at 684	4.00	172.0
CO_2 at 704	1.00	27.0
Air at 735	1.00	29.5
Argon at 684	1.00	43.0
CO_2 at 704	0.70	18.8
Air at 735	0.70	21.0
Argon at 684	0.70	30.2

Mixed Adsorption of Argon—Argon and Carbon Dioxide.—The adsorption of the two gases was measured at various mole fractions of pure argon and carbon dioxide, maintaining a constant total quantity (1×10^{-3} g. mole) of carbon dioxide and of argon. The conventional procedure of analysis for the carbon dioxide content was compared with the use of a radioactive tracer (A^{37}). Isotope A^{37} has a half life of 34.1 days[17] and it was prepared in the Ohio State University cyclotron by bombardment of potassium chloride. The results for the adsorption of carbon dioxide in the presence of argon are shown in Fig. 4. No

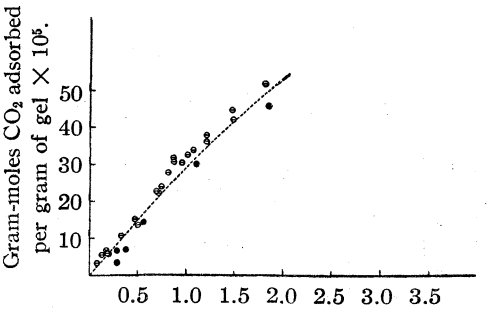


Fig. 4.—Mixed adsorption of argon and carbon dioxide: on silica gel, adsorption of CO_2 from A–CO_2 mixtures compared to adsorption of pure CO_2: total g. moles A + CO_2 = 1×10^{-3}; temp., 25°; av. wt. gel, 0.75 g.; -----, adsorption isotherm of pure CO_2; ⊖, adsorption of CO_2 from A–CO_2 mixtures by pressure change and CO_2 analysis; ●, adsorption of CO_2 from A–CO_2 mixtures by pressure change and use of radioactive argon (A^{37}) as tracer.

significant change in the adsorption of carbon dioxide in the presence of argon was detected. The results of the conventional method were slightly higher, in general, than the simple adsorption isotherm for carbon dioxide, while those obtained using A^{37} were slightly below the isotherm. Figure 5 shows the adsorption of stable argon from mixtures with carbon dioxide as determined by the use of radioactive argon. There was no measurable change in the adsorption of argon due to the pressure of carbon dioxide.

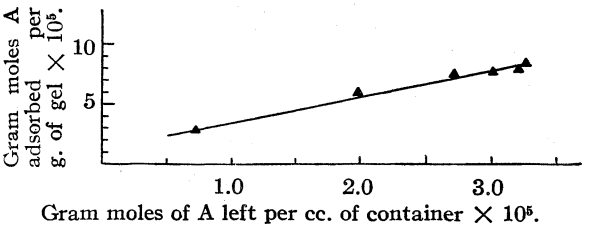


Fig. 5.—Mixed adsorption of argon and carbon dioxide, adsorption of argon on silica gel: adsorption of A from A–CO_2 mixtures, total g. moles A + CO_2 = 1×10^{-3}; temp., 25°, av. wt. gel., 0.75 g.

Argon and Air.—It has been reported that argon and nitrogen, and argon and oxygen mutually increase one another's adsorption at 0°.[18,19] Using radioactive argon similar results were obtained. Radioactive argon is added to

(17) P. K. Weimer, M. L. Pool and J. D. Kurbatov, *Phys. Rev.*, **66**, 209 (1944).

(18) B. Lambert and H. S. Heaven, *Proc. Roy. Soc.* (*London*), **A153**, 584 (1936).

(19) G. Damkohler, *Z. physik. Chem.*, **B23**, 58, 69 (1933).

air and the adsorption of the stable argon from air is traced. Approximately 13% of the total argon present in air was found to be adsorbed.

In these studies with radioactive argon it has been found that the use of radioactive tracer for mixed gas adsorption is feasible and gives more consistent results than the conventional method. In cases where the chemical analysis of the gas mixture is difficult by ordinary means, the use of a radioactive tracer, if available, provides a convenient method for studying mixed adsorption. It is recognized that the technique described here using separate samples of silica gel for each experiment does not insure that the adsorbent has exactly the same adsorption properties in each experiment. Experiments in which the only variable was the sample of silica gel used showed this error to be of the order of 3%.

Acknowledgment.—The authors greatly appreciate the support given to this research by Professor Alpheus Smith and by Professor M. L. Pool. We also express our thanks to the Alumni Fund for a grant in aid for purchase of equipment.

Summary

1. An apparatus is described suitable for studying binary mixed gas adsorption in which one component is radioactive or contains radioactive atoms as a tracer. The apparatus is also suitable for certain mixed adsorption studies by conventional means. Simple adsorption isotherms were obtained for air, argon and carbon dioxide on silica gel at 25°.

2. Adsorption isotherms for radon in air, in argon and in carbon dioxide on silica gel at 25° were studied. The isotherm in air follows Henry's law and substantiates the Langmuir theory of mixed adsorption as applied to low concentrations. The adsorption of radon is slightly suppressed in carbon dioxide. The studies with radon in argon show that the adsorption of radon is enhanced in the presence of argon even though a very small fraction of the total surface of silica gel is covered by radon.

3. The heat of adsorption of radon in air and in argon was estimated from the data obtained to be of the order of magnitude of 9,000 calories per mole.

4. Methods are described for the use of radioactive argon to follow the adsorption of argon in mixtures with carbon dioxide and with air.

SYRACUSE, N. Y. RECEIVED JANUARY 2, 1948

NOTES

The Reduction of 6-Methyl-8-(4′-diethylamino-1′-methylbutylidene)-aminoquinoline

BY H. J. BARBER, D. H. O. JOHN AND W. R. WRAGG

The recent publication by Elderfield, *et al.*,[1] reporting a study of the synthesis of Plasmochin by the reductive condensation of 1-diethylaminopentanone-4 (I) with 6-methoxy-8-aminoquinoline (II), from which a satisfactory method did not ensue, is of considerable interest to us since we were concerned during the war with a similar process which gave Plasmochin in excellent yield. We wish therefore to record some additional data.

Early in our work we investigated a process revealed by Bergmann[2] for the reductive condensation of 6-methoxy-8-nitroquinoline with (I), following his conditions as closely as practicable (our palladium/barium sulfate catalyst was prepared by the method of Sabalitschka and Moses[3]), but we could not obtain any Plasmochin. A second Bergmann, patent[4] claims, but does not exemplify, the reductive condensation of (I) and (II).

Preparation of the Schiff base, 6-methoxy-8-(4′-diethylamino - 1′ - methylbutylidene) - aminoquinoline (III), was accomplished by Elderfield, *et al.*,[1] by the interaction of (I) and (II) using ethylbenzene as an entrainer to remove water, but condensation under these conditions was slow and far from complete. The Schiff base may be obtained in almost quantitative yield using the diethyl ketal of (I), instead of (I) itself, (*cf.* van Shelven[5]) by the procedure described[6] for 6-methoxy - 8 - amino - 1,2,3,4 - tetrahydroquinoline (IV). The Schiff base, without distillation, could then be reduced in ethyl acetate solution at 60° and 450 lb. hydrogen pressure in the presence of a platinum/charcoal catalyst, but the results were not consistent. Considerable improvement was effected by using an Adams platinum oxide catalyst[7] at the same pressure but at room temperature. Reproducible results were obtained and an 80% over-all yield (calculated on (II)) of distilled Plasmochin base was obtained on a production scale.

In our experience the reduction is very susceptible to minor changes in materials, catalyst or

(1) Elderfield, Kreysa, Dunn and Humphreys, THIS JOURNAL, **70**, 40 (1948).

(2) British Patent 547,302.

(3) Sabalitschka and Moses, *Ber.*, **60**, 800 (1927).

(4) British Patent 547,301.

(5) British Patent 388,087, Example 32.

(6) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).

(7) John, *J. Soc. Chem. Ind.*, **63**, 256 (1944).

reaction conditions and unless hydrogenation proceeds rapidly and smoothly, by-products are formed. In one explanation of the imidazole formation observed in their reductive condensations of (I) and (II), Elderfield and Kreysa[8] suggest that on reduction of the Schiff base (III), saturation of the pyridine ring occurs before substantial reduction of the azomethine linkage. This clearly requires qualification since under conditions now reported the reverse is the case. However, the more drastic hydrogenation conditions and the different catalyst used by Elderfield, *et al.*, might have caused the reaction to follow the alternative course. That these latter conditions led to extensive nuclear reduction is in accord with our experience since we used similar conditions except for the solvent employed, for making tetrahydro-Plasmochin and (IV), the published yield and analysis[6] of which have been overlooked by Elderfield, *et al.*[8]

It is of interest to note that Andersag also reports a failure to achieve more than a few per cent. yield of Plasmochin by the aminoketone route.[9]

A considerable part of this experimental work was carried out by H. G. Thompson and A. C. Benzie.

(8) Elderfield and Kreysa, THIS JOURNAL, **70**, 44 (1948).

(9) I. G. Elberfeld, *Jahresberichte*, 1940 (B. I. O. S. 116), Appendix 2).

RESEARCH LABORATORIES
MAY & BAKER LTD.
DAGENHAM, ESSEX
ENGLAND

RECEIVED MAY 1, 1948

The Preparation of 1-(*p*-Nitrophenyl)-1,3-butadiene

BY E. C. COYNER AND G. A. ROPP[1]

In the continuation of a study[2] on Diels–Alder reactions with 1-aryl-1,3-dienes, 1-(*p*-nitrophenyl)-1,3-butadiene and its adduct with maleic anhydride have been prepared and characterized.

The diene was synthesized in two steps by a modification of the procedure described in a review[3] of German war-time investigations on extensions of the Meerwein[4] reaction.

$$CH_2{=}CH{-}CH{=}CH_2 + ClN_2C_6H_4NO_2\text{-}p \longrightarrow ClCH_2{-}CH{=}CH{-}CH_2C_6H_4NO_2\text{-}p + N_2$$

$$ClCH_2{-}CH{=}CHCH_2C_6H_4NO_2\text{-}p + KOH \longrightarrow CH_2{=}CH{-}CH{=}CHC_6H_4NO_2\text{-}p + KCl + H_2O$$

The chlorobutene, obtained in the first step, may be distilled successfully in small quantities under high vacuum, but it was found that this operation could be omitted as well as the removal of impurities, chiefly *p*-nitrophenol, from the chlorobutene by steam distillation. Actually, inclusion of these operations, as described in the Germany report, give only very low yields of diene, whereas the abbreviated procedure given in detail below resulted in a yield of 61% of purified product based on *p*-nitroaniline. Furthermore, the product is described in the German report as an oil, but in this work 1-(*p*-nitrophenyl)-1,3-butadiene was found to crystallize in yellow needles, m. p. 78.0–78.8°. It reacts readily with maleic anhydride and has been kept at room temperature in dark bottles for several months with no apparent decomposition.

Studies are now underway on the reactions of 1-(*p*-nitrophenyl)-1,3-butadiene with unsymmetrical dienophiles.

(1) Research Corporation Fellow.

(2) For a previous publication see Coyner and Ropp, THIS JOURNAL, **69**, 2231 (1947).

(3) Müller, "The Action of Aromatic Diazo Compounds on Aliphatic Unsaturated Compounds," PB 737, Office of Technical Services, Department of Commerce, Washington, D. C.

(4) Meerwein, Buchner and van Emster, *J. prakt. Chem.*, **152**, 237–266 (1939).

Experimental

1-(*p*-Nitrophenyl)-4-chloro-2-butene.—Technical *p*-nitroaniline was recrystallized once from ethanol and 140 g. (one mole) was dissolved in a hot solution of 240 cc. concentrated hydrochloric acid and 100 cc. of water. The solution was stirred rapidly and cooled in an ice–salt-bath. After 100 g. of ice was added, a solution of 70 g. of sodium nitrite in 120 cc. of water was run in during one hour while the temperature was kept between −4 and +4.5°. Stirring was continued for an additional twenty minutes and the reaction mixture was filtered. The filtrate was kept at 0° while it was added over a period of ninety minutes to a well-stirred mixture of 1 liter of acetone, 80 g. of sodium acetate dissolved in 100 cc. of water, 30 g. of cupric chloride dissolved in 50 cc. of water, and 130 cc. of liquid butadiene. The reaction mixture was maintained at −3 to +5° by means of an ice–salt-bath during the addition and was then allowed to warm to room temperature. Stirring was continued for an additional sixteen hours. One liter of ether was then added to extract the oily product, and the ethereal solution was separated, washed four times with 1-liter portions of water and dried over anhydrous magnesium sulfate. Removal of the solvent on the steam-bath gave 187.5 g. (88.6%) of crude 1-(*p*-nitrophenyl)-4-chloro-2-butene as a dark brown oil.

1-(*p*-Nitrophenyl)-1,3-butadiene.—The crude chlorobutene was dissolved in a solution of 500 cc. of ligroin and 500 cc. of benzene and treated with 5 g. of activated charcoal under reflux for two hours. The charcoal was removed by filtration, the solvents were evaporated on the steam-bath and the residual oil was dissolved in 400 cc. of methanol. This solution was then stirred at 15–33° while a solution of 112 g. of potassium hydroxide in 600 cc. of methanol was added over thirty minutes. Stirring was continued for an additional five minutes and the precipitated light yellow crystalline diene was removed by filtration; it was washed thoroughly with water and dried in a vacuum desiccator to give 76.5 g. of product, m. p. 75.0–76.8. The methanolic filtrate was added to 1200 cc. of water to precipitate 41.5 g. of less pure, dark brown product, which upon recrystallization from 400 cc. of ligroin gave 30 g. of light yellow crystalline diene, m. p. 75.5–76.8°. The total yield of product, m. p. 75.0–76.8° is therefore 106.5 g. (61% based on *p*-nitroaniline). A highly purified sample, m.p. 78.0–78.8°, was prepared by repeated recrystallizations from ligroin and from methanol.

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.44, 68.44; H, 5.07, 4.96.

Adduct with Maleic Anhydride, 3-(*p*-Nitrophenyl)-1,2,3,6-Tetrahydrophthalic Anhydride.—A mixture of one-hundredth mole quantities of 1-(*p*-nitrophenyl)-1,3-butadiene (1.75 g.) and maleic anhydride (0.98 g.) was heated at 70° for fifteen minutes, during which time the melt solidified. The solidified cake was then heated under reflux with 3 cc. of xylene for ten minutes and cooled to room temperature. The solid product was re-

moved by filtration and recrystallized once from glacial acetic acid and three times from ethyl acetate to give pale yellow crystals, m. p. 170.9–172.0°.

Anal. Calcd. for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.06. Found: C, 61.33, 61.60; H, 4.04, 3.99.

UNIVERSITY OF TENNESSEE
KNOXVILLE, TENNESSEE

RECEIVED MARCH 8, 1948

Hydroxyethylmorphine

BY WARNER W. CARLSON AND L. H. CRETCHER

The typical result of alkylating the phenolic hydroxyl of morphine has been found to be the production of codeine-like effects, almost regardless of the chemical nature of the alkylating group.[1] However, since no reference could be found to the preparation of a hydroxyalkyl ether derivative of morphine, the alkaloid was hydroxyethylated by the procedure previously developed for use with nitrogenous phenols.[2]

Toxicity of the derivative was determined by the subcutaneous (abdominal) injection of graded doses of the compound in white mice (17 to 19 g. weight range). The results are given in Table I, along with the values listed by Small and Eddy[1] for the parent alkaloid and its methyl and ethyl ethers. Introduction of the hydroxyethyl group was found to produce a marked decrease both in acute toxicity and convulsant action. Hydroxyethylmorphine also failed to elicit the Straub reaction or circus movements in the animals. In its actions the hydroxyethyl derivative resembles γ-isomorphine, which has an LD 50 of 2000 mg./kg. and does not produce the Straub reaction or circus movements in mice.[1]

TABLE I

ACUTE TOXICITY OF HYDROXYETHYLMORPHINE TO WHITE MICE

Substituent at position 3	LD 50 mg./kg., as free base	Convulsant action, mg./kg.	Straub reaction
HO—	531	531	Present
CH_3O—	241	161	Present
C_2H_5O—	136	122	Present
HOC_2H_4O—	2500	2500	Absent

A preliminary estimate of analgesic potency in white mice was made by the method of Woolfe and MacDonald,[3] morphine and codeine being used as reference compounds. The results are given in Table II, from which it is estimated that codeine is approximately 1/10, and hydroxyethylmorphine 1/15, as analgesic as the parent alkaloid.

Experimental

Hydroxyethylmorphine.—A mixture of 5.7 g. of morphine, 8.3 g. of potassium carbonate, and 100 g. of ethylene carbonate[2] (in excess as solvent) was heated with stirring for seventy-five minutes at 98°, cooled, and poured into an excess of cold aqueous alkali. The solution was extracted three times with 50-cc. portions of chloroform, the extracts united and the product extracted by 20 cc. of 0.1 *N* hydrochloric acid. The solution was made alkaline and the product again extracted into chloroform; because of the marked water solubility of the derivative, it was not feasible to wash the extract. The chloroform solution was evaporated to a sirup under reduced pressure, the residue dissolved in boiling absolute alcohol, and the solution cooled, hydroxyethylmorphine crystallizing. Recrystallized from the same solvent (30 cc. of alcohol per g. of compound) the derivative was obtained as colorless crystals; m. p. 190°; yield, 4.6 g.; $[\alpha]_D$ −124.8° (methanol).

TABLE II

ANALGESIC POTENCY OF HYDROXYETHYLMORPHINE

Drug	Dose, mg./kg., as free base	Animals showing analgesia, %	Av. time to develop analgesia minutes	Average duration of analgesia minutes
Morphine	10	100	14	29
	20	100	12	80
Codeine	50	60	14	31
	100	100	14	41
Hydroxy-ethylmorphine	50	66	12	32
	100	66	12	34
	150	100	10	38
	200	100	10	58

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.26; H, 7.04; N, 4.26. Found: C, 69.02; H, 7.08; N, 4.36.

DEPARTMENT OF RESEARCH IN PURE CHEMISTRY
MELLON INSTITUTE
PITTSBURGH, PA.

RECEIVED JANUARY 28, 1948

The Ultraviolet Absorption Spectra of 1,1′- and 2,2′-Binaphthyl

BY VERNON L. FRAMPTON, JOSEPH D. EDWARDS, JR., AND HENRY R. HENZE

In a very recent article concerning the ultraviolet absorption spectra of some naphthalene derivatives, Friedel, Orchin and Reggel[1] call attention in a footnote to differences between the spectra as determined by them for 1,1′- and 2,2′-binaphthyl and those noted previously by Adams and Kirkpatrick.[2] The significance of these data is such as to warrant this communication to confirm the location of the absorption maxima reported by Friedel, Orchin and Reggel, since, as they appear to us, the ultraviolet absorption spectra of 1,1′-binaphthyl and, especially, of 2,2′-binaphthyl were of fundamental importance in the selection by Adams, *et al.*, of a binaphthyl as the basic nucleus of gossypol.

1,1′-Binaphthyl has been resynthesized[3] by three different procedures, namely: (a) by the Wurtz–Fittig reaction[4] starting with 1-chloronaphthalene; (b) according to the method of Ull-

(1) Small and Eddy, U. S. Public Health Reports, Supplement No. 138, U. S. Government Printing Office, Washington, D. C., 1938.

(2) Carlson and Cretcher, THIS JOURNAL, **69**, 1952 (1947).

(3) Woolfe and MacDonald, *J. Pharm. Exp. Therap.*, **80**, 300 (1944).

(1) Friedel, Orchin and Reggel, THIS JOURNAL, **70**, 199 (1948); see footnote (10).

(2) Adams and Kirpatrick, *ibid.*, **60**, 2181 (1938).

(3) These experimental data are drawn from a thesis presented by Joseph Daniel Edwards, Jr., to the Faculty of the Graduate School of the University of Texas in partial fulfillment of the requirements for the Master of Arts degree, January, 1948.

(4) Rodd and Linch, *J. Chem. Soc.*, 2178 (1927).

mann[5] using 1-bromonaphthalene; (c) utilizing the Grignard reaction[6] with 1-bromonaphthalene. The melting points of the samples of 1,1′-binaphthyl[7] prepared by these procedures were 157.5, 157.2 and 157.5°, respectively; a mixture of the three preparations melted at 157.5°.

In Fig. 1 are presented the ultraviolet absorption spectra for these three samples, which were determined with a Beckman quartz spectrophotometer using 95% ethyl alcohol as solvent, together with the data[8] taken from the Fig. 2 published by Adams and Kirkpatrick.[2] In our Fig. 1 are included also data recorded still earlier by Pestemer and Cecelsky[9] using a hexane solution of 1,1′-binaphthyl. The low wave length absorption band which we report is at 220–224 millimicrons, which is in satisfactory agreement with the band at 226 millimicrons reported by Friedel, *et al.*,[1]

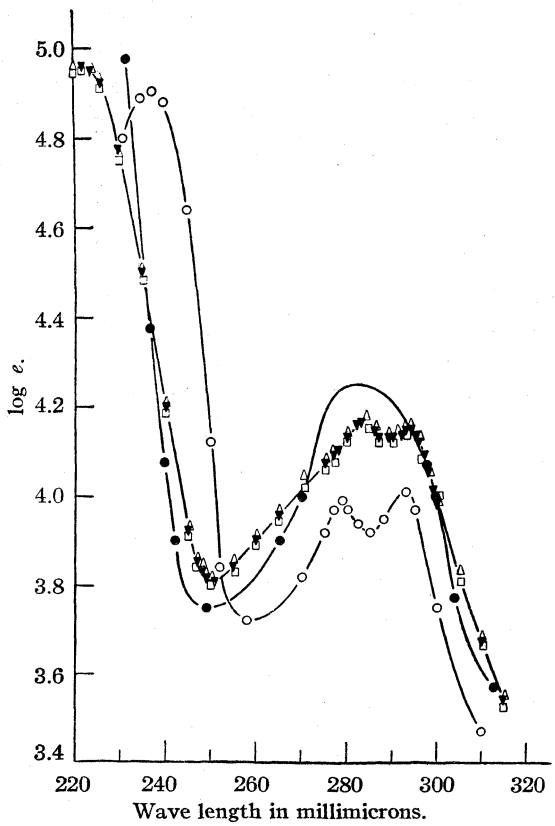


Fig. 1.—Ultraviolet absorption spectra for 1,1′-binaphthyl: ▼, 1,1′-binaphthyl prepared by the Wurtz–Fittig synthesis; △, Ullmann synthesis; □, Grignard synthesis; O, data of Adams and Kirkpatrick; ●, data of Pestemer and Cecelsky.

(5) Ullmann and Bielecki, *Ber.*, **34**, 2184 (1901).

(6) Sakellarios and Kyrimis, *ibid.*, **57**, 324 (1924).

(7) The melting point behavior is considerably influenced by the rate of heating. Samples can be shown to exhibit sintering at temperatures lower than the m. p. of 157.5° by very rapid heating. *Cf.* Orchin and Friedel, THIS JOURNAL, **68**, 573 (1946).

(8) These data were obtained using dioxane as solvent; however, identical data were reported utilizing ethyl alcohol as solvent.

(9) Pestemer and Cecelsky, *Monatsh.*, **59**, 119 (1932).

but is in disagreement with the location of the absorption band at 238 millimicrons according to Adams and Kirkpatrick.

2,2′-Binaphthyl,[10] melting at 187°, was synthesized through the Grignard reaction with 2-iodonaphthalene. The absorption spectrum for 2,2′-binaphthyl is presented in Fig. 2. In agreement with the findings of Friedel, *et al.*, a thorough investigation throughout the region 260–300 millimicrons did not yield evidence for the existence of an absorption maximum at 297 millimicrons, as reported by Adams and Kirkpatrick. Otherwise, the absorption spectra for 2,2′-binaphthyl are in reasonable agreement.

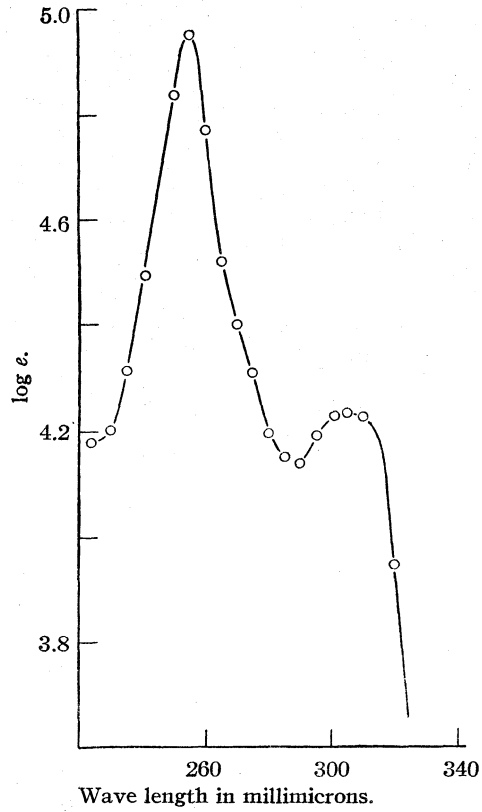


Fig. 2.—Ultraviolet absorption spectrum for 2,2′-binaphthyl.

(10) Vesely and Stursa, *Coll. Czechoslov. Chem. Commun.*, **4**, 139 (1932), reported m. p. of 187° for a sample of 2,2′-binaphthyl obtained using lithium as the coupling agent.

THE COTTON RESEARCH COMMITTEE OF TEXAS
AUSTIN, TEXAS, AND
THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN, TEXAS RECEIVED FEBRUARY 24, 1948

The Purification of Neopentane by Mercury Photosensitization[1]

BY B. DEB. DARWENT AND E. W. R. STEACIE

In a study of the mercury photosensitized reactions of neopentane it was found necessary to

prepare extremely pure samples of that hydrocarbon. The Grignard reaction of tertiary butyl chloride with methylmagnesium chloride was used to produce the neopentane. The product was washed with 85 and 95% sulfuric acid and then photobrominated to ensure the complete removal of unsaturates, since isobutene is the most likely impurity. The residual bromine and any hydrogen bromide formed were removed by distilling the mixture through 40% potassium hydroxide (aqueous) and over solid potassium hydroxide. The resulting neopentane was finally purified by low temperature distillation in a column of conventional design. The distillate was assumed to be pure when the temperature remained constant at 9.6° for thirty to sixty minutes under total reflux. This "pure" neopentane was taken off in four consecutive fractions, the purity of which was checked by determining the vapor pressure–temperature relations of large samples over a wide range of temperature. No indications of impurity could be detected.

Preliminary experiments showed that the rates of the mercury photosensitized reaction of different samples, though surprisingly low, were very variable. Samples of the unreacted and of the "partially decomposed" neopentane were analyzed by the mass spectrometer with the following results:

	Percentages					
Sample	A	B	C	D	E	F
Neopentane	96.4	99.6	99.9	100	100	100
n-Pentane	1.1	..	...	...	...	...
Dimethylcyclopropane	1.6	0.4	trace	...	...	...
C_6 hydrocarbons	1	..	...	...	...	...

in which Sample A was the "pure" unreacted neopentane and B to F were "partially decomposed" samples. It was stated by the analyst that samples D, E and F were "apparently of the same purity as the neopentane used for calibrating as obtained from Dr. F. D. Rossini, National Bureau of Standards, Standard Sample No. 299–5s. It is certified to be 99.96% pure; impurity 0.04 ± 0.02%."

Accordingly a large sample of crude (undistilled) neopentane (about 30 liters of gas) was subjected to prolonged mercury sensitization by circulating a mixture of gaseous neopentane and mercury through a quartz vessel illuminated by a low pressure mercury lamp, the radiation from which consisted largely of the unreversed 2537 Å. line, for seventy to eighty hours, roughly distilled into 5 fractions and analyzed on the mass spectrometer. The results were:

	Percentages				
Fraction no.	1	2	3	4	5
Neopentane	99 (8)[a]	99 (7)[a]	99 (6)[a]	99 (4)[a]	99 (0)[a]
Hexane	0.2	0.3	0.4	0.6	1.0

[a] The figures in parentheses are uncertain.

Hence, in the absence of very efficient fractionation, mercury photosensitization is an efficient method of obtaining neopentane of high purity. This method of purification is possible only because neopentane is remarkably resistant to attack by $Hg(^3P_1)$ atoms whereas the impurities react readily to give, ultimately, heavy polymers and non-condensable gases (hydrogen and methane) which are easily separated from the unreacted neopentane.

The Grignard reaction was carried out by Dr. A. Cambron and Mr. R. A. B. Bannard of these laboratories, and the mass spectrometer analyses by Dr. Fred L. Mohler of the National Bureau of Standards, Washington, D. C., to whom our thanks are due. The laboratory assistance of Mr. J. R. Pilon is gratefully acknowledged.

CONTRIBUTION NO. 1717 FROM THE
NATIONAL RESEARCH COUNCIL
DIVISION OF CHEMISTRY
NATIONAL RESEARCH LABORATORIES
OTTAWA, ONTARIO RECEIVED MARCH 19, 1948

The Reduction of *p*-Hydroxyformanilide by Lithium Aluminum Hydride to N-Methyl-*p*-aminophenol

BY JACOB EHRLICH

This reduction of an anilide to a secondary amine proceeds smoothly in tetrahydrofuran as solvent. The method is applicable to various amides using diethyl ether or tetrahydrofuran as solvent, to be reported in a later communication.

Experimental

A solution of 1.9 g. (0.05 mole)[1] of lithium aluminum hydride in 36 cc. of anhydrous tetrahydrofuran[2] was prepared in a 3-neck conical flask provided with sealed stirrer, thermometer, reflux condenser, hopper[3] and calcium chloride guard-tube.[4] The solution was brought to 20–25° and 2.75 g. (0.02 mole) of *p*-hydroxyformanilide was added in small portions during thirty minutes, cooling externally with ice-water to maintain this temperature. The hopper was flushed with 4 cc. of tetrahydrofuran and the charge stirred twenty minutes more at 20–25°. Dur-

(1) Assuming only one labile hydrogen (phenolic) in 1 mole of *p*-hydroxyformamilide, then 0.25 mole of $LiAlH_4$ would be destroyed prior to any reduction. The reduction of the formyl radical would consume a further 0.5 mole of $LiAlH_4$, making a 4:3 molar ratio of anilide:$LiAlH_4$. If the amido hydrogen is also labile, the ratio becomes 1:1. If the formyl hydrogen is labile, the ratio becomes 4:5. However, these calculations are only of academic interest, for the 0.02:0.05 molar ratio was arrived at empirically. If less $LiAlH_4$ is employed, the yield drops proportionally.

(2) The tetrahydrofuran was obtained from E. I. du Pont de Nemours and Co. This was rendered water and peroxide free by storing 500 cc. in an amber bottle over 75 g. of flake sodium hydroxide for two weeks, occasionally shaking. The clear, colorless supernatant liquor was decanted (from now discolored solids) for use in the reductions without further purification. On dissolving the $LiAlH_4$ in the tetrahydrofuran the heat of solution will raise the temperature to about 50°.

(3) Similar in construction (but smaller capacity) to that described by Swift and Billman, *Ind. Eng. Chem., Anal. Ed.*, **17**, 600 (1945). However, this may be omitted and the same results obtained by using a removable rubber stopper.

(4) In various reductions no special precautions, except the exclusion of atmospheric moisture, were employed, and no uncontrolled or explosive reaction was observed. However, as an added precaution, it would be desirable to conduct the reaction under an atmosphere of dry nitrogen.

ing this period a thin slush formed. The temperature was then raised to 63–66° and maintained for ten minutes. The pale pink slurry was then chilled to 20–25°, 77 cc.[5] of 3 *N* hydrochloric acid added *cautiously* from a dropping funnel (ice-water cooling as required), resulting in a pale slightly cloudy solution.

The charge then was steam-distilled (about 90 cc. distillate) to remove the solvent, digested while hot with 0.3 g. of Norit and 0.2 g. of Filter-Cel and filtered with suction. The colorless filtrate was cooled to 0–5°, 10 cc. of concentrated hydrochloric acid added, then titrated at this temperature with molar sodium nitrite solution to a strong blue streak (ten minutes end-point) on starch-iodide paper. Almost the theoretical amount was required. During the titration pale yellow nitrosamine needles separated. The crystals were filtered with suction, washed with water and dried at 55°; yield 2.66 g., m. p. 134–135°. The filtrate, on extraction with ether, yielded an additional 0.12 g.; total yield 92%.

On recrystallizing the combined crops from 10% ethanol, in the presence of a little Norit, the m. p. was raised to 135.5°, identical with purified N-nitroso-N-methyl-*p*-aminophenol prepared from photographic Metol as shown by mixed m. p.

(5) The first 20 cc. of 3 *N* hydrochloric acid must be fed very slowly, dropwise. During this period the main heat effect is evident and the bulk of the hydrogen gas evolved (by decomposition of the excess lithium aluminum hydride). Thereafter the balance may be added faster. Prior to the acid addition the calcium chloride tube is removed (*versus* any back pressure) and the flask vented to the hood.

CONTRIBUTION FROM THE
EHRLICH LABORATORY
BEVERLY HILLS, CALIFORNIA RECEIVED JANUARY 31, 1948

The Constitution of Citrinin

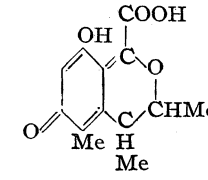
BY T. S. GORE, T. B. PANSE AND K. VENKATARAMAN

The structures originally assigned[1] to citrinin (I) and its degradation products (II) and (III) are untenable in the light of their behavior towards diazonium salts.[2] Cram[3] has now shown by synthesis and direct comparison that (III) is 4-methyl-5-ethylresorcinol, a conclusion at which we had arrived by circumstantial evidence. The 2,4 and 4,6-compounds were ruled out by the ability of (III) to form disazo dyes. Comparison of the absorption spectra and the color reactions of the bis-benzeneazo derivative of (III) with those of 2,4- and 4,6-bis-benzeneazoresorcinol and a series of analogous dyes showed that (III) is 5-methyl-4-ethylresorcinol (IV) or 4-methyl-5-ethylresorcinol (V). The absorption curves for 2,4-bis-benzeneazoresorcinol, 2,6-bis-benzeneazo-5-methyl-4-ethyl resorcinol and the bis-benzeneazo derivative of (III) had a well-defined, high intensity band in the visible region ($\lambda_{max.}$ ∽ 415 mμ; $\epsilon_{max.}$ ∽ 60,000). 4,6-bis-Benzeneazoresorcinol and 4,6-bis-benzeneazo-2-ethylresorcinol exhibited a band of relatively low intensity in the visible region ($\lambda_{max.}$ ∽ 415 mμ; $\epsilon_{max.}$ ∽ 20,000) and absorption maxima in the near ultraviolet ($\lambda_{max.}$ ∽ 340 mμ; $\epsilon_{max.}$ 36,000).

(1) Raistrick, Robinson, *et al.*, *Phil. Trans. Roy. Soc.*, **B220**, 269, 297 (1931).
(2) Gore, *et al.*, *Nature*, **157**, 333 (1946).
(3) Cram, THIS JOURNAL, **70**, 440 (1948).

Shah and Robinson's synthesis[4] of (IV) was repeated, and it was found to melt at 79–82° (Shah and Robinson, m. p. 75–80°), while (III) as a monohydrate melts at 68–69°, and after dehydration at 98–99°; the m. p. of (III) was considerably depressed by admixture with (IV). Cram[3] has quoted us erroneously as reporting a m. p. of 65–70° for (III). The bis-benzeneazo derivatives of (III) and (IV) melted, respectively, at 171° and 188°, and the mixed m. p. was lower. It followed therefore that (III) is 4-methyl-5-ethylresorcinol. However, this is in conflict with the observation of Hetherington and Raistrick[1] that neither of the acids obtained by oxidation of the dimethyl ether of (III) gave the anthrachrysone reaction. We prepared 3,5-dimethoxy-2-methylbenzoic acid (VII) by the methylation of the corresponding α-resorcylic acid,[5] and found that it readily gave a bordeaux-red color on warming with sulfuric acid (the anthrachrysone reaction); Cram has recorded that the acid (VI) synthesized by him corresponds in its properties to one of Hetherington and Raistrick's acids. The m. p. (157–158°) reported for (VI) by Cram is in agreement with ours, while Hetherington and Raistrick's two acids melted at 142–146° and 98–99°.

From the formulation of (III) as 4-methyl-5-ethylresorcinol, the properties of (II), including the formation of (III) from (II) by alkali fusion, are fully explained by the structure 4-methyl-5-(1-methyl-2-hydroxy)-propyl-resorcinol, proposed



by Cram. The experimental results of Hetherington and Raistrick[1] and the behaviour of citrinin towards diazonium salts[2] would then agree with the above constitution for citrinin.

(4) Shah and Robinson, *J. Chem. Soc.*, 1491 (1934).
(5) Woodward and Reed, THIS JOURNAL, **65**, 1569 (1943).

DEPARTMENT OF CHEMICAL TECHNOLOGY
THE UNIVERSITY
BOMBAY, INDIA RECEIVED APRIL 17, 1948

The Employment of Sodium Hydride as a Condensing Agent

BY NATHAN GREEN AND F. B. LAFORGE

Sodium hydride is now being produced on a large scale, and its advantages as a catalyst in various organic reactions have been indicated by Hansley and Carlisle.[1] Its use in this Laboratory in the preparation of ethyl β-oxocaprylate, ethyl β-carbethoxy-α-oxo-enanthate, and 5-carbethoxy-dihydrocinerone has been described in previous articles.[2,3] We have since employed this reagent in

(1) Hansley and Carlisle, *Chem. Eng. News*, **23**, 1332 (1945).
(2) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947).
(3) LaForge and Soloway, *ibid.*, **69**, 2932 (1947).

the preparation of carbethoxy derivatives of other ketones, and of their substitution products, for Claisen condensations of alkyl esters with ketones, and for cyclizations of the Dieckman type. It probably could be used with advantage for many reactions where powdered sodium or sodium ethylate is usually employed. We are therefore presenting some observations which we have made in the use of this catalyst in these reactions.

The reaction of ketones with ethyl carbonate starts promptly when the finely ground catalyst is employed, but with the coarser material there is a considerable lag, or occasionally the reaction may not start at all. Since at present sodium hydride is supplied only in the coarser size, which is easier and less hazardous to handle but less reactive, it is generally necessary to reduce the particle size by some means of grinding.

A laboratory apparatus for this purpose has been designed by V. L. Hansley[4] in which reactions are carried out in a revolving closed cylinder containing steel balls. Since this rather expensive equipment will not be generally available, we have employed the same principle in connection with the usual glass apparatus. When several ceramic spheres about 13 mm. in diameter are placed in the reaction flask with the solvent and the ethyl carbonate, and rolled slowly over the catalyst with a glass paddle stirrer for about thirty minutes, the particle size of the sodium hydride is reduced sufficiently so that the reaction starts soon on addition of a small quantity of the ketone. Care should be taken not to add very much of the ketone until the reaction, which is observed by the evolution of hydrogen, has definitely started. When the experiment is performed in this manner, the yield in the case of ethyl β-oxocaprylate is usually 80 to 85% of the theoretical.

In the preparation of sodium derivatives of β-keto esters the reaction starts at once regardless of the physical state of the sodium hydride, and the addition of the ester is regulated according to the rate of evolution of hydrogen. The solvent is generally anhydrous ether. Dioxane, in which most sodium enolates are soluble, is sometimes used.

Alcohol-free sodium alcoholates are conveniently prepared by dropping a slight excess of the alcohol on sodium hydride covered with benzene and, after refluxing, distilling off the solvent until it is alcohol-free, as shown by measurement of the refractive index. Sodium hydride dissolves more readily than sodium lumps or wire.

The following examples illustrate the employment of sodium hydride in reactions referred to above.[5]

Ethyl-3-oxo-6-octenoate[6] was prepared from 58 g. (2.4 moles) of sodium hydride covered with 300 ml. of dry ether and 283 g. (2.4 moles) of ethyl carbonate in a nitrogen atmosphere by dropping 136 g. (1.2 moles) of 5-heptene-2-one into the stirred suspension over a period of five hours. More ether was added as the contents of the flask thickened. Acetic acid was added in quantity equivalent to the sodium hydride diluted with ice and water, and the reaction product was isolated from the ethereal solution by removing first the ether and then the excess ethyl carbonate in vacuum: b. p. 110–120° (10 mm.), $n^{25}D$ 1.4460, yield 188 g. (85%).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.67; H, 8.80.

2,4-Nonanedione.—A mixture of 28.8 g. (0.2 mole) of ethyl caproate and 12.7 g. (0.22 mole) of dry acetone was added to 4.8 g. (0.2 mole) of sodium hydride covered with 10 ml. of dry ether. The evolution of hydrogen started after refluxing for several minutes, and more ether was added as solid material separated. Refluxing was continued for one hour. Ice and water containing a suitable quantity of sulfuric acid were added, and the reaction product was isolated from the ethereal solution and distilled from a modified Claisen flask: b. p. 94–98° (11 mm.), $n^{25}D$ 1.4222, yield 16.8 g. (54%).

2,5-Dioxo-1,4-cyclohexandicarboxylic Acid Diethyl Ester.—The Dieckman cyclization between two molecules of ethyl succinate occurs smoothly on addition of the ester to two equivalents of sodium hydride covered with a small quantity of ether and refluxing until the evolution of hydrogen has ceased. Upon addition of dilute acid the reaction product separates in crystalline form on removal of the ether and it can be recrystallized from ethanol (m. p. 130–131°).

Ethyl β-Carbethoxy-γ-oxo-pelargonate.—To 4.8 g. (0.2 mole) of sodium hydride covered with 100 ml. of ether, 37.2 g. (0.2 mole) of ethyl β-oxocaprylate was slowly added with stirring, more ether being added as the contents of the flask thickened. It was refluxed for thirty minutes, after which 37 g. (0.22 mole) ofe thyl bromoacetate was added dropwise at a rate to cause gentle refluxing of the ether. The reaction was completed by further refluxing for thirty minutes, after which the separated sodium bromide was dissolved by addition of water containing 5% of sulfuric acid. The ethereal layer was washed and dried and the solvent removed. The residue was distilled on a modified Claisen flask: b. p. 133–136° (0.4 mm.), $n^{25}D$ 1.4388. The yield was 46 g. (84.5%).

Anal. Calcd. for $C_{14}H_{24}O_5$: C_2H_5O, 32.4. Found: C_2H_5O, 33.0.

U. S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH ADMINISTRATION
BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
BELTSVILLE, MARYLAND
RECEIVED MARCH 10, 1948

(4) Private communication from V. L. Hansley of E. I. du Pont de Nemours and Co., Niagara Falls, N. Y.

(5) We wish to express our appreciation to the E. I. du Pont de Nemours and Co. for donating the sodium hydride we employed in this and previous work.

(6) Prepared in collaboration with S. B. Soloway.

The Action of Copper Sulfate on the Phenylosazones of the Sugars. VI.[1] Gentiobiose Phenylosotriazole[2]

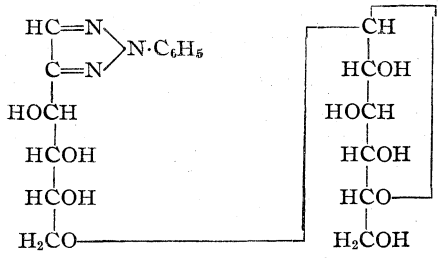
BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

In continuation of the investigation of the conversion of the sugar phenylosazones to the corresponding phenylosotriazoles through the action of copper sulfate, we have prepared the phenylosotriazole of gentiobiose. This phenylosotriazole differs from those described in the previous articles in that its crystals contain one molecular equivalent of ethanol which is tenaciously retained at ordinary temperatures even in moderately high

(1) Number V was published in THIS JOURNAL, **69**, 1461 (1947).

(2) Presented in part before the Division of Sugar Chemistry and Technology at the Chicago meeting of the American Chemical Society, April 19–23, 1948.

vacuum but is eliminated *in vacuo* at elevated temperatures. It is also unique in that its heptaacetate and heptabenzoate crystallize readily whereas, among the other disaccharide phenylosotriazoles investigated, only one crystalline acyl derivative has been obtained (cellobiose phenylosotriazole heptaacetate). Acid hydrolysis of gentiobiose phenylosotriazole produces a high yield (93%) of D-glucose phenylosotriazole and D-glucose (65%) as expected from the accompanying formula.



Gentiobiose Phenylosotriazole

We are indebted to Mr. Charles A. Kinser and Mrs. Betty Mount for the microchemical analyses.

Experimental

Gentiobiose Phenylosotriazole.—To a suspension of 10 g. of gentiobiose phenylosazone[3] in 900 ml. of boiling water was added a hot solution of 5.3 g. (1.1 molecular equivalents) of copper sulfate pentahydrate in 100 ml. of water. Solution of the phenylosazone took place rapidly and after refluxing for thirty minutes the solution was cooled, filtered, and the excess copper removed from the filtrate as the sulfide; the copper-free solution was neutralized with 10 g. of barium carbonate and following filtration, concentrated *in vacuo* to a thick reddish sirup. The sirup was dried by successive evaporations with three 25-ml. portions of absolute alcohol, and dissolved in 25 ml. of warm absolute alcohol, filtered to remove a small amount of inorganic contaminant and diluted with 35 ml. of ether; upon scratching, the product separated as somewhat gelatinous flocs which were recovered by filtration and washed with cold absolute alcohol and ether; yield 5.3 g. An additional 1.2 g. of product was obtained by concentration of the mother liquor; total yield 6.5 g. (71%). The material was recrystallized from 5 parts of absolute alcohol forming minute needles which melted at 91–93°[4] with foaming and rotated −34.3° in aqueous solution (*c*, 0.83). Analyses showed that the material contained one molecular equivalent of ethanol of crystallization which was retained tenaciously *in vacuo* at temperatures below the sintering point; at 97° *in vacuo* the alcohol was removed leaving an amorphous glassy material of no definite melting point; its analysis corresponded closely to that of an unsolvated disaccharide phenylosotriazole. The crystalline alcoholate was readily soluble in water, pyridine and hot alcohol and sparingly soluble in ether, acetone, ethyl acetate and cold alcohol. Upon separating from solution in impure form it shows a marked tendency to form gelatinous precipitates rather than discrete crystals.

Anal. Calcd. for $C_{18}H_{25}N_3O_9 \cdot C_2H_5OH$: C, 50.73; H, 6.60; loss on drying, 9.7. Found: C, 50.94; H, 6.39; loss on drying, 9.5.

Anal. (of the alcohol-free amorphous material). Calcd. for $C_{18}H_{25}N_3O_9$: C, 50.58; H, 5.90. Found: C, 50.56; H, 5.99.

On refluxing 1.2 g. of the crystalline alcoholate with 50 ml. of 0.5 *N* hydrochloric acid for six hours and chilling the solution, a 93% yield of D-glucose phenylosotriazole (m. p. 195–196°) was obtained and the concentrated aqueous mother liquor, after neutralization with silver carbonate, yielded 65% of D-glucose ($[\alpha]^{20}D$ +52.5°).

Gentiobiose Phenylosotriazole Heptaacetate.—A solution of 1.0 g. of gentiobiose phenylosotriazole monoalcoholate in a mixture of 8 ml. of acetic anhydride and 0.25 g. of fused sodium acetate was heated on the steam bath for two hours, cooled, and poured into ice water; the crystalline heptaacetate (1.6 g., quantitative) was recrystallized from 10 parts of alcohol and formed clumps of very fine needles melting at 144–146° and rotating −28.1° in chloroform solution (*c*, 0.84). It was readily soluble in chloroform, acetone–ether and warm alcohol and nearly insoluble in water and hexane.

Anal. Calcd. for $C_{32}H_{39}N_3O_{16}$: C, 53.26; H, 5.45; CH_3CO, 41.8. Found: C, 53.53; H, 5.62; CH_3CO, 41.6.

Gentiobiose Phenylosotriazole Heptabenzoate.—To a solution of 0.5 g. of gentiobiose phenylosotriazole monoalcoholate in 5 ml. of pyridine was added 2 ml. of benzoyl chloride; after standing at 25° for twenty-four hours the mixture was poured into ice water and the gummy precipitate washed by decantation with dilute sodium bicarbonate solution and water. The damp precipitate was digested on the steam-bath with 25 ml. of alcohol when spontaneous crystallization occurred; the cooled mixture was filtered and washed with alcohol yielding 1.2 g. (quantitative) of the heptabenzoate. The compound was recrystallized by dissolving it in 10 parts of chloroform and adding 20 parts of hexane or 50 parts of absolute alcohol; it crystallized as fine, short needles melting at 122–123° and rotating +1.5° in chloroform solution (*c*, 0.88). It is soluble in chloroform, ether, acetone and pyridine and sparingly soluble in water, hexane and hot alcohol.

Anal. Calcd. for $C_{67}H_{53}N_3O_{16}$: C, 69.60; H, 4.62; C_6H_5CO, 63.6. Found: C, 69.40; H, 4.57; C_6H_5CO, 63.3.

CONTRIBUTION FROM THE
FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE OF HEALTH
EXPERIMENTAL BIOLOGY AND
MEDICINE INSTITUTE
CHEMISTRY LABORATORY
BETHESDA, MARYLAND

RECEIVED MAY 3, 1948

(3) Berlin, THIS JOURNAL, **48**, 1107 (1926).

(4) The melting points were made with the stem of the thermometer fully immersed in the heated bath. The rotations are specific rotations $[\alpha]^{20}D$; the tube length was 4 dm. and *c* is the concentration in grams in 100 ml. of solution. All the crystalline compounds were recrystallized to constant m.p. and rotation.

The Separation of Iodine-131 from Tellurium

BY MILTON LEVY, ALBERT S. KESTON AND SIDNEY UDENFRIEND

The irradiated unit[1] supplied by the U. S. Atomic Energy Commission as a source of I^{131} contains 50 g. of tellurium. The chromic or nitric acid oxidations such as have been used in working up cyclotron targets proved cumbersome in the case of the pile units because of the large amount of tellurium. The following method based on fusion with sodium hydroxide has proven rapid and reliable.

The tellurium powder is transferred to a 100-ml. Pyrex kjeldahl flask (through a powder funnel) containing 5 g. of sodium hydroxide pellets. The

(1) Catalog item No. 37, "Radioisotopes," Catalog No. 2, revised September, 1947, U. S. Atomic Energy Commission, Oak Ridge, Tenn.

mixture is shaken and heated gently to drive out water and then to a dull red (above 452°, the m. p. of tellurium). The mixture is held at this high temperature for about five minutes with occasional shaking during the progress of heating. The flask is allowed to cool somewhat and then plunged into 100 ml. of water in a large mortar. The flask breaks and both it and the solid contents are coarsely powdered with a pestle. The aqueous layer with suspended tellurium is transferred to a liter erlenmeyer flask with suction and the residue in the mortar extracted with several 50-ml. portions of hot water until only minor amounts of radioactive materials are being transferred. The extracts and washings are heated to boiling to coagulate the precipitate. The solution is cooled and filtered to remove tellurium.

The remainder of the isolation requires an all-glass-standard taper distilling apparatus consisting of a 500-ml. flask, an adapter with addition tube, an adapter and condenser and a receiving adapter arranged to dip into a receiving solution. The filtered alkaline extract is run into the distilling flask, which contains a few boiling stones, and evaporated to a volume of about 50 ml. The distillate contains no radioactive material and is discarded. A concentrated solution of potassium permanganate is added in excess to oxidize all iodine in the alkaline solution to iodate. The receiving flask is changed to one containing a dilute solution of sodium sulfite and sodium carbonate (about 1 mg. of each in several ml. of water). The delivery tip is covered by this solution. Fifty ml. of concentrated sulfuric acid is added through the addition tube. Care is necessary because of the heat developed. After the sulfuric acid has been added, 1 g. of oxalic acid dissolved in a minimal amount of hot water is added. The iodate is reduced to iodine. The mixture is now distilled until substantially all of the radioactivity has collected in the receiver where the iodine is converted to iodide. The solution of iodide containing some carbonate, sulfite and sulfate is used directly in most of our work.

The tellurium residue when dissolved in nitric acid containing a small amount of chloride ion, gave, in the presence of excess dissolving silver, a silver chloride precipitate which contained relatively little radioactivity. When unirradiated tellurium to which I^{131} has been added is dissolved in this way, substantially all the radioactivity is coprecipitated with the silver chloride. Portions of the irradiated tellurium gave large amounts of I^{131} in the silver chloride precipitate. Since the tellurium residue from the pile unit contained little I^{131} and all other fractions except the final product contained not more than 10% of the radioactivity of the final product, we believe the yield to be 85–95% of the I^{131} originally present.

The exposures of the operators (two) during the working up of a unit by the method is minimized by the use of lead bricks, long handled tongs and rapid handling of materials. On pocket ionization chambers 0.04–0.06 roentgen was registered on the day of processing a unit. This is well below the allowed maximum of 0.1 roentgen per day. Film badges[2] worn during the week including the day of the preparation showed less than ten per cent. of the permitted maximum exposure for the week.

The irradiated tellurium units used in this investigation were supplied by the Clinton Laboratories and obtained on allocation from the U. S. Atomic Energy Commission.

This work was supported by a grant from the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

(2) Film Badge Service, Tracerlab, Inc., Boston, Mass.

DEPARTMENT OF CHEMISTRY
NEW YORK UNIVERSITY
COLLEGE OF MEDICINE
NEW YORK 16, N. Y.

RECEIVED MARCH 11, 1948

Preparation of *t*-Butylamine

BY D. E. PEARSON, J. F. BAXTER AND K. N. CARTER

Tertiary butylamine has been made by the hydrogenation of 2,2-dimethylethylenimine[1] and by the reaction of *t*-butylmagnesium chloride and methoxyamine.[2] Simple hydrolysis of the readily obtainable *t*-butylurea (E. K.) with aqueous alkali is too slow for satisfactory use. Smith and Emerson[3] accomplished the hydrolysis indirectly by reaction with phthalic anhydride and subsequent hydrolysis of the resulting phthalimide. It has now been found that the amine is readily prepared from *t*-butylurea by saponification in aqueous ethylene glycol solution. The procedure shown has been checked according to "Organic Syntheses" recommendations.

$$(CH_3)_3CHNHCONH_2 + 2NaOH \longrightarrow (CH_3)_3CNH_2 + NH_3 + Na_2CO_3$$

Procedure

A 1-liter round-bottomed, S. T. flask was equipped with an upright condenser, and a glass tubing was led from the top of the condenser to a small flask immersed in ice-water. The trap was unnecessary, if sufficiently cold water was used in the condenser. The flask was charged with sodium hydroxide (60 g., 1.5 moles) dissolved in 75 cc. of water, *t*-butylurea (70 g., 0.6 mole) and 225 cc. of ethylene glycol (practical grade), and the mixture refluxed for four hours. The liquid temperature was 115° when refluxing started and fell to 86° at the end. The *t*-butylurea gradually dissolved, and a gelatinous mass of sodium carbonate was formed. Shorter reflux gave lower yields; longer periods gave no increase. Lower concentrations of ethylene glycol gave proportionately lower yields. The flask was then cooled, equipped for distillation and the fraction boiling at 40–60° was collected in an ice-cooled receiver. The crude amine, including any in the trap, weighed 37–39 g. It was dried with 5–7 g. of solid sodium hydroxide. If a lower, aqueous

(1) Karabinos and Serijan, THIS JOURNAL, **67**, 1856 (1945); Campbell, Sommers and Campbell, *ibid.*, **68**, 140 (1946).

(2) Jones, *J. Chem. Soc.*, 781 (1946).

(3) Smith and Emerson, THIS JOURNAL, **67**, 1862 (1945).

layer formed, it was removed in a small separatory funnel, and the amine was redried with fresh sodium hydroxide for eight to ten hours. The filtered amine was then distilled through a short, Vigreux column into an ice-cooled receiver equipped with a soda-lime tube. The yield was 31–34 g. (71–78%), b. p. 44–46°, m. w. 73 by glass electrode titration. Double quantities also were used with no significant change in yields. It is suggested that the procedure, with obvious modifications in details, is probably applicable to the preparation of *t*-amylamine from *t*-amylurea.

FURMAN CHEMICAL LABORATORY
VANDERBILT UNIVERSITY
NASHVILLE 4, TENNESSEE RECEIVED FEBRUARY 12, 1948

Colored Complexes of Tungsten Hexafluoride with Organic Compounds

BY HOMER F. PRIEST AND WALTER C. SCHUMB

It was observed in the course of a study of the reduction of tungsten hexafluoride by organic compounds that when the hexafluoride was dissolved in certain of these compounds deep colors were produced. Apparatus was devised in which tungsten hexafluoride could be added as liquid to a sample of the organic liquid, an atmosphere of dry air being maintained above the solution. Solutions were also prepared quantitatively by distilling the pure hexafluoride into a known weight of organic solvent contained in weighed cylindrical comparison tubes for a Coleman spectrophotometer (Model 14). The tubes could be sealed off and reweighed so as to obtain the weight of added fluoride. Spectrometric traces were made, all values being obtained by use of the potentiometer drum rather than by direct galvanometer deflection.

The tungsten hexafluoride had been prepared from metallic tungsten and fluorine, followed by redistillation to eliminate any WOF_4 which might be present. Analysis of the hexafluoride showed it to be better than 99% pure. The organic solvents employed were of carefully selected purity; thus, analytical reagent grade, thiophene-free benzene; reagent grade acetone, toluene, *sym*-tetrachloroethane, ethyl alcohol and diethyl ether; Eastman Kodak Co. pure grade cyclohexane, cyclohexanone, and *n*-decane; dioxane free from unsaturated compounds. Most of the liquids were dried over anhydrous calcium sulfate and redistilled.

A summary of the qualitative observations made on the solution of tungsten hexafluoride in the different organic solvents is shown in Table I.

From these results it appears that the presence of certain functional groups in the solvents employed results in similar colors; thus the colors in benzene and toluene are similar, as are those in diethylcarbitol and diethyl ether. Ketones, such as acetone and cyclohexanone, give similar colors which intensify on standing and may be due to polymerization of the ketone rather than to the formation of a complex with the hexafluoride. Chlorinated solvents and hydrocarbons containing no functional groups give no colors. Alcohol also gives no color, but it is to be expected that alcoholysis of the hexafluoride could interfere with complex formation.

Because of the intense color given by benzene, a quantitative study was made of this solvent. At concentrations above 0.04 molar the color appeared to remain stable for several weeks. Solutions were made up at three concentrations of tungsten hexafluoride, 0.048, 0.118 and 0.121 molar, and the optical densities of these solutions were measured at 520, 550, 560 and 570 μ. A plot of optical density *vs.* concentration of tungsten hexafluoride gave straight lines, indicating that the colored material follows Beer's law, and that the concentration of the colored complex is directly proportional to the tungsten hexafluoride concentration. By absorption measurements carried out on four solutions of tungsten hexafluoride and benzene in carbon tetrachloride, results were obtained which led to the conclusion that the concentration of the colored complex also varies directly as the benzene concentration, from which fact it is concluded that the complex contains one molecule of benzene per molecule of the hexafluoride, $WF_6 \cdot C_6H_6$.

It has been noted previously by others,[1] as well

TABLE I

EFFECT OF DISSOLVING TUNGSTEN HEXAFLUORIDE IN ORGANIC LIQUIDS

Solvent	Color of solution	Effect of cooling to −78°	Effect of dilution	Remarks
Benzene	Red	White crystals	Orange–yellow	
Toluene	Red	None	Orange–yellow	Color retained when frozen
Acetone	Red	None	Orange	Color intensified on standing
Cyclohexanone	Red	None	Orange	Some intensification on standing
Ethyl alcohol	None	White crystals		
Carbon tetrachloride	None	White crystals		
sym-Tetrachloroethane	None	Solidified		
n-Decane	None	Solidified		
Cyclohexane	None	Solidified		
Diethylcarbitol	Violet–brown	None	Brown	
Diethyl ether	Violet–brown	None	Brown	
Dioxane	Pale red	White solid	Orange	Some crystals deposited

(1) See, for example, Fischer, *Z. anorg. Chem.*, **81**, 170 (1930); Kalischer, "Zur Kenntnis der Halogenide des höherwertigen Wolframs und Molybdäns," Berlin, 1902; Roscoe, *Ann.* **162**, 351 (1872).

as by ourselves, that colored solutions are also formed by tungsten hexachloride in various solvents; but we feel that the two cases are not comparable, for the following reasons. (1) Tungsten hexachloride itself has a blood-red color, so that solutions in various solvents showing a red, brown, or yellow color are reasonably to be expected, whereas tungsten hexafluoride itself is colorless. (2) The red solution of the hexafluoride in benzene freezes to a colorless crystalline solid, which on warming regains its color. (3) If the hexafluoride were reduced by solvent to lower valences of tungsten, the solution could not be expected to follow Beer's law, as was found to be the case. Furthermore, the colored solution of the hexafluoride in benzene remained unaltered for weeks, indicating lack of reaction, whereas the hexachloride solutions change gradually, owing to reduction of the tungsten.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

RECEIVED MARCH 11, 1948

Thiodiglycol Monoacetate by the Photochemical Addition of Mercaptoethanol to Vinyl Acetate

BY WALTER H. C. RUEGGEBERG, JACOB CHERNACK, IRA M. ROSE AND E. EMMET REID

The photochemical addition of mercaptans to olefins has been studied in this Laboratory[1] for several years. Recently, the photoaddition of ethanolmercaptan to vinyl chloride yielding 2-chloroethyl-2-hydroxyethyl sulfide (semi-mustard) was reported by Fuson and Ziegler[2] and from this Laboratory.[3] Inasmuch as the monoacetate of thiodiglycol has not been reported previously in the literature to the best of our knowledge, it appeared worthwhile to synthesize this half-ester through the photochemical addition of ethanolmercaptan to vinyl acetate.

It was soon learned, however, that the reaction rate depended strongly upon the purity of vinyl acetate used. Thus, for example, when freshly distilled vinyl acetate was mixed with mercaptoethanol, the mixture warmed up immediately. Titration of the residual mercaptan with iodine in methanol solution showed that 80% of the mercaptan had reacted after the first hour. On the other hand, if stabilized vinyl acetate (Eastman Kodak Co., practical grade) is employed in the process, no reaction is observed until the mixture is irradiated from an S-4, 100 watt mercury vapor lamp (General Electric Co.) in the presence of 1% of diphenyl disulfide, as catalyst.

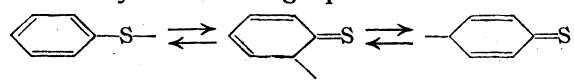
$$HOCH_2CH_2{-}S{-} + CH_2{=}CH{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \longrightarrow$$

$$HOCH_2CH_2{-}S{-}CH_2{-}\underset{\underset{O}{\|}}{CH}{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \quad (a)$$

$$HOCH_2CH_2{-}S{-}CH_2{-}\underset{\underset{O}{\|}}{CH}{-}O{-}CCH_3 + HOCH_2CH_2SH \longrightarrow$$

$$HOCH_2CH_2{-}S{-}CH_2CH_2{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH_3 + HOCH_2CH_2S{-} \quad (b)$$

Although disulfides such as diamyl disulfide are known to accelerate the photoaddition of mercaptoethanol to vinyl chloride,[3] it has been shown that diphenyl disulfide is a catalyst superior to aliphatic disulfides in this type of reaction.[1] Two reasons for this behavior may be cited. First, diphenyl disulfide absorbs light more strongly than dialkyl disulfides in the visible and near ultraviolet regions of the spectrum,[1] indicating that free radicals are more easily obtained; secondly, the stabilizing influence of resonance on the thiophenyl radicals should prolong their lives thus increasing reaction probability. The three resonance forms of the thiophenyl radicals may be represented by the following equilibria



In the disulfide-free reaction, the primary dissociation is that of the splitting of the S—H bond

$$HOCH_2CH_2SH + h\nu \longrightarrow HOCH_2CH_2{-}S{-} + H{-}$$

This reaction is then followed by a chain mechanism given by equations (a) and (b), above.

Thiodiglycol monoacetate, so prepared, is a water white liquid resembling thiodiglycol itself in odor and having the physical properties listed in Table I. It is soluble in water, benzene, carbon tetrachloride, chloroform, ethyl ether and acetone but insoluble in hexane or cyclohexane.

TABLE I

SOME PHYSICAL PROPERTIES OF THIODIGLYCOL MONOACETATE[a]

Temp., °C.	Density, g./ml.	Refractive index n^T_D	Molar refractivity[b] found	Viscosity, centipoises
9.5	1.1671	....	...	26.96
10	1.1666	1.4916	40.81	...
20	1.1576	1.4879	40.87	...
25	1.1531	....	...	12.43
30	1.1485	1.4841	40.92	...
35.8	1.1433	....	...	8.22
			Mean	40.87

[a] Surface tension at 28.9°, 41.2 dynes/cm. (du Nouy method). [b] The calculated value of the molecular refractivity is 40.78.

Experimental

Photosynthesis in the Absence of Catalysts.—Mercaptoethanol, 33.2 g., obtained from the Carbide and Carbon Chemicals Corporation was added slowly to 92.4 g. of freshly distilled, unstabilized vinyl acetate, originally obtained from Eastman Kodak Company. Immediately upon mixing, an exothermic reaction ensued. After

(1) Rueggeberg, *et al.*, reports on file at the Army Chemical Center; not currently available in the published literature.
(2) Fuson and Ziegler, *J. Org. Chem.*, **11**, 510 (1946).
(3) Rueggeberg, Cook and Reid, *ibid.*, **13**, 110 (1948).

standing one hour, an iodimetric titration of the reaction mixture in methanol indicated that about 80% of the mercaptan had undergone reaction. The mixture was allowed to stand at room temperature for one week prior to being distilled. Distillation of the product resulted in the recovery of unused mercaptoethanol and vinyl acetate and a residue yield of crude thiodiglycol monoacetate weighing 54.4 g. This material on distillation boiled at 137–138° at 8 mm.; yield of distilled product, 51%. *Anal.* Calcd. for $C_6H_{12}O_3S$: S, 19.5. Found: S, 19.2.

Photosynthesis in Presence of Diphenyl Disulfide.—Vinyl acetate, 90 g., (practical grade, stabilized) obtained from the Eastman Kodak Company was mixed with 78 g. of mercaptoethanol obtained from the Carbide and Carbon Chemicals Corporation. No reaction ensued. These reagents together with 0.8 g. of diphenyl disulfide (1% of the mercaptan used) were placed in a 300-ml. Pyrex test-tube and suspended in a water-bath at 20–25°. An S-4, 100-watt mercury vapor lamp was also suspended under water and placed 11 cm. from the center of the test-tube. On turning on the light the temperature of the reaction mixture rose from 22 to 34° receding slowly after about one hour of irradiation. Irradiation was continued for an additional two hours and subsequently, the reaction product was distilled. After two distillations 72 g. of a product was obtained boiling at 147.7 to 148° at 13–14 mm.

Anal. Calcd. for $C_6H_{12}O_3S$: C, 43.9; H, 7.4; S, 19.5. Found: C, 43.7; H, 7.4; S, 19.9.

Acknowledgment.—The authors are indebted to Messrs. N. Beitsch, S. Sass, E. A. Green and B. Zeffert for having performed the analytical and physical work presented in this paper.

CHEMICAL CORPS TECHNICAL COMMAND
ARMY CHEMICAL CENTER, MARYLAND

RECEIVED JANUARY 14, 1948

Preparation of Vanillonitrile and Vanillic Acid from Vanillin

BY CONRAD SCHUERCH, JR.

The acid catalyzed condensation of hydrazoic acid with aldehydes is included in the more general Schmidt reaction,[1] and in the case of acetaldehyde, benzaldehyde and *m*-nitrobenzaldehyde, results in the corresponding nitriles and N-substituted formyl derivatives.

$$\text{I.}\quad RCHO + HN_3 \xrightarrow{H^+} RC{\equiv}N + H_2O + N_2$$

$$\text{II.}\quad RCHO + HN_3 \xrightarrow{H^+} RNH{-}CHO + N_2$$

Vanillin has now been found to react readily in the presence of sulfuric acid according to equation I, and crystalline vanillonitrile has been easily isolated in a yield of about 70%. The formanilide, which was presumably formed at the same time according to equation II, did not interfere appreciably in the purification of the nitrile. When the original reaction mixture was diluted with water and boiled, hydrolysis of the nitrile occurred and almost pure vanillic acid crystallized in more than 70% yield from the liquors. This observation is of interest because vanillic acid is not readily available by the direct oxidation of vanillin, and because Pearl's catalytic oxidation with silver oxide[2] was found to be somewhat sensitive to obscure differences in the experimental conditions. Substitution of veratraldehyde for the vanillin used in the condensation with hydrazoic acid resulted in more than an 80% yield of crystalline veratric acid, and a small amount of 4-aminoveratrole (equation II) was also isolated from the hydrolysate.

As would be expected from the known reactions of ketones and the mechanism recently proposed for the Schmidt reaction[3,4,5,6] vanillin reacted with hydrazoic acid in the presence of reagents such as a dioxane solution of hydrogen chloride, that are milder than sulfuric acid. Although it is probable that a proper choice of solvent would give a homogeneous system and a smooth condensation with much smaller quantities of acid than those now used, the decrease might well alter the relative amounts of the products formed.[1]

Acknowledgment.—The author wishes to express his gratitude to Professor C. B. Purves for his kind interest and assistance in this and related work.

Vanillonitrile and Vanillic Acid.—One hundred grams (0.658 mole) of pure vanillin was dissolved completely in 375 ml. of concentrated reagent grade sulfuric acid kept at 0–10° in a 2-liter 3-necked flask, with mercury-sealed stirrer, condenser, thermometer and gas exit tube attached. Powdered sodium azide (45 g., 0.69 mole), contained in a small flask attached to the reaction vessel by means of a rubber connector, was added to the red solution at 0–11° over a period of one and one-half hours. The cooling bath was removed and the mixture was stirred for another half hour. The flask was again chilled and about 900 ml. of distilled water was added cautiously from a separatory funnel without allowing the temperature to rise above 18°. This addition caused the nitrile to separate as a yellow solid which completely filled the aqueous layer. When desired, the nitrile could be extracted with ether, and isolated after washing the extract with small amounts of sodium bisulfite and sodium bicarbonate solutions. The yield from smaller quantities of reactants was about 70% and most of the product melted at 87.5–88.3°; m. p. 89–90° is the recorded value for vanillonitrile.[7]

When vanillic acid was required, the original reaction mixture was diluted with 900 ml. of water as already described. The stirrer and thermometer were then removed and washed with 100 ml. of water which was added to the reaction flask, and the mixture boiled gently under reflux. Crystals of vanillic acid appeared after two and one-half hours, and after three hours of boiling the mixture was allowed to cool overnight. The crystals were filtered with suction under an efficient hood, washed five times with a total volume of 1700 ml. of distilled water and dried: yield of vanillic acid 81.5 g. or 73.8%; m. p., 201–203°; and neutralization equivalent (by electrometric titration to *p*H 7), 171. Calcd. for vanillic acid, neut. equiv., 168. Decolorization and recrystallization from water gave beautiful needles but raised the m. p. only slowly. A melting point of 208–210° was obtained,

(1) R. Adams, "Organic Reactions," Vol. 3, John Wiley and Sons, New York, N. Y., 1947, article by H. Wolfe, The Schmidt Reaction, p. 307.

(2) Pearl, THIS JOURNAL, **68**, 429 (1946).

(3) Sanford, Blair, Arroya and Sherk, *ibid.*, **67**, 1941 (1945).

(4) Smith, *ibid.*, **70**, 320 (1948).

(5) (a) Newman, Organic Chemistry Symposium, Boston, Mass., 1947; (b) Newman and Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

(6) Schuerch and Huntress, presented at the 112th Meeting of the American Chemical Society in New York, N. Y., September, 1947.

(7) Rupe, *Ber.*, **30**, 2449 (1898).

however, by extracting the crude crystals once with absolute ether in a Soxhlet apparatus. A mixed melting point with authentic vanillic acid[2] with the recorded m. p. 208–210°[8] was undepressed.

Veratric Acid and 4-Aminoveratrole.—The condensation of veratraldehyde 27.6 g., sodium azide 12.5 g. and concentrated sulfuric acid 118 ml. was essentially as described above but the time of hydrolysis was somewhat longer. Slightly discolored veratric acid, 25.4 g. or 84%, separated from the reaction mixture. One recrystallization from water and ethanol gave a pure product with the recorded[9] m. p. 179–181°. Extraction of the acid mother liquor with benzene gave less than 1 g. of oily crystals. The acidic solution was made strongly alkaline and extracted again with benzene. Evaporation of this extract and distillation of the residue under reduced pressure yielded 1.6 g. of colorless crystals that darkened in air. Their melting point of 87–88° agreed with that reported for 4-aminoveratrole.[10]

(8) Misani and Bogert, *J. Org. Chem.*, **10**, 355 (1945).

(9) Goldschmiedt, *Monatsh.*, **6**, 379 (1885).

(10) Buck and Ide in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 44.

DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY
MCGILL UNIVERSITY
MONTREAL, CANADA RECEIVED MARCH 9, 1948

[CONTRIBUTION FROM THE STEELE CHEMICAL LABORATORY OF DARTMOUTH COLLEGE, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MICHIGAN]

8-Amino-2,4-Dimethylquinoline[1]

BY WYMAN R. VAUGHAN[2]

As a consequence of the tremendous recent interest in the derivatives of 8-aminoquinoline as antimalarial drugs it was found desirable to develop a satisfactory synthesis for 8-amino-2,4-dimethylquinoline. The present procedure was found to be a rapid and efficient method for the preparation of this substance, one of its advantages being that it obviates any extensive purification of the intermediate 8-nitro-2,4-dimethylquinoline.

Experimental

8-Nitro-2,4-dimethylquinoline.—One mole (157 g., 150 ml.) of 2,4-dimethylquinoline[3] was cooled to 0° and treated with 250 ml. of concentrated sulfuric acid which was added as rapidly as possible with good mechanical stirring. The resulting solution was then cooled to 0° and treated with a solution of 115 g. of potassium nitrate in 300 ml. of concentrated sulfuric acid with vigorous mechanical stirring, the temperature being maintained between 0 and 5° by means of an ice–salt-bath. When all of the nitrating solution had been added, the mixture was stirred for an additional fifteen minutes without cooling and then was poured onto 2500 g. of cracked ice. The resulting mixture was treated with 1500 ml. of concentrated ammonia and diluted to 6 l. with cold water, cooled to room temperature and filtered. The filter cake was placed in a 2-l. beaker with 1 l. of cold water and stirred vigorously until a uniformly fine suspension was obtained. It was then filtered with good suction, and the moist filter cake was recrystallized from 1 l. of 95% ethanol using norit and a heated funnel: yield 113–115 g. (51–67%), m. p. 115–125°.[4] This impure product is a mixture of 8-nitro-2,4-dimethylquinoline with one or more isomers. A second isomer, m. p. 109.6–110.1° cor., was isolated from the mother liquors from the recrystallization of the major product, but the structure of this substance has not as yet been determined.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.86. Found: N, 14.0.

In view of the work of Price, Velzen and Guthrie[5] who isolated 6-nitro-2,4-dimethylquinoline, it would appear that this substance is either 5- or 7-nitro-2,4-dimethylquinoline, probably the former in view of the well-known resistance of the 7-position in quinoline toward nitration.[6]

8-Amino-2,4-dimethylquinoline.—A solution of 101 g. (0.5 mole) of 8-nitro-2,4-dimethylquinoline (m. p. 115–125°) in 375 ml. of concentrated hydrochloric acid was added from a dropping funnel to a well-stirred solution of 375 g. of stannous chloride dihydrate in 136 ml. of concentrated hydrochloric acid, the temperature being maintained at 40–50° by means of an ice-bath. Near the end of the reduction a yellow precipitate appeared. After complete addition of the nitro compound to the reducing solution there was added 2000 g. of cracked ice and a cooled solution of 850 g. of potassium hydroxide in 1 l. of water. The resulting mixture was vigorously stirred for 30 minutes and then filtered, and the residue was washed in the funnel with three portions of cold water totaling 1 l. The filter cake was pressed dry and then was dissolved in 1 l. of water containing 50 ml. of concentrated hydrochloric acid. In order to effect solution the mixture was boiled and then was treated at the boiling temperature with a liberal quantity of norit and filtered through a steam-heated funnel. Upon cooling there separated from the filtrate a mass of golden yellow needles, 71–87 g.[7] This product was dissolved in 500 ml. of boiling water, and the resulting solution was treated with 30 ml. of concentrated ammonia. The 8-amino-2,4-dimethylquinoline separated as an oil which solidified upon rapid cooling with continuous agitation. The mixture was allowed to stand for 30 minutes at room temperature, and then it was filtered: yield 51–61 g. (59–71%), m. p. 86–90°. If a very pure product is desired, the initial product may be recrystallized directly from 70–90° ligroin (10 ml. per g.) or converted to the hydrochloride, which is readily recrystallized from water. Highly purified 8-amino-2,4-dimethylquinoline is a colorless crystalline substance, m. p. 93.7–94.2° cor.[8]

Anal. Calcd. for $C_{11}H_{12}N_2$: N, 16.27. Found: N, 16.3, 16.23.

(1) Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Dartmouth College.

(2) Present address: Department of Chemistry, University of Michigan, Ann Arbor, Michigan.

(3) Vaughan, "Organic Syntheses," Vol. 28, in preparation; *cf.* Craig, THIS JOURNAL, **60**, 1458 (1938).

(4) Repeated recrystallization of a portion of this product from ethanol-water and finally from 95% ethanol yielded a very pure 8-nitro-2,4-dimethylquinoline, m. p. 147–147.5°. Price, Velzen and Guthrie give 149.5–150° cor., *cf.* ref. 5.

(5) Price, Velzen and Guthrie, *J. Org. Chem.*, **12**, 203 (1947).

(6) Bacharach, Haut and Caroline, *Rec. trav. chim.*, **52**, 413 (1933); *cf.* ref. 8.

(7) The hydrochloride thus obtained appears to be a dihydrate which loses some of its water of hydration upon standing in a dry atmosphere.

(8) Roberts and Turner, *J. Chem. Soc.*, 1856 (1927), give 89–92°.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 23, 1947

Some 2,3-Dialkylpyridines and their Derivatives[1]

BY HENRY M. WOODBURN AND MAX HELLMANN

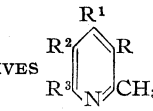
Our extension of Elderfield's work[2] on 2,3-dimethylpyridine to the synthesis of other 2,3-dialkylpyridines was interrupted by the war, and

(1) From the M.A. thesis of Max Hellmann, University of Buffalo, June, 1947.

(2) Elderfield and Tracy, *J. Org. Chem.*, **6**, 54 (1941).

TABLE I

PROPERTIES OF 2-METHYL-3-ALKYLPYRIDINE DERIVATIVES



R	R^1	R^2	R^3	M. p., °C.	B. p.,[a] °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
n-C_3H_7	OH	CO_2Et	OH	192–193		$C_{12}H_{17}O_4N$	60.2	59.7	7.18	7.15
n-C_4H_9	OH	CO_2Et	OH	182–184		$C_{13}H_{19}O_4N$	61.6	61.9	7.57	7.41
n-C_3H_7	OH	H	OH	330–332 dec.		$C_9H_{13}O_2N$	64.6	64.5	7.84	7.73
n-C_4H_9	OH	H	OH	348–350 dec.		$C_{10}H_{15}O_2N$	66.3	66.0	8.34	8.38
n-C_3H_7	Cl	H	Cl		259	$C_9H_{11}Cl_2N$	Cl 34.7	34.6		
n-C_4H_9	Cl	H	Cl		275	$C_{10}H_{13}Cl_2N$	Cl 32.5	32.1		
n-C_3H_7	H	H	H	130–131[b]	200–201	$C_{15}H_{16}N_4O_7$[c]	49.5	49.8	4.44	4.46
n-C_4H_9	H	H	H	124–125[b]	222–223	$C_{16}H_{18}N_4O_7$[c]	50.8	50.5	4.80	4.92

[a] Corrected. [b] M. p. of the picrate. [c] Formula and analysis of the picrate.

shortly after its resumption the appearance of an abstract of a paper by Wibaut and Kooyman[3] made it inadvisable to proceed further along those lines. The applicability of the reaction scheme having been proved, we wish to report the synthesis and properties of 2-methyl-3-*n*-propylpyridine and of 2-methyl-3-*n*-butylpyridine together with those of certain intermediates used in their preparation.

Ethyl α-*n*-butyl β-aminocrotonate, for which no literature reference was found, was prepared from ethyl α-*n*-butylacetoacetate, ammonia and ammonium nitrate. It had a melting point of 41–42° and a boiling point of 116–118° (10 mm.).

(3) Wibaut and Kooyman, *Rec. Trav. Chim.*, **63**, 231 (1944); *C. A.*, **41**, 450a (1947).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF BUFFALO
BUFFALO, NEW YORK RECEIVED FEBRUARY 26, 1948

Products of the Interaction of Potassium Dihydrogenphosphide and *n*-Heptyl Bromide in Liquid Ammonia

BY GEORGE W. WATT AND R. C. THOMPSON, JR.

Alkali and alkaline earth metal dihydrogenphosphides prepared by the reaction between phosphine and solutions of these metals in liquid ammonia[1,2] continue to find application in the synthesis of derivatives of phosphine.[3]

Several years ago we studied several reactions of potassium dihydrogenphosphide in liquid ammonia and since further work is not anticipated it seems worth while to report the synthesis of *n*-heptylphosphine and its conversion to a product believed to be *n*-heptyl-phosphonous acid.

Phosphine was prepared by the action of sodium hydroxide solution on phosphonium iodide and dried over potassium hydroxide pellets. The dry gas was led into a solution of 2.7 g. of potassium in approximately 100 ml. of anhydrous liquid ammonia (contained in a flask provided with a stirrer and reflux condenser) until the characteristic blue color of the potassium solution was discharged. All reactants were protected from contact with the atmosphere. *n*-Heptyl bromide (11.9 g.) was added to the resulting pale yellow solution of potassium dihydrogen phosphide and the reaction mixture was stirred for two hours at −33.5°. The ammonia was evaporated and the residual liquid was removed in an atmosphere of carbon dioxide, extracted with 2 *N* hydrochloric acid solution, and the acid-insoluble fraction was distilled in an atmosphere of carbon dioxide to provide 6 ml. of a clear liquid, b. p., 73–74° at 30 mm. Boiling point determinations using capillary tubes gave consistently a value of 169.5°. This is a reasonable value for the boiling point of the anticipated *n*-heptylphosphine[4] which was apparently the primary reaction product. Despite precautions taken to avoid atmospheric oxidation while handling samples for analysis, this product was oxidized to a substance having an analytical composition corresponding to *n*-heptylphosphonous acid.

Anal. Calcd. for $C_7H_{17}PO_2$: C, 51.19; H, 10.44; P, 18.89. Found: C, 50.91; H, 10.48; P, 19.10.

This substance gave a negative test for halogen, exploded upon contact with fuming nitric acid, and was soluble in glacial acetic acid. Upon exposure to the atmosphere for several hours, it was further oxidized to a viscous liquid that boiled above 225°.

With potassium dihydrogenphosphide in liquid ammonia at −33.5°, bromo and iodobenzene react slowly, and ammonium chloroacetate reacts more rapidly to form products that have not been identified.

(1) Joannis, *Compt. rend.*, **119**, 557 (1894); *Ann. chim phys.*, [8] **7**, 101 (1906).

(2) Legoux, *Compt. rend.*, **207**, 634 (1938); **209**, 47 (1939); *Bull. soc. chim.*, [5] **7**, 545 (1940); *Ann. chim.*, **17**, 100 (1942).

(3) Knunyants and Sterlin, *Compt. rend. acad. sci. U. R. S. S.*, **56**, 49 (1947).

(4) For *n*-octylphosphine, Möslinger [*Ann.*, **185**, 65 (1877)] has reported b. p., 184–187°.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN 12, TEXAS RECEIVED FEBRUARY 24, 1948

Reduction Products of *m*-Nitrostyrene

BY RICHARD H. WILEY AND NEWTON R. SMITH

The reduction of *m*-nitrostyrene to 3,3′-divinylazobenzene and to 2,2′-divinylbenzidine has been reported by Komppa.[1] These and two additional products, 3,3′-divinylazoxybenzene and 3,3′-divinylhydrazobenzene have been prepared in this study. Analytical data for these compounds are collected in Table I. The customary reagents were used for the transformations as described in

(1) Komppa, Inaugural Dissertation, Helsingfors, *Ber.*, **26**, Ref. 677 (1893).

TABLE I

REDUCTION PRODUCTS OF *m*-NITROSTYRENE

Compound	Yield, %	Color	M. p., °C., cor.	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3,3′-Divinylazoxybenzene	78	Yellow	39.5–41	$C_{16}H_{14}N_2O$	76.78	76.81	5.64	5.65	11.20	11.30
3,3′-Divinylazobenzene	81.5	Orange	84	$C_{16}H_{14}N_2$	82.02	82.21	6.02	6.16	11.96	11.87
3,3′-Divinylhydrazobenzene	74.5	Faint yellow	96.5–97	$C_{16}H_{16}N_2$	81.32	81.14	6.81	6.92	11.86	11.87
2,2′-Divinylbenzidine	30	White	123	$C_{16}H_{16}N_2$	81.32	81.06	6.81	6.92	11.86	12.10
3-Aminostyrene hydrochloride polymer	84	Brown	Dec.	$C_8H_{10}NCl$	...	...	..	..	9.00	9.17

the experimental part. The azoxy compound was formed with zinc and ammonium chloride instead of the hydroxylamine usually obtained with this reagent. Polymeric products were obtained in the reduction of nitro to amino with zinc and hydrochloric acid; of nitro to azo with stannous chloride; of azoxy to azo with iron filings; and of azo to hydrazo with zinc and alcoholic sodium hydroxide. The azoxy compound polymerized on heating with benzoyl peroxide and the benzidine and azo compounds on heating without catalyst. The hydrazo compound decomposed on heating with benzoyl peroxide apparently without polymerization.

Experimental

Yields, physical properties, and analyses for the following products are listed in Table I.

***m*-Nitrostyrene** was prepared by the decarboxylation of *m*-nitrocinnamic acid by a procedure similar to that previously attempted.[2] A mixture of 20 g. of *m*-nitrocinnamic acid (E. K. Co.), 75 ml. of quinoline, and 3 g. of copper powder were heated at 185–190° so as to produce a steady evolution of carbon dioxide. After one and one-half hours of heating the mixture was acidified with 50% excess 3 *N* hydrochloric acid and steam distilled. The distillate was extracted with chloroform and the combined extracts were dried over anhydrous sodium sulfate. After distilling off the chloroform, the residue was fractionated from a modified Claisen flask to give 9.3 g., 60% of the theoretical amount, of *m*-nitrostyrene, b. p. 90–96° (3.5 mm.), $n^{20}D$ 1.5836. Refractionation through a partial take-off column, 0.75 × 8 in. packed with Fenske rings gave a center cut, b. p. 96° (3.5 mm.), $n^{20}D$ 1.5830. With larger quantities longer reaction times were required and lower yields were obtained than in the above experiment.

3,3′-Divinylazoxybenzene was prepared by the reduction of *m*-nitrostyrene with sodium methoxide in methanol[3] or by reduction with zinc and ammonium chloride in aqueous ethanol.[4] Heating the fused solid at 80° with 0.5% benzoyl peroxide gave an insoluble, infusible polymer.

3,3′-Divinylazobenzene.—To 0.68 g. of 3,3′-divinylhydrazobenzene in 75 ml. of ethanol was added 10 g. of ferric chloride hexahydrate in 25 ml. of hot water. After fifteen minutes water was slowly added to precipitate the azo compound which was twice recrystallized from alcohol–water. Oxidation with sodium hypobromite or air in alcoholic sodium hydroxide also converted the hydrazo to the azo compound. Attempts to convert the azoxy to the azo compound by heating with iron filings gave polymeric products. The sample analyzed melted at 84° (cor.); Komppa[1] reported a m. p. of 38°. Heating at 110° for twenty-four hours gave an insoluble polymer which decomposed before melting when heated.

3,3′-Divinylhydrazobenzene was prepared by zinc and alcoholic sodium hydroxide reduction[5] of *m*-nitrostyrene. Attempts to reduce the azo to hydrazo compound with zinc and alcoholic sodium hydroxide gave only a polymer. On heating a mixture of solid the hydrazo compound and 0.5% benzoyl peroxide to 110° decomposition without apparent polymerization occurred.

2,2′-Divinylbenzidine was prepared in 30% yield by treating 3,3′-divinylhydrazobenzene with concd. hydrochloric acid in ether,[6] m. p. 123° (cor.); reported[1] m. p. 124°. Heating to 135° converted the benzidine to an infusible, insoluble polymer.

***m*-Aminostyrene Polymer.**—Reduction of *m*-nitrostyrene with zinc and hydrochloric acid gave a polymer which was precipitated as the hydrochloride on addition of excess hydrochloric acid to its aqueous acid solution.

(2) Walling and Wolfstirn, THIS JOURNAL, 69, 852 (1947).

(3) Sudborough and James, "Practical Organic Chemistry," D. Van Nostrand and Company, New York, N. Y., 1934, p. 252.

(4) Sudborough and James, *ibid.*, p. 253.

(5) Gattermann–Wieland, "Laboratory Methods of Organic Chemistry," The Macmillan Company, New York, N. Y., 1932, p. 174.

(6) Gattermann–Wieland, *ibid.*, p. 176.

VENABLE CHEMICAL LABORATORY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C.

RECEIVED MARCH 13, 1948

p-Alkoxybenzyl Grignard Reagents

BY M. G. VAN CAMPEN, DONALD F. MEISNER[1] AND STANLEY M. PARMERTER[2]

The alkoxybenzylmagnesium halides are valuable intermediates in the synthesis of stilbene derivatives particularly in the study of synthetic estrogenic agents. However, the general impression exists that these Grignard reagents cannot be prepared. This impression is probably due to the fact that in attempts to form the Grignard from such halides as *p*-methoxybenzyl chloride by the usual procedure, a nearly quantitative yield of the *p*,*p*′-dialkoxybibenzyl is obtained. By using a modification of the method reported by Gilman[3] for the preparation of allyl Grignard reagents, it is possible to prepare *p*-alkoxybenzylmagnesium chlorides in acceptable yields. This is accomplished primarily by the use of a large excess of magnesium powder and slow addition of a dilute ether solution of the benzyl halide to the magnesium. Using the following general procedure 90% yields of *p*-methoxybenzylmagnesium chloride and *p*-benzyloxybenzylmagnesium chloride are consistently obtained.

Procedure.—A mixture of 2 to 2.5 g. atoms of magnesium turnings and 2 to 2.5 g. atoms of magnesium

(1) Present address: C. J. Patterson Co., Kansas City 2, Missouri.

(2) Present address: Eastman Kodak Research Laboratories, Rochester, New York.

(3) Gilman and McGlumphy, *Bull. soc. chim.*, [4] 43, 1322 (1928).

powder is vigorously stirred under 1 liter of refluxing anhydrous ether. One mole of the alkoxybenzyl halide dissolved in 1 l. of ether is added over a two to five hour interval. The resulting Grignard reagent is then filtered through glass cotton to remove the finely divided magnesium powder, which if not removed usually reacts with objectionable vigor during the ultimate decomposition with water or dilute acid. The yield is estimated by the usual acidimetric titration.

RESEARCH LABORATORIES OF
THE WM. S. MERRELL COMPANY
CINCINNATI, OHIO

RECEIVED MARCH 8, 1948

COMMUNICATIONS TO THE EDITOR

CHEMICAL REACTIONS IN MOVING BOUNDARY SYSTEMS OF WEAK ELECTROLYTES

Sir:

In moving boundary systems containing partially neutralized weak acids or bases there exists the possibility of chemical reactions at the moving boundary which cause the mobility calculated from the boundary velocity and the conductivity of the leading solution to be lower than the ionic mobility.[1] This is illustrated by experiments 2 and 3 in which the indicator electrolyte is a salt of weak acid (cacodylic acid) having a higher pK than the leading weak electrolyte (acetic acid). The following reaction goes to completion

$$\mathrm{Cac^-} + \mathrm{HOAc} \rightleftharpoons \mathrm{HCac} + \mathrm{OAc^-} \quad K_{25^\circ} = 25 \quad (1)$$

to the right at the moving boundary so that none of the acetic acid remains behind that boundary. The concentration of the sodium acetate is 0.05 N (at 0°) in all experiments, and it has been shown that the concentration and pH of the indicator electrolyte (α solution) is unimportant over a wide range.

The moving boundary equation[2] cannot be applied to acetate ion in the presence of acetic acid, but a term may be added for the acetic acid as follows so that the moving boundary equation for acetate constituent becomes

$$T^{\gamma}_{\mathrm{OAc^-}} = V^{\beta\gamma}(C^{\gamma}_{\mathrm{OAc^-}} + C^{\gamma}_{\mathrm{HOAc}}) = \frac{u^{\gamma}_{\mathrm{OAc^-}} C^{\gamma}_{\mathrm{OAc^-}}}{\kappa^{\gamma}\ 1000/F} \quad (2)^3$$

From equation (2) we see that the mobility, u, calculated from the boundary velocity in this case is the "constituent" mobility. The acetate ion mobility, $u^{\gamma}_{\mathrm{OAc^-}}$

$$u = V^{\beta\gamma}\kappa^{\gamma}\frac{1000}{\mathrm{F}} = u^{\gamma}_{\mathrm{OAc^-}}\frac{(C^{\gamma}_{\mathrm{OAc^-}})}{(C^{\gamma}_{\mathrm{OAc^-}} + C^{\gamma}_{\mathrm{HOAc}})} \quad (3)$$

calculated from the constituent mobility obtained in experiments 2 and 3 by using equation (3) are -17.62×10^{-5} and -17.55×10^{-5} in agreement with the average value, -17.53×10^{-5}, obtained in experiments 1 and 4.

However, in systems containing weak electrolytes the constituent mobility is not always obtained as illustrated by experiment 5. Whether or not a chemical reaction takes place depends upon the pK and relative mobility of the indicator ion. In this experiment the mobility calculated is slightly lower than the ionic mobility because the acetate ion does not disappear in the $\beta\gamma$ boundary, owing to the slight dissociation of the acetic acid left behind the moving boundary.

TABLE I[a]

	Moving Boundary System[b] γ		β	α	$u \times 10^5$ (0° C.)
(1)	NaOAc(0.05)	←	NaCac	::NaCac	−17.47
(2)	NaOAc(0.05), HOAc(0.05)	←	NaCac, HCac	::NaCac	− 8.81
(3)	NaOAc(0.05), HOAc(0.01)	←	NaCac, HCac	::NaCac	− 5.85
(4)	NaOAc(0.05)	←	NaT	::NaT	−17.59
(5)	NaOAc(0.05), HOAc(0.05)	←	NaT, HOAc	::NaT	−16.54

[a] OAc, acetate; Cac, cacodylate; T, trichloroacetate. [b] The conventions recommended by Longsworth, THIS JOURNAL, **67**, 1109 (1945), are used.

Since proteins and buffers used in electrophoresis are weak electrolytes, reactions such as the above occur and must be considered in the quantitative interpretation of electrophoretic patterns.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN
ROBERT A. ALBERTY
J. C. NICHOL

RECEIVED MAY 25, 1948

SYNTHESIS OF DL-THREONINE

Sir:

The structure α-amino-β-hydroxy-n-butyric acid contains two dissimilar asymmetric carbon atoms and hence exists as four optical isomers and

(1) Dr. Harry Svensson, Institutes of Physical and Biological Chemistry, Upsala, Sweden, has independently recognized this fact in work initiated in September, 1946 (*Acta Chem. Scand.*, in press), personal communication.

(2) Weber, *Sitzungsber. Akad. Wissensch. Berlin*, 936 (1897); Svensson, *Ark. Kem. Min. Geol.*, **17A**, No. 14 (1943); Longsworth, THIS JOURNAL, **67**, 1109 (1945).

(3) The symbols have the meanings used by Longsworth ($C_{\mathrm{OAc^-}}$ is taken as negative).

two racemic modifications. Attempts to synthesize one of these racemic modifications, the essential amino acid DL-threonine, have invariably given poor results, though some of the syntheses have produced the diastereoisomeric DL-allothreonine in good yields. Efforts to convert DL-allothreonine into DL-threonine have met with little success.

It has now been found that esters of N-acyl-DL-allothreonine are converted into DL-threonine in high yield by transformation into the corresponding oxazolines followed by hydrolysis of the latter with mineral acid.

N-Benzoyl-DL-allothreonine was treated with diazomethane and the methyl ester (m. p. 110–111°. *Anal.* Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.36. Found: C, 60.86; H, 5.99.) on reaction with excess thionyl chloride at room temperature gave 2-phenyl-5-methyl-4-carbomethoxyoxazoline hydrochloride, m. p. 118–119°, in quantitative yield. *Anal.* Calcd. for $C_{12}H_{13}O_3N\cdot HCl$: C, 56.36; H, 5.52. Found: C, 56.50; H, 5.71. Hydrolysis with dilute hydrochloric acid followed by isolation and recrystallization gave pure D-threonine in 70% yield. *Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.35; H, 7.70; N, 11.46. By the same sequence of steps N-benzoyl-DL-threonine was converted into pure DL-allothreonine in 77% over-all yield.

A practical synthesis of DL-threonine from acetoacetic ester has been developed by the use of this inversion. Ethyl α-acetamidoacetoacetate, obtained in 88% yield from acetoacetic ester via reductive acetylation of ethyl α-phenylazoacetoacetate, was hydrogenated in aqueous solution with Adams catalyst to give on concentration a mixture of diastereoisomeric ethyl α-acetamido-β-hydroxy-*n*-butyrates containing 80–85% N-acetyl-DL-allothreonine ethyl ester. A purified sample of this product melted at 76–77°. *Anal.* Calcd. for $C_8H_{15}O_4N$: C, 50.78; H, 7.99. Found: C, 50.54; H, 8.04. The crude hydrogenation product was treated with thionyl chloride, and the solution was refluxed with water to decompose the intermediate oxazoline. An isolated sample of this 2,5-dimethyl-4-carbethoxyoxazoline hydrochloride melted at 105–106°. *Anal.* Calcd. for $C_8H_{13}O_3N\cdot HCl$: C, 46.27; H, 6.79; N, 6.75; N. E., 207.7. Found: C, 46.11; H, 6.87; N, 6.97; N. E., 202.2. The aqueous solution was concentrated dry and the amino acid hydrochloride taken up in isopropanol and precipitated with aniline. The crude product (89% yield from ethyl α-acetamidoacetoacetate) was a mixture of DL-threonine and DL-allothreonine containing 83% of the former (microbial assay).

Pure DL-threonine was obtained by separation of the sodium salt from anhydrous alcohol, reconversion into the free acid and recrystallization by precipitation from aqueous solution with alcohol. The over-all yield of DL-threonine from acetoacetic ester was 57%. *Anal.* Found: C, 40.42; H, 7.32; N, 11.82. This product was found 100% pure by microbial assay and better than 99% pure by solubility analysis.

Additional work now in progress indicates that the "oxazoline inversion" described may be a general method for the interconversion in high yield of diastereoisomeric α,β-amino alcohols.

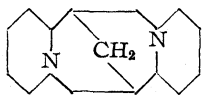
KARL PFISTER, 3rd.
RESEARCH LABORATORIES C. A. ROBINSON
MERCK & CO., INC. A. C. SHABICA
RAHWAY, N. J. MAX TISHLER

RECEIVED MAY 12, 1948

THE TOTAL SYNTHESIS OF SPARTEINE

Sir:

We wish to report a convenient total synthesis of *dl*-sparteine (I). The *Lupin* alkaloid *l*-



I

sparteine was first isolated in 1851 and the correct structure (I) was confirmed by Clemo and Raper[1] in 1933. *l*-Sparteine is used in medicine chiefly as a cardiac stimulant and a diuretic.[2] *d*-Sparteine and the naturally occurring alkaloid pachycarpine[3] have been shown to be identical.[4]

Our synthesis of *dl*-sparteine proceeds in two steps from ethyl 2-pyridylacetate. The first step was the preparation of 1-carbethoxy-4-keto-3-(2′-pyridyl)-pyridocoline by condensation of ethyl orthoformate with ethyl 2-pyridylacetate in the presence of acetic anhydride according to the method of Clemo, Morgan and Raper.[5] The second step was that of reductive cyclization, which was reported first from this Laboratory[6] for the synthesis of pyrrolizidines. 1-Carbethoxy-4-keto-3-(2′-pyridyl)-pyridocoline in dioxane was hydrogenated over copper chromite at 250° and 350 atm. in one and one-half hours. The product was separated into three fractions: b. p. 90–120°, 120–126°, 140–148° (1.25 mm.). The second and largest fraction gave a **monopicrate** (m. p. 136–137°; *Anal.* Calcd. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.55; H, 6.49; N, 15.18) and a **dipicrate** (m. p. 208°; *Anal.* Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 46.76; H, 4.88; N, 16.28). The analyses and melting points of the derivatives are consistent with the assignment of the *dl*-sparteine structure to the synthetic free base. Clemo and Leitch[7] reported a **monopicrate**

(1) Clemo and Raper, *J. Chem. Soc.*, 644 (1933).
(2) Wood and Osol, "United States Dispensatory," J. B. Lippincott Company, Philadelphia, Pa., twenty-third edition, 1943, p. 1012; "The Merck Index," Merck and Company, Rahway, N. J., fifth edition, 1940, p. 524.
(3) Orechov, Rabinowitch and Konovalova, *Ber.*, **66**, 621 (1933).
(4) Galinovsky and Stern, *ibid.*, **77**, 132 (1944).
(5) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1025 (1936).
(6) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).
(7) Clemo and Leitch, *J. Chem. Soc.*, 1811 (1928).

(m. p. 135°) and a **dipicrate** (m. p. 206–207°) of *dl*-sparteine, which they obtained from naturally occurring *dl*-lupanine. As a further proof of identity, our *dl*-sparteine was converted to *dl*-oxysparteine, m. p. 110–111°, by treatment with alkaline potassium ferricyanide. The melting point of *dl*-oxysparteine has been reported as 110–111°,[5] 112–113°,[4] 113°.[7] Finally, the infrared absorption spectra of our synthetic *dl*-sparteine dipicrate and an authentic sample of *l*-sparteine dipicrate (m. p. 208°) were found to be identical in solution.[8]

We are aware of the desirability of resolving *dl*-sparteine and of isolating the other two racemates of I. We also foresee the applicability of our method to the synthesis of other bases related to sparteine.

(8) The authors are indebted to Mrs. James L. Johnson for determination of the infrared absorption spectra.

THE NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS
NELSON J. LEONARD
ROGER E. BEYLER

A CRYSTALLINE FACTOR FUNCTIONALLY RELATED TO FOLIC ACID

Sir:

In a systematic study of factors functionally related to *p*-aminobenzoic acid and folic acid and occurring in liver extracts used for the treatment of pernicious anemia, a factor was discovered which prevented the toxic action of methylfolic acid[1] upon the growth of *Leuconostoc mesenteroides* 8293. In a medium previously described[2] but supplemented with 300 γ of thymine per 10 cc., the ratio of methylfolic acid to folic acid just necessary for maximum inhibition was 3,000. The addition of this factor in adequate amounts (equivalent to 0.01–0.03 γ of crystalline material per 10 cc.) increases the antibacterial index about tenfold.

A medium suitable for quantitative assay was obtained by the addition of 0.03 γ of folic acid and 200 γ of methylfolic acid per 10 cc. to the above medium. Under these conditions increasing concentrations of the factor resulted in increasing growth levels.

Employing this assay, a principle has been isolated from hog liver in crystalline form. Recrystallized from isopropyl alcohol, this principle appears as fine, colorless prisms, m. p. 189–190°. Under the testing conditions, the factor is several times as active as folic acid in promoting a half-maximum growth response.

Extracts prepared from either liver, hog duodenal mucosa, or grass are highly active, but milk, muscle tissue and yeast extract are relatively poor sources of active material. Liver extracts used in treatment of pernicious anemia are relatively potent, and some experimental extracts of high potency (determined clinically) assayed by the above method appear to contain as much as 1% of this factor.

Preliminary investigation of the structure of the compound indicated that it was thymidine[3] or a structurally related compound.

We acknowledge our indebtedness to Eli Lilly and Company for their coöperation. Particular thanks are due Drs. Ewald Rohrmann and Edward D. Campbell for their coöperation in furnishing experimental extracts and analytical facilities.

(1) Crude mixture from the condensation of α,β-dibromobutyraldehyde, 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid obtained from Dr. E. L. R. Stokstad [Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947)].

(2) Snell, *et al.*, *ibid.*, **143**, 519 (1942).

(3) Since this paper was submitted, we have obtained a sample of thymidine originally isolated from desoxyribonucleic acid by Levene and London (*J. Biol. Chem.*, **83**, 793 (1929)). The X-ray diffraction pattern and the biological properties of this sample are identical with those of the isolated factor.

THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH, AUSTIN, TEXAS
WILLIAM SHIVE
ROBERT E. EAKIN
W. M. HARDING
JOANNE M. RAVEL
JUDITH E. SUTHERLAND

RECEIVED APRIL 16, 1948

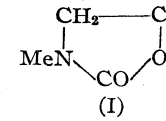
THE KINETICS OF THE POLYMERIZATION OF CARBONIC ANHYDRIDES

Sir:

Carothers (*Chem. Rev.*, **8**, 353 (1931)) has divided polymerizations into two types, "addition" and "condensation." In the former type, initiation, propagation, transfer and termination reactions are involved (*cf.* Bamford and Dewar, *Proc. Roy. Soc.* (*London*), **192**, 309 (1948)), but in condensation polymerizations only chain-growth occurs, and in this reaction every species reacts with every other. There is, however, a third type of polymerization in which there are only two reactions, initiation, and a propagation reaction where the polymers do not react with each other, but only with the monomer. The polymerizations of carbonic anhydrides (*e. g.*, I) appear to belong to this third type, and are also important since they can be used to synthesize polypeptides of some complexity. The reactions involved are

$$M + A \longrightarrow X + CO_2 \quad (k_1) \qquad (1)$$
$$M + X \longrightarrow X + CO_2 \quad (k_2) \qquad (2)$$

where M denotes the carbonic anhydride, X any polymer species, and A the initiator which may be a hydroxylic or amino compound.



(I)

$$MeNHCH_2CO(NMeCH_2CO)_nNMeCH_2CONMe_2$$

(II)

Although a complete formal solution of the kinetic equations is impossible, the following methods are available for the absolute determina-

tion of the velocity constants k_1 and k_2. If (M) = M_0 and (A) = A_0 when $t = 0$, and (A) = A_∞ when (M) = 0, it can be shown that

$$k_2/k_1 = (M_0 - A_0 + A_\infty)/(A_0 \log (A_0/A_\infty) - A_0 + A_\infty) \quad (3)$$

Since end-group estimation gives $A_0 - A_\infty$, this equation enables k_2/k_1 to be evaluated.

The experimental conditions can be adjusted so that the concentration of initiator (A) is approximately constant, when it can be shown that there is a maximum rate given by

$$[\mathrm{d(M)/d}t]^2_{\max.} = \frac{1}{27} k_1 k_2 A_0 (2M_0 + k_1 A_0/k_2)^3 \quad (4)$$

A simpler procedure, however, is to use the preformed polymer to initiate the polymerization, so that the second step (equation (2)) is isolated. The molar concentration of polymer (X_0), is thus constant, and the rate of disappearance of carbonic anhydride is given by

$$-\mathrm{d(M)/d}t = k_2 X_0 (\mathrm{M}) \quad (5)$$

The kinetics of the polymerization of sarcosine carbonic anhydride (I) is being investigated. The polymer (II) used for initiating is obtained as a colorless, hygroscopic solid by the action of dimethylamine on the anhydride (I) in dioxane.

The polymerization in nitrobenzene is followed manometrically by the evolution of carbon dioxide. In accordance with equation (10) the reaction shows first-order dependence on (M); this confirms the assumption that k_2 is independent of the molecular weight of the polymer, for molecular weights between about 500 and 5000. Preliminary measurements indicate that the velocity constant, k_2, can be expressed by the equation

$$k_2 = 1600e^{-5,800/RT} \text{ liters mole}^{-1} \text{ sec.}^{-1}$$

The low value of the frequency factor is noteworthy.

We hope to extend this investigation to other carbonic anhydrides and to co-polymerizations.

COURTAULDS, LIMITED
MAIDENHEAD, BERKS. S. G. WALEY
ENGLAND J. WATSON

RECEIVED APRIL 20, 1948

NEW BOOKS

Chemical Insect Attractants and Repellents. By VINCENT G. DETHIER, A.M., Ph.D., Professor of Zoology and Entomology, The Ohio State University; formerly Entomologist, Inter-Allied Malaria Control Commission, Gold Coast, B. W. A. The Blakiston Company, Philadelphia, Pennsylvania, 1947. xv + 298 pp. Illustrated. 15.5 × 23.5 cm. $5.00.

The manner in which various chemicals attract or repel insects is of considerable interest to both chemists and entomologists working in economic entomology, to students of insect ecology and to others. The subject has also intrigued biologists not so well acquainted with the peculiarly specialized behavior of the insect world. Although the literature on attractants and repellents is extensive, most of the effort has been expended on research by the trial-and-error method, with not enough consideration of the chemical, physical, physiological and botanical factors involved. In an effort to remedy the situation and to impart a greater impetus to research in this field, Dr. Dethier has undertaken the difficult task of assembling and correlating the widely scattered literature. In this respect he has done a commendable piece of work.

The text is not a compilation of formulas of attractant and repellent substances. Rather it represents a theoretical approach to the study of the subject. The book is divided into ten chapters. An introductory chapter is followed by six that deal specificially with attractants, one with repellents, and two that are devoted to a more general discussion. There are approximately 750 literature citations.

Although the importance of research on insect repellents, especially for those insects that transmit disease, such as malaria-carrying mosquitoes, is pointed out, no mention is made of the extensive studies carried on during the recent war by the Bureau of Entomology and Plant Quarantine, United States Department of Agriculture; neither are the excellent fundamental studies on repellents by DeLong at the Ohio State University, nor is adequate treatment given the work of Granett at Rutgers University. The important subject of mothproofing warrants more than a brief paragraph. The book contains numerous errors in chemical nomenclature and in the structural formulas of compounds. These errors might have been avoided if the manuscript had been submitted to an organic chemist for review. Nevertheless the book is a valuable one and meets a definite need for both the chemist and the entomologist.

H. L. HALLER

Fundamentals of Photographic Theory. By T. H. JAMES, Ph.D., and GEORGE C. HIGGINS, Ph.D., Research Laboratories of Eastman Kodak Company. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1948. vii + 286 pp. 14 × 22 cm. Price, $3.50.

The recognized standing of the authors, not to mention coöperation by members of the Eastman staff, arouses in the reader expectations which are not disappointed. By concentrating upon black and white photography, exclusive of cameras or accessories, a coverage of the central theme admirable from physical, chemical and psychophysical standpoints is achieved. Consistent use of the sensitivity-speck basis for the latent image, together with the Gurney–Mott hypotheses, resolves in plausible fashion a great variety of complicated or at first sight contradictory phenomena. The chemistry of essential dark-room procedures is set forth in detail, but some will regret the omission of intensification, reduction and toning. Conflicting theories are critically examined in the light of data and of physico-chemical generalizations. Objective and subjective evaluations of photographic images are

carefully distinguished, then aptly correlated. Outstanding is the graphic solution of the complete problem of tone reproduction, first suggested by L. A. Jones, which gives due weight to the sensitivity relations of the human eye. A short list of well-chosen references is found at the end of each chapter.

Few photographers are sufficiently equipped, instrumentally or through training, to put the entire book into practice. But it is at least consoling to realize that as an art photography has anticipated not a few theoretical conclusions.

GEORGE S. FORBES

Radioactive Tracers in Biology. An Introduction to Tracer Methodology. By MARTIN D. KAMEN, Associate Professor of Chemistry, Chemist to the Edward Mallinckrodt Institute of Radiology, Washington University, St. Louis, Missouri. Academic Press, Inc., 125 East 23rd Street, New York, N. Y., 1947. xiii + 281 pp. 38 figs. 16 × 23.5 cm. Price, $5.80.

This long-needed book on tracer techniques reviews the pertinent underlying concepts of nuclear physics, surveys contemporary tracer methods, and indicates their potentialities and limitations. As the Academic Press' first volume in a series of monographs on Organic and Biological Chemistry, which has subsequently come under the editorship of Louis F. Fieser and Mary Fieser, Dr. Kamen's book was an immediate sell-out. Doubtless the second printing, which buyers are now awaiting, will include corrections of numerous misprints and small errors which inevitably resulted from Dr. Kamen's speed record of less than three months for the actual writing of the entire book. If this speed left rough spots, nevertheless all the new workers in the many fields of application of radioactive isotopes should read Dr. Kamen's book, and will be grateful to him for providing it.

The first four chapters, of nearly a hundred pages, contain the essential facts necessary to the worker in any field of science or engineering who would use radioactive tracers. The balance of the book specializes these principles to specific applications in the life sciences, especially in studies of intermediary metabolism where radioactive tracers are an indispensable tool. Every new user of radioactive isotopes should certainly become conversant with the contents of this book. Seasoned workers will feel the book is introductory, but a small reader-survey has shown this reviewer that engineers, some chemists, radiologists, and physicians find the book advanced enough to require at least one or two rereadings.

Recently there have been a number of Isotope Conferences on a variety of scientific subjects, at each of which much time was consumed in reviews of elementary principles because this material was not conveniently available. The planners of future Isotope Conferences should presuppose that the audience and the conferees have at least mastered the topics presented in Kamen's book, and should now pitch their programs at the intermediate level instead of at the introductory level.

Among detection techniques, Kamen rightly advocates simple devices such as the Lauritsen electroscope wherever they can be used. The detailed instructions for building a Geiger–Müller counter were cogent in June, 1946, when the manuscript was completed, but since then a large variety of counters and electronic auxiliaries have become available commercially. Most new workers will prefer to buy rather than to build. Similarly, the homemade standards using uranium oxide should now be replaced by radium D-E beta ray standards distributed by the National Bureau of Standards.

The description of general methods and techniques deals primarily with C^{11} and C^{14} which are taken as prototypes of all other isotopes. Thus C^{11} presents the difficulty of a short half-period (twenty minutes), but emits easily detected energetic positron beta-rays (maximum energy 0.98 Mev) as well as the corresponding annihilation radiation (0.51 Mev) which can be measured readily using gamma-ray detecting instruments. Whereas C^{11} requires cyclotron production and, like other positron emitters, cannot be prepared by irradiation in a uranium pile, the long-lived C^{14} is now readily obtainable from the pile. However, the long half-period of C^{14} is associated, as usual, with a very low energy radiation (maximum energy of beta rays 0.15 Mev) which makes its detection correspondingly difficult. Also the very long half-period (5000 years) of C^{14} argues against its use in many investigations, especially in human subjects, because of the persistence of its radiation and the possible accumulation of biologically harmful total radiation doses.

Unfortunately, an extensive table of radioactive isotopes and their properties was not included in the first printing. A 4-page table of organic syntheses with radioactive isotopes is provided and should prove valuable and convenient for reference.

ROBLEY D. EVANS

Organic Analytical Reagents. By FRANK J. WELCHER, Ph.D., Associate Professor of Chemistry, Extension Division, University of Indiana. D. Van Nostrand and Co., Inc., 250 Fourth Avenue, New York, N. Y. Vol. I, xv + 442 pp. + 63 tables, 1947; Vol. II, xi + 530 pp. + 69 tables, 1947; Vol. III, xi + 593 pp. + 111 tables, 1947; Vol. IV, xiii + 624 pp. + 68 tables, 1948. All 15 × 23 cm. $8.00 per volume; price for set $28.00.

The first half of the twentieth century has been characterized by an extraordinary increase in the rate of magnitude of production of scientific data. In the field of organic chemistry, for example, this has resulted in the discovery and/or synthesis of an appalling number of new compounds. Unfortunately, however, the extension of prior means and the development of new tools for recording and organizing this mass of information has not kept a corresponding pace. Consequently, there has now resulted a condition in which new evidence daily accumulates that unless systematic, convenient and economically practicable means for location and evaluation of all the facts relevant to a desired compound or method are soon developed, further progress will be seriously retarded or even significantly impaired. For this reason all means whose objectives are primarily to systematize, classify, coördinate and organize this flood of data comprise a contribution to scientific progress which may (at its best) be just as valuable as the original components of the discoveries themselves. This four-volume work by Dr. Welcher represents an example of an effort to overcome in a particular area the serious inadequacies mentioned.

The principal objective of this work has been to assemble in one place a description of all organic compounds used through 1945 in the analysis of inorganic substances and to discuss their mode of employment. The scope of the book does *not* include application of organic reagents to the detection, determination, or identification of organic compounds.

The four volumes comprise a total of sixty-seven chapters; these cover 827 organic reagents and require 9042 citations of the literature. The organization is such that all information relative to a particular compound is brought together in one place, extensive diversification in its uses being there systematically subclassified. Chemically related reagents are grouped together in chapters within which the sequence is alphabetical. With the text for each reagent is associated the corresponding series of citations to the original literature. Each volume includes an alphabetical name index of the organic reagents and also a subclassified index in which, under headings representing applications, the various reagents of the particular volume are alphabetically listed. However, no cumulative master index covering all four volumes is given.

Since the arrangement of topics is somewhat arbitrary it can, perhaps, best be surveyed by a review of the chapter sequences and headings. Volume I begins with

five short general chapters as follows: electronic theory of valence, coördination compounds, chelate compounds, types of chelate rings, and the effect of structure on solubility. The subsequent twelve chapters are devoted to hydrocarbons, substitution products of hydrocarbons, alcohols, phenols, miscellaneous phenolic compounds, aminophenols, phenolsulfonic acids, 8-hydroxyquinoline and its derivatives, azo derivatives of 8-hydroxyquinoline, ethers, aldehydes and ketones.

Volume II comprises ten chapters treating the following: organic acids, halogenated acids, hydroxy acids, amino acids, miscellaneous acids, acyl halides, acid anhydrides, esters, amines (255 pages) and quaternary ammonium compounds.

Volume III contains nineteen chapters headed as follows: pyridine and its derivatives, quinoline and quinoline derivatives, dipyridyl and related compounds, pyrazolone derivatives, miscellaneous heterocyclic nitrogen compounds, dioximes, acyloin oximes, hydroxyoximes, isonitroso compounds, nitrosophenols, miscellaneous oximes, cupferron and neocupferron, nitrosoamines, rhodanine and its derivatives, carbazides and thiocarbazides and semicarbazides, carbazones, thiocarbazones and miscellaneous imino compounds.

Volume IV concludes the set with seventeen chapters dealing with acidic nitro compounds, arsonic acids, dithiocarbamates, xanthates, miscellaneous sulfur compounds, sulfonic acids, sulfuric acids, seleninic acids, alkaloids, diazonium compounds, carbohydrates, miscellaneous natural substances, miscellaneous compounds, lake-forming dyestuffs, hydroxyanthraquinone dyes, miscellaneous dyes and dyes used in the detection of nitrite.

For the preparation of the various organic reagents the author, guided by the principle that it be the most adaptable in the average chemistry laboratory, has selected only one. This severe restriction is to be deplored as in some cases organic chemists would regard the choice as inadequate. The organic nomenclature is generally definite, but some peculiar sequences are employed. References to Beilstein are associated with many (but not all) compounds, but much inconsistency exists in the method. Although reference is made to the main series of Beilstein's fourth edition, references to the equally important first supplementary series are not always included and the even more important second supplementary series seems to have been ignored.

The set of books will be of most value to chemists concerned with inorganic analysis.

ERNEST H. HUNTRESS

The Chemistry of Acetylenic Compounds. Vol. I. The Acetylenic Alcohols. By A. W. JOHNSON, PH.D. with a foreword by Sir Ian Heilbron, D.S.O., D.Sc., F.R.S. Edward Arnold and Co., London, England. Longmans, Green and Company, New York, N. Y., 1946. xvii + 394 pp. 14.5 × 22 cm. Price $9.50.

This first volume of a projected three volume set dealing with the acetylenic compounds presents an excellent discussion of the chemistry of the acetylenic alcohols up to September, 1945. The author has subdivided the acetylenic alcohols into three groups, (I) compounds containing one acetylenic bond and one hydroxyl group, (II) compounds containing one acetylenic bond and more than one hydroxyl group and (III) hydroxyl compounds containing more than one acetylenic bond. Each group of compounds is discussed in a logical manner under the headings, historical, nomenclature, formation, physical properties, reactions of the hydroxyl group, reactions of the acetylenic bonds, reactions involving the free ethynyl group and reactions involving the whole molecule. The main body of this book was written before 1940 and in order to bring it up to date an appendix has been added which covers the more recent developments in the field. Chapters on the chemistry of the rubenes, on the application of acetylenic carbinol reactions in the sex hormone field, and on physical constants of acetylenic alcohols are also included as appendices to the main body of the book.

This is a very valuable critical résumé of the chemistry of acetylenic alcohols and will be indispensable to research workers in the field. It will also serve as interesting reading for anyone who wants to become informed on these highly useful reactions and the properties of this group of organic compounds.

C. S. MARVEL

BOOKS RECEIVED

April 10, 1948–May 10, 1948

ERNEST DAVID BERGMANN. "Isomerism and Isomerization." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y., 1948. $3.50. 138 pp.

WALTER BOAS. "An Introduction to the Physics of Metals and Alloys." John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 193 pp. $3.50. First published, October, 1947.

WILLIAM CROCKER. "Growth of Plants." Reinhold Publishing Corporation, 330 West 42nd Street, New York 18, N. Y. 459 pp. $10.00. Published April 5, 1948.

R. H. HARRINGTON. "Modern Metallurgy of Alloys." John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 209 pp. $3.50. Copyright, 1948.

DAVID H. KILLEFFER. "The Genius of Industrial Research." Reinhold Publishing Corporation, 330 West 42nd Street, New York 18, N. Y. 263 pp. $4.50. Published April 9, 1948.

JAMES W. PERRY. "Chemical Russian Self-Taught." Journal of Chemical Education, 20th and Northampton Streets, Easton, Pennsylvania. 221 pp. $3.00. Copyright, 1948.

A. W. RALSTON. "Fatty Acids and Their Derivatives." John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 986 pp. $10.00. Published January, 1948.

L. ROSENFELD. "Nuclear Forces. I." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 181 pp. $5.00. Published 1948.

FRANK T. SISCO. "Modern Metallurgy for Engineers." Second Edition. Pitman Publishing Corporation, 2 West 45th Street, New York 19, N. Y. 499 pp. $5.00. Copyright, January, 1941.

W. THEILHEIMER. "Synthetische Methoden der Organischen Chemie." S. Karger, Ltd., New York, N. Y., 309 pp. Sfr. 35.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

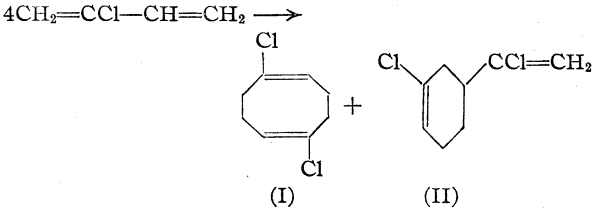
VOLUME 70 AUGUST 2, 1948 NUMBER 7

[CONTRIBUTION NO. 244 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

Cycloöctadienes from Dienes

BY R. E. FOSTER AND R. S. SCHREIBER

It has been reported[1] that an 8-carbon ring dimer was isolated from still residues obtained during the purification of monomeric chloroprene (2-chloro-1,3-butadiene). This dimer was assigned the structure 1,5-dichloro-1,5-cycloöctadiene (I) and presumably was formed by the spontaneous dimerization of chloroprene. The 6-membered ring dimer (II) was also isolated.



(I) (II)

Further, at the Reconstruction Finance Corporation Neoprene Plant, Louisville, Ky., operated by the E. I. du Pont de Nemours and Company, Mallonee and and Wooding isolated a third, lower-boiling product which tentatively has been assigned the structure 3-chloro-1-vinyl-1,3-cyclohexadiene. This material probably was formed by the dehydrochlorination of 1,3-dichloro-1-vinyl-3-cyclohexene, an isomer of (II).

Carothers[2] demonstrated earlier that a mixture of dimers was obtained by heating monomeric chloroprene. The components of this mixture were not identified, but it seems probable on the basis of comparable boiling points that two, or perhaps all three, of these compounds were present in the "β-polychloroprene" described by Carothers.

The purpose of this paper is to report the confirmation of the dimerization of chloroprene to a mixture of 6- and 8-membered ring compounds and to record two additional examples of the dimerization of conjugated dienes, 1,3-butadiene itself and 2,3-dichloro-1,3-butadiene,[3] to the corresponding cycloöctadienes.[4]

By heating chloroprene at 80° for one hundred and twenty hours in the presence of phenothiazine to inhibit polymerization and activated charcoal,[5] greater than 20% conversion to dichloro-1,5-cycloöctadiene was obtained.[5a] In addition, the two 6-membered ring compounds mentioned above were isolated. The structures of the carbon skeletons of these three materials were established by the reduction of the chloro compounds over platinum oxide in the presence of sodium acetate to the known saturated hydrocarbons. The fraction boiling at 147–149° was presumed to be impure cycloöctane on the basis of its boiling point and freezing point (9°); the 8-carbon ring was confirmed by oxidation with nitric acid to suberic acid.

The dimerization of 1,3-butadiene at 100–120° proceeded to give a preponderance of vinylcyclohexene, although the presence of 1–5% of an 8-membered ring dimer was demonstrated. The total dimerization product was hydrogenated and fractionated. The infrared spectra of the final fractions were compared with those of known mixtures of cycloöctane and ethylcyclohexane (see Fig. 1), and the proportion of cycloöctane in the

(1) Brown, Rose and Simonsen, *J. Chem. Soc.*, 101 (1944).

(2) Carothers, Williams, Collins and Kirby, THIS JOURNAL, **53**, 4211 (1931).

(3) Carothers and Berchet, U. S. Patent 1,965,369.

(4) During the preparation of this paper, it was brought to our attention that Dr. Karl Ziegler has reported the conversion of 1,3-butadiene at temperatures above 200° to a mixture of vinylcyclohexene, cycloöctadiene, and octahydrobiphenyl. Details of this work have not been published. Ziegler, "A New Approach to the Cycloöctane Series," meeting of the German Chemical Society, Heidelberg, April 15–18, 1947.

(5) Although the evidence is not unequivocal, there are indications that the yield of dimers is improved by the inclusion of activated charcoal, possibly as a result of the increased surface area.

(5a) Cope and Bailey, THIS JOURNAL, **70**, 2205 (1948), have developed a modified procedure for conducting this dimerization at atmospheric pressure.

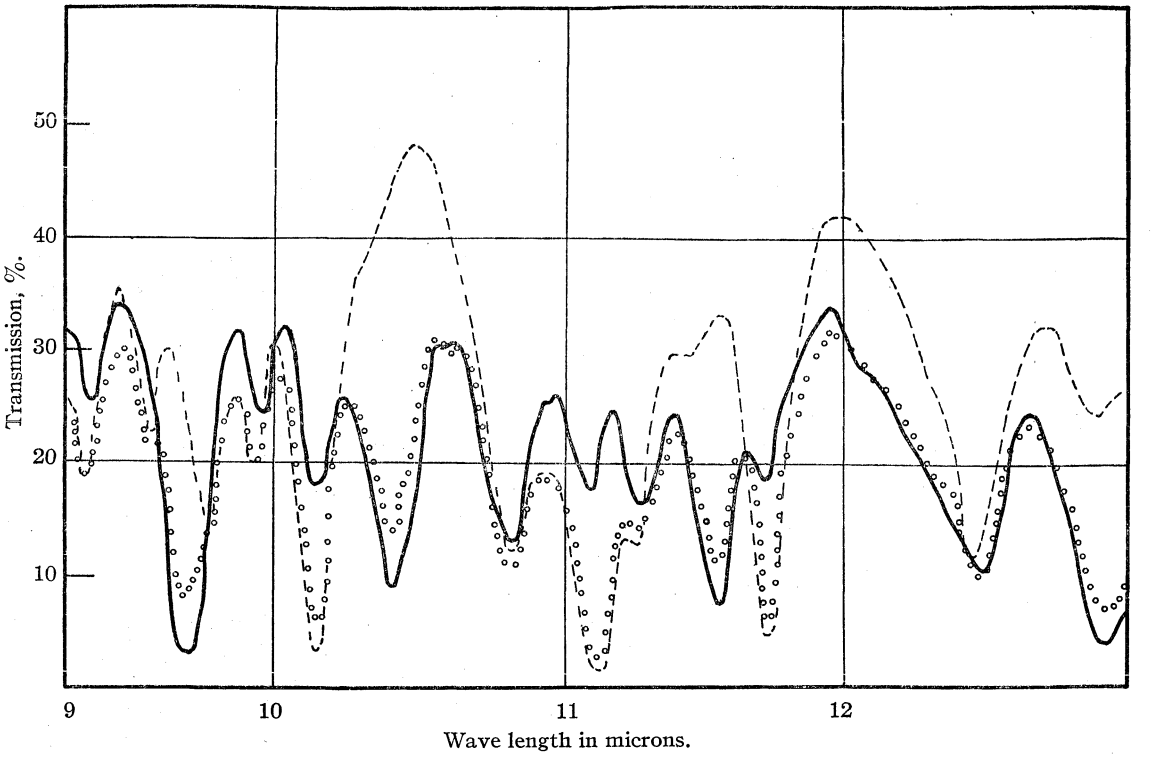


Fig. 1.—Infrared absorption spectra of cycloöctane, —; ethylcyclohexane, ---; and 1:1 cycloöctane–ethylcyclohexane, O-O-O.

total reduced dimer mixture was readily calculated. The identity of the final fractions was established by isolating cycloöctane in the pure state and subsequently oxidizing it to suberic acid.

The dimerization of 2,3-dichloro-1,3-butadiene was carried out at 80° for one hundred and twenty hours. Only one dimeric product, formed in 12.5% yield, was isolated; the remainder was converted to polymer. The dimer was shown to possess an 8-carbon ring by reduction to cycloöctane.

Experimental

Dimerization of Chloroprene.—One hundred and fifty grams of chloroprene, 3 g. of phenothiazine, and 10 g. of Darco (Grade S-51) were sealed in a pressure bottle under nitrogen and agitated at 80° for one hundred and twenty hours. The dark, mobile product was filtered to remove a small amount of polymer and charcoal (15 g.) and the filtrate (119 g.) was distilled. Unchanged monomer (25 g.) was removed at atmospheric pressure and the remainder was distilled under reduced pressure. The following fractions were obtained: (A) 3-chloro-1-vinyl-1,3-cyclohexadiene (15 g., 16%) 67–70° (17 mm.); (B) 3-chloro-1-α-chlorovinyl-3-cyclohexene (19 g., 20%) 96–100° (17 mm.); (C) dichloro-1,5-cycloöctadiene (28.2 g.) 109–118° (17–18 mm.). Infrared data indicated this last fraction to contain 75% 8-membered ring compound which corresponds to 22% yield of dichloro-1,5-cycloöctadiene. The total yield of dimeric products was 66% based on 96 g. of chloroprene, the amount consumed during the reaction.

These samples were refractionated for analysis. Fraction A: B. p. 61–62° (8.5 mm.), $n^{25}D$ 1.5138, d^{25}_4 1.051, *Anal.* Calcd. for C_8H_9Cl: C, 68.33; H, 6.45; Cl, 25.22; mol. wt., 141. Found: C, 67.45, 67.31; H, 6.49, 6.51; Cl, 27.02, 26.75; mol. wt., 154, 155 (ebullioscopic method in benzene).

Fraction B: B. p. 89–89.5° (8 mm.), $n^{25}D$ 1.5138, d^{25}_4 1.169. *Anal.* Calcd. for $C_8H_{10}Cl_2$: C, 54.26; H, 5.69; Cl, 40.05. Found: C, 54.91, 54.96; H, 5.83, 5.94; Cl, 39.62, 39.73.

Fraction C: B. p. 105–106° (8 mm.), $n^{25}D$ 1.5312; d^{25}_4 1.203. *Anal.* Calcd. for $C_8H_{10}Cl_2$: C, 54.26; H, 5.69; Cl, 40.05. Found: C, 54.47, 54.77; H, 5.97, 5.99; Cl, 39.42, 39.45.

Reduction of Fraction C.—A mixture of 9 g. of the dimer boiling at 109–118° (17–18 mm.), 50 ml. of glacial acetic acid, 13 g. of hydrated sodium acetate, and 1 g. of platinum oxide was agitated under 45 lb. hydrogen pressure until the reduction in pressure was 18 lb. (theory, 17.5 lb.). This mixture was filtered into water and subsequently extracted with an ether–benzene solution (1:1, by volume). The organic layer was dried over magnesium sulfate and distilled through a small column. The cycloöctane, boiling at 147–149°, 2.2 g. (34.4%), was employed in the following oxidation.

One gram of the hydrocarbon was added to 10 ml. of concentrated nitric acid (sp. gr. 1.42) and heated at 78–80° for twenty-four hours. The mixture was cooled in an ice-bath and the crystalline solid, 0.35 g., was isolated by filtration. The crude material crystallized from water as white plates, m. p. 140–141°. A mixture with an authentic sample of suberic acid melted at 140–141°.

Reduction of Fractions A and B.—In a manner similar to that described above, Fractions A and B were hydrogenated to give in each case ethylcyclohexane, b. p. 130–131°, $n^{25}D$ 1.4342.

Dimerization of Butadiene.—A mixture of 4800 g. of butadiene, 480 g. of Darco (Grade S-51), and 100 g. of *p-t*-butylcatechol was heated in a 3-gal. autoclave at 120° for sixty hours. At the end of this time, 490 g. of butadiene was recovered by venting the autoclave through a Dry Ice trap. The product was filtered (3861 g.) and hydrogenated at room temperature under 1500 lb. pres-

sure in the presence of 15 g. of ruthenium dioxide. From the reduced hydrocarbon mixture, ethylcyclohexane (2355 g.) was removed at 130–131°, or 68–69° (100 mm.), $n^{25}D$ 1.4312. The residue was rapidly distilled through a short-path still to remove the hydrocarbon from *p*-butylcatechol. This distillate was separated by distillation through a 10-inch helices-packed column into the following fractions: (D) b. p. 135–142°, $n^{25}D$ 1.4480, 18.5 g.; (E) b. p. 143–150°, $n^{25}D$ 1.4531, 30.8 g.; (F) b. p. 151–153°, $n^{25}D$ 1.4551, m. p. 6–7°, 1.1 g. On the basis of refractive indices and infrared data, these fractions contain: (D) 66% cycloöctane; (E) 86% cycloöctane; (F) 94% cycloöctane. The total yield of cycloöctane amounted to approximately 1%. Fractionation and infrared analyses of smaller preparations indicated cycloöctane yields of 3–5%. Fraction F was conclusively identified by nitric acid oxidation to a solid acid, m. p. 140–141°, which showed no depression in melting point when mixed with an authentic sample of suberic acid.

Dimerization of 2,3-Dichloro-1,3-butadiene.—A mixture of 91.3 g. of 2,3-dichloro-1,3-butadiene,[3] 3 g. of phenothiazine, and 5 g. of Darco (Grade S-51) was agitated in a pressure bottle at 80° for one hundred and twenty hours. The resulting solid mass was extracted with several 200-ml. portions of ethanol. The alcohol was removed through a Vigreux column and the tarry solid was distilled at reduced pressure to give 11.3 g. (12.5%) of a solid, b. p. 140–146° (3.6 mm.). This was the only distillable product, and on crystallization from an acetone–alcohol–water mixture (5:5:1, by volume) gave white plates, m. p. 98–99°. The material appeared to be a very stable compound.

Anal. Calcd. for $C_8H_8Cl_4$: Cl, 57.66; mol. wt., 246. Found: Cl, 57.0, 56.8; mol. wt., 241, 241 (ebullioscopic method in benzene).

This material was hydrogenated in acetic acid solution in the same manner as that described for the dimer from 2-chloro-1,3-butadiene. The reduction mixture was added to water, and the hydrocarbon was isolated by extraction with benzene. The organic solution was dried and distilled, and the fraction boiling at 140–150° was shown to be approximately 80% cycloöctane by comparison of its infrared absorption curve with that of an authentic sample of cycloöctane.

The Removal of Chlorine from Dichloro-1,5-cycloöctadiene.—The action of sodium in liquid ammonia was found to effect the removal of the halogens from dichloro-1,5-cycloöctadiene without simultaneous reduction of the carbon–carbon double bonds.

Thirty-six grams of dichloro-1,5-cycloöctadiene was mixed with 200 ml. of liquid ammonia and approximately 100 ml. of absolute ether was added to effect homogeneity. Ten grams of sodium was added in small pieces and the mixture was stirred and allowed to reflux under a Dry Ice condenser until the sodium had dissolved. This required about two hours. The ammonia was then allowed to evaporate and the residue was filtered. There was obtained 43.4 g. of black solid (theory for NaCl is 23.2 g.), suggesting that considerable polymerization of the product had occurred. The filtrate was dried and distilled; the product boiling at 149–160° weighed 3.9 g., which corresponded to a 19% yield of cycloöctadiene. This was redistilled, and the pure material boiling at 150–152° was presumed to be 1,5-cycloöctadiene.

Anal. Calcd. for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.78, 88.99; H, 10.94, 11.11.

Cope and Bailey[5] have found conditions for this reaction which give a 56% yield of the product.

Acknowledgment.—The authors are indebted to Dr. J. W. Stillman, under whose supervision the microanalyses were carried out, and to Miss Doris Huck for the infrared curves.

Summary

The dimerization of chloroprene to a mixture of 6- and 8-membered ring compounds has been confirmed. This unusual dimerization to 8-membered ring compounds has been extended to 1,3-butadiene and 2,3-dichloro-1,3-butadiene.

WILMINGTON, DELAWARE RECEIVED FEBRUARY 28, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. II. Synthesis of Cycloöctatetraene from Chloroprene[1]

BY ARTHUR C. COPE AND WILLIAM J. BAILEY[2]

Cycloöctatetraene has been prepared by the thirteen-step Willstätter synthesis from pseudopelletierine,[3,4] and by a catalytic process from acetylene.[5] We have continued an investigation of synthetic routes to cycloöctatetraene in a search for a reasonably short synthesis which could be adapted to the preparation of functional derivatives of cycloöctatetraene, which are not accessible through any reactions reported for the hydrocarbon.[5] This paper describes a seven-step synthesis of cycloöctatetraene from chloroprene (2-chloro-1,3-butadiene).

A method for the preparation of a cyclic dimer of chloroprene containing an eight-membered ring (previously isolated from chloroprene distillation residues[6]) has been developed by Foster and Schreiber.[7] By a modification of their procedure, chloroprene was heated in the presence of phenothiazine as a polymerization inhibitor and converted into a mixture of dimers. The eight-membered ring dimer (I) was separated from six-membered ring dimers by fractional distillation, treatment with alcoholic alkali to remove a dimer containing reactive chlorine which otherwise was difficult to separate, and refractionation. The eight-membered ring structure of I is established by its hydrogenation to cycloöctane,[6,7] which we have

(1) Presented at the Tenth National Organic Chemistry Symposium, Boston, Massachusetts, June 13, 1947.

(2) Arthur D. Little Postdoctorate Fellow, 1946–1947.

(3) Willstätter and Waser, *Ber.*, **44**, 3423 (1911); Willstätter and Heidelberger, *ibid.*, **46**, 517 (1913).

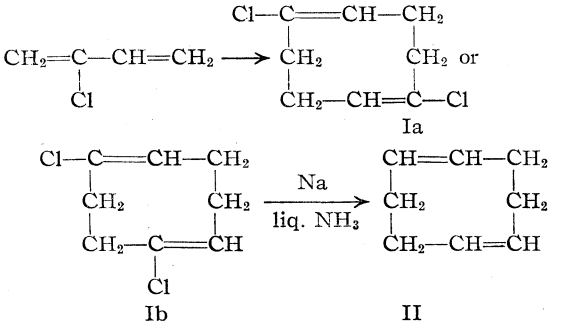
(4) Cope and Overberger, THIS JOURNAL, **70**, 1433 (1948).

(5) Described in Department of Commerce reports of German technological developments, including a translation of a paper by W. J. Reppe reprinted in "German Synthetic Fiber Developments," p. 631, Textile Research Institute, New York, N. Y., 1946 (P. B. 7416).

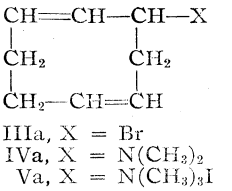
(6) Brown, Rose and Simonsen, *J. Chem. Soc.*, 101 (1944).

(7) Foster and Schreiber, THIS JOURNAL, **70**, 2303 (1948).

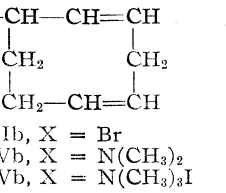
confirmed. The chloroprene units in the dimer may be joined head to tail (Ia) or head to head (Ib), or both structures may be present. These possibilities were not investigated, because the chlorine was replaced by hydrogen and the possibility for isomerism removed in the next step of the synthesis. The dehalogenation was accomplished by reaction of I with sodium in liquid ammonia.[7] Highest yields (56%) of 1,5-cycloöctadiene (II) were obtained with a low reaction temperature (−75 to −50°) and a short reaction time (three minutes), after which sodium compounds were neutralized and excess sodium decomposed by adding solid ammonium nitrate. These conditions minimized the polymerization which occurred as a side reaction. Titration showed that 90% of the chlorine in I was removed as ionic chlorine under these conditions. The structure of II was established by quantitative hydrogenation to cycloöctane, and by ozonization followed by oxidation with hydrogen peroxide, which gave succinic acid.



Reaction of an excess of II with N-bromosuccinimide in the presence of benzoyl peroxide[8] gave a stable monobromo substitution product (III) in 45–57% yield. Although the methylene groups in 1,5-cycloöctadiene are equivalent, rearrangement could occur either during the substitution reaction (through an intermediate free radical) or through an allylic shift of the bromo compound. Consequently the product may have structure IIIa, IIIb or be a mixture of the two. Reaction of III with dimethylamine gave a 61% yield of a dimethylaminocycloöctadiene (IV), which likewise may have structure IVa or IVb; the displacement reaction presents an added possibility for an allylic rearrangement.



IIIa, X = Br
IVa, X = $N(CH_3)_2$
Va, X = $N(CH_3)_3I$



IIIb, X = Br
IVb, X = $N(CH_3)_2$
Vb, X = $N(CH_3)_3I$

IV was proved to be a dimethylaminocycloöctadiene by quantitative hydrogenation to dimethylaminocycloöctane, which was identified as the methiodide. IV reacted with methyl iodide to give a methiodide, V, which was converted to the quaternary base and distilled to give a cycloöctatriene, VI. VI differed in index of refraction, density and ultraviolet absorption spectrum (Fig. 1) from 1,3,5-cycloöctatriene (prepared from pseudopelletierine).[4] Comparison of the ultraviolet absorption curves of VI and 1,3,5-cycloöctatriene (also shown in Fig. 1) indicates that VI probably is a mixture of 1,3,5-cycloöctatriene (VIa) and 1,3,6-cycloöctatriene (VIb), such as might be formed from a mixture of quaternary salts (Va and Vb). The ultraviolet absorption curve for 1,3,5-cycloöctatriene has a maximum at 2650 Å.[4] In VI the maximum is displaced to 2500 Å., while for structure VIb the maximum would be expected to fall nearer 2200 Å.

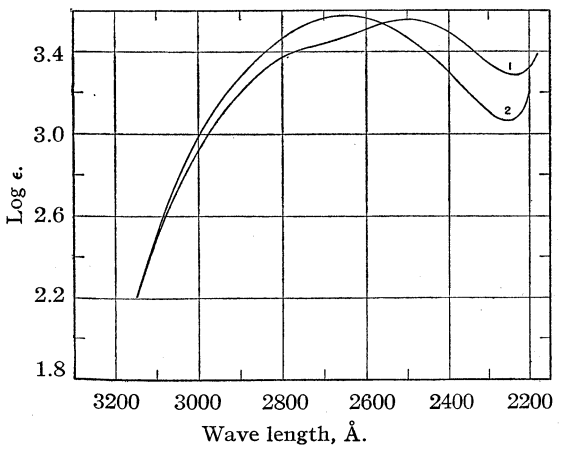
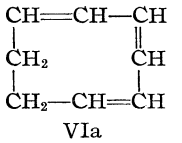
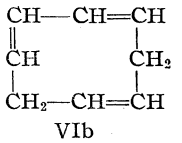


Fig. 1.—Curve 1, absorption spectrum of cycloöctatriene (VI); curve 2, absorption spectrum of 1,3,5-cycloöctatriene (ref. 4).



VIa



VIb

The possibility of conducting a similar sequence of reactions beginning with a dibromo derivative of cycloöctadiene was next investigated. 1,5-Cycloöctadiene (II) reacted with two molar equivalents of N-bromosuccinimide in the presence of benzoyl peroxide to give a dibromo compound, which was treated directly with an excess of dimethylamine. In this way a bis-(dimethylamino)-cycloöctadiene (VII) was obtained in an over-all yield of 34% from II. VII might be expected to be a mixture from its method of preparation, but proved to be practically homogeneous and identical with the compound believed to be 1,6-bis-(dimethylamino)-2,4-cycloöctadiene which is an intermediate in the Willstätter synthesis of cycloöctatetraene. Identity of the diamines from the two syntheses was established by correspondence

(8) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942); Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

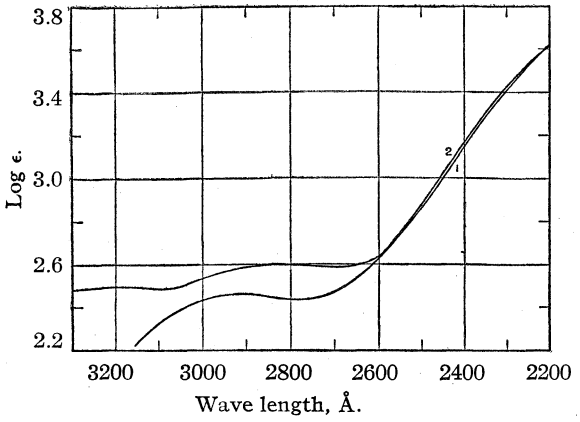


Fig. 2.—Curve 1, absorption spectrum of 1,6-bis-(dimethylamino)-2,4-cycloöctadiene (VII) derived from 1,5-cycloöctadiene; curve 2, absorption spectrum of 1,6-bis-(dimethylamino)-2,4-cycloöctadiene prepared from pseudopelletierine (ref. 4).

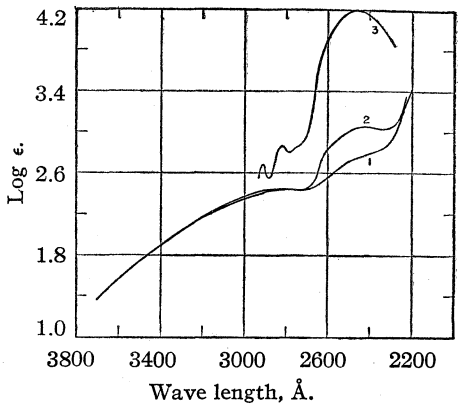
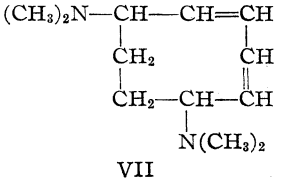


Fig. 3.—Curve 1, absorption spectrum of cycloöctatetraene prepared from acetylene; curve 2, absorption spectrum of cycloöctatetraene (containing approximately 8% of styrene) prepared from chloroprene; curve 3, absorption spectrum of styrene.[12]

in melting points of the dipicrates and dimethiodides, and comparison of ultraviolet absorption spectra (Fig. 2). Also VII was hydrogenated to 1,4-bis-(dimethylamino)-cycloöctane, which was identified as the dipicrate and dimethiodide. The formation of VII from II can be explained by rearrangement during the bromination of II, yielding 1,6-dibromo-2,4-cycloöctadiene, or by formation of 3,4-dibromo-1,5-cycloöctadiene followed by a double allylic rearrangement either before or during the displacement reaction with dimethylamine. The tendency of the double bonds to become conjugated undoubtedly accounts for the formation of VII, regardless of the step at which the rearrangements occur.



VII

The remaining steps in the synthesis of cycloöctatetraene followed the sequence of reactions used by Willstätter. VII was converted to the dimethiodide, which with silver hydroxide gave the quaternary base. Very slow distillation of the latter at 0.15–1 mm. gave a 15.5% yield of cycloöctatetraene, which was established as identical with a sample prepared from acetylene by correspondence in index of refraction, melting point, mixed melting point, ultraviolet (Fig. 3) and infrared[9] absorption spectra. The spectra indicated the presence of approximately 8% of styrene in this sample of cycloöctatetraene, presumably formed by rearrangement during decomposition of the quaternary base.

(9) We are indebted to Dr. R. C. Lord, Jr., and Mr. R. S. McDonald for the infrared data.

Experimental[10]

Dichloro-1,5-cycloöctadiene (I).—A stabilized 50% solution of chloroprene in xylene[11] was distilled rapidly in a nitrogen atmosphere without appreciable fractionation to obtain chloroprene containing 10–12% xylene. This distillate (2.5 kg.) and 45 g. of phenothiazine were placed in a 3-liter three-necked flask equipped with a thermometer, a mercury-sealed stirrer and a reflux condenser which was connected to a nitrogen cylinder through a line containing a mercury pop-valve. Air in the system was displaced with nitrogen, and the mixture was stirred slowly under nitrogen and heated at a temperature which maintained a slow reflux. The temperature of the liquid rose from 61 to 80° during sixty hours and was kept at 80–84° for an additional seventy hours by regulating the bath temperature. Hydrogen chloride escaped through the pop-valve during the heating period. The mixture was transferred to a 2-liter round-bottomed flask connected to a water-cooled condenser, receiver, Dry Ice trap and a water pump, and distilled as rapidly as possible under reduced pressure without fractionation. After separation of recovered chloroprene, which collected in the Dry Ice trap, the distillation was continued at 20–30 mm. and completed at a pressure of about 1 mm. with an oil pump protected from hydrogen chloride with soda-lime towers. This operation separated polymer and phenothiazine from the distillate containing dimers. The distillate was fractionated fairly rapidly under nitrogen at 3 mm. pressure through a total condensation, variable take-off column with a 30 × 2 cm. section packed with glass helices. This distillation separated an additional portion of recovered chloroprene, xylene, and crude six-membered ring dimers (b. p. up to 76° (3 mm.)) from the highest boiling fraction, b. p. 76–90° (3 mm.), containing the eight-membered ring dimer (and some six-membered ring dimers). The last fraction was heated for twenty-four hours at 60° with a solution equivalent to 90 g. of sodium hydroxide in 1400 ml. of absolute alcohol (prepared by adding sodium and water to absolute alcohol). The alcoholic solution was added to 2 l. of water and the product was extracted with four-400 ml. portions of benzene. The extracts were dried over anhydrous magnesium sulfate and concentrated. The residue was fractionated carefully through the 30 × 2 cm. helix-packed column in an atmosphere of nitrogen. Several such

(10) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mr. Philip H. Towle and Mrs. Louise W. Spencer for analyses.

(11) Obtained from the Organic Chemicals Department, E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

preparations yielded the following data: xylene present in the chloroprene dimerized, 10–12%; chloroprene recovered, 13–16%. The following percentages are based on the weight of chloroprene actually consumed in the reaction (subtracting the amount recovered): polymer formed, 9–23%; yield of crude six-membered ring dimers, 40–46%; yield of the fraction containing the eight-membered ring dimer from the first fractionation, 23–25%; yield of dichloro-1,5-cycloöctadiene (I) after alkali treatment and refractionation, 10–13%; b. p. 88–89° (3.3 mm.); 92–94° (3.8 mm.); $n^{25}D$ 1.5300–1.5310.

Anal. Calcd. for $C_8H_{10}Cl_2$: C, 54.26; H, 5.69; Cl, 40.05. Found: C, 54.11; H, 5.74; Cl, 39.9.

Preliminary fractionation to remove most of the six-membered ring dimers should precede alkali treatment of the product, as in the procedure described. Otherwise a compound which corresponded closely in analysis to $C_8H_{10}(OC_2H_5)Cl$ was formed in an amount corresponding to about half of the yield of I. This compound, evidently derived from a 6-membered ring dimer containing a reactive chlorine atom, boiled approximately 3° higher than I and its presence complicated the fractionation.[12]

A sample (10.00 g.) of the dichloro-1,5-cycloöctadiene in 60 ml. of glacial acetic acid was hydrogenated in the presence of 14.5 g. of anhydrous sodium acetate and 1.1 g. of pre-reduced Adams platinum oxide catalyst; 101% of four molar equivalents of hydrogen was absorbed. The solution was made basic with sodium carbonate and extracted with ether. Fractionation through a 15 × 1.2 cm. helix-packed column yielded 3.74 g. (59%) of cycloöctane, b. p. 148–149°; $n^{25}D$ 1.4557; m. p. 12.0°.

1,5-Cycloöctadiene (II).—Sodium (39.3 g., 1.7 moles) was dissolved in 2.5 l. of liquid ammonia in a 3-liter three-necked flask equipped with a stirrer, dropping funnel and thermometer. The ammonia solution was cooled to −75° in a Dry Ice–trichloroethylene-bath and a solution of 75 g. (0.42 mole) of dichloro-1,5-cycloöctadiene in 100 ml. of dry ether (also cooled with Dry Ice) was added with stirring during three-quarters of one minute. The mixture was stirred for two minutes, during which time the temperature of the liquid rose to −55 to −45°. Powdered ammonium nitrate (80 g.) was then added rapidly (one-half minute) and the ammonia was allowed to evaporate through a water-cooled reflux condenser while the reaction mixture stood overnight. Water was added to the residue and the product was extracted with ether, dried over magnesium sulfate and distilled. The yield of 1,5-cycloöctadiene was 25.4 g. (56%); b. p. 148–149°; $n^{25}D$ 1.4905; d^{25}_4 0.8818.[13]

Anal. Calcd. for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 89.13; H, 11.22.

A polymeric residue of 13.2 g. remained after distillation of the product. Titration of an aliquot portion of the aqueous solution after separation of the product showed the presence of 90% of the theoretical 0.84 equivalent of chloride ion.

Hydrogenation of a 1.21-g. sample of 1,5-cycloöctadiene in 20 ml. of glacial acetic acid in the presence of 0.1 g. of reduced platinum oxide required 101% of two molar equivalents of hydrogen. The product was identified as cycloöctane by its physical properties after purification by extraction from alkaline solution and distillation through a Craig micro column[14]; $n^{25}D$ 1.4555; m. p. 11.2°.

A 1.00-g. sample of 1,5-cycloöctadiene in 25 ml. of ethyl acetate was ozonized at −30°. The ethyl acetate was removed under reduced pressure and the ozonide was decomposed by heating on the steam-bath for three hours with 12 ml. of 30% hydrogen peroxide in 20 ml. of glacial acetic acid. After concentration under reduced pressure, the residue was dissolved in a sodium bicarbonate solution, which was extracted with ether to remove any neutral material. The alkaline solution was acidified and extracted with ether in a continuous extractor for two days. The ether extract was distilled and the residue recrystallized from water. Succinic acid was isolated in a yield of 1.62 g. (74%), m. p. and mixed m. p. with a known sample 186–187°.

Reaction of 1,5-Cycloöctadiene with N-Bromosuccinimide.—1,5-Cycloöctadiene (16.4 g.) in 50 ml. of dry carbon tetrachloride was stirred under reflux (80°) for one hour with 9.0 g. of N-bromosuccinimide and 0.25 g. of benzoyl peroxide. The succinimide formed was removed by filtration and the solution was fractionated through a 15 × 1.2 cm. helix-packed column. The recovery of 1,5-cycloöctadiene was 10.7 g. (determined by the weight of carbon tetrachloride–1,5-cycloöctadiene mixture recovered, and comparison of its refractive index with a linear plot of the refractive indices of known mixtures), and 5.4 g. (57% based on the N-bromosuccinimide) of bromocycloöctadiene (III) was obtained, b. p. 64° (1.9 mm.); $n^{25}D$ 1.5410; d^{25}_4 1.3420.

Anal. Calcd. for $C_8H_{11}Br$: C, 51.35; H, 5.93; Br, 42.72. Found: C, 51.27; H, 6.07; Br, 42.84.

Dibromocycloöctadiene was isolated in one instance from the reaction of 10.8 g. of 1,5-cycloöctadiene and 36 g. of N-bromosuccinimide in 100 ml. of dry carbon tetrachloride, which were heated under reflux with stirring in the presence of 0.5 g. of benzoyl peroxide for one hour. The succinimide formed was removed by filtration and the filtrate was washed with water, dried over Drierite and distilled under nitrogen. The dibromocycloöctadiene (14.2 g., b. p. 110–116° (2 mm.)) turned black after standing at room temperature for a few minutes, and in subsequent preparations was not isolated, but was treated directly with dimethylamine as outlined under the preparation of VII.

Dimethylaminocycloöctadiene (IV).—Bromocycloöctadiene (12.6 g.) and 250 ml. of a 20% solution of dimethylamine in benzene were allowed to stand for three days at room temperature. The mixture was extracted with 15% hydrochloric acid solution, which was then made basic with 20% sodium hydroxide and extracted with ether. The extracts were dried over magnesium sulfate, concentrated, and the residue was distilled under nitrogen through a 15 × 1.2 cm. helix-packed column. The yield of dimethylaminocycloöctadiene was 6.2 g. (61%); b. p. 58–60° (1.2 mm.); $n^{25}D$ 1.4972.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.33; N, 9.26. Found: C, 79.39; H, 11.45; N, 9.17.

Dimethylaminocycloöctadiene was also prepared in about the same over-all yield from 1,5-cycloöctadiene in a similar preparation in which the intermediate bromo compound was not isolated, and was obtained as a by-product in the preparation of 1,6-bis-(dimethylamino)-2,4-cycloöctadiene (see below).

Dimethylaminocycloöctadiene methiodide (V) was prepared from 12.8 g. of dimethylaminocycloöctadiene and 30 g. of methyl iodide in 70 ml. of absolute alcohol. The solution was allowed to stand for thirty minutes and heated under reflux for one hour. The crystalline methiodide (V) separated on cooling in a yield of 22.6 g. (91%), m. p. 163–166° (dec.). An analytical sample which was recrystallized twice from absolute alcohol melted at 168–169° (dec.).

Anal. Calcd. for $C_{11}H_{10}NI$: C, 45.05; H, 6.88; N, 4.77; I, 43.28. Found: C, 44.76; H, 6.95; N, 4.66; I, 43.14.

Although this methiodide had a relatively sharp melting point (with decomposition) it is believed to be a mixture of isomers (Va and Vb), for further recrystallization raised the m. p. to 174–175°; moreover, a mixed m. p. of V with the isomeric α-des-dimethylgranatenine methiodide[4] was not depressed but intermediate between the two decomposition points (174–176° dec.), proving that

(12) We are indebted to Dr. Calvin L. Stevens for these data.

(13) Impure 1,5-cycloöctadiene containing about 20% of a bicycloöctene has been prepared by the Hofmann exhaustive methylation procedure from des-dimethylgranatanine; Willstätter and Veraguth, *Ber.*, **38**, 1979 (1905); *ibid.*, **40**, 960 (1907); Willstätter and Kametka, *ibid.*, **41**, 1482 (1908); Harries, *ibid.*, **41**, 672 (1908).

(14) Craig, *Ind. Eng. Chem., Anal. Ed.*, **9**, 441 (1937).

the decomposition points of mixtures of such isomeric methiodides can be sharp and not markedly lowered.[12]

A 2.24-g. sample of dimethylaminocycloöctadiene in 70 ml. of absolute alcohol was hydrogenated in the presence of 0.4 g. of prereduced platinum oxide catalyst. Hydrogen absorption was 99.5% of two molar equivalents. The dimethylaminocycloöctane produced was isolated by distillation in a Craig micro column; $n^{25}D$ 1.4717 (ref. 4, $n^{25}D$ 1.4707).

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.02. Found: C, 77.36; H, 13.46; N, 9.15.

Dimethylaminocycloöctane methiodide was prepared as a derivative and recrystallized from absolute alcohol; m. p. 273–274° (dec.) (ref. 4, m. p. 274–275° dec.).

Anal. Calcd. for $C_{11}H_{24}NI$: C, 44.44; H, 8.13; N, 4.71; I, 42.70. Found: C, 44.16; H, 8.09; N, 4.63; I, 42.46.

Cycloöctatriene (VI).—Dimethylaminocycloöctadiene methiodide (21.4 g.) in 300 ml. of water and the silver hydroxide prepared from 37.5 g. of silver nitrate and 8.8 g. of sodium hydroxide were stirred at room temperature for one and one-half hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. The quaternary base was decomposed by continuing the distillation at a pressure of 20 mm. and a bath temperature of 90°. The distillate, which was collected in a receiver cooled with Dry Ice, was extracted with ether, and the extracts (to which 1% of *t*-butylcatechol was added as a polymerization inhibitor) were dried over magnesium sulfate. Distillation through a 15 × 1.2 cm. helix-packed column under nitrogen yielded 6.1 g. (78%) of cyclooctatriene, b. p. 76° (90 mm.); $n^{25}D$ 1.5187; d^{25}_4 0.8971.

Anal. Calcd. for C_8H_{10}: C, 90.50; H, 9.50. Found: C, 90.28; H, 9.47.

1,6-bis-(Dimethylamino)-2,4-cycloöctadiene (VII).—1,5-Cycloöctadiene (21.6 g., 0.2 mole) in 300 ml. of dry carbon tetrachloride, 72.g. (0.4 mole) of N-bromosuccinimide and 1 g. of benzoyl peroxide were stirred vigorously and heated under reflux (80°) for one hour. Succinimide was separated by filtration and most of the carbon tetrachloride was removed from the filtrate by distillation under reduced pressure. To the residue was added 500 ml. of a 22.5% solution of dimethylamine in benzene, and the mixture was allowed to stand for ten days at room temperature. Fifteen per cent. hydrochloric acid was added until the mixture was acid (*p*H 2), and the amine salts were extracted with two portions of 0.01 *N* hydrochloric acid. The acid extracts were made basic with 20% sodium hydroxide and the amines were extracted three times with ether. The ether was distilled and the residue was heated at 60° for three minutes with 400 ml. of 2 *N* hydrochloric acid to hydrolyze substituted vinyl amine types. The solution was cooled, extracted with ether to remove any neutral material, and made basic with 20% sodium hydroxide. The product was extracted with ether and the extracts were dried over magnesium sulfate. The ether was distilled and the residue fractionated under nitrogen through a 15 × 1.2 cm. helix-packed column. Dimethylaminocycloöctadiene (IV) (5.1 g., 17%) was obtained as a low boiling fraction, followed by 13.3 g. (34%) of 1,6-bis-(dimethylamino)-1,4-cyclooctadiene (VII), b. p. 90° (1 mm.); $n^{25}D$ 1.4995; d^{25}_4 0.932 (ref. 4, $n^{25}D$ 1.4990; d^{25}_4 0.9317).

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.16; H, 11.41. Found: C, 73.94; H, 11.06.

1,6-bis-(Dimethylamino)-2,4-cycloöctadiene dipicrate was prepared as a derivative and recrystallized from 95% alcohol; m. p. 194–195° (dec.) (ref. 4, m. p. 194.6–195.2°, dec.).

Anal. Calcd. for $C_{24}H_{28}N_8O_{14}$: C, 44.17; H, 4.33; N, 17.17. Found: C, 44.01; H, 4.52; N, 17.26.

1,6-bis-(Dimethylamino)-2,4-cycloöctadiene dimethiodide was prepared from 6.2 g. of 1,6-bis-(dimethylamino)-2,4-cycloöctadiene and 15 g. of methyl iodide in 50 ml. of absolute alcohol by refluxing for one hour. The salt which separated on cooling solidified on standing and was crystallized from a mixture of 90% alcohol and petroleum ether; yield 13.4 g. (87%), m. p. 172–173° (dec.); m. p. after recrystallization from absolute alcohol 172–173° (dec.)[12] (ref. 4, m. p. 173–174°, dec.).

Anal. Calcd. for $C_{14}H_{28}N_2I_2$: C, 35.16; H, 5.90; N, 5.86; I, 53.08. Found: C, 35.06; H, 5.91; N, 5.78; I, 53.28.

The above methiodide was separated from a much smaller amount (2–5%) of an isomeric dimethiodide which was relatively insoluble in alcohol. After two recrystallizations from alcohol and benzene the isomer (which may be a stereo or position isomer) darkened at 237–239° but did not liquefy or decompose with gas evolution below 285°.[12]

Anal. Calcd. for $C_{14}H_{28}N_2I_2$: C, 35.16; H, 5.90; N, 5.86; I, 53.08. Found: C, 35.25; H, 6.09; N, 6.01; I, 52.94.

A 2.30-g. sample of 1,6-bis-(dimethylamino)-2,4-cycloöctadiene in 30 ml. of absolute alcohol absorbed 110% of two molar equivalents of hydrogen slowly (during thirteen hours) in the presence of 0.5 g. of pre-reduced platinum oxide. The 1,4-bis-(dimethylamino)-cyclooctane formed was distilled through a Craig micro column: $n^{25}D$ 1.4820; d^{25}_4 0.9155 (ref. 4, $n^{25}D$ 1.4823, d^{25}_4 0.9166).

Anal. Calcd. for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.13. Found: C, 72.62; H, 12.99; N, 14.07.

1,4-bis-(Dimethylamino)-cycloöctane dipicrate was prepared as a derivative and recrystallized from 95% alcohol; m. p. 173–174° (dec.) (ref. 4, m. p. 171.5–172.2°, dec.).

Anal. Calcd. for $C_{24}H_{32}N_8O_{14}$: C, 43.90; H, 4.90; N, 17.07. Found: C, 43.98; H, 5.04; N, 16.95.

1,4-bis-(Dimethylamino)-cycloöctane dimethiodide was prepared as a second derivative and recrystallized from 90% alcohol and petroleum ether; m. p. 255–256° (dec.) (ref. 4, m. p. 258–259°, dec.).

Anal. Calcd. for $C_{14}H_{32}N_2I_2$: C, 34.86; H, 6.69. Found: C, 34.81; H, 7.04.

Cycloöctatetraene.—1,6-bis-(Dimethylamino)-2,4-cycloöctadiene dimethiodide (22 g.), 100 ml. of water and the silver hydroxide prepared from 25.5 g. of silver nitrate and 6.0 g. of sodium hydroxide were stirred for one hour at room temperature and one hour at 50°. The mixture was filtered and the filtrate was concentrated under reduced pressure. The final stages of concentration and decomposition of the quaternary base were conducted at a pressure of 0.15–1 mm. and a bath temperature of 50° during four hours. The flask was heated at 100° for twenty minutes after the decomposition appeared to be complete. The distillate, which was collected in a receiver cooled with Dry Ice, was extracted with ether. The extracts were dried over magnesium sulfate, concentrated, and the residue distilled through a Craig micro column. The yield of cycloöctatetraene was 0.74 g. (15.5%); $n^{25}D$ 1.5342 (ref. 4, $n^{25}D$ 1.5342).

Anal. Calcd. for C_8H_8: C, 92.26; H, 7.74. Found: C, 91.92; H, 7.88.

The cycloöctatetraene obtained melted at −8.7 to −7.9°, and gave a mixed melting point with a sample of cycloöctatetraene prepared from acetylene (m. p. −5.9 to −5.3°) of −7.6 to −6.5°.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra of compounds VI, VII and the cycloöctatetraene prepared in this way were determined in purified cyclohexane solution with a Beckmann quartz ultraviolet spectrophotometer. Absorption curves are shown in Figs. 1–3, in which curves for VII prepared from pseudopelletierine and cycloöctatetraene prepared from acetylene[4] are included for comparison.

Summary

Cycloöctatetraene has been prepared by a seven-step synthesis from chloroprene.

CAMBRIDGE, MASS. RECEIVED FEBRUARY 28, 1948

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

The Preparation and Properties of Some Substituted Benzyl Fluorides[1]

BY JACK BERNSTEIN,[2,3] JAY S. ROTH[4] AND WILLIAM T. MILLER, JR.

The substituted benzyl halides are of special importance because of their theoretical interest and because of their suitability for experimental investigation. Since a series of substituted benzyl fluorides had not been prepared previously, a general method for their preparation was sought in order to permit a study of their properties and relative reactivities. Benzyl fluoride and *p*-nitrobenzyl fluoride are the only compounds in this series which have been previously reported. They were prepared and characterized by the Ingolds[5]: benzyl fluoride itself by the thermal decomposition of benzyltrimethylammonium fluoride and *p*-nitrobenzyl fluoride by the nitration of benzyl fluoride. Swarts[6] had previously reported benzyl fluoride to be a liquid which decomposed very readily, but he did not describe his method of preparation or characterize the product. Ray and Ray[7] reported the preparation of benzyl fluoride by the action of thallous fluoride on benzyl bromide in absolute alcohol solution The product isolated by them was a yellow lachrymatory liquid which decomposed, and apparently was impure since benzyl fluoride is a colorless non-lachrymatory liquid. Attempts to prepare benzyl fluoride by the action of silver fluoride on benzyl chloride[8] and by the decomposition of phenyldiazomethane in 40% hydrofluoric acid[9] were unsuccessful.

In this research, benzyl fluoride was first prepared by thermally decomposing benzyl trimethylammonium fluoride according to Ingold's procedure. Poor yields were obtained, 22 to 29%, based on the starting benzyl chloride, due to polymerization which occurred during the decomposition of the quaternary salt. In addition, Ingold had shown that this method of preparation was not a general one, so that various other procedures had to be investigated. The reactions of benzyl halides with antimony fluoride, thallous fluoride,[7] silver fluoride and potassium fluoride were tried, but in no case could any benzyl fluoride be isolated from the reaction mixtures.

The method of synthesis finally found satisfactory as a general procedure consisted of treating mercuric fluoride[10] with benzyl bromides in chloroform solution. The replacement of the side-chain bromine by fluorine lowered the boiling point of the product sufficiently, about 40°, so that the benzyl fluorides could be easily separated from unreacted bromide by distillation. Absolutely anhydrous conditions were essential for satisfactory fluorinations since the presence of traces of water resulted in the formation of hydrogen fluoride which caused the polymerization of the benzyl fluoride. In general, the catalytic properties of hydrogen fluoride[11] greatly complicate the preparation and study of organic fluorine compounds as compared with the other halides and reactions leading to the formation of hydrogen fluoride are likely to be autocatalytic.

An attempt was made to prepare benzyl fluoride by the reaction of mercuric fluoride with benzyl chloride in benzene solution. From this reaction no benzyl fluoride was obtained, but a considerable quantity of diphenylmethane was isolated. The formation of this compound probably occurred through a Friedel–Crafts type reaction of either benzyl chloride or benzyl fluoride, catalyzed by the mercuric salts or by hydrogen fluoride. Calloway[12] has found that alkyl fluorides are the most reactive of the alkyl halides in Friedel–Crafts alkylation. The reaction of *p*-chlorobenzyl fluoride with benzene did not take place in the absence of a catalyst at moderate temperature. However, in the presence of boron trifluoride,[13] the benzyl fluorides reacted smoothly with aromatic hydrocarbons and diphenylmethane derivatives were isolated.

As indicated by Ingold, benzyl fluoride polymerizes very rapidly in the presence of catalysts. In this work the stability of the substituted benzyl fluorides was found to vary greatly with the substituent. No evidence was obtained for the polymerization of *p*-nitrobenzyl fluoride, and even *p*-bromobenzyl fluoride did not polymerize in the presence of a trace of sulfuric acid, which caused a very violent reaction when added to benzyl fluoride itself. In general, ring inactivating substituents made the benzyl fluoride more stable. This effect was consistent with a Friedel–Crafts type polymerization reaction as was the ready formation of diphenylmethane derivatives by reaction

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at Atlantic City, September 10, 1941. Abstracted from the thesis submitted by Jack Bernstein to the Graduate School of Cornell University in partial fulfillment of the requirements for the Ph.D. degree, June, 1941; and from the thesis submitted by Jay S. Roth in partial fulfillment of the requirements for the M.S. degree, June, 1941.

(2) Sage Fellow in Chemistry, 1940–1941.

(3) Present address: Squibb Institute for Medical Research, New Brunswick, N. J.

(4) Present address: Department of Chemistry, Rutgers University, New Brunswick, N. J.

(5) Ingold and Ingold, *J. Chem. Soc.*, 2249 (1928).

(6) Swarts, *Bull. soc. chim.*, [4] **35**, 1533 (1924).

(7) Ray and Ray, *J. Indian Chem. Soc.*, **13**, 427 (1936).

(8) Tronov and Kruger, *J. Russ. Phys.-Chem. Soc.*, **58**, 1270 (1926).

(9) Tseng, Chia and Ho, *Science Reports*, National Univ. Peking, **1**, 9 (1936).

(10) Henne and Midgley, THIS JOURNAL, **58**, 884 (1936).

(11) Simons, *Ind. Eng. Chem.*, **32**, 178 (1940).

(12) Calloway, THIS JOURNAL, **59**, 1474 (1937).

(13) Compare: Burwell and Archer, *ibid.*, **64**, 1032 (1942).

with benzene.[14] The polymerization may be catalyzed by boron trifluoride or boron trifluoride etherate. Ingold had already reported that sulfuric acid, hydrogen fluoride and even soft glass catalyzed the decomposition of benzyl fluoride. When pure or in the presence of traces of bases, the benzyl fluorides were found to be stable in Pyrex glass at room temperature for long periods of time. Some samples of *p*-chlorobenzyl fluoride have remained undecomposed after seven years storage, although other samples decomposed violently after standing for several weeks. In general, the marked tendency to polymerize increased the difficulty of the preparation of the benzyl fluorides although the use of rigorously anhydrous conditions and reagents, and reasonable care to prevent thermal decomposition during distillation resulted in fairly satisfactory yields of products.

The benzyl fluorides are pleasant smelling compounds with odors similar to the parent hydrocarbons. They show typical halide reactivity in many reactions, and with the exception of the Friedel and Crafts reactions are in general considerably less reactive than the chlorides. Reaction in aqueous alcoholic sodium hydroxide led to the formation of the corresponding ether and alcohol. In dilute aqueous alcoholic hydrogen chloride, significantly, the corresponding ether was also formed. By refluxing the fluoride in a mixture of hydrochloric acid and dioxane, the fluorine could be replaced by chlorine, possibly through the alcohol. The reaction of a fluoride with sodium phenolate in excess phenol led to the formation of the phenyl ethers. These ethers are crystalline compounds, easily purified, and would be suitable as derivatives for the identification of the fluorides which are mostly liquids. The preparation of esters was attempted using the method of Reid.[15] Under conditions which give almost quantitative yields of esters from *p*-nitrobenzyl chloride in three hours, or from *p*-nitrobenzyl bromide in fifteen minutes, practically no reaction had occurred in forty-six hours with *p*-nitrobenzyl fluoride. A small yield of acetate was obtained by reaction with potassium acetate in acetic acid.

Several attempts were made to prepare a Grignard reagent from benzyl fluoride, since benzyl chloride forms a Grignard reagent with great ease. At reflux temperature with ethyl ether no reaction took place while under more vigorous conditions in di-*n*-butyl ether polymerization of the benzyl fluoride occurred. It was found possible to obtain dibenzyl by heating benzyl fluoride in ether solution with Gilman's[16] activated magnesium catalyst in a bomb tube at 100° for ten days, although using ordinary magnesium under similar conditions gave no reaction. Under these vigorous conditions, any Grignard reagent formed would be expected to enter into secondary reactions and consequently would not have been detected. A Wurtz–Fittig reaction was carried out in ether solution, using lithium metal, to form dibenzyl.

(14) Compare: Henne and Leicester, THIS JOURNAL, **60**, 864 (1938).

(15) Reid, *ibid.*, **39**, 124 (1917).

(16) Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

Experimental Part

Preparation of Benzyl Fluorides

Benzyl Bromides.—The substituted benzyl bromides were prepared from the corresponding toluenes by direct bromination, usually at the boiling point, in Pyrex all-glass apparatus, illuminated by a mercury vapor lamp. Their physical properties and the yields obtained, based on the starting toluenes, are summarized in Table I.

TABLE I

Substituent	% Yield	Physical properties
m-CH_3[a]	50	B. p. 96–98° at 11 mm.
p-CH_3[a]	51	B. p. 96° at 12 mm., m. p. 36–37°
m-F[b]	54	B. p. 80° at 13 mm.
p-F[b]	57	B. p. 75–76° at 11 mm.
o-Cl[c]	52	B. p. 107° at 12 mm.
m-Cl[d]	57	B. p. 103–104° at 10 mm.
p-Cl[d]	71	B. p. 108° at 12 mm.; m. p. 49.0–49.5°
o-Br[b]	56	B. p. 118–120° at 9 mm.; m. p. 31–32°
m-Br[b]	60	B. p. 122–124° at 12 mm.; m. p. 41.5–42.5°
p-Br[b]	65	B. p. 117–119° at 10 mm.; m. p. 62–63°
m-I[e,g]	28	M. p. 49–50°
p-I[e,g]	28	M. p. 77–79°
m-NO_2[f,h]	30	B. p. 130° at 3 mm.; m. p. 56.5–57.0°
p-NO_2[f,i]	55	M. p. 97.5–99°

[a] Atkinson and Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907). [b] Shoesmith and Slater, *ibid.*, 214 (1926). [c] Leonard, *ibid.*, **109**, 570 (1916). [d] Jackson, *Am. Chem. J.*, **1**, 93 (1879). [e] Shoppee, *J. Chem. Soc.*, 696 (1932). [f] *Org. Syntheses*, **16**, 54 (1936). [g] Bromination temperature 170–180°. [h] Bromination temperature 160°. [i] Bromination temperature 150°.

Mercuric Fluoride.—Mercuric fluoride was prepared by the fluorination of anhydrous mercuric chloride (powder) in a rotating brass reaction vessel according to the general method of Henne.[10] An improved reaction vessel was designed to permit more complete utilization of the fluorine. This consisted of a brass tube 52 cm. long and 5 cm. in diameter which was fitted with interchangeable screw caps. The tube was divided in the middle by a diaphragm with a center opening of 1.5 cm. Mercuric chloride, 0.3 mole and a nickel rod the length of the chamber, to prevent caking of the solid, were placed in each side. The tube was rotated at 30 r. p. m. and fluoride from a closed type nickel electrolysis cell[17] was passed in until the charge in the side into which the fluorine entered was completely converted to mercuric fluoride, as shown by a negative test for chloride ion. This chamber was then emptied and refilled with mercuric chloride. The reaction vessel was then reversed so that the fluorine passed first into the chamber containing partially converted mercuric chloride and the process repeated. The mercuric fluoride was either used directly or stored in a tightly closed copper container fitted with a metal cap and a lead gasket.

Benzyl Fluorides.—The fluorination reactions were carried out in 1-liter three-necked flasks which were fitted with a mercury-sealed stirrer, a reflux condenser and a section of 1.25″ rubber tubing which was closed just above the neck of the flask by a screw clamp. The reflux condenser was fitted with a drying tube and contained a thermometer suspended inside so that its bulb dipped into the chloroform solution. The apparatus was all carefully dried. Chloroform, usually 650 cc., and from 0.2

(17) Miller, unpublished work.

TABLE II

PHYSICAL PROPERTIES OF SUBSTITUTED BENZYL FLUORIDES

Substituent	M. p., °C.	B. p. °C.	B. p. Mm.	d^{20}_4	$n^{20}D$	Fluorine, % Calcd.	Fluorine, % Found	MR_D Calcd.	MR_D Found
None[a]		50	27						
m-CH_3		48.5	8.5	1.0089	1.4952	15.31	15.3	35.55[b]	35.91
p-CH_3	19.5–20.0	46.5–47	8	1.0037	1.4918	15.31	15.2	35.55	35.89
m-F		41	15	1.1592	1.4660	29.66	29.9[c]	30.92	30.61
p-F		54	28	1.1573	1.4667	29.66	29.8[c]	30.92	30.69
o-Cl		58.5	9	1.2224	1.5159	13.15	13.2	35.80	35.72
m-Cl		65	11	1.2157	1.5158	13.15	13.0	35.80	35.83
p-Cl	3–4	72–73	16	1.2127	1.5149	13.15	13.1	35.80	35.95
		64	10.5						
o-Br		84–85	18	1.5557	1.5470	10.05	10.0	38.70	38.53
m-Br		83	13	1.5450	1.5448	10.05	10.1	38.70	38.67
p-Br	32.9–33.2	80.0–81.5	10–11			10.05	10.1		
m-I		68.0–68.5	2.5	1.8052	1.5933	8.05	7.98	43.73	44.32
p-I	51.5–52[d]	75	4			8.05	8.00		
m-NO_2		91	3.5	1.3019	1.5381	12.25	12.2	37.13	37.27
p-NO_2	38.2–38.5[e]					12.25	12.2[f]		

[a] First prepared by Ingold, who reported the b. p. as 55° at 30 mm. [b] See Gilman, "Organic Chemistry," Vol. II, 1938, p. 1737. The value of 1.09 used for the atomic refraction of fluorine was determined by Ingold. [c] Sodium peroxide decompositions were run on these samples to determine total fluorine. [d] Recrystallized from petroleum ether (b. p. 30–60°). [e] First prepared by Ingold, who reported the m. p. 38.5°. Sample was recrystallized from ether–petroleum ether mixture (1:1). [f] Treatment of *p*-nitrobenzyl fluoride with sodium ethoxide solution caused the formation of a dark brown solution. Upon steam distillation, a solid precipitated out, which was filtered off. The filtrate was treated with decolorizing carbon and then analyzed for F^-.

to 0.6 mole of the benzyl bromide were poured into the flask and about 50 cc. of chloroform distilled out, with the reflux condenser temporarily replaced by a condenser arranged for distillation, to assure removal of traces of water. The reflux condenser was then replaced. Freshly prepared mercuric fluoride, usually 0.3 mole, was placed in the rubber addition tube attached to the reaction flask and the open end stoppered. The solution was stirred vigorously and the mercuric fluoride added slowly by opening the screw clamp on the rubber tubing. The first portions of mercuric fluoride turned red-orange in color, but upon continued stirring the color changed to pale yellow and the temperature of the reaction mixture started to rise. When the temperature reached about 35°, the flask was cooled in water to prevent a more vigorous reaction. The addition of the mercuric fluoride was continued at 35° with occasional cooling of the reaction flask in a cold water-bath. About forty minutes were ordinarily required for the addition of the mercuric fluoride.

The reaction mixture was then stirred for from one-half to seventy hours. The longer times of reaction did not result in improved yields. The usual time of stirring was from two to four hours. The reaction mixture was then filtered and the residue washed with chloroform. The chloroform solutions were combined and washed once with saturated sodium carbonate solution, once with dilute nitric acid (1:10), again with saturated sodium carbonate solution, and finally with water. Two drops of pyridine or other tertiary amine were added to prevent polymerization of the fluoride and the chloroform solution dried over calcium chloride. After drying overnight, the chloroform was removed by distillation through an efficient column. The residue was then distilled under reduced pressure from a modified Claisen flask and then either redistilled or crystallized for further purification. In this redistillation, no pyridine was added.

A modified procedure was evolved for the preparation of benzyl and methyl-, fluoro- and *o*-chlorobenzyl fluorides which showed a great tendency to polymerize during the preparative reaction. One cc. of dry pyridine was added to the chloroform solution of the bromide before the addition of the mercuric fluoride. The addition of the mercuric fluoride then produced no immediate temperature rise and the solid in the reaction became red-orange in color. Continued stirring did not change this color, but upon gentle warming to about 40° the color changed to light yellow, and the reaction mixture had to be cooled in ice-water to prevent a rapid rise in temperature. When the temperature of the reaction mixture fell to 35°, the addition of the mercuric fluoride was continued. Stirring was continued for thirty minutes after all the mercuric fluoride had been added, 1 cc. of pyridine was added and the stirring continued for three hours. The remainder of the procedure was the same as indicated above.

The yields of benzyl fluorides isolated ranged from 40 to 60% but no attempt was made to secure maximum yields since higher still pot temperatures near the end of the distillations tended to cause thermal decomposition of the fluoride and result in polymerization of the distillate. The physical properties of the benzyl fluorides are given in Table II.

The purity of the benzyl fluorides was checked by analyses for fluorine and molecular refractivity determinations. The absence of any unreacted benzyl bromides in the products was shown by a completely negative test for bromide with boiling alcoholic silver nitrate solution.

Fluorine was determined by refluxing 1-g. samples of the fluorides with sodium ethoxide solution, prepared by dissolving 2.3 g. of sodium in 30 cc. of absolute alcohol, for forty-eight hours. Water, 100 cc., was added and the solution steam distilled to remove organic matter. Fluoride ion was then titrated in an aliquot with standard cerous nitrate solution using a divided titration vessel.[18] In the case of the fluorobenzyl fluorides sodium peroxide decompositions were run to determine total fluorine. A value of 17.5% F was found for *p*-fluorobenzyl fluoride using the sodium ethoxide decomposition indicating partial removal of ring as well as side chain fluorine.

Reactions of Benzyl Fluorides.—The observed reactions of the benzyl fluorides are listed below under reactants.

Aromatic Hydrocarbons.—*p*-Chlorobenzyl fluoride, 5.8 g., was refluxed for four hours in the absence of added catalyst with 40 cc. of dry benzene while a slow stream of

(18) Batchelder and Meloche, THIS JOURNAL, **53**, 2131 (1931); Hubbard and Henne, *ibid.*, **56**, 1078 (1934); Miller, unpublished work. This titration has recently been carefully investigated by Nichols and Olsen in this laboratory and an improved procedure described; *Ind. and Eng. Chem., Anal. Ed.*, **15**, 342 (1943).

nitrogen was passed through the reaction vessel. About 0.1% of the theoretical quantity of hydrogen fluoride was evolved. *m*-Bromobenzyl fluoride, 10.0 g., in 56.0 g. of *p*-xylene was refluxed for seven hours as above. About 1% of the theoretical amount of hydrogen fluoride was formed. The mixture was distilled. When about 75% of the *p*-xylene had been removed a vigorous reaction occurred with the copious evolution of hydrogen fluoride. Separation of the resulting mixture yielded 1.0 g. of starting fluoride, b. p. 82° at 10 mm., and 8.1 g. of viscous liquid, b. p. 185–186° at 10–12 mm. The latter material was indicated as 2,5-dimethyl-3-bromodiphenylmethane by analysis after redistillation at 0.5 mm. Calcd. for $C_{15}H_{15}Br$: Br, 29.1. Found: Br, 28.4.

p-Chlorobenzyl fluoride, 5.8 g., dissolved in 100 cc. of benzene was treated with gaseous boron trifluoride. Reaction was observed after two minutes and the boron trifluoride flow was stopped after four minutes. The solution was refluxed for an additional hour. Five grams of *p*-chlorobenzyl fluoride in 40 cc. of benzene was caused to react as above. The combined products yielded 11.4 g. of main fraction, b. p. 147–148° at 8 mm. This product, 4-chlorodiphenylmethane, on oxidation yielded *p*-chlorobenzophenone, m. p. 76–77°; reported m. p. 77–78°.[19]

m-Bromobenzyl fluoride, 11 g., dissolved in 100 g. of toluene was treated with gaseous boron trifluoride at Dry Ice temperature for six minutes. An immediate cloudiness was observed. On warming to room temperature without further addition of boron trifluoride the cloudiness disappeared and gas was evolved. The mixture was heated to reflux for thirty minutes. Distillation yielded a main fraction of 8.5 g., b. p. 170–173° at 7–8 mm. This product was characterized as 3-bromo-4′-methyldiphenylmethane by oxidation, with 10 g. of sodium dichromate in 15 cc. water and 10 cc. concentrated sulfuric acid at reflux temperature, to yield 3-bromo-4′-carboxybenzophenone. The purified acid had a neutral equivalent of 304.5; calcd. 305.

Sodium Hydroxide in Aqueous Alcohol.—Nine grams of *p*-chlorobenzyl fluoride dissolved in 200 cc. of 95% alcohol was mixed with 100 cc. of 0.99 *N* sodium hydroxide and heated at reflux on a steam-bath for one hundred hours. Extraction with petroleum ether and distillation yielded 7.5 g. of liquid, b. p. 104° at 15 mm., and 0.8 g. of solid residue. The residue after recrystallization from petroleum ether melted 69–70° and was shown to be *p*-chlorobenzyl alcohol. The redistilled liquid fraction, b. p. 220–223° at 746 mm., d^{14}_4 1.101, as compared with b. p. 225°, d^{14}_4 1.121 reported for ethyl *p*-chlorobenzyl ether, was cleaved with 48% hydrobromic acid to form ethyl bromide, converted to propionanilide m. p. 101–103°,[20] and *p*-chlorobenzyl bromide m. p. 48.5–49.5°, no depression in m. p. with authentic sample.

Hydrochloric Acid in Aqueous Alcohol.—Eleven grams of *m*-xylyl fluoride dissolved in 250 cc. of 95% alcohol was mixed with 125 cc. of 0.93 *N* hydrochloric acid and heated at reflux for seventy hours. Extraction with petroleum ether and distillation yielded 8.0 g. of liquid, b. p. 91–93° at 14 mm., without appreciable forerun or residue. The redistilled liquid had a b. p. 204–205° at 749 mm., d^{20}_4 0.939 as compared with b. p. 202° at 740 mm., d^{17}_4 0.930 reported for ethyl *m*-xylyl ether. Cleavage of the ether with 48% hydrobromic acid yielded ethyl bromide, b. p. 37–40°, which was converted into ethyl mercuric bromide,[21] m. p. 192–193°, and *m*-xylyl bromide, b. p. 215–217° at 747 mm., which was converted through the Grignard reagent into *m*-methylphenylacetic acid of m. p. 59.5–60.5°; reported m. p. 61°.

Hydrochloric Acid in Dioxane.—*p*-Nitrobenzyl fluoride, 2.0 g., dissolved in 20 cc. of dioxane was mixed with 5 cc. concentrated hydrochloric acid, and heated to reflux for sixteen hours. The mixture turned light brown and separated into two layers during this time. Distillation of the dioxane and extraction of the residue with hot 75% alcohol yielded 1.5 g. of crystals m. p. 64–67°. Two recrystallizations yielded m. p. 71–72° as compared with m. p. 71° reported for *p*-nitrobenzyl chloride.

m-Bromobenzyl fluoride was treated similarly to yield *m*-bromobenzyl chloride, m. p. 22°, as compared with reported m. p. 22.4°.

Sodium Phenolate.—Two grams of *p*-chlorobenzyl fluoride was heated for two hours in an oil-bath at 140° with a solution of sodium phenolate prepared by dissolving 0.5 g. of sodium in 5.0 g. of phenol. The reaction mixture was poured into 200 cc. of dilute sodium hydroxide and 3.0 g. of brown crystalline material separated. The solid was recrystallized from alcohol and melted at 86°; reported for *p*-chlorobenzylphenyl ether, m. p. 85.5–86.5°.

m-Bromobenzyl fluoride by a similar procedure yielded phenyl *m*-bromobenzyl ether, m. p. 37.5–38.0°, as compared with a reported m. p. of 36–37°. *p*-Chlorobenzyl fluoride yielded phenyl *p*-chlorobenzyl ether, m. p. 81°; reported m. p. 81°. *p*-Nitrobenzyl fluoride yielded phenyl *p*-nitrobenzyl ether, m. p. 91–92°; reported m. p. 91°.

Potassium Acetate.—Appreciable reaction did not occur when *p*-nitrobenzyl fluoride was refluxed in 67% aqueous alcohol solution with potassium or magnesium acetates for periods up to forty-six hours. Partial conversion to the acetate occurred when a solution of 2.0 g. of *p*-nitrobenzyl fluoride and 4 g. of potassium acetate in 30 cc. of glacial acetic acid was refluxed for twenty-four hours. Unreacted fluoride was slowly sublimed from the water insoluble product and a 0.3-g. residue obtained, m. p. 76°; m. p. with authentic *p*-nitrobenzyl acetate 77°.

Lithium and Magnesium Metals.—Lithium metal, 0.4 g. scraped and cut into small pieces under xylene, was added to 20 cc. of dry ether with nitrogen blanketing. Benzyl fluoride, 3.0 g., was added and the mixture warmed to reflux. A white deposit formed on the surface of the metal but after one and one-half hours the solution gave a negative test for benzyl lithium with Michler ketone.[22] After twelve hours, evaporation of the ether solution yielded 1.5 g. of dibenzyl, m. p. 51–52° after recrystallization from alcohol.

Thirteen grams of benzyl fluoride dissolved in 80 cc. of sodium dry ether was placed in the dropping funnel of a thoroughly dried Grignard set-up provided with nitrogen blanket. Freshly turned magnesium metal, 3.7 g., was introduced into the conical three-necked reaction flask and 20 cc. of the ether solution added. The mixture was stirred for several hours and warmed with no apparent reaction. Addition of iodine crystals or of Gilman activated magnesium catalyst[16] failed to produce any signs of reaction. Addition of phenylmagnesium bromide also failed to initiate reaction. Three cc. samples of the ethereal solution of benzyl fluoride were heated in glass bomb tubes with freshly turned magnesium and with the activated magnesium alloy at 100° for ten days. At the end of this period negative tests were obtained for the presence of Grignard reagent but the solution from the tube containing activated magnesium yielded crystals of dibenzyl, m. p. 51°. No dibenzyl could be obtained from the tube containing ordinary magnesium.

Summary

A general procedure for the preparation of benzyl fluorides by the reaction of mercuric fluoride with the corresponding benzyl bromide has been developed.

The benzyl fluorides underwent the typical Friedel–Crafts type reaction with aromatic hydrocarbons in many cases with great ease. They underwent typical halide replacement type reactions but at much slower rates than the corresponding chlorides.

The Grignard reagent could not be prepared

(19) Montagne, *Rec. trav. chim.*, **26**, 263 (1907).

(20) Underwood and Gale, THIS JOURNAL, **56**, 2117 (1934).

(21) Marvel, Gauerke and Hill, *ibid.*, **47**, 3009 (1925).

(22) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

from benzyl fluoride. Attempts to prepare it under vigorous conditions led to the formation of dibenzyl.

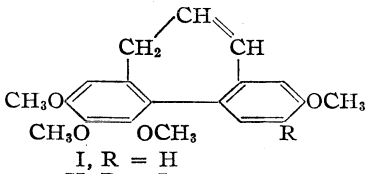
ITHACA, NEW YORK RECEIVED APRIL 1, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

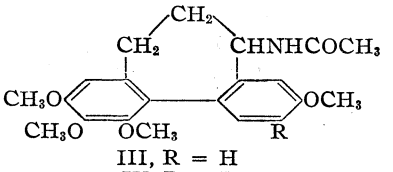
Studies on the Structure of Colchicine.[1] Syntheses in the Biphenyl Series

BY H. RICHARD FRANK,[2a] PAUL E. FANTA[2b] AND D. STANLEY TARBELL

Degradation studies on deaminocolchinol methyl ether[3] I and its iodine derivative[1] II have provided evidence for the presence of the central seven-membered ring. Assuming that no rearrangement of the carbon skeleton occurred during the formation of I or II from N-acetyl-(iodo)-colchinol methyl ether the latter compounds must have structures III and IV. It is obviously necessary, in order to establish the constitution of colchicine, to provide synthetic evidence for structures I–IV. Furthermore, the importance which colchicine and its derivatives have assumed in research on the cancer problem as a result of their antimitotic properties makes it highly desirable to explore possible methods of synthesizing compounds of this type.[4]

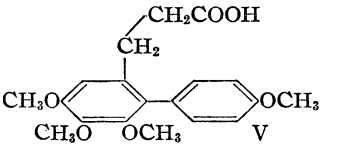


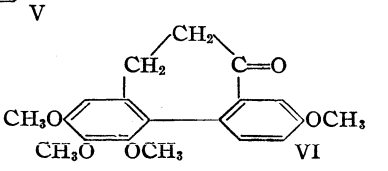
I, R = H
II, R = I



III, R = H
IV, R = I

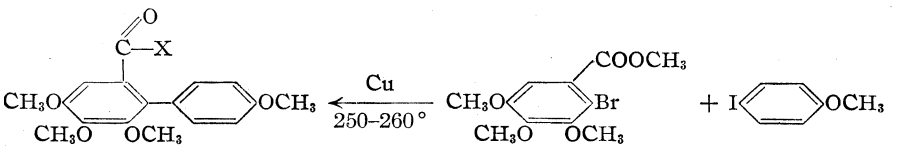
Our work was designed to lead to structures I and III through the synthesis of the biphenylpropionic acid V and its ring closure to the ketone VI, which could be converted by obvious methods to compounds I and III.



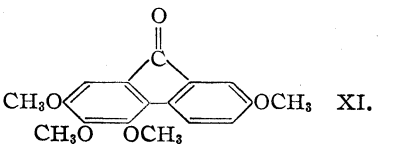


The biphenyl aldehyde VIII seemed to offer a feasible approach to the acid V, since the propionic acid side chain could be readily built up from the aldehyde by condensation with malonic acid followed by decarboxylation and reduction.

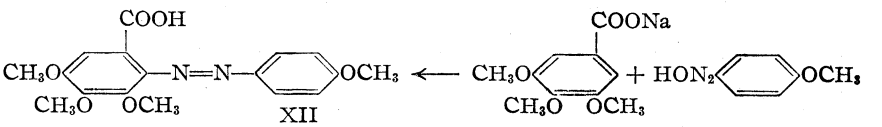
The acid VII was therefore prepared in 25–35% yield by the crossed Ullmann[5] reaction from *p*-iodoanisole and methyl 2-bromo-3,4,5-trimethoxybenzoate. The Ullmann synthesis using the iodo ester, methyl 2-iodo-3,4,5-trimethoxybenzoate and iodoanisole, yielded the two symmetrical products to the exclusion of the desired unsymmetrical compound VII.



VII, X = OH
VIII, X = H
IX, X = Cl
X, X = OCH_3



XI.



XII

Some preliminary experiments on the preparation of the acid VII by the Gomberg reaction from diazotized *p*-anisidine and sodium 3,4,5-trimeth-

(1) In memory of H. Richard Frank, died March 21, 1948; for the preceding paper see Tarbell, Frank and Fanta, THIS JOURNAL, **68**, 502 (1946).

(2) (a) Abbott Laboratories Fellow, 1946–1947. (b) Present address, Department of Chemistry, Harvard University, Cambridge, Massachusetts.

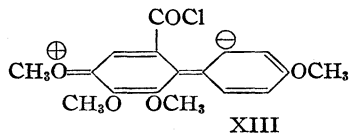
(3) (a) Buchanan, Cook and Loudon, *J. Chem. Soc.*, 325 (1944); (b) Barton, Cook and Loudon, *ibid.*, 176 (1945).

(4) For a discussion of colchicine and other compounds as chemotherapeutic agents for cancer, see Greenstein, "The Biochemistry of Cancer," Academic Press, New York, N. Y., 1947, pp. 170–172.

(5) For a review of the Ullmann reaction see Fanta, *Chem. Rev.*, **38**, 139 (1946).

oxybenzoate were unsuccessful, the product being the azo compound XII. The same product was obtained by the action of N-nitroso-N-acetyl-*p*-anisidine on ethyl trimethoxybenzoate, followed by hydrolysis.[6]

When the acid VII was converted to the acid chloride IX even under mild conditions, the latter lost hydrogen chloride spontaneously to form the orange-red 2,3,4,7-tetramethoxyfluorenone XI.[7]



XIII

The ester of VII failed to form a hydrazide,[8] yielding instead what may have been the bis-hydrazide.

In a more successful approach to the synthesis of V, β-(3,4,5-trimethoxyphenyl)-propionic acid was prepared by the previously reported method,[9] with modifications, according to the scheme

$$\underset{\text{XIV}}{\text{ArCOCl}} \xrightarrow{H_2,\ Pd} \underset{\text{XV}}{\text{ArCHO}} + \underset{\text{XVI}}{\text{ArCOOCH}_2\text{Ar}}$$

(Ar = 3,4,5-Trimethoxyphenyl)

$$\text{ArCHO} + \text{CH}_2(\text{COOH})_2 \longrightarrow \underset{\text{XVII}}{\text{ArCH=CHCOOH}} \xrightarrow[\text{NaOH}]{H_2,\ Ni} \underset{\text{XVIII}}{\text{ArCH}_2\text{CH}_2\text{COOH}}$$

In agreement with previous reports,[10] it was found that the Rosenmund reduction of 3,4,5-trimethoxybenzoyl chloride gave variable yields; a by-product, which in some runs was the main product, was shown to be the ester XVI, by hydrolysis to the expected compounds. This product has been observed by previous workers[11] but was not identified. Reduction of the cinnamic acid XVII by sodium amalgam[9] gave a product which was difficult to purify, but the Raney nickel and hydrogen reduction of the sodium salt in aqueous solution[12] gave a practically quantitative yield of the pure hydrocinnamic acid XVIII.

The trimethoxyphenylpropionic acid XVIII was next iodinated, best with iodine monochloride, to yield β-(2-iodo-3,4,5-trimethoxyphenyl)-propionic acid XIX which was esterified with diazomethane to the ester XX. The iodo ester was then coupled with *p*-iodoanisole (in excess) at 250° with copper powder, and the unsymmetrical acid V was isolated in 55% yield.

In order to prevent ring-closure of V from forming the hydrindone XXVII, the free position in the trimethoxylated ring was blocked by bromination, yielding β-2-(3-bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic acid XXI.

The structure of XXI was proved by brominating the trimethoxyphenylpropionic acid XVIII, to yield the monobromo derivative XXIII, which was iodinated by iodine monochloride to the bromoiodo compound XXIV. The ester XXV, on coupling with *p*-iodoanisole under the usual conditions, gave a small amount of the same bromo acid which had been obtained previously by direct bromination of the biphenyl acid V.

The problem of cyclizing the acid XXI to the desired ketone XXVI proved very troublesome. The acid was entirely unaffected by anhydrous hydrogen fluoride at room temperature,[13] and it seemed to be sulfonated to give water-soluble products when treated with sulfuric acid. Treatment of the acid chloride of XXI with phosphorus oxychloride in benzene or toluene gave a small amount of neutral material which proved to be the methyl ester XXII of the acid, apparently formed by intermolecular demethylation. The acid chloride of XXI when treated with stannic chloride in benzene gave no crystalline product.

Treatment of the acid chloride with aluminum chloride in tetrachloroethane gave variable results; in one case an impure carbonyl compound was obtained, which from the percentage composition of its oxime and semicarbazone, seemed to be nearly bromine free, and hence might be the desired ketone VI. Structure XXVII was considered as a possible one for this ketonic product, which could be formed from the bromo acid chloride by removal of the bromine[14] followed by ring-closure. The ketone XXVII was actually prepared by cyclization of the unbrominated acid V, and it had quite different properties from the product obtained by the cyclization of the bromo acid XXI

Although the product from the bromo acid thus appeared to have the desired structure, the poor

(6) These results were not entirely unexpected, since Grieve and Hey, *J. Chem. Soc.*, 108 (1938), found that diazotized aniline did not yield a biphenylcarboxylic acid with sodium benzoate. The diazonium compound has two possible modes of reaction, one as the ion ArN_2^+, to give an azo compound, and the other as the radical Ar· to form a biaryl. It is known (Grieve and Hey, *J. Chem. Soc.*, 1797 (1934)) that the radical reaction goes more slowly with toluene than with nitrobenzene, and hence seems to be retarded by electron-donating groups. The work of Fieser, Clapp and Daudt, THIS JOURNAL, **64**, 2052 (1942), shows that the methylation of aromatic systems by methyl radicals from lead tetraacetate goes more readily on polynitrated benzenes than on benzene or nitrobenzene. The three methoxyl groups in trimethoxybenzoic acid, being electron-donating groups, inhibit the attack on the ring by a free radical, and promote the attack by the electrophilic diazonium ion.

(7) This fact, while unfavorable for the immediate synthesis of the aldehyde, was nevertheless encouraging evidence for the feasibility of the general synthesis, since it implied that the *m*-methoxyl group in the acid V would not be an insuperable obstacle to cyclization in the desired manner. Recent observations of Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945), indicate that cyclization *meta* to a methoxyl group is not as difficult as had previously been supposed. The extremely facile cyclization of IX is doubtless due to the high electron density in the 2′-position, caused by contributions from resonance forms such as XIII.

(8) This was desired in order to investigate the McFadyen-Stevens method of obtaining aldehydes (*J. Chem. Soc.*, 584 (1936)).

(9) Slotta and Heller, *Ber.*, **63**, 3029 (1930).

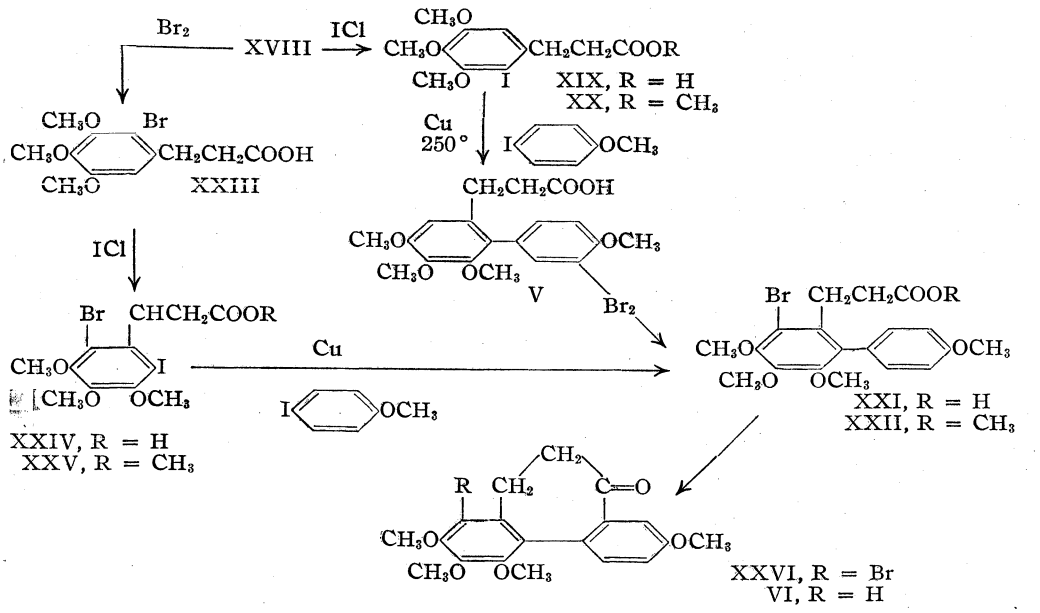
(10) Cook and Graham, *J. Chem. Soc.*, 322 (1944).

(11) (a) Späth, *Monatsh.*, **40**, 141 (1919); (b) Mauthner, *J. prakt. Chem.*, **129**, 283 (1931).

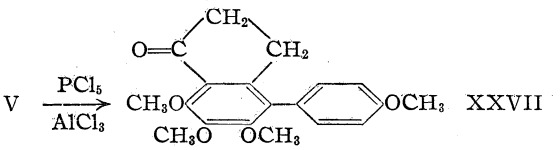
(12) Koelsch and Boekelheide, THIS JOURNAL, **66**, 414 (1944).

(13) *Cf.* Johnson and Shelberg, ref. 7.

(14) Halogen migration in aromatic compounds under the influence of acidic catalysts is discussed by Meerwein, Hofmann and Schill, *J. prakt. Chem.*, **154**, 266 (1940).

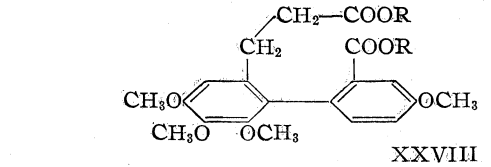


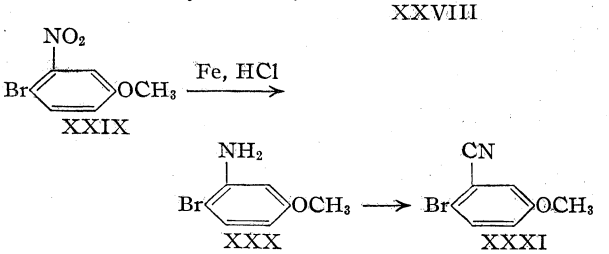
yield and erratic character of the reaction made it impractical for further synthetic operations. By



using nitrobenzene as solvent for the ring-closure' a small yield of crystalline product was obtained which had the percentage composition expected of the bromo ketone XXVI.[14a]

The difficulties mentioned above in the cyclization caused some effort to be spent on the synthesis of XXVIII, which could be converted to the desired ketone VI by a Dieckmann ring-closure.

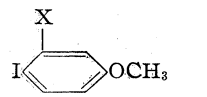




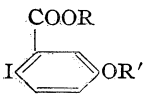
Some of the intermediates prepared for the synthesis of this compound will be described briefly.

3-Nitro-4-bromoanisole XXIX[1,15] was reduced with iron powder and acid and converted into the nitrile XXXI; the compound, however, was unchanged by refluxing with copper powder at 270°.

The preparation of the corresponding iodo compound was accordingly undertaken. 3-Nitro-4-iodoanisole[16] was prepared by a modified procedure, and the nitro group reduced with iron and acid. The crude amino compound XXXIII exploded violently during distillation, and attempts



XXXII, X = NO_2
XXXIII, X = NH_2
XXXIV, X = CN



XXXV, R = R' = H
XXXVI, R = CH_3, R' = H
XXXVII, R = H, R' = CH_3
XXXVIII, R = R' = CH_3

to prepare a number of derivatives from the crude product failed. The nitrile XXXIV was obtained from the crude amine by the Sandmeyer method, but in such small yield as to preclude further synthetic work.

The iodination of *m*-hydroxybenzoic acid, reported[17] to give 2-iodo-5-hydroxybenzoic acid XXXV, yielded in our hands 4-iodo-3-hydroxybenzoic acid[18]; the desired 2-iodo acid XXXV was obtained by a modification of the method of Brenans and Prost,[18] but methylation of the acid to the ether-ester XXXVIII proved extremely troublesome. The usual methods of methylation yielded only the carboxylic ester XXXVI. The desired product was finally obtained by treating the phenolic acid XXXV with a large excess of ethereal diazomethane over a period of several days.

The crossed Ullmann reaction between XXXVIII and the iodotrimethoxyphenylpropi-

(14a) Note added in proof: H. T. Huang in these laboratories recently has found that the bromo ketone obtained in this way possesses a five-membered ring. Work is being continued to determine the nature of the reaction.

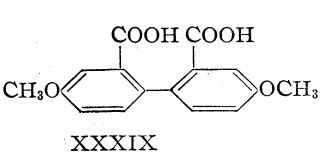
(15) Hodgson and Dyson, *J. Chem. Soc.*, 947 (1935).

(16) Hata, Tatematsu and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935); *Chem. Zentr.*, **107**, I, 546 (1936).

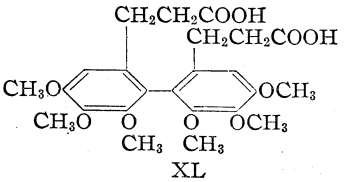
(17) Datta and Prosad, THIS JOURNAL, **39**, 448 (1917).

(18) (a) Brenans and Prost, *Compt. rend.*, **178**, 1285 (1924); (b) Henry and Sharp, *J. Chem. Soc.*, 856 (1935).

onic ester XX has not yielded the unsymmetrical product XXVIII; the two symmetrical acids XXXIX and XL have however been obtained and characterized.



XXXIX



XL

Acknowledgment.—We are indebted to Dr. Virgil Boekelheide for his interest and helpful suggestions during this work.

Experimental[19]

3,4,5-Trimethoxybenzoic acid was prepared by methylating gallic acid.[20]

***p*-Iodoanisole.**[21]—A solution of 337 g. (3.12 moles) of anisole in 300 cc. of glacial acetic acid was stirred with cooling, while 508 g. (3.12 moles) of iodine monochloride was added during fifteen minutes. The reaction was completed by refluxing gently for two hours. The product was washed with an excess of sodium hydroxide solution containing a small amount of sodium sulfite. The colorless product was distilled through a Vigreux column, giving a forerun of 93 g. of material, and 459 g. of pale amber liquid, b. p. 70–78° (3 mm.). This partly solidified at room temperature, and, upon warming with 400 cc. of methanol, followed by cooling to 0°, yielded 337 g. (46%) of large white crystals of *p*-iodoanisole, m. p. 50–51°.

4,5,6,4′-Tetramethoxybiphenyl-2-carboxylic Acid (VII).—To 10 g. of methyl 2-bromo-3,4,5-trimethoxybenzoate[22] dissolved in 30–40 g. of *p*-iodoanisole in a large test-tube was added 25 g. of copper bronze. The mixture was immersed in a metal-bath held at 250–260° and stirred vigorously. After ten to fifteen minutes, when the mass had become too viscous for stirring, heating was continued at 260–265° for about twenty minutes. The hot reaction mixture was then transferred to a beaker, broken up, cooled and extracted repeatedly with acetone or benzene. The extracts were evaporated to dryness in a stream of air, taken up in methanol, and saponified by adding aqueous alkali to the refluxing solution. After two to three hours, when the saponification was complete, water was added and the alcohol removed by evaporation. After cooling the solution, 4,4′-dimethoxybiphenyl and unchanged iodoanisole were removed by filtration, and the filtrate shaken with Raney nickel and hydrogen at 3 atm. for three hours.[23] After removal of the catalyst by centrifugation, excess anisole present was removed by steam distillation and the residue carefully acidified. The combined oily acids were extracted with boiling water to remove trimethoxybenzoic acid. The residue was extracted with boiling benzene, which left undissolved the symmetrical 3,4,5,3′,4′,5′-hexamethoxybiphenyl-2,2′-dicarboxylic acid of m. p. 252–253°.[24] The benzene extract was evaporated to dryness, leaving a residue of the desired acid VII, which, recrystallized from alcohol, melted at 163.5–164.5°, solidifying and remelting at 173–174°. The yield was 25–37%. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.20; H, 5.66.

3,4,5-Trimethoxy-2-(4-methoxyphenylazo)-benzoic Acid (XII).—One mole of *p*-anisidine in a solution containing two moles of hydrochloric acid was diazotized at 0° with sodium nitrite. One mole of sodium acetate and one mole of the sodium salt of trimethoxybenzoic acid in the minimum volume of water were added to the diazonium solution and the mixture warmed up to room temperature. The acidic, orange azo-compound XII was obtained by acidifying the mixture, collecting the precipitate by filtration and washing the filter cake with methyl alcohol. The residue on the funnel, after recrystallization from ethanol or acetic acid, melted at 221°. *Anal.* Calcd. for $C_{17}H_{18}O_6N_2$: C, 58.95; H, 5.24. Found: C, 58.88; H, 5.31. From the methanol washings unchanged trimethoxybenzoic acid was isolated.

2,3,4,7-Tetramethoxyfluorenone (XI).—A solution of 1 g. of 4,5,6,4′-tetramethoxybiphenyl-2-carboxylic acid VII in 5 cc. of dry benzene was treated with the calculated amount of phosphorus pentachloride and refluxed for two hours. The reaction mixture was extracted with hot sodium bicarbonate solution and the benzene evaporated. The residue was crystallized from ethanol, giving orange-red needles of the fluorenone, m. p. 117–118°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.97; H, 5.37. The fluorenone was also obtained when the evaporation of the phosphorus oxychloride present was attempted in high vacuum.

2-Carbomethoxy-4,5,6,4′-tetramethoxybiphenyl (X), obtained from the acid VII with ethereal diazomethane, crystallized from dilute alcohol as colorless plates, m. p. 63°. *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.08. Two grams of the ester in 20 cc. of alcohol were refluxed for two hours with 1 cc. of hydrazine hydrate: on cooling, crystals of m. p. 81° separated, which were insoluble in dilute acid. *Anal.* Calcd. for $C_{17}H_{20}N_2O_5$ (the hydrazide): C, 61.43; H, 6.07. Calcd. for $C_{34}H_{36}N_2O_{10}$ (the bis-hydrazide): C, 64.54; H, 5.74. Found: C, 64.66, 64.84; H, 6.66, 6.61.

3,4,5-Trimethoxybenzaldehyde (XV) was prepared in 30–50% yield by the Rosenmund reduction of 3,4,5-trimethoxybenzoyl chloride.[25]

3,4,5-Trimethoxybenzyl 3,4,5-Trimethoxybenzoate (XVI).—From some runs of the Rosenmund reduction, 3,4,5-trimethoxybenzoic anhydride, m. p. 160°,[26] and a product of m. p. 107° previously obtained by Späth and Mauthner[11] were isolated; the latter, insoluble in water and alkali, and unaffected by permanganate in boiling water, was saponified with alcoholic alkali. 3,4,5-Trimethoxybenzoic acid, m. p. 171°, and 3,4,5-trimethoxybenzyl alcohol (3,5-dinitrobenzoate, m. p. 147°[10]) were isolated from the saponification reaction. The compound of m. p. 107° is therefore the ester XVI. *Anal.* Calcd. for $C_{20}H_{24}O_8$: C, 61.22; H, 6.17. Found: C, 60.81; H, 6.03.

Isopropyl 3,4,5-Trimethoxythiolbenzoate.—This compound was prepared to see if the desulfuration procedure[27] could be used to obtain 3,4,5-trimethoxybenzaldehyde. A solution of 12.04 g. of trimethoxybenzoyl chloride and 7.4 g. (100% excess) of isopropylmercaptan in 30 cc. of pyridine was heated on the steam-bath for one hour. The product was obtained in 89% yield (crude), and, after recrystallization for analysis from aqueous methanol, melted at 47–48°. *Anal.* Calcd. for $C_{13}H_{18}O_4S$: C, 57.75; H, 6.70. Found: C, 57.96; H, 6.80.

A 4-g. portion of the thiol ester was refluxed with 25 g. of freshly prepared Raney nickel[28] in 100 cc. of 70% alcohol for twenty-four hours. The product was 1.97 g. of an oil which did not give an aldehyde test with dinitrophenylhydrazine reagent. The oil gave a poor yield of 3,4,5-trimethoxybenzyl 3,5-dinitrobenzoate, m. p. 143.5–

(19) Melting points corrected; microanalyses by the Micro-Tech Laboratories.

(20) "Organic Syntheses," Coll. Vol. I, 2nd Ed., p. 537.

(21) *Cf.* Blicke and Smith, THIS JOURNAL, **50**, 1229 (1928).

(22) Bogert and Plaut, *ibid.*, **37**, 2726 (1915).

(23) For this method of purifying products of an Ullmann reaction, *cf.* Carlin, THIS JOURNAL, **67**, 928 (1945).

(24) Herzig and Polak (*Monatsh.*, **29**, 270 (1908)) report a m. p. of 240° for this acid.

(25) Nierenstein, *J. prakt. Chem.*, **132**, 200 (1931); *cf.* Slotta, *ibid.*, **133**, 129 (1932).

(26) Sharp, *J. Chem. Soc.*, 1234 (1936).

(27) Wolfrom and Karabinos, THIS JOURNAL, **68**, 1455 (1946).

(28) Pavlic and Adkins, *ibid.*, **68**, 1471 (1946).

146.5° (reported,[10] 147–148°).[29] In other runs, using old Raney nickel in refluxing 70% alcohol, or shaking with fresh nickel at room temperature, unreacted ester was the only product obtained.[30]

3,4,5-Trimethoxycinnamic acid (XVII) was prepared by the procedure of Slotta and Heller,[9] by condensing the aldehyde with malonic acid in pyridine with 1% of piperidine as catalyst.

β-(3,4,5-Trimethoxyphenyl)-propionic Acid (XVIII).—A solution of 10 g. of 3,4,5-trimethoxycinnamic acid in 50 cc. of water and the calculated amount of sodium hydroxide was shaken for three hours with hydrogen at 4 atm. in the presence of Raney nickel. The catalyst was removed by filtration, the solution was cooled in ice and carefully acidified. The crystalline acid of m. p. 104° separated from the solution in practically quantitative yield. The previously reported m. p.'s are 98°[9] and 100–102°.[10]

β-(2-Iodo-3,4,5-trimethoxyphenyl)-propionic Acid (XIX).—To a solution of 50 g. of the trimethoxyphenylpropionic acid XVIII in 75 cc. of acetic acid and 300 cc. of water at 40° was added a 20% excess of iodine monochloride. After the exothermic reaction had subsided, the reaction mixture was allowed to stand for another hour, then decolorized with sodium bisulfite, and diluted with water to 800 cc. The iodo acid separated in 95% yield as granular crystals, which were purified by dissolving in sodium carbonate and reprecipitating from about 600 cc. of solution with hydrochloric acid. Crystallization from carbon tetrachloride or dilute methanol gave material of m. p. 124–125°. *Anal.* Calcd. for $C_{12}H_{15}IO_5$: C, 39.36; H, 4.13; neut. equiv., 366. Found: C, 39.00; H, 4.09; neut. equiv., 369. This method of iodination was far superior to that employing iodine and mercuric oxide, which was also used.

The methyl ester (XX) was obtained from the acid with ethereal diazomethane. After removal of the ether, the ester was used directly in the Ullmann reaction. An analytical sample, purified by vacuum distillation, had b. p. 175° (2.5 mm.), m. p. 36–37.5°. *Anal.* Calcd. for $C_{13}H_{17}IO_5$: C, 41.07; H, 4.51. Found: C, 41.00; H, 4.72.

β-2-(4,5,6,4′-Tetramethoxybiphenyl)-propionic Acid (V).—An Ullmann reaction between methyl β-(2-iodo-3,4,5-trimethoxyphenyl)-propionate (XX) and *p*-iodoanisole was carried out by a procedure similar to that described above for compound VII. The iodo ester (3.6 g.), *p*-iodoanisole (20 g.) and copper bronze (10 g.) were heated with stirring for one-half to one hour at 250–255°, and the products worked up as before. The aqueous solution of the saponified products was acidified, the oily acids taken up in benzene, and the fine needles, which formed almost immediately, were recrystallized from benzene; the product retained benzene of crystallization very tenaciously. The acid was very soluble in alcohol and acetone, slightly soluble in carbon tetrachloride, and melted, after crystallization from dilute ethanol, at 106.5–107°. *Anal.* Calcd. for $C_{19}H_{12}O_6$: C, 65.88; H, 6.40. Found: C, 65.58; H, 6.34.

β-2-(3-Bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic Acid (XXI).—To 6 g. of the biphenylpropionic acid V in 10 cc. of acetic acid at 0–5° was added dropwise with stirring a solution of 3 g. of bromine in 10 cc. of acetic acid. The mixture was allowed to stand for several hours at room temperature, then an equal volume of water was added. The crystalline acid, which separated on cooling in ice, was collected and dissolved in hot saturated sodium bicarbonate solution. From this, the crystalline sodium salt precipitated on cooling. The salt was collected, dissolved in hot water and converted to the acid by adding mineral acid. The purified acid, after crystallization from ethanol, melted at 169–171°. *Anal.* Calcd. for $C_{19}H_{21}BrO_6$: C, 53.67; H, 4.98. Found: C, 53.67; H, 4.88.

The methyl ester (XXII) was prepared from the acid with ethereal diazomethane or by heating the dry sodium salt with dimethyl sulfate for thirty minutes on the steam-bath. Crystallization from methanol gave a product melting at 92–93°. *Anal.* Calcd. for $C_{20}H_{23}BrO_6$: C, 54.68; H, 5.28. Found: C, 54.85; H, 5.73. The methyl ester in methanol solution was heated with hydroxylamine and dilute sodium hydroxide on the steam-bath for ten minutes, cooled, filtered and saturated with carbon dioxide. The **hydroxamic acid** which precipitated melted at 172–173°, dec.; for analysis, see below.

β-(2-Bromo-3,4,5-trimethoxyphenyl)-propionic Acid XXIII.—A solution of 1.60 g. of bromine in 5 cc. of glacial acetic acid was added slowly to 2.4 g. of trimethoxyphenylpropionic acid XVIII in 5 cc. of acetic acid, cooled in an ice-bath. The solution was allowed to stand for two hours at room temperature, until the color of bromine had disappeared, and 10 cc. of water was then added. On cooling in the refrigerator, crystals separated; a second crop was obtained by diluting with more water. β-(2-Bromo-3,4,5-trimethoxyphenyl)-propionic acid, crystallized from carbon tetrachloride–petroleum ether, had the m. p. 92.5–93.5°. *Anal.* Calcd. for $C_{12}H_{15}BrO_5$: C, 45.16; H, 4.74; neut. equiv., 319. Found: C, 45.06; H, 4.65; neut. equiv., 322.

β-(2,6-Dibromo-3,4,5-trimethoxyphenyl)-propionic acid was prepared from XVIII for reference in the same manner as the monobromo acid XXIII, except that an excess of bromine in acetic acid was added. When the reaction was complete, the excess of bromine was reduced with sodium bisulfite solution. The dibromo acid may be purified through its sodium salt, which is only slightly soluble in cold water. The free acid, recrystallized from benzene-petroleum ether, melted at 119.5°, then solidified and remelted at 122°. *Anal.* Calcd. for $C_{12}H_{14}Br_2O_5$: C, 36.22; H, 3.54. Found: C, 36.46; H, 3.55.

β-(2-Bromo-6-iodo-3,4,5-trimethoxyphenyl)-propionic Acid XXIV.—A solution of 1.3 g. of the bromo acid XXIII in 3 cc. of acetic acid was treated with excess of iodine monochloride in acetic acid in the cold. The solution was slowly warmed on the water-bath, then cooled, and the excess halogen removed with bisulfite. On dilution with water, the iodobromo acid precipitated in fine plates. The acid was purified by crystallizing the slightly water-soluble sodium salt from benzene, then regenerating the acid. Final crystallization from dilute ethanol yielded an acid of m. p. 130–132°. The product was not analytically pure, but the presence of iodine and bromine is borne out by the analysis. *Anal.* Calcd. for $C_{12}H_{14}O_5BrI$: C, 32.38; H, 3.17. Found: C, 33.95; H, 3.27.

β-2-(3-Bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic Acid XXI by the Ullmann Reaction.—The methyl ester of the above acid XXIV (0.4 g.) was heated with copper powder (2.5 g.) and *p*-iodoanisole (3 g.) for fifteen minutes at 250–260°. The mixture was extracted and saponified as in previous Ullmann reactions. The acids liberated consisted of a mixture of product and starting material, and were separated by the differential solubility of their dry sodium salts in benzene. The combined sodium salts were taken up in hot benzene. On cooling to room temperature the salt of the phenylpropionic acid XXIV precipitated out completely, leaving most of the biphenylpropionic acid XXI in solution. On evaporation of the solution and acidification, crystals were obtained (from ethanol) of m. p. 169–171°, giving no depression of mixed melting point with acid XXI prepared by the procedure described above.

Cyclization Experiments on the Acid XXI.—Only the following experiments are described in any detail; other methods tried are listed in the introduction.

With Phosphorus Oxychloride.—To 1 g. of the acid in 50 cc. of benzene (or toluene) was added the calculated weight of phosphorus pentachloride for conversion to the acid chloride The reaction mixture was refluxed for four hours, then cooled and extracted with cold concentrated

(29) Prelog and co-workers (*Helv. Chem. Acta*, **29**, 360, 684 (1946)) have observed reduction of thiol esters to primary alcohols by refluxing with Raney nickel.

(30) This work was carried out before the appearance of the paper by Spero, McIntosh and Levin, THIS JOURNAL, **70**, 1907 (1948), describing the use of partially deactivated Raney nickel for this reaction.

sodium bicarbonate solution. The residue from the organic layer was treated for an hour with hot concentrated sodium bicarbonate solution. A small amount of neutral oil, which remained undissolved, was crystallized from methanol, and melted at 91.5–92.5°; it gave no depression on mixed m. p. with the methyl ester XXII described above.

The hydroxamic acid, prepared as above, gave no depression on mixed m. p. with the authentic sample, and melted at 172–173°, dec. *Anal.* Calcd. for $C_{19}H_{22}BrNO_6$: N, 3.18. Found: N, 3.63. Both the ester and the hydroxamic acid yielded acid XXI on saponification.

With Aluminum Chloride.—A solution of the acid XXI (1 g.) in tetrachloroethane (50 cc.) was treated with the calculated weight of phosphorus pentachloride. The solution was heated to 80° for ten minutes to bring about complete conversion to the acid chloride and thereupon cooled to −10 to −5° in an ice–salt mixture. To the cold solution was added 0.33 g. of finely powdered aluminum chloride, some of which failed to go into solution despite vigorous agitation. The mixture, after being heated at 90° for ten minutes, was poured into 50 g. of ice and 10 cc. of concentrated hydrochloric acid to extract aluminum salts. The organic layer, after being washed with aqueous sodium bicarbonate, was evaporated at reduced pressure, and the residue extracted for one to two hours with hot concentrated sodium bicarbonate solution. The oily neutral residue (100–150 mg.) yielded in one case crystals of m. p. 141–144° from ethanol. The crude product yielded a semicarbazone, crystallized from ethanol, m. p. 210–212°, dec. *Anal.* Calcd. for $C_{20}H_{22}BrN_3O_5$: C, 51.85; H, 4.78; N, 9.05. Calcd. for $C_{20}H_{23}N_3O_5$: C, 62.32; H, 6.01; N, 10.90. Found: C, 59.62; H, 5.68; N, 11.24.

An oxime was also obtained which, crystallized from chloroform–ethanol, had m. p. 209–212°. Other fractions had m. p. 206–217°. *Anal.* Calcd. for $C_{18}H_{20}NBrO_5$: C, 54.04; H, 4.77. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17. Found: C, 65.46; H, 5.98.

In Nitrobenzene.—To 1 g. of the biphenylpropionic acid XXI in 25 cc. of nitrobenzene was added 0.5 g. of phosphorus pentachloride, the mixture being warmed to 80° to complete formation of the acid chloride. After cooling to 0°, 0.33 g. of aluminum chloride was added and the solution swirled vigorously. Heating for five minutes in a bath at 90° dissolved the aluminum chloride. The product was purified by extracting the nitrobenzene layer repeatedly with cold dilute hydrochloric acid and then with hot sodium bicarbonate solution. The dried organic layer was freed from solvent by vacuum distillation. The bromo ketone of m. p. 145° was obtained on crystallization from ethanol. *Anal.* Calcd. for $C_{19}H_{19}O_5Br$: C, 56.03; H, 4.70. Found: C, 55.88; H, 5.03.

An oxime, prepared from a less pure sample of ketone, gave a poor analysis for carbon.

4-(*p*-Methoxyphenyl)-5,6,7-trimethoxyhydrindone (XXVII).—A solution of 0.88 g. of β-(2-(4,5,6,4′-tetramethoxy)-biphenyl)-propionic acid in 25 cc. of tetrachloroethane was treated with the calculated weight of phosphorus pentachloride. After addition to the ice-cold solution of 0.33 g. of aluminum chloride, the mixture was swirled for ten minutes while immersed in an oil-bath at 90°. After decomposition of the reagents, removal of the solvent, and extraction with dilute alkali, there remained 0.24 g. of a compound, m. p. 86°, which when crystallized from ethanol, formed stout needles of m. p. 89°. The acid was not cyclized by anhydrous hydrofluoric acid. *Anal.* Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.70; H, 5.94. The oxime crystallized in colorless prisms, m. p. 217°, dec., from a mixture of ethanol and chloroform. *Anal.* Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.24; H, 6.01; N, 4.46.

3-Amino-4-bromoanisole XXX.—A 23.2-g. portion of 3-nitro-4-bromoanisole[16,31] (0.1 mole) in 100 cc. of 50% alcohol, and 17 g. (0.3 mole) of iron powder (J. T. Baker purified by hydrogen) were heated to refluxing on the steam-bath and stirred with a tantalum Hershberg stirrer, while 1.2 cc. of concentrated hydrochloric acid was added dropwise. The addition was very slow at first, and a vigorous reaction ensued. After all of the acid had been added, refluxing and stirring were continued for several hours. The solid material was removed from the hot product by centrifuging, the clear solution was brought to a slightly alkaline reaction with potassium hydroxide, and the flocculent precipitate was centrifuged down. The solution was boiled until a heavy oil separated and commended to steam distill. The oil was taken up in benzene, the solution clarified by centrifuging, the solvent removed by flash-distillation and the product distilled, giving 69% (13.9 g.) of pale yellow oil, b. p. 76–98° (2 mm.). The hydrochloride melted, after crystallization from water, at 183.5–184°, dec.[32] An attempted selective catalytic reduction of the nitrobromoanisole with hydrogen and platinum[33] was unsuccessful.

2-Bromo-5-methoxybenzonitrile XXXI.—The amine obtained above (13.9 g.) was diazotized and the clear dark red diazonium solution was poured into an ice-cold solution, which had been prepared by dissolving 9.3 g. of cuprous cyanide and 15.3 g. of sodium cyanide in 40 cc. of water. A thick brown mass was formed, and hydrogen cyanide was evolved; the mixture was heated on the steam-bath with stirring until a heavy oil settled out. This was taken up in 200 cc. of benzene, washed with dilute sodium hydroxide and hydrochloric acid, clarified by centrifuging, the solvent removed and the residue distilled at 2 mm., with precautions to prevent solidification in the side arm. A slightly yellow solid (8.2 g., 56%) was obtained, m. p. 84–97°. After crystallization from benzene an analytical sample was obtained as long, colorless needles, m. p. 98.5–99.5°. *Anal.* Calcd. for C_6H_6BrNO: C, 45.31; H, 2.85. Found: C, 45.41; H, 2.84. Hydrolysis of the nitrile with potassium hydroxide in diethylene glycol yielded 2-bromo-5-methoxybenzoic acid, m. p. 157–158°.[34] A portion of the nitrile was heated at the reflux temperature (about 270°) with copper bronze. The metal remained bright and no reaction seemed to occur.

3-Nitro-4-iodoanisole XXXII.—The published procedure[16] was modified as follows. A suspension of 44 g. of finely divided 3-nitro-4-aminoanisole in 250 cc. of ice and water was diazotized at −5°. The diazonium solution was poured into a cold solution of 65 g. (50% excess) of potassium iodide in 65 cc. of water. Heat and gases were evolved, and the mixture was heated on the steam-bath until a heavy oil separated, which solidified on cooling. It was taken up in benzene, washed with concentrated hydrochloric acid and with dilute sodium hydroxide solution containing a little sodium sulfite; after evaporation of the benzene, a 90% yield of crude material was obtained, which formed fine orange needles, m. p. 60.5–61.5° after crystallization from aqueous methanol.

3-Amino-4-iodoanisole (XXXIII).—Reduction of the nitro compound XXXII with iron and hydrochloric acid, by the method described above for the bromo compound, gave, in a small run, 52% yield of a red oil, b. p. 92–112° (0.2 mm.). Repetition of the reaction on a 1 mole scale was terminated by a violent explosion during the vacuum distillation.

The only crystalline compound that could be obtained from the crude aminoiodoanisole was the nitrile below. Reduction of the 3-nitro-4-iodanisole with stannous chloride, with ferrous hydroxide in ammonium hydroxide, or electrolytically, yielded either *m*-anisidine or intractable products.

2-Iodo-5-methoxybenzonitrile XXXIV.—The crude amine (5.7 g.) was diazotized and added to a solution of 4.03 g. of cuprous cyanide and 6.75 g. of sodium cyanide

(31) Samant, *Ber.*, **75**, 1008 (1942).

(32) The reported value[15] is 186°; the reduction was carried out previously,[15] but details were not given.

(33) *Cf.* Adams, Cohen and Rees, THIS JOURNAL, **49**, 1093 (1927).

(34) Pschorr, *Ann.*, **391**, 26 (1912), reports a m. p. of 161–162° for this compound.

n 20 cc. of water. The mixture was heated on the steam-bath, the heavy oil which separated was taken up in benzene, washed with acid and base, and the benzene was evaporated. The black tar remaining was subjected to vacuum sublimation, yielding a mushy yellow solid, which on resublimation and crystallization from benzene–petroleum ether, formed colorless plates, m. p. 98–100°. *Anal.* Calcd. for C_8H_6INO: C, 37.09; H, 2.34. Found: C, 37.46; H, 2.43.

3-Hydroxy-4-iodobenzoic Acid.—This reaction is described because this procedure is reported[17] to yield 2-iodo-5-hydroxy-benzoic acid XXXV. A solution of 13.8 g. of *m*-hydroxybenzoic acid in 200 cc. of concentrated ammonium hydroxide was stirred while a solution of 23.4 g. of iodine and 18.2 g. of potassium iodide in 100 cc. of water was added during five minutes. A precipitate of nitrogen triiodide was formed and reacted rapidly. The resulting green solution was stirred for an additional ten minutes and acidified to congo red by adding 180 cc. of concentrated hydrochloric acid. The thick precipitate was collected, and crystallized from a mixture of 100 cc. of water and 20 cc. of alcohol, giving a nearly quantitative yield of white needles, m. p. 225–227° dec; the acetyl derivative melted at 199.5–201.5°. The product was therefore the 3-hydroxy-4-iodobenzoic acid, which is reported[18a] to melt at 226° (acetyl derivative, 203°), and not the 2-iodo-5-hydroxy isomer.

2-Iodo-5-hydroxybenzoic Acid (XXXV).—The procedure of Brenans and Prost[18a] was modified as follows. An ice-cold solution of benzenediazonium chloride prepared from 37.2 g. of aniline was added with stirring to a solution of 55.2 g. of *m*-hydroxybenzoic acid and 48 g. of sodium hydroxide in 400 cc. of water. A sticky orange-red precipitate formed which dissolved on warming to 50°, the dark red solution was heated and stirred while a solution of 144 g. of sodium hydroxide in 150 cc. of water was added, followed by 210 g. of solid sodium hydrosulfite. With the solution at 80–90°, more sodium hydrosulfite was added in 5-g. portions at one-minute intervals until the dark red color was discharged. The solution was cooled to 30°, 500 g. of ice was added and the solution brought to a *p*H of 5.5 with concentrated hydrochloric acid. The pale yellow precipitate of 2-amino-5-hydroxybenzoic acid was collected, and diazotized at 0° with 67 cc. of concentrated sulfuric acid, 400 g. of ice and 26 g. of sodium nitrite. The diazonium solution was poured into a solution of 84 g. of potassium iodide in 150 cc. of water; the reaction which ensued was completed by heating on the steam-bath for an hour. Cooling to 0° gave 67.6 g. (64%) of dark purple crystalline product, which was purified by boiling with 15 g. of Nuchar in 700 cc. of water for an hour. Cooling to 0° yielded 52 g. (49% over-all from *m*-hydroxybenzoic acid) of nearly white needles which melted to a red liquid at 201–202.5°. The reported[18a] m. p. is 196–198°.

Methyl 2-iodo-5-hydroxybenzoate (XXXVI) was obtained from the acid with a slight excess of ethereal diazomethane solution. The product was isolated by vacuum sublimation followed by crystallization from benzene–petroleum ether; it formed white granular crystals, m. p. 102–103°. *Anal.* Calcd. for $C_8H_7IO_3$: C, 34.55; H, 2.54. Found: C, 34.90; H, 2.72.

Methyl 2-iodo-5-methoxybenzoate (XXXVIII) was obtained when 2.64 g. of 2-iodo-5-hydroxybenzoic acid was treated with a five-fold excess of ethereal diazomethane, and allowed to stand several days. The solution was washed with sodium hydroxide, dried, and the ether removed, leaving 1.81 g. (62%) of crude ester. This was distilled at 150° (0.8 mm.), giving a very pale yellow oil, $n^{22}D$ 1.6000. *Anal.* Calcd. for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 37.34; H, 3.27. Hydrolysis of this compound yielded 2-iodo-5-methoxybenzoic acid (XXXVII), which could not be obtained analytically pure; apparently there was some loss of iodine during saponification.

4,4′-Dimethoxydiphenic Acid (XXXIX).—A 1.00-g. portion of methyl 2-iodo-5-methoxybenzoate was mixed with 1.00 g. of copper bronze, and heated at 280–300° for twenty minutes. The product was extracted with two 7 cc. portions of benzene, which, on evaporation, yielded a dark oil. This was saponified with Claisen alkali; acidification produced a brown precipitate which was refluxed with Nuchar in aqueous methanol until the color had been removed. Upon cooling, a white powder was obtained which was crystallized from nitrobenzene; the fine white crystals melted at 245–248° on the heated stage. *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.78; H, 4.84.

2,2′,3,3′,4,4′-Hexamethoxy-6,6′-di-(β-carboxyethyl)-biphenyl (XL).—Methyl β-(3,4,5-trimethoxy-2-iodophenyl)-propionate (1.5 g.) and 1.5 g. of copper dust were heated in a test-tube in a Wood's metal bath at 265–270° for twenty minutes. The product was extracted with hot benzene, the extract was evaporated on the steam-bath and the residue was saponified by heating with Claisen alkali. Acidification gave an amber oil which was vacuum sublimed. A portion of the sublimate was crystallized from aqueous acetic acid, when it formed a white powder which sintered at 188–189° and melted to an amber liquid at 189–193°. *Anal.* Calcd. for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 59.98; H, 6.06.

Crossed Ullmann Reaction.—A mixture of equivalent quantities of methyl β-(3,4,5-trimethoxy-2-iodophenyl)-propionate and methyl 2-iodo-5-methoxybenzoate was heated with copper powder and the reaction product was converted to the free carboxylic acids in the usual way. The material thus obtained was subjected to an eight-plate multiple countercurrent extraction, using ether and 2 *M* phosphate buffer of *p*H 5.9 in 60-cc. separatory funnels.[35] The two symmetrical reaction products were separated in this way, but none of the desired unsymmetrical acid was obtained.

Summary

β-2-(3-Bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic acid has been synthesized, its structure proved, and its ring-closure to the bromo ketone studied. 4,5,6,4′-Tetramethoxybiphenyl-2-carboxylic acid has been prepared, and found to cyclize spontaneously to the fluorenone, when converted to the acid chloride A number of new compounds have been prepared and characterized in connection with these syntheses.

ROCHESTER, NEW YORK RECEIVED JANUARY 21, 1948

(35) Craig, Hogeboom, Carpenter and du Vigneaud, *J. Biol. Chem.*, **168**, 669 (1947), and earlier papers.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Streptomyces Antibiotics. XVII. Heptabenzoylstreptidine from Streptomycin

BY ROBERT L. PECK, FREDERICK A. KUEHL, JR., CHARLES E. HOFFHINE, JR., ELIZABETH W. PEEL AND KARL FOLKERS

Streptomycin has been degraded to heptabenzoylstreptidine which served as a key product for the determination of the position of the linkage of streptobiosamine to streptidine.[1] The details of the formation and characterization of heptabenzoylstreptidine and certain of its reactions are described herein.

A suspension of crystalline streptomycin trihydrochloride-calcium chloride double salt[2] in benzoyl chloride and pyridine was heated for about twenty minutes. The crude reaction product was purified by chromatography on charcoal to give a low yield of benzoylated streptomycin as an amorphous white powder. The analytical data were in agreement with the formula for undecabenzoylstreptomycin.

The presence of some dodecabenzoylstreptomycin in the benzoylated streptomycin was possible, since the streptose moiety of streptomycin contains a tertiary hydroxyl group. Although this hydroxyl group is difficult to acylate,[3,4] a bis-*p*-nitrobenzoate of bis-desoxystreptose[3] was obtained. The presence of some of the dodecabenzoyl derivative in the undecabenzoylstreptomycin would be of no consequence in the present study; however, it is essential that the streptidine moiety in the product be completely (hepta) benzoylated.

The molecular weights of undeca- and dodecabenzoylstreptomycin are 1727 and 1831, respectively. Ebullioscopic molecular weight determinations of benzoylated streptomycin in benzene gave values of 1625–1650 ± 165 for two different preparations.

Alkaline hydrolysis of benzoylated streptomycin gave maltol by isolation, and substantiated the presence of the intact streptomycin carbon skeleton[4] in the benzoylated product. This hydrolysis also gave benzoic acid in a yield of 10.9 moles of benzoic acid per mole of undecabenzoylstreptomycin.

The treatment of benzoylated streptomycin with one to three equivalents of hydrogen bromide in chloroform–glacial acetic acid solution at room temperature cleaved the glycosidic linkage between the streptidine and streptobiosamine moieties. Crystalline heptabenzoylstreptidine was obtained from this reaction in 72% yield.

Heptabenzoylstreptidine melted at 256–258° when crystallized from benzene–methanol. When crystallized from benzene a molecule of solvent of crystallization was present which could be removed by drying at 110° *in vacuo*. Analyses and molecular weight measurements were in agreement with the formula, $C_8H_{11}N_6O_4(C_6H_5CO)_7$. Heptabenzoylstreptidine was found to be optically active, $[\alpha]^{25}D$ + 58° (in chloroform), $[\alpha]^{25}D$ −3° (in glacial acetic acid). Further characterization was provided by conversion of heptabenzoylstreptidine to acetylheptabenzoylstreptidine, m. p. 156–160°, $[\alpha]^{25}D$ + 3° (in chloroform), to anisoylheptabenzoylstreptidine, m. p. 213–216°, $[\alpha]^{25}D$ −12° (in chloroform), and to octabenzoylstreptidine, m. p. 263–264°, $[\alpha]D$ 0.

The significance of the optical activity of heptabenzoylstreptidine is detailed in conjunction with the results of the degradation of this compound to α,γ-dibenzamido-β-hydroxyadipaldehyde, which are described in an accompanying paper.[5]

Both heptabenzoylstreptidine and octabenzoylstreptidine yielded a crystalline monobenzoylstreptidine upon treatment with sodium methoxide in pyridine–methanol solution. The isolation of the monobenzoyl derivative may have been due to its insolubility in the reaction medium. Further treatment of this monobenzoyl derivative with acid readily yielded streptidine which was optically inactive, as were streptidine preparations produced by hydrolysis of streptomycin directly.[6,7] It has been observed that octaacetylstreptidine,[6,8] is deacetylated to streptidine at room temperature in methanol containing ammonia.

It was found that streptidine could be benzoylated, under conditions similar to those applied to streptomycin, to give optically inactive octabenzoylstreptidine. A hexabenzoylstreptidine has also been obtained. Octabenzoylstreptidine was distinguished from heptabenzoylstreptidine by melting point and by the fact that only the latter compound (obtained by cleavage of benzoylated streptomycin) is optically active.

Octabenzoylstreptidine was remarkably stable to hydrogen bromide, since it was recovered in nearly quantitative yield after a solution of the substance in glacial acetic acid containing excess hydrogen bromide was refluxed for one hour. Octaacetylstreptidine[6,8] formed a crystalline dihydrobromide when treated with hydrogen bromide in glacial acetic acid at room temperature. This salt hydrolyzed in aqueous solution, and the substance was partially deacetylated.

(1) Kuehl, Peck, Hoffhine, Peel and Folkers, THIS JOURNAL, **69**, 1234 (1947).

(2) Peck, Brink, Kuehl, Flynn, Walti and Folkers, *ibid.*, **67**, 1866 (1945).

(3) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2405 (1946).

(4) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).

(5) Kuehl, Peck, Hoffhine and Folkers, *ibid.*, **70**, 2325 (1948).

(6) Peck, Graber, Walti, Peel, Hoffhine and Folkers, *ibid.*, **68**, 29 (1946).

(7) Carter, Clark, Dickman, Loo, Skell and Strong, *Science*, **103**, 540 (1946).

(8) Fried and Stavely, THIS JOURNAL, **69**, 1549 (1947).

Thus, it is clear that heptabenzoylstreptidine could not have been derived from the presence and hydrolysis of octabenzoylstreptidine as a contaminant in benzoylated streptomycin. The cleavage reaction took place at room temperature, and the yield of heptabenzoylstreptidine was high. It is also clear from the data given above that the atom in the unbenzoylated functional group of heptabenzoylstreptidine is attached to the carbon atom of streptidine which is linked glycosidically to streptobiosamine.

Evidence for the presence of a free hydroxyl group in heptabenzoylstreptidine was provided by the action of chromic acid in 90% acetic acid on octa-, hepta- and hexabenzoylstreptidine at 45°. Only the heptabenzoylstreptidine was affected by this oxidizing reagent and gave crystalline dibenzoylguanidine, m. p. 165–166°.[9] The yield of dibenzoylguanidine was greater than one mole per mole of heptabenzoylstreptidine which showed that each guanido group in the streptidine moiety of benzoylated streptomycin possessed two benzoyl groups. This result provided evidence that streptobiosamine was linked to streptidine through an oxygen atom rather than through a nitrogen atom. Since hexabenzoylstreptidine was unaffected by chromic acid, there is presumably no free hydroxyl group present.

Previous indication that the linkage of streptobiosamine and streptidine was through an oxygen rather than a nitrogen atom was furnished by the ultraviolet absorption spectra of heptabenzoylstreptidine and octabenzoylstreptidine; their spectra were practically identical. Hexabenzoylstreptidine showed distinctly different absorption maxima. These spectra substantiate the interpretation that both guanido groups of heptabenzoylstreptidine contain two benzoyl groups each, as otherwise a change in position of the absorption maxima would be expected.

Dihydrostreptomycin has also been benzoylated under the conditions used for streptomycin. Analyses on benzoylated dihydrostreptomycin were in agreement with the formula for dodecabenzoyldihydrostreptomycin. Cleavage of dodecabenzoyldihydrostreptomycin also yielded heptabenzoylstreptidine.

Experimental

Benzoylation of Streptomycin.—Twenty-five grams of crystalline streptomycin trihydrochloride–calcium chloride double salt was suspended in a mixture of 150 cc. of pyridine and 55 cc. of benzoyl chloride, and the suspension was heated on a steam-bath for ten minutes and then heated at reflux temperature for ten minutes. At the end of the heating period, all of the suspended solid had dissolved. The solution was partially cooled and diluted with 300 cc. of chloroform. The chloroform solution was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution, and water. The chloroform solution was dried over magnesium sulfate, filtered, concentrated *in vacuo* to a volume of about 200 cc., and then poured with stirring into 2 l. of petroleum ether. The precipitated crude undecabenzoylstreptomycin was collected on a filter and dried; yield, 49 g. For purification, a solution of this material in about 150 cc. of benzene was allowed to flow into a dry chromatographic column containing a mixture of 500 g. of Darco G-60 and 150 g. of filter paper pulp. Fresh benzene was added to the column, and five eluates were collected. A 1:1 acetone–benzene mixture was used next and three more eluates were collected. Chloroform was used to produce the ninth eluate. The eluates were concentrated to *ca.* 25-cc. volume *in vacuo* and the concentrates were poured into about ten volumes of petroleum ether, which caused the precipitation of the benzoylated streptomycin. The details of this chromatographic experiment are summarized in Table I.

TABLE I

CHROMATOGRAPHY OF BENZOYLATED STREPTOMYCIN

Eluate no.	Volume of eluate, cc.	Weight of product, g.	$[\alpha]^{25}D$ (chloroform)
1	300	0.4	+60°
2	500	2.30	+34°
3	1000	2.50	+27.6°
4	1000	1.10	+19.7°
5	1800	0.98	+12.7°
6	1400	0.81	−18.6°
7	700	6.90	−43°
8	800	2.50	−64.5°
9	2100	1.23	−38°

The product from eluate 1 was reprecipitated by dissolving it in 3 cc. of chloroform and pouring the solution dropwise into 80 cc. of boiling petroleum ether. The precipitate was a white amorphous powder; 0.37 g., $[\alpha]^{25}D$ +59° (*c*, 1.0 in chloroform).

Anal. Calcd. for $C_{21}H_{27}N_7O_{12}(C_6H_5CO)_{12}$: C, 68.88; H, 4.79; N, 5.36; mol. wt., 1831: Calcd. for $C_{21}H_{28}N_7O_{12}(C_6H_5CO)_{11}$: C, 68.16; H, 4.85; N, 5.68; mol. wt., 1727. Found: C, 68.53; H, 4.84; N, 5.38; mol. wt. (ebullioscopic in benzene), 1625 ± 163.

A methanol solution of this product showed ultraviolet absorption maxima at 2325 Å. (*E*% 680) and at 2750 Å. (*E*% 285), and a shoulder at 2550 Å. (*E*% 350). A tetrachloroethane solution of this product showed infrared absorption bands at 5.77, 6.25, 6.37, 7.88, 8.50, 9.04, 9.14 and 9.36 μ.

The product from eluate 2 was analyzed without further reprecipitation.

Anal. Found: C, 68.72; H, 5.12; N, 5.38; mol. wt., 1651 ± 165.

The analytical data on the products from eluates 1 and 2 correspond closely to the composition of undecabenzoylstreptomycin and dodecabenzoylstreptomycin. The product obtained from eluate 1 in an analogous experiment had the composition: C, 69.05; H, 4.86; N, 5.46; $[\alpha]^{25}D$ +42° (*c*, 1.0 in chloroform).

The product from eluate 8 was reprecipitated by using chloroform and petroleum ether; 2.1 g.; $[\alpha]^{25}D$ −41° (*c*, 1.0 in chloroform).

Anal. Found: C, 63.17; H, 5.08; N, 6.20; mol. wt., 1100.

The product in eluate 8 was clearly less completely benzoylated.

Cleavage of Undecabenzoylstreptomycin to Maltol.—A sample of undecabenzoylstreptomycin (from eluate 2) weighing 431 mg. was suspended in 5 cc. of methanol and the solution was heated to the reflux temperature. Three cubic centimeters of aqueous 2.5 *N* sodium hydroxide was added to the methanol solution, and the mixture was heated at the reflux temperature for fifteen minutes. The yellow-brown solution was then concen-

(9) Korndörfer (*Arch. Pharm.*, **241**, 449 [1903]) reported dibenzoylguanidine, m. p. 215°, as the product of benzoylation of guanidine in aqueous solution. Walther and Wlodkowski (*J. prakt. Chem.*, **59**, 266 [1899]) and we have found that this reaction gives dibenzoylurea, m. p. 215°.

trated under reduced pressure until the methanol was removed. The residual solution was diluted with 10 cc. of water and extracted three times with chloroform. The chloroform extracts were discarded. The alkaline aqueous solution was then saturated with carbon dioxide, and extracted four times with chloroform. The chloroform extracts were dried and evaporated to dryness to give 28.5 mg. of a crystalline residue. The crystals gave a reddish-purple color with ferric chloride solution which was identical with that given by maltol. The residue was recrystallized from chloroform–ether to give crystals which melted at 159–160°. When this product was mixed with an authentic sample of maltol (m. p. 159–160°), the melting point of the mixture was 159–160°.

The chloroform-extracted aqueous solution was acidified with sulfuric acid to *p*H 2, and extracted three times with chloroform. The extract was dried and evaporated to dryness to yield 332 mg. of benzoic acid (neutral equivalent: calcd., 122; found, 125). This represents a yield of 10.9 moles of benzoic acid per mole of undecabenzoylstreptomycin.

Cleavage of Undecabenzoylstreptomycin to Heptabenzoylstreptidine.—One hundred thirty-five milligrams of undecabenzoylstreptomycin (from eluate 1) was dissolved in 3.0 cc. of chloroform, and to the solution was added 0.11 cc. of a 16% solution of hydrogen bromide in glacial acetic acid. The solution was allowed to stand at room temperature for twenty-four hours, diluted with 5 cc. of chloroform, and the mixture was extracted twice with saturated aqueous sodium bicarbonate solution. The chloroform solution was washed with water, dried and evaporated *in vacuo* to give 124.5 mg. of an amorphous glassy residue. The residue was dissolved in 1 cc. of warm benzene, and diluted with 2 cc. of methanol. A white granular crystalline precipitate quickly separated. The precipitate was collected on a filter and washed with methanol; yield, 55.7 mg. (yield, 72%); m. p. 245–252° (micro-block). Recrystallization of this product from benzene–methanol yielded heptabenzoylstreptidine of melting point 256–258° (micro-block); $[\alpha]^{25}D$ +58° (*c*, 1.24 in chloroform).

Anal. Calcd. for $C_{57}H_{46}N_6O_{11}$: C, 69.15; H, 4.68; N, 8.49; mol. wt., 991. Found: C, 69.10; H, 4.71; N, 8.72; mol. wt., (ebullioscopic in benzene), 1116 ± 112.

In the ultraviolet, an ethanol solution of heptabenzoylstreptidine showed maxima at 2350 Å. (E_M 59,000), 2530 Å. (E_M 53,000) and 2770 Å. (E_M 43,500).

Heptabenzoylstreptidine contained benzene of crystallization when it was recrystallized from benzene–acetone solution upon removal of acetone by evaporation.

Anal. Calcd. for $C_{57}H_{46}N_6O_{11}\cdot C_6H_6$: C, 70.77; H, 4.90; solvent of crystallization, 7.3. Found: C, 70.45; H, 4.89; weight loss on drying two hours at 110° *in vacuo*, 7.3.

Acetylheptabenzoylstreptidine.—A solution of 428 mg. of heptabenzoylstreptidine in 10 cc. of acetic anhydride was refluxed for forty-five minutes. The solution was evaporated *in vacuo* to a thick glassy residue. The residue was dissolved in hot benzene, and the solution was diluted with methanol, whereupon crystals separated quickly; yield, 400 mg.; m. p. 156–160° (micro-block); $[\alpha]^{25}D$ +3° (*c*, 2.98 in chloroform). This product contained benzene of crystallization.

Anal. Calcd. for $C_{59}H_{48}N_6O_{12}\cdot 2C_6H_6$: C, 71.71; H, 5.09. Found: C, 71.48; H, 4.54.

Anisoylheptabenzoylstreptidine.—A mixture of 507 mg. of heptabenzoylstreptidine, 1.0 cc. of anisoyl chloride and 10 cc. of pyridine was heated at the reflux temperature for thirty minutes, cooled, and diluted with chloroform. The chloroform solution was washed and evaporated to a volume of 5 cc., and poured into 50 cc. of petroleum ether. The precipitate of crude anisoylheptabenzoylstreptidine was dissolved in 10 cc. of benzene and the solution was chromatographed on Darco G-60 to yield anisoylheptabenzoylstreptidine in the first eluates. The first eluates on evaporation left a crystalline residue which was recrystallized from ether–methanol; yield, 251 mg.; m. p. 212–216° (micro-block). One further crystallization from acetone–methanol gave material which melted at 213–216° (micro-block), and which showed $[\alpha]^{25}D$ −12° (*c*, 2.29 in chloroform).

Anal. Calcd. for $C_{65}H_{52}N_6O_{13}$: C, 69.38; H, 4.66; N, 7.47; OCH_3, 2.76. Found: C, 69.22; H, 4.40; N, 7.49; OCH_3, 3.44.

A chromatographic fraction which was crystallized from acetone melted at 218–220° (micro-block), and contained acetone of crystallization.

Anal. Calcd. for $C_{74}H_{70}N_6O_{16}$: C, 68.40; H, 5.43; OCH_3, 2.39. Found: C, 68.32; H, 5.16; OCH_3, 2.08.

Octabenzoylstreptidine from Heptabenzoylstreptidine.—One hundred twenty milligrams of heptabenzoylstreptidine was dissolved in a mixture of 2 cc. of pyridine and 0.2 cc. of benzoyl chloride. The solution was refluxed for thirty minutes, diluted with chloroform, washed with dilute acid and aqueous sodium bicarbonate and then water. The chloroform solution was dried and evaporated *in vacuo*. The residue was crystallized from benzene–methanol to give 54 mg. of octabenzoylstreptidine which melted at 261–263° (micro-block). When this product was mixed with heptabenzoylstreptidine, the melting point of the mixture was depressed. When this product was mixed with octabenzoylstreptidine, which was prepared by benzoylation of streptidine, the melting point was unchanged.

Anal. Calcd. for $C_{64}H_{50}N_6O_{12}$: C, 70.19; H, 4.60. Found: C, 70.23; H, 4.79.

Octabenzoylstreptidine.—Four grams of streptidine dihydrochloride was mixed with 67 cc. of pyridine and 27 cc. of benzoyl chloride. The mixture was heated at the reflux temperature for twenty minutes, evaporated *in vacuo* to a thick sirup, and then the residue was dissolved in 50 cc. of chloroform. The chloroform solution was washed with dilute hydrochloric acid, saturated aqueous sodium bicarbonate, and water. It was then dried over magnesium sulfate and filtered through a layer of Darco G-60. The filtrate was poured into 900 cc. of petroleum ether to give a granular, tan precipitate. The crude product, which weighed 13.9 g., was dissolved in 30 cc. of benzene and the solution was allowed to flow through a column containing 135 g. of aluminum oxide. The first 200 cc. of eluate yielded 12 g. of solid on evaporation. This product was dissolved in 25 cc. of hot benzene and 60 cc. of methanol was added. On cooling, crystals separated; yield, 7 g. (three crops). This product melted and resolidified in the range of 120–140° and on continued heating melted at about 250–260° (micro-block). Rechromatography of this product and recrystallization of the major chromatographic fraction from benzene–methanol gave 4.65 g. of crystals which showed a transition of 125–140° and then melted at 261–264°. Further recrystallization of this product from benzene–methanol gave octabenzoylstreptidine which melted constantly at 263–264°; $[\alpha]_D$ 0.

Anal. Calcd. for $C_{64}H_{50}N_6O_{12}$: C, 70.19; H, 4.60; N, 7.68; mol. wt., 1095. Found: C, 70.74; H, 4.65; N, 7.69; mol. wt. (ebullioscopic in benzene), 1267 (±10%).

In the ultraviolet, an ethanol solution of octabenzoylstreptidine showed maxima at 2375 Å. (E_M 77,800), 2550 Å. (E_M 63,500) and 2750 Å. (E_M 50,400).

Hexabenzoylstreptidine (1,3-benzoylguanido-2,4,5,6-tetrabenzoyloxycyclohexane).—The chromatograph columns used for the purification of octabenzoylstreptidine were subsequently eluted with chloroform. Evaporation of the chloroform extracts to dryness, and crystallization of the residue from acetone and from acetone–benzene gave a white crystalline product. This material melted partially at 165–175° and then melted fully at 220–225° when heated on the micro-block; $[\alpha]_D$ 0 (*c*, 2.0 in acetone).

Anal. Calcd. for $C_8H_{12}N_6O_4(C_7H_5O)_6$: C, 67.71; H, 4.77; N, 9.47. Found: C, 67.20; H, 4.90; N, 9.88.

This substance showed no evidence of oxidation when treated with chromic acid in 90% acetic acid solution. An ethanol solution showed a single maximum in the ultraviolet at 2625 Å. with E_M 35,000.

This evidence is in agreement with a 1,3-benzoylguanido-2,4,5,6-tetrabenzoyloxycyclohexane for the structure of hexabenzoylstreptidine.

Treatment of Octabenzoylstreptidine with Hydrogen Bromide.—One and one-half grams of octabenzoylstreptidine was dissolved in 15 cc. of chloroform and 15 cc. of 2.8 *N* hydrogen bromide in glacial acetic acid was added. The solution was refluxed (76°) for one hour, cooled, diluted with 25 cc. of chloroform, washed with saturated aqueous sodium bicarbonate and with water. The dried chloroform solution was evaporated *in vacuo* to give 1.5 g. of residue. This residue was crystallized from a mixture of 3 cc. of benzene and 10 cc. of methanol to give 1.35 g. of crystals which showed a transition at 120–160° and melted at 255–263°. One further crystallization gave 1.2 g. of recovered octabenzoylstreptidine which showed the transition at 120–150° and melted at 261–263° (micro-block).

Anal. Calcd. for $C_{64}H_{50}N_6O_{12}$: C, 70.19; H, 4.60. Found: C, 70.20; H, 4.57.

Octaacetylstreptidine Dihydrobromide.—A solution of 178 mg. of octaacetylstreptidine[6,8] in 1 cc. of glacial acetic acid containing 15% of hydrogen bromide was allowed to stand at room temperature, and white crystals began to separate in about ten minutes. After twenty-four hours, the mixture was diluted with 6 cc. of chloroform, and evaporated *in vacuo*. The residue was recrystallized from methanol–ether solution to give 139 mg. of crystals which melted at 175–185° (micro-block). A second crop of crystals weighing 61 mg. was obtained from the mother liquors. After recrystallization from methanol–ether, the product weighed 100 mg. and melted over the range 183–190°. The substance appeared to be octaacetylstreptidine dihydrobromide.

Anal. Calcd. for $C_8H_{10}N_6O_4(C_2H_3O)_8 \cdot 2HBr$: C, 37.92; H, 4.77; N, 11.05; Br, 21.02; CH_3CO, 45.23. Found: C, 38.91; H, 4.97; N, 10.89; Br, 21.7; CH_3CO, 40.4.

The ultraviolet absorption spectrum of the product in ethanol showed maxima at 2150 Å. (E_M 22,200) and 2550 Å. (E_M 27,500).

A solution of 1 g. of octaacetylstreptidine in 6 cc. of glacial acetic acid containing 15% of hydrogen bromide deposited crystals. The product was collected on a filter, washed with ether, and dried; yield, 702 mg., m. p. 180–195° (micro-block).

Anal. Calcd. for $C_8H_{10}N_6O_4(C_2H_3O)_8 \cdot 2HBr$: C, 37.92; H, 4.77; Br, 21.02. Found: C, 37.34; H, 4.84; Br, 20.85.

A 545-mg. portion of octaacetylstreptidine dihydrobromide was treated with a little water. Some crystalline material remained which was collected on a filter and washed with water. These crystals weighed 4.4 mg., and melted at 250–257° (micro-block) corresponding to octaacetylstreptidine. The aqueous filtrate was neutralized with sodium bicarbonate, and the precipitate was extracted with chloroform. The chloroform extract was evaporated to give 245 mg. of crystalline residue which melted at 170–230°. This material appeared to be partially deacetylated.

Hydrolysis of Octaacetylstreptidine to Streptidine Carbonate.—A solution of 229 mg. of octaacetylstreptidine in 100 cc. of absolute methanol was saturated at 0° with gaseous ammonia. After three hours, the solution was evaporated *in vacuo*, and the residue was extracted with chloroform to remove acetamide. The chloroform-insoluble residue weighed 110 mg. and appeared to be a mixture of streptidine and streptidine carbonate. A portion of this residue was converted to the picrate, which melted at 281–283° (micro-block). The melting point of this product on admixture with authentic streptidine picrate was not depressed. Twenty-eight milligrams of the residue was dissolved in 1.5 cc. of water; the solution was strongly alkaline. The addition of 2 cc. of methanol caused the separation of a crystalline product, which weighed 14 mg. and decomposed gradually above 240° (micro-block).

Anal. Calcd. for $C_8H_{18}N_6O_4 \cdot H_2CO_3 \cdot H_2O$: C, 31.58; H, 6.48; N, 24.55. Found: C, 31.25; H, 6.31; N, 24.54; acetyl, nil.

Stepwise Hydrolysis of Octabenzoylstreptidine to Monobenzoylstreptidine and Streptidine Dihydrochloride.—A solution of 504 mg. of octabenzoylstreptidine in 10 cc. of dry pyridine was mixed with 10 cc. of absolute methanol containing approximately 3 mg. of sodium methoxide. The solution was heated at the reflux temperature for three hours, during which time a crystalline solid separated. The crystals were removed, washed with methanol, and dried; weight 158 mg.; m. p. 232–235° (dec.) (micro-block). An aqueous solution of the product was alkaline and showed an ultraviolet absorption maximum at 2575 Å. (E_M 15,700).

Anal. Calcd. for $C_8H_{17}N_6O_4(C_6H_5CO)$: C, 49.17; H, 6.05; N, 22.94. Found: C, 48.50; H, 6.16; N, 22.09.

Nineteen milligrams of monobenzoylstreptidine was converted to a crystalline sulfate by treatment with a dilute sulfuric acid–acetone solution; yield, 24 mg. The crystals decomposed gradually when heated above 245° (micro-block).

Anal. Calcd. for $C_8H_{17}N_6O_4(C_6H_5CO) \cdot H_2SO_4 \cdot 2H_2O$: C, 36.00; H, 5.64; N, 16.79; S, 6.41. Found: C, 36.03; H, 6.62; N, 16.02; S, 5.63.

Another sample of the monobenzoylstreptidine was heated for two hours at the reflux temperature with 6 *N* hydrochloric acid. The hydrolysis mixture yielded benzoic acid and streptidine dihydrochloride. The latter was identified by conversion, in good yield, to octaacetylstreptidine.

Hydrolysis of Heptabenzoylstreptidine to Monobenzoylstreptidine.—Using the procedure described for the hydrolysis of octabenzoylstreptidine, a sample of heptabenzoylstreptidine weighing 2.004 g. was debenzoylated with methanol and sodium methoxide. The monobenzoyl derivative, which separated, was converted to the crystalline sulfate; yield, 379 mg. The crystalline salt decomposed gradually above 240° (micro-block).

Anal. Calcd. for $C_8H_{17}N_6O_4(C_6H_5CO) \cdot H_2SO_4 \cdot 2H_2O$: C, 36.00; H, 5.64; N, 16.79. Found: C, 36.17; H, 5.13; N, 17.41.

This product showed an ultraviolet absorption maximum which shifted with a change in the *p*H of the solution. In *N* hydrochloric acid, the maximum appeared at 2400 Å. (E_M 15,500). At *p*H 7, the maximum was at 2550 Å. (E_M 12,000). In 0.2 *N* sodium hydroxide, the maximum was at 2600 Å. (E_M 12,500). An aqueous solution of the compound showed a maximum at 2575 Å. (E_M 18,700).

Chromic Acid Oxidation of Heptabenzoylstreptidine; Isolation of Dibenzoylguanidine.—One and two-tenths grams of heptabenzoylstreptidine was dissolved in 20 cc. of acetic acid and the solution was mixed with 90 cc. of a 10% solution of chromic acid in 90% acetic acid. The solution was allowed to stand at 45° for five hours, and at room temperature for sixteen hours, and was then frozen and dried from the frozen state. The residue was dissolved in water, and the solution was neutralized to *p*H 7.0 with sodium bicarbonate and extracted four times with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to give a crystalline residue weighing 357 mg. The residue was dissolved in hot benzene, and the solution was filtered through a small pad of Darco G-60. The filtrate deposited white needles which weighed 100 mg., m. p. 163–164° (micro-block).

Anal. Calcd. for $CH_3N_3(C_7H_5O)_2$: C, 67.40; H, 4.90; N, 15.72; mol. wt., 267.3. Found: C, 67.25; H, 4.86; N, 15.44; mol. wt. (ebullioscopic in benzene), 264 ± 3.

Further recrystallizations from benzene and from

benzene–petroleum ether gave material which melted constantly at 165–166° (micro-block).

Anal. Calcd. for $CH_3N_3(C_7H_5O)_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.58; H, 5.15; N, 15.63.

This substance exhibited two maxima in the ultraviolet at 2450 Å. with E_M 32,000 and 2750 Å. with E_M 32,000 in methanol solution.

The data obtained on this oxidation product were in agreement with a dibenzoylquinidine, but the melting point was lower than that reported in the literature (m. p. 215°; Korndörfer, *Arch Pharm.*, **241**, 449 [1903]). Accordingly, a 28.7-mg. sample was dissolved in 3.0 cc. of concentrated hydrochloric acid and the solution was refluxed for ninety minutes. The hydrolysis solution was diluted with water and extracted with ether. Evaporation of the ether extracts left a crystalline residue of practically pure benzoic acid; yield, 23.7 mg. The residual acid aqueous solution was evaporated to dryness to give a crystalline residue which was dissolved in 3.0 cc. of water. Addition of 2.0 cc. of saturated aqueous picric acid caused a crystalline precipitate to separate. The picrate was recrystallized once from hot water; yield, 25.9 mg., m. p. 335–336° (micro-block). Admixture with authentic guanidine picrate (m. p. 335–336°) did not alter the melting point of the product.

Anal. Calcd. for $CH_5N_3 \cdot C_6H_3N_3O_7$: C, 29.17; H, 2.80; N, 29.17. Found: C, 29.33; H, 3.10; N, 29.39.

The oxidation product is thus established to be dibenzoylguanidine. The yield of dibenzoylguanidine from heptabenzoylstreptidine would be 28% if one dibenzoylguanido moiety were present in the latter molecule, or 56% if both guanido groups were di-benzoylated. The yields of dibenzoylguanidine obtained in three oxidation experiments were 48, 30 and 43%, respectively.

Dodecabenzoyldihydrostreptomycin.—Benzoylation of 2.80 g. of dihydrostreptomycin trihydrochloride, using the conditions described above for streptomycin, gave 5.82 g. of buff-colored benzoylated dihydrostreptomycin. Chromatographic purification of 5.5 g. gave a first-eluate fraction in the form of a white amorphous powder weighing 0.5 g., $[\alpha]^{25}D$ +51° (*c*, 1.78 in chloroform).

Anal. Calcd. for $C_{21}H_{29}N_7O_{12}(C_7H_5O)_{12}$: C, 68.81; H, 4.90; N, 5.35. Found: C, 68.40; H, 5.25; N, 5.66.

Heptabenzoylstreptidine from Dodecabenzoyldihydrostreptomycin.—A 347-mg. sample of dodecabenzoyldihydrostreptomycin was dissolved in 6.62 cc. of chloroform and 0.16 cc. of 30% hydrogen bromide in glacial acetic acid was added. The solution was allowed to stand overnight, then diluted with chloroform and extracted with water and aqueous sodium bicarbonate. The chloroform solution was dried, evaporated to dryness, and the residue was dissolved in 0.5 cc. of benzene and 2.5 cc. of methanol. On standing, there was deposited 101 mg. of crystalline precipitate. Recrystallization of the precipitate from benzene–acetone and from benzene–methanol gave 22 mg. of white crystals of heptabenzoylstreptidine which melted at 256–258°, and showed $[\alpha]^{32}D$ +54° (*c*, 0.98 in chloroform). There was no change in the melting point of this material when mixed with heptabenzoylstreptidine (m. p. 256–258°) obtained from undecabenzoylstreptomycin.

Acknowledgment.—The authors wish to express their thanks to Dr. N. R. Trenner and his associates for carrying out ultraviolet and infrared absorption measurements, to Dr. J. B. Conn and his associates for molecular weight determinations, and to Mr. R. Boos and his associates for the microanalyses.

Summary

Streptomycin was benzoylated to give undecabenzoylstreptomycin, which was degraded by alkali to maltol and by hydrogen bromide to heptabenzoylstreptidine.

Dihydrostreptomycin was also benzoylated to give dodecabenzoyldihydrostreptomycin, which was likewise cleaved by hydrogen bromide to give heptabenzoylstreptidine.

Heptabenzoylstreptidine was further characterized by acetyl and anisoyl derivatives and by conversion to octabenzoylstreptidine. A hexabenzoylstreptidine and a monobenzoylstreptidine were also characterized. Hydrolysis of octabenzoyl-, heptabenzoyl- and octaacetylstreptidine yielded streptidine, showing that acylation and hydrolysis reactions involved no change in the structure of streptidine.

Heptabenzoylstreptidine gave more than one equivalent of dibenzoylguanidine upon chromic acid oxidation showing that streptobiosamine is linked to streptidine through an oxygen atom.

RAHWAY, N. J. RECEIVED FEBRUARY 14, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Streptomyces Antibiotics. XVIII. Structure of Streptomycin

BY FREDERICK A. KUEHL, JR., ROBERT L. PECK, CHARLES E. HOFFHINE, JR., AND KARL FOLKERS

The degradation of streptomycin to N,N′-dibenzoyldesoxystreptamine, and the oxidation of this degradation product to show that streptobiosamine is linked glycosidically at position 4 of streptidine, have been reported.[1]

The unbenzoylated functional group of heptabenzoylstreptidine[2] is attached to the carbon atom of streptidine which is linked glycosidically to streptobiosamine. This unbenzoylated functional group was considered to be a hydroxyl group because of the facile methanolysis[3] of streptomycin, and because of the formation of more than one mole of dibenzoylguanidine[2] per mole of heptabenzoylstreptidine upon chromic acid oxidation. Conclusive evidence excluding a nitrogen-atom linkage was obtained in the present study.

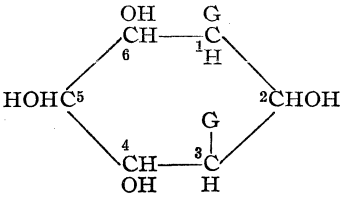
Streptidine and octabenzoylstreptidine[2] are optically inactive, showing that they are *meso* forms and have *cis* guanido groups; however, heptabenzoylstreptidine is optically active.[2] This optical activity proves that the unbenzoylated hy-

(1) Kuehl, Peck, Hoffhine, Peel and Folkers, THIS JOURNAL, **69**, 1234 (1947).

(2) Peck, Kuehl, Hoffhine, Peel and Folkers, *ibid.*, **70**, 2321 (1948).

(3) Brink, Kuehl and Folkers, *Science*, **102**, 2655 (1945); Brink, Kuehl, Flynn and Folkers, THIS JOURNAL, **68**, 2557 (1946).

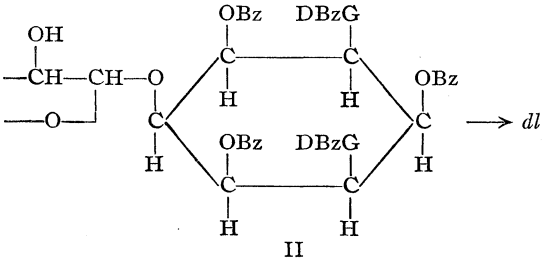
droxyl group in heptabenzoylstreptidine cannot be either at positions 2 or 5 of streptidine (I),



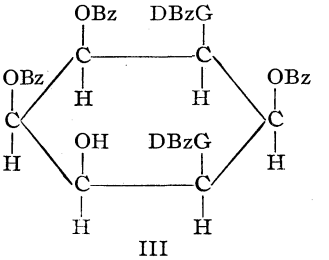
I, G = guanido

since these positions are in the plane of symmetry, and a heptabenzoylstreptidine with a free hydroxyl group at either position 2 or 5 would be optically inactive. The configuration of the groups about carbon atoms 4 and 6 is identical in streptidine and in the heptabenzoylstreptidine since there is no evidence of a Walden inversion in the formation of the latter compound. On the basis of these considerations of optical activity, the unbenzoylated hydroxyl group in heptabenzoylstreptidine is at position 4 (position 6 is equivalent).

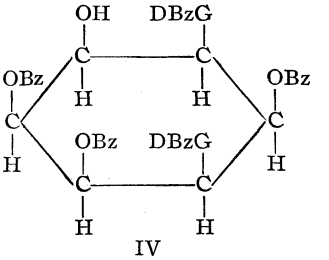
If streptobiosamine were linked glycosidically to position 5 of *meso*-streptidine, and if in the cleavage reaction an acyl group migrated from position 4 to position 5, such a migration might also be expected to occur from position 6 to result in a *dl*-heptabenzoylstreptidine. This hypothetical reaction is illustrated by the structures II, III, and IV, using one of the eight *meso* forms arbitrarily. The optical activity of the isolated heptabenzoylstreptidine eliminates such a rearrangement, unless an asymmetric rearrangement is considered possible.



II



III



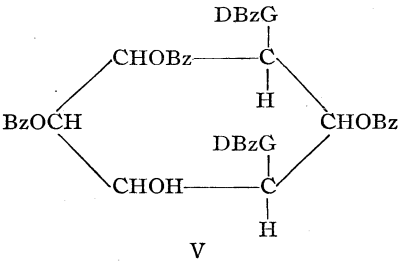
IV

DBzG = dibenzoylguanido
Bz = benzoyl-

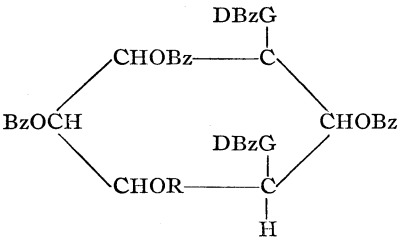
The determination of the position of the free hydroxyl group in heptabenzoylstreptidine by a series of degradative reactions led to a conclusion which is in agreement with that based on stereochemical considerations.

The most promising degradative method for locating the free hydroxy group appeared to be that of converting the >CHOH group to a $>CH_2$ group, because it seemed that the desoxy derivative would withstand the anticipated hydrolytic reactions.

Heptabenzoylstreptidine (V) reacted with methanesulfonyl chloride and toluenesulfonyl chloride to give mesylheptabenzoylstreptidine



V

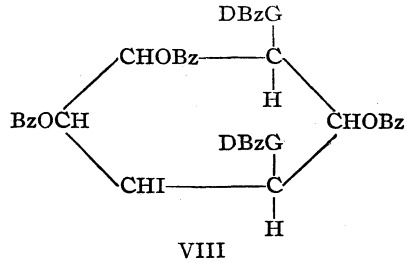


VI. R = CH_3SO_2—
VII. R = *p*-$CH_3C_6H_4SO_2$—

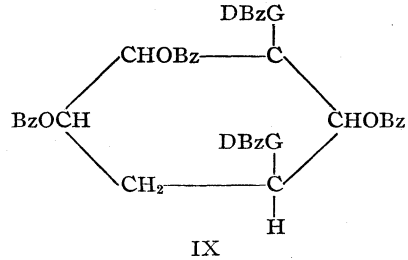
(VI) and tosylheptabenzoylstreptidine (VII), respectively. Mesyl derivatives of secondary alcohols in contrast to the corresponding tosyl derivatives have been reported[4] to react readily with sodium iodide to give the iodides. The mesyl derivative (VI) reacted with sodium iodide in acetone at 100° to give the iodoheptabenzoylstreptidine (VIII), and this mesyl derivative was used preparatively for this reaction. It was found later that the tosyl derivative (VII) also reacted readily with sodium iodide to give the iodo derivative (VIII). The formation of iodoheptabenzoylstreptidine constitutes conclusive evidence for an oxygen atom rather than a nitrogen atom linking streptidine to streptobiosamine.

Although iodoheptabenzoylstreptidine did not undergo hydrogenolysis over a palladium catalyst,

(4) Helferich and Gnuchtel, *Ber.*, **71B**, 712 (1938).



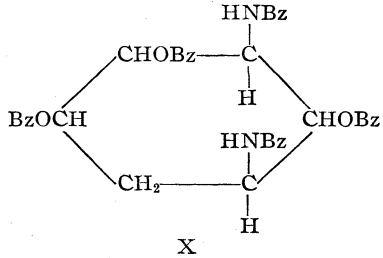
VIII



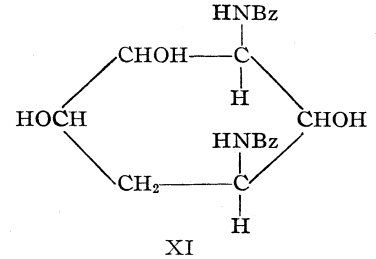
IX

the desired reduction product, heptabenzoyldesoxystreptidine (IX), was obtained when Raney nickel catalyst was used.

Heptabenzoyldesoxystreptidine (IX) was debenzoylated in methanol solution with barium methoxide. The resulting desoxystreptidine was then hydrolyzed to desoxystreptamine by baryta in the manner described for the conversion[5] of streptidine to streptamine. Desoxystreptamine was benzoylated to give pentabenzoyldesoxystreptamine (X), which was selectively debenzoylated in methanol solution with barium methoxide to N,N′-dibenzoyldesoxystreptamine (XI).

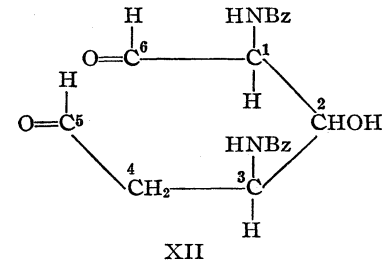


X

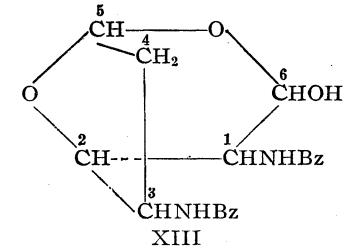


XI

Titration of N,N′-dibenzoyldesoxystreptamine with sodium periodate showed the consumption of one mole of periodate in seventeen hours and no further reaction in forty hours. The oxidation product was readily isolable as a crystalline compound which had a composition in agreement with that for α,γ-dibenzamido-β-hydroxyadipaldehyde (XII). The sharply defined consumption of one

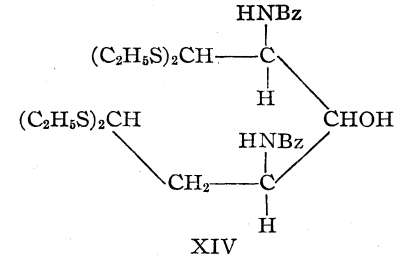


XII



XIII

mole of periodate was shown by treating the N,N′-dibenzoyldesoxystreptamine with excess periodate in aqueous solution, whereupon the same oxidation product crystallized directly from the solution after several days. In connection with the possibility that the aldehyde oxidation product actually has the cyclized structure XIII, the infrared absorption spectrum of the oxidation product was examined and a band for the aldehydic carbonyl group was not found. Only bands at 2.82, 6.38, 6.20 and 6.53 μ were observed Furthermore, the product exhibited a stability which is more compatible with structure XIII than the free aldehyde structure XII. The potential dialdehydic nature of the oxidation product was demonstrated, however, by the reaction of the compound with ethyl mercaptan and hydrogen chloride to give a crystalline derivative of the composition $C_{28}H_{40}N_2O_3S_4$; this derivative corresponds to structure XIV.

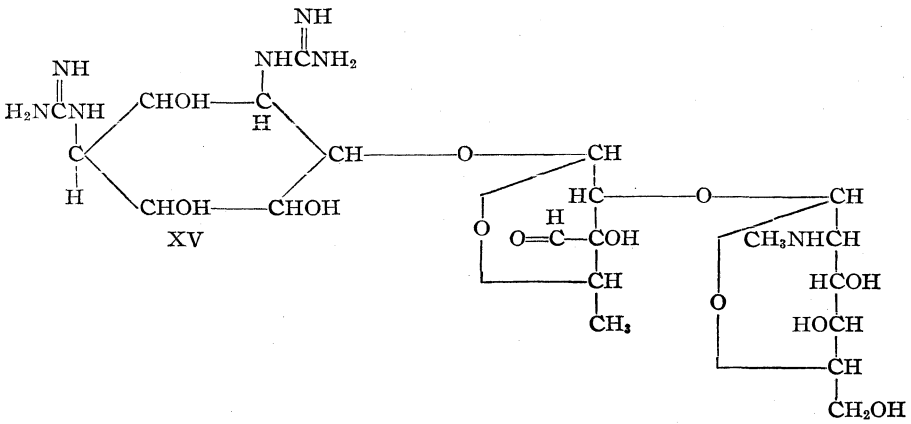


XIV

If the methylene group were positions 2 or 5 in desoxystreptamine, an aldehyde corresponding to structure XII or XIII could not have been formed. Thus, desoxystreptamine has the methylene group in position 4, and on the basis of the partial structure of streptomycin previously proposed,[6] the linkage of streptobiosamine to streptidine may be represented by structure XV. Structure XV for

(5) Peck, Hoffhine, Peel, Graber, Holly, Mozingo and Folkers, THIS JOURNAL, **68**, 776 (1946).

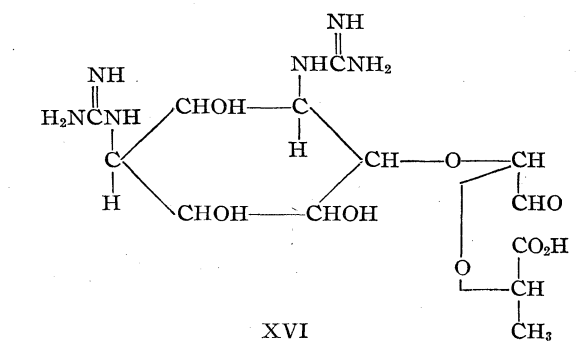
(6) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).



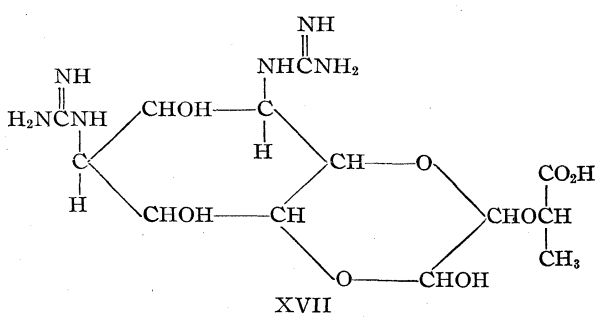
XV

streptomycin possesses a free formyl group. This group might also exist in hemiacetal form as a result of intramolecular cyclization.

Other workers[7] have treated streptomycin in aqueous solution with excess periodate, and obtained an oxidation product which yielded streptidine, glyoxal and an unidentified acid upon mild hydrolysis. They interpreted this result as strongly indicating that streptobiosamine is attached at carbon atom 5, although attachment at carbon atom 4 could not be entirely disregarded. On the basis of structure XV for streptomycin, perhaps the periodate oxidation data might be explained by intermediary formation of a product of structure XVI as the combined result of oxidation and hydrolytic reactions. Our experience has shown that streptose derivatives oxidize rapidly and streptidine oxidizes very slowly. Cyclization o the aldehydic product (XVI) might give the six-membered hemiacetal (XVII) which could be sufficiently stable to block oxidation of the streptidine nucleus.



XVI



XVII

(7) Carter, Loo and Skell, *J Biol. Chem.*, **168**, 401 (1947).

Experimental

Mesylheptabenzoylstreptidine.—A solution of 1.543 g. of heptabenzoylstreptidine in 20 ml. of pyridine was cooled to 5° and treated with 1.5 ml. of methanesulfonyl chloride. After remaining at 5° for fourteen hours, the reaction mixture was treated dropwise with 1 ml. of water at 5° to decompose the excess reagent. This mixture was poured into water, and the resulting oily suspension was extracted three times with chloroform. The combined chloroform extract was washed successively with dilute hydrochloric acid, sodium bicarbonate solution and water. The residue obtained from the dried chloroform solution was dissolved in 3 ml. of chloroform and at the boiling point of the solution was treated dropwise with methanol. Crystallization began quickly and after the mixture was cooled in ice-water for several hours, 1.520 g. of mesylheptabenzoylstreptidine was obtained, m. p. 241–242°. This product melted at 241.5–242° after a second recrystallization from the same solvent mixture; $(\alpha)^{25}D$ +18° (*c*, 0.8 in chloroform).

Anal. Calcd. for $C_{58}H_{48}N_6O_{13}S$: C, 65.16; H, 4.53; N, 7.85; S, 2.99. Found: C, 65.40; H, 4.29; N, 8.15 S, 2.46.

Iodoheptabenzoylstreptidine from Mesylheptabenzoylstreptidine.—A solution of 2.831 g. of mesylheptabenzoylstreptidine and 7 g. of dry sodium iodide in 50 ml. of anhydrous acetone was heated in a sealed tube for two hours at 100°. The acetone was removed *in vacuo*, and the yellow residue was shaken with a mixture of 50 ml. of water and 50 ml. of chloroform. The water layer was extracted three times with chloroform. The combined chloroform extract was washed successively with dilute sodium bicarbonate solution, sodium thiosulfate, water, and then dried over anhydrous magnesium sulfate. The colorless chloroform residue, 2.932 g., was dissolved in 5 ml. of chloroform and treated with 25 ml. of methanol. This solution yielded 2.542 g. of iodoheptabenzoylstreptidine, m. p. 153–154°, $(\alpha)^{25}D$ +23° (*c*, 0.08 in chloroform). Further recrystallization from the same solvent mixture did not alter the melting point.

Anal. Calcd. for $C_{57}H_{45}N_6O_{10}I$: C, 62.18; H, 4.12; I, 11.54. Found: C, 61.88; H, 4.05; I, 11.83.

Tosylheptabenzoylstreptidine.—A mixture of 275 mg. of heptabenzoylstreptidine, 115 mg. of tosyl chloride and 1.5 ml. of pyridine was allowed to stand in the cold room overnight. The clear solution was mixed with 10 ml. of cold water and allowed to stand for thirty minutes. The precipitated material was extracted with chloroform, and the chloroform solution was washed, dried over magnesium sulfate, and evaporated to dryness. The residue was crystallized from benzene–methanol; yield, 190 mg.; m. p. 200–203° (micro-block); $(\alpha)^{25}D$ +33° (*c*, 3.43 in chloroform).

Anal. Calcd. for $C_{64}H_{52}N_6O_{13}S$: C, 67.12; H, 4.58; N, 7.34; S, 2.80. Found: C, 67.40; H, 4.76; N, 7.47; S, 2.92.

Iodoheptabenzoylstreptidine from Tosylheptabenzoylstreptidine.—A mixture of 378 mg. of tosylheptabenzoylstreptidine, 3.4 g. of sodium iodide and 15 ml. of acetone was sealed in a bomb tube and heated at 100° for two hours. The contents of the tube were evaporated and water was added to the residue. The mixture was extracted with chloroform, and the chloroform extracts were washed with water and a little aqueous sodium thio-

sulfate. The colorless chloroform solution was evaporated to a volume of 2 ml. and diluted with 10 ml. of methanol. The first crop of iodoheptabenzoylstreptidine weighed 148 mg. and melted at 149–152° (micro-block). The second crop weighed 120 mg. and melted at 149–152°. Recrystallization of the combined material gave iodoheptabenzoylstreptidine, m. p. 151–153°.

Anal. Calcd. for $C_{57}H_{45}N_6O_{10}I$: C, 62.18; H, 4.12; I, 11.54. Found: C, 61.91; H, 4.40; I, 10.77.

Heptabenzoyldesoxystreptidine.—A solution of 5.58 g. of iodoheptabenzoylstreptidine in 330 ml. of aqueous 80% dioxane was reduced catalytically for one hour at 40 lb. pressure in the presence of about 25 g. of Raney nickel catalyst. After removal of the catalyst the solution was concentrated *in vacuo* to *ca.* 10-ml. volume. This solution was extracted several times with chloroform and distillation of the chloroform gave a colorless glassy residue. The residue was dissolved in a small amount of chloroform and crystallization was aided by adding methanol. The yield of crystalline product was 4.437 g., m. p. 187–191°. A number of recrystallizations alternately from chloroform–methanol and ethyl acetate–methanol was required to obtain pure heptabenzoyldesoxystreptidine, m. p. 198–199°.

Anal. Calcd. for $C_{57}H_{46}N_6O_{10}$: C, 70.21; H, 4.76; N, 8.62. Found: C, 70.25; H, 4.76; N, 8.49.

Pentabenzoyldesoxystreptamine.—A suspension of 321 mg. of heptabenzoyldesoxystreptidine in 150 ml. of absolute methanol containing 5 ml. of 0.4 *N* methanolic barium methoxide was stirred overnight at room temperature. The resulting clear solution was treated with carbon dioxide and concentrated *in vacuo* to a residue. This residue was leached with 20 ml. of 50% methanol, and after removal of the solvent from the extract, 119 mg. of desoxystreptidine carbonate was obtained as a white powder. A solution of desoxystreptidine in 20 ml. of saturated baryta was boiled for twenty-three hours, and then concentrated to *ca.* 10-ml. volume. Excess hydrochloric acid was added, and the solution was concentrated to dryness. This residue of desoxystreptamine hydrochloride and barium chloride was leached with 30 ml. of boiling methanol. The methanol-soluble material was again leached with 10 ml. of hot methanol. Removal of the methanol gave crude desoxystreptamine hydrochloride which was benzoylated at 5° with 20 ml. of pyridine and 3 ml. of benzoyl chloride. After standing overnight, the reaction mixture yielded pentabenzoyldesoxystreptamine which was crystallized from chloroform–ether; yield, 67 mg., m. p. 293–294°. After two recrystallizations from the same solvent mixture, the pentabenzoyldesoxystreptamine melted at 298–299°.

Anal. Calcd. for $C_{41}H_{34}N_2O_8$: C, 72.12; H, 5.02; N, 4.10. Found: C, 72.37; H, 5.10; N, 4.19.

N,N′-Dibenzoyldesoxystreptamine.—A suspension of 43 mg. of pentabenzoyldesoxystreptamine in 25 ml. of absolute methanol containing 2 ml. of 0.4 *N* methanolic barium methoxide was shaken at room temperature for ten minutes. The resulting clear solution was maintained at a temperature of 5° for fourteen hours and then treated with carbon dioxide. The solvent was removed *in vacuo*, and the residue was leached with 5 ml. of hot 50% methanol. This methanol-soluble portion, after removal of the solvent, was again leached with 5 ml. of hot methanol, and 18 mg. of methanol-soluble material was obtained which was redissolved in 1 ml. of methanol. Ten milligrams of N,N′-dibenzoyldesoxystreptamine was obtained; m. p. 287–289°; $(\alpha)^{25}D$ −4° (*c*, 1.1 in 50% acetic acid). The melting point remained unchanged after a second recrystallization from acetone–water.

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.50. Found: C, 64.72; H, 6.21; N, 7.80.

Titration of N,N′-Dibenzoyldesoxystreptamine with Sodium Periodate.—A 10.4-mg. sample was dissolved in 5 ml. of water and treated with 3.0 ml. of sodium periodate solution (1 ml. ≅ 6.355 ml. of 0.01 *N* arsenite solution); the total volume was adjusted to 10.0 ml. One-milliliter aliquots were removed and titrated periodically with 0.01 *N* standard arsenite solution. The data on the titration are given in Table I.

TABLE I

TITRATION OF N,N′-DIBENZOYLDESOXYSTREPTAMINE

Time in hours	0.01 *N* arsenite utilized	Moles of $NaIO_4$ consumed
17	0.580	1.03
21	.585	1.04
24	.580	1.03
41	.570	1.02

Oxidation of N,N′-Dibenzoyldesoxystreptamine to α,γ-Dibenzamido-β-hydroxyadipaldehyde.—A solution of 106.5 mg. of N,N′-dibenzoyldesoxystreptamine in 100 ml. of hot water was treated with 10.8 ml. of sodium periodate solution (1 ml. ≅ 5.67 mg. of $NaIO_4$). After forty hours, when titration indicated the consumption of 0.8 mole of oxidizing agent, the solution was concentrated *in vacuo* to a residue. Trituration of the residue with acetone gave 102 mg. of acetone-soluble material which was dissolved in 15 ml. of hot water. α,γ-Dibenzamido-β-hydroxyadipaldehyde crystallized from the aqueous solution; yield, 32 mg.; m. p. 148–149°; $(\alpha)^{25}D$ +12° (*c*, 1.0 in methanol) (initial). The melting point did not change upon recrystallization from acetone–water.

Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.18; H, 5.48; N, 7.60. Found: (sample dried at 100°) C, 65.37; H, 5.57; N, 7.57.

α,γ-Dibenzamido-β-hydroxyadipaldehyde Tetraethyl Mercaptal.—A suspension of 38 mg. of α,γ-dibenzamido-β-hydroxyadipaldehyde in 15 ml. of ethyl mercaptan was saturated with anhydrous hydrogen chloride. After shaking for fifteen minutes, the crystals dissolved and the clear solution was allowed to stand overnight at room temperature. The ethyl mercaptan was removed *in vacuo*, and the 64-mg. residue was dissolved in 5 ml. of ether. The ethereal solution was allowed to flow into a column containing 5 g. of acid-washed alumina. Elution of the alumina with 15 ml. of ether gave a residue which crystallized from benzene–petroleum ether; yield, 15 mg.; m. p. 143–144°. Further elution with 10 ml. of chloroform resulted in the isolation of 14 mg. of material, m. p. 146–146.5°. The melting point of α,γ-dibenzamido-β-hydroxyadipaldehyde tetraethyl mercaptal remained at 146–146.5° after repeated recrystallizations.

Anal. Calcd. for $C_{28}H_{40}N_2O_3S_4$: C, 57.79; H, 6.94; N, 4.81; S, 22.03. Found: C, 57.90; H, 6.82; N, 5.17; S, 22.40.

Acknowledgment.—The authors wish to thank Miss Mary Neale Bishop for technical assistance, Dr. N. R. Trenner for the infrared analysis, and Mr. R. N. Boos and his associates for microanalyses.

Summary

Heptabenzoylstreptidine reacted with methane sulfonyl chloride and tosyl chloride to give mesylheptabenzoylstreptidine and tosylheptabenzoylstreptidine, respectively. Treatment of both the mesyl or tosyl derivatives with sodium iodide gave iodoheptabenzoylstreptidine. Hydrogenolysis of the iodo derivative gave heptabenzoyldesoxystreptidine, which was converted stepwise into pentabenzoyldesoxystreptamine and N,N′-dibenzoyldesoxystreptamine.

Oxidation of N,N′-dibenzoyldesoxystreptamine with sodium periodate gave α,γ-dibenzamido-β-

hydroxyadipaldehyde. The adipaldehyde derivative was also characterized as the tetraethyl mercaptal.

These results show that streptobiosamine is linked glycosidically at position 4 of streptidine.

RAHWAY, N. J. RECEIVED FEBRUARY 14, 1948

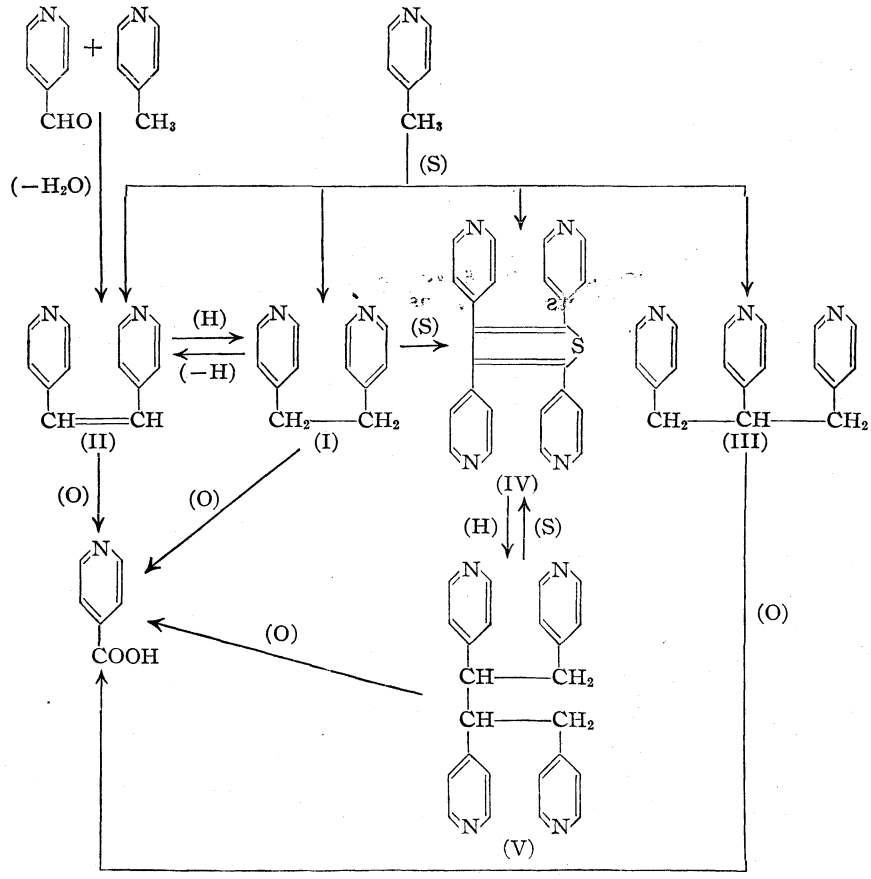
[CONTRIBUTION FROM KOPPERS CO., INC., MULTIPLE FELLOWSHIP ON TAR SYNTHETICS, MELLON INSTITUTE]

Action of Sulfur on Certain Pyridine and Quinoline Derivatives. I. Action of Sulfur on 4-Picoline

BY HELEN I. THAYER AND B. B. CORSON

The dehydropolymerizing action of sulfur on the picolines has not been previously noted, but certain examples of this action have been recorded in the methylbenzene series. For example, it is known that sulfur converts toluene to stilbene and tetraphenylthiophene, and xylenes to dimethylstilbenes and dimethylbenzyls.[1]

This paper describes the synthesis of several higher molecular weight bases from 4-picoline by the action of sulfur. Five products were obtained: hydrogen sulfide, 1,2-di-(4-pyridyl)-ethane (I), 1,2-di-(4-pyridyl)-ethylene (II), 1,2,3-tri-(4-pyridyl)-propane (III) and 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV). In the absence of sodium hydroxide the yield of tetrapyridylthiophene (IV) was negligible, but it was the main product (85–90% yield) when the reaction mixture contained a catalytic amount of sodium hydroxide and the final reaction temperature was in the vicinity of 300°. In general, the presence of sodium hydroxide favored the production of the unsaturated compounds of dipyridylethylene (II) and tetrapyridylthiophene (IV) at the expense of the saturated compounds of dipyridylethane (I) and tripyridylpropane (III). The product-distribution was also affected by temperature, length of reaction time, and sulfur–picoline ratio.



At the lower temperatures, sulfur-free compounds (I, II, and III) resulted, whereas at the higher temperatures the main product was the sulfur-containing tetrapyridylthiophene (IV). These results are similar to those of Aronstein and von Nierop,[1] who treated toluene with sulfur at 200° and 250–300° to obtain stilbene and tetraphenylthiophene, respectively. Likewise, Oddo and Raffa[2] obtained the sulfur-free compound 3,3′-biindole by treating indole with sulfur at 115–125° and sulfur-containing products at higher reaction temperatures.

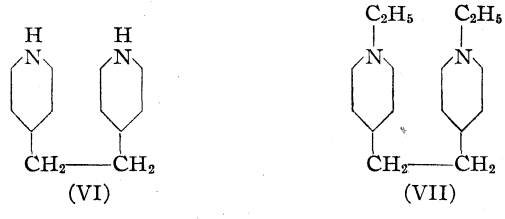
The structures of I and II were established as follows: (1) oxidation of these compounds to isonicotinic acid; (2) hydrogenation of II to I; (3) dehydrogenation of I to II; and (4) the synthesis of 1,2-di-(4-pyridyl)-ethylene (II) by the condensation of 4-pyridylaldehyde with 4-pico-

(1) Aronstein and von Nierop, *Rec. trav. chim.*, **21**, 448 (1902).

(2) Oddo and Raffa, *Gazz. chim. ital.*, **69**, 562 (1939).

line. The structure of 1,2,3-tri-(4-pyridyl)-propane (III) was based on its oxidation to isonicotinic acid. Evidence for the structure of 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV) was threefold: (1) its synthesis from 1,2-di-(4-pyridyl)-ethane (I); (2) its conversion to the sulfur-free compound (V); (3) the similarity of its spectrum in the region 280–370 mμ (Fig. 1) to that of 2,3,4,5-tetraphenylthiophene. The synthesis of IV from 1,2-di-(4-pyridyl)-ethane (I) was accomplished by heating the latter with sulfur as in the synthesis of tetraphenylthiophene from dibenzyl and sulfur,[3] and tetrapyridylthiophene (IV) was degraded to tetrapyridylbutane (V) with zinc and hydrochloric acid as in the reductive fission of tetraphenylthiophene to tetraphenylbutane.[4] The structure of 1,2,3,4-tetra-(4-pyridyl)-butane (V) was based on its oxidation to isonicotinic acid, and the conversion of V to IV by reaction with sulfur.

Catalytic hydrogenation of 1,2-di-(4-pyridyl)-ethane (I) in cyclohexane solution gave 1,2-di-(4-piperidyl)-ethane (VI), whereas hydrogenation in ethanol gave the di-N-ethyl derivative (VII).[5]



The various reaction mixtures were scrutinized for intermediate produc to serve as clues to the reaction mechanism. In the benzene series, polymeric thiobenzaldehyde, benzyl mercaptan and dibenzyl sulfide have been hypothesized as intermediates in the reaction of toluene with sulfur because they pyrolyze to certain of the end-products of this reaction, *viz.*, stilbene and tetraphenylthiophene.[1] However, in the present case, no analogous intermediates were isolated to justify the postulation of a reaction mechanism.

Experimental

4-Picoline.—The 4-picoline (95+% pure, b. p. 144.2–144.4° (743 mm.), $n^{20}D$ 1.5050, d^{20}_4 0.953) was a product of the Koppers Company, Inc.

Reaction of 4-Picoline with Sulfur (below 200°).—Yield data on several experiments are listed in Table I. The general procedure was to heat a mixture of 4-picoline with flowers of sulfur (with or without sodium hydroxide) in a 3-neck flask equipped with condenser, stirrer and thermometer. The mixture darkened and hydrogen sulfide was evolved. The final temperature of the reaction mixture depended upon the length of the heating period. After cooling, unreacted picoline was removed through a short column at about 45 mm. pressure, distillation being discontinued when the pot temperature reached 180°. Redistillation of the overhead showed it to be at least 90% 4-picoline; no higher boiling material was present. The reaction product residue was stirred into a mixture of ice and 50% sulfuric acid; unreacted sulfur was removed by filtration, and the filtrate was made alkaline with 30% sodium hydroxide solution. The oil layer was separated while warm. The water layer was extracted with benzene and the extract was added to the oil. The crude product, dark brown and semi-solid after removal of water and benzene, was distilled at about 3 mm. into several fractions. These distillates crystallized in the receiver and were purified by crystallization; the pot residue was a black, charred solid.

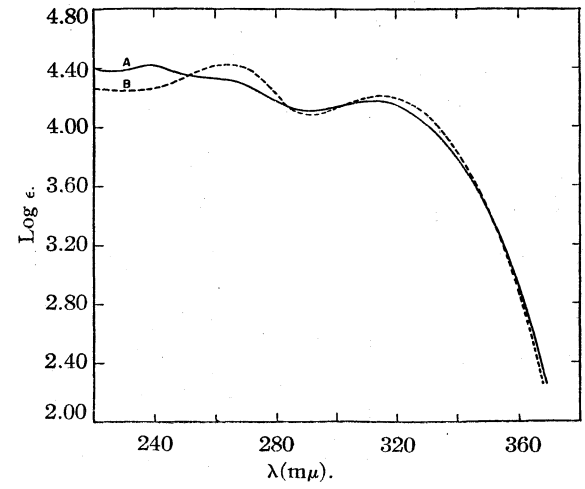


Fig. 1.—Absorption curves of tetraphenylthiophene (A) and tetra-(4-pyridyl)-thiophene (B) in 95% ethanol.

Effect of Reaction Variables (Table I).—In the absence of sodium hydroxide the main product was dipyridylethane; there was considerable tripyridylpropane, but little dipyridylethylene. Doubling the relative amount of sulfur (*e. g.*, increasing the sulfur–picoline ratio from 1:2 to 1:1) did not change the product-distribution, but it increased the picoline conversion somewhat. The effect of lengthening the reaction time was to increase the picoline conversion, partly due to the resulting higher final reaction temperature. As remarked above, the effect of sodium hydroxide was to favor the formation of dipyridylethylene and tetrapyridylthiophene at the expense of dipyridylethane and tripyridylpropane.

1,2-Di-(4-pyridyl)-ethane (I).—Repeated crystallization of the fraction melting at 107–110° (b. p. 167–174° at 3 mm.) from cyclohexane–benzene (3:1) gave compact, colorless crystals, m. p. (capillary) 110–111°, f. p. (cooling curve) 110.9–110.2°.[6]

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.2; H, 6.6; N, 15.2; mol. wt., 184. Found: C, 77.8; H, 6.9; N, 15.0; mol. wt., 189.[7]

The hydrochloride was precipitated from an alcohol solution of the base by hydrogen chloride; white crystalline powder, 95% yield, m. p. 329–330° (dec.).

Anal. Calcd. for $C_{12}H_{12}N_2 \cdot 2HCl$: Cl, 27.6. Found: Cl, 27.5.

1,2-Di-(4-pyridyl)-ethylene (II).—Three fractions boiling at 175–189° (2.5 mm.), 175–205° (2 mm.) and 193–220° (2 mm.), respectively, were combined and fractionally crystallized from benzene to yield impure I and II, the latter being long, white needles, m. p. 151–152°, f. p. 151.5–151.2°.

(3) Szperl and Wierusz-Kowalski, *Chem. Polski*, **15**, 19 (1917); through *Chem. Zentr.*, **89**, I, 909 (1918).

(4) Fromm and Achert, *Ber.*, **36**, 534 (1903).

(5) This is another example of simultaneous N-alkylation-hydrogenation, see King, Baltrop and Walley, *J. Chem. Soc.*, 277 (1945); Adkins, Kuick, Farlow and Wojcik, THIS JOURNAL, **56**, 2425 (1934).

(6) All melting points were corrected. The cooling curve temperatures listed were the initial and the final temperatures (when about 50% of the sample was frozen).

(7) Molecular weights were determined by the method of Hanson and Bowman, *Ind. Eng. Chem., Anal. Ed.*, **11**, 440 (1939).

TABLE I

REACTION OF 4-PICOLINE WITH SULFUR (BELOW 200°)

Hr.	T, °C.	Reactants, moles			Pic reacted, %	Products, wt. %					
		Pic[a]	S	NaOH		$C_2H_4P_2$	$C_2H_2P_2$	$C_3H_5P_3$	TP_4	Pot residue	Unaccounted for
9	143–166	4	4	0	71	52	2	21	0	9	16
12	137–174	3	3	0	77	46	6	22	0	15	11
12	140–155	3	1.5	0	53	60	4	14	0	10	12
24	140–171	3	1.5	0	71	48	4	24	0	8	16
7	135–160	4	8	0.075	65	32	15	4	0	17	32
12	140–199	4	8	0.075	94	9	0	0	72	13	6
12	135–161	3	3	0.15	78	28	20	11	1	16	24
12	135–162	3	3	0.30	77	26	15	0	26	9	24

[a] Pic, $C_2H_4P_2$, $C_2H_2P_2$, $C_3H_5P_3$, TP_4 = 4-picoline, 1,2-di-(4-pyridyl)-ethane, 1,2-di-(4-pyridyl)-ethylene, 1,2,3-tri-(4-pyridyl)-propane, 2,3,4,5-tetra-(4-pyridyl)-thiophene, respectively.

TABLE II

REACTION OF 4-PICOLINE WITH SULFUR (ABOVE 200°)

Hr.	T, °C.	Reactants, moles			Pic:S	Products		
		Pic	S	NaOH		H_2S % Yield	S, g.	P_4T % Yield
2.5	150–300	0.05	0.075	0.00025	4:6	101	0	89[a]
2.8	175–330	.05	.0875	.00025	4:7	98	0.02	83[b]
2.5	160–290	.05	.100	.00025	4:8	97	0.5	90[b]
2.5	160–290	.05	.125	.00025	4:10	100	1.5	78[b]

[a] Based on sulfur. [b] Based on picoline.

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.1; H, 5.5; N, 15.4; mol. wt., 182. Found: C, 78.8; H, 5.3; N, 15.6; mol. wt., 180.

Its hydrochloride, precipitated from alcohol in 99% yield, was a white crystalline solid, m. p. 347° (sealed tube, dec.).

Anal. Calcd. for $C_{12}H_{10}N_2 \cdot 2HCl$: Cl, 27.8. Found: Cl, 27.8.

1,2,3-Tri-(4-pyridyl)-propane (III).—The fraction boiling at 230–242° (2 mm.) was repeatedly crystallized from ethyl acetate to yield pale yellow crystals, m. p. 110–111°, f. p. 109.9–109.3°. Its melting point was depressed 10–12° by admixture with an equal amount of di-(4-pyridyl)-ethane (I) which also melted at 110–111°.

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.5; H, 6.2; N, 15.3; mol. wt., 275. Found: C, 78.8; H, 6.3; N, 15.2; mol. wt., 282.

Its hydrochloride, precipitated from alcohol in 85% yield, was a white hygroscopic powder, m. p. 230–232° (dec.).

Anal. Calcd. $C_{18}H_{17}N_3 \cdot 3HCl$: Cl, 27.7. Found: Cl, 27.4.

Reaction of 4-Picoline with Sulfur (above 200°).—At temperatures above 200° in the presence of catalytic amounts of sodium hydroxide, the main products were 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV) and hydrogen sulfide. The data listed in Table II were obtained from small experiments in which hydrogen sulfide was swept out of the reaction mixture by nitrogen and collected in Ascarite preceded by pumice–sulfuric acid. Approximately the theoretical amount of hydrogen sulfide was recovered; the maximum utilization of sulfur was at the picoline–sulfur ratios of 4:6 and 4:7. The decreased yield of tetrapyridylthiophene obtained at the smallest picoline:sulfur ratio of 4:10 (as compared with the theoretical ratio of 4:7) was probably due to inclusion of product in the recovered excess sulfur. In typical larger scale reactions, a mixture of 4 moles of picoline, 8 moles of sulfur, and 0.025 mole of sodium hydroxide was heated for fourteen hours (final temperature *ca.* 245°). The reaction mixture was poured into acid and unreacted sulfur was removed by filtration; the acid filtrate was made alkaline and the precipitated tetrapyridylthiophene isolated (85–90% yield).

2,3,4,5-Tetra-(4-pyridyl)-thiophene (IV).—The crude product gave about 80% yield of compound IV, m. p. 251.8–252.6°, pale yellow crystals from methanol or pyridine.

Anal. Calcd. for $C_{24}H_{16}N_4S$: C, 73.4; H, 4.1; N, 14.3; S, 8.2; mol. wt., 393. Found: C, 73.6; H, 4.0; N, 14.2; S, 8.4; mol. wt., 401.

The hydrochloride, precipitated from ethanol in 95% yield, was a pale yellow hygroscopic solid, m. p. 283–285° (dec.).

Anal. Calcd. for $C_{24}H_{16}N_4S \cdot 4HCl$: Cl, 26.3. Found: Cl, 26.0.

Proof of Structure

Oxidation of Compounds I, II, III and V.—1,2-Di-(4-pyridyl)-ethane (1.84 g.) in 100 cc. of water was oxidized at about 60° with 6 g. of potassium permanganate added in several portions during one and one-half hours. From the filtrate (at *p*H 3.6) two crops of isonicotinic acid were obtained, 1.81 g. (m. p. 317–319° (dec.)) and 0.36 g. (m. p. 314–316° (dec.)). The neutral equivalents were 124.3 and 125.6, respectively, compared with the theoretical of 123.1. The yield of isonicotinic acid was therefore 87%. In similar manner, 1,2-di-(4-pyridyl)-ethylene, 1,2,3-tri-(4-pyridyl)-propane, and 1,2,3,4-tetra-(4-pyridyl)-butane were oxidized to isonicotinic acid in 76, 84 and 74% yields, respectively.

Synthesis of 1,2-Di-(4-pyridyl)-ethylene (II) from 4-Pyridylaldehyde and 4-Picoline.—Selenium dioxide oxidation of 4-picoline in wet dioxane at 90° under nitrogen produced a small yield of 4-pyridylaldehyde, b. p. 68–74° (11 mm.), $n^{25}D$ 1.5382, m. p. of phenylhydrazone 177.5–178.5°.[8] 4-Pyridylaldehyde (1.79 g.) was heated with 1.56 g. of 4-picoline and 2.28 g. of zinc chloride for sixteen hours at 200–215°. The reaction mixture was cooled, dissolved in 20 cc. of 3 *N* sulfuric acid and two 5-g. portions of sodium hydroxide pellets were added. The cooled alkaline solution was repeatedly extracted with ether followed by chloroform. Removal of the solvent left a semi-solid product which was filtered; the filtrate was distilled (b. p. 182–189° (4 mm.)) to yield a distillate which partially solidified. The weight of the combined solids was 0.41 g. (13% yield). Three crystallizations from benzene with boneblacking gave colorless needles

(8) Wibaut, Kooyman and Boer, *Rec. trav. chim.*, **64**, 30 (1945).

which melted at 151–152° and showed no depression in melting point when admixed with di-(4-pyridyl)-ethylene (II).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.1; H, 5.5; N, 15.4. Found: C, 78.9; H, 5.3; N, 15.7.

Hydrogenation of 1,2-Di-(4-pyridyl)-ethylene (II) to 1,2-Di-(4-pyridyl)-ethane (I).—Hydrogenation of dipyridylethylene in methanol with platinum gave a 76% yield of product which melted at 111–112° and did not depress the melting point of 1,2-di-(4-pyridyl)-ethane (I).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.2; H, 6.6; N, 15.2. Found: C, 78.2; H, 6.7; N, 15.3.

Dehydrogenation of 1,2-Di-(4-pyridyl)-ethane (I) to 1,2-Di-(4-pyridyl)-ethylene (II).—Dipyridylethane (117 g.) was passed over 60 g. of a ferruginous dehydrogenation catalyst[9] at 600°, atmospheric pressure, and one second contact time, with 15 volumes of diluent steam. The catalyst carbonized to the extent of 10.9 weight per cent. The catalyzate was a mixture of solid, oil and water (ammoniacal odor), from which were separated 30 g. of unchanged dipyridylethane, 20 g. of dipyridylethylene, and 14 g. of 4-picoline (identified as methiodide, m. p. and mixed m. p. 152–153.5°).

Sulfuration of 1,2-Di-(4-pyridyl)-ethane to 2,3,4,5-Tetra-(4-pyridyl)-thiophene.—A mixture of 3.68 g. of 1,2-di-(4-pyridyl)-ethane (I) and 1.60 g. of sulfur was heated for eight and one-half hours at 170–240°; 0.85 g. of hydrogen sulfide was evolved, 0.75 g. of sulfur was recovered, and 2.5 g. of a reddish-brown solid was obtained. Crystallization from methanol gave 1.69 g. of solid melting at 246–250°, and recrystallization gave yellow crystals melting at 251.5–252.5° whose melting point was not depressed by admixture with 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV).

Anal. Calcd. for $C_{24}H_{16}N_4S$: C, 73.4; H, 4.1; N, 14.3. Found: C, 73.6; H, 4.2; N, 14.2.

Reductive Desulfurization of 2,3,4,5-Tetra-(4-pyridyl)-thiophene (IV) to 1,2,3,4-Tetra-(4-pyridyl)-butane (V).—A mixture of 7.84 g. of tetrapyridylthiophene, 20 g. of zinc dust, and 100 cc. of 25% hydrochloric acid was refluxed for two hours; 25 cc. of 25% hydrochloric acid was added and the refluxing was continued for another hour. The grayish solid was filtered, boiled for a short time with 25% caustic to decompose the zinc chloride complex, and the mixture was filtered. The solid was extracted with dilute hydrochloric acid, and the nitrogen base (4.21 g., 57% yield) was precipitated from the extract by caustic (m. p. 262–265° after recrystallization from 96% ethanol).

Anal. Calcd. for $C_{24}H_{22}N_4$: C, 78.6; H, 6.1; N, 15.3; mol. wt., 366. Found: C, 78.5; H, 6.1; N, 15.4; mol. wt. (Rast), 347.

Sulfuration of 1,2,3,4-Tetra-(4-pyridyl)-butane (V) to 2,3,4,5-Tetra-(4-pyridyl)-thiophene (IV).—A mixture of 1.44 g. of tetrapyridylbutane and 0.75 g. of sulfur was heated for two and one-half hours at 140–245° in a slow stream of nitrogen; 0.38 g. of hydrogen sulfide was collected in Ascarite and 0.31 g. of sulfur was recovered. The filtrate was made alkaline and 1.36 g. (89% yield) of tan-colored precipitate was filtered. Recrystallization from methanol gave pale-yellow crystals (m. p. 251.5–252.5°) whose melting point was not depressed by admixture with 2,3,4,5-tetra-(4-pyridyl)-thiophene (IV).

Anal. Calcd. for $C_{24}H_{16}N_4S$: C, 73.4; H, 4.1; N, 14.3; S, 8.2. Found: C, 73.7; H, 4.3; N, 14.6; S, 7.8.

Hydrogenation of 1,2-Di-(4-pyridyl)-ethane (I) to 1,2-Di-(4-piperidyl)-ethane (VI).—Dipyridylethane (114 g.) was hydrogenated in 300 cc. of cyclohexane at 135 atm. and 175–190° with nickel.[10] Distillation yielded 86 g. of material boiling at 125–130° (2 mm.) which solidified in the receiver. Crystallization from Skellysolve B–benzene (6:1) gave 68 g. of colorless crystals (m. p. 110–113.5°) which rapidly formed a carbonate on exposure to air. A recrystallized sample of carbonate-free material melted at 113–114°.

Anal. Calcd. for $C_{12}H_{24}N_2$: C, 73.4; H, 12.3; N, 14.3. Found: C, 73.4; H, 12.1; N, 14.3.

The hydrochloride (colorless powder, 96% yield) melted at 366–368° (dec.).

Anal. Calcd. for $C_{12}H_{24}N_2 \cdot 2HCl$: Cl, 26.3. Found: Cl, 26.0.

Hydrogenation of 1,2-Di-(4-pyridyl)-ethane (I) to Di-(N-ethyl-4-piperidyl)-ethane (VII).—Dipyridylethane (18 g.) was hydrogenated in ethanol at 90 atm. and 200–220° with nickel. The crude product (21 g.) boiled at 139–143° (1.5 mm.); redistilled product ($n^{20}D$ 1.4836, d^{20}_4 0.9005) boiled at 153–156° (3.5 mm.). The colorless liquid base formed a solid hydrate which dehydrated over phosphorus pentoxide. The hydrochloride was obtained in 91% yield, a white, hygroscopic powder.

Anal. Calcd. for $C_{16}H_{32}N_2 \cdot 2HCl$: Cl, 21.8. Found: Cl, 21.8.

The picrate, yellow needles from benzene, melted at 178.5–180°.

Anal. Calcd. for $C_{16}H_{32}N_2 \cdot 2C_6H_3N_3O_7$: C, 47.3; H, 5.4. Found: C, 47.7; H, 5.4.

Ethylation of 1,2-Di-(4-piperidyl)-ethane (VI).—An ethanol solution (25 cc.) of 5.9 g. of dipiperidylethane and 9.8 g. of ethyl iodide was refluxed for two and one-half hours. The solid (9.8 g.), which separated on standing overnight, was filtered and treated with 65 cc. of 4% potassium hydroxide. The mixture was ether extracted, and the solid recovered from the ether was shaken with benzenesulfonyl chloride in 10% caustic. The solid sulfonamide of the non-ethylated dipiperidylethane was filtered and the filtrate was ether extracted. Double distillation of the ether-soluble oil gave a heart-cut (b. p. 149–150° (2.5 mm.) $n^{20}D$ 1.4839) which formed a picrate (m. p. 178.5–180°) which showed no depression with the picrate of compound VII.

Anal. Calcd. for $C_{16}H_{32}N_2 \cdot 2C_6H_3N_3O_7$: C, 47.3; H, 5.4. Found: C, 47.0; H, 5.3.

Acknowledgment.—Thanks are expressed to J. E. Nickels, B. F. Tatterson, and J. J. McGovern for assistance in dehydrogenation, hydrogenation and spectroscopy, respectively, and to J. L. Keller for initiation of the early phases of the work.

Summary

1,2-Di-(4-pyridyl)-ethane, 1,2-di-(4-pyridyl)-ethylene, 1,2,3-tri-(4-pyridyl)-propane and 2,3,4,5-tetra-(4-pyridyl)-thiophene were obtained from the reaction of 4-picoline with sulfur, the product-distribution depending upon the conditions.

2,3,4,5-Tetra-(4-pyridyl)-thiophene was converted to 1,2,3,4-tetra-(4-pyridyl)-butane by reductive desulfurization.

1,2-Di-(4-pyridyl)-ethane and 1,2,3,4-tetra-(4-pyridyl)-butane reacted with sulfur to form 2,3,4,5-tetra-(4-pyridyl)-thiophene.

1,2-Di-(4-pyridyl)-ethane was hydrogenated in cyclohexane solution to 1,2-di-(4-piperidyl)-ethane, and in ethanol solution to 1,2-di-(N-ethyl-4-piperidyl)-ethane.

PITTSBURGH, PA. RECEIVED FEBRUARY 13, 1948

(9) Kearby, U. S. Patent 2,395,875 (1946).

(10) Ipatieff and Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Preparation of Some Polymerizable Esters of Long-Chain Saturated Aliphatic Acids with Unsaturated Alcohols

BY DANIEL SWERN AND E. F. JORDAN, JR.

If long-chain aliphatic compounds could be copolymerized with olefinic monomers of low molecular weight, the long chain would be chemically bound in the polymer molecule and the problems of exudation, evaporation and leaching of the modifying agent would be eliminated. The intramolecularly modified polymer would retain its original properties for a long time and perhaps for its entire period of use. By the proper selection of monomers and the relative proportions of low molecular weight olefinic monomer to fatty compound, a wide range of modified polymers could be obtained. The major obstacle, perhaps, to the preparation of such intramolecularly modified copolymers in the past has been the unavailability of pure long-chain compounds containing the necessary functional groups.

In a previous publication we described a series of polymerizable esters of oleic acid, and discussed briefly polymers obtained from some of them, as well as their copolymers with vinyl acetate.[2] The copolymers or intramolecularly modified polymers displayed a wide range of properties (hard, glass-like products to tough or soft rubber-like materials or viscous liquids), depending on the content of oleate ester. When only 1% of the more reactive and also the more promising oleate esters (vinyl, 2-chloroallyl, methallyl and allyl) were employed, insoluble hard, glass-like copolymers, which differed only slightly from unmodified polyvinyl acetate, were obtained. Since soluble, thermoplastic copolymers with a wide range of physical properties are of great industrial importance and their production is steadily increasing, we undertook the preparation of reactive monofunctional esters from long-chain, saturated aliphatic acids for use as intramolecular modifiers for low molecular weight olefinic monomers.

The purpose of the present paper is to describe the preparation and some of the physical properties of the vinyl, 2-chloroallyl, methallyl, allyl, 3-buten-2-yl, crotyl and furfuryl esters of caproic, caprylic, pelargonic, capric, lauric, myristic, palmitic and stearic acids, as well as to report briefly on the polymerization and copolymerization of some of the more reactive esters.

Examination of the literature revealed that some of the esters we wished to prepare had been described by earlier workers, primarily in patents and usually with little or no experimental details, and, in general, the products were incompletely characterized. Furthermore, in these publications no information regarding the purity of the starting materials or final products was given. Inasmuch as commercially available long-chain saturated fatty acids, which the earlier workers apparently employed, are not pure compounds and are almost invariably contaminated with unsaturated acids, it is highly probable that the products reported in the literature were impure and, more important, were not monofunctional. In preparing soluble, thermoplastic, intramolecularly modified copolymers of the type described earlier in this paper, the purity of the monomers, especially with respect to their functionality, is of the utmost importance. In fact, the difficulty experienced by earlier investigators in preparing soluble copolymers of high molecular weight in which one of the monomers is a long-chain compound, was undoubtedly due to the presence of polyfunctional impurities in the long-chain compound.

Vinyl esters of long-chain saturated aliphatic acids have been described in patents[3,4] and in a recent publication.[5] 2-Chloroallyl laurate[6] and stearate,[6] and the methallyl esters of long-chain acids from caprylic to stearic have also been reported in recent patents.[7] Allyl caproate,[8,9] pelargonate,[10] laurate,[11] palmitate[8,12] and stearate[12] have been described in several papers and patents. Furfuryl palmitate has been described in two publications.[13,14] No reference to the preparation or properties of crotyl and 3-buten-2-yl esters of long-chain fatty acids could be found.

The vinyl esters were prepared by the procedure of Toussaint and MacDowell.[4] The results are summarized in Table I. The vinyl esters were colorless, mobile liquids, with the exception of the palmitate and stearate, which were crystalline solids melting at 27 and 35°, respectively. They were insoluble in water and soluble in organic solvents. The short-chain esters had fruit-like odors and the long-chain esters were odorless.

When the purified vinyl esters were analyzed, low iodine and high saponification numbers were

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. This paper was presented at the meeting of the American Chemical Society held in Chicago, Ill., April 19–23, 1948.

(2) Swern, Billen and Knight, THIS JOURNAL, **69**, 2439 (1947).

(3) Reppe, German Patent 588,352 (1933); U. S. Patent 2,066,075 (1936).

(4) Toussaint and MacDowell, Jr., U. S. Patent 2,299,862 (1942).

(5) Powers, *Ind. Eng. Chem.*, **38**, 837 (1946).

(6) Coleman and Hadler, U. S. Patent 2,208,960 (1940).

(7) Price and Kapp, U. S. Patent 2,341,060 (1944); Brit. Patent 545,415 (1942).

(8) Golendeev, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1408 (1940).

(9) Moffett and Smith, U. S. Patent 2,390,164 (1945).

(10) Alekseeva and Isaev, *Masloboino-Zhurovaya Prom.*, **16**, No. 5/6, 54 (1940).

(11) Dean, U. S. Patent 2,374,081 (1945).

(12) Golendeev, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 1841 (1936).

(13) Tatiiri, *J. Chem. Soc. Japan*, **60**, 442 (1939).

(14) Norris and Terry, *Oil and Soap*, **21**, 193 (1944).

TABLE I

VINYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Iodine no.[b] Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	d^{30}_4	$n^{30}D$(Abbe)[c]	Molecular refraction Calcd.	Found
Caproate	40	98–99	100	178.5	173.1	67.57	67.53	9.92	9.87	0.8837	1.4159	40.33	40.38
Caprylate	55	134–135	100	149.1	144.3	70.56	70.21	10.66	10.60	.8719	1.4256	49.57	49.95
Pelargonate	55	133–133.5	50	137.8	136.0	71.69	71.94	10.94	11.19	.8689	1.4291	54.19	54.70
Caprate	45	148	50	128.0	125.6	72.68	72.60	11.18	11.38	.8670	1.4320	58.81	59.33
Laurate	55	142	10	112.2	110.5	74.30	74.36	11.58	11.84	.8639	1.4368	68.04	68.65
Myristate	60	147–148	4.8	99.8	97.9	75.53	75.22	11.88	11.93	.8617	1.4407	77.28	77.92
Palmitate[d]	35	168–169	4.5	89.8	87.7	76.53	76.74	12.13	12.21	.8602[e]	1.4438	86.51	87.18
Stearate[f]	30	187–188	4.3	81.7	79.4	77.36	77.58	12.34	12.46	.8517[g]	1.4423[g]	95.75	96.46

[a] Pure products after two to three distillations, with the exception of the stearate, which was purified by recrystallization of the once-distilled product from acetone. [b] One-hour Wijs method and a 200% excess of iodine chloride solution. [c] Δn per degree = −0.0004. [d] M. p. 26.7–27.1°. [e] d^{35}_4 0.8571. [f] M. p. 35–36°. [g] At 40°.

obtained.[2] The failure to obtain correct iodine numbers was attributed to the reduction in the rate of addition of iodine chloride to the double bond because of the effect of the electron-attracting acyloxy group in reducing the nucleophilic properties of the double bond.[15] Reasonably

$$R—CO_2 \leftarrow CH=CH_2$$

satisfactory iodine numbers (97 to 99%) (Table I) were obtained by allowing the iodine number determination to proceed for twenty-four hours or, preferably, by employing a 200% excess of Wijs solution and a one-hour reaction period. Since it was noticed that the saponification number increased as the reflux time was lengthened, the anomalous saponification number was attributed to the consumption of alkali by acetaldehyde, the tautomer of vinyl alcohol. The procedure finally employed consisted in a five-minute reflux period followed by rapid chilling of the sample in ice water and immediate titration. Fairly satisfactory results were obtained in this way (saponification numbers ranging from 95 to 105% of theoretical values), but difficulty was experienced in duplicating the analyses. For this reason saponification numbers are not listed in Table I.

Polymerization of the vinyl esters in the presence of 0.5% benzoyl peroxide as catalyst[16] yielded soft, elastic polymers, with the exception of polymerized vinyl palmitate and stearate, which were white wax-like solids.[3,17] The iodine numbers of the polymers were usually less than five, thus indicating fairly complete polymerization, although occasionally somewhat higher iodine numbers were obtained. The polymerized vinyl esters were thermoplastic. They were readily soluble in benzene and hot amyl acetate and, with the exception of polymerized vinyl caproate, insoluble or slightly soluble in acetone and glacial acetic acid, and insoluble in water.

Copolymerization of the vinyl esters with vinyl acetate or styrene[16] yielded products which ranged in physical appearance from hard and glass-like (low content of long-chain ester) to very soft and elastic (high content of long-chain ester), with the exception of the copolymers of vinyl stearate with vinyl acetate, which were hard wax-like solids at room temperature. The products containing styrene showed indications of incompatibility, particularly at high contents of long-chain esters. All the copolymers were thermoplastic and colorless, or slightly straw-yellow when styrene was a monomer. They were readily soluble in benzene and amyl acetate, and either slightly soluble or insoluble in acetone and acetic acid, particularly at high contents of long-chain esters. The copolymers were insoluble in water.

The wide range of physical properties attainable in copolymers containing vinyl esters of long-chain fatty acids suggests numerous potential uses for the products.[5,17,18] Furthermore, the polyvinyl esters themselves may be useful as modifying agents for other polymers, particularly where intramolecular modification is either not feasible or is undesirable.

The 2-chloroallyl esters were prepared by direct esterification of the alcohol with the appropriate acid, naphthalene-2-sulfonic acid being employed as catalyst and the water formed during the reaction being azeotropically removed.[2] The results are summarized in Table II. The esters, with the exception of 2-chloroallyl stearate, which decomposed extensively on heating to its boiling point, were isolated in 85 to 95% yields by vacuum distillation of the reaction mixture, and they were substantially pure without further treatment. On redistillation, 60 to 85% yields of pure esters were obtained. The stearate was purified by recrystallization to constant melting point from acetone. The 2-chloroallyl esters were colorless, mobile liquids, with the exception of the stearate, which was a crystalline solid. They were soluble in organic solvents and insoluble in water. The 2-chloroallyl esters were unstable, liberating hydrogen chloride rapidly at elevated temperatures and slowly at room temperature. Products stored for some time gradually became discolored and contained free hydrogen chloride.

(15) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943.

(16) Guile and Huston, "A Revised Laboratory Manual of Synthetic Plastics and Resinous Materials," Michigan State College. 1944, p. 99.

(17) Reppe, Starck and Voss, U. S. Patent 2,118,864 (1938).

(18) Fikentscher, Off. Tech. Serv. Report PB A 76327 (1937).

TABLE II

2-CHLOROALLYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	d^{30}_4	$n^{30}D$ (Abbe)[b]	Molecular refraction Calcd.	Molecular refraction Found
Caproate	75	80	4.5	56.74	56.90	7.93	7.88	1.0067	1.4389	49.82	49.81
Caprylate	80	107–107.5	4.7	60.40	60.61	8.77	9.05	0.9825	1.4431	59.05	59.00
Pelargonate	75	120	5	61.92	61.85	9.10	9.44	.9719	1.4447	63.67	63.76
Caprate	85	129	4.2	63.27	63.20	9.39	9.46	.9635	1.4458	68.29	68.30
Laurate	80	151–152	4.2	65.55	65.45	9.91	10.16	.9493	1.4484	77.52	77.64
Myristate	75	173	4.0	67.41	67.31	10.33	10.28	.9377	1.4505	86.76	86.75
Palmitate[c]	60	190–191	4.0	68.96	68.17	10.66	10.85	.9291[d]	1.4524	96.00	96.25
Stearate[e]	85	200–202 (dec.)	2	70.25	69.98	10.95	10.96	.9149[f]	1.4497[f]	105.2	105.3

[a] Pure products after two to three distillations with the exception of the stearate, which was purified by recrystallization from acetone. [b] Δn per degree = −0.0004. [c] M. p. 28–29°. [d] d^{40}_4 0.9216. [e] M. p. 36–37°. [f] At 40°. d^{45}_4 0.9112.

TABLE III

METHALLYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Sapon. equiv. Calcd.	Sapon. equiv. Found	Iodine no.[b] Calcd.	Iodine no.[b] Found	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	d^{30}_4	$n^{30}D$ (Abbe)[c]	Molecular refraction Calcd.	Molecular refraction Found
Caproate	55	135	100	170.2	170.6	149.1	150.1	70.56	70.40	10.66	10.70	0.8760	1.4250	49.57	49.68
Caprylate	45	147–148	50	198.3	198.6	128.0	129.1	72.68	73.00	11.18	11.20	.8703	1.4308	58.81	59.05
Pelargonate	40	163–164	50	212.3	213.1	119.4	119.8	73.54	73.79	11.35	11.44	.8684	1.4335	63.42	63.60
Caprate	50	175	50	226.3	227.2	112.2	113.1	74.30	74.52	11.58	11.64	.8665	1.4354	68.04	68.15
Laurate	40	165	10	254.4	255.7	99.8	99.4	75.53	75.65	11.88	11.86	.8638	1.4392	77.28	77.45
Myristate	35	164–165	4	282.5	283.1	89.8	90.5	76.53	76.75	12.13	12.36	.8617	1.4423	86.51	86.85
Palmitate	35	186–186.5	4	310.5	311.0	81.7	81.3	77.36	77.49	12.34	12.24	.8604	1.4450	95.75	96.16
Stearate[d]	40	204–205	4.6	338.6	339.2	75.0	76.0	78.03	78.45	12.51	12.73	.8593	1.4471	105.0	105.2

[a] Pure products after two distillations. [b] One hour Wijs method. [c] Δn per degree = −0.0004. [d] This compound solidified only after standing for several months at about 25°. M. p. 30.5–31°.

2-Chloroallyl caprate, myristate and stearate were converted to dark-yellow or brown viscous oils when polymerized in the presence of benzoyl peroxide as catalyst.[16] Copolymers of these esters with vinyl acetate were tough, elastic, colorless products when not more than 10% of long-chain ester was employed. As the proportions of 2-chloroallyl ester were increased, the products became darker and softer, and at the maximum content of long-chain ester (60%) they were yellow to brown viscous oils. The copolymers containing 40% of 2-chloroallyl caprate were readily soluble in hot acetone, acetic acid, amyl acetate and benzene. Those containing 40% of 2-chloroallyl myristate were slightly soluble in hot acetone and glacial acetic acid and readily soluble in the other solvents, and the copolymers containing 40% of 2-chloroallyl stearate were slightly soluble in amyl acetate, acetic acid and acetone but readily soluble in benzene.

Although it has been reported in the literature that methallyl esters of long-chain acids can be prepared by a direct esterification technique in which toluenesulfonic acid is employed as catalyst,[7] we observed that considerable isobutyraldehyde was obtained[19] and that the esters were difficult to purify. For these reasons, we employed the alcoholysis method previously described,[2] and had no difficulty in obtaining the pure esters in fair yields (35 to 55%) from the methyl esters of the acids and methallyl alcohol containing dissolved sodium. The results are summarized in Table III. The methallyl esters were colorless, mobile, stable liquids, insoluble in water and soluble in organic solvents.

Under the conditions employed in the polymerization of the vinyl and 2-chloroallyl esters, the methallyl esters of the long-chain acids showed little tendency to polymerize. This was demonstrated by the fact that the iodine numbers of the products after polymerization were only about 10% lower than those of the pure monomers In this respect they were similar to the methallyl esters of short-chain acids.[20] Copolymers containing methallyl esters were not prepared.

The allyl, 3-buten-2-yl and crotyl esters were prepared in 80 to 90%, 55 to 85% and 50 to 85% yields, respectively, by direct esterification of the acids with the alcohols, with naphthalene-2-sulfonic acid as catalyst, the water formed during the reaction being azeotropically removed.[2] We also prepared several of the crotyl esters by alcoholysis[2] of the methyl esters, but the yields were considerably lower than by the direct method. The results are summarized in Tables IV, V and VI. The physical properties of a given crotyl ester prepared by either esterification technique were identical, indicating that the acid catalyst did not cause isomerization of the crotyl portion of the molecule. The allyl, 3-buten-2-yl and crotyl esters were colorless, stable, mobile liquids with the exception of allyl stearate, which was a solid melting at 37°. They were insoluble in water and

(19) Hearne, Tamele and Converse, *Ind. Eng. Chem.*, **33**, 805 (1941).

(20) Ryan and Shaw, THIS JOURNAL, **62**, 3469 (1940).

TABLE IV

ALLYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Sapon. equiv. Calcd.	Found	Iodine no.[b] Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	d^{30}_4	$n^{30}D$ (Abbe)[c]	Molecular refraction Calcd.	Found
Caproate	80	92.5–93.0	30	156.2	156.4	162.4	161.7	69.19	69.07	10.32	10.28	0.8800	1.4200	44.95	44.93
Caprylate	80	87–88	5.5	184.3	183.7	137.7	137.5	71.69	72.00	10.94	10.79	.8729	1.4271	54.19	54.21
Pelargonate	85	151	50	198.3	198.2	128.0	128.3	72.68	72.80	11.18	11.33	.8702	1.4302	58.81	58.89
Caprate	90	113–114	5.2	212.3	211.8	119.4	118.8	73.54	73.60	11.35	11.03	.8684	1.4326	63.42	63.44
Laurate	90	136	4.5	240.4	239.8	105.6	105.3	74.95	74.71	11.74	11.53	.8648	1.4370	72.66	72.85
Myristate	90	157	4.3	268.4	267.0	94.5	94.7	76.06	75.58	12.02	11.89	.8627	1.4404	81.89	82.00
Palmitate	85	[d]		296.5	294.8	85.6	84.8	76.96	77.25	12.23	12.35	.8609[e]	1.4431	91.13	91.20
Stearate	85	[f]		324.5	323.7	78.2	78.6	77.72	77.71	12.42	12.29	.8524[g]	1.4420[g]	100.4	100.7

[a] Pure products after two distillations, with the exception of the palmitate and stearate, which were purified by recrystallization from acetone at −20° and 0°, respectively. [b] One hour Wijs method. [c] Δn per degree = −0.0004. [d] M. p. 25.3–25.5°. [e] d^{35}_4 0.8581. [f] M. p. 37.1–37.3°. [g] At 40°. d^{45}_4 0.8491.

TABLE V

3-BUTEN-2-YL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Sapon. equiv. Calcd.	Found	Iodine no.[b] Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	d^{30}_4	$n^{30}D$ (Abbe)[c]	Molecular refraction Calcd.	Found
Caproate	55	189	753	170.2	171.4	149.1	150.6	70.56	70.74	10.66	10.56	0.8644	1.4179	49.57	49.59
		123	99												
Caprylate	60	150	75	198.3	197.9	128.0	128.9	72.68	72.61	11.18	11.29	.8609	1.4251	58.81	58.93
Pelargonate	85	173	100	212.3	212.3	119.4	119.8	73.54	74.06	11.35	11.68	.8596	1.4280	63.42	63.63
Caprate	65	185–186	100	226.3	225.8	112.2	112.8	74.30	74.20	11.58	11.70	.8586	1.4308	68.04	68.28
Laurate	80	156–157	10	254.4	254.3	99.8	100.0	75.53	75.70	11.88	12.30	.8567	1.4350	77.28	77.55
Myristate	70	180	10	282.5	281.8	89.8	90.3	76.53	76.40	12.13	12.20	.8556	1.4384	86.51	86.77
Palmitate	70	180	4.3	310.5	310.0	81.7	81.9	77.36	77.34	12.34	12.39	.8546	1.4413	95.75	95.99
Stearate	65	199	4.2	338.6	338.8	75.0	75.7	78.03	77.80	12.51	12.20	.8538	1.4440	105.0	105.3

[a] Pure products after two to three distillations. [b] One hour Wijs method. [c] Δn per degree = −0.0004.

TABLE VI

CROTYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Sapon. equiv. Calcd.	Found	Iodine no.[b] Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	d^{30}_4	$n^{30}D$ (Abbe)[c]	Molecular refraction Calcd.	Found
Caproate	60	141	100	170.2	170.0	149.1	147.8	70.56	70.87	10.66	10.75	0.8789	1.4279	49.57	49.82
Caprylate	55	154–154.5	50	198.3	197.6	128.0	128.4	72.68	72.84	11.18	10.74	.8730	1.4335	58.81	59.08
	85[d]														
Pelargonate	85[d]	165	50	212.3	211.7	119.6	118.8	73.54	73.33	11.35	12.02	.8709	1.4358	63.43	63.70
Caprate	65	181	50	226.3	225.0	112.2	112.9	74.30	74.64	11.58	11.48	.8687	1.4378	68.04	68.36
Laurate	65	167–168	10	254.4	254.3	99.8	99.8	75.53	75.79	11.88	12.14	.8656	1.4411	77.28	77.62
Myristate	50	170	4.3	282.5	282.0	89.8	89.7	76.53	76.06	12.13	12.67	.8632	1.4442	86.51	86.94
Palmitate	70	188–189	3.8	310.5	310.1	81.7	81.4	77.36	77.70	12.34	12.28	.8616[e]	1.4466	95.75	96.20
Stearate[f]	35	209	4.5	338.6	337.3	75.0	75.2	78.03	77.96	12.51	12.51	.8566[g]	1.4467[g]	105.0	105.5
	85[d]														

[a] Pure products after two distillations. [b] One hour Wijs method. [c] Δn per degree = −0.0004. [d] Yield by direct esterification of crotyl alcohol with the fatty acid. All other yields in this table are for the alcoholysis reaction. [e] d^{35}_4 0.8581. [f] M. p. 30.5–31°. [g] At 35°.

soluble in organic solvents. The short-chain allyl esters had fruit-like odors, whereas the long-chain compounds were odorless.

The allyl esters also showed little tendency to polymerize when heated with 0.5% benzoyl peroxide as catalyst,[16] the iodine numbers of the products being only 10 to 20% lower than those of the corresponding monomers. Copolymers of the allyl esters with diallyl phthalate ranged from tough to soft colorless gels as the content of allyl ester was increased from 1 to 20%. These copolymers were insoluble in acetone, amyl acetate, benzene and acetic acid.

Because of the known lack of polymerizability of the 3-buten-2-yl and crotyl esters,[2] their polymers or copolymers were not prepared.

The furfuryl esters were obtained in only 30 to 50% yields by alcoholysis of the methyl esters of the long-chain acids with furfuryl alcohol containing dissolved sodium.[2] The results are summarized in Table VII. They were pale-yellow, mobile liquids, with the exception of the stearate, which was a solid melting at 41°. The furfuryl esters were insoluble in water and soluble in organic solvents. The stearate, isolated by distillation, was pale-yellow when molten. When recrystallized from acetone, it was a beautiful crystalline solid which was colorless when molten and had physical properties identical with those of the product purified by distillation alone, indicating that the discoloration of the products was caused by impurities present only in traces.

Experimental

All the reactions and distillations described were conducted in an atmosphere of nitrogen.

Starting Materials.—Pure caproic, caprylic, pelargonic and capric acids were prepared from the 90% commercial grades of these acids by repeated distillation under vacuum

TABLE VII

FURFURYL ESTERS OF SATURATED ALIPHATIC ACIDS

Ester	Yield,[a] %	Boiling point °C.	Mm.	Sapon. equiv. Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	d^{30}_4	$n^{30}D$ (Abbe)[b]	Molecular refraction Calcd.	Found
Caproate	50	149–150	50	196.2	194.1	67.32	66.98	8.22	8.13	1.005	1.4550	53.16	53.10
Caprylate	30	139	10	224.3	222.0	69.58	69.32	8.98	9.24	0.9789	1.4560	62.40	62.32
Pelargonate	40	151.5–153.0	10	238.3	236.0	70.55	70.29	9.31	8.87	.9637	1.4563	67.02	66.88
Caprate	35	167	10	252.3	251.0	71.40	71.08	9.58	9.58	.9600	1.4570	71.63	71.54
Laurate	35	167–168	3.8	280.4	279.1	72.84	72.11	10.07	10.15	.9462	1.4578	80.87	81.00
Myristate	40	187–187.5	3.9	308.5	306.9	74.00	73.85	10.46	10.64	.9352	1.4588	90.11	90.26
Palmitate	30	205–206	3.8	336.5	334.0	74.95	74.75	10.78	10.93	.9226[c]	1.4580[c]	99.34	99.70
Stearate[d]	35	211–213	2.5	364.6	363.2	75.76	75.31	11.06	10.52	.9086[e]	1.4549[e]	108.6	108.9

[a] Pure products after two distillations. [b] Δn per degree = −0.0004. [c] At 35°. [d] M. p. 40.7–41.4°. [e] At 45°.

through efficient fractionating columns. Pure lauric acid was prepared from the purest commercial grade by two recrystallizations from acetone (10 ml. of solvent per gram of solute) at −40°, followed by fractional distillation under vacuum. Pure myristic acid was similarly prepared, except that two crystallizations at −20° were employed. Pure palmitic acid was prepared by repeated crystallization of the purest commercial grade from acetone (10 ml. of solvent per gram of solute) at 0° until a constant melting point was obtained. Pure stearic acid was prepared by two recrystallizations from acetone at 0° of the fatty acids obtained from completely hydrogenated soybean oil. The methyl esters were prepared from the acids by refluxing them for six hours with a large molar excess (500%) of anhydrous methyl alcohol containing a small quantity (2% by weight of the acid) of 95% sulfuric acid as catalyst. The reaction mixture was poured with thorough mixing into a large quantity of warm water (40–50°) in a separatory funnel, and the lower aqueous layer was separated and discarded. The esters were washed with warm water until free of sulfuric acid and dried by heating to 100° under moderate vacuum in a stream of inert gas. They were then distilled under vacuum through an efficient fractionating column. The products employed in the reactions described had the theoretical neutralization or saponification equivalents, and their physical properties (m. p., b. p., and n_D [Abbe]) agreed with the best values reported in the literature.[21,22,23]

The unsaturated alcohols were distilled through efficient fractionating columns before use.

Vinyl acetate, styrene and diallyl phthalate, were obtained from the commercial grades by fractional distillation. These substances were used immediately after isolation.

Vinyl Esters.—The procedure of Toussaint and MacDowell[4] was employed. The yield of once-distilled ester was 50 to 70%, and upon redistillation in the presence of sufficient sodium bicarbonate to neutralize the small quantities of free acid which these esters usually contained, 30 to 60% yields of pure vinyl esters were obtained. Negligible residues were obtained on redistillation, with the exception of the distillations of vinyl palmitate and stearate, the two highest boiling vinyl esters prepared. Vinyl stearate was most conveniently purified by recrystallization of the once-distilled product from acetone (3 ml. of solvent per gram of solute) at 0°. It was a crystalline solid, and its physical properties and those of the product purified by redistillation were identical. The results are summarized in Table I.

2-Chloroallyl, Allyl, 3-Buten-2-yl and Crotyl Esters.—The azeotropic method previously described[2] was employed, and refluxing was continued until the theoretical quantity of water was evolved. In the preparation of the 3-buten-2-yl esters, eighteen to twenty-four hours of reflux time was usually required, whereas only three to six hours was required when the primary alcohols were employed. The esters were isolated from the reaction mixture by vacuum distillation, with the exception of allyl and 2-chloroallyl stearate and allyl palmitate, which were recrystallized to constant melting point from acetone (3 to 4 ml. of solvent per gram of solute) after recovery of the unreacted alcohol. Some of the crotyl esters were also prepared by the alcoholysis method,[2] but the yields were much lower than by the direct method. The results are summarized in Tables II, IV, V and VI.

Methallyl and Furfuryl Esters.—The alcoholysis method previously described was employed.[2] The results are summarized in Tables III and VII.

Polymerization of Vinyl, 2-Chloroallyl, Methallyl and Allyl Esters.—Approximately 5-ml. portions of the freshly distilled esters were weighed into test-tubes, 0.5% by weight of benzoyl peroxide was added and the polymerizations were conducted in a thermostatically controlled oven.[15] Solubilities were determined in benzene, acetone, glacial acetic acid and amyl acetate at room temperature, and in the case of those solvents in which the polymers were insoluble, also at 100° or at the boiling point, whichever was reached first. The results obtained have been discussed earlier in the manuscript.

Copolymerization of Vinyl, 2-Chloroallyl and Allyl Esters.—The vinyl esters were copolymerized[16] with vinyl acetate and also with styrene, the 2-chloroallyl esters with vinyl acetate only, and the allyl esters with diallyl phthalate. Benzoyl peroxide (0.5% on a total monomer basis) was employed as catalyst. When vinyl acetate was employed as a monomer, copolymers were prepared containing from 1 to 60% of long-chain ester, on a total monomer basis. When styrene and diallyl phthalate were employed as monomers, copolymers were prepared containing a maximum content of long-chain ester of 40 and 20%, respectively.

Acknowledgment.—We are indebted to C. L. Ogg and associates for the carbon and hydrogen analyses, to Geraldine N. Billen for some of the density and refractive index determinations, and to R. E. Koos for most of the iodine number and saponification equivalent determinations.

Summary

Vinyl, 2-chloroallyl, methallyl, allyl, 3-buten-2-yl, crotyl and furfuryl esters of caproic, caprylic, pelargonic, capric, lauric, myristic, palmitic and stearic acids have been prepared, and some of their properties have been determined. Modified procedures for the determination of the iodine and saponification numbers of the vinyl esters are described.

The polymerization of the vinyl, 2-chloroallyl, methallyl and allyl esters, with benzoyl peroxide as catalyst, has been studied briefly. The polymerized vinyl esters are soft, colorless, elastic masses, with the exception of polymerized vinyl palmitate and vinyl stearate, which are white, wax-like solids. The polymerized 2-chloroallyl es-

(21) Dorinson, McCorkle and Ralston, THIS JOURNAL, **64**, 2739 (1942).

(22) Pool and Ralston, *Ind. Eng. Chem.*, **34**, 1104 (1942).

(23) Markley, "Fatty Acids," published by Interscience Publishers, Inc., New York, N. Y., 1947.

ters are dark-yellow or brown viscous oils. The methallyl and allyl esters display little tendency to polymerize.

The vinyl esters have been copolymerized with vinyl acetate and also with styrene, the 2-chloroallyl esters with vinyl acetate only and the allyl esters with diallyl phthalate. The wide range of properties attainable in the copolymers suggests numerous potential uses for the products.

PHILADELPHIA 18, PA. RECEIVED JANUARY 22, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY, SECTION OF MATHEMATICAL BIOPHYSICS, UNIVERSITY OF CHICAGO, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Equilibrium Equations for a Model of Antibody–Antigen Combination

BY MANUEL F. MORALES, JEAN BOTTS AND TERRELL L. HILL

Application of statistical procedures to models of antibody–antigen combination yields expressions involving certain thermodynamic constants of the equilibrium; such expressions enable the calculation of these constants from conventional measurements, and may therefore be of interest. We wish to present here certain relations of this sort based on a useful model proposed recently by Teorell.[1,2,3]

In Teorell's model, antibody (A) is assumed univalent,[4] and antigen (G) is assumed n-valent; the aggregate compounds have therefore the formulas, A_iG, and the equilibrium is formally similar to that of ampholyte dissociation[5]

$$\left.\begin{aligned} A + A_{i-1}G &\rightleftarrows A_iG \\ K_i &= [A_iG]/[A][A_{i-1}G] \end{aligned}\right\} \quad i = 1, 2, \ldots, n \qquad (1)$$

We shall assume in what follows that the total concentrations of antibody and antigen, A_0 and G_0, respectively, are known experimentally. Deferring until later a discussion of the matter, we shall also suppose that the concentration ratio of total bound antibody to total bound antigen in the initial solution

$$R = \sum_{i=1}^{i=n} i[A_iG] / \sum_{i=1}^{i=n} [A_iG]$$

is measurable (actually this ratio is measurable only in the precipitate which subsequently forms). Clearly, $\lim_{A_0 \to \infty} R = n$, the antigen valence. In certain cases it will be further required to know the amounts of bound A and G. Various assumptions regarding the aggregation will now be considered separately.

I. The reactivity of a vacant reactive site on the surface of an A–G aggregate is assumed to be completely independent of the remainder of the structure on which it exists. In this case it may be shown that

$$R = \frac{K_1[A](1 + K_1[A]/n)^{n-1}}{(1 + K_1[A]/n)^n - 1} \qquad (2)$$

If A_0 and G_0 be given special values, A_0' and G_0' such that [A] becomes equal to n/K_1, then R takes on a special value, $R' = (n/2)/(1 - 1/2^n)$, which is very nearly $n/2$ for $n \geqq 4$. Conversely, one may vary A_0 and G_0 experimentally until R becomes, say, $n/2$; at that point [A] equals n/K_1, and one may also show that on this account

$$K_1 = n/(A_0' - R'G_0') \qquad (3)$$

K_1 is thus obtainable from the usual concentration measurements. All other equilibrium constants are derivable from K_1 by means of the formula

$$K_i = (K_1/n)(n - i + 1)/i \qquad (4)$$

II. The antibody molecules on the surface of the same antigen are assumed to attract or repel one another. It is assumed (rather reasonably) that these interactions can be represented as an A–A bond energy, E_{AA}, and that they operate only between nearest neighbor molecules. To treat this case one must make specific assumptions about the surface lattice formed by the reactive sites on the antigen. We shall here consider three such lattices, corresponding to the contact points on any sphere[6] in the (a) hexagonal closest packing of spheres, (b) cubic closest packing of spheres, and (c) simple cubic packing of spheres. In this case we have

$$R = \frac{\sum_{i=1}^{i=n} \sum_{p} i(K_1[A]/n)^i W_i^{(p)} \exp(-pE_{AA}/kT)}{\sum_{i=1}^{i=n} \sum_{p} (K_1[A]/n)^i W_i^{(p)} \exp(-pE_{AA}/kT)} \qquad (5)$$

where, for a given lattice, $W_i^{(p)}$ is the number of microscopically different ways in which i antibody molecules may be placed on an antigen molecule in such a manner that among the antibody molecules there will be p nearest neighbor pairs. The calculation of the $W_i^{(p)}$ is considered elsewhere.[7]

(1) Teorell, *Nature*, **151**, 696 (1943).

(2) Teorell, *J. Hyg.*, **44**, 227 (1946).

(3) Teorell, *ibid.*, **44**, 237 (1946).

(4) The unsettled rivalry between this model, which goes back to the concepts of Bordet, and the framework model proposed independently by Marrack and Heidelberger and later greatly elaborated by Pauling (THIS JOURNAL, **62**, 2643 (1940)) is acknowledged. The same methods here used, however, appear applicable to the latter case, although with more difficulty.

(5) Analogs to our cases I and II below have been given for ampholyte dissociation by Kirkwood in Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, pp. 290–294. The specific model treated, however, is quite different.

(6) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.

(7) Morales and Botts, *J. Chem. Phys.*, **16**, 587 (1948).

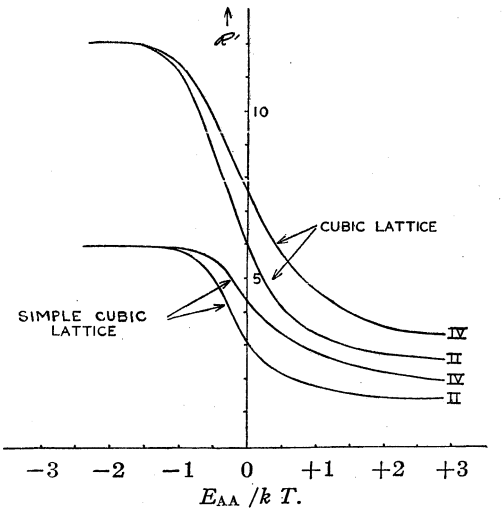


Fig. 1.—Critical value of R as a function of E_{AA}/kT, for two different lattices and for two degrees of approximation (cases II and IV of the text).

Suffice to say here that the value of R, *viz.*, R', at which $K_1 = n/(A_0' - R'G_0')$ is now no longer $n/2$, but depends also upon E_{AA}. Once E_{AA} is known, as from colligative property measurements on concentrated solutions of pure antibody, then R' is calculable (see, for example, Fig. 1, curves II). The relation between the K_i and K_1 is given by

$$K_i = \frac{K_1 \sum_p W_i^{(p)} \exp(-pE_{AA}/kT)}{n \sum_p W_{i-1}^{(p)} \exp(-pE_{AA}/kT)} \quad (6)$$

III. A and G are assumed to be spherical molecules of approximately the same mass and radius, and the moment of inertia of A_iG is assumed to be the same as that of an equivalent sphere having the aggregate mass and volume of $i + 1$ molecules. The inclusion now demanded of the translational and rotational effects upon the equilibrium can only be done very approximately, employing gas-type partition functions, but the results have some comparative value over those derived in section I. One finds that

$$R = \frac{Q(Q+1)^4(1 + K_1[A]/16n)^n}{(Q+1)^4(1 + K_1[A]/16n)^n - 1} \quad (7)$$

where Q^k stands for the operation, $\partial/\partial \log[A]$. In this case $K_1 = 16n/[A]$ when R takes on a definite value $R'(n)$ readily calculable from (7). However, it will in general be required to measure [A] at this point (as distinct from simply knowing A_0). The formula for K_i is

$$K_i = (K_1/16n)[(i+1)/i]^4(n - i + 1)/i \quad (8)$$

IV. The conditions in II and III above are to be combined. For this case

$$R' = \frac{\sum_{i=1}^{i=n} i(i+1)^4 \sum_p W_i^{(p)} \exp(-pE_{AA}/kT)}{\sum_{i=1}^{i=n} (i+1)^4 \sum_p W_i^{(p)} \exp(-pE_{AA}/kT)} \quad (9)$$

the value of R when $K_1 = 16n/[A]$, can be plotted for a given lattice (Fig. 1, curves IV) as a function of E_{AA}. It is, as in Case III, required to know [A] experimentally. For K_i we have

$$K_i = (K_1/16n)[(i+1)/i]^4 \frac{\sum_p W_i^{(p)} \exp(-pE_{AA}/kT)}{\sum_p W_{i-1}^{(p)} \exp(-pE_{AA}/kT)} \quad (10)$$

In the foregoing cases, I–IV, we have considered varying degrees of approximation to the description of the equilibrium (1) presumably in the *solution* phase; however, we have already indicated that total amounts, ratios, etc., are actually measured in the precipitate which appears upon completion of the "secondary reaction" or flocculation, this secondary reaction customarily being aided by the application of a centrifugal field. It is now necessary to discuss the relation between the solution composition (as described by the equations above) and the precipitate composition. The simplest hypothesis of all, and the one with which we will content ourselves for the present, is to assume (as have Teorell and others) that $[A_iG]_{sol'n.} = [A_iG]_{ppt.}$ Rash as this may sound, it is nevertheless possible to imagine situations in which it may be approximately true. On the basis of a monovalent antibody the qualitative reason for the insolubility of the A-G aggregates (compared to A and G) is ascribed to the occlusion[8] by A-G bond formation of sites which ordinarily would interact strongly with the solvent, and confer an appreciable solubility on the molecule. If we suppose that the "primary" reaction (1) reaches equilibrium and then a precipitating condition (*e. g.*, centrifugation or flocculation by quite a different mechanism) is *suddenly* applied, one would obtain

$$R_{ppt} = \frac{\sum_i i\{[A_iG]_{sol'n.} - [A_iG]_{sat.}\}}{\sum_i \{[A_iG]_{sol'n.} - [A_iG]_{sat.}\}} \quad (11)$$

where $[A_iG]_{sat.}$ is the molar solubility of the A_iG aggregate in the presence of the suddenly applied condition. If, in particular, all $[A_iG]_{sat.}$ are near zero,[9] then we are left with the R dealt with in cases I–IV. Quite a different justification for the assumption $[A_iG]_{sol'n.} = [A_iG]_{ppt.}$ has been suggested by Teorell,[2] namely, that molecules of the size and nature (number of reactive sites) involved here may, as it were, be "precipitated in part" or, more specifically, that sites on the structure which have not reacted may participate in the solution equilibrium; the fact that certain enzymes (*e. g.*, beef catalase) when acting as antigens can catalyze their specific reaction even after having been pre-

(8) Boyd, "Fundamentals of Immunology," Interscience Publishers, New York, N. Y., 1947.

(9) This restriction may be lightened by developing approximate expressions for $[A_iG]_{sat.}$ based on Meyer's solubility equation (see Mark, "The Physical Chemistry of High Polymeric Systems," Interscience Publishers, New York, N. Y., 1940, p. 249).

cipitated in A-G form is cited by him as indicating the plausibility of the phenomenon. It is certainly true that neither of the two foregoing arguments is thoroughly convincing, and the assumption must be regarded as provisional, even though the experimental comparison of equations based upon it is quite encouraging.[8] Probably the most satisfactory treatment would be to introduce definite solubilities for the aggregate molecules and treat the solution–precipitate equilibrium in the standard way. This has been done for the restricted case of bivalent antibody and bivalent antigen (corresponding, so far as mechanical considerations are concerned, to our case I) by Pauling, *et al.*[10] It can also be done, although with considerable awkwardness, for the present cases.

So long as the numerical values are not taken too literally but viewed, rather, in a comparative sense, it may be of some interest in closing to examine numerically the effect on the equilibrium constants of including the perturbations of cases II, III, and IV. Previous treatments (corresponding to case I) do not appear to have included them, or, when allowing for perturbations of any sort, have not specified how they can be calculated. Let us consider, for example, a system where A and G are spherical molecules of molecular weight, 100,000 g., and radius, 75 Å., the temperature is 37°, and the surface lattice of reactive sites on G is the hexavalent lattice, (c). To estimate the effect of translation and rotation we may compare the results of case I with those of case III. By the method of case I the K_1 are determined only up to a multiplicative constant (involving the translational and rotational factors) which is supposed to be independent of i. This is also clearly the case in ordinary thermodynamic formulations and in so-called "kinetic" derivations, wherein no method is provided for calculating the proportionality constant on the basis of mechanical information about the reactant molecules. Actually, as a result of translation and rotation and A-A interactions (cases II–IV), the "constant" does depend on i. Since we cannot compute the absolute value of $K_i^{(I)}$, we cannot examine the effect (say, translation and rotation) of this dependence upon the ratio, $K_i^{(I)}/K_i^{(III)}$; however, we may consider instead the function $(K_1^{(III)}/K_6^{(III)})/(K_1^{(I)}/K_6^{(I)})$, in which the proportionality "constant" does not appear, and which, if translational–rotational effects are negligible, should be unity. Actually, it turns out to be about 8.7 in this example. The effect of even very slight A-A interactions can be estimated by a comparison of case I and case II.[7] Assuming a repulsion, $E_{AA} = +kT$, one finds $K_1^{(I)}/K_1^{(II)} = 1$, $K_3^{(I)}/K_3^{(II)} = 4.9$, and $K_6^{(I)}/K_6^{(II)} = 328$, again emphasizing that such interactions are not to be disregarded. Still a third instructive computation is an estimate of the absolute value of the equilibrium constants and therefore of the standard free energy change per reaction site. (This is admittedly quite rough, because the system for which a good value of ΔH has been measured does not conform too well with our particular numerical example.) Using a hemocyanin as an antigen and horse antibody, Boyd, *et al.*,[11] found the ΔH (or what we shall here assume as equivalent, ΔE) per site to be about $-40{,}000$ cal. This leads[12] to a $K_1^{(III)}$ value of 1.18×10^8 li. mole^{-1}, and a ΔF_1° of $-11{,}400$ cal. Assuming that an A–G bond is really the composite of several "weak" bonds of bond energy *ca.* 5,000 cal.,[6] one finds for our example a free energy change per individual weak bond of about -1400 cal., which is not an unreasonable value.

The authors are indebted to Professors Linus Pauling and William C. Boyd for criticisms helpful in the preparation of this manuscript.

Summary

Assuming a polyvalent antigen and a monovalent antibody, there are derived by conventional statistical methods certain relations between measurable concentrations of the reactants and the dissociation constants characterizing the equilibrium. From these relations it is possible to calculate the constants, given the appropriate concentration data. This is done for various assumptions regarding the nature of the reaction. Rough estimates made on the basis of existing information suggest that certain perturbations of the equilibrium, such as the interaction between nearest neighbor antibody molecules on the same antigen molecule or the effects of translation and rotation, may not be negligible as usually has been assumed in the past.

CHICAGO, ILL.
ROCHESTER, N. Y. RECEIVED FEBRUARY 24, 1948

(10) Pauling, *et al.*, THIS JOURNAL, **64**, 3003 (1942).

(11) Boyd, *et al.*, *J. Biol. Chem.*, **139**, 787 (1941).

(12) Under the assumptions of case III, the absolute expression for K_1 is

$$K_1 = \frac{2^4 N_0 n e^{-E_{AG}/kT}}{(2\pi mkT/h^2)^{3/2}(8\pi^2 ma^2 kT/h^2)^{3/2}\sqrt{\pi}}$$

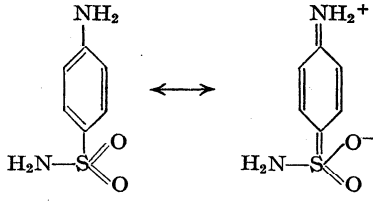
where N_0 is the Avogadro number, m the mass, k the Boltzmann constant, T the absolute temperature, h the Planck constant, and a the radius of the molecule.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

The Fine Structure of Sulfanilamide

BY A. WEIZMANN

The physical properties of sulfanilamide (its solubility, low in non-polar, and high in polar solvents, its absorption spectrum,[1] its high electric moment[2]) may be explained by the assumption of a charged structure contributing to the actual state of the molecule. The possibility that S=O double bonds participate in such resonating systems as



has, however, been doubted occasionally on the strength of the hypothesis that S=O is not a real double bond, but a "semipolar" bond system.[3]

A decision appeared possible by the application of a method first used by Birtles and Hampson[4] in the case of 4-nitroaniline. If the high dipole moment of sulfanilamide is due to a contributing charged structure, ortho-substituents bulky enough to prevent the necessary monoplanar arrangement of the substituents of the double bond, should make the charged form incapable of existence and should, therefore, reduce the electric moment.

2,3,5,6-Tetramethylsulfanilamide has, indeed, a lower moment (5.3 ± 0.8) than the parent substance (6.63). According to Kumler and Halverstadt[2] the theoretical value for the moment of sulfanilamide (and, of course, its tetramethyl derivative), should be 5.82, if the classical formula is correct.

For the sake of comparison, it is interesting to note that in contradistinction with the behavior of sulfanilamide, the moments of methyl 2,3,5,6-tetramethylbenzoate (2.6 ± 0.4) and 2,3,5,6-tetramethylphenylurethan (3.1 ± 0.8 in benzene; 3.2 ± 0.4 in dioxane) are somewhat higher than those of the parent substances, methyl benzoate (1.9 ± 0.5)[5] and phenylurethan (2.56 ± 0.03), respectively. The reason for this phenomenon is obscure; in neither case a significant contribution of a charged form is to be expected; in the latter, the acylation of the amino-group prevents its participation in such a formula.[6]

Some preliminary observations on the biological activity of tetramethyl-sulfanilamide may be of interest.[7] The substance showed no bactericidal or bacteriostatic action *in vitro*, perhaps due to its low solubility in water. *In vivo*, however, it showed approximately the same activity as sulfaguanidine, especially against gram-negative bacteria.

Experimental

Durene was prepared according to v. Braun and Nelles[8] and aminodurene according to Willstätter and Kubli,[9] who also described briefly the **N-acetyl derivative** (m. p. 207°). If in its preparation (5 g. of aminodurene, 15 cc. of acetic anhydride on the water-bath for thirty minutes; cooling; filtration; recrystallization from glacial acetic acid) the reaction mixture is heated to the boiling point, the **N,N-diacetyl derivative**, m. p. 137°, is formed.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2. Found: C, 72.0; H, 8.3.

By treatment with the theoretical amount of 15% methanolic potassium hydroxide solution (two hours), one acetyl group is split off.

The N-Acetyl-2,3,5,6-tetramethylaminobenzenesulfonamide.—N-Acetylaminodurene (0.9 g.) was added slowly to chlorosulfonic acid (10 g.) at 10–15°. The reaction was completed at 55–60° (ninety minutes) and the product poured on ice, filtered, washed with water and boiled for ten minutes with 15% aqueous ammonia; from glacial acetic acid, m. p. 262°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.3; H, 6.7. Found: C, 53.6; H, 6.7.

Boiling 15% aqueous potassium hydroxide, 10% alcoholic potassium hydroxide solution or 10% alcoholic hydrochloric acid left the substance unattacked; the last-mentioned reagent at 180° gave aminodurene, m. p. 75°.

For the synthesis of tetramethylsulfanilamide, the following route proved more successful:

N-Carbethoxyaminodurene (2,3,5,6-tetramethylphenylurethan).—To a well-agitated mixture of aminodurene (1 g.), sodium carbonate (0.53 g.) and benzene (15 cc.), ethyl chlorocarbonate (2 g.) was added at room temperature. The reaction was completed at 80° (ten minutes) and the reaction product recrystallized successively from dilute acetic acid and benzene or petroleum ether. It formed needles of m. p. 154–155°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.6; H, 8.6. Found: C, 70.8; H, 8.8.

N-Carbethoxy-2,3,5,6-tetramethylaminobenzenesulfonamide.—The preceding substance (0.5 g.) was added slowly with agitation and cooling (0°) to chlorosulfonic acid (10 cc.). After thirty minutes at room temperature, the product was poured on ice, and the waxy solid filtered, washed with ice water and boiled for five minutes with 15% aqueous ammonia. It crystallized from 50% acetic acid in platelets, m. p. 225° (dec. 230°); yield, 61%.

Anal. Calcd. for $C_{13}H_{20}O_4N_2S$: C, 52.0; H, 6.7. Found: C, 52.0; H, 6.6.

2,3,5,6-Tetramethyl-aminobenzenesulfonamide.—The N-carbethoxy- compound was hydrolyzed with boiling

(1) Kumler and Strait, THIS JOURNAL, **65**, 2349 (1943); Kumler, *ibid.*, **68**, 1184 (1946). See also Halverstadt and Kumler, *ibid.*, **63**, 624 (1941); Kumler and Daniels, *ibid.*, **65**, 2190 (1943).

(2) Kumler and Halverstadt, *ibid.*, **63**, 2182 (1942).

(3) See, *e. g.*, Arndt and Martius, *Ann.*, **499**, 228 (1932).

(4) Birtles and Hampson, *J. Chem. Soc.*, 10 (1937).

(5) Previous values: 2.06, 1.8, 1.91, 1.83, 1.9 (*Trans. Faraday Soc.*, **30**, LI (1934)). See also Halverstadt and Kumler, THIS JOURNAL, **64**, 2988 (1943).

(6) Prof. Norman R. Jones has also found some unexpected features in the absorption spectra of the above substances. He will report on his findings independently.

(7) Thanks are due for these data to Dr. Olitzki of the Department of Hygiene, Hebrew University, Jerusalem.

(8) v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).

(9) Willstätter and Kubli, *ibid.*, **42**, 4151 (1909).

c	δ	ϵ	n^2	P	$P_{E^1/2}$	$\overline{P}$	$\overline{P}_E$	$\overline{P}_{A+O}$
(1) Methyl benzoate in benzene; t = 26.0°								
0	0.8744	2.2700	2.2231	26.629	25.834	....	...	....
0.0148	.8788	2.3115	2.2237	27.297	25.996	78.11	36.81	41.30
.0251	.8818	2.4270	2.2243	29.042	26.113	126.62	36.97	89.65
.0312	.8836	2.5131	2.2261	30.286	26.203	146.92	37.68	109.24
$\overline{P}_{A+O}$ (average) = 80.06; μ = 1.9 ± 0.5								
(2) Methyl 2,3,5,6-tetramethylbenzoate in benzene; t = 26.5°								
0	0.8716	2.2690	2.2228	26.596	25.916	....	...	....
0.0060	.8737	2.3138	2.2238	27.430	26.088	173.24	54.78	118.56
.0076	.8743	2.3392	2.2240	27.844	26.148	187.21	55.77	131.44
.0123	.8759	2.4331	2.2249	29.307	26.279	247.36	55.48	191.88
$\overline{P}_{A+O}$ (average) = 147.29; μ = 2.6 ± 0.4								
(3) 2,3,5,6-Tetramethylsulfanilamide in dioxane; t = 35.0°								
0	1.0248	2.2290	2.0079	24.930	21.567	....	...	....
0.0017	1.0279	2.2792	2.0087	25.658	21.597	450.66	39.11	411.55
.0024	1.0288	2.3288	2.0096	26.368	21.620	626.60	43.74	582.76
.0031	1.0297	2.3861	2.0107	27.141	21.642	742.79	45.92	696.87
$\overline{P}_{A+O}$ (average) = 563.76; μ = 5.3 ± 0.8								
(4) Phenylurethan in benzene; t = 26.8°								
0	0.8710	2.2684	2.2201	26.615	25.889	....	...	....
0.0068	.8734	2.3204	2.2225	27.498	26.049	157.24	23.67	133.57
.0097	.8745	2.3342	2.2231	27.750	26.109	149.99	22.75	127.24
.0156	.8766	2.3910	2.2238	28.678	26.225	129.20	21.59	137.61
$\overline{P}_{A+O}$ (average) = 132.81; μ = 2.56 ± 0.03								
(5) 2,3,5,6-Tetramethylphenylurethan in benzene; t = 35.0°								
0	0.8619	2.2720	2.2171	26.950	26.117	....	...	....
0.0045	.8662	2.3041	2.2177	27.509	26.211	151.73	47.10	104.63
.0060	.8676	2.3569	2.2183	28.303	26.248	253.20	48.02	205.18
.0088	.8703	2.4430	2.2189	29.581	26.312	324.91	48.20	276.71
$\overline{P}_{A+O}$ (average) = 195.51; μ = 3.1 ± 0.8								
(6) 2,3,5,6-Tetramethylphenylurethane in dioxane; t = 35.0°								
0	1.0366	2.2310	2.0079	24.695	21.351	....	...	....
0.0055	1.0368	2.2935	2.0116	25.785	21.583	223.60	63.69	159.91
.0069	1.0369	2.3529	2.0133	26.652	21.653	308.32	65.12	243.20
.0090	1.0370	2.3711	2.0161	26.964	21.760	277.93	67.00	210.93
P_{A+O} (average) = 204.68; μ = 3.2 ± 0.4								

15% aqueous sodium hydroxide solution (forty-five minutes), the solution carefully neutralized with acetic acid and the product recrystallized from 50% alcohol. It formed needles of m. p. 177–178°.

Anal. Calcd. for $C_{10}H_{16}O_2N_2S$: C, 52.6; H, 7.0; N, 12.3. Found: C, 52.5; H, 7.2; N, 12.4.

2,3,5,6-Tetramethylbenzoic Acid.—The Grignard compound, prepared from bromodurene (10 g.) and magnesium (10 g.) in ether–benzene (75 and 30 cc.), was treated with dry gaseous carbon dioxide. The acid was recrystallized from dilute alcohol and had m. p. 178°; yield, 50%.[10] The **methyl ester**, from the acid (0.4 g.) and dimethyl sulfate (2.5 g.) at room temperature, was best purified by sublimation *in vacuo* (100–110° (25 mm.)). It formed prismatic plates of m. p. 60–61°.[11]

(10) Beilstein, Vol. IX, p. 564.

Measurements

c = concentration; δ = density; ϵ = dielectric constant; n = refractive index; $P^1/_2$ = total polarization of the solution, $P_{E^1/_2}$ = electron polarization of the solution; $\overline{P}$,$\overline{P}_E$ = the same for the solute; $\overline{P}_{A+O}$ = atomic and orientation polarization for the solute.

REHOVOTH, ISRAEL RECEIVED OCTOBER 27, 1947

(11) Jacobson, *Ber.*, **22**, 1223 (1889); Meyer and Woehler, *ibid.*, **29**, 2572 (1896).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Study of the Exchange of Nickel in Certain Complex Compounds Using Radioactive Nickel[1]

BY J. ENOCH JOHNSON[2] AND NORRIS F. HALL

In general, it has been found that exchange of the central atom in a complex ion or compound proceeds rapidly only when the bonds present approach ionic rather than covalent character. This has been assumed by many investigators (*e. g.*, Steigman[3]) to be the basis of the success of the Szilard–Chalmers method of concentrating radioactive isotopes. Certain exceptional cases have been discussed by Seaborg[4] and others[5] but in the majority of cases a satisfactory correlation has been demonstrated between exchange data and other types of evidence for covalent bonds. Magnetic susceptibility, interpreted in the light of quantum theory by Pauling,[6] gives evidence of bond type for complexes whose central atom can undergo a redistribution of electrons in changing from ionic or weak covalent bonds to strong covalent bonds. In certain 4-coördinated complexes,[7] X-ray data have definitely indicated covalent bonding by demonstrating a square planar arrangement of the coördinated groups.

Nickel forms a number of complex compounds and ions of the coördination type. Pauling pointed out that it is possible by pairing up all the electrons in the 3d shell of the nickel ion to obtain strong covalent (sp^2d) bonds resulting in a square planar structure, in contrast to the tetrahedral structure of weak covalent (sp^3) bonds. In the planar structure the nickel atom should be diamagnetic rather than paramagnetic as in the weak covalent tetrahedral structure and the simple nickel ion. A number of 4-coördinated nickel compounds have been found to be diamagnetic and X-ray examination has shown such diamagnetic nickel compounds to have a planar structure. Sugden[8] has prepared two diamagnetic geometrical isomers of nickel derivatives of several unsymmetrical glyoximes, which can be explained by assuming a planar structure.

Nickel also forms 6-coördinated complex ions such as $(Ni\ dipyridyl_3)^{++}$, some of which have been separated into optical isomers. Where optical resolution of coördination complexes has been demonstrated, strong covalent bonding is generally assumed.[9] According to the Pauling theory, the magnetic susceptibility of the nickel atom in 6-coördinated nickel complexes can give no evidence of covalency, because in either case there would be two unpaired electrons.

Due to these considerations, it was expected that exchange studies would show no exchange of simple nickel ions with 4-coördinated nickel compounds for which strong covalent bonds are indicated by magnetic susceptibility, X-ray examination and demonstration of geometrical isomers. Also 6-coördinated complex nickel ions for which strong covalent bonds are indicated by resolution of optical isomers should not show exchange with simple nickel ions. Nickel complexes having predominantly ionic or weak covalent bonds were expected to exhibit interchange of the nickel atoms.

Experimental

Preparation of Compounds.—The nickel complex compounds were prepared by procedures described in the literature references cited in footnotes to Table I. These compounds were analyzed for nickel by the gravimetric dimethylglyoxime method. The analytical results are given in Table I.

Radioactive Nickel.—The radioactive nickel (Ni^{65}, 2.6 hour half-life) used in this investigation was obtained by neutron bombardment of metallic zinc, nickel or an aqueous suspension of nickel dimethylglyoxime containing a little nickel chloride. The neutrons were produced by the bombardment of lithium or beryllium by deuterons accelerated by the voltage gradient supplied by an electrostatic generator in the University of Wisconsin physics department. Best results were obtained by bombarding metallic zinc with (Li + D) neutrons.

The irradiated metallic zinc was dissolved in hydrochloric acid and filtered. The residue was dissolved in perchloric acid and a little cupric chloride and nickel chloride added to the combined solutions. The nickel was precipitated by the addition of dimethylglyoxime and sodium acetate. The precipitate was dissolved in nitric acid–hydrochloric acid mixture (1:4) and evaporated to dryness to obtain the nickel chloride. This was taken up in water, neutralized with aqueous ammonia and diluted to give the desired concentration of nickel chloride. Alternatively, the metallic zinc was dissolved in nitric acid and the nitric acid removed by evaporating with hydrochloric acid before precipitating the nickel with dimethyl glyoxime.

Acetone, methyl cellosolve and ethyl cellosolve solutions of radioactive nickel perchlorate were prepared similarly except that the last precipitate of dimethylglyoxime was dissolved in dilute (30%) perchloric acid solution and evaporated nearly to dryness to decompose the organic part of the molecule. The residue was taken up in water, neutralized with aqueous ammonia, nickel perchlorate added to approximate the desired amount and the solution evaporated nearly to dryness. The residue was taken up in the appropriate solvent and diluted to give the concentration desired for the experiment.

The irradiated metallic nickel was dissolved in boiling hydrochloric acid solution, precipitated by dimethyl glyoxime and treated as above. The irradiated nickel dimethylglyoxime was filtered from the suspension and the active nickel chloride solution was treated as above. It was found that the specific activity of the nickel ions was ten to fifteen times the specific activity of the nickel

(1) This paper is based on a thesis presented by J. Enoch Johnson in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of Wisconsin, February, 1942.

(2) Present address: Chemistry Division, Naval Research Laboratory, Washington 20, D. C.

(3) Steigman, *Phys. Rev.*, **59**, 498 (1941).

(4) Seaborg, *Chem. Rev.*, **27**, 199 (1940).

(5) Ruben, *et al.*, THIS JOURNAL, **64**, 2297 (1942).

(6) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

(7) Mellor, *Chem. Rev.*, **33**, 137 (1943).

(8) Sugden, *J. Chem. Soc.*, 246 (1932).

(9) Johnson, *Trans. Faraday Soc.*, **28**, 845 (1932).

TABLE I

EXCHANGE OF NICKEL[a] IN COMPLEX COMPOUNDS

Complex compound	Analyses, % Ni Calcd.	Found	Solvent	Time of interaction, minutes	Specific activity Complex	Ni^{++} ion	Ratio *i* of spec. act.
bis-Methylbenzylglyoxime nickel[b]	13.31	13.44	Acetone	5	0.0	10.9	0.00
				60	0.0	10.7	.00
bis-Methyl-*n*-butylglyoxime nickel[c]	15.74	15.34	Me Cello-	5	1.3	39.4	.03
			solve	5	0.8	39.5	.02
				60	1.3	40.0	.03
				60	1.3	38.6	.03
bis-N,N-Di-*n*-propyldithiocarbamate nickel[c]	14.27	14.15	Acetone	5	0.2	17.7	.01
				60	0.2	17.6	.01
				5	11.0	8.2	1.34[k]
				60	9.6	9.2	1.04[k]
				30	23.3	17.0	1.37[k]
				30	0.9	31.0	0.03
bis-N,N-Di-isoamyldithiocarbamate nickel[c]	11.22	11.13	Acetone	5	0.1	32.6	0.00
				60	0.2	35.8	0.01
				30	21.8	19.3	1.13[k]
				30	0.5	35.5	0.01
bis-Salicylaldoxime nickel[d]	17.75	17.65	Me Cello-	5	5.0	4.4	1.14
			solve	60	4.3	4.7	0.91
				5	18.3	16.8	1.09
				60	17.3	18.1	0.96
bis-Salicylaldehyde nickel dihydrate[e]	17.42	17.16	Me Cello-	5	11.1	9.4	1.18
			solve	5	10.0	11.5	0.87
				60	11.1	10.5	1.06
				60	11.1	11.3	0.98
bis-Salicylaldimine nickel[f]	19.63	19.32	Me Cello-	5	28.8	31.0	0.93
			solve	60	32.3	30.3	1.06
				5	9.0	9.8	0.92
				60	8.5	8.8	0.97
bis-Salicylaldehyde-ethylenediamine nickel[g]	18.07	17.85	Et Cello-	5	0.2	21.7	0.01
			solve	5	0.0	22.6	0.00
				60	0.0	21.6	0.00
				60	0.0	21.2	0.00
tris-Ethylenediamine nickelous chloride dihydrate[h]	16.97	16.58	Water	5	14.0	14.7	0.95
				60	14.2	13.9	1.02
				5	8.2	8.1	1.01
				60	8.0	7.7	1.04
tris-α,α'-Dipyridyl nickelous chloride heptahydrate[i]	8.16	7.80	Water	5	5.5	22.1	0.25
				60	9.9	13.3	0.75
				5	12.3	35.2	0.35
				40	19.4	23.5	0.83
				90	20.9	21.6	0.97

[a] The radioactive nickel salt used was nickel perchlorate, except for the runs using water as the solvent, in which cases nickel chloride was used. [b] Sugden, *J. Chem. Soc.*, 246 (1932). [c] Cavell and Sugden, *ibid.*, 621 (1935). [d] Cox, *et al.*, *ibid.*, 459 (1935). [e] Tyson and Adams, THIS JOURNAL, **62**, 1228 (1940). [f] Pfeiffer and Buchholz, *J. prakt. Chem.*, **129**, 163 (1931). [g] Dubsky and Sokol, *Coll. Czech. Chem. Comm.*, **3**, 548 (1931). [h] Werner, *Z. anorg. Chem.*, **21**, 201 (1899). [i] Pfeiffer and Tappermann, *Z. anorg. allgem. Chem.*, **215**, 273 (1933). [j] This ratio is obtained by dividing the specific activity of the complex by the specific activity of the simple nickel ion. [k] In these experiments, concentrated aqueous ammonia was added immediately before precipitation of the complex by dilution with water.

in the nickel dimethylglyoxime, demonstrating the application of the Szilard–Chalmers principle, and giving strong indication that there is no exchange between the two forms of nickel involved.

Exchange Procedure.—The general method of determining the exchange of nickel between the 4-coördinated nickel compounds and simple nickel ions was to mix at room temperature (about 25°) a solution (in acetone, methyl cellosolve or ethyl cellosolve) of the complex compound with a solution of radioactive nickel perchlorate in the same solvent. After an appropriate time interval, the complex compound was separated from the solution by dilution with several volumes of water. In the case of bis-methylbenzylglyoxime nickel and bis-salicylaldimine nickel, sodium chloride was added to salt out the complex compound.

The activity of the complex compound was measured on the solid precipitate or on a solution of the compound in dilute hydrochloric acid or, in the case of the dithiocarbamate compounds, in acetone. The activity of the

nickel ions in the filtrate was determined by precipitation by the usual method with dimethylglyoxime, dissolving this precipitate in dilute hydrochloric acid solution and diluting to the desired volume. The activity measurements were made on the solution or on the dimethyl glyoxime precipitate.

The determination of exchange of nickel between 6-coördinated complex nickel ions and radioactive nickel chloride was made by mixing the aqueous solutions. The tris-ethylenediamine nickel ion was separated by precipitation with chloroplatinic acid or sodium thiosulfate solution. The precipitate was redissolved in 60% perchloric acid to determine its activity. In the case of the tris-dipyridyl nickel ion, the nickel ion was separated from the solution by precipitating with dimethylglyoxime, leaving the dipyridyl nickel ion in solution. The filtrate was evaporated to a small volume, filtered again and diluted with water to the desired volume.

Analysis for Nickel.—All the analyses for nickel were made by the gravimetric method using dimethylglyoxime. The weight of nickel was obtained by using the value of 20.3% as the percentage of nickel in the dimethylglyoxime precipitate. In case the solution to be analyzed contained nickel combined with an organic substance besides dimethylglyoxime, the solution was evaporated with 60% perchloric acid until it fumed strongly. The solution was cooled, diluted with water and handled in the usual manner. If the solution contained an organic solvent such as acetone, this was evaporated off before treatment with perchloric acid. It was found necessary to fume strongly with sulfuric acid in analysis of solutions containing dipyridyl to decompose it prior to nickel analysis.

Measurements and Calculations.—The activity of the nickel samples was determined by the use of a Geiger–Mueller counter. For counting dry samples the counter tube was contained in a felt-padded brass jacket fitted into a lead box built in two parts. The sample contained on a small watch glass was placed on a brass holder and slipped into a slot below the counter tube. Solution samples were run into an annular glass jacket which was slipped over the counter tube. Solutions whose activity was to be measured were usually made up to 25 ml. in a volumetric flask. Since the volume of the annular jacket was approximately 15 ml., it was completely filled each time so that all measurements were made under the same conditions.

The observed activity (counts/min.) was corrected for background count (12–15 counts/min.), for counting losses and for the decay of the radioactive nickel. The specific activity (counts per minute per milligram of nickel) was calculated by dividing the corrected counts per minute by the number of milligrams in the sample. The samples contained approximately 10–20 mg. of nickel. The corrected activity for active samples was usually 100–400 counts per minute.

The results of the exchange experiments are given in Table I. The values given under the heading "Ratio of Specific Activities" is the ratio of the specific activity of the nickel in the complex compound to the specific activity of the simple nickel ion. The value of this ratio should be 1.00 when complete exchange has occurred.

Behavior with Dimethylglyoxime.—In preliminary experiments to find satisfactory means of separating the complex nickel compounds from the nickel perchlorate and nickel chloride, the behavior of these compounds of nickel in the presence of dimethylglyoxime was studied. These observations seemed noteworthy because of the striking correlation with the exchange data for these compounds. Nickel tris-dipyridyl chloride in aqueous solution gave no precipitate with dimethylglyoxime whereas the nickel tris-ethylenediamine ion gave an immediate precipitate of nickel dimethylglyoxime. The addition of 1% alcoholic dimethylglyoxime to the acetone solutions of the nickel complexes with the two glyoximes, the two dithiocarbamates and disalicylaldehyde-ethylenediamine did not give a precipitate even after an hour. An immediate precipitate of nickel dimethylglyoxime was formed when the dimethylglyoxime solution was added to the methyl cellosolve solution of bis-salicylaldoxime nickel and bis-salicylaldehyde nickel. bis-Salicylaldimine nickel in acetone solution did not give an immediate precipitate, but after dilution with water a precipitate of nickel dimethylglyoxime formed after a short time.

Results and Discussion

bis-Methylbenzylglyoxime Nickel.—Sugden[8] found this compound to be diamagnetic and he succeeded in separating two geometrical isomers which he called the α-form, m. p. 168°, and the β-form, m. p. 75–77°. Sugden concluded that this isomerism is made possible by the planar configuration of the four Ni–N bonds. The α-isomeride (m. p. 167–168°) was used in these exchange experiments. As was expected, the data in Table I show that no exchange occurred between the nickel atoms in bis-methylbenzylglyoxime nickel and nickel perchlorate within sixty minutes under the conditions of the experiment.

bis-Methyl-*n*-butylglyoxime Nickel.—Cavell and Sugden[10] reported that this compound is diamagnetic and that it occurs in two steroisomeric forms. Because of this proof of a planar configuration of the bonds, no exchange was expected to occur between the nickel atoms of the compound and nickel ions in homogeneous solution. The results of the activity measurements are interpreted to mean that no exchange had occurred. The slight activity of the nickel complex is attributed to the fact that the precipitate of the nickel glyoxime was not wet appreciably by the wash water, which could allow radioactive nickel ions to remain adsorbed on the precipitate.

***bis*-N,N-Di-*n*-propyldithiocarbamate Nickel.**—Malatesta[11] and Cavell and Sugden[10] found this compound to be diamagnetic. Malatesta stated further that the dithiocarbamates of nickel in general maintain the diamagnetic state in solution as well as in the fused condition. Cavell and Sugden were unable to isolate stereoisomers of this compound and concluded that this was probably due to a symmetrical structure of the molecule. Peyronel,[12] on the basis of X-ray measurements, found this compound to be planar. The sum of this information made it seem likely that no exchange of nickel atoms would be found with this compound. The exchange data show that no exchange had occurred when separation of the complex compound from the nickel perchlorate was made by simply diluting with water. In the experiments where concentrated aqueous ammonia was added to facilitate the precipitation of the complex, complete exchange was obtained within five minutes. Because this did not agree with the results obtained when the ammonia treatment was omitted, this phenomenon was further investigated with the di-isoamyl dithiocarbamate complex of nickel.

bis-N,N-Di-iso-amyldithiocarbamate Nickel.—Although no structural data were available

(10) Cavell and Sugden, *J. Chem. Soc.*, 621 (1935).
(11) Malatesta, *Gazz. chim. ital.*, **67**, 738 (1937).
(12) Peyronel, *Z. Krist.*, **103**, 157 (1941).

for this compound, there was no reason to believe that it should behave differently from the di-*n*-propyl derivative. The exchange experiments were performed in essentially the same way as with the propyl compound. The data show that no appreciable exchange had occurred when the separation of the complex from the nickel perchlorate was made by merely diluting with water. However, when concentrated aqueous ammonia was added to the acetone solution before dilution with water, complete exchange occurred. The time elapsing between the addition of ammonia and the complete separation of the precipitated complex compound by filtration was less than two minutes. It was concluded that the presence of ammonia has a profound effect upon the stability of the nickel dithiocarbamate structures. Ammonia apparently weakens the bonds of the complex units to the nickel so much that thermal exchange may occur in a short time at room temperature.

bis-Salicylaldoxime Nickel.—Cox[13] and coworkers found that the nickel and palladium compounds of salicylaldoxime are isomorphous, which is significant since all quadricovalent palladium compounds are planar in structure. The nickel compound was found by them to be diamagnetic. However, Malatesta[14] reported that bis-salicylaldoxime nickel is paramagnetic to the extent of 2.70 magnetons. The results of the exchange experiments given in Table I show complete interchange of the nickel atoms within five minutes in methyl cellosolve solution. This might seem to substantiate Malatesta in regard to the magnetic susceptibility of this compound. However, Willis and Mellor[15] recently reported this compound to be diamagnetic in the solid state and in benzene solution, but to be paramagnetic to the extent of 1.1 and 3.1 Bohr magnetons in chloroform and pyridine, respectively. They postulated, in the case of pyridine, the formation of an octahedral complex containing pyridine in equilibrium with the planar molecules. But they felt that chloroform would be unlikely to form such a complex. They agreed that the difference of stability of square and tetrahedral complexes may in some cases be so small that the solvent may cause partial conversion to the tetrahedral structures as was earlier suggested by French, Magee and Sheffield[16] in the case of bis-formylcamphor–ethylenediamine nickel in methanol solution. The present authors feel that the exchange observed with bis-salicylaldoxime nickel in methyl cellosolve solution does indicate a change of bond type.

bis-Salicylaldehyde Nickel.—This compound is paramagnetic in the solid state and in pyridine solution and is therefore believed to have predominantly ionic or weak covalent bonds. As was expected from this information, complete exchange occurred with nickel ions in methyl cellosolve solution within five minutes.

bis-Salicylaldimine Nickel.—Tyson and Adams[17] found this compound to be diamagnetic in the solid state as did Willis and Mellor,[15] although the latter found it to be paramagnetic to the extent of 2.3 Bohr magnetons in pyridine solution. The results of the exchange experiments show complete exchange within five minutes in acetone solution. The addition of sodium chloride in the separation of the complex compound is not believed to have caused the exchange of nickel atoms because the addition of sodium chloride was used in the separation of bis-methylbenzylglyoxime nickel which showed no exchange. It is more probable that the covalent bonds of the diamagnetic solid compound are modified sufficiently by the solvent to allow thermal exchange.

bis-Salicylaldehyde-ethylenediamine Nickel.—Willis and Mellor[15] recently reported this compound to be diamagnetic both in the solid state and in pyridine solution. The exchange study of this compound was made in ethyl cellosolve solution and the results show definitely that there was no exchange of nickel atoms within an hour. The presence of another five-membered ring in this complex molecule apparently stabilizes the molecule which is otherwise similar in structure to bis-salicylaldimine nickel and bis-salicylaldoxime nickel.

tris-Ethylenediamine Nickelous Chloride Dihydrate.—Rosenbohm[18] and Cambi, Cagnasso and Tremolada[19] found this compound to have a magnetic susceptibility sufficient to show two unpaired electrons just as in the simple nickel ion. However, Pauling's explanation of the stability of 6-coördinated nickel complexes does not require pairing of all the valence electrons. Consequently, magnetic susceptibility measurements are of no value in predicting stability. Bucknall and Wardlaw[20] were able to resolve the tartrates and *d*-camphor sulfonates of this complex ion, but the optical activity was lost on conversion of these salts to the chloride. The results in Table I show that the nickel atoms in the ethylenediamine complex ion exchanged completely with nickel ion in water within five minutes. This was not unexpected due to the failure to resolve this complex ion into stable optical isomers.

tris-α,α'-Dipyridyl Nickelous Chloride Heptahydrate.—Morgan and Burstall[21] were able to resolve this complex nickel chloride into its optical isomers. This has been substantiated by others. These optically active salts racemize in aqueous solution. For example, it was reported that racemization is complete after 115 minutes at

(13) Cox, *et al.*, *J. Chem. Soc.*, 459 (1935).
(14) Malatesta, *Gazz. chim. ital.*, **68**, 319 (1938).
(15) Willis and Mellor, THIS JOURNAL, **69**, 1237 (1947).
(16) French, Magee and Sheffield, *ibid.*, **64**, 1924 (1942).
(17) Tyson and Adams, THIS JOURNAL, **62**, 1228 (1940).
(18) Rosenbohm, *Z. physik. Chem.*, **93**, 693 (1919).
(19) Cambi, Cagnasso and Tremolada, *Gazz. chim. ital.*, **64**, 758 (1934).
(20) Bucknall and Wardlaw, *J. Chem. Soc.*, 2739 (1928).
(21) Morgan and Burstall, *Nature*, **127**, 854 (1931); *J. Chem. Soc.*, 2213 (1931).

17°, or in about sixty minutes at 20°. The fact that this salt is resolvable indicates that its complex ion is quite stable. The results in Table I show that the nickel atom in the complex ion exchanges at a measurable rate with the simple nickel ion in water solution. No attempt was made to establish the rate of this exchange under varying conditions. The observed interchange indicates that racemization of the optical isomers may be due to partial dissociation of the complex ion. This exchange of the nickel atom in the dipyridyl complex is interesting because Ruben, *et al.*,[5] found a slow exchange of iron atoms between ferrous ion and ferrous α,α'-dipyridyl ion, although the latter is diamagnetic so that no exchange was predicted.

Acknowledgments.—The authors wish to thank Dr. Truman P. Kohman who made helpful suggestions, Dr. J. L. McKibben who built the counting apparatus and operated the electrostatic generator for the preparation of the radionickel and Mr. Dave Frisch who also operated the generator. This work was supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

Summary

1. The nickel exchange of ten nickel coördination compounds was studied using Ni^{63} as the tracer. In the main the results, which are discussed in detail, show a satisfactory correlation with predictions of bond type based on other criteria.

2. bis-Methylbenzylglyoxime nickel, bis-methyl-*n*-butylglyoxime nickel, bis-N,N-di-*n*-propyldithiocarbamate nickel, bis-N,N-di-iso-amyldithiocarbamate nickel and bis-salicylaldehyde-ethylenediamine nickel was found not to exchange under the experimental conditions used in accordance with expectation based on the magnetic and other structural evidence for strong covalent bonds. The two dithiocarbamate compounds of nickel did, however, show exchange with nickel perchlorate in the presence of ammonia.

3. bis-Salicylaldehyde nickel and tris-ethylenediamine nickel chloride were found to exchange as predicted.

4. bis-Salicylaldoxime nickel and bis-salicylaldimine nickel, although diamagnetic in the solid state, were found to exchange. This is believed to be evidence that these compounds exhibit a change of bond type when dissolved in methyl cellosolve.

5. Although tris-α,α'-dipyridyl nickel chloride heptahydrate has been resolved into its optical isomers and was not therefore expected to exchange, it did exchange at a measurable rate. This may be connected with the racemization observed for this compound.

MADISON, WISCONSIN RECEIVED FEBRUARY 3, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Reaction of Ferrous and Ferric Iron with 1,10-Phenanthroline. I. Dissociation Constants of Ferrous and Ferric Phenanthroline

BY T. S. LEE, I. M. KOLTHOFF AND D. L. LEUSSING

The intensely red colored complex of divalent iron and phenanthroline is used extensively for the colorimetric determination of iron and as an oxidation–reduction indicator. The dissociation constants of ferrous and ferric phenanthroline have hitherto not been determined, nor has a systematic study been made of the effect of acid on the dissociation of these complexes. Moreover, no study has been made of the kinetics of the formation and the dissociation of either complex. Such information is of general and especially of analytical interest.

The present paper is divided into three parts: (1) the basic strength of phenanthroline, (2) dissociation of "ferroin" (the ferrous phenanthroline complex) and (3) the dissociation of "ferriin" (the ferric phenanthroline complex).

In a subsequent paper the kinetics of formation and dissociation of ferroin and ferriin will be discussed.

Experimental

Materials Used.—1,10-Phenanthroline ("ortho-phenanthroline") monohydrate was obtained from the G. Frederick Smith Chemical Co. The phenanthroline content of several different samples of this compound was found by conductometric titration with acid to be 100 ± 1% of theoretical. Standard solutions of phenanthroline and phenanthrolium chloride were prepared by dissolving the calculated amount of phenanthroline in water or in standard hydrochloric acid.

Standard solutions of the following compounds were prepared from analytical reagent chemicals and standardized by accepted procedures: ferrous sulfate, sulfuric acid, hydrochloric acid, ceric sulfate and potassium chloride.

Potentiometric Titration of Phenanthroline with Hydrochloric Acid.—One-hundredth *M* phenanthroline solution in water was titrated at room temperature with 0.2 *N* hydrochloric acid. The *p*H was measured with a glass electrode (Leeds and Northrup *p*H Meter, Model No. 7661).

Determination of *p*H of Mixture of Phenanthrolium Chloride and Phenanthroline.—Solutions were prepared which were 0.0200 *M* in phenanthroline, 0.0100 *M* in hydrochloric acid, and 0.001, 0.010, 0.100, 0.500 or 1.00 *M* in potassium chloride. The *p*H of these solutions was measured at 25 ± 0.1° with the apparatus described above.

Conductometric Titration of Phenanthroline with Hydrochloric Acid.—One hundredth *M* phenanthroline solution in water was titrated with 0.2 *N* hydrochloric acid. The titration was carried out at room temperature in a titration conductance cell with freshly platinized elec-

trodes. The conductance bridge used was model RC-1B, Industrial Instruments, Inc.

Conductometric Determination of the Acid Dissociation Constant of Phenanthrolium Ion.—The equivalent conductances of the following solutions were determined: (1) 0.00100 *M* in phenanthroline and 0.00100 *M* in hydrochloric acid, (2) 0.0060 *M* in phenanthroline and 0.00100 *M* in hydrochloric acid and (3) 0.00100 *M* hydrochloric acid. The temperature of the solutions was maintained at 25 ± 0.1°. The cell constant was determined with 0.01 *M* hydrochloric acid using the value 412.0 for the equivalent conductance of this solution.[1]

Determination of Ferroin in Equilibrium Mixtures of Phenanthroline, Ferrous Sulfate and Sulfuric Acid.—Equilibrium mixtures were prepared by pipetting the appropriate quantities of reagent solutions into volumetric flasks and diluting to the mark. The reaction mixtures were allowed to stand in a thermostat at 25 ± 0.1° for one or two days, after which time equilibrium had been established. A portion of the solution was removed and the extinction of the solution was measured at 500 mμ with a Beckman Model DU Spectrophotometer. The concentration of ferroin was found by comparing the extinction with that on a calibration curve determined with known concentrations of ferroin. The extinction of ferroin was found to be unaffected by ionic strength, at least up to a value of 1 *M* (sodium sulfate used as the electrolyte).

Measurement of E. m. f. of the Cell Au|Fe^{++}, Fe^{+++}, H_2SO_4|$FePh_3^{++}$, $FePh_3^{+++}$, H_2SO_4|Au (Ph denotes phenanthroline).—One of the half cells consisted of a gold electrode immersed in a solution $2.5\cdot10^{-3}$ *M* in ferrous sulfate, $2.5\cdot10^{-3}$ *M* in ferric sulfate and *a M* in sulfuric acid. The other half cell consisted of a gold electrode and a solution $2.5\cdot10^{-3}$ *M* in ferrous phenanthroline sulfate, $2.5\cdot10^{-3}$ *M* in ferric phenanthroline sulfate and *a M* in sulfuric acid. This solution was prepared by adding ferrous phenanthroline sulfate to the calculated quantity of ceric sulfate (of known sulfuric acid content) and sulfuric acid solution. The two half cells were connected by a bridge containing *a M* sulfuric acid. The concentrations, *a*, of sulfuric acid used in different experiments were 0.05, 0.5, 1, 2 and 8 *M*. The temperature of the cell was maintained at 25 ± 0.1° by means of a thermostat. The Leeds and Northrup instrument mentioned above was used to measure the E. m. f. The E. m. f. of the cell was found to vary with time due to the slow dissociation of ferroin and ferriin in the acid solution. The E. m. f. of the cell at zero time (time of addition of ferroin to sulfuric acid and ceric sulfate) was found by plotting E. m. f. against time and extrapolating to zero time.

Acid Strength of Phenanthrolium Ion.—Although the phenanthroline molecule possesses two basic nitrogen atoms it was found to combine with only one proton in acid solution The reason for this is that the nitrogen atoms are separated by a distance of only about 2.5 Å. and occupy such positions in the molecule that electrostatic or steric forces or both prevent two protons from combining with the phenanthroline (see Fig. 1).

The experimental points obtained in a potentiometric titration of phenanthroline with hydrochloric acid are plotted in Fig. 2. A relatively large change in *p*H occurs in the region corresponding to approximately one mole of acid per mole of phenanthroline. Little change in *p*H occurs in the region corresponding to approximately two moles of acid per mole of phenanthroline. The drawn curve in Fig. 2 is the theoretical curve calculated for the titration of phenanthroline with acid assuming that phenanthroline is a mono-acid base

(1) T. Shedlovsky, THIS JOURNAL, **54**, 1411 (1932).

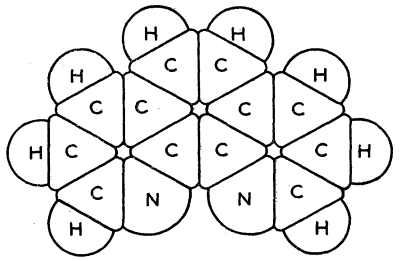


Fig. 1.—Fisher–Hirshfelder–Taylor steric model of 1,10-phenanthroline. All atoms of the phenanthroline molecule lie in the same plane.

and that the dissociation constant of the phenanthrolium ion is 1.1×10^{-5} (see below). It is seen that the calculated curve agrees with the experimental data.

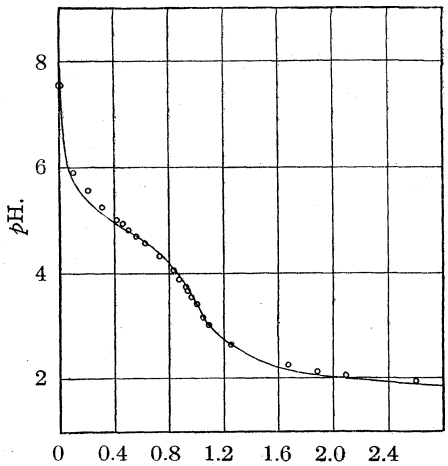


Fig. 2.—Potentiometric titration of phenanthroline with hydrochloric acid (curve is calculated, dots are experimental points).

The acid constant of the phenanthrolium ion K_A was determined potentiometrically by measuring the *p*aH (hydrogen ion activity) of solutions which were 0.01 *M* in phenanthroline and 0.01 *M* in phenanthrolium chloride, and which contained potassium chloride at various concentrations. The results are given in Table I.

TABLE I

DEPENDENCE OF HYDROGEN ION ACTIVITY OF 0.01 *M* PHENANTHROLINE–0.01 *M* PHENANTHROLIUM CHLORIDE BUFFER ON IONIC STRENGTH

Concentration of KCl, *M*	Observed *p*aH	Total ionic strength, μ	γ_{PhH^+}
0.001	4.81	0.011	0.91
.010	4.83	.020	.87
.100	4.91	.11	.73
.500	5.03	.51	.55
1.00	5.12	1.01	.45

In Figure 3 the observed values of *p*aH are plotted against the square root of the ionic

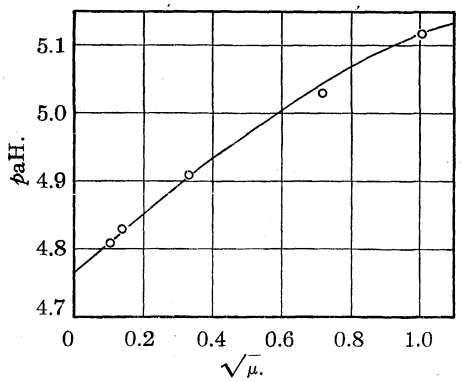


Fig. 3.—Dependence of hydrogen ion activity of phenanthrolium chloride–phenanthroline solution on ionic strength.

strength. It is seen that the curve is nearly linear at low ionic strengths and extrapolates to a value of *pa*H of 4.77 at zero ionic strength. This value corresponds to a hydrogen ion activity of 1.7×10^{-5}, hence the acid dissociation constant K_A of the phenanthrolium ion is about 1.7×10^{-5} at 25°. The data of Table I involve a small error due to the liquid junction potential between the saturated potassium chloride solution in the salt bridge and the potassium chloride, phenanthrolium chloride solution under investigation.

For use in calculations described below approximate activity coefficients of the phenanthrolium ion were calculated. The equation employed was

$$\gamma_{PhH^+} = \frac{a_{H^+}\gamma_{Ph}(Ph)}{K_A(PhH^+)} \qquad (1)$$

where γ represents activity coefficient, a represents activity, and parentheses indicate molar concentrations. The values of γ_{PhH^+} given in Table I are subject to an error due to liquid junction potential.

Figure 4 shows the results of the conductometric titration of 0.01 *M* phenanthroline with 0.2 *N* hydrochloric acid. (The conductivity of the solution was corrected for the small change in volume which occurred during the titration.) It is seen that phenanthroline behaves as a mono-acid base. Only one mole of hydrogen ion combines with one mole of phenanthroline.

The degree of hydrolysis, *h*, of the phenanthrolium ion in 0.001 *M* phenanthrolium chloride solution was determined by means of the relation

$$h = (\Lambda_1 - \Lambda_2)/(\Lambda_3 - \Lambda_2) \qquad (2)$$

where Λ_1 is the equivalent conductance of 0.001 *M* phenanthrolium chloride, Λ_2 is the equivalent conductance of 0.001 *M* phenanthrolium chloride in the presence of an excess of phenanthroline (to repress hydrolysis), and Λ_3 is the equivalent conductance of 0.001 *M* hydrochloric acid. The value of Λ_1 was found to be 136.0 at 25°, and the value of Λ_2 104.5. Taking the value of Shedlovsky[1] of 421.4 for the equivalent conductance of 0.001 *M* hydrochloric acid at 25°, we find that *h*

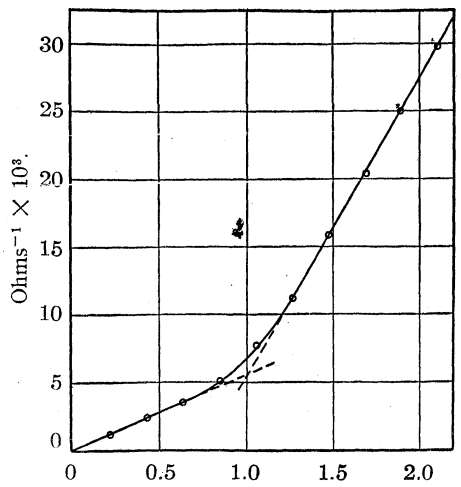


Fig. 4.—Conductometric titration of phenanthroline with hydrochloric acid.

for 0.001 *M* phenanthrolium chloride is 1.0×10^{-1}. From this value the acid dissociation constant of the phenanthrolium ion is calculated to be 1.1×10^{-5}. The computation involves the assumption that the activity coefficient of phenanthrolium ion is equal to that of the hydrogen ion in a solution of an ionic strength of 0.001 *M*. From the value of the acid constant, 1.1×10^{-5} at 25°, it is found that the ionization constant of the base phenanthroline in water is about 9×10^{-10} at 25°.

Dissociation of Ferroin.—It is known that in ferroin the iron is joined to three phenanthroline molecules.[2,3] The formula may be represented by $FePh_3^{++}$. Gould and Vosburgh[4] found that complexes with one and with two phenanthroline molecules per iron atom do not exist in spectrophotometrically detectible amounts in neutral aqueous mixtures of ferrous iron and ferroin. As will be described in a subsequent paper we found evidence that the complexes $FePh^{++}$ and $FePh_2^{++}$ exist in acid solutions at appreciable concentrations if the iron concentration is very high. However, for the present purposes only $FePh_3^{++}$ need be considered.

In acid solutions with a *p*H of 3 or less phenanthroline is present chiefly as the phenanthrolium ion rather than as free phenanthroline, and the equilibrium between ferroin and a strong acid may be represented by

$$FePh_3^{++} + 3H^+ \rightleftharpoons Fe^{++} + 3PhH^+ \qquad (3)$$

The value of the equilibrium constant, K_c', of reaction (3) was found by determining the concentration of ferroin in equilibrium with known concentrations of ferrous sulfate and sulfuric acid. The results are given in Table II.

(2) F. Blau, *Monatsh.*, **19**, 666 (1898).

(3) Smith and Richter, "Phenanthroline and Substituted Phenanthroline Indicators," G. Frederick Smith Chemical Co., Columbus, Ohio, 1944.

(4) Gould and Vosburgh, THIS JOURNAL, **64**, 1630 (1942).

TABLE II

EQUILIBRIUM OF FERROUS IRON WITH PHENANTHROLINE IN ACID SOLUTIONS

Reaction mixture	Initial concn. of H_2SO_4, M	Initial concn. of $FeSO_4$, $M \times 10^5$	Initial concn. of phen., $M \times 10^5$	Concn. of ferroin found, $M \times 10^5$	Concn. of Fe^{++} calcd., $M \times 10^5$	Concn. of PhH^+ calcd., $M \times 10^5$	Concn. of H^+ calcd., M	Concn. equilib. const. $K_c' \times 10^7$	Activity equilib. const.[a] $K' \times 10^7$
1	0.00536	10.4	9.97	1.63	8.8	5.08	0.0089	9.7	8.4
2	.0511	10.3	99.7	6.42	3.9	80.4	.0687	9.7	5.2
3	.505	10.3	1000	5.80	4.5	983	.572	39	5.2
4	.501	253	100	0.790	252	97.6	.584	15	2.0
5	.502	253	200	4.75	248	186	.584	17	2.3
6	.512	239	199	4.16	234	187	.595	17	2.1
7	.502	496	200	7.70	487	164	.584	14	1.8

[a] In calculating the activity equilibrium constant from the concentration equilibrium constant the values 0.87, 0.71 and 0.47 were used for the activity coefficients of phenanthrolium ion in mixtures 1, 2, and 3–7, respectively. The values 0.92, 0.85 and 0.92 were used for the activity coefficients of hydrogen ion in reaction mixtures 1, 2, and 3–7, respectively.

The concentration equilibrium constant

$$K_c' = \frac{(Fe^{++})(PhH^+)^3}{(FePh_3^{++})(H^+)^3} \qquad (4)$$

where parentheses represent concentrations, was calculated for each of the reaction mixtures. The concentration of phenanthrolium ion was calculated from the expression

$$(PhH^+) = (Ph)_t - 3 \times (FePh_3^{++}) \qquad (5)$$

where $(Ph)_t$ represents the total initial concentration of phenanthroline. The concentration of ferrous iron was calculated from the relation

$$(Fe^{++}) = (Fe^{++})_t - (FePh_3^{++}) \qquad (6)$$

where $(Fe^{++})_t$ represents the total initial concentration of iron. The concentration of hydrogen ion was estimated by assuming that the first hydrogen ion of sulfuric acid is completely dissociated and that the second dissociation constant is 0.012.[5] The calculated value of the hydrogen ion concentration depends on the values used for the activity coefficients of hydrogen ion, hydrogen sulfate ion, and sulfate ion. These activity coefficients were estimated by the individual ion activity coefficient method.[6] This method involves the assumption that the activity coefficients of potassium ion and chloride ion are equal in any given solution, and that the activity coefficient of an individual ion depends on the nature of the ion and on the total ionic strength of the solution but does not depend on the nature of electrolyte.

In evaluating the activity constant

$$K' = a_{Fe^{++}} a^3_{PhH^+} / a_{FePh_3^{++}} a^3_{H^+} \qquad (7)$$

it was assumed that $\gamma_{Fe^{++}} = \gamma_{FePh_3^{++}}$ where γ denotes activity coefficient. The values for γ_{PhH^+} were taken from Table I.

In experiments 1–3 of Table II the total concentration of iron was held constant and the acid and phenanthroline concentrations were varied. The values of K' were nearly the same in the three experiments. In experiments 4 and 5 the acid and iron concentrations were held constant and the phenanthroline concentration was varied. In experiments 6 and 7 the acid and phenanthroline concentrations were held constant and the iron concentration was varied. The total variation in K' was from 1.8 to 8.4 $\times 10^{-7}$. Considering the uncertainty in activity coefficients, especially in 0.5 M sulfuric acid, the reported values of K' may be considered as reasonably constant. The average value of K' at 25° is 4×10^{-7}. In view of the fact that the hydrogen ion concentration was varied by a factor of 100 in these experiments and that the hydrogen ion activity occurs in equation (7) as a cube power it may be stated that the experimental data confirm the validity of equation (7) over the range of concentrations studied.

Equilibrium "constants" for the hypothetical reaction

$$FePh_3^{++} + 6H^+ = Fe^{++} + 3PhH_2^{++} \qquad (8)$$

were also calculated from the data of Table II. The "constant" calculated for reaction (8) changes by a factor of about one million when the sulfuric acid concentration is changed from 0.005 to 0.5 M. This result substantiates the conclusion given in the previous section that phenanthroline is a mono-acid base.

The constant for the dissociation of ferroin, represented by the equations

$$FePh_3^{++} = Fe^{++} + 3Ph \qquad (9)$$

$$K_{diss.\ ferroin} = a_{Fe^{++}} a^3_{Ph} / a_{FePh_3^{++}} \qquad (10)$$

can be calculated from the equilibrium constant K' of reaction (7) and the acid constant of the phenanthrolium ion. The relation is $K_{diss.\ ferroin} = K'K_A^3$. The values 4×10^{-7} and 1.1×10^{-5} for K' and K_A, respectively, give a value of 5×10^{-22} for $K_{diss.\ ferroin}$ at 25°. In a subsequent paper it will be shown that this value is in agreement with a value determined by an entirely independent method.

Knowledge of the nature of the dissociation of ferroin in acid solution (equation 3) and of the value of K' can be applied to the colorimetric determination of iron. The quantitative conversion of ferrous iron to ferroin is dependent on the ratio of phenanthroline to acid. If the colorimetric determination of iron is carried out at relatively high acidity, the concentration of excess

(5) W. Hamer, THIS JOURNAL, **56**, 860 (1934).

(6) Lewis and Randall, "Thermodynamics," McGraw-Hill Book Co., Inc., New York, N. Y., 1923, p. 381.

phenanthroline must be correspondingly high. In order that the reaction be 99% complete, the ratio of excess phenanthrolium ion to hydrogen ion should be 0.035 or greater. Thus if the hydrogen ion concentration is 10^{-3} M, the concentration of excess phenanthrolium ion must be 3.5×10^{-5} M or greater.

Dissociation Constant of Ferriin.—The constant for the dissociation of ferriin (a reaction analogous to reaction 9) was calculated from the dissociation constant of ferroin and the equilibrium constant for the reaction of ferrous iron with ferriin

$$Fe^{++} + FePh_3^{+++} = Fe^{+++} + FePh_3^{++} \quad (11)$$

The equation expressing this relation is

$$K_{\text{diss. ferriin}} = \frac{a_{Fe^{+++}} a^3_{Ph}}{a_{FePh_3^{+++}}} = \frac{a_{Fe^{+++}} a_{FePh_3^{++}}}{a_{Fe^{++}} a_{FePh_3^{+++}}} K_{\text{diss. ferriin}} \quad (12)$$

The equilibrium constant K'' for the reaction of ferrous iron with ferriin was calculated by two different methods: (1) from the e. m. f. of the cell $Au|Fe^{++}, Fe^{+++}, H_2SO_4|FePh_3^{++}, FePh_3^{+++}, H_2SO_4|Au$, and (2) from the formal potentials of the ferroin-ferriin couple and of the ferrous–ferric couple. The former method is somewhat more direct and is thought to be more reliable. The experimental data for method (1) are given in Table III. The data for use in method (2) were taken from the literature.[7,8,9,10]

The values of the dissociation constant of ferriin calculated from the experimental data using equation (12) were found to be 8.0×10^{-15} in 0.05 M sulfuric acid, 2.5×10^{-15} in 0.5 M, 1.0×10^{-15} in 1 M, 2.9×10^{-16} in 2 M, and 7.5×10^{-21} in 8 M. In the calculations it is assumed that the activity coefficients of ferric and ferriin ions are approximately equal.

(7) Walden, Hammett and Chapman, THIS JOURNAL, **55**, 2649 (1933).

(8) Hume and Kolthoff, *ibid.*, **65**, 1895 (1943).

(9) Smith and Richter, *Ind. Eng. Chem., Anal. Ed.*, **16**, 580 (1944).

(10) E. H. Swift, "System of Chemical Analysis," Prentice-Hall, New York, N. Y., 1939, p. 540.

TABLE III

EQUILIBRIUM CONSTANT FOR THE REACTION OF FERRIC IRON WITH FERROIN

Concn. of H_2SO_4, M	E. m. f. of cell, volts	K'' From e. m. f.	K'' From formal potentials
0.05	0.425	$1.6\ 10^7$	....
0.5	.395	$5.0\ 10^6$	....
1	.373	$2.1\ 10^6$	$4.4\ 10^6$
2	.340	$5.8\ 10^5$	$9.1\ 10^5$
8	.110	$1.5\ 10$	$2.3\ 10$

The dissociation constant of ferriin appears to decrease with increasing sulfuric acid concentrations. This variation is opposite to that which would be expected if the effect were due merely to complexing of the ferric ion with sulfate. The variation is also opposite to that which would be expected if the activity coefficient of ferriin were greater than the activity coefficient of ferric ion. (The ferriin ion is larger and might be expected to have the larger activity coefficient.) The variation may be explained if it is assumed that the ferriin ion possesses a proton in solutions of high acidity, $FeHPh_3^{++++}$. This will be discussed in a subsequent paper.

Acknowledgment is made to the Graduate School of the University of Minnesota for a grant which enabled us to carry out this investigation. The authors also wish to thank Professor R. T. Arnold for helpful suggestions.

Summary

1,10-Phenanthroline has been found to behave as a typical mono-acid base in aqueous solutions. The acid dissociation constant of the phenanthrolium ion is 1.1×10^{-5} at 25°.

The dissociation constants of ferrous and ferric phenanthroline have been evaluated. The constant of ferrous phenanthroline in various concentrations of sulfuric acid is 5×10^{-22} at 25° and that of ferric phenanthroline in 0.05 M sulfuric acid is 8×10^{-15} at 25°.

MINNEAPOLIS, MINNESOTA RECEIVED MARCH 5, 1948

[CONTRIBUTION FROM GULF RESEARCH AND DEVELOPMENT COMPANY'S MULTIPLE FELLOWSHIP, MELLON INSTITUTE]

Differential Heats of Adsorption of Nitrogen on Carbon Blacks

BY L. G. JOYNER AND P. H. EMMETT

It has long been realized that measurements of the heat evolved during the physical adsorption of gases upon solids might yield considerable information concerning the nature of the solid surface. Of particular interest would be the variations of the differential heat with the amount of gas adsorbed.

Unfortunately, very little accurate work has been done by either the calorimetric or the isosteric method for measuring heats of adsorption and few attempts have been made to compare the two methods. Such attempts as have been made have been well summarized and discussed by Brunauer.[1]

In recent years calorimetric technique has been so improved, especially by Beebe[2] and his coworkers, that it is possible to detect variations in the differential heat of adsorption which are smaller than the experimental error involved in much of the early work in the field. More precise methods for measuring the adsorption of gases on solids have also been developed. In view of the fact that calorimetric measurements such as Beebe's are rather complicated and time consuming, it seemed worthwhile to ascertain whether the simpler isosteric method for measuring the heat of adsorption was capable of detecting the same details of the heat curve as the calorimetric method. To this end, we have carried out and are here reporting detailed adsorption studies of nitrogen on portions of the same samples of carbon black for which Beebe, Biscoe, Smith and Wendell[2a] have recently reported the most complete calorimetric measurements of the heat of adsorption of nitrogen that have so far been published. The samples were kindly given to us by Dr. Beebe.

Experimental

Materials.—Two carbon blacks were selected for the present investigation. These were the same samples used by Beebe, Biscoe, Smith and Wendell[2a] and have been described in detail in their paper. The two carbon blacks were Spheron Grade 6 and Graphon. The Spheron Grade 6 is a medium processing channel black (MPC). Graphon is a partially "graphitized" carbon black formed by heating MPC black to 3200°.

The nitrogen adsorbate was Airco Prepurified nitrogen. It was merely dried in a liquid nitrogen trap prior to being used.

Apparatus.—The adsorption apparatus was a modified version of the type described by Emmett.[3] Pressures above 1 cm. were determined to 0.1 mm. on a 10-mm. bore manometer with a vernier reader. Lower pressure determinations were made on a special manometer read by means of a microscope cathetometer. This was similar to the system described by Harkins and Jura.[4] The precision of these low-pressure readings was about 0.01 mm. The normal vapor pressure of nitrogen (P_0) was determined continuously and directly by means of a separate manometer and bulb partially filled with liquid nitrogen and placed in the low-temperature bath in close proximity to the adsorption bulb.

The adsorption isotherms at −183 and −195° were made using a liquid oxygen and a liquid nitrogen bath, respectively. The isotherms at −205° were made in a specially designed, low temperature system, details of which will be published in the near future. Briefly, the lower temperature was obtained by decreasing the pressure over liquid nitrogen. By means of a vapor pressure controller, relay and pump, the pressure was kept constant to within a few tenths of a mm. The total temperature variation over an entire run was less than 0.1°.

All surface area values were obtained by a linear plot of the adsorption data according to the Brunauer, Emmet and Teller (B.E.T.) equation[5,6]

$$\frac{x}{V(1-x)} = \frac{1}{V_m C} + \frac{(C-1)x}{V_m C} \qquad (1)$$

where x is the relative pressure at which the volume V of gas (S.T.P.) is adsorbed, V_m is the volume of gas required to form a monolayer and C is a constant proportional to exp. $(E_1 - E_L)/RT$. E_1 is defined[5] as the "average heat of adsorption for the first layer" and E_L the heat of liquefaction of the adsorbate.[7]

Results

Figure 1 shows the nitrogen adsorption isotherms for Grade 6 Spheron at −183.1° and −194.6°. Similar isotherms for Graphon at −182.8°, −194.8° and −204.7° are shown in Fig. 2. In Fig. 3 the low pressure regions of the Graphon isotherms are given in more detail. All of the isotherms are actually composites of several separate runs. Many more points were taken

(1) Brunauer, "The Adsorption of Gases and Vapors—Physical Adsorption," Princeton Press, Princeton, N. J., 1943, Chapter 8.

(2) (a) Beebe, Biscoe, Smith and Wendell, THIS JOURNAL, **69**, 95 (1947). (b) Beebe and Orfield, *ibid.*, **59**, 1627 (1937). (c) Beebe and Dowden, *ibid.*, **60**, 2912 (1938). (d) Beebe and Stevens, *ibid.*, **62**, 2134 (1940).

(3) P. H. Emmett, "American Society for Testing Materials, Symposium on New Methods for Particle Size Determination," 1941, p. 95.

(4) Harkins and Jura, THIS JOURNAL, **66**, 1366 (1944).

(5) Brunauer, Emmett and Teller, *ibid.*, **60**, 309 (1938).

(6) Cassie, *Trans. Faraday Soc.*, **41**, 450 (1945).

(7) It must be kept in mind that E_1 does not and should not necessarily agree with direct experimental values for the heat of adsorption in the first layer.[2a] To begin with, E_1 is evaluted from plotting adsorption data by equation 1 for relative pressures ranging from 0.05 to about 0.3. Accordingly, the E_1 as deduced from the constant C in equation 1 is more nearly the average heat of adsorption for the less active part[5] of the surface since most of the first layer would have been completed already at a relative pressure of 0.05 for many adsorbates. Furthermore, since C is defined as

$$\frac{a_1 b_2}{a_2 b_1} \text{ exp. } (E_1 - E_L)/RT$$

it is possible to obtain E_1 from C only by evaluating the term a_1b_2/a_2b_1. Actually this term is frequently assumed equal to unity though recent calculations[6,8] suggest that it may differ from unity by a factor of 10 to 100. Accordingly, equation 1 can be expected to yield only an approximate value for E_1 and at best gives an E_1 characteristic of the less active parts of the surface.

(8) Emmett, THIS JOURNAL, **68**, 1784 (1946).

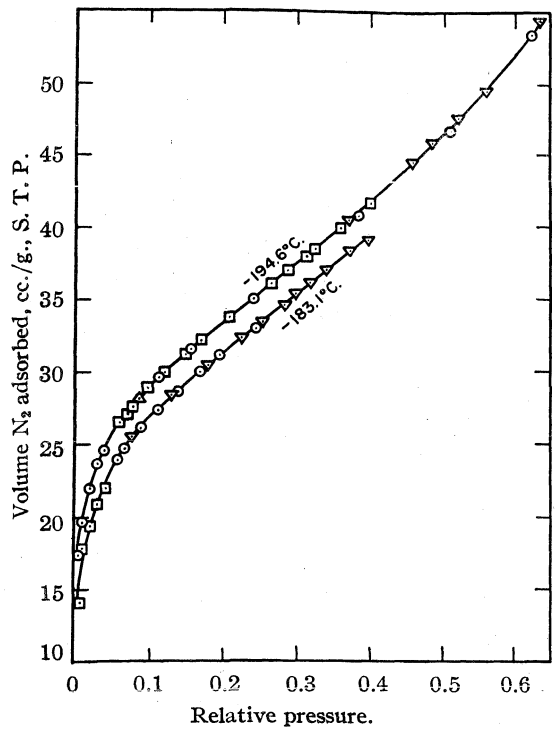


Fig. 1.—Adsorption of nitrogen on Grade 6 Spheron at −183.1 and −194.6°.

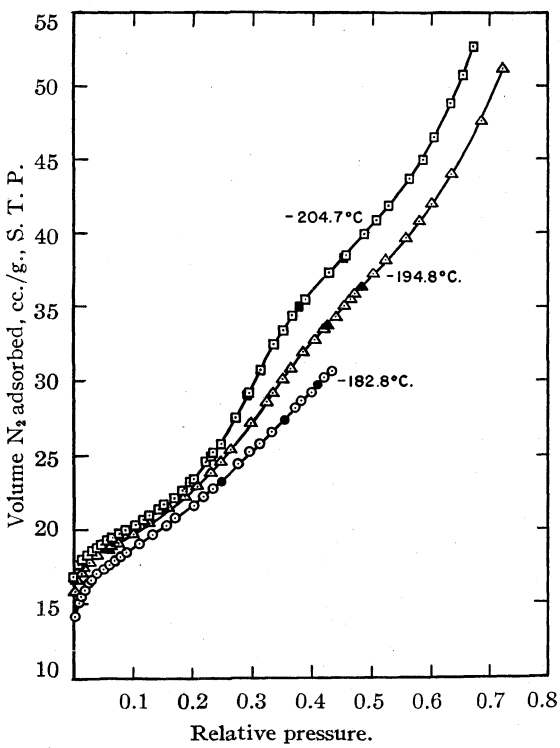


Fig. 2.—Adsorption of nitrogen on Graphon at −182.8, −194.8 and −204.7°. Solid symbols are desorption points.

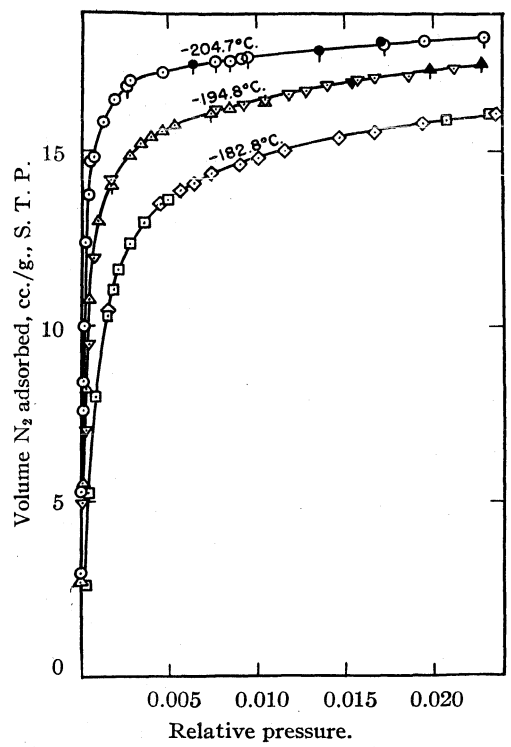


Fig. 3.—Low pressure detail of the adsorption of nitrogen on Graphon at −182.8, −194.8 and −204.7°. Different symbols represent separate runs. Solid symbols are desorption points.

than are shown.[9] Those given in the figures, however, are representative and serve to illustrate the precision of the measurements. Separate runs are indicated by the different symbols in Fig. 3. The −183° isotherms could not be carried above a a relative pressure of about 0.4 because of the limitations of the apparatus. That the carbon blacks are probably non-porous is indicated by the superposition of the desorption points on the adsorption curve in the region above 0.4 relative pressure, this being the region in which hysteresis usually occurs for porous substances. The desorption points were taken after the maximum volume of gas shown by the curves in Fig. 2 had been adsorbed.

Calculations and Discussion

Calculation of the Heat of Adsorption.—The differential heat of adsorption was calculated from the Clausius–Clapeyron equation in the form[10]

(9) For additional data order Document 2530 from American Documentation Institute, 1719 N St., N. W., Washington 7, D. C., remitting 50¢ for microfilm or 50¢ for photoprints.

(10) Wilkins, *Proc. Roy. Soc.* (*London*), **A164**, 496 (1938), has suggested that the correct method of applying the Clausius–Clapeyron equation to adsorption data entails the use of a constant fraction of the surface covered rather than a constant volume of adsorbed gas at the several temperatures being used. If such calculations are made for the data in the present paper for constant values of V/V_m (V_m varying with temperature as indicated in column 3 Table I) the resulting ΔH value is smaller in absolute value than the curves

$$\Delta H = 2.303R\left(\frac{T_1T_2}{T_2 - T_1}\right)(\log P_2 - \log P_1)_{\text{const. } V} \quad (2)$$

For each isotherm log P was plotted against the volume of gas adsorbed, V. Figure 4 show this plot for the three isotherms on Graphon. The vertical distance between the lines was measured at a given value of V and inserted into Equation 2; ΔH for various given values of V was then calculated.

In Figure 5 are plotted as a function of V/V_m the differential heat of adsorption for nitrogen on Spheron measured isosterically as above (solid line) and the calorimetric results for the same system (symbols) as measured by Beebe and his co-workers.[2a] Figure 6 shows a similar comparison for the nitrogen–Graphon system.

Since Equation 2 is very sensitive to small variations in the pressure, especially in the low pressure region, vertical lines are used in Figs. 5 and 6 to indicate the maximum variation observed. The extent of this variation in terms of pressure is indicated by the envelope lines for the −194.8° curve in Fig. 4. Variations of only 0.01 to 0.02 mm. in the low pressure region have a considerable effect upon the calculated heat value, whereas at higher pressures even larger variations have negligible effect.

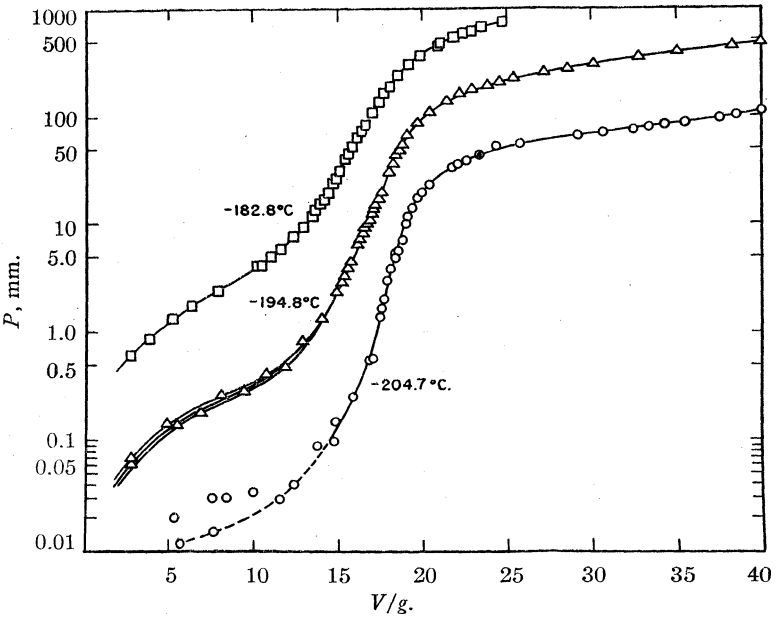


Fig. 4.—Logarithmic plot of the Graphon isotherms for purposes of calculating the differential heat of adsorption, showing the experimental deviations at extreme low pressures.

Changes in ΔH, ΔF and ΔS during the Adsorption of Nitrogen on Carbon Blacks.—It is apparent from Figs. 5 and 6 that the agreement between the differential heats of adsorption as calculated from the isotherms by Equation 2 and those determined calorimetrically by Beebe[2a] is remarkably good. The isosteric heats of adsorption of nitrogen on the Graphon sample are of better precision than those on Grade 6 Spheron, due to an improvement of the apparatus. It is doubtful, however, that this lower precision for the Spheron data can account for the rather large discrepancy observed for Spheron in the region of the monolayer between the isosteric heats and the portion of the calorimetric heats represented by the closed circles. It may be noted that the calorimetric data represented by the open circles and triangles are much closer to the isosteric line in this region than are points shown as closed circles.

For the adsorption of nitrogen on Graphon the agreement between the isosteric and calorimetric heats is especially good. The isosteric data reproduce faithfully the rather unusual calorimetric curve. Since for this system the isotherm was determined at three temperatures, there are three possible ways of calculating the differential heats by Equation 2. The various results are indicated in the figure by separate symbols. Above 0.7 monolayer the heats calculated from all three pairs of isotherms agree very well. Below 0.7 monolayer the −204.7° isotherm involves a larger possible error because of the low absolute pressure and cannot be used to calculate an isosteric heat with accuracy. It is not surprising, therefore, that the heat values calculated from the −204.7° and the −182.8° isotherms and shown by open triangles are in poor agreement with the other isosteric and with the calorimetric values.

The isotherms of the Graphon system shown in Fig. 2 all have an unusual hump starting at a relative pressure of about 0.2. This hump was also obtained but not discussed by Beebe[2a] and is not directly associated with the large rise in the differential heat curve since the latter occurs at 0.75 monolayer while the isotherm hump is much higher. There is, however, a much smaller rise in the heat curve at 1.75 monolayers which is associated with the isotherm hump. It is remarkable that the second and smaller rise in the differential

shown in Figs. 5 and 6 by 100 to 400 calories. However, the justification of this proposed method of applying the Clausius–Clapeyron equation is not clear at the present writing. Certainly the two papers of Wilkins (also Wilkins, *Proc. Roy. Soc.* (London), **A164**, 510 (1938)) dealing with the subject appear to be so full of misprints as to be unsuitable as a theoretical guide to the problem. Our own data show definitely that any heat of adsorption values calculated on the basis of constant fraction of the surface covered will be smaller than those calculated by equation 2 with volume of adsorbed gas constant. Wilkins' theoretical treatment led to what seems to be an erroneous conclusion that the heat of adsorption is larger if calculated by constant fraction of the surface covered than by constant volume.

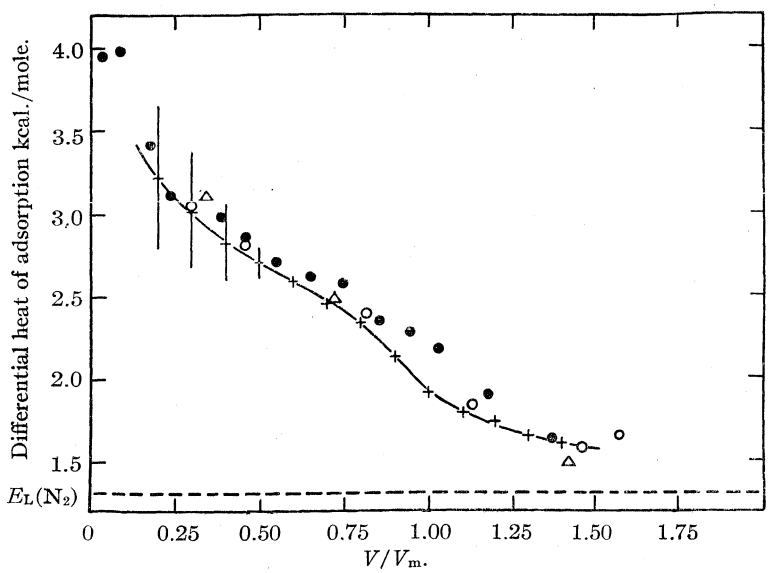


Fig. 5.—Differential heats of adsorption for nitrogen on Grade 6 Spheron as determined calorimetrically by Beebe, Biscoe, Smith and Wendell,[2a] (O, ●, △), and isosterically by the authors (+). The length of the vertical lines represents the total spread of the values calculated from the isosteric data.

heat curve is almost exactly one monolayer separated from the larger rise. It would almost seem that whatever forces cause the first rise are carried through and repeated in the second layer.

If one considers the process

$$N_2 \text{ (liquid)} \longrightarrow N_2 \text{ (adsorbed)}$$

it is a simple matter to calculate from the foregoing data the change in heat content, (ΔH); the free energy change, (ΔF); and the entropy change, (ΔS). ΔH is simply the difference between the differential heat of adsorption and the heat of liquefaction. ΔF is given by

$$\Delta F = RT \ln P/P_0 \qquad (5)$$

The free energy change so calculated was found to be independent of the temperature at least over the range of temperature studied. The entropy change is then obtained from the relation $T\Delta S = \Delta H - \Delta F$.

Figures 7 and 8 show how these properties vary with V/V_m for the two carbon blacks studied. Although the portion of the ΔS curve for Spheron below a V/V_m value of 0.5 is quantitatively questionable, ΔS undoubtedly remains negative down to at least a value of V/V_m equal to 0.2. For Graphon, the value of ΔS is positive up to a V/V_m value of 0.3 and again for a V/V_m value between 1.0 and 1.5.

Beebe and his co-workers[2a] have pointed out that on the basis of calculations by Barrer[11] the observed decrease in the heats for the Spheron with the amount of surface coverage cannot be accounted for by interaction between adsorbed molecules. However, as they point out, it is possible that such interaction forces may account for the increase in heats over the V/V_m range between 0.5 and 1.0 in the case of Graphon.

If one accepts Beebe's[2a] suggestion that the heat treatment to which Spheron is subjected when it is converted to Graphon eliminates most of the highly active centers found on the Spheron a possible explanation of the entropy curves is suggested. In the case of the Spheron where active points are present, the adsorbed phase is more or less ordered with a resulting negative entropy change over the entire course of the adsorption. In the Graphon system the first molecules are adsorbed in a very random or disordered manner giving rise to the positive portion of the entropy curve. Once the surface is partially covered, interaction forces, such as those discussed by Barrer[11] may cause a more orderly adsorption of the remainder of the monolayer, hence giving rise to the negative entropy change. It must be admitted, however, that it stretches

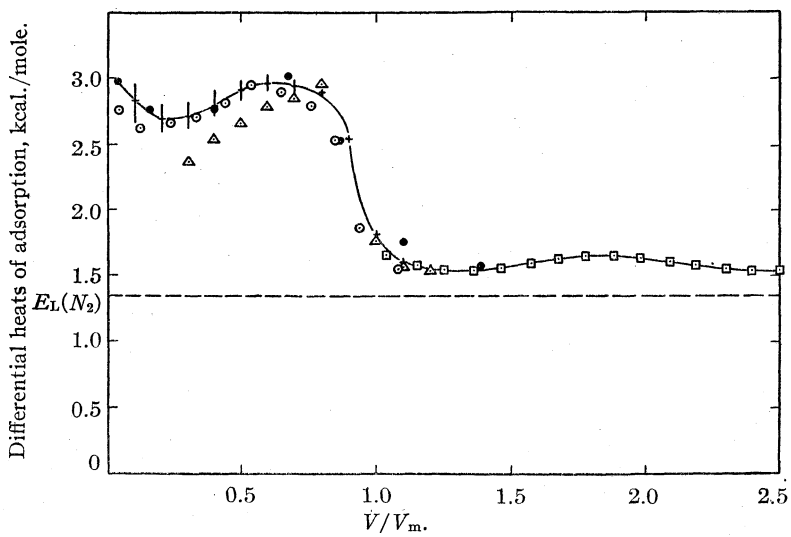


Fig. 6.—Differential heats of adsorption for nitrogen on Graphon as determined calorimetrically by Beebe, Biscoe, Smith and Wendell,[2a] (O,●), and isosterically by the authors (+, −194.8 to −182.8°; △, −204.7 to −182.8°; □, −204.7 to −194.8°). The length of the vertical lines represents the total spread of the values calculated from the isosteric data.

(11) Barrer, *Proc. Roy. Soc.* (*London*), **161A**, 476 (1937).

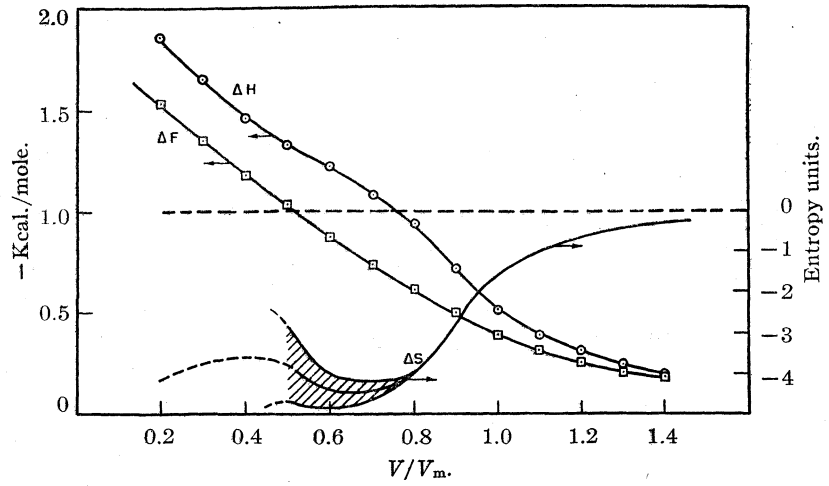


Fig. 7.—Variation in free energy change, change in heat content and entropy change for the transfer of nitrogen from the liquid state to the adsorbed state on Grade 6 Spheron with the system at −194.6°.

this picture rather far to imagine this process being repeated to explain the positive entropy which appears in the second layer.

Surface Area Measurements on the Carbon Blacks.—In Figure 9, the data for the adsorption of nitrogen on Graphon are plotted according to the usual B.E.T. linear equation. At all three temperatures excellent straight lines are obtained up to 0.2 relative pressure. Above this pressure the experimental points fall below the B.E.T. plot. This behavior has been noted twice before in the literature, once with butane on silica gel[5] and once with nitrogen on activated magnesia.[12] There has been little basis for judging the course of this behavior in the first two instances. The points could fall below the B.E.T. curves either because E_2, the heat of adsorption in the second layer was higher than E_L, or as suggested by Walker and Zettlemoyer[13] because of the presence of a considerable amount of surface characterized by a low C value (2 to 10) in addition to the surface having the usual C value (50 to 150). In the B.E.T. plots of the nitrogen adsorption on Graphon shown in Fig. 9, it seems reasonable to attribute the behavior to the same cause that is responsible for a rise in the heat of adsorption in the range between adsorption volumes equivalent to 0.5 and 0.9 fraction of a monolayer and 1.6 and 1.8 monolayers. It seems extremely unlikely that the explanation suggested by Walker and Zettlemoyer[13] can explain the results in Fig. 9 because on no carbon black so far studied has C ever been lower than about 100 and because such low C values as would be necessary have never been observed for nitrogen adsorption on any solid except hide.[14]

V_m for Graphon was calculated by the usual B.E.T. method from the linear portion below 0.2 relative pressure. The cross-sectional area of the nitrogen molecule was calculated for the various temperatures from the equation given by Emmett and Brunauer[15] using the data of Yost and Russell,[16] for the density of liquid nitrogen. V_m and the cross-sectional area factor F (in sq. m./cc.) are given in Table I.

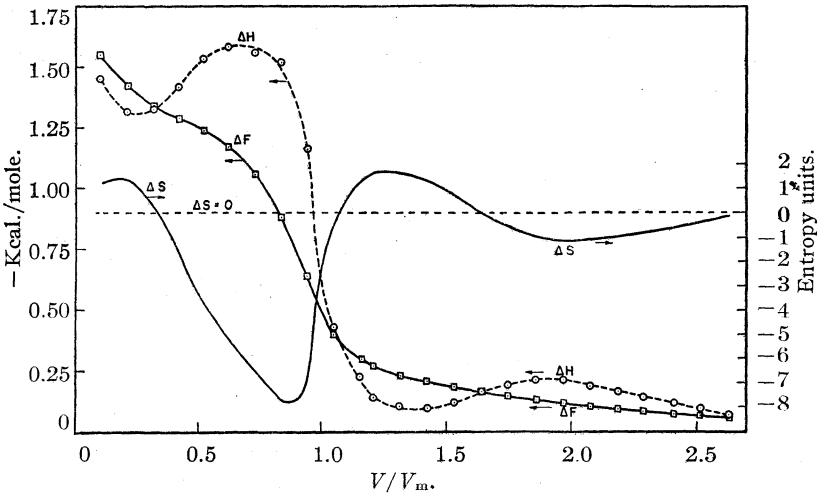


Fig. 8.—Variation in the free energy change, change in heat content and entropy change for the transfer of nitrogen from the liquid state to the adsorbed state on Graphon with the system at −194.8°.

TABLE I

V_m, surface area and C values for Graphon and for Grade 6 Spheron at various temperatures as determined from the B.E.T.[5] plot of the nitrogen adsorption isotherms.

	Temp., °C.	V_m, cc./g.	Vol. factor F, sq. m./cc.	Area, sq. m./g.	C
Graphon	−182.8	17.48	4.605	80.50	285
	−194.8	18.28	4.394	80.32	273
	−204.7	18.97	4.240	80.43	263
Spheron	−183.1	26.23	4.601	120.7	100
	−194.6	27.41	4.398	120.5	166

(12) Zettlemoyer and Walker, *Ind. Eng. Chem.*, **39**, 69 (1947).

(13) Walker and Zettlemoyer, *J. Phys. and Colloid Chem.*, **52**, 47 (1948).

(14) Zettlemoyer, Schweitzer and Walker, *J. Am. Leather Chemists' Assoc.*, **41**, 253 (1946).

(15) Emmett and Brunauer, THIS JOURNAL, **59**, 1553 (1937).

(16) Yost and Russell, "Systematic Inorganic Chemistry," Prentice-Hall Inc., New York, N. Y., 1944, p. 5.

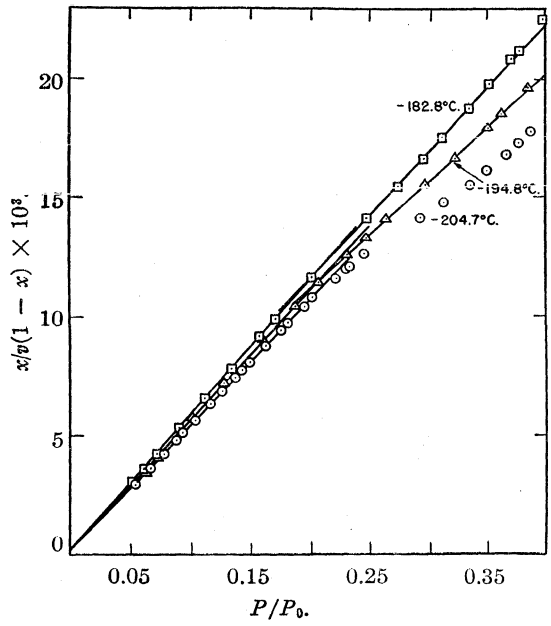


Fig. 9.—B. E. T.[5] plots of the three isotherms of nitrogen on Graphon.

The areas calculated by multiplying these two agree for all three temperatures within one per cent. This is an excellent confirmation of the variation with temperature of the cross-sectional area of the adsorbed nitrogen molecule as calculated by the equation of Emmett and Brunauer.[15] It also justifies the selection of the lower linear portion of Fig. 9 for the determination of V_m since no such agreement occurs if the upper, apparently linear, portion is used.

This break in the B.E.T. plot for the Graphon data accounts for the discrepancy between the value of V_m of Beebe, Biscoe, Smith and Wendell[2a] and that reported here. In determining V_m they used an average straight line and hence their value of 19.17 cc. is 5.5% above that obtained from the lower linear portion of the −194.8° curve in Fig. 9. In Fig. 6, Beebe's value of V_m was used to calculate the fraction of the surface covered in order to keep both heat values on the same basis.

Figure 10 shows the Graphon data plotted according to the method of Harkins and Jura.[4] Again two linear portions occur with the break occurring at 0.2 relative pressure. This pressure is almost exactly where the hump in the isotherm begins. Indicated in Fig. 10 is the slope which the −194.8° line should have if it is to give the same area by the Harkins and Jura[4] method as was obtained by the B.E.T. method. The slope of the linear portion occurring at low pressure is closer to this slope than that of the higher pressure data. A $\pi-\sigma$ plot of the Graphon data showed no evidence of a phase change occurring in this system.

Both the B.E.T. and the Harkins and Jura plot of the Spheron isotherms are quite normal.

Table II gives the area of the two carbon blacks as determined by the B.E.T. method at the various temperatures and also the area obtained from the −194.8° isotherm by the Harkins and Jura[4] method using 4.06 for the proportionality constant k. Isotherms at temperatures other than −194.8° could not be used for Harkins and Jura determinations since k is not known for nitrogen except at that temperature. The B.E.T. results for both blacks are surprisingly self-consistent, the maximum variation among the areas for a given adsorbent being less than 1%. The agreement between the B.E.T. values and the Harkins and Jura value is also remarkably good, being within about 10%. As a matter of fact, it is interesting to note that the cross-sectional areas that have to be assigned to the nitrogen molecule to obtain surface areas by the B.E.T. method in agreement with those obtained by Harkins and Jura plots exhibit the same relationship to the constant C shown by one of the authors[8] to exist for numerous adsorptions being 17.93 Å.^{2} and 17.04 Å.^{2} for C values of 273 and 166, respectively.

Utilizing the slope of the Harkins and Jura plot of the isotherms at temperatures other than −194.8° and the area, calculated from the −194.8° data by their method, it is possible to calculate a value of the Harkins and Jura[4] proportionality constant k at the other temperatures. The results of such calculations are shown in the last two columns of Table II. The agreement between calculated k values for the two non-porous carbon blacks at −182.8° is remarkable and is an excellent confirmation of the self-consistency of the Harkins and Jura[4] method when applied to non-porous substances. Incidentally, the varia-

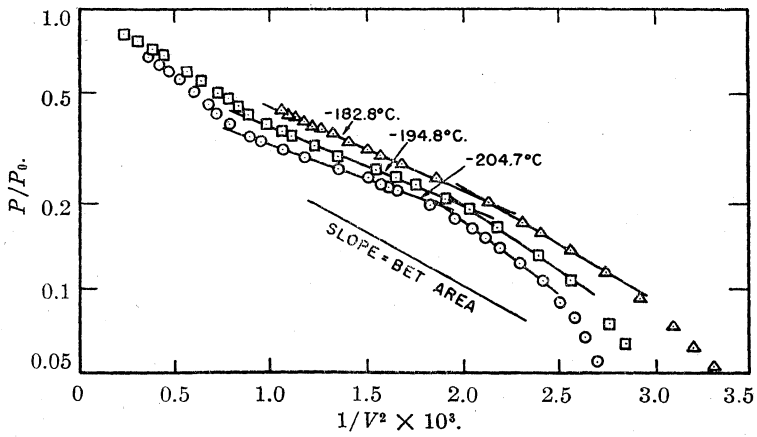


Fig. 10.—Harkins and Jura[4] plots of the three isotherms of nitrogen on Graphon. For comparison is shown the slope required to equal the B. E. T.[5] area for the −194.8° isotherm.

tion of k with temperature in Table II is in approximate agreement with the prediction of Davis and DeWitt[17] that the Harkins and Jura k value for a given adsorbate should be proportional to $1/T^{1/2}$.

TABLE II

Comparison of areas of Graphon and Grade 6 Spheron as determined by the B. E. T. method[5] at three temperatures and by the Harkins and Jura method[4] at −195°.

	Area, sq. m./g.					k calculated from H & J area at −195°C.
	B.E.T.			H & J k = 4.06		
Temp., °C.	−195	−183	−205	−195	−183	−205
Graphon	80.3	80.5	80.4	88.7	4.47	3.86
Spheron	120.4	120.7		126.3	4.47	

Summary

1. Adsorption isotherms for nitrogen on two samples of carbon black were determined at −205, −195 and −183°.

2. The differential heats of adsorption of nitrogen on the two samples of carbon black were measured isosterically.

3. Excellent agreement with the calorimetric data of Beebe and his co-workers[2a] for the same samples of carbon black was obtained. ΔF and ΔS values for the process liquid nitrogen going to adsorbed nitrogen were determined as a function of the surface covered and a possible interpretation of the results is suggested.

4. The areas of the various samples as calculated by the B.E.T.[5] theory were compared to the areas calculated by the method of Harkins and Jura.[4]

(17) Davis and DeWitt, THIS JOURNAL, **70**, 1135 (1948).

RECEIVED NOVEMBER 8, 1947

[CONTRIBUTION FROM GULF RESEARCH AND DEVELOPMENT COMPANY'S MULTIPLE FELLOWSHIP, MELLON INSTITUTE]

Differential Heats of Adsorption and Desorption of Nitrogen on Porous Glass

BY L. G. JOYNER AND P. H. EMMETT

Gleysteen and Deitz[1] recently calculated by the Clausius-Clapeyron equation from the data of Lambert and Clark[2] the differential heat of adsorption and the differential heat of desorption of benzene on ferric oxide gel. They found the heat of desorption to be about 760 calories larger in the region where hysteresis occurs and suggested that this value could be used in conjunction with the Brunauer, Deming, Deming and Teller[3] adsorption equation to account approximately for the hysteresis observed in this benzene–iron oxide gel system.

It was felt that these observations of Gleysteen and Deitz[1] were of sufficient importance to warrant their being checked by another set of data. To this end we have determined the adsorption and desorption isotherms for nitrogen at −204.8° and −194.6° on a sample of porous glass.

Experimental

Materials.—The porous glass sample was one of a number furnished by the Corning Glass Company (Hood and Nordberg, U. S. Patent 2,106,774). It was one of the samples used by Emmett and Cines[4] for adsorption work at −195°.

The nitrogen adsorbate was Airco prepurified nitrogen. It was merely dried in a liquid nitrogen trap prior to being used.

Apparatus.—The adsorption and temperature controlling apparatus and the procedure were the same as for the preceding paper.[5] All surface area values were calculated by the standard B. E. T. equation.[6]

(1) Gleysteen and Deitz, *J. Research Nat. Bur. Standards*, **35**, 285 (1945).

(2) Lambert and Clark, *Proc. Roy. Soc.*, **A122**, 497 (1929).

(3) Brunauer, Deming, Deming and Teller, THIS JOURNAL, **62**, 1723 (1940).

(4) Emmett and Cines, *J. Phys. & Colloid Chem.*, **51**, 1248 (1947).

(5) Joyner and Emmett, THIS JOURNAL, **70**, 2353 (1948).

(6) P. H. Emmett, "American Society for Testing Materials, Symposium on New Methods for Particle Size Determination," 1941, p. 95.

Results

The adsorption and desorption data for nitrogen on the porous glass have been plotted in Fig. 1. For each temperature, adsorption and desorption points for two separate runs are shown. The agreement between the separate runs was excellent. The isotherms are what have been called "Type IV" and resemble somewhat the isotherms obtained by Lambert and Clark[2] for benzene on iron oxide gel.

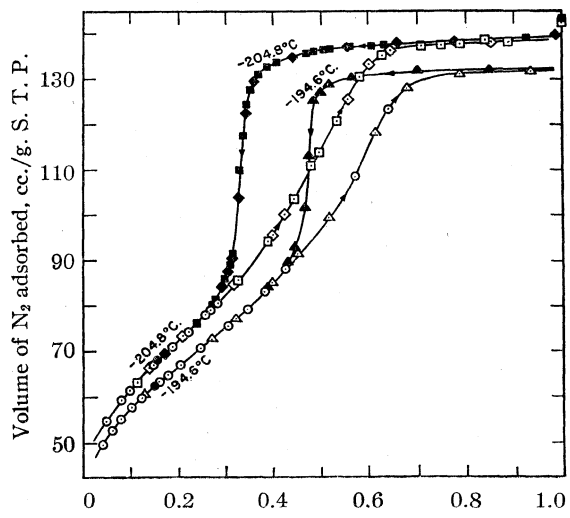


Fig. 1.—Adsorption of nitrogen on porous glass at −204.8 and −194.6°. Solid symbols are desorption points.

Calculations and Discussion

Comparison of the Heat of Adsorption of Nitrogen with the Heat of Desorption.—Brunauer, Deming, Deming and Teller[3] de-

veloped a general adsorption theory by which five types of adsorption isotherms may be deduced from the single equation

$$V = V_m \left[\frac{x}{1-x} + A\right] \quad (1)$$

where A is a complicated function of C, x, $\bar{n}$ and h. V_m is the volume of gas required to form a monolayer on the surface and x is the relative pressure. In the function A of equation 1, $\bar{n}$ is the maximum number of layers that can fit into a capillary; C is related to the heat of adsorption of the first layer in the same way as in the regular B.E.T. equation[6]; and $h = (\bar{n}C^2 - C^2 + 2C)\exp. Q/RT$ where Q is an additional energy term associated with the last layer to enter the capillary.

Brunauer, Deming, Deming and Teller[3] applied the above equation to the data of Lambert and Clark[2] for the adsorption of benzene on ferric oxide gel and obtained reasonably good agreement. Gleysteen and Deitz[1] showed that if all the constants of Equation 1, as calculated from the adsorption data, are held fixed except for the value of Q and, if this is increased by the 760 calories that they had calculated as the amount by which the heat of desorption of benzene on ferric oxide gel exceeded the heat of adsorption, a reasonable facsimile of the experimental desorption curve is obtained.

In applying the suggestion of Gleysteen and Deitz[1] to our data we have elected to assign such excess heat to the Q for desorption as is needed to make the desorption isotherm for $-194.6°$ as calculated from equation 1 agree with that shown in Fig. 1. The curve for this calculated excess Q (labeled calcd. B.D.D.T.) is shown in Fig. 2. It is apparent that no single value for the amount by which the Q for the desorption curve exceeds that for the adsorption curve would suffice to give agreement between the experimental and calculated isotherms. Furthermore, it is evident that at low relative pressures and at high relative pressures the heats of adsorption and desorption will be equal.

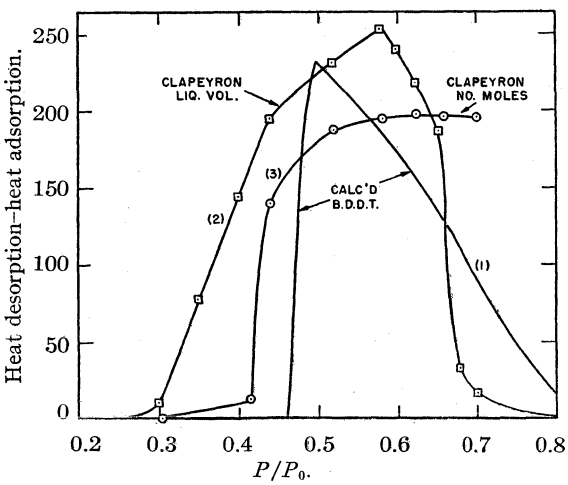


Fig. 2.—Excess of the heat of desorption over the heat of adsorption for nitrogen (in calories per mole) on porous glass over the hysteresis region, as calculated by three different methods.

Some explanation of how the calculated curve (marked B.D.D.T. calcd. in Fig. 2) for the heat of desorption minus the heat of adsorption was obtained may be in order. The values for V_m and C for the $-194.6°$ isotherm were obtained in the usual manner from the simple B.E.T. plot (see equation 1 of the preceding[5] paper). The values of the parameters $\bar{n}$ and Q which gave the best fit of Equation 1 to the adsorption isotherm were then determined by a trial and error method. The Q so determined may be designated as $Q_{ads.}$ Agreement between experiment and theory was obtained to about the same degree as was obtained by Brunauer, Deming, Deming and Teller[3] for the benzene–ferric oxide system. Using the values of V_m, C and $\bar{n}$ from the adsorption part of the curve, values of V and x from the desorption isotherm were inserted into Equation 1 and $Q_{des.}$ calculated. The calculated curve of Fig. 2 is simply $Q_{des.} - Q_{ads.}$ plotted as a function of the relative pressure at $-194.6°$.

The conventional isosteric calculation of heats of adsorption and desorption by the Clausius–Clapeyron equation is fraught with considerable uncertainty when applied to data such as shown in Fig. 1. As pointed out by McBain[7] it is impossible to construct isosteres for the higher relative pressure regions for those cases in which the volume of gas adsorbed (S.T.P.) at saturation varies with temperature. The difficulty can apparently be avoided if one applies the Clausius–Clapeyron equation at constant liquid volume (and hence constant volume of pore space filled with adsorbate) rather than to constant volume of gas adsorbed. The amount by which the heat of desorption exceeds the heat of adsorption per mole is shown in Fig. 2 as a function of the relative pressure (for the $-194.6°$ isotherm) when calculated both on the basis of constant liquid volume of adsorbate and also when calculated for constant number of moles of adsorbate on the porous glass.

From what has already been said, it follows that curve 3 cannot be extended above about 0.7 relative pressure because at this point the isotherm for $-194.6°$ levels off and becomes independent of pressure.

The three curves shown in Fig. 2 are in remarkably good agreement considering the assumptions involved in the Brunauer, Deming, Deming and Teller[3] theory and the methods used in calculating curve 2. They all combine to indicate that the quantity of heat involved in desorbing adsorbate from capillaries is greater than the heat evolved during adsorption. This excess heat is probably of fundamental importance in determining the cause of the hysteresis loop, though the exact relationships involved may remain obscure until

(7) McBain, "The Sorption of Gases and Vapors by Solids," G. Routledge and Sons Ltd., London, 1932, p. 141.

more is learned concerning the phenomenon of hysteresis.

Variation of the Inception of Desorption Hysteresis with Temperature.—One other observation relative to the isotherms in Fig. 1 is of interest. A few years ago, Cohan,[8] on the basis of an "open pore" theory of adsorption, predicted that the lower relative pressure at which the desorption branch of an isotherm rejoins the adsorption branch should decrease as the temperature decreases. Qualitatively our data shown by the plots in Fig. 1 and similar data by Lambert and Clark[2] for benzene adsorption on ferric oxide agree with Cohan's hypothesis.[8] However, the agreement with his prediction is not quantitative. Thus, the value of the relative pressure corresponding to the beginning of hysteresis at −204.8° should be 0.305 according to Cohan[8] if, as in Fig. 1, the corresponding relative pressure in the −194.6° isotherm is 0.420. Actually, the hysteresis at −204.8° begins at about 0.265 relative pressure.

Surface Area Measurements on Porous Glass.—The adsorption data at both temperatures yield excellent linear portions when plotted according to either the B.E.T.[6] or the Harkins and Jura[9] method. The B.E.T. areas and C values for porous glass as calculated from both the −194.6° and the −204.8° isotherms are given in Table I. The Harkins and Jura area was calculated from the −194.6° isotherm by the use of 4.06 for the proportionality constant k. The agreement between the B.E.T. areas, although not as good as for the carbon blacks of the preceding paper, is still within 2%. Again the Harkins and Jura area is somewhat higher than but nevertheless is in reasonable agreement with that obtained by the B.E.T. method. We find as in the preceding paper[5] that the cross-sectional area (16.9 Å.²) that has to be assigned to the nitrogen molecule to obtain a surface area by the B.E.T. method in agreement with that obtained by the Harkins and Jura[9] plot exhibits the same relationship to the constant C (123) which has been shown to exist by one of the authors.[10]

TABLE I

Calculation of the surface areas and related constants by the B. E. T.[6] and by the Harkins and Jura[9] methods from the nitrogen adsorption isotherms:

Temperature, °C.	−194.6	−204.8
V_m, cc./g.	55.90	59.21
B.E.T. area, sq. m./g.	245.8[a]	250.9[a]
H. & J. area, sq. m./g.	255.2	
k calculated from H. & J. area at −194.6°C.		3.35
B.E.T. C	123	147

[a] The cross-sectional molecular areas for nitrogen for −194.6° and −204.8° were taken as 16.26Å.² and 15.67 Å.², respectively, for these area calculations.

(8) Cohan, THIS JOURNAL, **66**, 98 (1944).

(9) Harkins and Jura, THIS JOURNAL, **66**, 1366 (1944).

If we utilize the slope of the Harkins and Jura[9] plot for the −204.8° isotherm and calculate a value of the Harkins and Jura proportionality constant k required to yield the same value of the surface area as was obtained by their method from the data at −194.6°, we obtain a value for k of 3.35 for the porous glass. A similar calculation in the preceding paper[5] for the non-porous solid Graphon at the same temperature yielded a k value of 3.86. This difference of about 17% in the value of k found between the porous and non-porous substances at −204.8° is to be compared to the perfect agreement between k values found for the two non-porous carbon blacks at −183° in the preceding paper.[5] These two examples are insufficient to warrent final conclusions but they do suggest that the temperature coefficient of k may be different for porous and non-porous substances.

Summary

1. Adsorption isotherms for nitrogen on a sample of porous glass were determined at −204.8° and −194.6°.

2. The differential heat of adsorption and the differential heat of desorption of nitrogen on the porous glass were measured isosterically.

3. For the porous glass the differential heat of desorption was shown to be in excess of the differential heat of adsorption over the hysteresis region by as much as 250 calories. The excess heat of desorption over the heat of adsorption was correlated with the hysteresis loop by means of the Brunauer, Deming, Deming and Teller[3] theory of multilayer adsorption in a way similar to that suggested by Gleysteen and Deitz.[1]

4. The area of the porous glass as calculated by the B.E.T.[6] theory from the adsorption data at −194.6° was compared to and found to agree with the area calculated by the method of Harkins and Jura.[9]

PITTSBURGH, PENNSYLVANIA

RECEIVED NOVEMBER 8, 1947

(10) Emmett, THIS JOURNAL, **68**, 1784 (1946).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Chemical and Physical Adsorption of Gases on Carbon Dust

BY ROBERT H. SAVAGE AND CALLAWAY BROWN

The clean-up of hydrogen by fresh carbon or graphite wear-dust,[1] at room temperature, has been interpreted as a chemical adsorption resulting from the opening of the graphite lattice during the process of frictional seizure. The amount of hydrogen adsorbed by the dust was found to be 10^5 times greater than that adsorbed by a typical activated charcoal at the same temperature and pressure, and represented a chemically-active surface of the order of one square meter per gram. The supposition was made that the *total* surface of the dust was considerably greater than this, as roughly indicated by the color of the material; and this possibility was strengthened by a subsequent study with an electron microscope which revealed[2] that the carbon particles occurred in a wide distribution of size and showed a fineness extending beyond the resolving power of the instrument. The suggestion was then made that a determination of the total surface of this carbon by nitrogen adsorption at low temperature[3] would complete the data relating the chemically active surface to the total (physical) surface.

For carbon we have not found published information relating the two types of adsorption. According to the work of Lowry and Hulett,[4] after a charcoal has been outgassed thoroughly at 900–1000° and has been allowed to cool in vacuum to room temperature, such gases as hydrogen, nitrogen, carbon monoxide, can be admitted and subsequently recovered quantitatively at room temperature. The adsorption of these gases is clearly no more than physical. Yet surface films held by primary valences evidently occur since there are recovered large quantities of hydrogen as well as oxides of carbon during the degassing of charcoal[5] at 600 to 1200°. Nitrogen, also, has been recovered in the degassing of graphite[6] at temperatures up to 2200°, and is the predominant gas evolved in the range 1700 to 2200°.

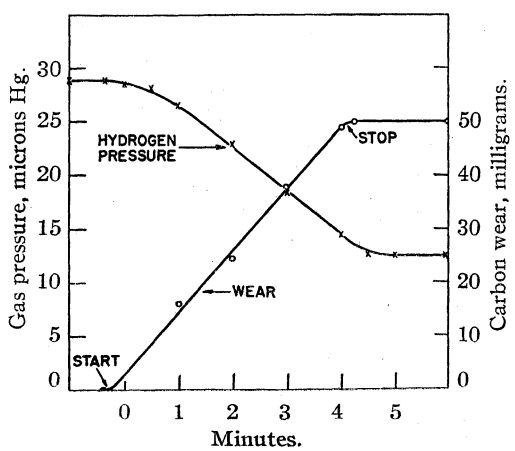


Fig. 1.—Clean-up of hydrogen by graphite wear-dust.

The lack of a detailed knowledge of the surface films on carbon seems to result from the fact that previous work has been concerned almost exclusively with the determination of adsorption characteristics of carbons which are already saturated chemically and which are not cleaned by the usual activation methods involving bake-outs at relatively low temperatures. Since an important part of the surface film may not be removed by such heating alone, the carbon wear-dust as a research material offers the novel advantage of providing *clean* carbon surfaces of exceptional extent by a simple mechanical process, so that the *formation* of the primary films may be measured. Employing the carbon dust we have observed an irreversible (chemical) clean-up at room temperature of hydrogen, nitrogen, oxygen, carbon dioxide, carbon monoxide and methane. This report is concerned particularly with (A) the hydrogen clean-up in relation to (B) a low temperature nitrogen adsorption performed after the clean-up to determine the total surface area.

Experimental

Part A.—Carbon wear-dust was made by operating graphite rods (brushes) against a rotating copper disk in a friction apparatus[1] containing hydrogen at a low pressure. (In the absence of certain vapors required for graphite lubrication, the graphite seizes to the moving base and rapidly disintegrates into a black dust which immediately cleans up the hydrogen. The clean-up is substantially the same whether the dust is formed in hydrogen directly or whether it is formed in vacuum and the hydrogen admitted after wear has stopped. Further, it occurs independently of the presence of copper in the moving base; *i. e.*, it is observed also with graphite rods sliding on a graphite disk.)

The observed wear (brush-volume) and the hydrogen clean-up were measured, as shown by Fig. 1. From the observed pressure drop in the system of 5.3-liter volume

TABLE I

CHEMICAL ADSORPTION

Sample, wear dust	Trial a	Trial b
Wear volume from rod, cc.	0.0263	0.0206
Apparent rod density, g./cc.	1.9	1.9
Calcd. weight of dust, g.	0.050	0.0392
Hydrogen adsorbed at S. T. P., cc.	0.101	0.078
Specific adsorption, cc./g.	2.00	1.98
Specific surface (chemical), sq. m./g.	5.16	5.12

(1) R. H. Savage, *J. Applied Phys.*, **19**, 1 (1948).

(2) Ernest F. Fullam and Robert H. Savage, *ibid.*, July, 1948.

(3) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309 (1938).

(4) H. H. Lowry and G. A. Hulett, *ibid.*, **42**, 1408 (1919).

(5) Robert B. Anderson and P. H. Emmett, *J. Phys. and Colloid. Chem.*, **51**, 1308 (1947).

(6) F. J. Norton and A. L. Marshall, *Trans. Am. Inst. Mining Met. Engrs., Inst. Metals Div.*, **156**, 351 (1944).

we have calculated the adsorption, and also the specific area, of the *chemically active surface*, Table I. For reasons to be discussed, the area saturated per hydrogen molecule was assumed to be 9.6×10^{-16} sq. cm. (the area of two C atoms in the plane perpendicular to the graphite hexagonal plane). Several additional runs were then made to increase the amount of dust, and to check these results, after which the bell-jar was removed and a sample of the dust transferred to a small Pyrex tube for determination of surface area.

Part B.—The tube was next sealed into an adsorption apparatus[7] by means of a spherical ground-glass joint. The carbon sample was degassed in vacuum at room temperature and again for one hour at 500°, and the adsorption of nitrogen at −195° was determined after each pumping in the usual manner with helium as the reference gas. (Only the results following the 500° bake-out will be included because these are indicated to be more representative; the other data agreed however within 20%.) The dust was then removed and was replaced, first, with a sample of the original graphite "stock-powder" from which (with the addition of about 2% coked-binder) the brush had been made by pressing and firing to 1350°; and second, with samples of finished graphite rods of apparent density 1.9 g. per cc. Nitrogen adsorption at −195° was determined for each of these and the results are summarized, for comparison with the wear-dust, in Table II. The surface areas were calculated from these adsorption data, shown in Fig. 2, using the Brunauer, Emmett, Teller adsorption equation[8] and the value 16.2×10^{-16} sq. cm. for the area covered by a nitrogen molecule.

TABLE II

PHYSICAL ADSORPTION

Sample	g.	V_m (from BET plot) cc. N_2	Specific V_m cc. N_2/g.	Sp. surface (total) m^2/g.
Wear dust	0.0786	7.86	100.0	435
Stock powder	2.579	4.53	1.76	7.65
Rod	0.281	0.084	0.30	1.30

Finally the work was extended to include graphite rods of contrasting physical properties, with the results shown in Table III. The electrographitized carbon shown under (2) had been fired to about 2800° in contrast to the natural graphite rod 1, fired at 1350°. The powder under (2) was formed by grinding one of the rods in a high-speed impact grinder to produce a surface area of 4.62 sq. m./g., in striking contrast to the 435 and 390 sq. m./g. areas shown for the two wear-dust samples. The three samples of rod 1 of different cross-section and history show the reproducibility of the results.

Discussion

Tables I and II show the changes in surface which accompany the processes of rod manufacture (pressing and bonding of graphite particles) and of rod wear. The stock powder is a relatively coarse graphite showing an area 7.65 sq. m./g., and this is decreased to 1.3 sq. m./g. as a result of the rod formation. The process of wear results in a fine subdivision of the individual graphite particles, increasing the surface by 335-fold, within the range of the fine colloidal carbon blacks (color blacks). Of the total surface, 99.7% is apparently fresh surface developed in the wearing process. Only a portion of this fresh surface can be chemically active toward hydrogen since the 1.98 cc./g. hydrogen adsorption, although many times larger

(7) E. O. Kraemer, "Advances in Colloid Science," (by P. H. Emmett), Interscience Publishers, New York, 1942, pp. 1–36.

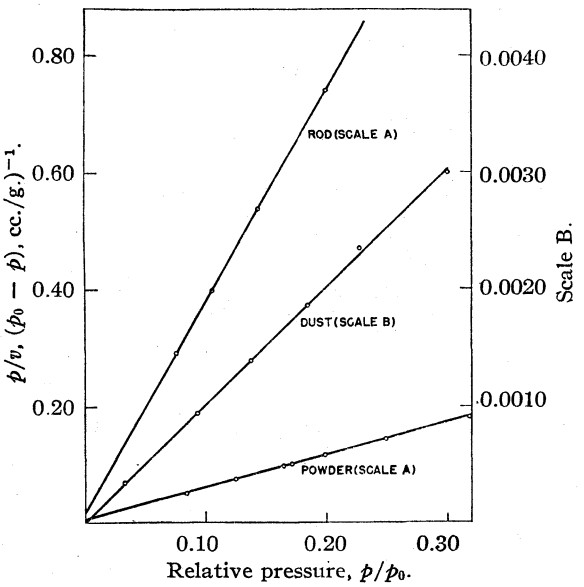


Fig. 2.—Adsorption of nitrogen at −195° on graphite (BET plots).

than that reported for any previous carbon, is only 2% of the monolayer nitrogen adsorption of 100 cc./g. The hydrogen adsorption would seem to represent the proportion of carbon atoms which have been exposed so as to show one or more strong valences of unsaturation, such as those of free radicals. This exposure would not occur if the graphite crystal is simply delaminated or scaled away, but would occur if the crystal is opened both along the main cleavage plane *and* at right angles to this plane (so as to uncover both face atoms and edge atoms).

The laminar structure of graphite, together with the indication that the chemically active surface represents only a small proportion of the total surface, suggests that the wear-dust particles are composed of thin plates, and that only edge atoms combine with hydrogen while face atoms in the main cleavage plane of graphite make up most of the total surface area. In this case the area of the chemically active surface and the fraction of the surface atoms which are chemically active may be readily calculated from the lattice dimensions. The main cleavage plane of graphite consists of carbon hexagons with the smallest interatomic distance 1.42 Å. and the separation between planes 3.39 Å. The area per carbon atom along an edge perpendicular to the main plane is therefore $1.42 \times 3.39 = 4.81$ sq. Å. If the hydrogen adsorption is due to one-to-one combination of hydrogen atom with edge carbon atoms, the chemically active surface covered by 1.98 cc. per gram is 5.12 sq. m./g. as listed in Table I. Any other lattice points reacting with hydrogen would lead to an even smaller value for the area of the chemically active surface. The remaining total surface, 430 sq. m./g., is considered to represent facial area. Each surface hexagon (equivalent to 2 carbon

atoms) occupies 5.24 sq. Å., so the total number of face atoms per g., $n_f = 430 \times 10^4/2.62 \times 10^{-16}$. The proportion of surface atoms which combine with the 1.98 cc. of hydrogen, presumably as edge atoms, is therefore $^1/_{155}$ or 0.65%. Although the "chemical" surface represents only a small fraction of the total surface, its absolute magnitude, 5.12 sq. m./g., is large compared with the *total surface* of the rod from which the dust was worn and is comparable with the *total surface* of natural graphite powders.

Size and Shape of Graphite Fragments.—The values of equivalent particle size in Table III

TABLE III

Sample	Specific surface, sq. m./g.	Equiv. part.-size, microns
No. 1		
Powder for making rod 1 (natural graphite)	7.65	0.349
Rod 1 (0.25 × 0.25 cm.² cross-section) (used for making dust)	1.3	2.05
Rod 1′ (0.51 × 0.63 cm.² cross-section) (other samples, same stock)	1.19	2.24
Rod 1″ (0.25 × 0.25 cm.² cross-section) (other samples, same stock)	1.13	2.35
Wear dust 1	435	0.0060
No. 2		
Rod 2 (electrographitized coke-bonded black-carbon)	1.88	1.42
Powder from grinding rod 2	4.62	0.58
Wear dust 2	390	0.0068

represent the diameter of hypothetical spheres (or the edge of cubes), calculated from the equation $d_3 = 6/\rho S$ where d_3 is in microns when S is in sq. m./g. and the density ρ is in g./cc. (2.25 for graphite). It is convenient to use the spherical model for comparison with the more usual forms of black carbon but a laminar model with a large ratio of area to thickness appears much more likely from the evidence discussed above. For a plate-like particle of area A and thickness t, the surface area may be considered as $2A$ with only a small error if the ratio of edge surface to total surface is small. The mass of the particle is $At\rho$, and the surface area per unit mass $S = 2/t\rho$. As long as the thickness t remains small compared with the area A, the specific surface area of the graphite is *independent of the size and shape* of the plates and is determined by the thickness. For wear-dust 1 with $S = 435 \times 10^4$ sq. cm./g., therefore, the indicated thickness $t = 20.4 \times 10^{-8}$ cm.

From the specific surface area alone there is no limitation on the size and shape of plate-like particles; only the thickness is determined. A probable limitation on the face to edge surface ratio appears in the ratio of total surface, from nitrogen adsorption at −195°, to "chemical" surface, from hydrogen clean-up at room temperature. The ratio of total surface atoms to hydrogen atoms adsorbed has been calculated to be 155. If this is assumed to represent the ratio of face atoms to edge atoms, the average size of the plates may be calculated. For a plate of area A, perimeter p, and thickness t, the total number of facial atoms $n_f = 10^{16} \times 2A/2.62$; the number of edge atoms in each basal plane $10^8\ p/1.42$, and the number of basal planes $10^8\ t/3.39$ approximately. The total number of edge atoms, therefore, $n_e = 10^{16}\ pt/4.81$ and the ratio of face to edge atoms, $n_f/n_e = 3.67\ (A/pt)$. When the thickness $t = 20.4$ Å. and the ratio $n_f/n_e = 155$, the ratio of area to perimeter, $A/p = 862 \times 10^{-8}$ cm.

In the limiting case of a circle of radius r, $A/p = r/2$; then $r = 1720$ Å. Circular plates of average radius 1720 Å. and thickness 20.4 Å. thus satisfy the requirements for both "total" and "chemical" surface, assuming combination of hydrogen with edge atoms. Plates of shape other than circular still satisfy the total surface requirement if the thickness is 20.4 Å. but must be of larger area than $\pi(1720 \times 10^{-8})$ sq. cm. in order for the ratio of face to edge atoms to remain at 155.

Evidence from Electron Microscope and X-Ray Diffraction.[8]—A typical electron micrograph of the wear-dust appears in Fig. 3. The electron microscope studies are discussed more fully elsewhere[2] but it is clear that a large range of sizes is present extending from 10000 Å. down to 100 Å. or less in diameter. A number of particles semi-transparent to the electron beam are present and these are certainly of a thickness considerably less than 100 Å. Furthermore the thin plates are

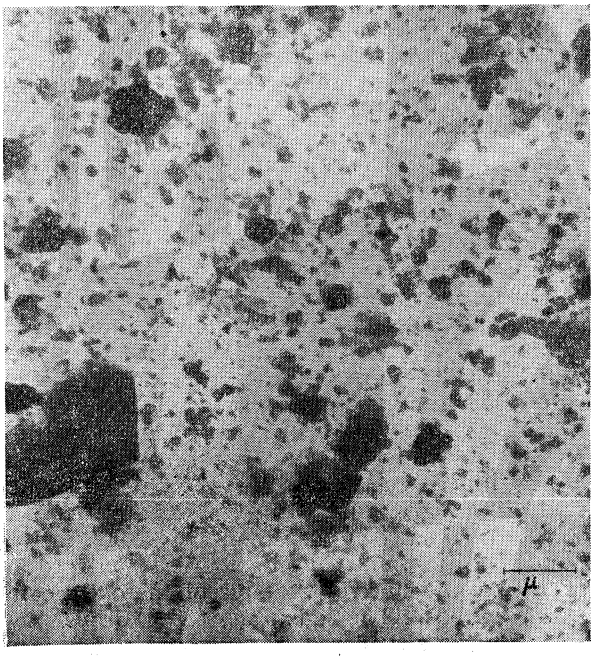


Fig. 3.—Electron micrograph of graphite wear-dust.

(8) The authors wish to thank Ernest F. Fullam for the electron micrograph, and David Harker for the X-ray data and its interpretation.

seen to vary in respect to thickness from opacity to invisibility; and since the gradation is continuous we cannot determine the concentration of particles too thin to be visible. Quantitative treatment is thus complicated by the large range of sizes present and by the transparency to the electron beam of very thin platelets.

X-Ray diffraction results provide interesting independent evidence for the structure of the wear-dust particles. Diffraction of copper Kα radiation from a thin layer of the wear-dust powder was carried out in a Geiger counter X-ray spectrometer. The output of the recorder, which plots intensity of the diffracted radiation against the diffraction angle, is shown in Fig. 4.

The sharp peak at 27° corresponds to the 00.2 reflection of massive graphite. (This reflection is from the cleavage planes.) The graphite crystals responsible for this reflection must be thicker than about 1000 Å. The sharp peak just mentioned is superimposed on a very broad maximum of about 10° width at half height. Such a diffraction effect is consistent with the assumption of either (a) distortion of the crystal lattice, (b) extremely small particle size or (c) both. The electron microscope evidence points toward alternative (b). If the line broadening is due entirely to particle size, the particles must be of the order of five times the interplanar distance or 20 Å. in thickness. This reflection provides no information on particle size in directions other than normal to the cleavage plane of graphite.

Thus the electron micrographs and X-ray diffraction show that the particles are predominantly very thin perpendicular to the hexagonal plane and of comparatively large diameter. Although a portion of the powder appears to consist of relatively thick fragments the results on the whole are in excellent agreement with the thin plate model. This supports the assumption that hydrogen reacts quantitatively with edge atoms. It should be noted that the estimate of 20 Å. thickness from the surface area is independent of the location of the chemisorbed hydrogen. Only the estimate of the face dimension depends on the ratio of edge to face atoms.

Clean-up of Other Gases.—Preliminary studies of nitrogen clean-up by the carbon wear-dust have indicated this is considerably less than for hydrogen. On two carbons it has been indicated to be 180 cu. mm. (STP)/g. or higher. The fact that it is appreciable seems to us to be rather remarkable since molecular nitrogen does not react with charcoal.[9] Preliminary data for methane showed an adsorption of roughly one-half that obtained with hydrogen; that is, roughly the same number of hydrogen atoms were involved per gram of carbon dust. The carbon monoxide adsorption was indicated to be somewhat higher than that of hydrogen.

(9) R. B. Anderson and P. H. Emmett, *J. Phys. Colloid. Chem.*, **51**, 1327 (1947).

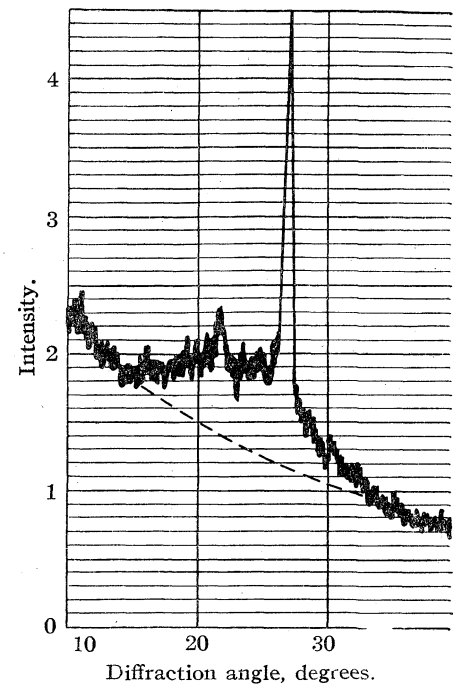


Fig. 4—X-Ray diffraction record for graphite wear-dust.

In measuring the chemical clean-up of these gases during the initial stages of the work, the bell-jar trap was chilled with liquid nitrogen to condense traces of water vapor. The trap was observed to collect a much larger proportion of the wear-dust when chilled than when held at room temperature, and because of the large carbon surface involved, there resulted considerable physical adsorption of such gases as nitrogen and methane at the low temperature. This complicated the chemical measurements, and to correct this difficulty in a later series of experiments the trap was retained at room temperature during the clean-up. Another complication was found to occur when the trap was warm, *viz.*, a slow evolution of water vapor which tended to compete in the clean-up and to modify the pressure reading. Further work is under way to bring the data on the other gases up to the degree of reproducibility found for hydrogen.

Summary

1. Carbon dust, formed by the high wear of graphite rods rubbing against a rotating base in vacuum, has been found to adsorb hydrogen, nitrogen, oxygen, carbon monoxide, carbon dioxide and methane irreversibly at room temperature. The hydrogen clean-up, 2 cc./g. of dust, is 10^5 times the adsorption shown by representative activated charcoals at room temperature and low pressures of the order of 10 microns.

2. In a typical case the *chemically active* specific surface of the dust is indicated by the hydrogen clean-up to be 5.12 sq. m./g. The total (physical) specific surface is found by nitrogen adsorption at −195° to be 435 sq. m./g., as calculated from the

measured adsorption of 100 cc. of N_2/g. for the monolayer. This total surface of the *graphite* dust is comparable with those of the best commercial activated carbons, and in addition 1.2% of this total surface showed a powerful chemical activity.

3. Nitrogen adsorption isotherms on graphite powder (raw material), finished graphite rods (brushes), and powder formed by pulverizing the rods in a high-speed impact grinder indicated surface areas of 7.7, 1.3 and 4.6 sq. m./g., respectively, compared with 435 sq. m./g. for the wear-dust.

4. It is shown that for a laminar model of graphite fragments in which the ratio of edge area to face area is small, the surface area per unit weight is independent of size and shape and depends only on the thickness of the fragments. A thickness of 20.4 Å. is indicated for the carbon wear-dust. A minimum average diameter of 3500 Å. is indicated for the face dimension on the assumption that hydrogen reacts quantitatively with edge atoms.

5. It is suggested that the chemically active portion of the dust represents unsaturated carbon valences at points of cleavage at right angles to the main cleavage plane. The wear dust appears to differ from previous carbon samples studied in that these strong valence bonds have been freshly opened, mechanically, and occur in large numbers; whereas the corresponding bonds in other carbons are ordinarily saturated by chemisorbed gas and are not opened by ordinary outgassing procedures.

SCHENECTADY, NEW YORK RECEIVED JANUARY 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Thermodynamics of Aqueous Solutions of Potassium Hydroxide[1]

BY G. C. AKERLOF[2] AND PAUL BENDER[3]

Introduction

The results presented in this paper represent a continuation of a program of studies of the thermodynamic properties of concentrated aqueous electrolytic solutions in which measurements on hydrochloric acid[4] and sodium hydroxide[5] solutions have already been reported. A detailed description of the experimental procedure and the method of calculation employed here has been given previously.[5] In the following all symbols agree with common usage or with those in earlier papers.

Preliminary Treatment of the Data.—The cell measured has the composition

$$Pt,H_2/KOH(m)/KxHg/KOH(m_r)/H_2,\ Pt$$

The cell reaction and the resulting electromotive force expression are given, respectively, by

$$KOH(m) + H_2O(m_r) + {}^1/_2H_2(m) \rightarrow KOH(m_r) + H_2O(m) + {}^1/_2H_2(m_r) \quad (1)$$

$$E = -\frac{RT}{F} \ln \frac{a_{KOH(m_r)} a_{H_2O(m)} a_{H_2(m_r)}^{1/2}}{a_{KOH(m)} a_{H_2O(m_r)} a_{H_2(m)}^{1/2}} \quad (2)$$

The reference concentration m_r was held constant at 0.09154 molal for twenty concentrations m of potassium hydroxide ranging from 0.2240 to 17.544 molal. The method employed to eliminate carbonate from the solutions has been described previously.[6] Measurements were made at ten-degree intervals from 0 to 70°; a small linear correction was applied to the observed electromotive force values to correct them to round temperatures.

A critical survey of the vapor pressure measurements of Smits,[7] Tammann,[8] Paranjpe[9] and Kobayashi[10] provided the information necessary for the correction of the observed electromotive forces to unit activity of hydrogen gas in each half-cell. Since all the measurements available were made by the static method, which tends to give too high values because of difficulty in the complete elimination of air from the solutions, somewhat greater weight was assigned to the lower vapor pressure values reported at a given concentration. The resulting correction reached a maximum value of 4.5 millivolts at 70° and 17.54 molal. The corrected electromotive force values are summarized in Table I; the average deviation of the observed points from smoothed values obtained by the method of least squares, assuming a quadratic dependence on the temperature, is less than 0.4 millivolt.

The water transfer potentials

$$\Delta E_{H_2O} = -\frac{RT}{F} \ln \frac{a_{H_2O(m)}}{a_{H_2O(m_r)}}$$

were evaluated by the method suggested by Akerlof and Kegeles[5] and more recently generalized by Stokes.[11] Their validity was checked by comparison with those calculated from the final log a_1 values; the agreement was well within the experimental error of the electromotive force measure-

(1) This paper is based on the dissertation presented in 1942 to the Faculty of the Graduate School of Yale University by Paul Bender in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Mellon Institute, Pittsburgh 13, Pennsylvania.

(3) Present address: Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin.

(4) Akerlof and Teare, THIS JOURNAL, **59**, 1855 (1937).

(5) Akerlof and Kegeles, *ibid.*, **62**, 620 (1940).

(6) Akerlof and Bender, THIS JOURNAL, **63**, 1085 (1941).

(7) Smits, *Arch. Neerland. 2*, **1**, 111 (1898); *Z. physik. Chem.*, **39**, 385 (1905).

(8) Tammann, *Mem. Acad. Petersburgh 7*, **35**, Nr. 9 and 64 (1887).

(9) Paranjpe, *J. Indian Inst. Sci.*, **2**, 59 (1918).

(10) Kobayashi, *J. Sci. Hiroshima Univ.*, **A2**, 274 (1931-32).

(11) Stokes, THIS JOURNAL, **67**, 1686 (1945).

TABLE I

OBSERVED ELECTROMOTIVE FORCE DATA, CORRECTED TO ROUND TEMPERATURES AND UNIT ACTIVITY OF HYDROGEN GAS

m	0°	10°	20°	30°	40°	50°	60°	70°
0.2240	0.0397	0.0418	0.0423	0.0437	0.0456	0.0474	0.0482	0.0492
.2847	.0497	.0515	.0533	.0551	.0567	.0584	.0591	.0611
.4829	.0742	.0779	.0808	.0826	.0852	.0868	.0907	.0924
.6997	.0915	.0954	.0996	.1021	.1042	.1076	.1094	.1129
.9956	.1104	.1148	.1183	.1226	.1256	.1290	.1325	.1351
1.9869	.1500	.1569	.1622	.1672	.1720	.1768	.1812	.1846
2.5141	.1681	.1723	.1785	.1846	.1890	.1942	.1993	.2038
2.9868	.1802	.1879	.1933	.1982	.2049	.2111	.2138	.2168
4.0565	.2107	.2173	.2239	.2308	.2380	.2429	.2471	.2520
5.0212	.2333	.2417	.2491	.2556	.2617	.2663	.2728	.2769
5.6545	.2515	.2574	.2648	.2714	.2773	.2816	.2861	.2879
7.0174	.2820	.2902	.2971	.3041	.3116	.3173	.3220	.3273
8.0473	.3046	.3145	.3217	.3278	.3347	.3412	.3459	.3490
9.0314	.3284	.3355	.3429	.3498	.3566	.3626	.3683	.3722
10.052	.3483	.3571	.3637	.3714	.3769	.3830	.3867	.3941
11.091	.3701	.3800	.3877	.3941	.4001	.4060	.4109	.4150
12.073	.3922	.4006	.4087	.4154	.4225	.4275	.4327	.4361
13.064	.4111	.4188	.4273	.4341	.4394	.4445	.4512	.4559
14.099	.4321	.4383	.4442	.4501	.4587	.4642	.4703	.4759
17.544	.4948	.5015	.5085	.5156	.5224	.5269	.5308	.5335

ments. The conclusion of Harned and Cook[12] that below four molal the water transfer potential is practically constant in the temperature range from 0 to 35° was confirmed.

Thermodynamic Properties of Solutions of Potassium Hydroxide.—The logarithm of the mean ionic activity coefficient of the solute was calculated using the equation

$$\log \gamma = \frac{-u\sqrt{m}}{1+\sqrt{2m}} + Bm + Cm^2 + Dm^3 + Em^4 \quad (3)$$

where u is the universal constant of the limiting law, and B, C, D, and E are empirical coefficients evaluated as functions of the temperature by the method of least squares. A summary of the results of this process is given in Table II. The extension of the calculation to the other thermodynamic properties of solute and solvent in terms of the constants of equation (3) has been given explicitly by Akerlof and Kegeles.[5] Figures 1 and 2 show the dependence on the concentration of log γ and of $(\log a_1)/m$ at the various temperatures at which measurements were made.

TABLE II

EMPIRICAL COEFFICIENTS USED FOR THE CALCULATION OF THE ACTIVITY COEFFICIENT OF THE SOLUTE IN AQUEOUS SOLUTIONS OF POTASSIUM HYDROXIDE

$B = 0.06629 + 0.0_36135t - 0.0_411018t^2 + 0.0_74096t^3$
$C = 0.010909 - 0.0_317108t + 0.0_516895t^2 - 0.0_87969t^3$
$D = -0.0_37351 + 0.0_59973t - 0.0_79347t^2 + 0.0_96215t^3$
$E = 0.0_415502 - 0.0_61980t + 0.0_818424t^2 - 0.0_{10}1764t^3$

Temp., °C.	u	Temp., °C.	u	Temp., °C.	u
0	0.487	25	0.506	50	0.534
10	.494	30	.511	60	.549
20	.502	40	.522	70	.565

(12) Harned and Cook, THIS JOURNAL, **59**, 496 (1937).

Discussion

The first amalgam cell measurements on potassium hydroxide solutions were made at 25° by Ming Chow,[13] who used flowing potassium amalgam and mercury–mercuric oxide electrodes. His results were considered unreliable by Knobel,[14] who repeated the work using hydrogen electrodes instead of the mercury–mercuric oxide type. Knobel's experimental results were subsequently recalculated, taking into account the water transfer potential, by Harned,[15] Scatchard,[16] and Harned and Akerlof.[17] In the latter calculations, in which the extrapolations were based on the Debye–Huckel theory, log γ values were obtained which are in fair agreement with those here reported. More recently amalgam cell measurements covering a concentration range up to four molal at temperatures from 0 to 35° were reported by Harned and Cook.[12] Our results are on the whole in good agreement with theirs over their entire measuring range.

The electromotive force measurements at 25° of Shibata and co-workers[18] are in excellent agreement with ours at hydroxide concentrations up to seven molal with an average deviation of 0.3 mv. between the two sets of results. This comparison suggests that contrary to previous opinion the mercury–mercuric oxide electrode might function reversibly without undesirable side reactions, at least in dilute alkali solutions. At higher concentrations investigated in the two researches greater deviations are observed. In this connection the

(13) Chow, *ibid.*, **42**, 488 (1920).
(14) Knobel, *ibid.*, **45**, 470 (1923).
(15) Harned, *Z. physik. Chem.*, **117**, 23 (1925).
(16) Scatchard, THIS JOURNAL **47**, 658 (1925).
(17) Harned and Akerlof, *Physik. Z.*, **27**, 426 (1926).
(18) Shibata, Murata and Toyoda, *J. Chem. Soc. Japan*, **52**, 627 (1931); Shibata and Murata, *ibid.*, **52**, 645 (1931).

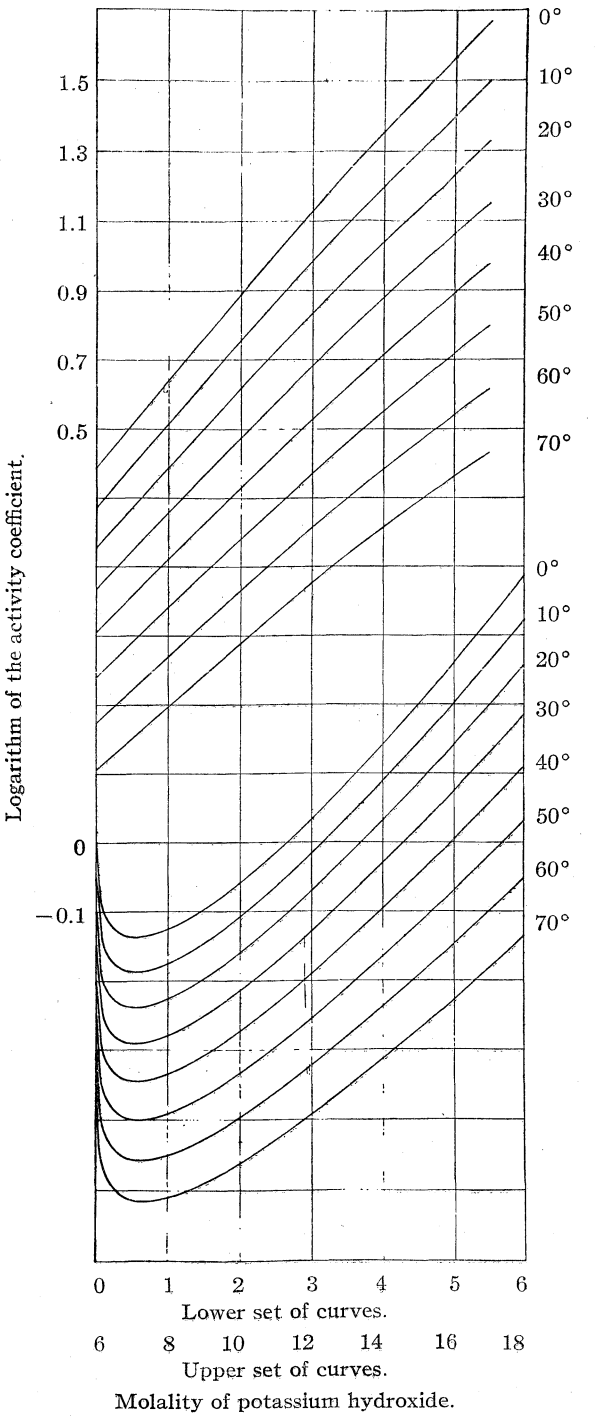


Fig. 1.—Isotherms for the logarithm of the activity coefficient of potassium hydroxide. The curves for the concentration range 6 to 17.5 molal are plotted on half the scale of those for the range 0 to 6 molal. The figures on the ordinates are for 0°; for each 10° rise in temperature the ordinate is shifted by 0.05 for the lower set of curves, and by 0.1 for the upper set.

possibility of specific effects arising in very concentrated hydroxide solutions cannot be ignored.

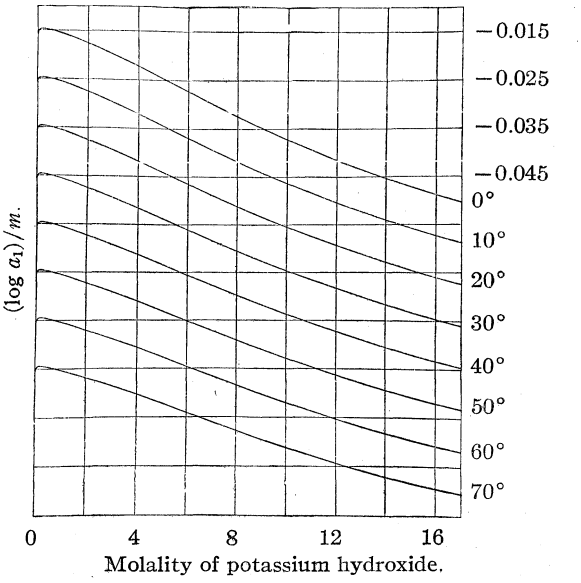


Fig. 2.—Isotherms for the function (log a_1)/m for aqueous solutions of potassium hydroxide. The figures on the ordinates are for 0°; for each 10° rise in temperature the ordinate is shifted by 0.010.

In a comparison of the curves for log γ for sodium and potassium hydroxides and hydrochloric acid we find that with increasing temperature and concentration they approach each other rapidly, the large individual differences observed at lower temperatures and moderate concentrations tending to disappear. A study of the behavior of these curves at concentrations or temperatures considerably above those previously employed would be of great interest.

A direct determination of log a_1 from electromotive force measurements on the cell $Pt,H_2/KOH_{(m)}/HgO\text{-}Hg$ has been attempted by Shibata, Kobayashi and Furukawa,[19] but the values reported by them differ appreciably from ours, which are in good agreement with the available experimental vapor pressure data.

An attempt to determine the relative partial molal heat contents and heat capacities subjects the original data to a very severe test, since the evaluation of these quantities involves the first and second differential coefficients of the original results with respect to the temperature. Values have been calculated for the relative partial molal heat content of the solute and compared with those of Harned and Cook[12] and Rossini,[20] whose computation was based on the calorimetric determinations of Richards and Rowe[21] and Pratt.[22] The calculation gives in both cases what might seem to be only fair agreement. This is due partly to the very high accuracy required in the basic experimental work, and partly to the method of compu-

(19) Shibata, Kobayashi and Furukawa, *J. Chem. Soc., Japan*, **52**, 404 (1931).

(20) Rossini, *Bur. Standards J. Research*, **6**, 791 (1931).

(21) Richards and Rowe, THIS JOURNAL, **43**, 770 (1921).

(22) Pratt, *J. Franklin Inst.*, **185**, 663 (1918).

tation employed. The use of quadratic equations instead of cubic equations for the coefficients of equation 3 changes the value of $\bar{L}_2$ by over 70 calories per mole at a concentration of 2 molal and 18°, although the changes so produced in the values of the coefficients themselves amount to a few tenths of a per cent. at most. Actually the agreement between our results and those obtained by Rossini is quite respectable, as is shown by the following comparison for a temperature of 18°

m	0.09	0.16	0.25	0.36	0.64	1.00	1.44	1.96
$\bar{L}_2$, cal./mole, this study	145	168	186	198	218	242	292	374
$\bar{L}_2$, cal./mole, Rossini	131	145	148	147	147	137	164	207

No direct comparison with the work of Shibata and associates[18] is possible, but from their measurements can be derived values of E and dE/dT for the cell

$$Hg-HgO/KOH(m)/K_xHg/KOH(m_r)/HgO-Hg$$

for which there holds the relation

$$FE - FT\,(dE/dT) = \bar{L}_2(m) - \bar{L}_2(m_r) + {}^1/_2\bar{L}_1(m_r) - {}^1/_2\bar{L}_1(m) \quad (4)$$

Values of the right-hand side of the equation calculated from their data differ by an average of 100 calories from those calculated for the left-hand side from our data, over a concentration range from one to twenty molal at 25°.

In the case of the relative partial molal heat capacity of the solute, our values differ from those of Harned and Cook[12] by an average of only one calorie per degree per mole for concentrations up to four molal in the temperature range from 0 to 25°. The average difference between our results and the direct calorimetric measurements of Gucker and Schminke[23] at 25° is less than three calories per degree per mole.

In the calculation of the relative partial molal entropy of the solute and solvent an interesting result was obtained. At high solute concentrations on each isotherm the values obtained for these quantities were constant within the experimental error, the entropy level for both solute and solvent changing almost linearly with the temperature. This behavior is illustrated for the solute in Fig. 3. The deviations of the entropy changes of the solvent in concentrated solutions from the requirements of the limiting law should be connected with definite structural changes, and they will be of the greatest interest when a more adequate theory is available. The practically constant values obtained for the relative partial molal entropies at high concentrations of potassium hydroxide would seem to suggest evidence for a structural constancy of the solutions over a large concentration range.

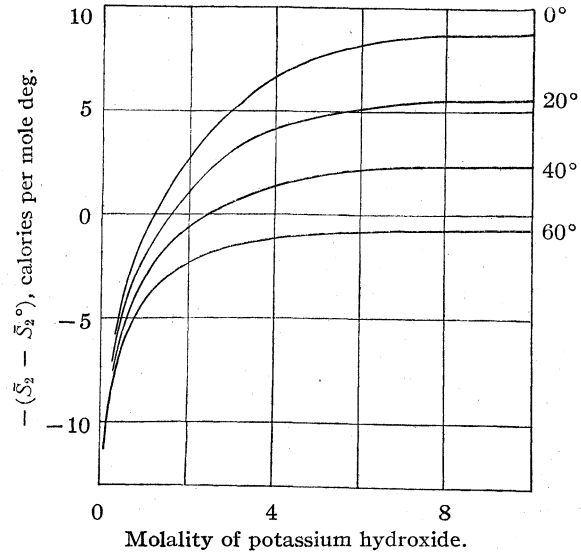


Fig. 3.—Isotherms for the relative partial molal entropy of the solute in aqueous solutions of potassium hydroxide.

Summary

The electromotive force of the cell $Pt,H_2/KOH(m)/K_xHg/KOH(m_r)/H_2,Pt$ has been measured at a number of hydroxide concentrations up to 17 molal over the temperature range from 0 to 70°. Various thermodynamic properties of both solute and solvent were computed and compared with earlier, pertinent data in the literature.

(23) Gucker and Schminke, THIS JOURNAL, **54**, 1358 (1932).

NEW HAVEN, CONN. RECEIVED FEBRUARY 27, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Characterization of Ion Exchange Resins. I. Acidity and Number of Constituent Cation Exchange Groups[1,2]

BY HARRY P. GREGOR AND J. I. BREGMAN[3]

Investigations of the resinous ion exchange process are possible only on an empirical level without a knowledge of the physio-chemical properties of the resins themselves. In order to determine the numbers and kinds of exchange groups making up a resin, two techniques were developed, the first being a direct titration of the resin with base in the presence of neutral electrolyte; the second procedure involved adding to the resin the salt of a weak acid and determining the extent of reaction by back-titration of the buffer. Resins made from known starting materials have been characterized.

Cation exchange resins are high molecular weight polyacids which are virtually insoluble in aqueous and non-aqueous media. The acid or acids which constitute the exchange groups are usually of the sulfonic, carboxylic or phenolic type, and are substituents in the resin structure (usually of the phenol-aldehyde type).[4] Their exchange properties can be ascribed as being entirely due to the exchange of various cations for the dissociable hydrogen ion. Resins of the phenol-sulfonic–phenol–formaldehyde type have been prepared and are commercially available which contain 10% sulfur, and a corresponding exchange capacity of 3.1 mmoles. per gram. Therefore, the $-SO_3H$ group itself must comprise at least 25% of the mass of the resin in the dry state. When the resin is placed in water it swells strongly, usually doubling its weight. Thus approximately 60% of the hydrated mass of the resin is the exchange group itself and the water associated with it. Therefore, a true picture of a cation exchanger is that of a structure containing large polar exchange groups held together by a three-dimensional hydrocarbon network.

If the direct titration of a cation exchange resin in the hydrogen state is attempted, there will be no *p*H change in the external solution until the end-point of the titration is reached if the exchanger contains only strong acid groups. The reaction can be written

$$R—SO_3H + NaOH = R—SO_3Na + H_2O$$

Here the actual titration is taking place within the pores of the resin, and the *p*H changes cannot be measured directly. An exact empirical expression[5] describing the exchange reaction is

$$\frac{(Na^+)_R}{(H^+)_R}\left[\frac{(H^+)_S}{(Na^+)_S}\right]^n = K$$

where the subscripts refer to the resin and external solution phases. Since the ratio of the activity coefficients of univalent cations is nearly equal to unity, concentrations are used in place of activities. If a large excess of a neutral sodium salt is added, the ratio $(Na^+)_R/(Na^+)_S$ becomes small because n is 0.8–1.0 and K is 0.5–2.0 for most resins. The ratio $(H^+)_S/(H^+)_R$ must become very large and virtually all of the hydrogen ions are in the solution phase. Thus the addition of neutral salt displaces an ion into solution upon dissociation, and yields results comparable to those which would be obtained if the resin were soluble. This is also the case for the weak acid resins.

For the buffer titration an acid resin is added to the salt of a weak acid. An excess of neutral salt is also required, and the reaction is

$$R—H + Na^+ + A^- = R—Na + H^+ + A^-$$

where R—H represents the acid resin and HA the weak acid. The number of exchangeable hydrogen ions of the resin equals the moles of hydrogen ions which are displaced at the equilibrium *p*H. The resin is filtered and the solution back-titrated with sodium hydroxide to the initial *p*H of the buffer salt solution; the number of displaced hydrogen ions in the resin is the equivalent of base required at the equilibrium *p*H. A plot of these capacity values as a function of *p*H is the equivalent of the titration curve of the resin acid.

The terms "number of exchangeable" hydrogen ions and the conventional term "exchange capacity" do not necessarily mean the same thing, for the number of cations taken up by a hydrogen exchanger may be greater[6] than the number of hydrogen ions displaced. This may be due to complex ions, and is usually found when polyvalent ions are exchanged.

Experimental

Selection and Treatment of Resins.—The resins were either ones prepared from the patent literature or commercial resins where the procedures for the synthesis were known. Since the chemicals were usually of technical grade, the resins themselves were, as a rule, not of high purity. In addition, the curing treatment which includes heating for prolonged periods at elevated temperatures may partially decompose the resins and introduce new exchange groups. The resins used included: (A) phenol–formaldehyde, alkaline condensed[7]; (B)

(1) Presented before the Division of Colloid Chemistry of the American Chemical Society, New York, N. Y., September 16, 1947.

(2) This work is abstracted from the Dissertation of J. I. Bregman presented in partial fulfillment of the requirements for the degree of Master of Science in Chemistry at the Polytechnic Institute of Brooklyn, October, 1947.

(3) Present address: Fels and Company, Philadelphia, Pa.

(4) R. J. Myers, "Advances in Colloid Science, Vol. I," Interscience Publishers, Inc., New York, N. Y., 1941.

(5) R. Griessbach, "Preparation and Applications of Ion Exchange Adsorbents," Verlag Chemie, Berlin, 1939.

(6) H. Chaya, B.S. Thesis, Polytechnic Institute of Brooklyn, May, 1947.

(7) B. A. Adams and E. L. Holmes, U. S. Patent 2,104,501, Jan. 4, 1938.

phenolsulfonic acid–phenol–formaldehyde, acid condensed[8]; (C) phenolsulfonic acid–phenol–formaldehyde, alkaline condensed[8]; (D) phenol–formaldehyde, alkaline condensed in the presence of sodium sulfite[9]; (E) phenol–formaldehyde, alkaline condensed, cured and dried, then treated with sodium sulfite[9]; (F) salicylic acid–phenol–formaldehyde, alkaline condensed[8]; (G) coal treated with 2 *M* sodium hydroxide at elevated temperatures in a bomb; (H) coal treated with hot concentrated sulfuric acid[10]; (J) polystyrene directly sulfonated with chlorosulfonic acid.[11]

The resins were wet screened to −20 + 30 mesh, and "conditioned," *i. e.*, treated alternately with large excesses of 1 *M* hydrochloric acid and 1 *M* sodium chloride to remove soluble components of the resin and displace any heavy metal cations present. The resins were regenerated, *i. e.*, converted to the hydrogen or acid state by passing a large excess of 1 *M* hydrochloric acid through a bed of the resin very slowly and then rinsed with carbon dioxide free distilled water to an effluent *p*H of 4. Due to resin solubility, *p*H values above 4 are usually not obtained at slow flow rates. The material was then air dried until the particles no longer adhered to one another, and its moisture content determined by drying over phosphorus pentoxide. Air dried resin was used for experiments because the desiccated form is very hygroscopic and frequently decrepitates in water. Resin ground to give particles of a smaller size was regenerated again to remove added impurities and to convert to the acid state any newly available exchange groups.

Direct Titration.—In order to obtain a resin containing different acidic groups, resin K was prepared by sulfonating phenol with an excess of fuming sulfuric acid, adding phenol and a slight excess of formaldehyde and condensing in the acid state. This resin showed an increased exchange capacity with increasing alkalinity, indicating the presence of "weak-acid" capacity.

A number of 0.5-g. portions of resin K were weighed into flasks containing 100 ml. of varying concentrations of sodium chloride made up in doubly distilled water. Different amounts of standard (0.5 *N*) sodium hydroxide were added to each flask, which was then shaken for twenty-four hours and which was sufficient for the establishment of equilibrium, as shown by tests to be described later. The equilibrium *p*H of the solution was measured with a Beckman "high *p*H" glass electrode. All values given hereafter are for 1 g. of moisture-free hydrogen resin.

Experimental values for the direct titration are shown in Fig. 1. These experimental curves, showing a displacement to lower values of *p*H as the neutral salt concentration is increased, are in qualitative agreement with curves calculated using the empirical expression given above.[5] Sodium chloride solutions more concentrated than 0.5 *N* gave the same results as the 0.5 *N* solution.

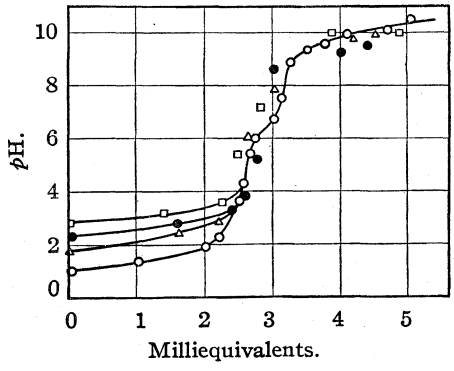


Fig. 1.—Direct titration of resin K with sodium hydroxide in sodium chloride solutions: □, 0.000 *N*; ●, 0.002 *N*; △, 0.028 *N*; ○, 0.500 *N*.

Resin K was also titrated rapidly in 0.5 *N* sodium chloride in the customary manner, and curves for −20 + 30 and −100 mesh material is shown in Fig. 2. The curve for 0.02 *N* hydrochloric acid is included for comparison.

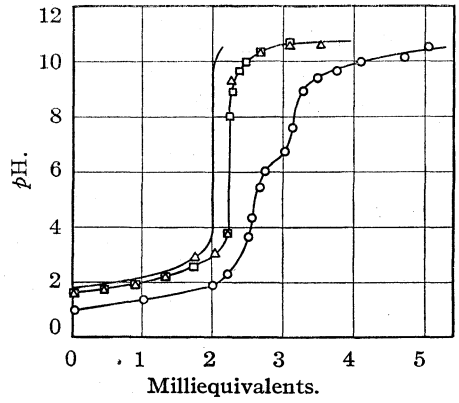


Fig. 2.—Rapid direct titration in 0.5 *N* sodium chloride of resin K: △, −20 + 30 mesh; □, −100 mesh; ○, −20 + 30 equilibrium value; —, 0.02 *N* hydrochloric acid.

Buffer Titrations.—These determinations were carried out by adding 0.5-g. samples of resin K to 100 ml. of 0.02 *M* solutions of sodium salts of weak acids in 0.5 *N* sodium chloride, shaking for twenty-four hours, filtering off resin and back titrating to the original *p*H of the solution with sodium hydroxide. Buffer salts were selected which covered the *p*H range from 3 to 10, and which gave a sharp back titration end-point. These included sodium tartrate, acetate, citrate, monohydrogen phosphate, carbonate and phosphate. The buffer titration curve for resin K is shown in Fig. 3, together with the direct titration curve for the same resin.

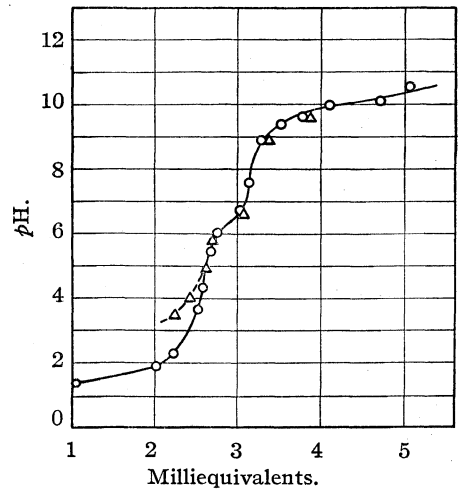


Fig. 3.—Direct (○) and buffer (△) titration curves for resin K.

Several variations of the above procedure were investigated. When sodium salts were replaced with those of lithium and potassium, identical titration curves were found. When the concentration of the buffer salt was varied from 0.01 to 0.1 *M*, the curves were unchanged when corrected to an ionic strength of 0.5. When the

(8) H. Wassenegger and K. Jaeger, U. S. Patent 2,204,539, June 11, 1940.

(9) H. Wassenegger, R. Griessbach and W. Sutterlein, U. S. Patent 2,228,159, Jan. 7, 1941.

(10) P. Smit, U. S. Patent 2,191,063, Feb. 20, 1940.

(11) G. F. D'Alelio, U. S. Patent 2,366,007, Dec. 26, 1944.

sodium chloride concentration was made lower than 0.2 *N* the titration curves became altered, presumably because insufficient neutral salt was present to displace all of the dissociated hydrogen ions.

When the −20 + 30 mesh resin was ground to −100 mesh, regenerated and titrated, the titration curve was found to be unchanged. However, when a lot of commercial resin was screened and each fraction tested, wide variations in the results frequently appeared.

The rate of exchange was determined by treating hydrogen resin with 0.5 *N* sodium chloride with rapid stirring, using a glass electrode to measure the rate. After a constant *p*H was reached, the resin was filtered and placed in a 0.02 *M* solution of disodium hydrogen phosphate in 0.5 *M* sodium chloride, and the rate measured as before. At equilibrium the process was repeated with trisodium phosphate. The milliequivalents of hydrogen ion displaced were calculated from the experimental *p*H values, using as a calibration curve the titration of that same buffer salt solution with hydrochloric acid.

While the rate was measured at a variable *p*H value, well defined results were obtained, as shown in Fig. 4 with resin C.

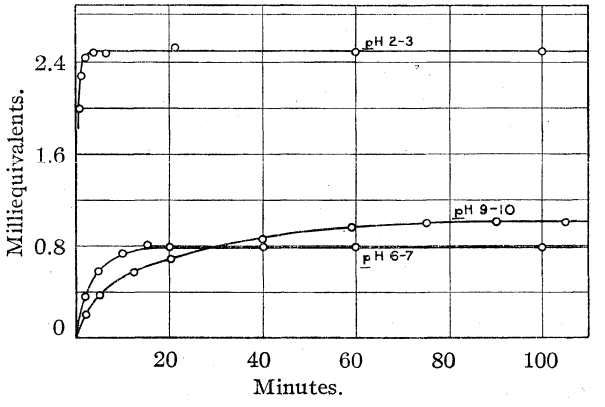


Fig. 4.—Rate of exchange at different *p*H levels for resin C.

Buffer titration curves for a number of different resins are shown in Figs. 5 and 6, the letters adjacent to each curve referring to the resins described earlier.

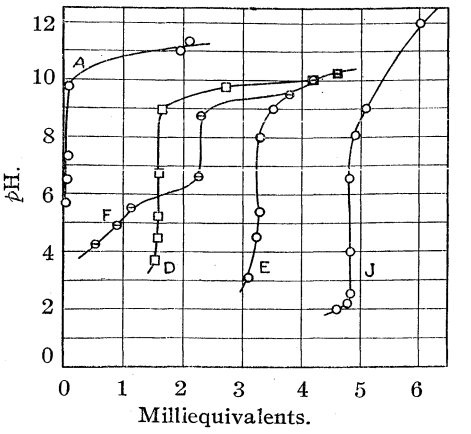


Fig. 5.

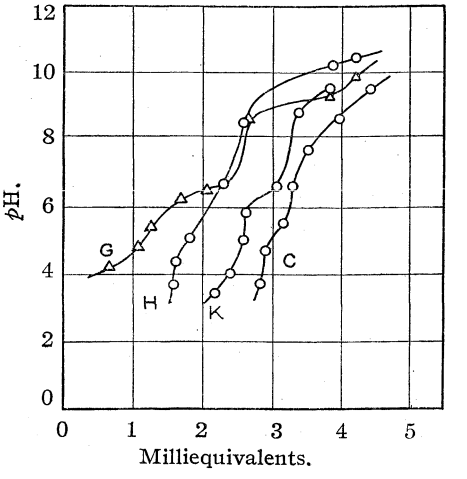


Fig. 6.

Discussion

The direct or buffer titration of a resin, when carried out in an excess of neutral salt, gives results comparable to those that would be obtained if the resin were in true solution. Since the process is one of displacement of the hydrogen ion, the nature of the cation used does not appreciably affect the results when only alkali metal cations are used.

The apparent anomalies in the rate studies can be explained by considering that the strong acid groups, by virtue of their high degree of hydration and large hydrated volume, are surrounded by a more open resin matrix than the smaller, weakly dissociated groups. Therefore the rate of diffusion of the exchanging ion to a strong acid group is greater than for a weak acid group. This is shown by the rate studies in Fig. 4. When the particle is reduced in size by grinding, the fractures probably occur at the wider pores, and the time for reaction of a weak acid group is reduced only by the time required for diffusion into the wider pores. Thus a rapid titration of even a resin of small particle size does not show the presence of weak acid groups. Further studies are in progress to test the validity of this postulate.

The electro-chemical nature of the acidic groups does not seem to be strongly affected by their being a part of the resin structure. The phenolic group has a *pKa* value of approximately 10, and the carboxyl group has a *pKa* value of 5.5. Resins prepared using sodium sulfite do not show the diverse groups which appear in the sulfonated resins, presumably as a result of the oxidizing sulfonating procedure. The two cation exchangers not of resinous nature show titration curves compatible with their preparative procedures. The gradual slopes of their curves indicate the complex nature of these natural products.

A true cation exchange resin can now be defined as a solid phase containing dissociable cations which will exchange for any other cation independently of the nature of the anion of the exchanging cation in solution. A base absorbent is a solid phase containing dissociable cations which will exchange for any other cation only when weak acid anions or hydroxyl ions are the anions of the exchanging cation in solution. A comparable

definition would restrict true cation exchange resins to those which contain only completely dissociated acidic groups, *i. e.*, strong acid resins.

BROOKLYN, N. Y. RECEIVED DECEMBER 27, 1947

[CONTRIBUTION NO. 75 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

Chain Transfer in the Polymerization of Styrene. II. The Reaction of Styrene with Carbon Tetrachloride[1]

BY R. A. GREGG AND FRANK R. MAYO

Using literature data on the uncatalyzed polymerization of styrene, a previous paper[2] from this Laboratory showed that the effects of solvents in reducing the molecular weight of polymerizing styrene could be correlated on the basis that the growing polymer radical captures an atom from the solvent molecule, resulting in a radical which starts a new chain[3] and in the incorporation of solvent in the polymer. Since these relations promised to be useful in making quantitative comparisons of the reactivities of solvents toward free radicals, a thorough test of the equations and concepts on the styrene–carbon tetrachloride system was begun. The present paper considers both the uncatalyzed and peroxide-catalyzed polymerization of styrene at 60–132° to give products averaging more than thirty styrene units per polymer molecule, or per incorporated carbon tetrachloride molecule. A succeeding paper[4] will consider formation of products averaging as low as two styrene units per carbon tetrachloride residue.

Experimental

Purification of Materials.—Dow styrene was freed from inhibitor by vacuum distillation and the middle fractions were partially crystallized by stirring in a Dry Ice-bath. The process was repeated from six to eight times until the freezing point became constant. The recrystallized material was distilled under nitrogen: b. p. 44.9–50° at 18 mm.; $n^{20}D$ 1.5465; f. p. −30.7° ± 0.1°. The styrene was stored in sealed, evacuated tubes in Dry Ice.

Reagent grade carbon tetrachloride was stirred with concentrated sulfuric acid and then with potassium hydroxide solution, washed with water, and dried over calcium chloride. It was distilled from paraffin wax[5] through a 1-meter helices-packed column: b. p. 76.8° at 760 mm.; $n^{20}D$ 1.4605.

Benzoyl peroxide was twice dissolved in cold chloroform and precipitated by pouring into cold methanol, collected on a sintered glass filter, and dried under vacuum at room temperature. It liberated 100.0–100.4% of the theoretical quantity of iodine from potassium iodide in glacial acetic acid.[6]

Preparation of Polystyrene Samples.—Weighed amounts of carbon tetrachloride and styrene (and benzoyl peroxide, when used) were placed in a flamed Pyrex tube equipped with a standard taper joint. The tube was attached to the vacuum line and the sample was frozen in liquid nitrogen. The tube was then evacuated and the sample was degassed twice by thawing and refreezing. The tube was then sealed at a pressure of 10^{-5} mm. Check experiments in which both the solvent and the styrene were distilled under high vacuum into the reaction tube showed no difference, even with large volumes of other solvents. The polymerizations were carried out in thermostats at 60 ± 0.05°, 100 ± 0.1°, and 132 ± 1°, and held to about ten per cent. conversion.

The polymer was precipitated with methanol and redissolved in twenty-five to fifty times its weight of benzene. This solution was then treated with three to five times its volume of methanol. An additional solution and precipitation was used for many of the samples whose molecular weights were determined osmometrically. The decanted precipitating medium was usually centrifuged to obtain any suspended polymer. The polymer was dissolved in benzene; the solution was frozen in Dry Ice, and the benzene was removed by sublimation.[7]

The above procedure results in loss of some of the very low molecular weight polystyrene; where the average molecular weight of the polymer was low, some of the precipitating solutions were rapidly concentrated by distillation *in vacuo* and the residue was dissolved in benzene and added to the main portion of the polymer. This procedure permits distillation of monomer from a *small* amount of *low* molecular weight polymer instead of from the whole polymer and gave products, marked in Table I, with appreciably lower average degrees of polymerization.

Determination of Number Average Molecular Weights from Osmotic Pressure.—These determinations were made by Drs. R. H. Ewart, H. C. Tingey and M. Wales.[8] The osmotic pressures were measured either in glass[9] or metal osmometers[10] with cellophane membranes and at three or more concentrations. Either butanone or benzene was used as the solvent, with identical end results.

Viscosity Determinations.—Solution viscosities were determined in benzene at 30°, using Fenske viscometers with 80–120 second flow times and neglecting kinetic energy corrections. Such corrections would give an increase of about 5% in intrinsic viscosities but would not affect the present molecular weight estimates from viscosity data. Where the molecular weight was determined independently, the intrinsic viscosity,[11] $[\eta]$, was obtained from specific viscosities at three or more polymer concentrations. Otherwise, the intrinsic viscosity was obtained from the specific viscosity of a single solution, measured in two

(1) This paper was presented before the Polymer Forum at the Atlantic City Meeting of the American Chemical Society, April 10, 1946.

(2) Mayo, THIS JOURNAL, **65**, 2324 (1943).

(3) Essentially the same development has been made independently by Hulburt, Harman, Tobolsky, and Eyring, *Ann. N. Y., Acad. Sci.*, **44**, 371 (1943), and by Medvedev, Koritskaya and Alekseeva, *J. Phys. Chem. U. S. S. R.*, **17**, 391 (1943).

(4) Mayo, paper submitted to THIS JOURNAL.

(5) Weissberger and Proskauer, "Organic Solvents," Oxford University Press, 1935, p. 156.

(6) Liebhafsky and Sharkey, THIS JOURNAL, **62**, 190 (1940).

(7) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1943).

(8) Ewart and Tingey, *Abstracts of Papers*, 111th Meeting American Chemical Society, April, 1947, p. 4Q.

(9) French and Ewart, *Ind. Eng. Chem., Anal. Ed.*, **19**, 165 (1947).

(10) Flory, THIS JOURNAL, **65**, 372 (1943).

(11) Kraemer and Lansing, *J. Phys. Chem.*, **39**, 153 (1935).

TABLE I

THERMAL POLYMERIZATION OF STYRENE IN CARBON TETRACHLORIDE

$\frac{[CCl_4]}{[Styrene]}$[a]	Time, hr.	Yield, %	k[b] × 10^4	[η]	No. av. mol. wt. × 10^{-3} (osmotic)	(Cl)[c]	Analyses, % Cl	$1/\bar{P}$ × 10^5 ([η])[d]	(Cl)[e]	C × 10^5 ([η])[f]	(Cl)[g]
Experiments at 60°											
0.000			1.1[i]	3.43[k]				10.1($1/\bar{P}_0$)			
.00291	85	6.8	1.00	2.94				12.6		830	
.00614	85	6.9	1.06	2.46	610 ± 60			16.1		950	
.0214	95	7.7	1.16	1.90	510 ± 40			23.1		1010	
.0186	115.4	9.14	1.02	1.70				27.1		870	
.0267	93	7.7	1.01	1.39	290 ± 40			35.9		920	
.0393	115.4	11.68	1.35	1.10				49.8		950	
.0413	112.2	8.8	1.00	1.06	237 ± 15	159	0.075	52.4	66	975	1270
.0704	112.2	9.1	1.08	0.826	131 ± 5			74.8		880	
.074	162.5	16.1	1.45	.69	125			95.7		1070	
.1000	85	5.4	0.78	.64	107 ± 10			106		930	
.1026	212	19.4	1.42	.60				117		940	
.1615	85	7.9	1.29	.494	82 ± 5			153		850	
.1643		6.28	0.89	.486		63	.212	156	167	860	920
.1958		5.22	0.60	.35		42	.339	247	260	1180	1250
.2595	85	9.0	1.63	.356	50[m]			242		850	
.3045	113.5	9.08	1.32	.314		30.3	.41	289	314		952
.3645	160	6.2	0.76	.26	< 50	27.9	.480	376	375		967
.4515	160	10.5	1.19	.25		26.5	.521	397	395		810
.471	159.2	11.9	1.38	.237		25.5	.541	429	410		798
.682	187.7	11.5	1.23	.196		18.3	.760	563	573		778
.853	185	7.23	0.86			13.7	1.02		769		854
.931	187.7	9.82	1.23	.168		14.8	0.94	696	709		712
.940	92.3	11.7	1.84	.155		14.4	0.967	780	730		721
1.000	192	5.12				13.4	1.04		784		752
1.052	285	12.25[h]	0.94			10.5	1.34		1002		885
1.051	285	12.25[h]	0.94			10.7	1.32		984		879
1.181	92.3	8.8	2.49	.142		12.7	1.10	890	830		657
2.043	252	2.68	0.36			6.87	2.05		1550		742
Experiments at 100°											
0.000	4.1	9.17	28.5[j]	1.81[k]				24.8($1/\bar{P}_0$)			
.00582	4.1	10.81	34.6	1.38				36.3		1860	
.0124	4.0	10.31	35.3	1.14	216	199	0.037	47.3	52	1710	2070
.0222	4.3	9.95	32.3	0.876	159	142	.066	68.4	74	1860	2080
.02643	5.3	10.90	27.3	.82				75.2		1810	
.0416	4.3	10.27	31.6	.628	105	80	.143	109	130	1930	2400
.0496	4.0	9.37	30.5	.573	93	82	.139	124	127	1910	1960
.0892	4.3	9.20	30.0	.428	58	48	.26	187	217	1730	2050
.194	4.3	8.32	27.5	.261		29.2	.45	374	358		1640
.3157	4.3	7.37	27.5	.204		18.5	.735	531	570		1660
.4943	6.6	8.90	30.8	.158		13.6	1.01	758	776		1450
.676	7.5	10.59	29.3	.133		10.8	1.28	969	978		1330
.683	8.0	4.70	13.7			7.95	1.75		1335		1870
.890	8.0	7.39[h]	20.6			6.90	2.02		1541		1640
1.023	12.0	13.1	27.1			6.06	2.30		1760		1630
1.228	11.0	8.08	15.9	.084		6.55	2.13	1860	1626		1248
1.980	16.6	*ca.* 10[h]				3.45	4.07		3155		1500
2.00	16.8	9.81	20.2			3.60	3.9		3010		1420
2.043	15.8	8.16	17.9			3.65	3.86		2980		1390
3.05	23.2	8.08	15.9			2.56	5.50		4300		1340
0.211[i]	45.4	10.33	20.6	.233				438		1860	
Experiments at 132°											
0.000	0.83	18.2	308[j]	.99[k]	171 ± 2.6		0.00	57.6($1/\bar{P}_0$)			
.0341	.83	19.0	331	.46		57	.172	169	185	2950	3370
.0713	.83	17.2	304	.31		33.5	.345	294	311		3260
.100	.9	19.55	344			29	.41		360		2730
.150	.9	15.57	269			19.4	.655		541		2980
.200	.9	16.25	290			15.0	.87		701		2970

[a] Initial molar solvent:monomer ratios. [b] Over-all second order rate constant in liters mole^{-1} hour^{-1}. [c] Equation (7). [d] Equations (2) and (8). [e] Equations (5–6). [f] Equation (3). [g] Equation (4). [h] Precipitating media concentrated to recover dissolved polymer. [i] Five volumes of benzene used as diluent for styrene–carbon tetrachloride mixture. [j] Average value from six experiments. [k] Averaged value, maximum deviation 0.05. [l] Single representative experiment. [m] For weight average and Z-average molecular weights, see Wales, Bender, Williams and Ewart, *J. Chem. Phys.*, **14**, 353 (1946).

different viscometers, and the equation

$$[\eta] = \frac{\sqrt{1 + 1.5\eta_{sp}} - 1}{0.75C_v} \qquad (1)$$

where C_v is the grams of polymer per 100 cc. of solution at the temperature of the viscosity measurement.

Chlorine Determinations (by Dr. O. W. Lundstedt and Mr. G. S. Mills).—For the determination of very small proportions of chlorine, the method of Shriner[12] was modified. A 20 mm. i. d., 80-cm. Vycor tube was heated in a furnace to about 800°. The tube had a 15 cm. section of crushed platinum foil in the hottest portion of the furnace and the remainder of the tube was packed with crushed Vycor interspersed with 50-mesh platinum disks. Oxygen, at a rate of 20 cc. per minute, was used to burn the sample which was heated by a mechanically-advanced auxiliary furnace. The products were absorbed in 5 ml. of 3% hydrogen peroxide and 1 ml. (20 mg.) of sodium acetate solution contained in a six bulb Will-Varrentrapp type absorber. The sample size was such that 2–10 ml. of silver nitrate were required. The halogen was titrated with 0.01 *N* silver nitrate in 50% acetone solution with dichlorofluorescein indicator according to the recommendations of Bullock and Kirk.[13] Blanks were negligible and analysis of a known sample agreed with the theoretical within two parts per thousand.

Results and Discussion

The Relation between Intrinsic Viscosity and Number Average Molecular Weight for Unfractionated Polystyrene.—In order to permit molecular weight determinations on unfractionated polystyrenes from viscosity measurements, the relation between number average molecular weight, $\overline{M}_n$, and intrinsic viscosity, $[\eta]$, was determined. Molecular weights of polystyrenes by osmotic pressure determinations in the molecular weight range 50,000–600,000 and by chlorine analyses in the range 10,000–200,000 are compared with intrinsic viscosities in Table I and Fig. 1. The figure shows that, within experimental error, over the range 10,000–600,000

$$\overline{M}_n = 184{,}000\ [\eta]^{1.40} \qquad (2)$$

and this relation was used to calculate number average molecular weights in all experiments where viscosities were determined.[14] Equation (2) is applicable only to polystyrenes prepared at low conversions where the molecular weight distribution is uncomplicated by changing solvent–monomer ratio or branching reactions.[15] The relation is apparently independent of the chain transfer solvent[8,14] and temperature.[16]

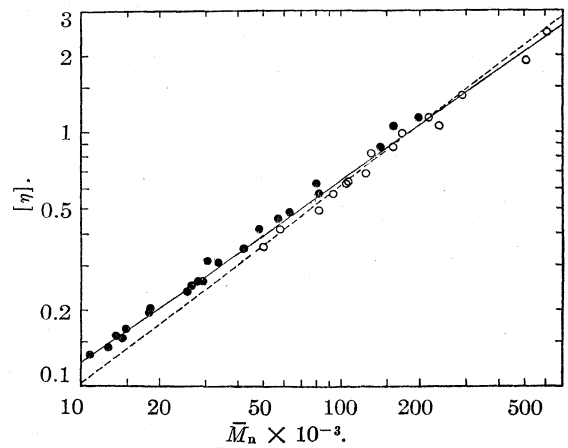


Fig. 1.—Relation between intrinsic viscosity, $[\eta]$, and number average molecular weight, $\overline{M}_n$, for unfractionated polystyrenes prepared at 60°, 100°, and 132° in presence of carbon tetrachloride: $\overline{M}_n$ by osmotic pressure, O, by chlorine analysis, ●. Solid line corresponds to Equation (2), broken line to older equation.[14]

Transfer Constant of Carbon Tetrachloride in the Thermal Polymerization of Styrene.—Table I summarizes results on the uncatalyzed polymerization of styrene in carbon tetrachloride. The reactions involved were discussed previously[2] and it was shown that

$$1/\overline{P} = C[S]/[M] + 1/\overline{P}_0 \qquad (3)$$

(12) Shriner, "Quantitative Analysis of Organic Compounds," Edwards Bros., Inc., Ann Arbor, Mich., 1944, pp. 26–27.

(13) Bullock and Kirk, *Ind. Eng. Chem., Anal. Ed.*, **7**, 178 (1935).

(14) A large number of osmotic determinations on polystyrenes of molecular weight 50,000–600,000, prepared in various other solvents, without catalysts at three temperatures and with benzoyl peroxide at 60°, had indicated the relation[5]

$$\overline{M}_n = 184{,}000\ [\eta]^{1.277}$$

used previously by Gregg and Mayo, *Trans. Faraday Soc.*, **43B**, in press (1947). For molecular weights above 50,000, the two equations give substantially the same results.

(15) Equation 2 is based upon polystyrenes with a distribution function (assumed to be) governed by termination through chain transfer and disproportionation and with the termination steps independent of chain length. If polystyrene chains in the absence of solvent terminate by combination of radicals, then $\overline{P}_0$ values calculated from intrinsic viscosities and Equation 2 should be too low by about 20%. However, osmotic determinations on polymers from pure styrene at 100 and 132° give $\overline{P}_0$ values agreeing with those calculated from Equation (2). For 60° polymers, osmotic determination of $\overline{P}_0$ is impractical, but plots of $1/\overline{P}$ (from osmotic determinations) against solvent:monomer ratio extrapolate to the $1/\overline{P}_0$ value calculated from intrinsic viscosity. The data thus reveal no different distribution of molecular weights in the absence of solvent.

(16) Similar equations have been proposed for polystyrene fractions and an effect of temperature of preparation of the polymer has been reported, Alfrey, Bartovics and Mark, THIS JOURNAL, **65**, 2319 (1943).

where $\overline{P}$ and $\overline{P}_0$ are the degrees of polymerization of styrene, in the presence and absence of solvent, respectively, at solvent and monomer concentrations [S] and [M], and where C, the transfer constant, is the ratio of the rate constants for chain transfer and chain growth for all polystyrene radicals. An effort was made to hold reaction of the styrene to 10% or less. The small variation in over-all second order rate constant with solvent:monomer ratio shows that the thermal reaction is not seriously complicated by traces of catalysts and justifies the assumption in deriving Equation (3) that the rate constants for chain initiation, growth, and termination do not change significantly with solvent or chain length.

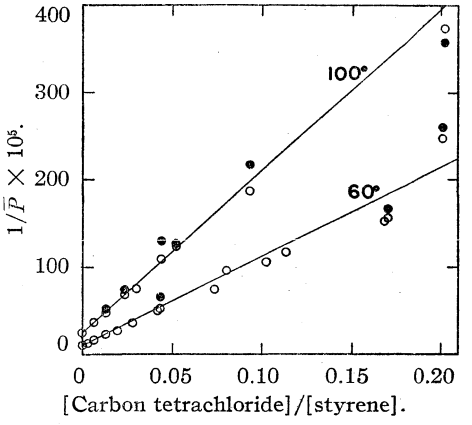


Fig. 2.—Thermal polymerization of styrene in carbon tetrachloride: $1/\overline{P}$ from intrinsic viscosity, O; from chlorine analysis, ●.

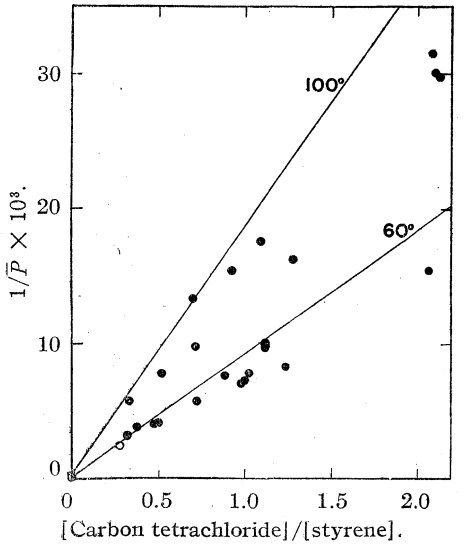


Fig. 3.—Thermal polymerization of styrene in carbon tetrachloride: $1/\overline{P}$ from intrinsic viscosity, O; from chlorine analysis, ●.

Except for low degrees of polymerization, where the proportion of monomer consumed in starting polymer chains cannot be neglected[4]

$$C[\mathrm{S}]/[\mathrm{M}] = \mathrm{d}[\mathrm{S}]/\mathrm{d}[\mathrm{M}] \quad (4)$$

where d[S]/d[M] is the molar ratio of solvent to monomer in the polymer being formed. The average degree of polymerization and number average molecular weight, $\overline{M}_n$, in Table I are calculated from chlorine analyses by the relations

$$\mathrm{d}[\mathrm{S}]/\mathrm{d}[\mathrm{M}] = 104.14/[(14183/\%\ \mathrm{Cl\ in\ polymer}) - 153.84] \quad (5)$$

$$1/\overline{P} = \mathrm{d}[\mathrm{S}]/\mathrm{d}[\mathrm{M}] + 1/\overline{P}_0 \quad (6)$$

$$\overline{M}_n = 104.14\,\overline{P}(1 + 153.84\,\mathrm{d}[\mathrm{S}]/104.14\,\mathrm{d}[\mathrm{M}]) = 104.14\,\overline{P}/(1 - 0.01085\%\ \mathrm{Cl}) \quad (7)$$

$\overline{M}_n$ is also determined from intrinsic viscosity by Equation (2); then

$$1/\overline{P} = (104.14\text{–}153.84/\overline{P}_0)/(\overline{M}_n - 153.84) \backsimeq 104/(\overline{M}_n - 154) \quad (8)$$

The transfer constant, C, is calculated from Equations (3) or (4).

Since, in each experiment, the styrene concentration decreases appreciably while the carbon tetrachloride concentration does not, *average* solvent:monomer ratios have been used in all calculations and plots. Calculations of transfer constants in Table I are based on all chlorine analyses and on intrinsic viscosities above 0.35 (where they have been standardized against osmotic molecular weights) and in Figs. 2 and 3 the same data for 60 and 120° runs have been plotted for graphical determination of transfer constants. The lines in Figs. 2 and 3 are based on experiments with solvent:monomer ratios below 0.4 and other experiments where low molecular weight material was recovered after polymer precipitation. The slopes of the lines are the transfer constants for carbon tetrachloride with styrene at 60° and 100°, 0.0092 (±0.0010) and 0.0185 (±0.0022), respectively, the experimental error being taken as the standard deviation of the transfer constants in Table I for those experiments on which the lines were based. The two 1:1 experiments at 60° where low molecular weight material was recovered fall slightly below the line only because of the failure of Equation (3) to apply to low degrees of polymerization and the failure of the shortest radicals to transfer normally,[4] but only part of the deviation of the best 100° experiments can be ascribed to these causes. Almost all other experiments at 60° and 100° at solvent:monomer ratios above 0.4 show the effects of loss of low molecular weight material in precipitating polymer. The linear relation between solvent:monomer ratio and $1/\overline{P}$ is taken as proof that the transfer constant, the ratio of the rate constants for chain transfer and chain growth, is substantially constant for radicals averaging 100–10000 styrene units.

The transfer constant at 132° is taken as the average of the six values in Table I, 0.0304 (±0.0023). From the values of the transfer con-

stant at 60, 100, and 132°, the activation energy for chain transfer is found to be about 4.5 kcal./mole higher than for chain growth and the frequency factor for transfer is then about eight times as large as for growth.

The reaction mixture in the last listed experiment at 100° was diluted with five volumes of benzene, which, in comparison with carbon tetrachloride, is substantially inert in chain transfer.[2,14] Since the rate of reaction and the molecular weight of the product were entirely consistent with the other experiments, the use of an inert diluent is justified in the experiments in Table II.

Transfer Constants from Peroxide Initiated Polymerizations.—In order to extend quantitative work on chain transfer to other monomers and to very low styrene concentrations, where uncatalyzed rates are very small or difficultly reproducible, the benzoyl peroxide–catalyzed polymerization of styrene was investigated. The relation between monomer and peroxide concentration and rate and degree of polymerization seems well established[17,18] and has recently been interpreted by Matheson[19] in this Laboratory. Matheson's equations and previous methods[2] have been used to derive Equation (9)

$$1/\bar{P} = C\frac{[S]}{[M]} + \frac{2(k_a k_3\,[\text{peroxide}])^{1/2}}{k_2[M]}\left(\frac{k_c[M]}{k_b + k_c[M]}\right)^{1/2} \quad (9)$$

Here k_a, k_b and k_c are, respectively, the rate constants for the primary dissociation of peroxide into radicals, the first order recombination of radicals from the peroxide, and the reaction of these radicals with styrene; k_2 and k_3 are the rate constants for chain growth and termination. Uncatalyzed initiation is neglected and the final factor is the fraction of peroxide radicals which initiate chains. This development assumes that the rate constants concerned are independent of the composition of the polymerizing system, a condition which is met in Table II, as shown by the over-all rates. The condition may not be met when the decomposition of the peroxide is affected by the solvent.[20] This equation may be applied for low conversions under either of two sets of conditions. If solvent and monomer concentration are kept constant while the peroxide concentration is varied, C is obtained from the intercept of the line formed by plotting $1/\bar{P}$ *vs.* $[\text{peroxide}]^{1/2}$. This method has thus far given poor results partly because of the extrapolation involved and the necessity for keeping conversions low and equal.

If the concentrations of both monomer and peroxide are held constant, C is the slope of the line formed by plotting $1/\bar{P}$ *vs.* [S]/[M]. Table II and Fig. 4 illustrate this method, benzene being used as an inert diluent. The slope of the line (determined by the least squares method, assuming no error in [S]/[M]) and the transfer constant are 0.0093, in excellent agreement with the value obtained in thermal polymerization. This method may be applied to monomers or solvents which cannot be freed of peroxides and to monomers which themselves undergo chain transfer.

(17) Schulz and Husemann, *Z. physik. Chem.*, **39A**, 246 (1941); Schulz and Blaschke, *ibid.*, **51A**, 75 (1942).

(18) Josefowitz and Mark, *Polymer Bull.*, **1**, 140 (1945).

(19) Matheson, *J. Chem. Phys.*, **13**, 584 (1945).

(20) Nozaki and Bartlett, THIS JOURNAL, **68**, 1686 (1946); Cass, *ibid.*, **68**, 1976 (1946).

TABLE II

PEROXIDE-INITIATED POLYMERIZATION OF STYRENE AT 60° AT VARIOUS CONCENTRATIONS OF CARBON TETRACHLORIDE[a]

[CCl_4]/Styrene	Conversion,[b] %	Rate %/hr./[peroxide]$^{1/2}$	[η]	$1/\bar{P} \times 10^{5}$[c]
0.0256	7.31	15.8	1.24	42
.0513	7.30	15.8	0.90	66
.0769	7.22	15.6	.72	90
.1026	7.35	15.9	.61	113
.1535	6.86	14.9	.40	205
.2053	6.79	14.7	.36	228
.2566	6.96	15.1	.35	247

[a] The carbon tetrachloride was added to 23.0-ml. aliquots of a solution of 0.0261 g. of benzoyl peroxide in 157.9 g. of styrene. Benzene was added until the volume of each run was 28.0 ml. [Styrene] = 7.14 moles/liter; [Bz_2O_2] 0.000507 mole/l. [b] In twenty and one-half hours. [c] Calculated from Equations (2) and (8).

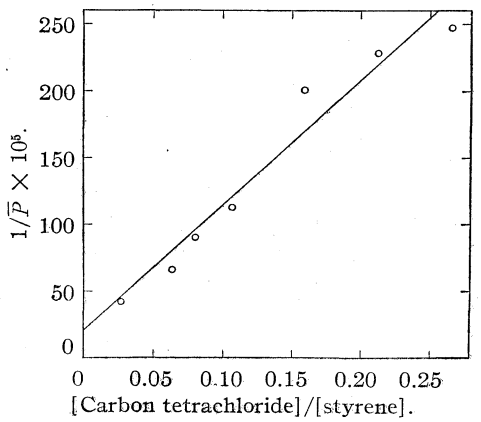


Fig. 4.—Benzoyl peroxide catalyzed polymerization of styrene in presence of carbon tetrachloride at 60°.

Summary

The polymerization of styrene in carbon tetrachloride has been studied over the temperature range 60–132°, over a range of solvent:monomer ratios from 0.003 to 3, and in the presence and absence of benzoyl peroxide as catalyst. Equations are presented which account for the average molecular weights (2500 to 1,000,000) of the products obtained. At 60°, the rate constant for the reaction of a growing polymer radical with carbon tetrachloride is 0.0092 times as large as the rate constant for addition of the radical to styrene. The temperature coefficient of this ratio shows that the chain transfer reaction has both a higher activation energy and a higher frequency factor. The constancy of this ratio and of the over-all rate con-

stant for polymerization indicate that the reactions of the growing polymer radical are independent of average chain length over the range 100 to 10,000 styrene units. The results establish the validity of a simple and accurate method for comparing the reactivities of solvents in general with the free radicals which occur in polymerizing systems.

Number average molecular weights of the products of thermal polymerizations of styrene at low conversions have been determined by osmotic pressure measurements and by chlorine analyses; they bear a simple relation to the intrinsic viscosities of the unfractionated polymers.

PASSAIC, N. J. RECEIVED JULY 19, 1947

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Monomers and Polymers. IV. Vinylthiophenes[1,2]

BY G. BRYANT BACHMAN AND LOWELL V. HEISEY

The desirable polymerization and copolymerization characteristics of the chlorinated styrenes[3] and alpha-methylstyrenes[2b] have suggested studying their analogs in the thiophene series. We have synthesized a representative group of compounds with one, two or three chlorine or bromine atoms and an alpha- or beta-vinyl or isopropenyl group substituted on the thiophene nucleus. These compounds have been found to polymerize and copolymerize similarly to the corresponding benzene compounds, the rates increasing with the number of chlorine atoms present on each thiophene nucleus. The polymers were all somewhat colored, however, in spite of careful purification of the monomers. This seems to be inherent in the alpha-halothiophenes themselves. Even 2-chlorothiophene, which is color stable in stoppered tubes at 70° for days, colors within a few hours at this temperature in the presence of peroxides.

The preparation of vinylthiophenes is a problem very similar in nature to that of preparing vinylbenzenes except that the thiophene nucleus is more reactive, less stable, and subject to different rules of orientation than the benzene nucleus. We have been especially interested in observing the results of exchange metallation in the thiophene series. Either an alpha-hydrogen or an alpha-halogen may be replaced by lithium when treated with alkyllithium compounds. Thus 2-chloro-, 2,5-dichloro- and 2,3,4,5-tetrachlorothiophenes gave the corresponding metallo-derivatives with lithium in the 2-position and chlorine in the 5-, 5- and 3,4,5-positions, respectively. Magnesium reacted with 2,5-dibromothiophene normally, but with 2-bromo-5-chloro- and with 2,3,4,5-tetrachlorothiophenes it reacted well only in the presence of a co-halide (ethyl bromide). These lithium reagents and the corresponding Grignard reagents gave alcohols (Table I) with acetaldehyde, propionaldehyde, or acetone which were readily dehydrated to the desired vinylthiophenes (Table II). Some of the tertiary alcohols dehydrated spontaneously during isolation. Other vinylthiophenes were prepared from the corresponding methyl thienyl ketones by reduction or by reaction with methylmagnesium halide followed by dehydration of the resulting alcohols.

α-Methylstyrenes with ortho halogen atoms have been shown[2b] not to polymerize or copolymerize freely, a fact which is attributed to the steric hindrance to free rotation of the isopropenyl group provided by the ortho substituent. This hindrance is not as extreme in the thiophene series. The angles between adjacent positions amount to about 72° for five-membered rings and only about 60° for six-membered rings. Models show that the isopropenyl group in 2,5-dichloro-3-isopropenylthiophene is free to rotate about a full circle, and in agreement with the model and the theory this vinyl compound copolymerizes satisfactorily with butadiene in an emulsion system. That it is a borderline case is indicated by the fact that its bulk polymer with maleic anhydride and its emulsion polymer with styrene were obtained in only small yields (about 5%).

Acknowledgment.—We wish to express our appreciation to the Purdue Research Foundation and to the General Tire and Rubber Company for financial support in the form of a fellowship.

Experimental

Unsubstituted Vinylthiophenes.—2-Vinylthiophene has been previously reported.[4] 2-Isopropenylthiophene was prepared by adding 2-acetylthiophene to an ether solution of methylmagnesium bromide (a different method from that used by Thomas[5]), and steam distilling the unstable hydrolyzed product with 2% sulfuric acid.

Anal. Calcd. for C_6H_6S: C, 67.7; H, 6.5. Found: C, 67.7; H, 6.5.

5-Bromo-2-vinylthiophenes.—2,5-Dibromothiophene,[6] 182 g. (0.75 mole), in 250 ml. of dry ether was converted to the mono-Grignard reagent with 18.3 g. (0.75 mole) of magnesium. Benzene, 200 ml., caused the ether-insoluble red oil to dissolve. Addition of acetaldehyde 34 g. (0.77 mole) or acetone 43.5 g. (0.75 mole) and hydrolysis with dilute acetic acid gave the corresponding alcohols mixed

(1) From the Ph.D. thesis of L. V. Heisey, Purdue University, June, 1947. Present address: McPherson College, McPherson, Kansas.

(2) For previous papers in this series see, (a) Bachman and Lewis, THIS JOURNAL, **69**, 2022 (1947), and (b) Bachman and Finholt, *ibid.*, **70**, 622 (1948).

(3) Michalek and Clark, *Chem. Eng. News*, **22**, 1559 (1944).

(4) Mowry, Renoll and Huber, THIS JOURNAL, **68**, 1105 (1946).

(5) Thomas, *Bull. soc. chim.*, **5**, 732 (1908); *Compt. rend.*, **146**, 642 (1908).

(6) Steinkopf and Köhler, *Ann.*, **532**, 250 (1937).

TABLE I

CHLORINATED THIOPHENE ALCOHOLS

Name[a]	Yield,[b] %	B. p., °C., mm.	$n^{25}D$	d^{25}_{25}	Formula	Chlorine, % Calcd.	Found
T—$CHOHCH_3$							
(2),5-Cl	A(81), B(71), C(27)	85–87 (2)	1.5556	1.264	C_6H_7OSCl	21.8	21.7
(3),2,5-diCl	B(90)	95–97 (1)	1.5630	1.413	$C_6H_6OSCl_2$	36.0	35.6
(2),3,4,5-triCl	C(87), D(79)	109–112 (2)	....[c]	...	$C_6H_5OSCl_3$	45.9	46.0
T—$C(CH_3)_2OH$							
(2),5-Cl	A(67), C(95)	83–85 (1)	1.5362	1.226	C_7H_9OSCl	20.1	19.9
(3),2,5-diCl	E(93)	104–105 (2)	1.5560	1.358	$C_7H_8OSCl_2$	33.6	33.3
(2),3,4,5-triCl	D(77)	118–122 (2)	....[d]	...	$C_7H_7OSCl_3$	43.3	42.8
T—$CHOHC_2H_5$							
(2),5-Cl	A(68)	100–101 (1)	1.5408	1.232	C_7H_9OSCl	20.1	19.8

[a] T stands for thienyl. Parenthetical numbers give positions of hydroxyalkyl groups. [b] Methods of preparation: A, hydrogen–lithium interchange followed by addition of RCOR′; B, reduction of acetylthiophene; C, preparation of thiophene–Grignard reagent followed by addition of RCOR′; D, halogen–lithium interchange followed by addition of RCOR′; E, acetylthiophene and CH_3MgX. [c] Solid, m. p. 52.5–53.5°. [d] Solid, m. p. 78.5–79.5°.

TABLE II

VINYLTHIOPHENES

Substituents[a]	Method[b] and yield, %	B. p., mm.	d^{25}_{25}	$n^{25}D$	Formula	Analyses, % Calcd.	Found
T—$CH=CH_2$							
(2),5-Br	A(34)	64–65 (5)	1.668	1.6160	C_6H_5SBr	S, 16.96	16.81
(2),5-Cl	B(72), C(48)	56–57 (7)	1.199	1.5780	C_6H_5SCl	Cl, 24.5	24.3
(3),2,5-diCl	B(64)	55–56 (1)	1.361	1.5908	$C_6H_4SCl_2$	Cl, 39.6	39.2
(2),3,4,5-triCl	B(70), C(0)	83–84 (1)	1.502	1.6106	$C_6H_3SCl_3$	Cl, 49.8	49.8
T—$C(CH_3)=CH_2$							
(2),none	D(59)	66–67 (20)[c]	1.022	1.5586	C_7H_8S	C, 67.7	67.7
						H, 6.50	6.50
(2),5-Br	A(53)	84–85 (3)	1.631	1.6038	C_7H_7SBr	S, 15.79	15.61
(2),5-Cl	C(84), D(51)	78–79 (10)	1.182	1.5720	C_7H_7SCl	Cl, 22.4	22.3
(3),2,5-diCl	B(83)	77–78 (1)	1.306	1.5831	C_7H_6SCl	Cl, 36.7	36.4
(2),3,4,5-triCl	B(63)	93–94 (2)	1.446	1.5920	$C_7H_5SCl_3$	Cl, 46.8	46.7
T—$CH=CHCH_3$							
(2),5-Cl	B(47)	80–82 (7)	1.157	1.5787	C_7H_7SCl	Cl, 22.4	22.1

[a] T stands for thienyl. Parenthetical numbers give positions of vinyl groups. [b] Methods of preparation: A, spontaneous dehydration of the alcohol prepared from 5-bromo-2-thienylmagnesium bromide and RCOR′; B, dehydration of the corresponding alcohol over activated Al_2O_3 at 300°; C, dehydration of the corresponding alcohol by heating with $KHSO_4$; D, dehydration of the alcohol from 2-acetylthiophene and CH_3MgX. [c] Reported by Thomas,[5] b. p. (727 mm.) 166–167°.

with their dehydration products. The mixtures were steam distilled with 2% sulfuric acid and the vinyl derivatives rectified and isolated with 34% and 53% yields, respectively. Their properties are listed in Table II.

2-Bromo-5-chlorothiophene.—2-Chlorothiophene, 118.6 g. (1.0 mole), in carbon disulfide, 200 ml., was brominated with 160 g. (1.0 mole) of bromine at 0°. After twenty-four hours the mixture was decolorized with 5% sodium sulfite solution, the solvent removed, and the residue heated on a steam cone with 5% sodium hydroxide solution for four hours. Rectification of the product through a short column gave 147 g. (74.6% yield) of a colorless liquid, b. p. (18 mm.) 69.5–70.0°; m. p. −22° to −20°; $n^{25}D$ 1.5924; d^{25}_{25} 1.803.

Anal. Calcd. for C_4H_2SClBr: C, 24.33; H, 1.00. Found: C, 24.31, 24.42; H, 1.19, 1.30.

5-Chloro-2-vinylthiophenes:—**(A) From 2-Chlorothiophene.**—A solution of 11.9 g. (0.1 mole) of 2-chlorothiophene in 25 ml. of dry ether was added at 0° to a solution of butyllithium prepared from 1.80 g. (0.26 mole) of lithium and 11.1 g. (0.12 mole) of *n*-butyl chloride in 45 ml. of dry ether. The resulting light yellow suspension was refluxed for six hours and then carbonated with Dry Ice to determine the structure of the lithium compound. A 10.4-g. yield (65%) of 5-chloro-2-thiophenecarboxylic acid,[7] m. p. 150–152°, was obtained. Similar solutions prepared with five to ten times as much of each reactant were treated with one and a half molar quantities of acetaldehyde, propionaldehyde and acetone, respectively, at 0°. The resulting mixtures were stirred for two hours at room temperature, hydrolyzed by dropwise addition of 10% aqueous sodium carbonate, and the organic materials separated, ether-extracted and fractionated under reduced pressure. The alcohols were colorless oily liquids.

Attempts to convert 2-chlorothiophene to 5-chloro-2-thienylmagnesium bromide by exchange metallation with ethylmagnesium bromide in boiling ether or benzene were unsuccessful. No ethane was evolved within two hours and carbonation with Dry Ice gave only propionic acid and recovered dichlorothiophene.

(B) From 2-Acetyl-5-chlorothiophene.—Reduction of 2-acetyl-5-chlorothiophene with aluminum isopropoxide and fractional distillation of the product gave a 71% yield of 5-chloro-2-(1′-hydroxyethyl)-thiophene.

(7) "Thiophene Chemicals," Socony-Vacuum Oil Co., Inc., New York, N. Y., 1946.

Treatment of 2-acetyl-5-chlorothiophene with methylmagnesium halide gave 5-chloro-2-isopropenylthiophene but none of the corresponding alcohol.

(C) From 2-Bromo-5-chlorothiophene.—The Grignard reagent from 29.0 g. (0.4 mole) of 2-bromo-5-chlorothiophene in 150 ml. of ether was treated with 26 g. (0.6 mole) of acetaldehyde in 100 ml. of ether and 150 ml. of benzene. The mixture was refluxed half an hour, worked up and distilled to obtain 6 g. (0.04 mole) of 5-chloro-2-vinylthiophene, 15 g. (0.11 mole) of 5-chloro-2-(1′-hydroxyethyl)-thiophene and 1.0 g. (0.02 mole) of 5,5′-dichloro-2,2′-dithienyl, m. p. 107–109.[8] Later attempts to prepare this Grignard reagent directly were unsuccessful, and it was found better to use a cohalide (ethyl bromide).

(D) From 2,5-Dichlorothiophene.—Carbonation of 5-chloro-2-thienyllithium prepared from about 0.3 mole of butyllithium and 30.6 g. (0.2 mole) of 2,5-dichlorothiophene gave a 63% yield of 5-chloro-2-thiophenecarboxylic acid, indicating the feasibility of preparing 5-chloro-2-vinylthiophenes by this approach. The method was not applied, however, because satisfactory results were obtained by the simpler syntheses already indicated.

The alcohols prepared by these syntheses were dehydrated as indicated in Table II. Dehydrations over alumina were accomplished in a furnace which consisted of a vertical, electrically heated, 25 mm. × 50 cm. Pyrex reaction tube packed with 4–8 mesh alumina. The top of the tube had two dropping funnels, one for the alcohol and the other for solvent to flush the system. The bottom of the reaction tube was connected to a water aspirator through a water-cooled condenser and a trap immersed in a Dry Ice–trichloroethylene bath. The alumina was activated before use by drawing a slow stream of air through it at 500° overnight.

The dehydrations were conducted by dissolving the alcohols in an equal volume of dry benzene and passing the solution through the furnace at 300° and 30–100 mm. at the rate of 100 ml. per hour. A similar amount of benzene was passed through the furnace after the main fraction to flush the system, and one hour was allowed for drainage before the product was removed.

Dehydrations with potassium hydrogen sulfate catalyst were done at a pressure which permitted dehydration but not distillation of the alcohol. The yields by this method were good only for the tertiary alcohols.

Trinitrobenzene was regularly used as an inhibitor to polymerization in distilling the vinyl compounds.

The 2,5-Dichloro-3-vinylthiophenes.—3-Acetyl-2,5-dichlorothiophene was prepared by the method of Steinkopf and Köhler[6] but their yield (16%) was greatly improved (to 84%) by using carbon disulfide as solvent instead of petroleum ether. The Perrier technique[4] gave only 57% yields in carbon disulfide. Hypochlorite oxidation of the above ketone gave 2,5-dichloro-3-thiophenecarboxylic acid.[8a]

Aluminum isopropoxide reduction of 3-acetyl-2,5-dichlorothiophene gave on distillation 2,5-dichloro-3-(1′-hydroxyethyl)-thiophene (90%). Treatment of the ketone with methylmagnesium halide gave 2,5-dichloro-3-(2′-hydroxyisopropyl)-thiophene (93%).

The above alcohols were dehydrated satisfactorily to the corresponding vinyl compounds in the vapor phase over alumina at 300°.

The 3,4,5-Trichlorovinylthiophenes.—2,3,4,5-Tetrachlorothiophene, 5.56 g. (0.025 mole), was added to a filtered solution of butyllithium (0.03 mole) in 50 ml. of ether. Refluxing for four hours, carbonation with Dry Ice, and isolation of the product gave 3.2 g. (55.4% yield) of 3,4,5-trichloro-2-thiophenecarboxylic acid, m. p. 223–224° (reported,[9] m. p. 224°).

Conversion of 2,3,4,5-tetrachlorothiophene to a Grignard reagent using a cohalide (C_2H_5Br) proceeded less satisfactorily. Reaction of either metallo derivative with acetaldehyde or with acetone instead of Dry Ice gave the desired alcohols. These were dehydrated at 300° over alumina. Other methods were unsuccessful.

Polymerization Studies.—Small samples of the vinyl compounds described were polymerized alone and with styrene, methyl methacrylate, vinyl acetate and maleic anhydride by heating at 70° in 3-inch test-tubes with 0.5% of benzoyl peroxide. The propenyl compound did not polymerize or copolymerize. The isopropenyl compounds did not polymerize alone but did copolymerize. However those compounds with the isopropenyl group in the 2-position and with a halogen in the 5-position polymerized on long exposure to sunlight. It is believed that this is the result of a partial photochemical decomposition yielding hydrogen halides which are known to catalyze the polymerization of isopropenylbenzene. The vinylthiophenes polymerized and copolymerized normally.

Rubbery copolymers with butadiene were prepared in a typical GR-S type emulsion system containing: butadiene 7.5 g., olefin 2.5 g., water 17.5 g., potassium persulfate 0.03 g., lauryl mercaptan 0.06 g. and soap 0.5 g. These copolymerizations were run in sealed tubes rotating in a water-bath at 40° until no further change occurred as evidenced by cessation of fall of the liquid meniscus in the tube. Evidence of copolymerization was determined by the amount and character of the precipitated and acetone-extracted copolymer. Satisfactory rubbers were obtained from all of the vinyl compounds except the 5-chloro-2-propenylthiophene, which did not copolymerize, and the 3,4,5-trichloro-2-isopropenylthiophene, which was not studied.

The copolymers of 2,5-dichloro-3-isopropenylthiophene were of especial theoretical interest and were therefore purified and analyzed. The product with styrene, obtained through an emulsion polymerization at 40–60° for three weeks, was precipitated with aqueous sodium chloride, washed with methanol, and extracted continuously with acetone for eight hours. The residue (5%) was a white powder.

Anal. Calcd. for $(C_8H_8 \cdot C_7H_6SCl_2)_x$: Cl, 23.9. Found: Cl, 21.47, 21.24.

The product with maleic anhydride, obtained through a bulk polymerization of the reactants at 70° for one month, was extracted continuously with benzene for six hours. The residue (5%) was a white powder.

Anal. Calcd. for $(C_4H_2O_3 \cdot C_7H_6SCl_2)_x$: Cl, 25.4. Found: Cl, 19.08, 18.84.

The product with butadiene, obtained in 90% yield in sixty-six hours as described above, was a brown rubbery solid.

Anal. Calcd. for $(3C_4H_6 \cdot C_7H_6SCl_2)_x$: Cl, 9.01. Found: Cl, 9.27, 9.14.

These data indicate that copolymerization occurred.

Summary

A number of halogenated thiophene alcohols have been prepared and dehydrated to the corresponding vinyl halogenated thiophenes in order to study the polymerization and copolymerization characteristics of these olefins.

LAFAYETTE, INDIANA RECEIVED DECEMBER 15, 1947

(8) Thöl and Eberhard, *Ber.*, **26**, 2945 (1893).

(8a) Recently described by Hartough and Conley, THIS JOURNAL, **69**, 3097 (1947), m. p. 147–148°.

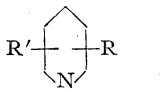
(9) Steinkopf, Jacob and Penz, *Ann.*, **512**, 136 (1934).

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

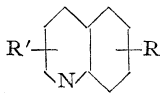
Monomers and Polymers. V. Vinylpyridines and Vinylquinolines[1,2]

BY G. BRYANT BACHMAN AND D. DONALD MICUCCI

The examination of synthetic rubbers prepared by the copolymerization of butadiene with various olefins has shown that the nature of the olefin exerts a considerable influence on the properties of the rubbers obtained. Relative to butadiene–styrene rubbers the butadiene–dichlorostyrene rubbers are more easily milled and processed and show better hot tensile strength. The butadiene–vinylpyridine rubbers are outstanding in tensile strength but are nervy and tough and mill poorly. It was hoped that, by combining the effects of halogen atoms and heterocyclic nuclei in the same molecule, monomers might be obtained which would give rubbers of outstanding value. The present paper reports the preparation of vinylpyridines and vinylquinolines, some of which contain nuclearly substituted halogen atoms, and describes preliminary experiments to determine the polymerizing and copolymerizing characteristics of each. The following compounds were studied.



I, R = 2-C(CH$_3$)=CH$_2$, R′ = H
II, R = 3-C(CH$_3$)=CH$_2$, R′ = H
III, R = 3-C(CH$_3$)=CH$_2$, R′ = 5-Br
IV, R = 3-CH=CH$_2$, R′ = 5-Br
V, R = 3-C(CH$_3$)=CH$_2$, R′ = 5-Cl



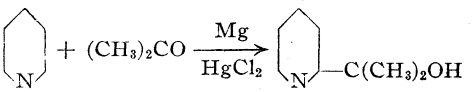
VI, R = 2-CH=CH$_2$, R′ = H
VII, R = 2-CH=CH$_2$, R′ = 6-Cl
VIII, R = 2-C(CH$_3$)=CH$_2$, R′ = H
IX, R = 2-C(CH$_3$)=CH$_2$, R′ = 6-Cl

Of these I,[3,4] II[5] and VI[6,7] have been prepared previously by others, but their polymerization characteristics are not reported. Compound VII was not obtained as a monomer since it polymerized very readily and attempts to prepare it by methods analogous to those used successfully for VI gave only a polymer.

In accord with our previous observations[2] the vinyl compounds of this series polymerized and copolymerized satisfactorily, while the alpha-methylvinyl compounds did not polymerize alone but did copolymerize with butadiene and other polymerizable vinyl compounds. The 2-alpha-methylvinyl derivatives of both pyridine and quinoline were however exceptional in that they did not copolymerize satisfactorily with butadiene, although they did form hard, black, brittle solids with maleic anhydride.

The introduction of halogen atoms seems to increase the rate of copolymerization of the vinyl heterocyclic monomers with butadiene and to soften the resulting rubbers somewhat but the effect is not as great as was hoped for. Our preliminary examination of these rubbers indicates that it would be desirable to introduce at least two halogen atoms per molecule of vinyl compound to obtain greater internal plasticization of the butadiene copolymers. This could probably be achieved more easily in the quinoline series than in the pyridine series since the number of positions available on the pyridine nucleus is limited. Furthermore, halogen atoms in 2, 4 and 6-positions of pyridine are readily hydrolyzed. This leaves only the 3- and 5-positions free for halogen atoms and the 2(6)- or 4-positions for the vinyl groups. It has been shown that alpha-methylvinyl groups in the 2(6)-position do not copolymerize, and the same may very well be true of such groups in the 4-position. Among quinoline compounds only the 2- and 4-positions hold readily hydrolyzable halogens. The 5, 6, 7 and 8 positions of the benzene ring and the 3-position of the pyridine ring offer suitable points of attachment of both halogen atoms and vinyl groups. The preparation of some of these compounds will be described at a later date.

The vinyl compounds studied were prepared by dehydrating corresponding alcohols. The (CH$_3$)$_2$-C(OH)– group in the 3-position of pyridine dehydrated more easily than the same group in the 2-position. Most of the alcohols were prepared from the corresponding acids by well-known methods, but the alcohols corresponding to I[3] and VI[8] were obtained by special methods. Emmert and Asendorf[3] have reported a little known but very interesting reaction for the preparation of 2-(2′-hydroxy-2′-propyl)-pyridine which involves a heterogeneous bimolecular reduction of acetone and pyridine in the presence of magnesium and mercuric chloride.



After improving the published procedure for this reaction we found it to be well suited for the synthesis of I.

Considerable time was spent studying syntheses for 5-chloro- and 5-bromonicotinic acids, intermediates for the preparation of III, IV and V. These acids are both known but the reported syntheses are difficult and give poor yields. We found that nicotinic acid chloride hydrochloride could be brominated directly to give the 5-substituted acid in excellent yields (87%) at 170°.

(1) From the Ph.D. thesis of D. Donal Micucci, Purdue University, February, 1948.

(2) For previous papers in this series see THIS JOURNAL, **69**, 2022 (1947); **70**, 622, 2378 (1948).

(3) Emmert and Asendorf, *Ber.*, **72B**, 1188–1194 (1939); *C. A.*, **33**, 7300 (1939).

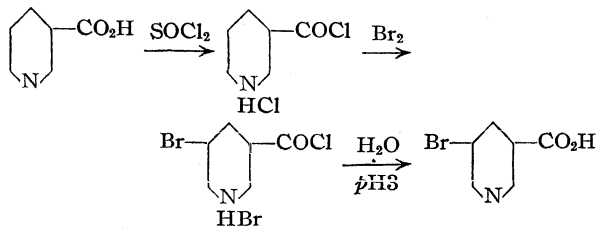
(4) Loffler and Grosse, *Ber.*, **40**, 1328 (1907).

(5) Oparina, *J. Russ. Phys.-Chem. Soc.*, **57**, 319–341 (1925); *C. A.*, **20**, 2499 (1926).

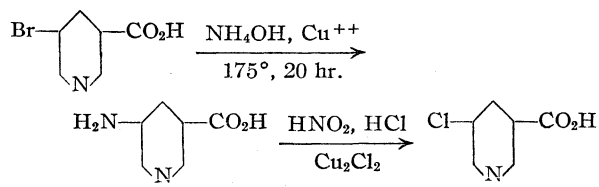
(6) Methner, *Ber.*, **27**, 2689 (1894).

(7) Einhorn and Lehnkering, *Ann.*, **246**, 172 (1888).

(8) Koenigs, *Ber.*, **32**, 224 (1899).



A similar reaction involving picolinic acid gave only tars. Many attempts were made to prepare 5-chloronicotinic acid by direct chlorination, but with only moderate success. On a small scale the desired product was obtained, but on a larger scale rapid sublimation, incomplete fusion of the acid chloride hydrochloride, and failure to form a perchloride complex interfered. Eventually the 5-chloro acid was prepared from the 5-bromo acid *via* the 5-amino acid.



A convenient new synthesis, suitable for laboratory scale preparations, was also developed for ethyl quinaldinate and its 6-chloro analog, intermediates for VIII and IX.

Acknowledgment.—The authors are indebted to the General Tire and Rubber Company for support in the form of a fellowship.

Experimental

2-Isopropenylpyridine

2-(2′-Hydroxy-2′-propyl)-pyridine.—A mixture of 24 g. (0.088 mole) of mercuric chloride, 24.3 g. (1.0 mole) of magnesium turnings and 200 g. (2.53 moles) of pyridine was warmed on the steam-bath until it acquired an opaque gray color. Then 200 g. (3.45 moles) of acetone was added dropwise with stirring during one and one-half hours. After an additional hour the magnesium had disappeared. The mixture was poured over ice and excess potassium carbonate solution, and the brown oil was separated and distilled. The fraction, b. p. 85–95° (12 mm.), was dissolved in dilute hydrochloric acid and steam distilled to remove volatile impurities. The product was recovered by treatment with bases and redistilled; yield 40 g. (29.3% based on the magnesium), b. p. 85–90° (10 mm.), m. p. 49–50° (from chloroform). These properties correspond with those previously reported by Sobecki[9] and by Emmert and Asendorf.[3]

2-Isopropenylpyridine.—The procedure of Emmert and Asendorf[3] gave a 67% yield of an oil b. p. 63–67° (10 mm.), $n^{25}D$ 1.5241, d^{25}_{25} 0.9962 (reported[3] b. p. 172–176°).

3-Isopropenylpyridine

3-(2′-Hydroxy-2′-propyl)-pyridine.—This alcohol was prepared by Graf and Langer,[10] who gave no details of procedure. A solution of 137 g. (1.0 mole) of methyl nicotinate in 1000 ml. of anhydrous ether was added dropwise with stirring to a solution of 540 g. (3.25 mole) of methylmagnesium iodide in 900 ml. of ether. The yellow suspension was stirred and refluxed for three hours and then poured over chopped ice containing acetic acid. The solution was made just alkaline; the product was extracted with ether and distilled; yield 78 g. (57%), b. p. 130° (10 mm.); reported,[10] b. p. 130° (11 mm.), m. p. 53°.

3-Isopropenylpyridine.—Dehydration of the above alcohol with a mixture of sulfuric and acetic acids by the procedure of Oparina[5] gave 3-isopropenylpyridine in 79% yield, b. p. 75° (10 mm.), $n^{25}D$ 1.5381, d^{25}_{25} 0.9775, methiodide, m. p. 103–104° (reported[5] b. p. 187–188°, d^{20}_{20} 0.9771).

Dehydration by heating with half molar quantities of phosphorus pentoxide in benzene for several hours gave a 65% yield but only a 25% conversion to the same compound.

5-Bromo-3-isopropenylpyridine

5-Bromonicotinic Acid.—Nicotinic acid was converted to the acid chloride hydrochloride with thionyl chloride, heated ten hours at 150–170° (oil-bath temperature) with an equimolecular amount of bromine, and then cooled. Ice water was added, the *p*H was adjusted to 3 with base and the precipitated product was filtered and recrystallized (Norit) from ethanol; yield 87%, m. p. 183°.[11] Treatment with thionyl chloride and then dilute base gave the acid chloride, m. p. 75°,[11] in 86% yield.

5-Bromo-3-(2′-hydroxy-2′-propyl)-pyridine.—5-Bromonicotinyl chloride was treated with 3.5 moles of methylmagnesium iodide to obtain the desired tertiary alcohol, a colorless and very viscous oil, b. p. 135–140° (3 mm.), $n^{25}D$ 1.5615, d^{25}_{25} 1.47; methiodide, m. p. 208–210°, dec.

Anal. Calcd. for $C_8H_{10}NOBr$: C, 44.47; H, 4.67. Found: C, 44.80; H, 4.70.

5-Bromo-3-isopropenylpyridine.—Dehydration of the above alcohol by heating with 20% sulfuric acid in acetic acid or by passing the vapors over alumina at 300° (50 mm.) gave 89 and 78% yields, respectively, of product, b. p. 85–87° (3 mm.), $n^{25}D$ 1.5820, d^{25}_{25} 1.4204; methiodide, m. p. 228°, dec.

Anal. Calcd. for C_8H_8NBr: N, 7.07. Found: N, 6.91.

5-Bromo-3-vinylpyridine

Ethyl 5-Bromonicotinate.—A 95% yield of the desired ester, m. p. 38–39°, was obtained by adding excess absolute ethanol to 5-bromonicotinyl chloride, refluxing for thirty minutes, distilling off the excess alcohol, and making the residue alkaline. The crude material was recrystallized from petroleum ether (60–70°).

Anal. Calcd. for $C_8H_8NO_2Br$: N, 6.08. Found: N, 5.86.

3-Acetyl-5-bromopyridine.—This ketone was prepared by three different procedures: (A) from 5-bromonicotinyl chloride and methylmagnesium bromide, yield 18%; (B) from 5-bromonicotinyl chloride and dimethylcadmium. This procedure was more laborious, but gave a slightly better yield (25%). (C) From ethyl 5-bromonicotinate *via* ethyl 5-bromonicotinylacetate: a solution of 0.32 mole of anhydrous sodium ethoxide in 108 ml. of xylene was prepared and added to a mixture of 46 g. (0.2 mole) of ethyl 5-bromonicotinate, 33.4 g. (0.38 mole) of ethyl acetate, and 50 ml. of xylene. After being heated and stirred for six hours and standing overnight, the mixture was poured into 800 ml. of ice water, acidified with 40 ml. of concentrated hydrochloric acid, and hydrolyzed by heating on a steam-bath for five hours. The xylene was removed by distillation, the residue was made basic, and the solid ketone which precipitated was separated by filtration. Recrystallization from petroleum ether (60–70°) gave 30 g. (75% yield) of white plates, m. p. 90°.

Anal. Calcd. for C_7H_6NOBr: C, 42.03; H, 3.04. Found: C, 42.11; H, 3.04.

5-Bromo-3-(1′-hydroxyethyl)-pyridine.—Reduction of 20 g. (0.1 mole) of 5-bromo-3-acetylpyridine with 0.1 mole of aluminum isopropoxide by the standard procedure[12] and isolation by vacuum distillation gave 20 g. (85% yield) of

(9) Sobecki, *Ber.*, **41**, 4103 (1908).

(10) Graf and Langer, *J. prakt. Chem.*, **146**, 103 (1937).

(11) Graf, *et al.*, *ibid.*, **138**, 244–258 (1933).

(12) Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 203.

the desired alcohol as a viscous oil, b. p. 134–136° (3 mm.), $n^{25}D$ 1.5728, d^{25}_{25} 1.5378.

Anal. Calcd. for C_7H_8NOBr: N, 6.93. Found: N, 7.00.

5-Bromo-3-vinylpyridine.—A 103-g. sample of 5-bromo-3-(1′-hydroxyethyl)-pyridine was dehydrated over alumina by the vapor phase method described previously. The 5-bromo-3-vinylpyridine fraction obtained amounted to 63 g. (67% yield), b. p. 74–75° (3 mm.), $n^{25}D$ 1.5810, d^{25}_{25} 1.4823.

Anal. Calcd. for C_7H_6NBr: N, 7.61. Found: N, 7.46.

5-Chloro-3-isopropenylpyridine

5-Aminonicotinic Acid.—One mole, 202 g., of 5-bromonicotinic acid, 400 ml. of ammonium hydroxide solution (sp. gr. 0.9) and 50 g. of copper sulfate pentahydrate were heated to 170–180° for twenty hours in a glass-lined autoclave. The dark-colored solution was removed after cooling and treated with aqueous sodium sulfide to remove copper ions. The filtered solution was adjusted to *p*H 4–5 and the precipitated acid was filtered off, washed with water, and recrystallized from water (Norite). A yield of 96 g. (69%), m. p. 292–294°, was obtained. Graf[11] reports no yield and a m. p. of 288–290° for a product prepared similarly from 5-chloronicotinic acid.

5-Chloronicotinic Acid and Its Chloride.—A sample of 96 g. (0.7 mole) of 5-aminonicotinic acid dissolved in 400 ml. of concd. hydrochloric acid was cooled in an ice–salt-bath to 0° and diazotized with a cold solution of 50.4 g. (0.77 mole) of sodium nitrite in 145 ml. of water. The mixture was poured into a solution of 80 g. (0.7 mole) of cuprous chloride in 400 ml. of concentrated hydrochloric acid. After three hours of stirring the mixture was heated to 60° to complete the reaction, diluted with an equal volume of water, and treated with aqueous sodium sulfide to precipitate the copper ions. The filtered solution deposited the crude chloro acid at *p*H 3. Recrystallization from hot water (Norite) gave 20 g. (18% yield) of 5-chloronicotinic acid, m. p. 169–170°. Graf,[11] who obtained a 25–30% yield of this acid by long heating of nicotinic acid with excess thionyl chloride, eventually in a sealed tube, reports m. p. 170–171°. The acid chloride, m. p. 53°, was prepared in 90% yield with the aid of thionyl chloride by the procedure of Graf and Meyer,[13] who report the same m. p. but give no yield.

5-Chloro-3-(2′-hydroxy-2′-propyl)-pyridine.—Following the procedure for the corresponding 5-bromo compound but starting with 20 g. (0.12 mole) of 5-chloronicotinyl chloride gave 14.2 g. (73% yield) of the desired alcohol, b. p. 115° (3 mm.), $n^{25}D$ 1.5377, d^{25}_{25} 1.199.

Anal. Calcd. for $C_8H_{10}NOCl$: N, 8.17. Found: N, 8.25.

5-Chloro-3-isopropenylpyridine.—Dehydration of 12 g. (0.7 mole) of the above alcohol by the procedure used for the 5-bromo analog gave 8.5 g. (79% yield) of the desired olefin, b. p. 70–73° (3 mm.), $n^{25}D$ 1.5554, d^{25}_{25} 1.1520.

Anal. Calcd. for C_8H_6NCl: N, 9.12. Found: N, 9.15.

2-Vinylquinoline

2-(2′-Hydroxyethyl)-quinoline.—Condensation of quinaldine with formaldehyde by the procedure of Koenigs[8] gave a 30% yield of this alcohol.

2-Vinylquinoline.—A mixture of 10 g. of the above alcohol, 1.5 g. of powdered potassium hydroxide, and 0.1 g. of phenyl-β-naphthylamine was heated in an oil-bath at 140–150° under reduced pressure (5 mm.) until distillation stopped. The oily product was redistilled to obtain 4.2 g. (46.9% yield) of the vinyl compound.

2-Vinylquinoline was also prepared directly from a quinaldine–formaldehyde reaction mixture. Quinaldine, 200 g. (1.4 moles), formalin 180 g. (2.4 moles of formaldehyde), 100 ml. of ethanol and 100 ml. of water were heated twenty-four hours on a steam-bath. The solvents were distilled off, 5 g. of powdered sodium hydroxide and 1 g. of phenyl-β-naphthylamine were added, and the mixture was heated at 7 mm. pressure until distillation ceased. Redistillation gave 103 g. (49% yield) of product, b. p. 120–125° (7 mm.), $n^{20}D$ 1.6439, d^{25}_{25} 1.0692.

Anal. Calcd. for $C_{11}H_9N$: N, 9.04. Found: N, 9.06.

2-Isopropenylquinoline

Ethyl Quinaldinate.—A solution of 111 g. (0.66 mole) of silver nitrate in 660 ml. of water was added carefully with stirring to a solution of 83 g. (0.22 mole) of 2-tribromoquinaldine in 800 ml. of ethanol. The mixture was refluxed for thirty minutes, filtered, acidified with 40 ml. of hydrochloric acid, and concentrated under vacuum to 300 ml. The solution was made strongly basic, the oily product was separated by decantation and ether extraction and was then purified by distillation; yield 25 g. (55%), b. p. 131–136° (1 mm.); reported,[14] b. p. 131–136° (0.3 mm.), $n^{20}D$ 1.5973.

2-(2′-Hydroxy-2′-propyl)-quinoline.—Ethyl quinaldinate was treated with 3.3 moles of methylmagnesium bromide to obtain 16 g. (86%) of the alcohol, m. p. 67°.[15]

2-Isopropenylquinoline.—Dehydration of 17 g. of the above alcohol was accomplished by heating with 50 ml. of concentrated sulfuric acid in an oil-bath at 120–130° for three hours. The mixture was cooled, poured into cold water, made basic, and ether extracted. Distillation gave a pale yellow oil, 7.0 g. (45.5% yield), b. p. 119–120° (3 mm.), $n^{25}D$ 1.6281, d^{25}_{25} 1.0600.

Anal. Calcd. for $C_{12}H_{11}N$: N, 8.28. Found: N, 8.05.

6-Chloro-2-isopropenylquinoline

6-Chloroquinaldine.—The following procedure gives over three times the yield reported previously.[16] A mixture of 80 g. (0.625 mole) of 4-chloroaniline, 500 ml. of absolute ethanol, 53 ml. of concentrated hydrochloric acid, 270 g. of ferric chloride hexahydrate and 10 g. of zinc chloride was heated to 60–65°. Crotonaldehyde, 35 g. (0.5 mole) was added dropwise in two hours. The mixture was refluxed two hours, let stand overnight, distilled under vacuum to remove the alcohol, and then made strongly basic and steam distilled. The distilled solid, after drying, weighed 70 g. (79% yield), m. p. 92–93° (reported,[16] m. p. 91°).

6-Chloro-2-tribromoquinaldine.—A solution of 227 g. (1.44 mole) of bromine in 61 ml. of glacial acetic acid was added in the course of one hour to a mixture of 245 g. (2.98 moles) of anhydrous sodium acetate, 85 g. (0.49 mole) of 6-chloroquinaldine, and 610 ml. of glacial acetic acid at 75–80°. After heating at 90–95° for one hour and standing overnight, the solid product was separated and recrystallized from petroleum ether (60–70°); yield 133 g. (67%), m. p. 59–60°.

Anal. Calcd. for $C_{10}H_5NBr_3Cl$: Br, 57.86; Cl, 8.56. Found: Br, 57.5, 57.6; Cl, 8.5, 8.5.

Ethyl 6-Chloroquinaldinate.—The procedure developed for the preparation of ethyl quinaldinate gave a 44% yield of the 6-chloro analog, m. p. 91–92°.

Anal. Calcd. for $C_{12}H_{10}NO_2Cl$: N, 5.94. Found: N, 5.94.

6-Chloro-2-isopropenylquinoline.—The reaction of 13 g. (0.055 mole) of ethyl 6-chloroquinaldinate with approximately 0.18 mole of methylmagnesium bromide in ether according to the procedure previously described using ethyl quinaldinate gave 7.5 g. of a viscous oil, chiefly 6-chloro-2-(2′-hydroxy-2′-propyl)-quinoline, which was not further characterized but was dehydrated directly with concd. sulfuric acid (20 ml.) at 120° for three hours. The olefin was a pale yellow oil which crystallized from an ethanol–water mixture; yield 4.3 g. (62.5%), m. p. 50°.

Anal. Calcd. for $C_{12}H_{11}NCl$: N, 6.84. Found: N, 6.67.

(13) Graf and Meyer, *Ber.*, **61**, 2210 (1928).

(14) Campbell, *et al.*, THIS JOURNAL, **68**, 1841 (1946).

(15) Emmert and Pirot, *Ber.*, **74B**, 718 (1941).

(16) Bartow and McCollum, THIS JOURNAL, **26**, 703 (1904).

Polymerization Experiments

Compounds I, VIII and IX gave no polymers alone or copolymers with butadiene, styrene, or methyl methacrylate, in the presence of benzoyl peroxide. Of the remaining compounds II, III, and V gave no polymers alone but copolymerized readily with the above olefins. Compounds IV and VI polymerized readily alone and also copolymerized with the above olefins. Several attempts were made to prepare 6-chloro-2-vinylquinoline (VII) by procedures analogous to those used for 2-vinylquinoline (VI). In every case rapid polymerization interfered with isolation of the monomer. The bulk polymers were prepared by heating the monomers at 70° in stoppered test-tubes with 0.5% benzoyl peroxide catalyst. Equal weights of monomers were used for the copolymers. The emulsion polymers with butadiene were prepared in sealed tubes at 40° (thermostat) using the formula: butadiene 7.5 g., vinyl monomer 2.5 g., water 18 g., soap 0.5 g., potassium persulfate 0.03 g., lauryl mercaptan (OEI) 0.06 g.

Summary

A series of vinylpyridines and vinylquinolines, some containing nuclear halogens, have been prepared and a preliminary study made of their polymerizing and copolymerizing characteristics.

LAFAYETTE, INDIANA RECEIVED DECEMBER 23, 1947

[CONTRIBUTION NO. 145 FROM THE GOODYEAR TIRE AND RUBBER CO., RESEARCH LABORATORY]

Viscosity–Molecular Weight and Viscosity–Temperature Relationships for Polystyrene and Polyisobutylene[1,2]

BY THOMAS G FOX, JR., AND PAUL J. FLORY

The simple empirical relationship[3]

$$\log \eta = A + C\overline{M}_w^{1/2} \qquad (1)$$

where η is the viscosity, $\overline{M}_w$ the weight average molecular weight and A and C are constants for a specified temperature, has been found to apply with remarkable accuracy to linear polyesters,[3,4] polyamides,[5] and to certain non-linear polymers as well.[5] Extension of this relationship to addition polymers of unsaturated compounds such as polyethylene[6] and polyisobutylene[7] and to polymeric dimethyl silicones[8] has been attempted recently with indications of success. However, either the molecular weights (weight average) were unreliably determined or the range was too limited for positive assurance that equation (1) may be applied to these polymers.

In the present investigation viscosities of two representative hydrocarbon polymers, polystyrene and polyisobutylene, of simple chain structure have been measured over wide ranges of molecular weight, molecular weight distribution and temperature. In addition to providing data with which to test the generality of equation (1), the present results demonstrate the nature of the dependence of the viscosity–temperature coefficient on molecular weight, molecular weight distribution and temperature. Apparent discrepancies which have appeared in the literature on viscosity–temperature coefficients for polystyrene have been accounted for. It is hoped that the results of this investigation will provide a basis for the better understanding of flow mechanisms in high polymers.

(1) The work presented in this paper comprises a program of fundamental research on rubber and plastics being carried out under a contract between the Office of Naval Research and the Goodyear Tire and Rubber Company.

(2) Presented before the High Polymer Forum at the Atlantic City Meeting of the American Chemical Society, April 15, 1947.

(3) P. J. Flory, THIS JOURNAL, **62**, 1057 (1940).

(4) W. O. Baker, C. S. Fuller and J. H. Heiss, *ibid.*, **63**, 2142 (1941).

(5) J. R. Schaefgen and P. J. Flory, forthcoming publication.

(6) G. J. Dienes and H. F. Klemm, *J. Applied Phys.*, **17**, 458 (1946).

(7) R. L. Zapp and F. P. Baldwin, *Ind. Eng. Chem.*, **38**, 948 (1946).

(8) A. J. Barry, *J. Applied Phys.*, **17**, 1020 (1946).

Experimental

Preparation and Fractionation.—Seven polymers of styrene varying in viscosity average molecular weight ($\overline{M}_v$) from 7000 to 350,000 were prepared by bulk polymerization at 60°. An average molecular weight in the desired range was obtained in each case by using appropriate concentrations of benzoyl peroxide and dodecyl mercaptan as shown in Table I. The reactions were stopped at conversions of approximately 25%. The polymers were separated by precipitation in an excess of vigorously stirred methanol, and were dried *in vacuo* at 60°.

Four polyisobutylenes with molecular weights as listed in Table I were fractionated.[9] Thus, the polymer known commercially as "Vistanex-LMH" with a viscosity average molecular weight of 69,000, was separated into a series of polymer fractions identified as PB1F1, PB1F2, and so on. The polymer PB5 consisted of a mixture of two large coarse fractions separated from PB2 and PB3.

All polymers were fractionated by single precipitation methods carried out at 30.0°. Solvent–precipitant combinations employed were methyl ethyl ketone–methyl alcohol for polystyrene and benzene–acetone for polyisobutylene. In each case the precipitant was added slowly with stirring to a solution containing 1.3 to 2.5 g. of polymer per 100 ml. of solvent (Table I) until a condition of permanent turbidity was reached. After adding an appropriate excess of the precipitant, the solution was warmed until it became clear, then subjected to gentle stirring while cooling slowly to 30.0°. The insoluble gel which settled out on standing overnight at this temperature was separated from the clear solution by decantation, washed with the non-solvent, and dried first on a steam

(9) The polyisobutylene was supplied by the Standard Oil Co. of New Jersey. We are indebted to Mr. D. W. Young of the Esso Laboratories who made available to us PB7, a laboratory sample of low molecular weight.

TABLE I

THE POLYMERS USED FOR FRACTIONATION

Polystyrene

Polymer	Mole % peroxide	Mole % mercaptan	Extent of reaction	$\overline{M}_v$	Fractionation initial concn., g./100 ml.
14A	0.04	0	26%	349,000	2.0
11A	0.50	0	22	150,000	2.0
8A	1.0	0.010	28	60,000	2.0
6A	1.0	0.024	24	70,000	2.0
3D	1.0	0.055	28	45,000	2.0
4C	1.0	0.22	22	41,000	2.2
16A	4.0	6.5	20	7,060	2.0

Polyisobutylene

Polymer	Commercial designation	$\overline{M}_v$ (approximate)	Fractionation initial concn., g./100 ml.
PB1	Vistanex LMH	69,000	2.00
PB2	100,000 Grade	1,000,000	1.25
PB3	100,000 Grade	1,000,000	1.25
PB4	Vistanex LMS	45,000	2.50
PB5	.....	1,000,000	1.33
PB7	.....	3,100	2.5

bath and then *in vacuo* at 60°. By repeating this procedure a series of fractions was obtained from each polymer, the individual fractions usually representing 5 to 25% of the whole polymer (Table VIII). PB5F1 appears to be a notable exception, as it represents 46% of PB5. However, it represents only 23% of polyisobutylene B-100 since PB5 was obtained by combining fractions representing approximately half of that polymer.

Fractionation of the low molecular weight polystyrene 16A was carried out from acetone solution using as precipitant a mixture containing equal volumes of water and methanol. The acetone-soluble portion of 4C (about two-thirds of the whole) was fractionated in a similar manner.

Inasmuch as the *weight average* molecular weight on which the melt viscosity depends (*cf. seq.*) lies close to the *viscosity average* deduced from intrinsic viscosity measurements, it is evident that efficient fractionation should be unnecessary. Nevertheless, to confirm this expectation experimentally, polystyrene 3D was fractionated by the double precipitation method previously described.[10] The melt viscosity of one of these fractions did not differ significantly from that of a fraction of the same intrinsic viscosity which had been obtained by the single precipitation method. Hence all subsequent fractionations were carried out employing the single precipitation technique.

Molecular Weight Determination.—Molecular weights of the polystyrene fractions have been calculated from their intrinsic viscosities, $[\eta]$, in freshly distilled benzene, using the relationship obtained by Ewart[11]

$$\log \overline{M}_v = (\log[\eta] + 4.013)/0.74 \qquad (2)$$

where $\overline{M}_v$ is the viscosity average molecular weight.[10] Molecular weights of the polyisobutylenes have been obtained from their intrinsic viscosities in carbon tetrachloride, using the equation[12]

$$\log \overline{M}_v = (\log[\eta] + 3.345)/0.64 \qquad (3)$$

The carbon tetrachloride was purified by successive washings with concentrated sulfuric acid, water, 10% sodium carbonate, and water, followed by drying over sodium sulfate and distilling. For the fractionated polymers it is permissible to replace $\overline{M}_v$ with $\overline{M}_w$.

The solution viscosities were measured at 30.08 ± 0.01° using a Ubbelohde no. 1 viscometer the calibration of which included the kinetic energy term.[13]

Relative viscosities, η_r, for solutions of the polystyrene fractions at different concentrations agreed with the relationship reported by Tingey[14]

$$(\ln \eta_r)/c = [\eta] - 0.125\,[\eta]^2 c \qquad (4)$$

where c is expressed in g./100 ml. Consequently it was possible to determine the intrinsic viscosity from the efflux time for a single solution.

The value of $(\ln \eta_r)/c$ for polyisobutylene solutions with relative viscosities between 1.18 and 1.22 was arbitrarily taken to represent $[\eta]$. This value differs by approximately 2% from that obtained by extrapolation to infinite dilution. In some cases, particularly for high molecular weight samples, values of $(\ln \eta_r)/c$ for η_r in the above prescribed range were obtained by extrapolation from measurements in solutions of higher relative viscosities, the error thus introduced being less than 4%.

Molecular weights reported here are generally reproducible to ±3%. For certain of the polymers of higher molecular weight this uncertainty may be ±5%.

Capillary Viscometers.—Melt viscosities in the range of 1 to 10^6 poises were determined according to the procedure previously described.[3] The viscometers consisted of straight capillary tubes, 1.0 to 2.0 mm. in diameter, each marked at four points at appropriate distances from the lower tip. The time required to fill the viscometer capillary from one mark to the next under a predetermined pressure differential was measured. In this way three determinations could be carried out successively. Absolute viscosities in poises were calculated from

$$\eta = ktp \qquad (5)$$

(10) P. J. Flory, THIS JOURNAL, **65**, 372 (1943).

(11) R. H. Ewart, paper presented at the Atlantic City Meeting of the American Chemical Society, April 14, 1947. Recently A. I. Goldberg, W. P. Hohenstein and H. Mark, *J. Polymer Sci.*, **2**, 503 (1947), have proposed yet another intrinsic viscosity–molecular weight relationship for polystyrene. We prefer the Ewart expression for our purposes since it is derived from measurements made over a range similar to that covered in our experiments. Use of the Goldberg, Hohenstein and Mark equation, however, would not affect the general nature of the relationships reported in this paper.

(12) See reference 10. We are indebted to Dr. John Rehner, Jr., of the Esso Laboratories for providing information on the relationship between intrinsic viscosities of polyisobutylene in carbon tetrachloride compared to those in diisobutylene, the solvent originally used[10] in establishing the intrinsic viscosity–molecular weight relationship. According to Rehner, the ratio $[\eta]_{CCl_4}/[\eta]_{diisobutylene}$ is 1.255 ± 0.005 for all molecular weights.

(13) The calibration method outlined in ASTM Designation D445-39T was employed.

(14) H. C. Tingey, unpublished data referred to by R. H. Ewart, "Advances in Colloid Science," Vol. II, Interscience Publishers, New York, N. Y., 1946, p. 210.

where t is the measured time, p the pressure differential (2 to 30 cm. of mercury), and k is a calibration constant computed according to Poiseuille's law from the accurately measured dimensions of the tubes. As a check on the reliability of these calibrations, the constants k for several of the viscometers were independently determined from their tp products for an oil of accurately known viscosity, 493 poises at 30.0°, obtained from the National Bureau of Standards. The two methods agreed within ±1%.

Construction of the Coaxial Viscometer.—To measure viscosities in the range of 10^5 to 10^{11} poises there was constructed a coaxial falling-cylinder viscometer (shown schematically in Fig. 1) of the type described by Segel,[15] systematically studied by Traxler and Schweyer,[16] and used by various other workers.[17] It consists of a steel block 4″ × 3.5″ × 2″ containing a cylindrical cavity of diameter B and length L, the axis of the cavity coinciding with the long axis of the block. A steel rod of smaller diameter, A, is centered coaxially in the cavity, the ends of the rod projecting beyond the respective ends of the viscometer block. The annular space around the steel rod is filled with the sample. With the viscometer suspended with its long axis in a vertical position, the rate of fall, V, of the steel rod under the influence of a suspended weight, W, is observed. The viscosity is calculated from

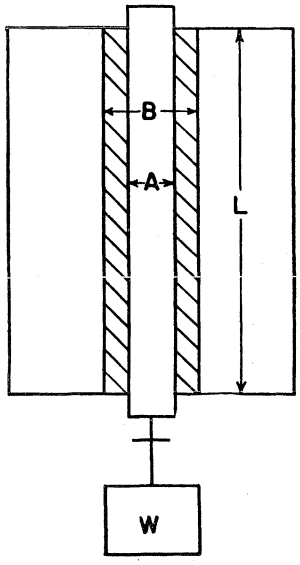


Fig. 1.—Schematic cross-sectional view of the coaxial falling-cylinder viscometer. The values of L, B and A are 10.16 cm., 1.122 cm. and 0.795 cm., respectively.

$$\eta = KW/V \qquad (6)$$

where K is a constant determined from the dimensions of the instrument according to the equation

$$K = (g/2\pi L)\ln(B/A) \qquad (7)$$

where g is the gravitational constant. The instrument was designed with provisions for: (1) molding of the polymer in the annular space about the central rod, (2) obtaining adequate temperature control and (3) the application of a load to, and observation of the rate of fall of, the central cylinder. Important features of the construction are shown schematically in Figs. 2 and 3 (omitting the screws, guide pins, and other details which would make the drawings hopelessly complex).

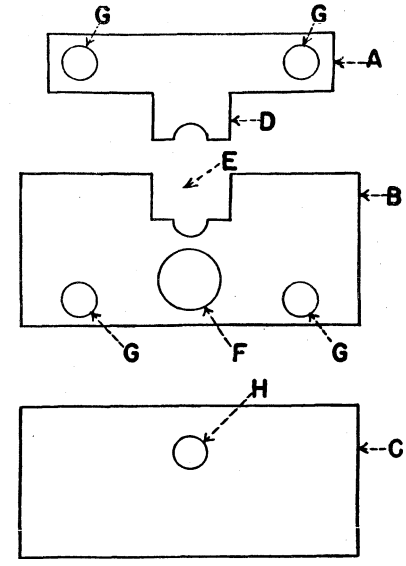


Fig. 2.—End view of the coaxial viscometer. Drawn approximately to scale.

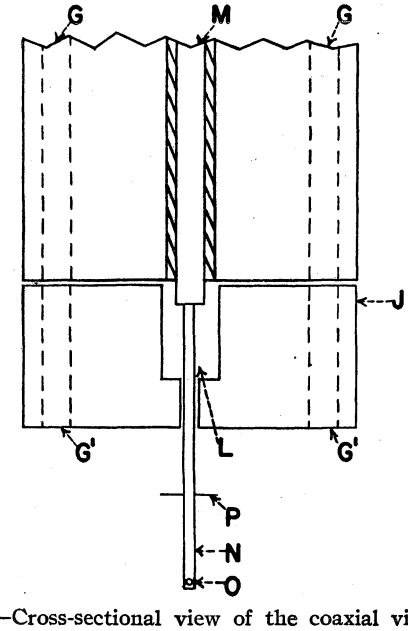


Fig. 3.—Cross-sectional view of the coaxial viscometer; not drawn to scale.

In order to permit molding of the sample within the instrument, the outer block was constructed in two parts, as illustrated by the end view of Fig. 2. As the two sections are brought together the projecting portion (D) of the top member (A) fits snugly into the trough (E) in the bottom section (B), thus providing the necessary compression of the polymer. Positioning of the steel rod in the

(15) M. Segel, *Physik. Z.*, **4**, 493 (1903).

(16) R. N. Traxler and H. E. Schweyer, *Am. Soc. Testing Materials Proc.*, **36**, 523 (1936).

(17) A. Pochettino, *Nuovo cimento*, **8**, 77 (1914); C. J. Mack, *J. Phys. Chem.*, **36**, 2901 (1932); H. L. D. Pugh, *J. Sci. Instruments*, **21**, 177 (1944).

cavity during the molding operation is accomplished by two metal plates (C) which can be secured to the ends of the bottom section of the viscometer, each plate being provided with a hole (H) about 0.001″ larger in diameter than the rod.

Four symmetrically placed $^3/_8$″ holes (G) were bored through the length of the block for the insertion of either cartridge-type electrical heaters or copper tubes containing a cooling liquid. A larger hole (F) directly under the cylindrical cavity provides for the insertion of a Fenwal thermoswitch, which in conjunction with an electronic relay provides temperature control. To insure uniform temperature throughout the length of the polymeric cylinder, 1.5″ steel blocks (J in Fig. 3) can be attached at both ends of the viscometer. These blocks are provided with appropriate holes (G′, L) to permit insertion of the heaters and to allow for motion of the inner cylinder and its attachments.

Two thermocouple holes are provided, one being drilled in the core of the steel rod and the other in the side of the viscometer block, the latter reaching within 5 mm. of the annular cavity.

As shown in Fig. 3, a thin steel tube (N) attaches to the end of the steel rod (M) and projects out into the space below the instrument. Weights may be hung from a hole (O) which is drilled at the lower end of this tube. A needle (P) is fastened perpendicular to its length, providing a reference for observing the motion of the falling cylinder. Two rods projecting from the sides of the viscometer provide for its suspension between a pair of iron posts firmly bolted to a cast iron base.

Operation of the Coaxial Viscometer.—In preparation for the molding operation, the end plates (C) are first attached to the lower block (B) of the viscometer and the steel rod is inserted through the holes (H) in the end-plates. The upper and lower blocks are brought to temperature, usually 160°. An amount of polymer slightly in excess of that needed to fill the cavity is distributed evenly in the trough (E) and the upper block is set in place on the lower. The assembly is placed in a press equipped with heated platens and again brought to temperature. A load of 10,000 to 30,000 pounds is applied to close the viscometer assembly, the excess polymer being forced out through three vents drilled in the top of the viscometer. After about ten minutes the viscometer is cooled to room temperature under pressure, the pressure is removed and the two sections of the viscometer are securely fastened together with screws.

In order to make ready for viscosity measurements, the insulating end pieces (J) are substituted for the end plates (C), the heaters and the thermoswitch are inserted in the cavities (G, F) and the necessary electrical connections are made. The steel tube (N) is secured to the steel rod, the thermocouples are set in place, and the assembly is insulated with asbestos board and glass fabric. The instrument is mounted with its axis vertical and brought to the desired temperature. The desired weight is hung on the end of the steel tube and the position of the needle observed at various intervals.

In the experiments reported here, the temperature was controlled within ±2° between −9 and 200°, the readings of the two thermocouples agreeing within ±1°. A traveling microscope accurate to ±0.0005 cm. was used for most of the observations; one of lower accuracy, ±0.003 cm., was used in the initial experiments. Rates of fall varying from 1.5×10^{-7} to 3.5×10^{-3} cm./sec. were observed. Usually ten or more observations were made while the cylinder moved 0.15 to 0.30 cm., after which the viscometer was inverted and the load attached to the other end. Observations were repeated while the cylinder traveled in the opposite direction. The velocity of fall was observed to be independent of the direction of motion of the cylinder.

High Temperature Stability.—Both the melt viscosity and the intrinsic viscosity were observed to decrease on heating polystyrene to 217° in the presence of either air or nitrogen for periods of five minutes to two hours. However, in several instances an insoluble portion appeared and an increase in the intrinsic viscosity of the soluble portion was observed. It appears that degradation and cross-linking reactions occur simultaneously under these conditions. Addition of phenyl β-naphthylamine eliminated all evidence of gelation and reduced degradation to a negligible amount when polysytrene was heated at 217° in a nitrogen atmosphere for up to two hours. Accordingly, approximately 0.5% of this compound was incorporated into all high molecular weight polystyrenes by addition to a benzene solution of the polymer and subsequent evaporation.

No signs of gelation and only a slight decrease in the intrinsic viscosity were observed when polyisobutylene was heated to 217° in the presence of an inert atmosphere for periods of thirty to ninety minutes.

The $\overline{M}_w$ values reported here are derived from intrinsic viscosities measured after the melt viscosity had been determined. In most cases the molecular weights before and after melt viscosity determination agree within 5%.

Results

The Coaxial Viscometer.—The deformation taking place within the coaxial viscometer approaches simple shear; the difference between the outer and inner cylinder diameters being relatively small, the rate of shear is nearly uniform throughout the polymer. If the polymer undergoes Newtonian flow, (1) the motion of the falling cylinder will be linear with time, (2) the observed viscosity will be independent of the applied load and (3) the viscosity values will agree with those obtained by the capillary method.

Results shown in Table II and in Fig. 4 illustrate the constancy of the rate of displacement of the cylinder with polyisobutylenes at viscosities up to 10^{10} poises and loads up to 500 g.

TABLE II

THE DISTANCE (d) TRAVELED BY THE FALLING CYLINDER IN TIME (t)

Polyisobutylene

$\overline{M}_w$ = 660,000

Load 558 g., T = 160° C.[a]			Load 158 g., T = 160° C.[a]		
t, sec.	d obs.	d calcd.[b]	t, sec.	d obs.	d calcd.[b]
0	0 cm.	0 cm.	0	0 cm.	0 cm.
87	0.088	0.088	263	0.078	0.074
128	.130	.129	510	.149	.144
191	.191	.193	667	.191	.188
294	.293	.294	809	.229	.228
348	.350	.351	1007	.285	.284

Load 58 g., T = 160° C.[a]			Load 527 g., T = 8° C.[c]		
t, sec.	d obs.	d calcd.[b]	t, sec. × 10^{-3}	d obs.	d calcd.[b]
0	0 cm.	0 cm.	0	0 cm.	0 cm.
146	0.016	0.016	97.2	0.0132	0.0150
320	.035	.035	153.9	.0223	.0237
674	.073	.073	183.6	.0280	.0283
809	.086	.087	270.0	.0414	.0416
1021	.110	.110	500.4	.0773	.0771

[a] $\eta = 3 \times 10^6$ poises at 160°. [b] d calcd. = Vt, where V is the "best value" for the velocity in cm./sec. [c] $\eta = 2 \times 10^{10}$ poises at 8°.

However, in many cases, particularly at the higher viscosities, there was observed an initial non-linear dependence of displacement on time which later became linear (*i. e.*, the straight lines in Fig. 4 do not go through the origin). It was assumed that the non-linear portion was due to a time-dependent elastic deformation which, however, reached completion in a relatively short time.[18] Since the elastic deformation was of no interest in this work, sufficient time was allowed in most of the experiments for the completion of the elastic deformation prior to observing the fall of the cylinder. Hence, the times recorded in Table II are referred not to the time of application of the load but rather to some arbitrary time thereafter.

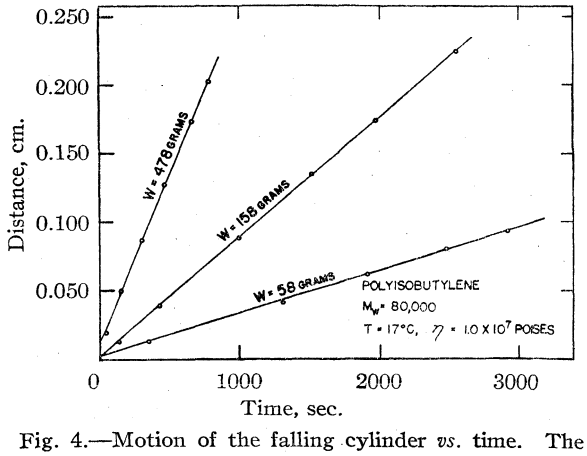


Fig. 4.—Motion of the falling cylinder *vs.* time. The initial observation (distance 0 at zero time) was made as soon as possible after attaching the weight.

Observed viscosity values for polyisobutylenes are independent of the applied load at least up to 500 g., provided the viscosity be less than 10^9 poises. Typical data illustrating this point are given in Table III. The apparent viscosity decreases with increasing load for higher values.

TABLE III

THE APPARENT VISCOSITY AS A FUNCTION OF APPLIED LOAD

Polyisobutylene, $\overline{M}_w$ = 660,000

	T = 160°		T = 8°	
Direction of motion	Load, g.	η, poises	Load, g.	η, poises
Out	558	2.97 × 10^6	3970	0.84 × 10^{10}
In	558	2.95	2140	1.50
Out	213	3.00	1020	1.55
In	158	3.02	527	1.84
Out	58	2.88	Extrapolated	1.97 × 10^{10}
In	58	2.85	to zero load	poises
Average (2.95 ± 0.05) × 10^6 poises				

The viscosity at zero load, where the limiting flow characteristics may be assumed to correspond to ideal Newtonian behavior, was obtained in such cases by linear extrapolation (Fig. 5).

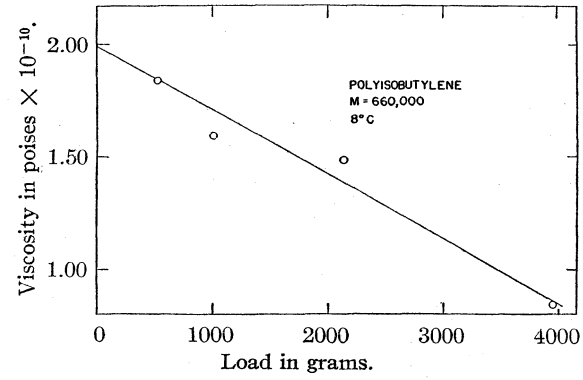


Fig. 5.—The apparent viscosity *vs.* load, employing the coaxial falling-cylinder viscometer.

Measurement of the viscosity of polyisobutylene of molecular weight 80,000 by this method yielded 88,000 poises at 87° which, from the temperature coefficient of flow (*cf. seq.*), corresponds to 79,000 poises at 89°. A similar determination at the latter temperature using a capillary viscometer yielded 80,700 poises. Thus, the two methods are consistent.

Attempts to measure accurately the viscosity of high molecular weight polystyrene in the coaxial viscometer were unsuccessful. Frequently the apparent viscosity was observed to vary with time and/or with the applied load. The results

(18) A. P. Alexandrov and J. S. Lazurkin, *Acta Physicochim. U. R. S. S.*, **12**, 647 (1940).

TABLE IV

VISCOSITY–TEMPERATURE RELATIONS FOR POLYSTYRENE[a]

Polymer	M	$T°$	η_T, poises	Polymer	M	$T°$	η_T, poises
11AF3	134,000	217	11,400	16AF5	4900	217	1.03
		190.5	68,000			190.5	2.1
		160	1,350,000			160	8.7
						138	43.8
6AF3	80,000	217.2	1,703			110	950
		210.2	2,525			99.5	3750
		201.2	4,315			88.5	28,300
		190.7	9,200			81.7	182,000
		177.8	27,400				
				16AF6	3700	138	3.44
8AF4	32,200	217	131			110	25.6
		190.5	709			88	229
		160	12,900			74.0	2360
		138	375,000			64.5	8400
		130	2,320,000			53.0	197,000
4CF2	25,700	217	70.3				
		201.1	168				
		177.8	1060				
		156.5	11,500				

[a] The same sample of each polymer fraction was used for measurements at the several temperatures.

which appeared most reliable were lower than the corresponding values obtained with capillary viscometers by a factor of at least three. These discrepancies are believed to have been caused by air bubbles trapped in the polystyrene. All efforts to mold high molecular weight polystyrenes in the viscometer so that they were reasonably free of bubbles failed. On the other hand, polyisobutylene could be molded almost bubble-free with no great difficulty.

Viscosity–Temperature Relationships.—The viscosities of fifteen polystyrene fractions ranging in molecular weight from 3700 to 134,000 were measured with capillary viscometers at various temperatures. The maximum temperature range covered was 217 to 53°. Representative data are given in Table IV, and the data for thirteen of the fractions are plotted as log (η_T/η_{217}) *vs.* $1/T$ (°A.$^{-1}$) in Fig. 6. The viscosity ratio is employed in order to facilitate comparison of results for polymers differing in molecular weight. The relationship between log (η_T/η_{217}) and $1/T$ is non-linear. The data for eight fractions with molecular weights from 25,700 to 134,000 may be represented by a single curve (curve 1 of Fig. 6) when plotted in this manner. For fractions of lower molecular weight, a series of curves are obtained, their slopes being lower the lower the molecular weight. This dependence of the viscosity–temperature coefficient on the molecular weight is further illustrated in Fig. 7 where log (η_T/η_{217}) for temperatures of 160, 176 and 190° are plotted *vs.* the molecular weight. (The molecular weights employed here and in Tables IV, V and VI are based on intrinsic viscosity measurements and, hence, to the extent that the particular type of average requires specification when dealing with fractionated samples, they represent viscosity averages. For reasons which will appear later, however, the particular average is not specified.) The temperature-coefficient for polystyrene at a given temperature increases with increasing molecular weight up to approximately

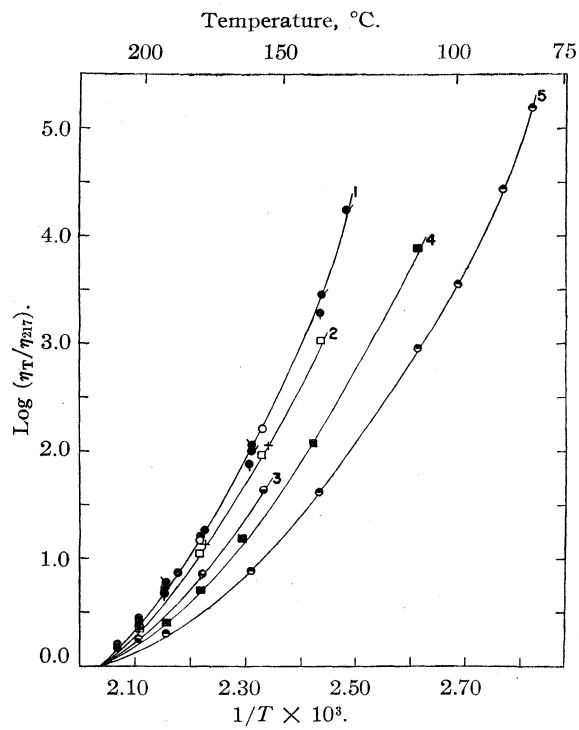


Fig. 6.—Log (η_T/η_{217}) *vs.* $1/T$ (°A.$^{-1}$) for polystyrene fractions of various molecular weights: curve 1, ◉ 134,000, ● 80,000, 69,500, 49,700, 44,000, ◉ 32,200, ○ 26,600, ◉ 25,500; curve 2, +13,500, □ 11,000; curve 3, ◒ 7400; curve 4, ■ 5100; curve 5, ◓ 4900.

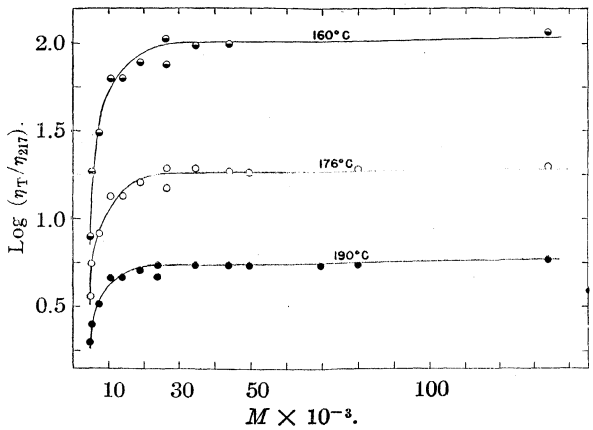


Fig. 7.—Log (η_T/η_{217}) *vs.* M for polystyrene fractions.

25,000 beyond which it is approximately constant.

Corresponding results for polyisobutylene over the molecular weight range from 11,200 to 660,000 are presented in Table V.

TABLE V

VISCOSITY–TEMPERATURE RELATIONS FOR POLYISOBUTYLENE[a]

Polymer	T, °C.	η_T, poises	Method of measurement
PB2F2	217	7.6×10^5	Capillary
M = 660,000	160	2.95×10^6	Coaxial
	141	5.28×10^6	Coaxial
	119	1.20×10^7	Coaxial
	100	2.57×10^7	Coaxial
	78	7.80×10^7	Coaxial
	28	2.04×10^9	Coaxial
	8	1.97×10^{10}	Coaxial
PB4F1	217	1100	Capillary
M = 80,000	190	2090	Capillary
	160	4800	Capillary
	138	10,100	Capillary
	89	80,700	Capillary
	87	8.8×10^4	Coaxial
	78.5	1.38×10^5	Coaxial
	38	1.83×10^6	Coaxial
	17	1.0×10^7	Coaxial
	3.5	4.1×10^7	Coaxial
	−9	2.58×10^7	Coaxial
PB1F3	216.5	1150	Capillary
M = 81,500	201.0	1640	Capillary
	179.0	2810	Capillary
	156.0	5600	Capillary
PB1F4	217	340	Capillary
M = 56,500	201.4	485	Capillary
	181.5	880	Capillary
	157.0	1750	Capillary
	110.0	9830	Capillary
PB1F5	217.0	119	Capillary
M = 38,200	200.8	168	Capillary
	178.6	305	Capillary
	155.6	634	Capillary
PB1F7	216.5	22.9	Capillary
M = 22,400	181.0	56.1	Capillary
	137.7	206	Capillary
	110.0	643	Capillary
	80.5	2760	Capillary
PB1F8	217.2	6.45	Capillary
M = 11,200	181.9	14.2	Capillary
	138.1	57.6	Capillary
	110.0	184	Capillary
	79.0	884	Capillary
	55.5	3530	Capillary

[a] The same sample of each polymer fraction was used for measurements at the several temperatures.

TABLE VI

THE APPARENT ENERGY OF ACTIVATION FOR VISCOUS FLOW

Polyisobutylene

Mol. wt. range	217°	200°	E_T, kcal./mole 150°	100°	50°	0°
11,200 to >1,000,000	10.3	10.6	12.0	13.2	13.7	19.3

Polystyrene

Polymer	M	E_T, kcal./mole 217°	200°	175°	150°	138°	125°	100°	88°	82°
Several	>25,000	24	30	38	52	66	>100	..	..	..
4CF3	19,000	22	27	35	42	..	...	..	..	..
4CF5	7,400	18	23	27	35	..	...	..	..	..
4CF6	5,100	8	21	26	32	..	...	..	..	..
16AF5	4,900	7	12	20	28	32	35	44	60	85
16AF6	3,700	..	..	..	..	..	22	27	32	37

Both types of viscometers were employed for measurements on each of the two highest molecular weight fractions. The capillary method alone was employed for the other polyisobutylenes. The data for the various fractions are represented by a single curve in Fig. 8. The viscosity-temperature coefficient appears to be independent of molecular weight over the range investigated. The corresponding curve for high molecular

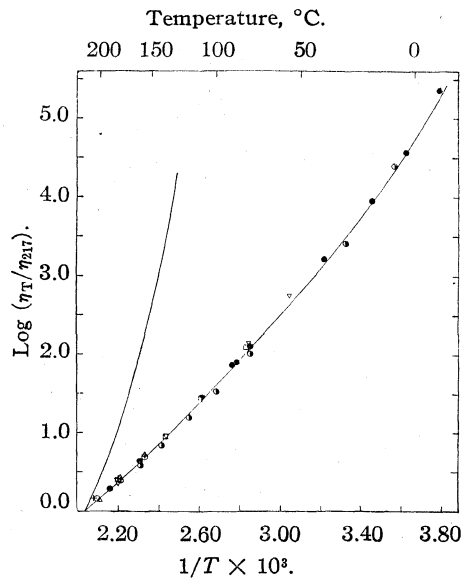


Fig. 8.—Log (η_T/η_{217}) *vs.* $1/T$ (°A.$^{-1}$) for polyisobutylene fractions of various molecular weights: ◑ 660,000, ● 80,000, ○ 81,500, + 56,500, △ 38,200, □ 22,400, ▽ 11,200. The curve to the left, representing high molecular weight polystyrene, is a duplicate of curve 1 of Fig. 6.

weight polystyrene (curve 1 of Fig. 6) has been included for comparison.

The present results are in good agreement with those of Ferry and Parks[19] on the viscosity of an unfractionated polyisobutylene of cryoscopic molecular weight 4900, as obtained from falling sphere and rotating cylinder measurements. As shown in Fig. 9, their data fall on or near the curve for polyisobutylene (from Fig. 8) provided the viscosity of their polymer at 217° (which they did not determine) is assumed to be 7.94 poises.

Both polymers exhibit a non-linear relationship between log η_T and $1/T$. The "apparent" energy of activation, E_T, for viscous flow at temperature T, defined as $2.3R[d(\log \eta)/d(1/T)]$, increases with decreasing temperature for both polystyrene and polyisobutylene. As shown in Table VI (see also Fig. 8), E_T for high molecular weight polystyrene in this temperature range is greater than the corresponding value for polyisobutylene and it increases more rapidly with decreasing temperature. The dependence of the viscosity–temperature coefficient for polystyrene on molecular weight below 25,000 is reflected in the diminished values of E_T in this range.

Viscosity and Molecular Weight.—The viscosities of the lower polyisobutylenes were measured at 217° by capillary viscometers; the coaxial method was used in most cases on the higher polymers. These latter measurements were carried out at several lower temperatures and the corresponding values at 217° were obtained by extrapolation using the viscosity–temperature dependence presented above. The validity of these extrapolations is confirmed by close agreement between values extrapolated from measurements at different temperatures, as shown in Table VII. Viscosities for polystyrene at 217° were obtained by the capillary method.

TABLE VII

EXTRAPOLATION OF COAXIAL VISCOMETER DATA TO 217°

Polymer	T, °C.	log η_T	Extrapolated log η_{217}	Average log η_{217}
PB5F1	160	8.05	7.40	7.40
PB5F2	160	7.69	7.04	7.02 ± 0.03
	115	8.34	6.99	
PB5F3	160	6.74	6.09	6.08 ± 0.01
	112	7.47	6.07	
PB2F4	88	6.38	4.50	4.51 ± 0.01
	38	7.73	4.51	

All of the above data as obtained at 217° or extrapolated to that temperature are summarized in Table VIII and in Figs. 10 and 11 where log η_{217} is plotted against $\overline{M}_w^{1/2}$. Curves drawn through the sets of points for the two polymers are of the same general character. While certain limited portions of the data may be approximated by straight lines, no linear relationship is valid over a wide molecular weight range. For polystyrenes below 25,000 the viscosity–molecular weight relationship is of little significance since for these polymers the viscosity–temperature behavior is dependent on the molecular weight. However, for convenience these data have been included and a dotted line has been drawn through the points.

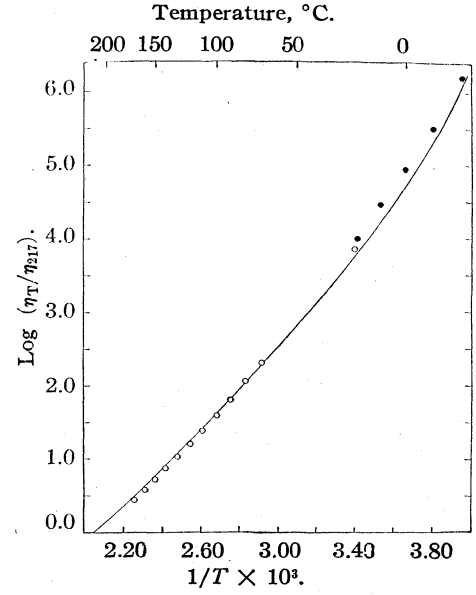


Fig. 9.—Log (η_T/η_{217}) *vs.* $1/T$ (°A.$^{-1}$) for polyisobutylene. The solid line is a reproduction of the curve for polyisobutylene in Fig. 8. The points represent data obtained by Ferry and Parks (ref. 19) on an unfractionated polyisobutylene of cryoscopic molecular weight 4900. The open circles represent falling sphere data; the dark circles represent data obtained with a rotating cylinder viscometer. The value of η_{217}, which they did not measure, was arbitrarily taken as 7.94 poises.

The similarity in behavior of these two polymers is further illustrated if these data are plotted as log η_{217} *vs.* log $\overline{M}_w$. In such plots, the two sets of points may be represented fairly satisfactorily by two straight lines, with identical slopes. However, the approximate linearity of these log–log plots probably is of limited significance, the correct function being of a more complicated nature.

The Viscosities of Mixtures.—Any choice of a particular molecular weight average in Figs. 7, 10, and 11 is necessarily arbitrary so far as the foregoing data are concerned, inasmuch as the various molecular weight averages, $\overline{M}_n$, $\overline{M}_v$, and $\overline{M}_w$ for fractionated samples are similar. In order to establish the particular averages (if any) on which the viscosity and the viscosity–temperature coefficients depend explicitly, seven mixtures of polystyrene fractions and two of polyisobutylene were prepared as detailed in Table IX by evaporating benzene solutions of two fractions of widely separated molecular weights. The melt viscosities of the mixtures were observed at 217° and several lower temperatures (Table IX). In Table X val-

(19) J. D. Ferry and G. S. Parks, *Physics*, **6**, 356 (1935).

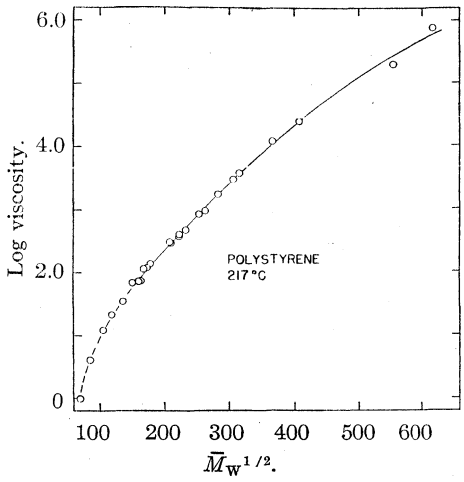


Fig. 10.—Log η_{217} *vs.* $\bar{M}_W^{1/2}$ for polystyrene fractions: measurements were made with capillary viscometers. The viscosity–temperature curves for polystyrenes below 25,000 are not parallel; hence the dotted line through the points for these polymers is for convenience only.

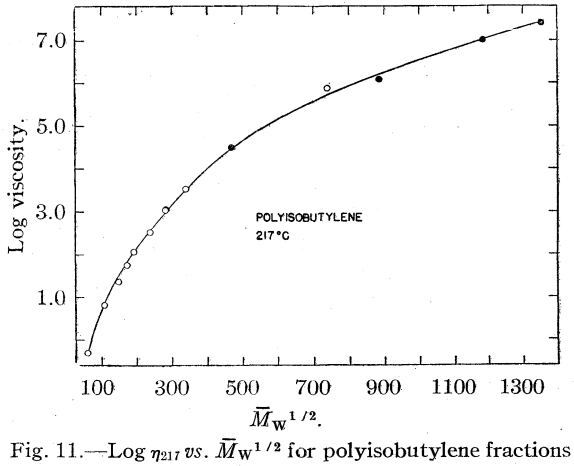


Fig. 11.—Log η_{217} *vs.* $\bar{M}_W^{1/2}$ for polyisobutylene fractions: observations with the coaxial viscometer(extrapolated), ●; with capillary viscometers, ○.

ues of $\bar{M}_n$, $\bar{M}_v$ and $\bar{M}_w$ for these mixtures are given (Columns 6, 2, and 4, respectively) as calculated by the usual equations

$$\bar{M}_n = \sum_i w_i \Big/ \sum_i (w_i/M_i), \qquad (8)$$

$$\bar{M}_v = \left[\sum_i w_i M_i^a \Big/ \sum_i w_i\right]^{1/a} \qquad (9)$$

$$\bar{M}_w = \sum_i w_i M_i \Big/ \sum_i w_i \qquad (10)$$

where w_i is the weight fraction of the species of molecular weight M_i, and a is the exponent in the equation relating the intrinsic viscosity to molecular weight. The experimental values of $\bar{M}_v$ (Column 3), obtained from intrinsic viscosities, agree rather well with the calculated values, although for the higher molecular weight mixtures discrepancies as great as 6% occur.

TABLE VIII

VISCOSITY–MOLECULAR WEIGHT RELATIONSHIPS

Polymer fraction	% of unfractionated polymer	$\bar{M}_w$	η_{217},[a] poises	Method of measurement
		Polyisobutylene		
PB5F1	46.0	1,830,000	2.5×10^7	Coaxial extrapolated to 217°
PB5F2	23.6	1,400,000	1.0×10^7	Coaxial extrapolated to 217°
PB5F3	24.7	783,000	1.2×10^6	Coaxial extrapolated to 217°
PB2F2	25.0	548,000	7.6×10^5	Capillary at 217°
PB2F4	15.4	221,000	3.2×10^4	Coaxial extrapolated to 217°
PB1F2	14.4	115,000	3390	Capillary at 217°
PB1F3	11.1	81,500	1150	Capillary at 217°
PB4F1	20.0	80,000	1100	Capillary at 217°
PB1F4	12.0	56,500	330	Capillary at 217°
PB1F5	10.0	38,200	118	Capillary at 217°
PB1F6	9.0	29,900	55.8	Capillary at 217°
PB1F7	6.4	22,400	22.8	Capillary at 217°
PB1F8	7.8	11,200	6.5	Capillary at 217°
PB7F4	4.0	3,500	0.50	[b]
		Polystyrene		
14AF2	26.0	381,000	7.5×10^5	Capillary at 217°
14AF3	19.4	307,000	2.0×10^5	Capillary at 217°
14AF4	11.2	229,000	8.5×10^4	Capillary at 217°
11AF2	22.2	186,000	3.6×10^4	Capillary at 217°
14AF5	6.0	167,000	2.5×10^4	Capillary at 217°
11AF3	11.5	134,000	1.2×10^4	Capillary at 217°
8AF1	31.3	100,000	3710	Capillary at 217°
3DF3	5.8	94,000	2970	Capillary at 217°
6AF3	40.8	80,000	1703	Capillary at 217°
3DF3′	19.5	69,500	930	Capillary at 217°
3DF6	9.5	63,800	803	Capillary at 217°
3DF7	7.0	54,400	459	Capillary at 217°
6AF4	29.5	49,700	368	Capillary at 217°
3DF4′	21.7	49,700	398	Capillary at 217°
7AF3	20.0	44,000	287	Capillary at 217°
3DF8	9.2	43,300	299	Capillary at 217°
8AF4	15.0	32,200	131	Capillary at 217°
3DF5′	18.3	30,100	118	Capillary at 217°
3DF10	6.0	28,500	112	Capillary at 217°
6AF5	13.7	26,600	70.5	Capillary at 217°
16AF2	8.5	25,500	71.2	Capillary at 217°
4CF2	15.8	25,700	70.3	Capillary at 217°
3DF11	4.0	22,800	67	Capillary at 217°
4CF3	20.6	18,900	34	Capillary at 217°
3DF6′	12.1	14,200	21.5	Capillary at 217°
4CF4	21.3	11,000	12.0	Capillary at 217°
4CF5	11.5	7,200	4.1	Capillary at 217°
16AF5	14.0	4,900	1.0	Capillary at 217°

[a] Some of the viscosity values represent averages obtained from measurements at 217° on two or more samples of the same polymer fraction. These are generally reproducible to ±5% or better, although the uncertainty in the extrapolation of the coaxial data to 217° (Table VII) may be as high as ±15%. [b] A special pipet type viscometer consisting of a fine capillary and a small bulb was employed in measurements on this lowest fraction.

TABLE IX

THE VISCOSITIES OF MIXTURES

Designation	Mol. wts. and proportions of components[a]		η_T in poises 217°	190°	160°	138°	$\log\left(\frac{\eta_{190}}{\eta_{217}}\right)$	$\log\left(\frac{\eta_{160}}{\eta_{217}}\right)$
			Polystyrene					
A	389,000(0.5)	78,000(0.5)	80,500	....	....	..	...	...
B	389,000(0.5)	35,000(0.5)	50,000	....	....	..	...	...
C	100,000(0.5)	31,000(0.5)	796	4560	88,000	..	0.758	2.044
D	78,000(0.5)	31,000(0.5)	532	2820	55,000	..	0.724	2.014
E	138,000(0.25)	8,240(0.75)	67.4	307	2720	..	0.658	1.606
F	44,000(0.5)	5,180(0.5)	22.4	80	681	6710	0.553	1.483
G	26,000(0.5)	5,180(0.5)	9.2	33.4	273	2590	0.560	1.472
			Polyisobutylene					
H	233,000(0.5)	38,200(0.5)	4960	9240	216,000	..	0.270	0.639
I	81,500(0.5)	30,000(0.5)	321	....	.....	..	...	...

[a] Figures in parentheses represent proportions by weight.

TABLE X

MOLECULAR WEIGHTS OF THE MIXTURES

Designation	$\overline{M}_v$ calcd.	$\overline{M}_v$ obs.	$\overline{M}_w$ calcd.	$\overline{M}_{217}$	$\overline{M}_n$ calcd.	$\overline{M}_T$
			Polystyrene			
A	217,000	212,000	233,000	219,000	130,000	.....
B	190,000	179,000	213,000	195,000	64,000	.....
C	63,800	60,600	65,500	62,500	47,500	$\geq$ 25,000
D	51,600	53,600	54,500	55,200	44,200	$\geq$ 25,000
E	32,500	33,000	40,700	24,700	10,800	10,000
F	22,300	20,900	24,500	14,900	9,250	7,500
G	14,700	13,800	15,600	9,400	8,600	7,500
			Polyisobutylene			
H	121,000	121,000	135,000	134,000	66,000	Normal
I	53,700	52,700	55,800	55,700	44,000	.....

The quantity designated as "$\overline{M}_{217}$" (Column 5) represents the molecular weight of a homogeneous fraction exhibiting the same viscosity at 217° as the mixture; the $\overline{M}_{217}$ values have been deduced from the measured viscosities of the mixtures at 217° (Table IX) and the previously established curves relating viscosity to molecular weight for the fractions (Fig. 10 or 11). Values of $\overline{M}_{217}$ for both of the polyisobutylene mixtures and for the polystyrene mixtures for which $\overline{M}_n$ is greater than 25,000 are in good agreement with the corresponding *weight average* molecular weights. For each of the polystyrene mixtures for which $\overline{M}_n$ is less than 25,000 (E, F, G), $\overline{M}_{217}$ lies between the number average and viscosity average molecular weights.

The quantity designated as "$\overline{M}_T$" (Column 7) represents the molecular weight of the polystyrene fraction having the same viscosity–temperature relationship as that of the mixture, as deduced from the observed values of (η_T/η_{217}) for the mixture (Table IX) and the curves of Fig. 7. For the two polystyrene mixtures with $\overline{M}_n$ greater than 25,000 (C, D) the viscosity–temperature coefficients are identical with those previously observed to be characteristic of polystyrene fractions having molecular weights in excess of 25,000. For each of the mixtures of lower molecular weight (E, F, G), $\overline{M}_T$ is approximately equal to the *number average* molecular weight of the mixture.

The ratio η_T/η_{217} for polyisobutylene mixture H at $T = 160°$ and 190° (Table IX) was observed to be in agreement with the corresponding value for the polyisobutylene fractions. As with the fractions, no dependence on molecular weight is evident.

Generalizing the above results obtained on simple mixtures of fractions, we conclude that the melt viscosities of polystyrenes for which the *number average* molecular weight is greater than 25,000 and of all polyisobutylenes (above a molecular weight of 11,200 at least) are explicit functions of the *weight average* molecular weight, regardless of the degree of molecular weight heterogeneity. Further, the viscosity–temperature coefficients for these polymers are independent of molecular weight distribution as well as of molecular weight. For polystyrenes of $\overline{M}_n$ less than 25,000, the viscosity–temperature coefficient varies with, and is determined by, the *number average* molecular weight, being otherwise independent of the molecular weight distribution. The melt viscosities of polystyrenes in this molecular weight (number average) range are not uniquely determined by any specific average molecular weight.

Discussion

Failure of equation (1) to accurately represent the dependence of melt viscosities of polystyrene and polyisobutylene on molecular weight is surprising in the face of the number of instances, covering a variety of polymers, in which the square root relationship has been reported to hold. Perusal of these various sets of results reveals, however, either that the molecular weight range covered generally was too limited for a conclusive decision or that the molecular weights were determined by methods which fail to yield an accurate measure of the weight average or something consistently proportional to it. These aspects of previous investigations on the applicability of equation (1) are summarized in Table XI. Only

in the case of the glycol–dibasic acid polyesters has the relationship been demonstrated to apply precisely over a manifold range; it probably applies similarly to the polyamides. The results for polyesters and polyamides are limited to moderate molecular weights, however; it is conceivable that the square root relationship may fail for higher molecular weight polymers of these series.

TABLE XI

Polymer	Mol. wt. range	Mol. wt. determination	Reference
Glycol–dibasic acid polyesters	500–20,000 (40-fold)	End-group titration	3
Polyundecanoates	5,000–22,200 (4-fold)	End-group titration	4
Polyamides	2,880–37,100 (13-fold)	Stoichiometric proportion of reactants	5
Polydimethylsiloxane	2,500–160,000 (64-fold)	Osmotic pressure[a]; end group titration; light scattering	8
Polyisobutylene	134,000–545,000 (4-fold)	Intrinsic viscosity	7
Polyethylene	12,000–36,000 (3-fold)	Staudinger viscosity[b]	6
Paraffin wax–polyethylene mixtures	400–17,000 (42-fold)	Staudinger viscosity[b]	6

[a] Since these three methods were applied to different polymers none of which were fractionated, the results should not be strictly comparable on a weight average basis. [b] Molecular weights by this method are undoubtedly of limited significance.

The difference in the nature of the viscosity–molecular weight relationship for polystyrene and polyisobutylene on the one hand and that for polyesters and polyamides on the other cannot be dismissed as a mere consequence of the displacement of the respective molecular weight ranges covered. Enlarged plots of log η *vs.* $\bar{M}_w^{1/2}$ using the data for polystyrene and polyisobutylene fractions within the molecular weight range covered for the polyesters and polyamides (or, preferably, over the same range of chain lengths) show definite deviations from linearity which considerably exceed the experimental error; the polyester and polyamide plots, on the other hand, are precisely linear.[3] The conclusion cannot be avoided that the square root relationship applies to certain polymers such as the polyesters (at least up to moderate molecular weights), but that it cannot be applied to other polymers such as those investigated here, except, perhaps, as a short range rough approximation.[20] It may be significant that these polyesters and polyamides possess regularly occurring polar groups conducive to crystallization whereas polyisobutylene and polystyrene are nonpolar in character.

It is noteworthy that the melt viscosity appears to be determined explicitly by the weight average molecular weight (except for low molecular weight polystyrenes) in all cases where the effect of molecular weight heterogeneity has been tested.

Recently attempts have been made to interpret the effects of polymer molecular weight and of plasticizer content on softening points[21] and brittle temperatures[22] through the use of relationships based on equation (1). In the light of our results, which refute the general applicability of equation (1), these treatments are of questionable value.

Both polystyrene and polyisobutylene, in common with linear polyesters[3] and many other complex liquids,[23] exhibit non-linear relationships between ln η and $1/T$. If the usual relationship

$$\eta = De^{E/RT} \qquad (11)$$

where E is the activation energy for viscous flow, is to be applied here, either D or E (or both) must be temperature dependent. Hence, to regard the value of $R[\mathrm{d}(\ln \eta)/\mathrm{d}(1/T)]$ as the energy of activation probably is incorrect. The value of E_T considered here is merely a measure of the slope of the log η *vs.* $1/T$ curve at the specified temperature, although for convenience it has been designated as an apparent energy of activation.

There exists in the literature much disagreement concerning the temperature coefficient of viscosity of polystyrene. Spencer and Williams arrived at an estimate for E_T of 8 to 12 kcal. from viscosity measurements between room temperature and 100° on concentrated solutions of polystyrene in several aromatic solvents.[24,25] The linear extrapolation involved in obtaining E_T from the properties of solutions in which the maximum concentration was 50% by weight of polystyrene is of doubtful validity. The viscosity–temperature coefficient as deduced by the same authors[24] from Nason's results[26] on the rates of extrusion at high stresses is of uncertain significance. Observations of Foote[27] on the flow of polystyrene in capillary molds under high pressures indicated a dependence of E_T on temperature, his estimates varying from 40 to 80 kcal. between 200 and 100°. Many of these experiments involved high stresses and the accuracy was admittedly low. Wiley's measurements[28] on the elongation of a strip of polystyrene under a constant load permit a calculation of E_T of 18 kcal. and 79 kcal. at 190 and 150°, respectively, a variation in excess of that reported here. Perhaps, as has been suggested elsewhere,[21] the viscous and elastic effects have not been separated in this case.

Thus, while the confusion concerning the viscosity–temperature coefficient of polystyrene may be due in part to the variation of E_T with tempera-

(20) Investigations now in progress on the viscosities of very low molecular weight polyisobutylene and of polyesters of exceptionally high molecular weight are expected to clarify the difference in the behavior of polymers of these two series.

(21) R. F. Tuckett, *Trans. Faraday Soc.*, **39**, 158 (1943).

(22) R. F. Boyer and R. S. Spencer, "Advances in Colloid Science," Vol. II, Interscience Publishers, New York, N. Y., 1946, p. 28; R. F. Boyer and R. S. Spencer, *J. Polymer Sci.*, **2**, 157 (1947).

(23) R. H. Ewell, *J. Applied Phys.*, **9**, 252 (1938).

(24) R. S. Spencer and J. L. Williams, *J. Colloid Sci.*, **2**, **117** (1947).

(25) J. D. Ferry, THIS JOURNAL, **64**, 1330 (1942).

(26) H. K. Nason, *J. Applied Phys.*, **16**, 338 (1945).

(27) N. M. Foote, *Ind. Eng. Chem.*, **36**, 244 (1944).

(28) F. E. Wiley, *Ind. Eng. Chem.*, **33**, 1377 (1941).

ture and with molecular weight (for $\overline{M}_n$ less than 25,000), it is chiefly attributable to the low accuracy and unreliability (for this purpose) of much of the data on which previous estimates were based.[29]

Tuckett[21] has suggested that any apparent increase of E_T with decreasing temperature above a value of 20 kcal. is due to the simultaneous occurrence of a slow time-dependent elastic deformation, the activation energy of which he assumes to be greater than that for viscous flow. Elastic effects and other non-Newtonian disturbances were eliminated in the present work by operating at low rates of shear and at relatively large deformations. Results obtained with the capillary viscometers invariably were found to be independent of the pressure employed; the highest viscosities, determined with the coaxial viscometer, were derived from measurements made after elastic deformation appeared to have reached equilibrium. The successful elimination of any complicating elastic effects in our experiments is confirmed by the independence of the viscosity–temperature coefficient of molecular weight (except for polystyrenes for which $\overline{M}_n$ is less than 25,000). This behavior is contrary to that predicted by Tuckett on the basis of the aforementioned assumptions. Tuckett's assumption that E_T for viscous deformation is approximately independent of temperature and that it may not exceed 20 kcal. is not substantiated.

Since the viscosity–temperature coefficient has been observed to depend on the *number average* molecular weight, a commercial polystyrene with a high intrinsic viscosity will not necessarily possess the limiting viscosity–temperature coefficient for high molecular weight polystyrene. The presence of even a small amount of low molecular weight material (*e. g.*, unreacted monomer or an impurity) may cause the number average molecular weight to be less than 25,000, although the weight average molecular weight may be high. This suggests also that the efficiency of low molecular weight compounds as plasticizers for polystyrene is perhaps due to their ability to lower $\overline{M}_n$ (and thus E_T).

Acknowledgment.—The authors wish to acknowledge the assistance of Mr. Robert E. Marshall in carrying out the fractionations and measuring solution viscosities.

(29) Since this manuscript was written, Spencer and Dillon, *J. Colloid Sci.*, **3**, 163 (1948), have reported viscosity–temperature data for high molecular weight polystyrene which are in substantial agreement with the present results. They have also investigated the dependence of viscosity on shearing stress. According to their results, our viscosity values for polystyrenes above 100,000 should in no case be in error by more than about 10% due to failure to extrapolate to zero shearing stress.

Summary

1. The viscosities of polystyrene and polyisobutylene fractions over molecular weight ranges of 4900 to 381,000 and 3,500 to 1,830,000, respectively, have been determined at 217°. The viscosities of polystyrene fractions covering the molecular weight range of 3,700 to 134,000 were measured at several temperatures, the maximum range being 53 to 217°. Similar data were obtained for polyisobutylene fractions in the molecular weight range of 11,200 to 660,000 over a maximum temperature range of −9 to 217°.

2. The viscosity–molecular weight relationships have been expressed in graphical form. Log η_{217} is not a linear function of $\overline{M}_w^{1/2}$ for either of these polymers over the wide range in the molecular weight investigated.

3. Both polymers exhibit non-linear relationships between log η and $1/T$. The viscosity–temperature coefficient is independent of molecular weight except for polystyrene fractions of molecular weight less than 25,000, for which the coefficient at a specified temperature decreases with decreasing molecular weight.

4. From the viscosities of mixtures of fractions of widely separated molecular weights at 217° and at several lower temperatures, the following generalizations have been made: (a) The melt viscosities of these polymers at a specified temperature are determined by the weight average molecular weights, regardless of heterogeneity, except for polystyrenes of number average molecular weight less than 25,000. For the latter the melt viscosity is not uniquely determined by $\overline{M}_n$, $\overline{M}_v$, or $\overline{M}_w$, but appears to be some function of the particular molecular weight distribution. (b) The viscosity–temperature coefficient of these polymers is independent of both molecular weight distribution and molecular weight except for polystyrenes with $\overline{M}_n$ less than 25,000. For the latter the viscosity–temperature coefficient is determined by the number average molecular weight, being otherwise independent of molecular weight distribution.

5. The results of previous investigations on the viscosity–molecular weight and viscosity–temperature relationships of polymeric materials have been discussed.

6. A coaxial falling-cylinder viscometer was designed for determining the viscosity of high molecular weight polyisobutylene. Details have been given concerning its construction and use.

AKRON, OHIO RECEIVED OCTOBER 10, 1947

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

Thiophosphoric Amides: Aminolysis

BY ALLEN C. BUCK[a] AND HERMAN P. LANKELMA

Mixed thiophosphoric triamides of the type $(RNH)_2PS(NHR_1)$ where R is an aromatic radical and R_1 an aliphatic radical have been prepared by Michaelis[1] by the stepwise aminolysis of thiophosphoryl chloride

$$2R_1NH_2 + PSCl_3 \longrightarrow (R_1NH)PSCl_2 + R_1NH_2\cdot HCl \quad (1)$$

$$(R_1NH)PSCl_2 + 4RNH_2 \longrightarrow (R_1NH)\underset{S}{P}(NHR)_2 + 2RNH_2\cdot HCl \quad (2)$$

Michaelis could not use this method to prepare mixed triamides in which both radicals were aromatic since the intermediate, $RNHPSCl_2$, lost hydrogen chloride to give RN=PSCl.

A new approach to the preparation of mixed thiophosphoric triamides was suggested by the addition of aniline to dimeric thiophosphoric anil anilide.[2] The addition of amines to dimeric thiophosphoric anil anilide could yield mixed thiophosphoric triamides

$$(C_6H_5N\text{—}\overset{S}{P}\text{—}NHC_6H_5)_2 + RNH_2 \longrightarrow 2(C_6H_5NH)_2\overset{S}{P}\text{—}NHR \quad (3)$$

When RNH_2 in equation (3) was benzylamine, in excess, the product at temperatures of 30 and 60° was a mixture containing triamides of both benzylamine and aniline. No pure mixed triamide could be isolated. When the reaction temperature was raised to 130° tribenzylthiophosphoric amide was isolated in good yield. This product could have formed only through the addition of benzylamine to dimeric thiophosphoric anil anilide and the replacement of aniline by benzylamine

$$(C_6H_5N\text{—}\overset{S}{P}\text{—}NHC_6H_5)_2 + 6C_6H_5CH_2NH_2 \longrightarrow 2(C_6H_5CH_2NH)_3PS + 4C_6H_5NH_2 \quad (4)$$

A second approach to the preparation of mixed thiophosphoric triamides appeared to be possible through the reaction of dithiophosphoric dianilide with amines according to the equation

$$(C_6H_5NH)_2PSSH + RNH_2 \longrightarrow (C_6H_5NH)_2\overset{S}{P}\text{—}(NHR) + H_2S \quad (5)$$

This reaction has already been carried out with aniline to give thiophosphoric trianilide. When dithiophosphoric dianilide was treated with benzylamine, tribenzyl thiophosphoric amide rather than a mixed triamide was obtained. Tribenzylthiophosphoric amide must have resulted from the concurrent formation of a mixed triamide by loss of hydrogen sulfide between dithiophosphoric dianilide and benzylamine and displacement of aniline by benzylamine

$$(C_6H_5NH)_2PSSH + 3C_6H_5CH_2NH_2 \longrightarrow (C_6H_5CH_2NH)_3PS + 2C_6H_5NH_2 + H_2S \quad (6)$$

The displacement of aniline by benzylamine with the formation of benzylamine triamide in each of these cases suggested the possibility of a similar reaction occurring also with a triamide. The reaction of triamides with primary aliphatic amines and with primary aromatic amines was therefore studied. This reaction could lead to mixed triamides $(RNH)_2\overset{S}{P}(NHR')$ and $(RNH)\overset{S}{P}(NHR')_2$ by partial displacement or to $(RNH)_3PS$ by complete displacement. The results of this study are shown in Table I.

The reaction of thiophosphoric trianilide with tributylamine and with dimethylaniline was tried to determine the effect of tertiary amines, which could not enter into displacement reactions.

When thiophosphoric trianilide was heated at 130° in a large excess of tributylamine, hydrogen sulfide was continuously evolved for twenty hours. Aniline and the phosphate ion were identified as decomposition products. Dimethylaniline promoted a similar decomposition, but required a much longer reaction time. In neither case could any thiophosphoric trianilide be recovered.

It is apparent that this decomposition not only resulted in the rupture of nitrogen–phosphorus bonds, but that the rate at which these bonds were broken was related to the basicity of the tertiary amine used. It would follow that thiophosphoric triamides heated in excess primary aliphatic or aromatic amines would have nitrogen-phosphorus bonds severed in an analogous fashion. In this case, however, a new triamide could form from the excess amine present. Thus is it possible that displacement reactions involving primary amines and thiophosphoric triamides with primary amine residues attached to phosphorus be expressed as a mobile equilibrium

$$(RNH)_3PS + 3R'NH_2 \longleftrightarrow (R'NH)_3PS + 3RNH_2 \quad (7)$$

The position of equilibrium would depend upon the relative stability of the phosphorus–nitrogen bond of the two triamides. The relative rates at which tertiary amines decomposed thiophosphoric acid trianilide indicated that the aliphatic amines would sever nitrogen–phosphorus bonds more rapidly than the less basic aromatic amines. It would follow in equation (7), that the nitrogen–phosphorus bonds of an aliphatic amine would be more stable than that of an aromatic amine. Under the conditions used with the triamides of primary

[a] Standard Oil Co., Ohio, Fellow in Chemistry 1946–1947; present address, E. I. du Pont de Nemours and Co., Parlin, New Jersey.

(1) Michaelis, *Ann.*, **326**, 129–258 (1903).

(2) Buck, Bartleson and Lankelma, THIS JOURNAL, **70**, 744 (1948).

TABLE I

	Triamide $(RNH)_3PS$	Amine	Temp., °C.	Time, hr.	Product
1	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	30–60	2	No reaction
2	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	130	2	A mixture of triamides of aniline and benzylamine
3	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	180	2	$(C_6H_5CH_2NH)_3PS$ 80% yield
4	$(n\text{-}C_3H_7NH)_3PS$	$C_6H_5CH_2NH_2$	150–160	4	$(C_6H_5CH_2NH)_3PS$ 84% yield
5	$(C_5H_{10}N)_3PS$[a]	$C_6H_5CH_2NH_2$	170	4	No reaction
6	$(C_6H_5NH)_3PS$	$p\text{-}ClC_6H_4NH_2$	130	2	A mixture of triamides of aniline and *p*-chloroaniline
7	$(C_6H_5NH)_3PS$	$p\text{-}ClC_6H_4NH_2$	180	2	$(p\text{-}ClC_2H_4NH)_3PS$ 40% yield
8	$(C_6H_5\cdot CH_2NH)_3PS$	$C_6H_5NH_2$	130 and 180		A mixture of triamides of benzylamine and aniline
9	$(n\text{-}C_3H_7NH)_3PS$	$C_6H_5NH_2$	180	8	$(C_6H_5NH)_3PS$, 40% yield
10	$(C_5H_{10}N)_3PS$[a]	$C_6H_5NH_2$	180	4	No reaction

[a] Piperidyl.

amines, the nitrogen–phosphorus bond of the triamide of a secondary amine, piperidine, was not severed by tertiary amines, either aliphatic or aromatic. Primary amines also would not be expected to sever these bonds under comparable reaction conditions. The establishment of an equilibrium and therefore displacement reactions could not occur. This was verified; Table I, number 5.

This equilibrium could also be shifted by mass action. This is shown by the reaction between thiophosphoric trianilide and benzylamine. Using a large excess of benzylamine, tribenzyl thiophosphoric amide was formed in high yield; Table I, number 3. The reverse displacement could not be accomplished under comparable reaction conditions. Since the boiling points of benzylamine and aniline lie close together, selective removal of the aniline could not be used to displace the equilibrium. However, this was accomplished by using tri-*n*-propylthiophosphoric amide. In this case the triamide with the weaker nitrogen–phosphorus bonds was formed due to the selective removal of the low boiling *n*-propylamine from the equilibrium mixture, Table I, number 9.

The displacement of aniline from thiophosphoric acid trianilide by *p*-chloroaniline, Table I, number 7, was accomplished by the addition of an excess of *p*-chloroaniline to the equilibrium mixture. The displacement of *n*-propylamine from tri-*n*-propylthiophosphoric amide by benzylamine, Table I, number 4, was accomplished with the use of excess benzylamine and the continuous removal of the low boiling *n*-propylamine displaced.

Experimental

Action of Benzylamine on Dimeric Thiophosphoric Anil Anilide.—Six grams of dimeric thiophosphoric acid anil anilide and 15 g. of benzylamine were heated at 180° for three hours. Crystallization of the product from alcohol gave 4 g. of tribenzyl thiophosphoric amide, m. p. 120–123°, a 44% yield. It was identified by a mixed melting point.

At a temperature of 30 and 60° a product melting at 70–80° was obtained. It could not be purified by crystallization from alcohol. It was shown to be a mixture of triamides by cleavage with acetic acid.[2] Acetanilide, benzylamine and phosphoric acid were identified in the cleavage products. At a temperature of 130° a 50% yield of the tribenzyl thiophosphoric amide was obtained.

Action of Benzylamine on Dithiophosphoric Dianilide.—Six grams of benzylamine and 5.6 g. of dithiophosphoric dianilide were heated to 140–150° for four hours. The product was washed with dilute hydrochloric acid and crystallized from alcohol; 1.5 g. of tribenzyl thiophosphoric amide melting at 123–125° was obtained. Aniline was identified in the acid washings by conversion to acetanilide.

Action of Tertiary Amines on Thiophosphoric Trianilide.—Three grams of thiophosphoric trianilide and 20 g. of tributylamine were heated at 130° in an atmosphere of nitrogen. The evolution of hydrogen sulfide was detectable for twenty hours. The mixture was made alkaline with sodium hydroxide solution and steam distilled. The distillate was extracted with ether and the amines recovered by evaporation of the ether. The aniline was separated and identified as the benzenesulfonamide. The aqueous solution from the steam distillation gave a strong test for phosphate ion with ammonium molybdate solution.

Action of Amines on Thiophosphoric Triamides.—The combinations of amine and triamide employed, with the reaction conditions and results, are shown in Table I. The triamides employed were prepared as follows: thiophosphoric acid trianilide from aniline and phosphorus pentasulfide[2]; tribenzyl, tri-*n*-propyl, and tripiperidyl thiophosphoric amides from the amine and thiophosphoryl chloride by the method of Michaelis[1] in yields of 57, 84 and 25%, respectively. The triamide formed in each case was identified by a mixed melting point and the displaced amine was identified as an acyl derivative. In two of the cases where a mixture of triamides was obtained, Table I, numbers 2 and 8, cleavage of the amides with acetic acid yielded a mixture of acetanilide and benzylamine.

Summary

The preparation of mixed thiophosphoric triamides by the addition of amines other than aniline to dimeric thiophosphoric anil anilide was prevented by aminolysis reactions. Similarly, the reaction of amines other than aniline with dithiophosphoric dianilide failed to yield mixed thiophosphoric triamides due to aminolysis reactions.

The primary amine thiophosphoric triamides underwent complete aminolysis reactions upon heating with other primary amines. The thiophosphoric triamide of the secondary amine, piperidine, did not undergo this reaction.

An interpretation of the aminolysis reactions has been presented.

CLEVELAND, OHIO RECEIVED SEPTEMBER 10, 1947

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

The Reaction of Aniline with Phosphorus Pentoxide: Phosphoric Anilides

BY ALLEN C. BUCK[1] AND HERMAN P. LANKELMA

The reaction of six and four moles of aniline with one mole of phosphorus pentasulfide has been shown to yield thiophosphoric trianilide and dithiophosphoric dianilide, respectively.[1a]

The reaction of six and four moles of aniline with one mole of phosphorus pentoxide under similar conditions gave aniline metaphosphate as the major reaction product along with small amounts of aniline orthophosphate. In addition to aniline metaphosphate, the reaction of four moles of aniline and one mole of phosphorus pentoxide at room temperature in an inert solvent such as toluene gave very low yields of phosphoric dianilide.

The formation of some phosphoric dianilide suggested that the reaction was similar to that with the sulfide, that is, the formation of a dianilide which subsequently reacts with aniline at higher temperatures to form a trianilide. However, the reaction of aniline with phosphorus pentoxide differed in that aniline metaphosphate was formed.

$$2C_6H_5NH_2 + P_2O_5 \longrightarrow (C_6H_5NH)_2POOH + HPO_3 \quad (1)$$

$$C_6H_5NH_2 + HPO_3 \longrightarrow C_6H_5NH_2\cdot HPO_3 \quad (2)$$

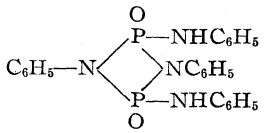
With phosphorus pentasulfide, however, the formation of dithiophosphoric dianilide was not interfered with by the formation of a salt of aniline.

Although phosphoric trianilide was not obtained by the action of aniline on phosphorus pentoxide, it has been prepared by Michaelis and Soden[2] from aniline and phosphorus oxychloride. Phosphoric trianilide, like thiophosphoric trianilide, was stable to prolonged refluxing in water, dilute acids and bases. It was also stable toward glacial acetic acid under conditions which effect a cleavage of thiophosphoric trianilide.[1a]

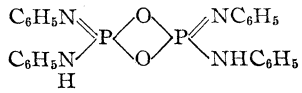
Michaelis and Silberstein[3,4] observed that phosphoric trianilide was thermally unstable when heated under a vacuum, losing aniline to form dimeric phosphoric anil anilide

$$2(C_6H_5NH)_3PO \longrightarrow (C_6H_5N{-}\overset{\overset{O}{\|}}{P}{-}NHC_6H_5)_2 + 2C_6H_5NH_2 \quad (3)$$

They recorded a melting point of 357° for this compound and suggested a cyclic amide structure (A), whereas Oddo[5] reported a melting point of 320–325° and suggested a cyclic isoamide structure (B)



(A)



(B)

Dimeric phosphoric anil anilide, prepared in this laboratory by thermal decomposition of phosphoric trianilide, melted at 357–358° as reported by Michaelis and Silberstein. It has been previously shown that thiophosphoric trianilide exhibited similar thermal instability.[1a]

Since dimeric thiophosphoric anil anilide had reacted with aniline to reform thiophosphoric trianilide,[1a] it appeared that phosphoric anil anilide might undergo a similar reaction. When dimeric phosphoric anil anilide was refluxed in excess aniline, it slowly dissolved with the formation of quantitative yields of phosphoric trianilide.

It has previously been shown that the nitrogen–phosphorus bond in thiophosphoric trianilide was ruptured by tributylamine and that aniline could be displaced from it with primary amines.[6] Phosphoric trianilide was not attacked by tributylamine under similar conditions. This suggested that the aniline might not be displaced by primary amines. Accordingly phosphoric trianilide was treated with excess benzylamine under conditions which had displaced aniline from thiophosphoric trianilide to give eighty per cent. yields of tribenzyl thiophosphoric amide.[6] The phosphoric trianilide was recovered unaltered.

The stability of phosphoric trianilide to displacement reactions suggested that mixed phosphoric triamides might be prepared by the addition of amines other than aniline to dimeric phosphoric anil anilide

$$(C_6H_5N{-}\overset{\overset{O}{\|}}{P}NHC_6H_5)_2 + 2RNH_2 \longrightarrow 2(C_6H_5NH)_2\overset{\overset{O}{\|}}{P}(NHR) \quad (4)$$

This reaction was first tried using *n*-propylamine as the amine. The solid product obtained from the reaction was a mixture which exhibited resistance to hot dilute acids and bases, a property of trianilides, from which phosphoric trianilide was isolated after several crystallizations. When this reaction was repeated with secondary amines, di-*n*-propylamine and piperidine, a mixture of products was again obtained and phosphoric trianilide was isolated after two crystallizations.

Theoretically, amines could react with dimeric phosphoric anil anilide in one or both of the following ways depending upon whether nitrogen–

(1) Standard Oil Co., Ohio, Fellow in Chemistry 1946–1947; present address, E. I. du Pont de Nemours and Co., Parlin, New Jersey.

(1a) Buck, Bartleson and Lankelma, THIS JOURNAL, **70**, 744 (1948).

(2) Michaelis and Soden, *Ann.*, **229**, 295–340 (1885).

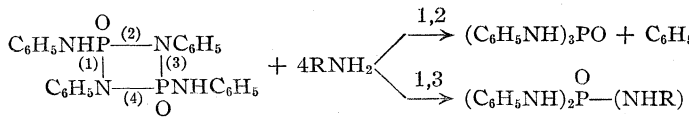
(3) Michaelis, *ibid.*, **407**, 310 (1915).

(4) Michaelis and Silberstein, *Ber.*, **28**, 716–733 (1896).

(5) Oddo, *Gazz. chim. ital.*, **29**, II, 340 (1899).

(6) Buck and Lankelma, THIS JOURNAL, **70**, 2396 (1948).

phosphorus bonds 1,2 or 1,3 of the ring were ruptured



Each pair of bonds would have an equal chance to be ruptured and a mixture of products would therefore be expected. The presence of phosphoric trianilide as one of the reaction products regardless of the nature of RNH_2 supported the view that the addition of amines to dimeric phosphoric anil anilide did occur by the rupture of bonds 1,2 above.

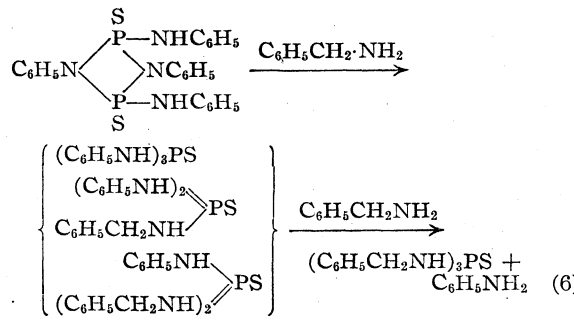
Since mixtures of products were obtained from which phosphoric trianilide was isolated only after repeated crystallization, it appeared quite likely that this mixture contained the two similar mixed phosphoric triamides suggested in equation (5) above. The similar solubilities of these mixed triamides prevented separation into the individual components.

The formation of phosphoric trianilide by the addition of two moles of an amine other than aniline to dimeric phosphoric anil anilide offers proof that the structure proposed by Michaelis[3] for dimeric phosphoric anil anilide is correct. The structure proposed by Oddo would not yield phosphoric trianilide but a mixed triamide.

By analogy with dimeric phosphoric anil anilide, the structure of dimeric thiophosphoric anil anilide previously reported[1a] would contain a four-membered nitrogen–phosphorus ring. This structure was supported by the fact that the addition of aniline gave thiophosphoric trianilide, a reaction comparable to that observed with dimeric phosphoric anil anilide. However, with amines other than aniline there was a difference in the type of triamide obtained. Whereas dimeric phosphoric anil anilide and amines at 180° gave mixtures of phosphoric triamides of which one component was always the trianilide, dimeric thiophosphoric anil anilide and amines such as benzylamine, gave excellent yields of a single triamide, tribenzyl thiophosphoric amide.[6] However, it has been shown previously that the action of excess benzylamine on dimeric thiophosphoric anil anilide at 30 and 60° gave mixtures of thiophosphoric triamides from which no individual triamide could be isolated. Also, displacement of aniline from thiophosphoric trianilide by benzylamine did not occur at 30 and 60° but occurred readily at 180°. It would appear, therefore, that the displacement of aniline in dimeric thiophosphoric anil anilide by benzylamine would not occur at the lower temperatures. The reaction of primary amines, such as benzylamine, with dimeric thiophosphoric anil anilide to form tribenzylthiophosphoric amide would involve severing of the ring to give a mixture of triamides followed by displacement of aniline.

In the case of dimeric phosphoric anil anilide the triamides resulting from the first reaction are stable.

Phosphoric dianilide, $(C_6H_5NH)_2POOH$, obtained in very low yields from aniline and phosphorus pentoxide has previously been prepared by Michaelis and Soden[2] from aniline and phosphorus oxychloride. Phosphoric dianilide was observed by Michaelis to be readily hydrolyzed by hot water and hot dilute acids to give aniline and phosphoric acid. It has previously been shown that thiophosphoric dianilide underwent a similar decomposition with these reagents.[1a]



Experimental

Reactions of Aniline with Phosphorus Pentoxide.—37.2 g. (0.4 mole) of aniline and 14.2 g. (0.1 mole) of phosphorus pentoxide in 100 ml. of toluene were heated at 50° for three hours with stirring. The principal product was aniline phosphate from which the aniline was liberated by treatment with cold 5% sodium hydroxide solution. The aniline was identified as benzene sulfonanilide, the phosphate ion as ammonium phosphomolybdate. In addition 3 g., a 6% yield, of phosphoric dianilide, m. p. 199–200°, was obtained. It was identified by a mixed melting point with a sample of the dianilide prepared by the method of Michaelis and Soden.[2] Using a 6:1 molar ratio of aniline and phosphorus pentoxide and heating at 200° for three hours only aniline phosphate was obtained.

Attempts to Hydrolyze Phosphoric Trianilide.—One gram samples of phosphoric trianilide were refluxed in water, 5% sodium hydroxide, 5% hydrochloric acid and glacial acetic acid for twenty hours without change.

Preparation of Dimeric Phosphoric Anil Anilide and its Reaction with Primary and Secondary Amines.—Nine grams of phosphoric trianilide was heated for thirty minutes at 225° under a vacuum of 30 mm. of mercury; 2.5 g. of aniline distilled over. The residual solid was washed with alcohol and filtered. Six grams of phosphoric anil anilide, m. p. 357–359°, was obtained. This is a yield of 94%.

Three grams of phosphoric anil anilide was heated with 15 g. of aniline at the boiling point for five hours. The excess aniline was removed by steam distillation and the residual solid recrystallized from alcohol and gave 3.9 g. (a 93% yield) of phosphoric trianilide, m. p. 213–215°.

Two grams of phosphoric anil anilide and 15 g. of *n*-propylamine heated at 180–190° in a sealed tube for five hours gave 1.0 g. of product melting at 70–205°. Recrystallizations from alcohol gave 0.2 g. of phosphoric trianilide. No other product could be separated.

Two grams of phosphoric anil anilide with 15 g. of di-*n*-propylamine gave 0.8 g. of phosphoric trianilide, and 7 g. of phosphoric anil anilide with 30 g. of piperidine gave 2 g. of phosphoric trianilide.

Stability of Phosphoric Acid Trianilide to Amines.—Phosphoric trianilide was heated with excess tributylamine for twenty hours at 130° and also with excess benzylamine for four hours at 170°. Unchanged trianilide was recovered in high yield and no reaction products were detected.

Summary

The reaction of aniline with phosphorus pentoxide gave aniline metaphosphate as the principal product.

A comparison of the properties of phosphoric and thiophosphoric anilides has been made.

Proof of structure of the dimeric phosphoric and thiophosphoric anil anilides has been given.

CLEVELAND, OHIO RECEIVED SEPTEMBER 10, 1947

[CONTRIBUTION NO. 53 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Preparation of Ethers of Triphenylcarbinol from the Triphenylcarbonium Ion

BY HILTON A. SMITH AND ROBERT J. SMITH

Several years ago Newman[1] reported a new method for the esterification of certain sterically hindered acids. The acids were dissolved in 100% sulfuric acid where they formed carbonium ions. The resulting solutions were poured into alcohols and the esters formed were subsequently recovered. Triphenylacetic acid is a sterically hindered acid which cannot be esterified by heating with an alcohol in the presence of an acid catalyst.[2] When an attempt was made to esterify this acid with methanol by Newman's method, the product was identified as the methyl ether of triphenylcarbinol. This is, perhaps, not surprising since it has already been shown[3] that triphenylacetic acid loses carbon monoxide quantitatively when treated with concentrated sulfuric acid. The mechanism for the formation of the ether is presumably

$$(C_6H_5)_3CCOOH + 2H_2SO_4 \longrightarrow (C_6H_5)_3CCO^+ + H_3O^+ + 2HSO_4^- \quad (1)$$

$$(C_6H_5)_3CCO^+ \longrightarrow (C_6H_5)_3C^+ + CO \quad (2)$$

$$(C_6H_5)_3C^+ + CH_3OH \longrightarrow (C_6H_5)_3COCH_3 + H^+ \quad (3)$$

While this method is a failure as far as the production of esters of triphenylacetic acid is concerned, it does indicate a quick and useful method for the preparation of ethers of triphenylcarbinol. The carbinol is dissolved in 100% sulfuric acid, where it forms the triphenylcarbonium ion according to the equation

$$(C_6H_5)_3COH + 2H_2SO_4 \longrightarrow (C_6H_5)_3C^+ + H_3O^+ + 2HSO_4^- \quad (4)^{4,5}$$

The carbonium ion may then be made to react with various alcohols in the manner indicated by equation (3). The yield of ether is essentially quantitative, and the product may be obtained in very pure form.

A search of the literature indicated that other methods which have been used to prepare ethers of triphenylcarbinol are usually quite long, and give smaller yields of impure products. Such methods include the reaction of triphenylmethyl chloride with an alcohol,[6,7,8] and the reaction of the chloride with sodium alcoholates. This latter method was employed by Norris and Young,[9] who prepared eleven different ethers of triphenylcarbinol in yields ranging from 10 to 60%. In the present research, six such ethers were prepared, the yields of purified products ranging from 86 to 97%. The same method could presumably be used for the formation of ethers of other carbinols which form similar carbonium ions in sulfuric acid (*i. e.*, have *i* factors of 4).

The preparation of pure ethers of triphenylcarbinol is, unfortunately, complicated by their decomposition into triphenylmethane and an aldehyde, as indicated for the ethyl ether by the equation

$$(C_6H_5)_3COC_2H_5 \longrightarrow (C_6H_5)_3CH + CH_3CHO \quad (5)$$

This reaction was extensively studied by Norris and Young[9] who found that the ease of decomposition increased with increasing complexity of the ether. In addition, the reaction is catalyzed by several ions, the most efficient of those studied being the bisulfate ion. The preparation of ethers of triphenylcarbinol from carbonium ions formed in sulfuric acid gives the product in the presence of bisulfate ions, and decomposition will occur for the higher members of the series unless the product is quickly removed.

Conditions were not found which would give the *s*-butyl, *t*-butyl and benzyl ethers. It might also be noted that Newman[1] was unable to prepare the *t*-butyl ester of trimethylbenzoic acid by an analogous method. The failure of such alcohols to give esters or ethers by reaction with the carbonium ions may be due to one of two reasons:

1. The effect of these branched-chain alcohols may be such as to materially decrease the rate of reaction (3).[10]
2. An equilibrium of the type

$$(C_6H_5)_3COR + H_2O \rightleftharpoons (C_6H_5)_3COH + ROH$$

(1) Newman, THIS JOURNAL, **63**, 2431 (1941).
(2) Smith and Burn, *ibid.*, **66**, 1494 (1944).
(3) Bistrzycki and Reintki, *Ber.*, **38**, 839 (1905); Bistrzycki and Mouron, *ibid.*, **43**, 2883 (1910); Dittmar, *J. Phys. Chem.*, **33**, 533 (1929); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 283.
(4) Hantzsch, *Z. physik. Chem.*, **61**, 257 (1908).
(5) Hammett and Deyrup, THIS JOURNAL, **55**, 1900 (1933).
(6) Friedel and Crafts, *Ann. chim. phys.*, [6] **1**, 502 (1884).
(7) Hemilian, *Ber.*, **7**, 1208 (1874).
(8) Helferich, Speidel and Tochdte, *ibid.*, **56**, 766 (1923).
(9) Norris and Young, THIS JOURNAL, **52**, 753 (1930).
(10) Smith, *ibid.*, **62**, 1136 (1940).

may exist in solution, and the effect of increased complexity of the alkyl group may be of such a nature as to shift the equilibrium toward the formation of the carbinol.

The ethers of triphenylcarbinol also form the triphenylcarbonium ion when dissolved in 100% sulfuric acid, and the triphenylcarbinol may be recovered in essentially quantitative yields if such solutions are poured into water.

In attempting to find the most advantageous procedure for the etherification reactions, a study was first made of the esterification of 2,4,6-trimethylbenzoic acid with methanol and ethanol. It was found that Newman's procedure[1] could be greatly simplified. In fact, the study indicated that, under conditions similar to those employed by Newman, both benzoic acid and 2,4,6-trimethylbenzoic acids may be almost completely esterified, but the benzoates are rapidly hydrolyzed. If the reaction mixture is poured into water rather than having water poured into it, good yields of the benzoates may be obtained. Apparently when water is poured into the sulfuric acid solution, local heating causes hydrolysis of the benzoates. A similar but much slower hydrolysis of the esters of the 2,4,6-trimethylbenzoic acid probably causes a slight reduction in the net yield of these esters. Conditions can be established which show that the fundamental differences between benzoic acid and the sterically hindered benzoic acids discussed by Newman do actually exist. This is shown by the fact that the sterically hindered 2,4,6-trimethylbenzoic acid is almost completely esterified in ten minutes, while the unhindered benzoic acid is not. The *i* factor of 4 for the hindered acid in sulfuric acid indicates a carbonium ion reaction while that of 2 for benzoic acid indicates that the ordinary type of acid-catalyzed esterification is involved.

Experimental

The 100% sulfuric acid was prepared by mixing suitable quantities of 96% sulfuric acid and oleum. It froze at 10° and analyzed 100.3% by dilution and titration with standard base.

Preparation of Ethers from Triphenylcarbinol.—For those ethers which were solids, 2 g. of triphenylcarbinol was dissolved in 6 to 12 g. of 100% sulfuric acid. The resulting yellow solution was added dropwise to 30 ml. of cold alcohol held at −10° by means of a salt–ice-bath. As soon as all of the solution was added, the resulting mixture was poured into 100 g. of a mixture of ice and water. The solid which separated was immediately filtered out, washed, and recrystallized from methanol.

For those ethers which were obtained as liquids, the following modifications were introduced. After pouring the sulfuric acid–alcohol solution into water, the organic layer was extracted with ether. The ether solution was treated with sodium carbonate solution, dried, and all readily volatile matter removed. The triphenylcarbinol ether which remained was fractionated in a small Vigreux column.

Hydrolysis of Ethers.—Several of the above ethers were dissolved in 100% sulfuric acid solution, and the resulting yellow solutions poured into ice water. The solid product which separated was filtered from the liquid, and identified as triphenylcarbinol by its melting point and mixed melting point with known triphenylcarbinol.

TABLE I

ETHERS OF TRIPHENYLCARBINOL

Alcohol used	Yield, %	Melting point or boiling point, °C.[b]
Methyl	97	96 –96.5
Ethyl	94	82.5–83
Propyl[a]	88	54.5–55.5
Isopropyl	86	113 –114
n-Butyl	87	208 at 5.5 mm.
Isoamyl	88	217.5 at 5.5 mm.

[a] It was usually necessary to extract this ether because of difficulty in inducing crystallization. [b] See Norris and Young, ref. 5, for melting or boiling points of the compounds.

Attempted Esterification of Triphenylacetic Acid.—Two grams of triphenylacetic acid was dissolved in 25 g. of 100% sulfuric acid. Some frothing was noted, indicating gas evolution. The resulting yellow solution was poured dropwise into 30 cc. of cooled methanol. This mixture was poured into 100 g. of ice and water. The precipitate was filtered and recrystallized from methanol to give 1.77 g. of white crystals, m. p. 96°.[11]

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.5, 87.5; H, 6.8, 6.6.

Esterification of Benzoic and 2,4,6-Trimethylbenzoic Acids.—Benzoic and 2,4,6-trimethylbenzoic acids were esterified in the manner described by Newman[1] (Method I) and by a modification of this method (Method II). The main difference between the two was that in the modified method the reaction mixture was poured into ice and water, while Newman added ice water to the reaction mixture. For each esterification, 2-g. samples of benzoic acid and 1-g. samples of 2,4,6-trimethylbenzoic acids were used.

In two parallel experiments using benzoic acid and ethanol, and allowing the mixture of alcohol, sulfuric acid and benzoic acid to stand for twelve hours, the product worked up by Method I showed 62.5% of acid recovered. Using Method II, no acid was obtained. When methanol and benzoic acid were used, and the mixture allowed to stand for only ten minutes, less than 50% of the acid was recovered by Method II. When the mixture was allowed to stand for one hour, only 10% of the acid was recovered.

In experiments with 2,4,6-trimethylbenzoic acid and methanol, using Method II, 6% of the acid was recovered whether the mixture was allowed to stand for ten minutes or for one hour.

It is much easier to estimate the ester yields from the percentage of acid recovered, than from ester yields. However the esters were isolated in a number of cases, and the amounts obtained were in accord with the results indicated on the basis of recovered acid.

Summary

A method for the formation of ethers of triphenylcarbinol from the triphenylcarbonium ion has been described; the method gives good yields of pure ethers. The esterification of benzoic and 2,4,6-trimethylbenzoic acids by Newman's method has been discussed.

KNOXVILLE, TENN. RECEIVED FEBRUARY 2, 1948

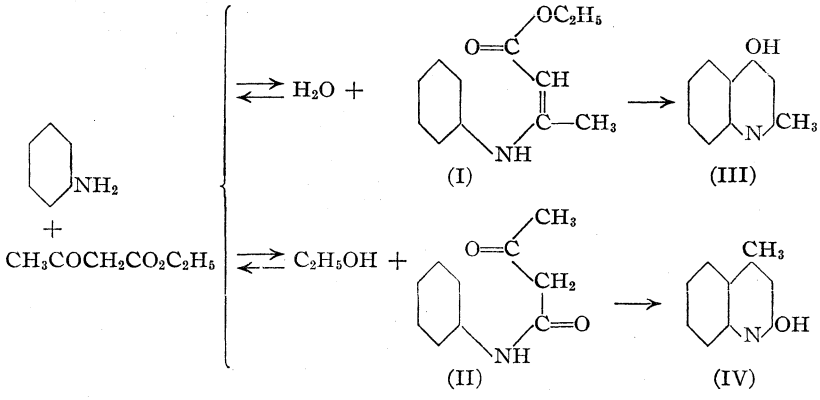
(11) The crystals from some of these preparations first melted at 84°, this being the melting point of a different crystalline form of the methyl ether of triphenylcarbinol. See Hatt, *J. Chem. Soc.*, 483 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Reactions of β-Keto Esters with Aromatic Amines. Syntheses of 2- and 4-Hydroxyquinoline Derivatives[1]

BY CHARLES R. HAUSER AND GEORGE A. REYNOLDS

Earlier workers have shown that ethyl acetoacetate and aniline react at room temperatures to form ethyl β-anilinocrotonate (I)[2] or the anil, whereas, at 130–140°, acetoacetanilide (II) is produced.[3] On cyclization these products form 2-methyl-4-hydroxyquinoline (III) and 4-methyl-2-hydroxyquinoline (IV), respectively.



We have found that both crotonate and anilide formations are reversible; the crotonate is converted to the anilide by heating with an equivalent of water and a trace of acid[4] at 130–140°, whereas the reverse transformation takes place upon boiling the anilide with ethanol and Drierite. Furthermore, in contrast to ethyl acetoacetate, 2-ethylbutyl and *n*-amyl acetoacetates were found to react with aniline to form mainly the corresponding crotonates even at 130–140°. The crotonates and the anilide were identified by cyclizations to (III) and (IV), respectively.[5] Conceivably differences in the volatility of the by-products govern the course the reaction takes. If at all temperatures considered the equilibrium favors the crotonate, anilide formation in the case of the ethyl ester[6] could be accounted for, because ethanol, the by-product of the anilide formation, is more volatile than water, which would result from crotonate production.[7] On the other hand, one might assume that at 130–140° the equilibrium favors the anilide, and then the results could be understood on the basis of the lower volatility of 2-ethylbutyl and *n*-amyl alcohols as compared to water. The facts at hand do not permit stating which, if any, of these alternatives applies. However, since the products are readily interconvertible, it seems likely that the temperature dependence of the course of reaction is due to displacement of equilibrium rather than to the existence of two competing reaction paths with sufficiently differing temperature coefficients[8] of rate.

In Table I are given the over-all yields of various 2- and 4-hydroxyquinolines obtained from β-keto esters and aromatic amines employing various methods of preparation of the intermediate crotonates and anilides. The crotonates were generally prepared more conveniently by refluxing the reactants with Drierite in ethanol (Method B)[9,10] than by the older procedure (Method A) which requires a much longer time. However, Method B has not been satisfactory with ethyl benzoylacetate with which a modification of Method A was finally adopted (see note *e*, Table

(1) This work was supported by a grant from the Duke University Research Council.

(2) (a) Knorr, *Ber.*, **16**, 2593 (1883); (b) Conrad and Limpach, *Ber.*, **20**, 944 (1887); (c) Cavallito and Haskell, THIS JOURNAL, **66**, 1166 (1944); (d) Coffey, Thomson and Wilson, *J. Chem. Soc.*, 856 (1936).

(3) (a) Knorr, *Ann.*, **236**, 69 (1886); (b) Roos, *Ber.*, **21**, 624 (1888); (c) Knorr and Reuter, *Ber.*, **27**, 1169 (1894); (d) Knorr, *Ann.*, **236**, 74 (1894).

(4) The reaction failed in the absence of a trace of acid. This is not surprising since Coffey, Thomson and Wilson (ref. 2d) have shown that the formation of the crotonate requires a trace of acid, which ordinarily is present in commercial ethyl acetoacetate.

(5) The anilide was also identified (after recrystallization) by its melting point. The crotonates have been distilled at reduced pressures but, since the distillates deposited small amounts of diphenylurea, they were not analyzed. The diphenylurea was formed apparently from anilide, small amounts of which were evidently produced during the heating at 130–140° or during the distillation. Oppenheim and Precht (*Ber.*, **9**, 1098 (1876)) reported that heating the anilide with aniline produced diphenylurea and acetone.

(6) Also isopropyl acetoacetate appears to form the anilide at 130–140°, since a low yield of (IV) has been obtained on cyclizing the crude product. However, in attempts to reproduce this result, the only product isolated was diphenylurea which was formed presumably from the anilide (see note 5).

(7) Knorr (3d) reported that the anilide was obtained from aniline and ethyl acetoacetate when they were heated in a sealed tube at 150° for a long time. An attempt to reproduce this result was unsuccessful.

(8) This is evidently the case, for example, in the reaction of alkali with anti-benzaldoxime acetate which yields mainly the anti-benzaldoxime at 0° but mainly the corresponding nitrile at 30° or above; Hauser and Jordan, THIS JOURNAL, **57**, 2450 (1935).

(9) A little more than the calculated amount of Drierite required to remove the by-product, water, has generally been employed, but one-third of this amount has given, after cyclization of the crotonate, only a slightly lower yield of (III). It was found advisable to add a trace of acetic acid as catalyst.

(10) This procedure has also been satisfactory for the reaction of ethyl ethoxalylpropionate and aniline; cyclization of the resulting intermediate gave 3-methyl-4-hydroxy-2-carbethoxyquinoline, m. p. 177–179°, in 50% yield. However, the procedure using Drierite, as well as the original one, failed with ethyl ethoxalylpropionate and 2-nitro-4-methoxyaniline.

TABLE I

QUINOLINE DERIVATIVES FROM $RCOCH_2CO_2R'$ AND AROMATIC AMINES BY CYCLIZATION OF INTERMEDIATE CROTONATES AND ANILIDES OBTAINED BY VARIOUS METHODS

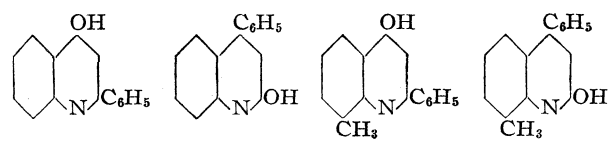
R	R′	Aromatic amine	Method	Substituted quinoline	M. p., °C.	Yield,[l] %
Methyl	Ethyl	Aniline	A	2-Methyl-4-hydroxy	229–230[a]	60
Methyl	Ethyl	Aniline	B	2-Methyl-4-hydroxy	229–230[a]	70
Methyl	*n*-Amyl[b]	Aniline	D	2-Methyl-4-hydroxy	229–230[a]	30
Methyl	2-Ethylbutyl[b]	Aniline	C, D	2-Methyl-4-hydroxy	229–230[a]	70
Methyl	Ethyl	*p*-Chloroaniline	B	2-Methyl-6-chloro-4-hydroxy	320–322[c]	68
Methyl	2-Ethylbutyl	*p*-Chloroaniline	C	2-Methyl-6-chloro-4-hydroxy	320–322[c]	70
Methyl	2-Ethylbutyl	*o*-Toluidine	C	2,8-Dimethyl-4-hydroxy	260–261[d]	68
Phenyl	Ethyl	Aniline	A[e]	2-Phenyl-4-hydroxy	253–254[f]	50
Phenyl	Ethyl	*o*-Toluidine	A	2-Phenyl-8-methyl-4-hydroxy	245–246[g]	38
Methyl	Ethyl	Aniline	D, E	4-Methyl-2-hydroxy	222–223[h]	50
Methyl	Ethyl	*o*-Toluidine	D, E	4,8-Dimethyl-2-hydroxy	217–218[i]	50
Phenyl	Ethyl	Aniline	F, G	4-Phenyl-2-hydroxy	259–260[j]	50
Phenyl	Ethyl	*o*-Toluidine	F, G	8-Methyl-4-phenyl-2-hydroxy	216–217[k]	38

[a] Conrad and Limpach, *Ber.*, **20**, 949 (1887). [b] Prepared by the method of Shivers, Dillon and Hauser, THIS JOURNAL, **69**, 119 (1947). [c] Kermac and Weatherhead, *J. Chem. Soc.*, 563 (1939). [d] Conrad and Limpach, *Ber.*, **21**, 524 (1888). [e] The reactants were allowed to stand ten days. The crotonate, obtained in 55% yield, melts at 92–93° (ref. 11). [f] Ref. 11. [g] Dziewonski, Moszew and Dortheimerowna, *Roczniki Chem.*, **12**, 925 (1932). [h] Camps, *Ber.*, **32**, 3230 (1901). [i] Ewins and King, *J. Chem. Soc.*, **103**, 107 (1913). [j] Ref. 12. [k] *Anal.* Calcd. for $C_{16}H_{13}NO$: C, 81.67; H, 5.61; N, 5.99. Found: C, 81.22; H, 5.80; N, 6.25. [l] Over-all yield base on the β-keto ester or aromatic amine.

I). Both Method A and B have failed with ethyl acetoacetate and *o*-nitroaniline or 2-nitro-4-methoxyaniline. Method C, which was used only with the higher alkylacetoacetates, is not generally as convenient as Method B. Method D, involving heating the reactant at 130–140°, produces the crotonates only with β-keto esters of sufficiently high boiling alcohols. The anilides were prepared from the ethyl β-keto esters either by Method D or by refluxing the reactants (Methods E and G).

It should be pointed out that, although cyclization of the crude crotonates prepared on a 0.1-mole scale by Method B gave quinolines of satisfactory purity, crude ethyl β-anilinocrotonate, prepared on a 0.5-mole scale, as a rule, gave products which were difficult to purify. When, however, the crotonate was purified by distillation under reduced pressure, the pure quinoline was always obtained.

Knorr reported that, like the crotonate, the anilide from aniline and ethyl benzoylacetate produces 2-phenyl-4-hydroxyquinoline (V) on cyclization.[11] He prepared the anilide by heating the reactants at 150° followed by treatment with dilute acid to hydrolyze ethyl β-phenylamidophenylacrylate, which was formed along with the anilide. However, we have found that heating the reactants at 150°, followed by recrystallization, produces essentially pure anilide, which, on cyclization, forms the expected 4-phenyl-2-hydroxyquinoline (VI). The two isomers, (V) and (VI), melt only a few degrees apart but a mixture of the two melts much lower and over a range. Moreover, treatment of (VI) with phosphorus oxychloride forms a chloro derivative the melting point of which is fifteen degrees higher than that reported for the chloro derivative of (V). Compounds (VII) and (VIII), which have been prepared from *o*-toluidine and ethyl benzoylacetate, melt almost thirty degrees apart. The present method of preparing 4-phenyl-2-hydroxyquinoline appears much more convenient than that described previously employing acetyl-*o*-amidobenzophenone.[12]



(V) (VI) (VII) (VIII)

Experimental[13]

General Procedures.—The crotonates were prepared by one or more of the following procedures using 0.1 mole each of β-keto ester and aromatic amine. Method A: the reactants were allowed to stand at room temperatures (20–30°) either alone for four to five days[2a,b,e] or in the presence of a trace of hydrochloric acid (or aniline hydrochloride) in a vacuum desiccator over concentrated sulfuric acid for one to three days.[2d] Method B: to the reactants was added 30–40 ml. of commercial absolute ethanol, about 35 g. of Drierite, and three or four drops of glacial acetic acid. The resulting mixture was refluxed on the steam-bath for three to four hours. The Drierite was filtered off and the ethanol was distilled at slightly above room temperatures by means of a water aspirator. Method C: the reactants were heated at 95–100° in an oil-bath for three to four hours in the presence of about 10 g. of Drierite and the Drierite then filtered off. Method D (applicable to β-keto esters of higher alcohols): the reactants were heated in an open Erlenmeyer flask or beaker for three or four hours in an oil-bath at 130–140° and then cooled to room temperatures.

The crude crotonate was added as rapidly as possible to 100 ml. of stirred refluxing (250–260°) Dowtherm[14] contained in a 200-ml. three-neck round-bottom flask equipped with a mercury-sealed stirrer and condenser. After fifteen

(11) Knorr, *Ann.*, **245**, 378 (1888).

(12) Camps, *Arch. Pharm.*, **237**, 683 (1899).

(13) Analyses by Oakwold Laboratory, Alexandria, Virginia.

(14) This cyclization has been effected previously under other conditions; Cavallito and Haskell (ref. 3c) effected the reaction in mineral oil.

to twenty minutes the stirring was stopped and the mixture allowed to cool, a light yellow solid usually separating. Approximately 200 ml. of Skellysolve "B" was then added. After shaking, the solid 4-hydroxyquinoline derivative was filtered off, washed several times with Skellysolve and recrystallized from water in the case of 2-methyl-4-hydroxyquinoline and from a mixture of water and ethanol in the other cases.

Acetoacetanilides were prepared from 0.1 mole each of ethyl acetoacetate and aromatic amine either by Method D described above or by refluxing the reactants three to four minutes[15] (Method E). The solid, obtained on cooling the mixture, was recrystallized from acetic acid and water and then from ethanol and water yielding acetoacetanilide (m. p. 82–83°)[3a] in 52% yield and acetoaceto-*o*-toluidide (m. p. 107–108°)[15] in 55% yield.

Benzoylacetanilides were prepared from 0.1 mole each of ethyl benzoylacetate and aromatic amine either by heating the reactants at 150° for five hours (Method F) or by refluxing the mixture for fifteen minutes (Method G). After recrystallization as described for acetoacetanilide, benzoylacetanilide (m. p. 107–108°)[11] was obtained in 50% yield, and benzoylaceto-*o*-toluidide (m. p. 130–131°) in a 65% yield.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.82; H, 5.96. Found: C, 75.51; H, 5.72.

The anilides were cyclized in concentrated sulfuric acid at 80–90° as described in "Organic Syntheses"[16] or by heating on the steam-bath for fifteen minutes. The 2-hydroxyquinoline derivatives were recrystallized from a mixture of water and ethanol. An attempt to cyclize acetoacetanilide (II) in Dowtherm at 250–260° as described above for the crotonate was unsuccessful.

The yields and the melting points of the quinoline derivatives are given in Table I. Admixture of the various samples of the same derivative showed no depression in melting point, but admixture of isomeric 2- and 4-hydroxyquinolines depressed the melting point.

2-Methyl-4-hydroxyquinoline (0.5 mole scale).—A mixture of 46.5 g. (0.5 mole) of aniline, 65 g. (0.5 mole) of ethyl acetoacetate, 100 ml. of commercial absolute ethanol, 135 g. of Drierite, and 1 ml. of glacial acetic acid was refluxed on the steam-bath for four hours. After removing the Drierite and the solvent, the residue was fractionated through a 30-cm. Vigreux column yielding 58 g. (57%) of ethyl β-anilinocrotonate, b. p. 155° at 10 mm.[17] The crotonate was cyclized in 200 ml. of Dowtherm yielding 38 g. (50%) of 2-methyl-4-hydroxyquinoline (m. p. 229–230°).

4-Phenyl-2-chloroquinoline.—A mixture of 10 g. (0.045 mole) of 4-phenyl-2-hydroxyquinoline (m. p. 259°) and 30 ml. of phosphorus oxychloride was heated in an oil-bath at 120° for two hours, the excess oxychloride distilled under reduced pressure and the light brown viscous oily residue poured onto ice. After standing in the refrigerator for one day the solidified oil was recrystallized from absolute ethanol yielding 10 g. (93%) of white crystals of 4-phenyl-2-chloroquinoline, m. p. 87–88°.

Anal. Calcd. for $C_{15}H_{10}NCl$: C, 75.15; H, 4.21; N, 5.86; Cl, 14.8. Found: C, 74.88; H, 4.70; N, 6.12; Cl, 14.68.

Conversion of Crotonate to Anilide.—To 0.1 mole of ethyl β-anilinocrotonate, b. p. 155° at 10 mm., was added 2 g. of water and five drops of concentrated hydrochloric acid and the mixture stirred and heated in an open flask in an oil-bath at 130–140° for three or four hours. The resulting crude anilide was cyclized[16] to form 4-methyl-2-hydroxyquinoline, m. p. 222–223°, in 35% over-all yield.

Conversion of Anilide to Crotonate.—A mixture of 0.1 mole of acetoacetanilide (m. p. 82–83°), 30 ml. of commercial absolute ethanol and 30 g. of Drierite was refluxed four hours and the Drierite then filtered off. After distilling the solvent, the residue was fractionated giving a 50% yield of ethyl β-anilinocrotonate (b. p. 139–143° at 6 mm.) which was cyclized in Dowtherm to 2-methyl-4-hydroxyquinoline, m. p. 229–230°, in 39% over-all yield from the anilide.

Summary

1. The factors governing the formation of crotonates and anilides from β-keto esters and aromatic amines have been considered.

2. Crotonates and anilides, prepared by various methods, have been cyclized to form 4- and 2-hydroxyquinolines, respectively.

3. In contrast to reports in the literature the anilide from ethyl benzoylacetate and aniline was found to form 4-phenyl-2-hydroxyquinoline on cyclization.

(15) Ewins and King, *J. Chem. Soc.*, **103**, 104 (1913), effected the reaction in one and one-half minutes.

(16) Lauer and Kaslow, "Organic Syntheses," Vol. 24, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 68.

(17) Distillation of the residue at a bath temperature of 120° until the forerun was removed and then at 140–160° gave ethyl β-anilinocrotonate, b. p. 128–130° at 2 mm., in 60–70% yield.

DURHAM, NORTH CAROLINA RECEIVED MARCH 19, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Bacterial Activity of "Racemized Casein," Caseose, and the Four Diastereoisomeric Leucylleucines[1,2]

BY SIDNEY W. FOX, YUTAKA KOBAYASHI,[3] SAMUEL MELVIN[3] AND FREDERICK N. MINARD[4]

Several of the antibiotics, particularly penicillin and gramicidin, are notable for their content of D-amino acid residues. In the case of penicillin, the D-amino acid residue is one of a number of critical structural features, since the L-analog is without activity.[5] D-Amino acids have been shown experimentally to inhibit bacterial growth[6,7] at relatively high concentrations. Recent reports, however, indicate medical utility of some of the simple amino acids, when used in relatively large amounts, in the control of infection.[8] In view of the above observations it is of interest to determine the antibacterial activity of structures re-

(1) Journal Paper No. J-1514 of the Iowa Agricultural Experiment Station, Project 897, in coöperation with the Veterinary Research Institute, and Project 980.

(2) The experiments with "racemized casein" were described before the American Society of Biological Chemists, May, 1947, at Chicago.

(3) This work was supported in part by the Industrial Science Research Institute of Iowa State College.

(4) Upjohn Company Fellow.

(5) du Vigneaud, Carpenter, Holley, Livermore and Rachele, *Science*, **104**, 431 (1946).

(6) Fox, Fling and Bollenback, *J. Biol. Chem.*, **155**, 465 (1944).

(7) Kobayashi, Fling and Fox, *ibid.*, **174**, 391 (1948).

(8) Mario, *Minerva med.*, **38**, I, 578 (1947).

lated to the D-amino acids and to the antibiotics in which these simple units are incorporate.[9]

Substances which include the D-amino acid residue repeated within a single large molecule are under investigation in this laboratory; interest in such materials and their behavior has also been expressed elsewhere.[10] The present report describes two types of such material, with some reference to their effects on bacteria.

The simpler type is represented by D-leucyl-D-leucine. For comparative experiments in the present study, all four diastereoisomeric leucylleucines were synthesized by the method of Fischer and Koelker.[11] D-Leucyl-D-leucine was of particular interest because of its relationship to D-valyl-D-valine, which had been isolated from partial hydrolyzates of gramicidin as the benzoyl derivative.[12] In the other type of molecule the D-amino acid residues were linked in the main-chain through both the amino and carboxyl groups. Such material was available through the racemization procedure of Dakin.[13,14] The fractions called by Dakin "racemized casein" and caseose were shown to contain inverted residues of valine, leucine, phenylalanine, proline, tyrosine, aspartic acid, glutamic acid, arginine, lysine and histidine. D-Isomers of the first three amino acids represent all of the D-forms which have been found in gramicidin and tyrocidine.[15–19]

TABLE I

GALVANOMETER READINGS OF *Escherichia coli* CULTURES IN NUTRIENT BROTH CONTAINING LEUCINE AND LEUCYLLEUCINE ISOMERS

Figures presented represent per cent. transmission.

Substance	Concentration, mg. per ml. 10	5.0	2.5	1.25	0.6	0.3
L-Leucine	70	74	71	74	72	75
D-Leucine	99	82	76	74	72	70
L-Leucyl-L-leucine	71	70	70	69	72	70
D-Leucyl-D-leucine	72	70	67	67	69	70
L-Leucyl-D-leucine	79	71	70	69	69	70
D-Leucyl-L-leucine	78	71	71	70	68	71

TABLE II

GROWTH OF *Escherichia coli* ON MEDIA CONTAINING CASEIN AND RACEMIZED CASEIN DERIVATIVES

O = no visible growth; S.G. = slight visible growth; G = visible growth

	Time, days 1	2	3
Smaco casein	O	O	O
Racemized casein	O	G	G
Caseose	S. G.	S. G.	S. G.

(9) Fling, Minard and Fox, THIS JOURNAL, **69**, 2466 (1947).
(10) Bergel, *Biochem. J.*, **41**, xxxvi (1947).
(11) Fischer and Koelker, *Ann.*, **354**, 39 (1907).
(12) Christensen, *J. Biol. Chem.*, **154**, 427 (1944).
(13) Dakin, *ibid.*, **13**, 357 (1912–1913).
(14) Dakin and Dudley, *ibid.*, **15**, 263 (1913).
(15) Hotchkiss, *ibid.*, **141**, 171 (1941).
(16) Christensen, Edwards and Piersma, *ibid.*, **141**, 187 (1941).
(17) Hotchkiss, *J. Bact.*, **45**, 64 (1943).
(18) Gordon, Martin and Synge, *Biochem. J.*, **37**, 86 (1943).
(19) Gordon, Martin and Synge, *ibid.*, **37**, 313 (1943).

In none of the tests with the described D-amino acid derivatives was antibacterial activity equal to that of D-leucine noted (Table I). The lack of activity of D-leucyl-D-leucine, as an analog of D-valyl-D-valine, is in agreement with the rapid loss of activity of gramicidin under gentle hydrolytic conditions.[20,21] The activity of gramicidin thus seems not to be even partially represented by contiguous D-amino acid residues. The experiments with racemized casein and with caseose indicate that a polypeptide preparation containing a larger proportion of D-amino acid residues than occurs in tyrocidine is without appreciable antibacterial activity.

The results recorded by Dakin and Dudley[22] for the action of pancreatic microbial cultures on racemized casein was in the main confirmed in this work, with *Escherichia coli*. It should be noted that in the present experiments, the effect of *E. coli* on native casein also was tested; no appreciable growth was observed.

The quantitative nature of the behavior of the leucylleucines as sources of L-leucine for *L. arabinosus 17-5* is striking. Table III represents a typical experimental result. The bacterium was capable of utilizing fully, during the experimental incubation period, the L-leucine residues of L-leucyl-L-leucine and of D-leucyl-L-leucine. As might be expected, it could not utilize D-leucyl-D-leucine. *L. arabinosus* was also unable to use L-leucyl-D-leucine. This behavior is in contrast to the utilizability of D-leucyl-L-leucine.[23]

TABLE III

L-LEUCINE ACTIVITY OF LEUCYLLEUCINE ISOMERS FOR GROWTH OF *Lactobacillus arabinosus 17-5* IN LEUCINE-FREE MEDIUM

Peptide	L-Leucine activity of peptide, %	
L-Leucyl-L-leucine	98	102
L-Leucyl-D-leucine	0	0
D-Leucyl-L-leucine	50	50
D-Leucyl-D-leucine	0	0

Experimental

Leucylleucines.—The D–D, D–L, L–D, and L–L leucylleucines were prepared by the same general procedure employed by Fischer and Koelker[11] and by Fischer.[24] The intermediate bromoisocaproylleucines prepared in the present work had the following m. p.'s (cor.): L-α-bromoisocaproyl-D-leucine, 145–7° (F. & K. 149°), L-α-bromoisocaproyl-L-leucine, 126–7°, (F. & K. 128°), D-α-bromoisocaproyl-D-leucine, 125–7°, (F. & K. 128°), and D-α-bromoisocaproyl-L-leucine, 144–6° (F. 149°). Each of the dipeptides was assayed for L-leucine content. Samples of 20 mg. of each dipeptide were dissolved in 5 ml. of 20% hydrochloric acid and autoclaved for three hours at 15 lb. steam pressure. The solutions were then neutralized with sodium hydroxide and each was diluted to 100 ml. The resultant solutions were then assayed against a stand-

(20) Schales and Mann, *Arch. Biochem.*, **13**, 357 (1947).
(21) Itschner and Fox, unpublished experiments.
(22) Dakin and Dudley, *J. Biol. Chem.*, **15**, 276 (1913).
(23) Taken in conjunction with the work of Ågren: *Acta. Physiol. Scand.*, **13**, 347 (1947), these results emphasize the importance of position of the amino acid residue.
(24) Fischer, *Ber.*, **39**, 351 (1906).

ard solution of DL-leucine turbidimetrically on a Coleman Model 11 Spectrophotometer at 600 mμ. The organism employed was *Lactobacillus arabinosus 17-5*, which responds only to the L-form of leucine. The medium employed was that of Kuiken, *et al.*[25]

Within the probable limits of error of the assay, the identity of the four leucylleucines was established. The L–L assayed 90–100% L-leucine, the L–D and D–L each 50% L-leucine (±5%), and the D–D hydrolyzate gave 0- < 1% L-leucine.

Partially Racemized Casein Fractions.—Smaco vitamin-free casein was partially racemized by the procedure of Dakin.[12] The $[\alpha]^{27}D$ for the original casein, the acid-precipitable racemized casein and the water-soluble caseose (precipitated by ammonium sulfate) were, respectively: $-104.7° \pm 0.8°$, $-52.0° \pm 0.8°$, and $-37.5° \pm 2.0°$ (0.3 g. in 25 ml. 0.5 *N* sodium hydroxide solution).

Inhibition Experiments.—The leucylleucines and leucines were first tested against *E. coli* in a dilution series. Twenty mg. of each compound was weighed into a small test-tube. Two ml. of nutrient broth[26] was added to each tube and solution was effected by warming. Half of this was mixed with medium in another tube, and this process repeated through a series of a total of six tubes. The tubes were plugged with cotton and autoclaved for ten minutes at 15 lb. steam pressure. The tubes were then inoculated from a fresh subculture of *E. coli*.

After twenty-five hours of incubation at 37°, the turbidities of the cultures were assessed in a Coleman Model 11 spectrophotometer at 650 mμ. The results are presented in Table I. The experiment was repeated with a synthetic medium consisting of 0.5% disodium phosphate, 0.5% dipotassium phosphate, 0.5% ammonium chloride, 0.02% magnesium sulfate and 0.5% glucose, brought to *p*H 7 with phosphoric acid. The visual results were similar to those in nutrient broth; only D-leucine at 10 mg./ml. showed total inhibition. No inhibition was found for any of the peptides tested against *L. arabinosus 17-5* in a yeast extract medium[27] with all other conditions the same as in the *E. coli* experiments. Because of the conceivability of racemization of the D-peptides during autoclaving,[28] the experiment of Table I was repeated with the glucose added aseptically after autoclaving, and again with the glucose replaced by glycerol. In both cases the results were identical with those in synthetic medium.

At concentrations of 10 mg./ml. of added racemized casein and of caseose, *E. coli* grew under the experimental conditions given above. *E. coli* was grown for the other inhibition experiments with nutrient broth as above, except for the added casein or racemized preparations. The racemized casein was dissolved in 2 *N* sodium hydroxide solution, neutralized, and Seitz-filtered for the tests. There was no inhibition of *L. arabinosus 17-5* by racemized casein at a concentration of 3.5 mg./ml. nor by caseose at a concentration of 15 mg./ml. in yeast extract medium at 37° for seventy-two hours.

A corresponding set of experiments with racemized gelatin (not isolated) gave similar results.

Experiments on Support of Growth.—For experiments on support of growth, casein, racemized casein, and caseose were made up in concentrations of 100 mg./ml. of 0.8% sodium carbonate solution containing traces of calcium chloride, magnesium sulfate and trisodium phosphate. No other protein was present. *E. coli* was the organism used. The results are presented in Table II.

Tests of replaceability of L-leucine by the leucylleucines were run in leucine-free synthetic medium[25] inoculated with *L. arabinosus*. The results are presented in Table III.

Summary

Racemized casein and caseose, containing numerous D-amino acid residues per molecule, failed to inhibit the growth of cultures of *Escherichia coli* or *Lactobacillus arabinosus 17-5*. None of the four isomeric leucylleucines showed as much antibacterial activity as D-leucine. The relationship of these experiments to the antibacterial activity of D-amino acids and of the antibiotics which are D-amino acid derivatives has been discussed.

The replaceability of L-leucine by leucylleucine isomers, in the medium for *L. arabinosus 17-5*, has been studied. The L-residues of L-leucyl-L-leucine and D-leucyl-L-leucine were fully utilized. None of the residues of L-leucyl-D-leucine nor of D-leucyl-D-leucine were available to this organism.

AMES, IOWA RECEIVED JANUARY 31, 1948

(25) Kuiken, Norman, Lyman, Hale and Blotter, *J. Biol. Chem.*, **151**, 615 (1943).

(26) Difco Laboratories, "Difco Manual," Detroit, Mich., 1943, p. 42.

(27) Difco Laboratories, "Difco Manual," Detroit, Mich., 1943, p. 178.

(28) Fling and Fox, *J. Biol. Chem.*, **160**, 329 (1945).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Action of Heat on D-Fructose. Isolation of Diheterolevulosan and a New Di-D-fructose Dianhydride

BY M. L. WOLFROM AND MARY GRACE BLAIR[1]

It is probable that the well-established tendency of D-fructose to form bimolecular cyclic anhydrides[2] accounts for some of the molasses formation occurring in cane sugar house processing. Such a view has been expressed by Sattler and Zerban.[3] These authors have investigated the non-fermented products formed on heating a concentrated aqueous solution of D-fructose. They established that the complex mixture obtained closely approximated in composition that required for a mixture of isomeric di-D-fructose dianhydrides. This work has now been repeated in our laboratory and the non-fermented products have been subjected to separation by chromatography on clay, a procedure established by Lew, Wolfrom and Goepp.[4] Two crystalline products were isolated in pure form and characterized. The one was the diheterolevulosan of Pictet and Chavan[5]

(1) Sugar Research Foundation Fellow of The Ohio State University Research Foundation (Project 190).

(2) For a review of the di-D-fructose dianhydrides see Emma J. McDonald, *Advances in Carbohydrate Chem.*, **2**, 253 (1946).

(3) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, **37**, 1133 (1945).

(4) B. W. Lew, M. L. Wolfrom and R. M. Goepp, Jr., THIS JOURNAL, **67**, 1865 (1945); **68**, 1449 (1946).

(5) A. Pictet and J. Chavan, *Helv. Chim. Acta*, **9**, 809 (1926).

and the other, designated diheterolevulosan II, was an isomeric substance (m. p. 250–252°, dec.; $[\alpha]^{25}D$ −39° in water) not identical with any known di-D-fructose dianhydride.

Pictet and Chavan[5] prepared their crystalline diheterolevulosan by treating D-fructose at low temperatures with concentrated hydrochloric acid. This work was repeated in our laboratory in order to obtain material for comparative purposes. The complex reaction product was subjected to chromatographic separation and the diheterolevulosan of Pictet and Chavan[5] was obtained with constants in agreement with those cited by these workers. In addition, diheterolevulosan II was obtained from this source. The crystalline hexaacetate of diheterolevulosan was prepared and was found to have properties in agreement with those described by Schlubach and Behre.[6] The hexaacetate of diheterolevulosan II was likewise obtained in crystalline form.

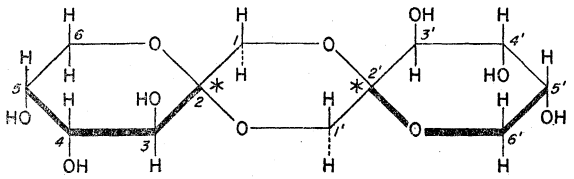
Pictet and Chavan[5] isolated an amorphous fraction which they termed "heterolevulosan" and which they considered to be a monomolecular anhydride of D-fructose. A material of similar properties was obtained on following their procedure. It was easily demonstrated by chromatographic methods, however, that this fraction was a complex mixture whose main component was the diheterolevulosan II. There thus exists no evidence for a monomolecular anhydride of D-fructose or for its "dimerization"[3,5] to a di-D-fructose dianhydride. Like "glutose,"[3] "heterolevulosan" has no existence in fact and the name should be stricken from the chemical literature.

Schlubach and Behre[6] methylated diheterolevulosan to a crystalline hexamethyl ether from which was obtained on acid hydrolysis a sirupy trimethyl-D-fructose, $[\alpha]^{20}D$ −73.5° in water, which formed an oily phenylosazone without demethylation. McDonald and Jackson[7] noted that diheterolevulosan absorbed four moles of periodate. To this we add that two moles of formic acid and no formaldehyde are produced in this oxidation. Upon these data the structure I (Fig. 1), di-D-fructopyranose 1,2′:2,1′-dianhydride, is evinced for diheterolevulosan. The methylation data do not meet the exacting criteria of crystallinity and are therefore inadequate. Fortunately, the periodate work is definitive and leads uniquely to formula I. The structure of diheterolevulosan is thus established save for the assignment of configurations to the anomeric spirane carbon atoms.

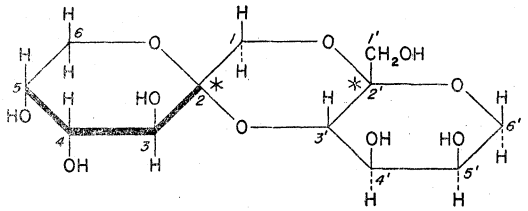
We can presently adduce for the structure of diheterolevulosan II only the results of periodate analysis which are that three moles of oxidant are consumed with the concomitant formation of one mole of formic acid and no formaldehyde. Formulas II and III satisfy these demands and for the sake of simplicity we favor III. Further data are required for an unequivocal proof of structure.

(6) H. H. Schlubach and C. Behre, *Ann.*, **508**, 16 (1934).

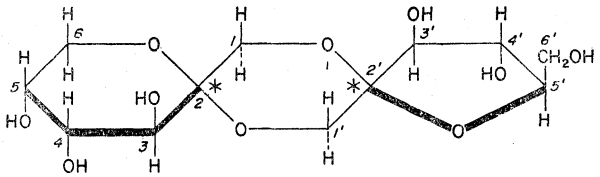
(7) Emma J. McDonald and R. F. Jackson, *J. Research Natl. Bur. Standards*, **35**, 497 (1945).



I. Diheterolevulosan (di-D-fructopyranose 1,2′:2,1′-dianhydride).



II. Di-D-fructopyranose 1,2′:2,3-dianhydride.



III. D-Fructopyranose-D-fructofuranose 1,2′:2,1′-dianhydride.

*Anomeric configuration unknown.

Fig. 1.—Di-D-fructose dianhydrides.

Experimental

Treatment of D-Fructose with Hydrochloric Acid and Recovery of the Crude Reaction Products.—Following Pictet and Chavan,[5] D-fructose (100 g.) was dissolved at 0° in 400 g. of concentrated hydrochloric acid (sp. gr. 1.19 at 15.56°) and the solution was maintained at 0° for seventy-two hours. Neutralization was then effected with basic lead carbonate and the dissolved lead chloride was removed from the filtered solution by ion exchange on Amberlites IR-100 and IR-4.[8] Unchanged D-fructose was removed from the solution (1500 ml.) by fermentation with 20 g. of baker's yeast (Fleischmann) at 30° for three days. Upon the cessation of fermentation, the yeast was removed by centrifugation and filtration through a filter-aid. The filtrate was deionized with Amberlites IR-100 and IR-4[8] and concentrated to a sirup which was dried by the addition of absolute ethanol and its subsequent removal by distillation under reduced pressure. Crystallization was effected from methanol; yield 28 g. in two crops (fraction A). The filtrate (150 ml.) was added dropwise to 1.5 liters of anhydrous ether and the precipitate so formed was removed by filtration; yield 4.7 g. (fraction B), $[\alpha]^{24}D$ −61.0° (*c* 4, water). The material was an amorphous, somewhat hygroscopic, white powder.

Diheterolevulosan from Fraction A.—Fraction A (28 g.) above was recrystallized several times from water to yield pure diheterolevulosan; yield 5.9 g., m. p.[9] 261–263° (dec.), $[\alpha]^{18}D$ −45.8° (*c* 4, water). This material was chromatographically pure; it showed only one zone when chromatographed according to the extrusion procedure described below. Pictet and Chavan[5] cite for

(8) Products of the Resinous Products and Chemical Co., Philadelphia, Pennsylvania.

(9) Unless otherwise noted, all melting points are uncorrected and were taken on a modified Berl–Kullmann block as described by F. W. Bergstrom, *Ind. Eng. Chem., Anal. Ed.*, **9**, 340 (1937). The substances were heated as rapidly as possible from room temperature to near the melting point.

diheterolevulosan the constants: m. p. 266–267°; $[\alpha]^{18}D$ −43.5° (*c* 4, water).

Anal. The substance (1 mole) consumed 4.2 moles of sodium metaperiodate and formed 2.0 moles of formic acid and no formaldehyde.

Acetylation of this material (0.5 g.) with pyridine (7 ml.) and acetic anhydride (4.5 ml.) by shaking mechanically at room temperature for four to five days, yielded hexaacetyldiheterolevulosan (recrystallized from absolute ethanol); yield 0.8 g., m. p. 172.5–173.5° (cor.), $[\alpha]^{28}D$ −59.0° (*c* 1, U. S. P.[10] chloroform). Schlubach and Behre[6] cite for hexaacetyldiheterolevulosan the constants: m. p. 171–173°; $[\alpha]^{20}D$ −59.1° (*c* 1, chloroform).

Diheterolevulosan II from Fraction A.—The aqueous mother liquor from the above-described preparation of diheterolevulosan was concentrated to a sirup; yield 22 g. An amount of 11 g. of this sirup was dissolved in 8 ml. of water, made into a slurry with clay–Celite[11] (5:1 by wt.) and treated with 200 ml. of 95% ethanol. The mixture was added to the top of a 2-liter pharmaceutical percolator packed with 1 kg. of the same clay–Celite mixture and saturated with 95% ethanol. To this mixture was added 95% ethanol until 6.3 liters of effluent was obtained. Evaporation of the filtered effluent yielded a sirup (fraction A-1). Additional development with 95% ethanol removed a negligible amount of material (very weak Molisch test). Changing of the developer to 80% ethanol slowly removed further material. From 5 liters of effluent there was recovered, in the manner described above, crystalline material identified as diheterolevulosan; yield 1.0 g., $[\alpha]^{27}D$ −45.4° (*c* 4, water).

Fraction A-1 was dissolved in water and deionized with Amberlite IR-100 and IR-4.[8] The deionized solution was concentrated under reduced pressure to a thick sirup and crystallized by the addition of methanol; yield 7.2 g., $[\alpha]^{26}D$ −39.5° (*c* 4, water). The material was recrystallized by solution in water, concentration to a thick sirup and addition to this of absolute methanol. This product contained some inorganic material which was removed by solution of the organic crystals in boiling absolute methanol and filtration. The solvent was removed and the procedure was repeated with 90% ethanol. Crystallization was effected by concentration of the dilute ethanol solution; yield 6.4 g., m. p. 250–252° (dec.), m. p. 239–243° on admixture with diheterolevulosan of m. p. 261–263° (dec.), $[\alpha]^{28}D$ −39° (*c* 4, water). The substance reduced Fehling solution after acid hydrolysis with 5% sulfuric acid for thirty minutes at 70°. It was chromatographically pure, showing only one zone when chromatographed on clay according to the procedure detailed below.

Anal. Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.28; H, 6.18. Periodate analysis: the substance (1 mole) consumed 3.0 moles of sodium metaperiodate and formed 1.0 mole of formic acid and no formaldehyde.

Hexaacetyldiheterolevulosan II.—This substance was prepared according to the procedure described above for hexaacetyldiheterolevulosan except that solution was readily effected in the acetylating mixture and two days standing at room temperature without shaking sufficed. It was obtained crystalline from absolute ethanol; m. p. 123–124°; $[\alpha]^{20}D$ −41.5° (*c* 4, U. S. P.[10] chloroform).

Anal. Calcd. for $C_{12}H_{14}O_{10}(CH_3CO)_6$: C, 49.99; H, 5.60; CH_3CO, 10.4 ml. 0.1 *N* NaOH per 100 mg.; mol. wt., 577. Found: C, 50.11; H, 5.72; CH_3CO, 10.4 ml.; mol. wt. (Rast), 604.

Deacetylation was effected by the procedure of Kunz and Hudson[12] (sodium hydroxide in dilute acetone at −15°). Acetone was removed from the neutralized solution by distillation under reduced pressure and inorganic ions were removed by passage through ion exchange columns (Amberlites IR-100 and IR-4[8]). Concentration to a thick sirup followed by methanol addition yielded the original crystalline diheterolevulosan II; m. p. 250–252°, $[\alpha]^{23}D$ −38.7° (*c* 4, water).

Investigation of Fraction B.—Fraction B above (4.7 g., $[\alpha]^{24}D$ −61° in water) corresponds to the amorphous material described by Pictet and Chavan[5] as "heterolevulosan," $[\alpha]^{24}D$ −66° (*c* 3, water), and considered by them to be a six carbon anhydro-D-fructose. Three grams of this fraction was dissolved in 45 ml. of water and 255 ml. of dioxane (distilled from sodium) was added. The resultant solution was chromatographed in 5-cc. portions on 25 g. of clay–Celite (5:1) in tapered tubes (23 mm. diam. at bottom and 25 mm. diam. at top). Development was effected with 70 ml. of 95% dioxane. Extrusion of the chromatograms and streaking with the alkaline permanganate indicator (1% potassium permanganate in 2 *N* sodium hydroxide) located three zones in each: C, 6–18 mm. from the top; D, 45–70 mm.; E, 95–125 mm. No significant amount of material was present in the effluents. The sectioned fractions were eluted with 80% ethanol. The collected material from the C zones yielded a small amount of crystalline substance that is under further investigation; m. p. 261–263° (dec.), $[\alpha]^{25}D$ −90° (*c* 4, water). Zone E yielded a sirup; yield 0.3 g. Zone D contained diheterolevulosan II; 0.8 g., $[\alpha]^{23}D$ −37° (*c* 4, water). Ash-free material was obtained on recrystallization as described above; m. p. 248–250° (dec.) undepressed on admixture with the material described above, $[\alpha]^{24}D$ −37° (*c* 4, water).

Anal. Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.08; H, 6.08.

Subjection of an Aqueous Solution of D-Fructose to the Action of Heat and Recovery of the Reaction Products.—Following the heat treatment procedure of Sattler and Zerban,[3] 100 g. of D-fructose was dissolved in 25 ml. of water and the resultant solution was refluxed gently for sixteen hours. The solution was then diluted to 700 ml. with sterile water and fermented and deionized as described previously. The resultant dried sirup was dissolved in 200 ml. of dry methanol and the solution added dropwise to 2 liters of dry acetone. The resultant flaky, cream colored, somewhat hygroscopic, amorphous solid was removed by filtration; yield 26 g., $[\alpha]^{24}D$ −23° (*c* 4, water). The precipitate was redissolved in water, treated with decolorizing charcoal, and the solution again evaporated to dryness under reduced pressure. The dry residue was further purified by two precipitations effected by the dropwise addition of its methanolic solution to acetone; yield 18 g., $[\alpha]^{24}D$ −32.6° (*c* 4, water). An amount of 16.4 g. of this material was crystallized from anhydrous methanol; yield 1.1 g. of crystals (fraction F), $[\alpha]^{22}D$ −37° (*c* 4, water). The mother liquor material will be designated fraction G.

Fraction F (1.1 g.) was dissolved in 15 ml. of water to which was then added 85 ml. of purified dioxane. This solution was chromatographed in 5-cc. portions exactly as described above for fraction B. Two zones were obtained: H, 8–23 mm. from the top; I, 36–72 mm. The collected material from the H zone yielded crystals on concentration of the eluate; yield 0.49 g., $[\alpha]^{30}D$ −48° (*c* 4, water). Pure material was obtained on several recrystallizations effected by solution in a minimum amount of hot water and addition of ethanol. It was identified as diheterolevulosan; m. p. 261–263° (dec.) undepressed on admixture with the above-described material from the acid treatment of D-fructose, $[\alpha]^{24}D$ −45.0° (*c* 4, water).

Anal. Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.23; H, 5.96.

The hexaacetate was prepared as described above; m. p. 172.5–173.5° (cor.) undepressed on admixture with material from the acid treatment of D-fructose, $[\alpha]^{28}D$ −58.0° (*c* 1, U. S. P.[10] chloroform).

(10) United States Pharmacopoeia.

(11) The clay employed was Florex XXX, a fuller's earth type of clay, produced by the Floridin Co., Warren, Pennsylvania. The Celite (no. 535) was a siliceous filter-aid produced by Johns-Manville Co., New York, N. Y. The mixture was purified by solvent extraction as described by Lew, Wolfrom and Goepp.[4]

(12) A. Kunz and C. S. Hudson, THIS JOURNAL, **48**, 1982 (1926).

The collected material from the above-described zone I was a sirup that crystallized on the addition of anhydrous methanol; yield 0.19 g. (fraction J), $[\alpha]^{20}D$ −37.6° (*c* 4, water). This material was combined below to form fraction K.

An amount of 12 g. of fraction G above was dissolved in 180 ml. of water and to this was added 1020 ml. of purified dioxane. The resultant solution was chromatographed in 5-ml. portions as described above for fraction B. Zones were obtained that were located in the same positions as those found in fraction B. The collected material from the bottom zones yielded a sirup that was not further investigated; yield 1.4 g. The material from the top zones was found to contain diheterolevulosan, identified by optical rotation, which was isolated as described above; yield 0.32 g. The collected material from the middles zones crystallized in part from methanol; yield 1.2 g., $[\alpha]^{28}D$ −39.0° (*c* 4, water). This crystalline material was combined with fraction J above to form fraction K which was further purified from methanol and 90% ethanol and was identified as diheterolevulosan II; m. p. 250–252° (dec.) undepressed on admixture with material obtained by the acid treatment of D-fructose, $[\alpha]^{28}D$ −39.0° (*c* 4, water).

Anal. Calcd. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.31; H, 6.20.

The material was non-reducing toward Fehling solution and yielded the above-described hexaacetate of diheterolevulosan II.

Summary

1. Diheterolevulosan (di-D-fructopyranose 1,-2′:2,1′-dianhydride, I) and a new di-D-fructose dianhydride, designated diheterolevulosan II, have been isolated in crystalline form by chromatographic methods from the products obtained by the action of heat or of hydrogen chloride upon concentrated aqueous solutions of D-fructose.

2. Periodate analysis of diheterolevulosan II (II) favors, but does not prove, a 1,2′:2,1′-dianhydride structure (III) formed between a mole of D-fructopyranose and one of D-fructofuranose.

3. The amorphous "heterolevulosan" of Pictet and Chavan is shown by chromatographic methods to be a complex mixture, the principal constituent of which is diheterolevulosan II.

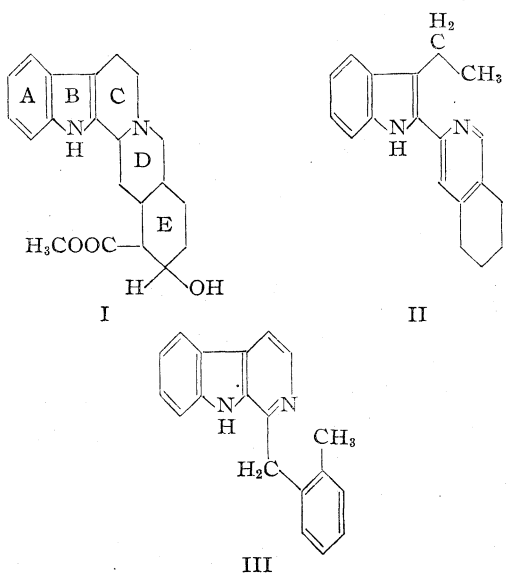
COLUMBUS, OHIO RECEIVED FEBRUARY 16, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Structure of Ketoyobyrine

BY R. B. WOODWARD AND BERNHARD WITKOP

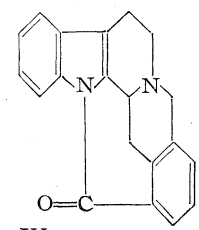
The selenium dehydrogenation of yohimbine (I) gives two bases, tetrahydroisoyobyrine (II), yobyrine (III) and ketoyobyrine, a neutral substance of the formula $C_{20}H_{16}ON_2$. The study of the basic products was of primary importance in deducing the structure of yohimbine, and the structures of the bases have been established beyond question.[1,2] On the other hand, no satisfactory formulation of ketoyobyrine has been forthcoming. Scholz[3] originally put forward the expression (IV); the facts that ketoyobyrine is optically inactive, that it is the product of a drastic dehydrogenation reaction, and in particular that it has no basic properties, are incompatible with that formula. The outstanding phenomenon in the chemistry of ketoyobyrine is the smooth cleavage of the molecule by amyl alcoholic potassium hydroxide to hemellitylic acid and norharmane.[3,4] This behavior has been adduced in support of an alternative formula (V),[2] which, however, still cannot be reconciled with the neutral character of the molecule.



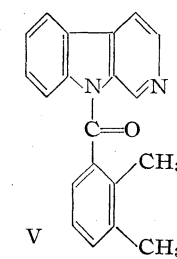
I

II

III



IV



V

In this communication, it is shown that in fact ketoyobyrine[5] has the structure (VI). This formula was deduced from that of yohimbine (I) on the basis of these considerations: (i) when yohimbic acid is heated with selenium, loss of the

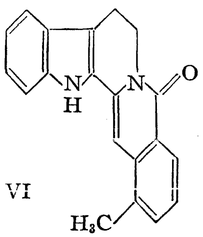
(1) Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).

(2) Witkop, *Ann.*, **554**, 83 (1943); *cf.* Clemo and Swan, *J. Chem. Soc.*, 617 (1946); Julian, *et al.*, THIS JOURNAL, **70**, 180 (1948).

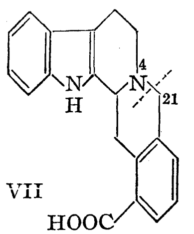
(3) Scholz, Diss. Eidgen. Techn. Hochschule, Zürich, 1934.

(4) Mendlik and Wibaut, *Rec. trav. chim.*, **50**, 91 (1931).

(5) It is clear that the term ketoyobyrine is a misnomer, but in view of long-established usage, we feel that a change is not desirable.

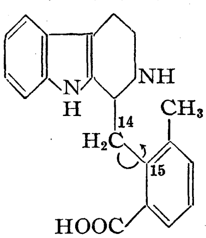


VI

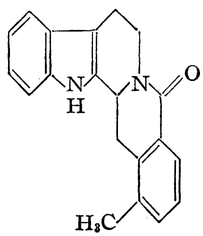


VII

hydroxyl group through dehydration may be followed to some extent by the dehydrogenation of ring E; (ii) the resulting intermediate (VII), as a benzylamine, should be subject to ready reduction cleavage between N.4 and C.21,[6] to give (VIII); (iii) by rotation through 180° about the



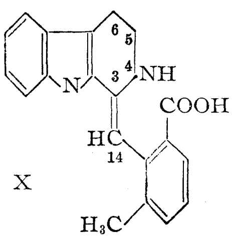
VIII



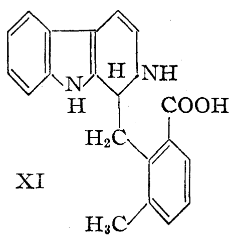
IX

C.14-C.15 bond, (VIII) is in a position to undergo lactamization to (IX); (iv) selenium may effect the further dehydrogenation of the dihydroisoquinolone (IX) to (VI). It is noteworthy that the latter contains a fully aromatic isoquinolone system, and that a compound of that structure should exhibit the high stability characteristic of ketoyobyrine.

The remarkable cleavage of ketoyobyrine by amyl alcoholic potassium hydroxide to norharmane and hemellitylic acid is readily explicable in terms of the structure (VI). Thus, opening of the amide link gives (X). The $\Delta^{3,14}$ double bond of

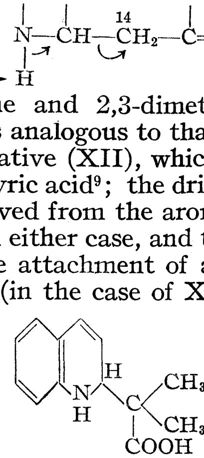


X



XI

(X) migrates to $\Delta^{5,6}$ by three prototropic shifts, for each of which ample analogy is available, *viz.*, enamine (HC=C—NH, 14, 3) → ketimine[7] (CH₂—C=N, 14, 3) ketimine (—C=N—CH₂, 3, 5) → isomeric ketimine[8] (—CH—N=CH, 3, 5), and finally ketimine → enamine[7] (N=CH—CH₂ → NH—CH=CH, 5, 6). The resulting dihydropyridine derivative (XI) then suffers loss of the side chain through the base-catalyzed process N—CH—$\overset{14}{CH_2}$—C=C—COOH, (HO⊖ → H) giving norharmane and 2,3-dimethylbenzoic acid. The cleavage is analogous to that of the dihydroquinoline derivative (XII), which leads to quinoline and isobutyric acid[9]; the driving force for the reaction is derived from the aromatization of the pyridine ring in either case, and the reaction is facilitated by the attachment of a carboxyl group either directly (in the case of XII) or through a

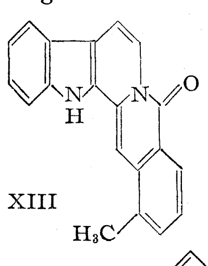


XII

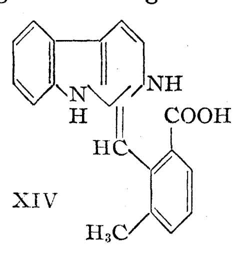
double bond (in the case of XI) to the carbon atom which must accept the electron pair from the broken bond.

The formula (VI) implies that in ketoyobyrine the yohimbine ring system is not fully aromatized. In accordance with that view, we have found that when ketoyobyrine is heated at 280° in the presence of palladium black, exactly one mole of hydrogen is released, and a new substance, $C_{20}H_{14}ON_2$, m. p. 345°, for which we propose the name dehydroketoyobyrine, is formed. The ultraviolet spectrum of the new compound differs considerably from that of its progenitor (*cf.* Fig. 1). It is clear that the structure (XIII) may be assigned to dehydroketoyobyrine.

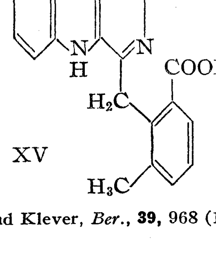
In marked contrast to ketoyobyrine, dehydroketoyobyrine, when treated with hot amyl alcoholic potassium hydroxide, is converted smoothly to a colorless *amino acid*, $C_{20}H_{16}O_2N_2$, which reverts readily to its precursor on heating, alone, or in a variety of solvents, *e. g.*, even on attempted recrystallization from alcohol. The nature of these changes is clear. Following the cleavage of the



XIII



XIV



XV

(6) Emde and Kull, *Arch. Pharm.*, **274**, 173 (1936).

(7) *Cf.* Auwers and Wunderling, *Ber.*, **64**, 2748, 2758 (1931); **65**, 70 (1932).

(8) Shoppee, *J. Chem. Soc.*, 696 (1932); 1225 (1931).

(9) Staudinger and Klever, *Ber.*, **39**, 968 (1906); **40**, 1149 (1907).

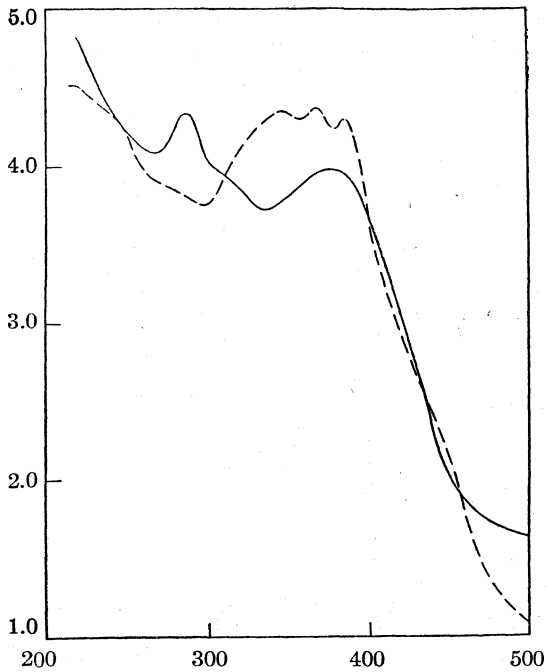
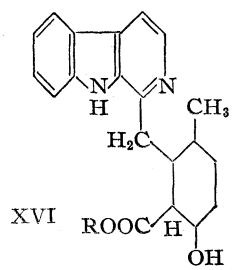


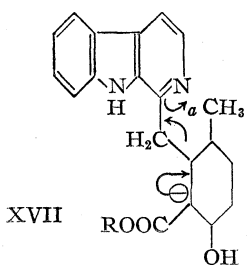
Fig. 1.—Dehydroketoyobyrine, —; ketoyobyrine ----.

amide link of (XIII) with the formation of (XIV), ring C becomes aromatic through migration of the $\Delta^{3,14}$ double bond to the $\Delta^{3,4}$ position. In this way, we arrive at the conclusion that the amino acid $C_{20}H_{16}O_2N_2$ is carboxyyobyrine (XV). This view is substantiated by the identity of the ultraviolet absorption spectrum of the amino acid in alkaline solution[10] with that of yobyrine[11] (III) (*cf.* Fig. 2). The reconversion of (XV) to (XIII) is readily understandable in the light of the well-known lability of the α-substituted pyridine ⇄ α-pyridone methine equilibrium. When attempts were made to effect the decarboxylation of (XV) to yobyrine itself, the facile reconversion to (XIII) supervened, and dehydroketoyobyrine was the sole isolable product.

The new view of the constitution of ketoyobyrine affords new support for the attachment of the carboxyl group of yohimbine at C.16. Hitherto the acceptance of this position has depended upon the formation of harmane and *m*-toluic acid from



XVI



XVII

(10) The spectrum was determined under alkaline conditions in order to minimize any possible additional contribution to absorption as a result of the conjugation of the carboxyl group of (XV) with the benzenoid ring.

(11) Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

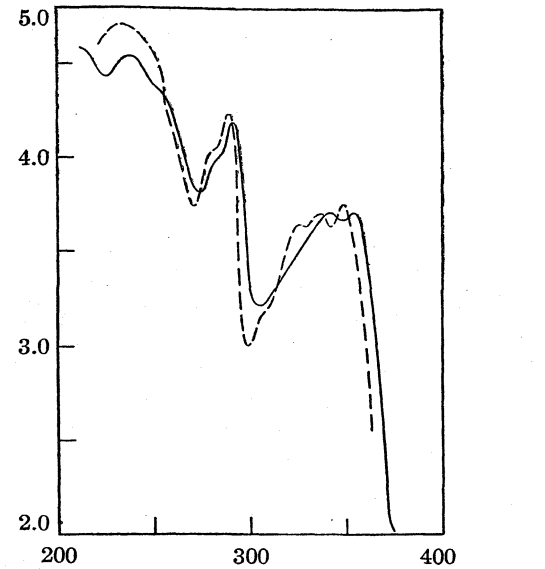


Fig. 2.—Carboxyyobyrine (sodium salt), —; yobyrine, ------.

"tetradehydroyohimbine"[12] (XVI)[2] on boiling with amyl alcoholic potassium hydroxide. The inference from this change is relatively clear, but the structural value of the evidence has been subject to some question in view of the fact that the nature of the cleavage has been obscure, the more so, since, in this reaction, scission of the C.14-C.15 bond occurs, in sharp contrast to the breaking of the C.3-C.14 bond of ketoyobyrine under very similar conditions. We should like to point out that the course of the cleavage of (XVI) is explicable in terms which we have applied elsewhere to the drastic alkaline degradation of alicyclic acids.[13] Thus, removal by base of the hydrogen atom, α to and activated by, the carbomethoxy group of (XVI) gives an anion (XVII), which undergoes a simple electronic shift (XVII, arrows), with cleavage of the C.14-C.15 bond; the acceptance of the liberated electron pair by C.14 is, of course, facilitated by the adjacent pyridine ring (*cf.* XVII, arrow *a*). The addition of a proton to the heterocyclic fragment leads to harmane, and the further changes which lead to *m*-toluic acid from the hydroaromatic fission product are unexceptional. We may point out that the course of this cleavage is in general terms very similar to that of ketoyobyrine, and that the difference in the actual points of cleavage receives a rational explanation in terms of the particular molecular environment present in the one or the other case.

In these circumstances, we consider that the attachment of the carbomethoxy group of yohimbine at C.16 is now entirely free of ambiguity.

Experimental

Ketoyobyrine.—The crude product obtained from the selenium dehydrogenation of yohimbic acid in about 4%

(12) Hahn, Kappes and Ludewig, *Ber.*, **67**, 686 (1934).

(13) Woodward and Brutschy, THIS JOURNAL, in press.

yield was first recrystallized from acetic acid (charcoal) and then extracted from a thimble with alcohol, in which it is moderately soluble; bright yellow rectangular prisms, m. p. 315–320°[14] (dark melt).

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.97; H, 5.37 Found: C, 79.98; H, 5.37.

Dehydroketoyobyrine.—A mixture of 100 mg. of ketoyobyrine and 200 mg. of palladium black was heated to 280° (metal-bath). After about fifteen minutes exactly the equivalent of one mole of hydrogen had been liberated; prolonged heating or higher temperature did not increase the amount of hydrogen (8.5 cc.). From the reaction mixture the dehydroproduct was obtained either by sublimation (280°, 0.001 mm.), or by recrystallization from a thimble with ethyl alcohol (twenty-four hours). The compound is very sparingly soluble in ethanol and forms fans of short needles of a yellowish-green color. The yield is almost quantitative. The crystals when powdered or sublimed have the same yellow color as ketoyobyrine and in solution they exhibit a similar powerful fluorescence; melting point 345–350° (transformation into prisms at 310°, mixed melting point with ketoyobyrine, 305–310°).

Anal. Calcd. for $C_{20}H_{14}ON_2$: C, 80.53; H, 4.69. Found: C, 80.32; H, 4.92.

Carboxyyobyrine.—Dehydroketoyobyrine (0.2 g.) was heated under reflux in 4 cc. of amyl alcohol containing 2 g. of caustic potash. A clear yellow solution was obtained after fifteen minutes, whereas ketoyobyrine requires many hours to go into solution under the same conditions. After ten hours water was added and the mixture was extracted with ether. The ethereal layer contained traces of ketoyobyrine, if that was a contaminant of the starting material, and traces of a fluorescent base yielding a picrate (4 mg.), m. p. 255°, showing no depression on admixture with norharmane picrate. The aqueous alkaline layer contained an acid which on acidification with glacial acetic acid separated as a colorless flocculent precipitate. When the alkaline cleavage was carried out in a glass vessel, silicic acid was precipitated first by adding mineral acid to the alkaline solution to *p*H 8.5. The flocculent amino acid (180 mg.) was obtained crystalline when its solution in dilute ammonia was allowed to stand overnight in a slightly evacuated desiccator. In another run, carboxyyobyrine was obtained in beautiful fine needles when it was reprecipitated from dilute alkaline solution with just the necessary amount of acetic acid and was allowed to stand for two days. The colorless aqueous acidic solution of the acid shows the characteristic pure blue harmane fluorescence. On heating the compound becomes yellow at about 100° and shows then the same melting point as dehydroketoyobyrine. For the analysis the substance has to be dried at room temperature.

Anal. Calcd. for $C_{20}H_{16}O_2N_2 \cdot H_2O$: C, 71.85; H, 5.40. Found: C, 71.46; H, 5.49.

Reconversion to Dehydroketoyobyrine.—When recrystallization of carboxyyobyrine was attempted by extracting it from a thimble with methanol in which the amino acid is sparingly soluble, all the yellow material which had crystallized overnight from the alcoholic solution consisted of dehydroketoyobyrine, m. p. 345°. When 20 mg. of carboxyyobyrine mixed with 40 mg. of soda lime was heated *in vacuo* to 350°, no yobyrine could be isolated from the negligible sublimate. The residue gave some dehydroketoyobyrine.

Acknowledgment.—We are indebted to Miss Adelaide Sutton who, through the courtesy of Dr. Elkan R. Blout (Polaroid Corporation, Cambridge), measured the ultraviolet spectra.

Summary

The structure of ketoyobyrine has been shown to be that of a lactam derived from carboxyyobyrine.

CAMBRIDGE 38, MASS. RECEIVED MARCH 15, 1948

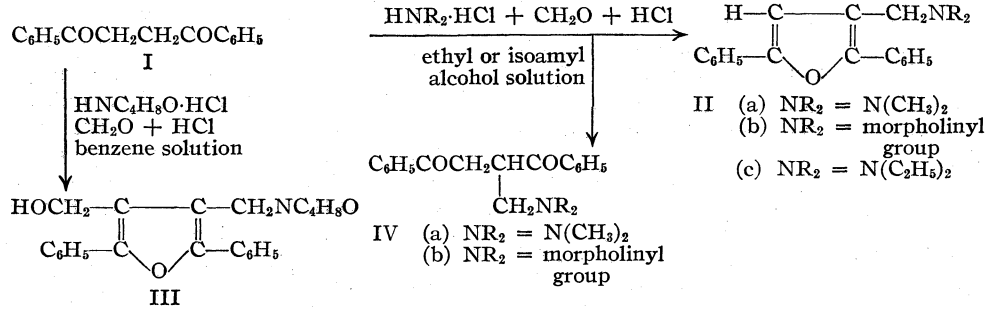
(14) All melting points are corrected.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Mannich Reaction with 1,2-Dibenzoylethane[1,2]

BY PHILIP S. BAILEY[3] AND ROBERT E. LUTZ

The Mannich reaction has been carried out with 1,2-dibenzoylethane, using secondary amine hydrochlorides and paraformaldehyde in ethyl or isoamyl alcohol solution and in benzene solution.[4]



In ethanol solution, using dimethylamine and morpholine hydrochlorides and refluxing for forty-eight hours, the products were the respective substituted furans (IIa and IIb), both of which have previously been made by other methods.[5] When

(1) A portion of the work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

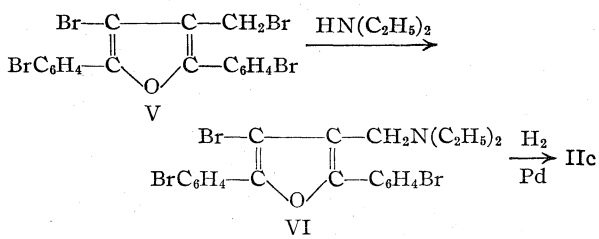
(2) Presented in combination with a paper from The University of Texas at the Chicago meeting of the American Chemical Society, April, 1948.

(3) Holder of Philip Francis du Pont Fellowships, 1942–1944. Present location, The University of Texas, Austin, Texas.

(4) For a discussion of the use of benzene as a solvent in the Mannich reaction see Fry, *J. Org. Chem.*, **10**, 259 (1945).

(5) Lutz and Bailey, THIS JOURNAL, **67**, 2229 (1945).

the reaction was carried out under less acidic conditions, low yields of the respective mono-(aminomethyl)-dibenzoylethanes (IV) were obtained. Never were any di-(aminomethyl)-dibenzoylethanes isolated. When diethylamine hydrochloride was used in ethanol solution, very little reaction occurred. When isoamyl alcohol was used as the solvent, however, a 32% yield of IIc was obtained. The structure of this compound was proved by the same method used in the proof of structure of the other (aminomethyl)-furans,[5] namely, conversions V to IIc.



When the reaction was carried out in benzene solution,[4] using morpholine hydrochloride, the product was a mixture from which was isolated some of the (morpholinylmethyl)-furan (IIb) and the known 3-(hydroxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran (III).[6,7] The respective yields of these products seem to vary with the acidity of the reaction medium. When 1% by volume of concentrated hydrochloric acid was used in the reaction mixture, compound III was the principal product, but when the amount of hydrochloric acid was cut in half, compound IIb was the principal product.

The basis for the structure assigned to compound III was its synthesis from compound IIb by a bromomethylation reaction followed by a hydrolysis of the resulting bromomethyl compound.[6] Further substantiating this structure was the reaction of the hydroxymethyl compound (III) with acetic anhydride and sulfuric acid or benzoic anhydride and sulfuric acid to yield the acetate or the benzoate, respectively.

Experimental[8]

Preparation of 1,2-Dibenzoylethane (I).—The 1,2-dibenzoylethane used in these reactions was prepared by the reduction of 1,2-dibenzoylethylene by means of stannous chloride and hydrochloric acid. Into a hot suspension of 200 g. of stannous chloride in a solution of 300 ml. of 8 *N* hydrochloric acid and 100 ml. of 95% ethanol, was poured with stirring a hot solution of 200 g. of *trans*-1,2-dibenzoylethylene in 1 liter of 95% ethanol. The mixture was then diluted with 100 ml. of water, cooled and filtered. Recrystallization of the crude dibenzoylethane (190 g., m. p. 125–133°) yielded 156 g. (76% yield) of material which melted at 145–147°.

3-(N-Diethylaminomethyl)-2,5-diphenylfuran Hydrochloride (IIc) (SN-3545)[9] from the Mannich Reaction in Isoamyl Alcohol Solution.—A mixture of 12 g. of 1,2-dibenzoylethane (I), 12 g. of diethylamine hydrochloride, 5 g. of paraformaldehyde, 1 ml. of concentrated hydrochloric acid and 50 ml. of isoamyl alcohol was refluxed for thirty hours, after which the solvent was evaporated under vacuum. An ether suspension of the residue was shaken with dilute hydrochloric acid until everything dissolved in one or the other of the layers, after which the ether layer was evaporated. From the residue was isolated 1.3 g. of 2,5-diphenylfuran which was identified by a mixture melting point with an authentic sample. The hydrochloric acid extract was neutralized with sodium carbonate and extracted with ether. The ether extract was washed with salt solution several times, dried over sodium sulfate and evaporated. An acetone solution of the residual oil was acidified with ethereal hydrogen chloride solution and diluted with dry ether. White crystals were obtained, which weighed 5.4 g. (32% yield) and melted at 168–175°. Several recrystallizations from acetone solution, by the addition of dry ether, raised the melting point to 177–179°.

Anal. Calcd. for $C_{21}H_{23}NO\cdot HCl$: C, 73.77; H, 7.08. Found: C, 73.74; H, 7.16.

The preparation also was attempted using other solvents. In the case of ethanol, reaction was obtained only when excess paraformaldehyde was added daily over a period of fifteen days; yield of IIc, 18%. When the reaction was carried out in benzene solution a mixture of basic products was obtained which was not studied further, due to difficulty in effecting a separation.

4-Bromo-2,5-di-(*p*-bromophenyl)-3-(N-diethylaminomethyl)-furan (VI).—A mixture of 2.8 g. of V[10] and 10 ml. of diethylamine in 25 ml. of isopropyl ether was allowed to react without attention for two days. The diethylamine hydrochloride which precipitated was filtered off and the filtrate was washed several times with salt water and dried over sodium sulfate. Evaporation of the ether solution and crystallization of the residue from 2-propanol gave 2.5 g. (91% yield) of white crystals, m. p. 95–98°; recrystallized from 2-propanol, m. p. 97–98°.

Anal. Calcd. for $C_{21}H_{20}Br_3NO$: C, 46.52; H, 3.72. Found: C, 46.34; H, 3.65.

In a separate experiment it was shown that 4-bromo-3-methyl-2,5-diphenylfuran will not react with amines under the above conditions.

3-(N-Diethylaminomethyl)-2,5-diphenylfuran (IIc) from 4-Bromo-2,5-di-(*p*-bromophenyl)-3-(N-diethylaminomethyl)-furan (VI).—Catalytic hydrogenolysis of 1 g. of VI in 50 ml. of ethanol with 1 g. of palladium-barium sulfate catalyst was carried out until the rate appreciably decreased, at which point 3.5 mole-equivalents of hydrogen had reacted. The reaction mixture was filtered and the filtrate evaporated; the residue was suspended in sodium carbonate solution and the mixture was extracted with ether. The ether extract was washed, dried over sodium sulfate and evaporated. An acetone solution of the residue, acidified with ethereal hydrogen chloride solution and diluted with absolute ether, yielded 0.6 g. of a white crystalline material (m. p. 177–178°), which was shown by a mixture melting point to be the same compound obtained from the Mannich reaction described above.

Oxidation of the furan with nitric acid in acetic acid solution gave an oil which resisted crystallization either as a free amine or as a hydrochloride.

3-(N-Morpholinylmethyl)-2,5-diphenylfuran Hydrochloride (IIb) from the Mannich Reaction in Ethanol Solution.—A mixture of 48 g. of dibenzoylethane (I), 25 g. of paraformaldehyde, 51 g. of morpholine hydrochloride, 200

(6) Lutz and Bailey, THIS JOURNAL, **68**, 2002 (1946).

(7) Due to an erroneous analysis, the fact was not at first apparent that this compound was identical with that reported in ref. 6. Thanks are due to Mr. Gene Nowlin, graduate student of The University of Texas, for subsequent work which led to the identification of III, and which will be reported soon in a paper from The University of Texas.

(8) All melting points reported here are corrected.

(9) The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned are tabulated in the monograph, F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Edwards Brothers, Ann Arbor, Michigan, 1947.

(10) Lutz and McGinn, THIS JOURNAL, **64**, 2583 (1942).

ml. of absolute ethanol and enough ethanolic hydrogen chloride to make the reaction mixture slightly acidic, was refluxed for one hundred and thirty-five hours. During this time an additional 2 g. of paraformaldehyde was added every twelve hours. The reaction mixture was worked up in a manner similar to that of the Mannich reaction using diethylamine hydrochloride. Thus was obtained 21 g. of 2,5-diphenylfuran and 30 g. of 3-(N-morpholinylmethyl)-2,5-diphenylfuran hydrochloride (IIb), both of which were identified by mixture melting points with known samples. The use of isoamyl alcohol as a solvent did not improve the yield.

1,2-Dibenzoyl-1-(N-morpholinylmethyl)-ethane (IVb) from the Mannich Reaction.—When a mixture of 4.7 g. of dibenzoylethane (I), 4.2 g. of morpholine hydrochloride, 1.8 g. of paraformaldehyde and 20 ml. of ethanol (no excess hydrogen chloride present) was refluxed for forty hours (1 g. of excess paraformaldehyde was added every twelve hours) and the reaction mixture was worked up as described above, 0.6 g. of dibenzoylethane was recovered in the non-basic extract and 1.6 g. (24% yield) of IVb (m. p. 80–82°) was found in the basic extract. It was isolated as the free amine and was identified by a mixture melting point with an authentic sample.[5]

3-(N-Dimethylaminomethyl)-2,5-diphenylfuran Hydrochloride (IIa) from the Mannich Reaction in Ethanol Solution.—A mixture of 12 g. of dibenzoylethane (I), 8 g. of dimethylamine hydrochloride, 5 g. of paraformaldehyde, 16 drops of concentrated hydrochloric acid and 50 ml. of absolute ethanol was refluxed for forty-three hours. On cooling, a precipitate formed and was filtered; 2.5 g., m. p. 75–135°; identified as dibenzoylethane after recrystallization. When the filtrate was worked up in the same manner as the Mannich reactions described above, 4.5 g. (31% yield) of white crystals (m. p. 217–220°) was obtained and identified as 3-(N-dimethylaminomethyl)-2,5-diphenylfuran hydrochloride (IIa) by a mixture melting point with an authentic sample.[5]

In another run in which one-half the amount of hydrochloric acid was used, 50% of the product was 1,2-dibenzoyl-1-(N-dimethylaminomethyl)-ethane hydrochloride (IVa); separated from the furan by fractional crystallization and identified by a mixture melting point with an authentic sample.[5]

The Mannich Reaction between 1,2-Dibenzoylethane (I), Paraformaldehyde and Morpholine Hydrochloride in Benzene Solution.—A mixture of 48 g. of dibenzoylethane (I), 51 g. of morpholine hydrochloride, 28 g. of paraformaldehyde, 200 ml. of benzene and 2 ml. of concentrated hydrochloric acid was refluxed for forty-eight hours. Two layers were present during the entire time. The solvent was then evaporated under reduced pressure and the residue was suspended in ether. When the resulting mixture was shaken with approximately 6 *N* hydrochloric acid, some material crystallized (15.3 g., m. p. 145–148°) and was identified as dibenzoylethane by a mixture melting point. The acid layer was separated and was neutralized with sodium carbonate. When this mixture was shaken with ether, some material crystallized and was filtered; 18 g., m. p. 152–165°. The filtrate was thoroughly extracted with ether and the ether extract, upon being washed, dried and evaporated, yielded an oil which was converted to a crystalline hydrochloride and identified as IIb by a mixture melting point; yield 1 g. The 18-g. batch of crystals melted at 176–177° after several recrystallizations from ethanol and was shown to be 3-(hydroxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran (III) by a mixture melting point with a known sample.[6] A small amount of the compound (III) was converted into a crystalline hydrochloride by acidifying an acetone solution of the material with ethereal hydrogen chloride solution; recrystallized from methyl ethyl ketone, m. p. 178–180° (it gave a large depression in a mixture melting point with the free amine).

Anal. Calcd. for $C_{22}H_{23}NO_3 \cdot HCl$: C, 68.47; H, 6.27. Found: C, 68.32, 68.29; H, 6.26, 6.11.

In another reaction in which only one-half the quantity of hydrochloric acid was used, the yield of III was one-third less, while the yield of IIb was 37%. In yet another experiment where the amount of paraformaldehyde was cut to one-half, the hydrochloric acid to one-fourth and the reaction mixture was refluxed for only one hour, IVb was the product in 8% yield. The recovery of dibenzoylethane was 91%.

3-(Acetoxymethyl)-4-(N-morpholinylmethyl)-2,5-diphenylfuran.—To a suspension of 2 g. of III in 9 ml. of acetic anhydride was added 7 drops of concentrated sulfuric acid. The mixture was allowed to stand for five minutes, after which time it was poured into water. The resulting mixture was neutralized with sodium carbonate and extracted with ether. After the ether extract was washed, dried and evaporated, the residue was converted into a hydrochloride by acidifying an acetone solution of it with ethereal hydrogen chloride solution. Upon cooling and filtering, 1.5 g. of material was obtained (m. p. 183–185°); recrystallized from 2-propanol, m. p. 187–188°.

Anal. Calcd. for $C_{24}H_{25}NO_4 \cdot HCl$: C, 67.36; H, 6.12. Found: C, 67.40, 67.52; H, 6.41, 6.18.

The acetoxy compound was not obtained when acetyl chloride was used in place of acetic anhydride.

The acetoxy compound was converted back to III by treatment with phosphorus pentachloride or methylmagnesium iodide followed by hydrolysis.

3-(Benzoyloxy)-4-(N-morpholinylmethyl)-2,5-diphenylfuran.—A mixture of 1 g. of III and 5 g. of benzoic anhydride was fused at 80°. To the fused mixture was added 4 drops of concentrated sulfuric acid. The reaction mixture was allowed to stand for fifteen minutes at 80°, after which time it was poured into water. The resulting aqueous mixture was extracted with ether and the ether extract was washed four times with dilute sodium hydroxide solution, dried over sodium sulfate, and evaporated. An acetone solution of the residue was acidified with ethereal hydrogen chloride solution, and the resulting crystals were filtered; yield, 1 g.; recrystallized from 2-propanol, m. p. 183–185°.

Anal. Calcd. for $C_{29}H_{27}NO_4 \cdot HCl$: C, 71.08; H, 5.76. Found: C, 71.16; H, 5.73.

The hydroxymethyl compound (III) was not affected by refluxing acetic acid–zinc dust mixture (thirty minutes).

Summary

The Mannich reaction with 1,2-dibenzoylethane has been carried out in benzene and in alcohol solutions. The products isolated were N-substituted 1-(aminomethyl)-1,2-dibenzoylethanes and 3-(aminomethyl)-2,5-diphenylfurans, and in one case 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran. Conditions favoring the formation of each type of product are described.

AUSTIN, TEXAS
CHARLOTTESVILLE, VIRGINIA

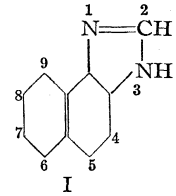
RECEIVED FEBRUARY 24, 1948

[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of 2- and 3-Substituted Naphth[1,2]imidazoles

BY EARL W. MALMBERG[1] AND CLIFF S. HAMILTON

Many of the compounds which have been synthesized in this Laboratory because of possible interest as antimalarial agents have included the benzoquinoline nucleus as part of the structure.[2] The syntheses of a number of similar compounds which are based on the naphth[1,2]imidazole nucleus (I) have been studied and are reported in the



I

present investigation. The antimalarial screening of one derivative of the proposed nucleus, 2-aminonaphth[1,2]-imidazole, was reported after the inception of this work; the quinine equivalent was less than 0.08.[3]

The Phillips reaction[4] was used in the preparation of the 2,3-disubstituted naphth[1,2]imidazoles. The parent diamine in the disubstituted series is 1-amino-2-methylaminonaphthalene. The most promising synthesis for this unreported diamine was by reduction of 1-nitroso-2-methylaminonaphthalene. The necessary aminonitroso compound was prepared very simply according to the method of Fischer, Dietrich, and Weiss.[5] Methods usually employed for the reduction of nitroso compounds failed because of the formation of extremely insoluble complexes between the aminonitroso compound and various metallic ions. Reduction with molecular hydrogen and Raney nickel catalyst proceeded very smoothly and in excellent yields.

Literature reports[6] and preliminary experiments with ethyl ϵ-diethylaminocaproate indicated that amino acids do not undergo the Phillips reaction, and so the tertiary amine groups which were desired in the final structure were introduced into the molecule after the ring closure; the secondary hydroxyl group could be present in the molecule of the carboxylic acid. The desired intermediates were therefore prepared from the acids listed below, chloroacetic acid and β-chlorolactic acid. The respective products, 2-chloromethyl-3-methylnaphth[1,2]imidazole and 2-(α-hydroxy-β-choroethyl)-3-methylnapth[1,2]imidazole, were then treated with morpholine and piperidine to give products of the desired structure.

The naphth[1,2]imidazoles which are substituted only in the 2-position can be regarded as derived from 1,2-diaminonaphthalene. However, the Phillips reaction could not be successfully applied to this diamine because of the insolubility of the amine salt in acid of the required strength. Attempts to prepare the desired intermediate by fusion of the diamine and chloro acids were also unsuccessful. Hydroxy compounds have been converted to chloro derivatives in the benzimidazole series quite readily[6,7] and therefore 2-hydroxymethylnaphth[1,2]imidazole was prepared by fusion of the diamine with glycolic acid, the method used by Sachs for the preparation of a perimidine.[8] However, preliminary experiments on the conversion of 2-hydroxymethylnaphth[1,2]imidazole to the desired chloromethyl compound by means of thionyl chloride showed no promise of success because of the insolubility of the hydroxy compound and therefore a third and successful approach was made. 1-Nitro-2-aminonaphthalene was converted to N-(1-nitro-2-naphthyl)-α-chloroacetamide by treatment with chloroacetyl chloride; the halogen on the acetyl group of this compound is active and readily reacted with an amine such as morpholine. The product of this reaction, N-(1-nitro-2-naphthyl)-α-morpholinoacetamide, was converted to the desired compound, 2-morpholinomethylnaphth[1,2]imidazole, by two different methods. Reductive ring closure,[9] refluxing the nitro amide in alcohol with zinc and hydrochloric acid, accomplished the transformation in one step. A somewhat longer but more satisfactory synthesis was through the catalytic reduction of the nitro compound to N-(1-amino-2-naphthyl)-α-morpholinoacetamide; the ring closure was then accomplished by the method of Kelly and Day.[9] In this series the placement of the hydrogen on either nitrogen of the ring is immaterial since the tautomeric nature of the structure has been demonstrated.[9] The compounds of the series with hydrogen on the heterocyclic nitrogen rather than a methyl group were characterized by a very high melting point, very low solubility in organic solvents, and solubility in both aqueous alkali and acid.

Experimental[10]

1-Nitrosonaphthol-2.—This nitroso compound was prepared by the direct nitrosation of naphthol-2.[11] For best results in the subsequent catalytic reduction it was

(1) Parke, Davis and Company Fellow.

(2) Benson and Hamilton, THIS JOURNAL, **68**, 2644 (1946).

(3) "A Survey of Antimalarial Drugs 1941–1945," ed. by F. Y. Wiselogle, J. W. Edwards, Ann Arbor, Mich., 1946, SN. 13,406.

(4) Phillips, *J. Chem. Soc.*, 2820 (1929).

(5) Fischer, Dietrich and Weiss, *J. prakt. Chem.*, **100**, 167 (1920).

(6) Hughes and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 209 (1938).

(7) Skolnik, Miller and Day, THIS JOURNAL, **65**, 1854 (1943).

(8) Sachs, *Ann.*, **365**, 108 (1909).

(9) Kelly and Day, THIS JOURNAL, **67**, 1074 (1945).

(10) All melting points are corrected for stem emergence. We wish to thank Mr. Anton Kashas for the performance of a number of the carbon and hydrogen analyses.

(11) Marvel and Porter, "Organic Syntheses," Coll. Vol. I, ed. 2, John Wiley and Sons, New York, N. Y., 1941, p. 411.

necessary to recrystallize the crude yield from 88–100° ligroin.

1-Nitroso-2-methylaminonaphthalene (II).—A mixture of 100 ml. of water and 127 ml. of aqueous methylamine (25% methylamine by weight, 0.94 mole) was cooled to 15° and 34.6 g. (0.2 mole) of recrystallized 1-nitroso-naphthol-2 was slowly added. The mixture was warmed to 35° to complete solution of the salt. The mixture was allowed to stand at room temperature for twenty-four hours, during which time the product crystallized out in black platelets. Purification by solution in dilute hydrochloric acid, filtration, and precipitation with dilute ammonium hydroxide was sufficient for excellent results with the subsequent catalytic reduction. The product weighed 33.5 g. (90%). A sample which was recrystallized from methanol melted at 145–146°; literature values vary from 141–142° to 148–149°.[5]

1-Amino-2-methylaminonaphthalene Dihydrochloride (III).—A suspension of 18.6 g. of II in 115 ml. of absolute ethanol was reduced at room temperature with Raney nickel catalyst and molecular hydrogen at 50 lb. pressure. The calculated quantity of hydrogen was absorbed in twenty to twenty-five minutes and the pressure was constant thereafter. After removal of the catalyst, dry hydrogen chloride was passed into the cooled alcoholic solution and the product isolated as the dihydrochloride; yield, 23.3 g. (95%).

This new diamine was found to be an unstable oil with a blue fluorescence; it was always isolated and used as the dihydrochloride. The dihydrochloride salt, after solution in hot water and treatment with charcoal and recrystallization from dilute hydrochloric acid melted with decomposition at 194–196°. The diamine was characterized by the conversion to a known derivative and to three new compounds which are described in the following four procedures; the Phillips reaction with acetic, chloroacetic, lactic and β-chlorolactic acid was used in these conversions. A known compound, 2,3-dimethylnaph[1,2]imidazole,[12] was formed with acetic acid; the identities of the other three products were confirmed by the elementary analysis and by the results of succeeding reactions.

2,3-Dimethylnaphth[1,2]imidazole (IV).—A mixture of 1.0 g. of III, 1.6 ml. of acetic anhydride, and 8 ml. of 4 *N* hydrochloric acid was heated under reflux for one hour. The cooled solution was neutralized with solid sodium bicarbonate, whereupon a quantitative yield of 2,3-dimethylnaphth[1,2]imidazole was obtained in crystalline form. When recrystallized from dilute alcohol and from benzene, the product melted at 142–143°, the same value as reported in the literature.[12]

2-(α-Hydroxyethyl)-3-methylnaphth[1,2]imidazole (V).—A mixture of 1.8 g. (0.02 mole) of lactic acid and 2.45 g. (0.01 mole) of III was refluxed in 24 ml. of 4 *N* hydrochloric acid for six hours. The reaction mixture was cooled in ice and neutralized carefully with solid sodium bicarbonate. The crude yield of crystalline product weighed 2.2 g. (96%). A sample which was recrystallized from benzene and from alcohol melted at 184.1–184.6°.

Anal. Calcd. for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24. Found: C, 74.22; H, 6.37.

2-Chloromethyl-3-methylnaphth[1,2]imidazole (VI).—Technical chloroacetic acid (5.64 g., 0.06 mole) was dissolved in 72 ml. of 4 *N* hydrochloric acid and the mixture was heated on a steam-bath. Three 1.23-g. portions of III (total of 3.69 g., 0.015 mole) was added at thirty-minute intervals during the first hour of heating. The mixture was heated a total of four hours, after which it was cooled in ice, a layer of ether added, and the mixture carefully neutralized with sodium bicarbonate. The tar which formed during the addition of the first half of the total amount of base was skimmed off before the product began to precipitate. The dried crude yield was extracted with 75 ml. of 2:1 benzene–ligroin, the extract was treated with charcoal, filtered, and the product crystallized from the cooled solution; yield 1.2 g. (34%).

(12) Meldola and Lane, *J. Chem. Soc.*, **85**, 1602 (1904).

VI, similar to an analogous compound in the benzimidazole series,[13] is a powerful skin irritant. The compound was crystallized from benzene–ligroin mixtures and from absolute alcohol. The substance turns yellow at 150–155° and melts with decomposition at 160–162°.

Anal. Calcd. for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81. Found: C, 67.70; H, 4.93.

2-(α-Hydroxy-β-chloroethyl)-3-methylnaphth[1,2]imidazole (VII).—A mixture of β-chlorolactic acid (7.46 g., 0.16 mole) and III (9.8 g., 0.04 mole) in 96 ml. of 3 *N* hydrochloric acid was heated on a steam-bath for seven hours. The subsequent procedure was the same as in the preparation of VI except that 135 ml. of benzene–ligroin was used for the extraction. A yield of 2.96 g. (29%) was obtained from experiments in which two of three separate lots of β-chlorolactic acid were used. With a third lot, identical with the other two as far as physical tests indicated, a yield of only 8–10% could be obtained. The product was recrystallized from benzene and from alcohol; m. p., 168.9–169.0°.

Anal. Calcd. for $C_{14}H_{13}ON_2Cl$: C, 64.49; H, 5.03. Found: C, 64.48; H, 5.11.

β-Chlorolactic Acid.—This acid was prepared by the oxidation of glycerol α-monochlorohydrin.[14] The chlorohydrin was made by the procedure of "Organic Syntheses" and redistilled before use[15]; the fraction which was collected between 117 and 120° at 13 mm. was used in the oxidation. The time required for the oxidation with nitric acid was considerably longer than that reported by Koelsch, but it was also noted that just a few degrees of variation in room temperature had a marked effect on the rate of this exothermic reaction.

A modified method of isolating the desired product was used. The oily crystalline mass of crude product was subjected to prolonged suction on a filter until practically all the oil was removed. The melting point of this product, 77–78°, was excellent, comparable to the values reported for recrystallized material, 77°[14] and 78.5–79.0°.[16]

2-Piperidinomethyl-3-methylnaphth[1,2]imidazole (VIII).—A solution of VI and a three-fold excess of piperidine in benzene was refluxed in benzene for two hours. The piperidine hydrochloride was removed by washing and the product isolated in 97% yield by evaporation of the benzene solution. The product was recrystallized from dilute alcohol and from ligroin; m. p., 134.8–135.0°.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58. Found: C, 77.46; H, 7.63.

2-Morpholinomethyl-3-methylnaphth[1,2]imidazole (IX).—The same procedure was used as in the preparation of VIII, with morpholine in place of the piperidine. This very similar product melted at 134.0–134.4°.

Anal. Calcd. for $C_{17}H_{19}ON_3$: C, 72.58; H, 6.81; N, 14.94. Found: C, 72.67; H, 6.82; N, 14.92.

2-(α-Hydroxy-β-piperidinoethyl)-3-methylnaphth[1,2]imidazole (X).—A solution of VII in piperidine was heated on a steam-bath for three hours. The resulting mixture was poured into water and the product allowed to crystallize; the crude yield was 95%. The product was recrystallized from dilute alcohol and from benzene–ligroin. The crystals which were obtained from anhydrous solvents or which were very carefully dried melted at 149.2–149.6°.

Anal. Calcd. for $C_{19}H_{23}ON_3$: C, 73.76; H, 7.49. Found: C, 73.83; H, 7.61.

2-(α-Hydroxy-β-morpholinoethyl)-3-methylnaphth[1,2]imidazole (XI).—This compound was prepared from VII and morpholine by the same procedure as for the preparation of X. The product possessed the same properties as X, with respect to solubility, etc.; the melting point was 168.4–169.0°.

(13) Bloom and Day, *J. Org. Chem.*, **4**, 14 (1939).

(14) Koelsch, THIS JOURNAL, **52**, 1105 (1930).

(15) Conant and Quayle, "Organic Syntheses," Coll. Vol. I, ed. 2, John Wiley, New York, N. Y., 1941, p. 294.

(16) Smith, *Z. physik. Chem.*, **81**, 366 (1913).

Anal. Calcd. for $C_{18}H_{21}O_2N_3$: C, 69.43; H, 6.80. Found: C, 69.27; H, 6.87.

N-(1-Nitro-2-naphthyl)-α-chloroacetamide (XII).—Seven grams (0.07 mole) of precipitated chalk was suspended in a solution of 12.1 g. (0.064 mole) of 1-nitro-2-aminonaphthalene in 32 ml. of dry dioxane, and to this mixture a solution of 9.6 g. (0.085 mole) of redistilled chloroacetyl chloride in 18.6 ml. of dry dioxane was slowly added. The mixture was stirred and kept between 20 to 25° during the addition and then allowed to stand at room temperature for several days. The product was precipitated by the slow addition of 200 ml. of water, and after acidification the product was collected by filtration. The crude product was purified by crystallization from ligroin. By use of a Soxhlet extractor a yield of 88% of the purified product was obtained. A sample which was crystallized from benzene and from alcohol melted at 119.8–120.6°.

Anal. Calcd. for $C_{12}H_9O_3N_2Cl$: C, 54.33; H, 3.42. Found: C, 54.39; H, 3.50.

N-(1-Nitro-2-naphthyl)-α-morpholinoacetamide (XIII).—A solution of 18.0 g. (0.075 mole) of XII and 16.3 g. (0.1875 mole) of morpholine in 120 ml. of 80% ethanol was refluxed for one hour. The resulting mixture was cooled slowly, finally to −10°, and 19.3 g. (82%) of very pure product crystallized. A sample which was recrystallized from benzene–ligroin and from absolute alcohol melted at 131.9–132.5°.

Anal. Calcd. for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.44. Found: C, 61.04; H, 5.50.

N-(1-Amino-2-naphthyl)-α-morpholinoacetamide (XIV).—Fifteen grams of XIII was dissolved in 100 ml. of warm absolute alcohol, Raney nickel catalyst was added, and hydrogen under 50 pounds pressure admitted. The calculated quantity of hydrogen was slowly absorbed and the pressure subsequently remained constant. The final solution was warmed to dissolve the product which crystallized during the reaction, filtered, and upon cooling 8.0 g. of pure product (58%) was obtained. By precipitating the product as the dihydrochloride a yield of 82% was obtained. A sample which was recrystallized from benzene–ligroin, acetone, and absolute ethanol melted at 163.9–164.4°.

Anal. Calcd. for $C_{16}H_{19}O_2N_3$: C, 67.34; H, 6.71. Found: C, 67.36; H, 6.76.

2-Morpholinomethylnaphth[1,2]imidazole Dihydrochloride (XV): Reductive Ring Closure.—One gram of XIII was dissolved in 100 ml. of warm alcohol, 1.0 g. of granulated zinc was placed in the flask, and the solution was refluxed for seven hours. During this time 10 ml. of concentrated hydrochloric acid was added very slowly. The salt of the ring closure product precipitated during the reaction. This salt was freed from inorganic impurities by solution in water and the free base was obtained as an amorphous white solid upon neutralization of the solution with sodium bicarbonate. The dihydrochloride salt was prepared by addition of hydrogen chloride to an ethereal solution of the free base; the characteristics of this salt are described in the following section.

Ring Closure of XIV in Xylene.—One gram of XIV was refluxed in 80 ml. of xylene for one hour. The product was extracted with acid, the solution treated with charcoal, neutralized, and finally the amorphous free base was again isolated as the dihydrochloride salt. The amorphous free base was soluble in dilute acid and alkali and in organic solvents. The dihydrochloride was purified by recrystallization from ethanol which contained 3 to 4% of water; m. p. 241–243°.

Anal. Calcd. for $C_{16}H_{17}ON_3 \cdot 2HCl$: C, 56.47; H, 5.63; Cl, 20.84. Found: C, 56.24; H, 5.73; Cl, 20.74.

N-(1-Nitro-2-naphthyl)-α-anilinoacetamide.—A solution of 1.2 g. (0.0045 mole) of XII and 1.9 g. (0.02 mole) of aniline in 25 ml. of absolute ethanol were heated on a steam-bath for six hours. During this time the volume of solvent was allowed to decrease to 15 ml., and upon cooling the final mixture a precipitate of pure crystalline product was obtained which weighed 1.3 g. (87%). This compound was insoluble in dilute acid, but could be recrystallized from benzene–ligroin and alcohol; m. p. 171–172°.

Anal. Calcd. for $C_{18}H_{15}O_3N_3$: C, 67.28; H, 4.71. Found: C, 67.44; H, 4.84.

1,2-Diaminonaphthalene (XVI).—1-Nitro-2-aminonaphthalene in alcoholic solution was reduced at room temperature with Raney nickel catalyst and molecular hydrogen at 50 lb. pressure. The solvent was evaporated to a small volume and the product precipitated by the careful addition of water; yield, 71%. The crude product melted at 91–92°; literature values vary from 90–96°.[17]

2-Hydroxymethylnaphth[1,2]imidazole (XVII).—A mixture of XVI (3.6 g., 0.023 mole) and glycolic acid (1.8 g., 0.024 mole) was heated slowly up to 150°. The initially fluid mixture became viscous after a considerable amount of water had been lost, and after twenty minutes of heating 10 ml. of glycerol was added. Heating was continued for a total of two hours, and then the mixture was poured into 100 ml. of water. Ten milliliters of 6 *N* hydrochloric acid was added to the mixture, the solution was heated to boiling, treated with charcoal, and filtered while hot. The hydrochloride of XVII crystallized from the filtrate upon cooling; yield, 45%.

The free base is soluble in dilute acid, dilute alkali, and alcohol; it is very sparingly soluble in other organic solvents, but it can be recrystallized from acetone; m. p. 253–255° (dec.).

Anal. Calcd. for $C_{12}H_{10}ON_2$: C, 72.71; H, 5.09. Found: C, 72.78; H, 5.18.

Summary

A new diamine, 1-amino-2-methylaminonaphthalene, was prepared by reduction of 1-nitroso-2-methylaminonaphthalene. Naphth[1,2]imidazoles which are substituted in the 2- and 3-positions were prepared by the Phillips reaction between this diamine and acetic, lactic, chloroacetic, and β-chlorolactic acids. The products from the latter two acids were treated with piperidine and morpholine to give compounds of the desired structures, 2-piperidinomethyl-3-methylnaphth[1,2]-imidazole, 2-morpholinomethyl-3-methylnaphth-[1,2]imidazole, 2-(α-hydroxy-β-piperidinoethyl)-3-methylnaphth[1,2]imidazole, and 2-(α-hydroxy-β-morpholinoethyl)-3-methylnaphth[1,2]imidazole.

Naphth[1,2]imidazoles which are substituted only in the 2-position were prepared by the chloroacetylation of 1-nitro-2-aminonaphthalene, reaction of the chloro compound with morpholine to give N-(1-nitro-2-naphthyl)-α-morpholinoacetamide, and conversion of this compound to 2-morpholinomethylnaphth[1,2]imidazole by two different methods.

LINCOLN, NEBRASKA RECEIVED JANUARY 14, 1948

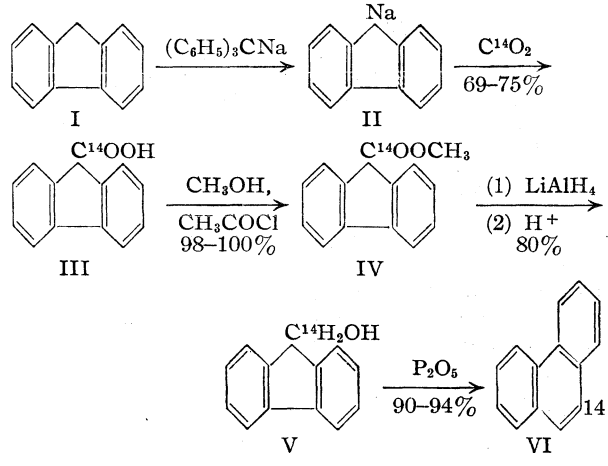
(17) Bamberger and Schieffelin, *Ber.*, **22**, 1376 (1889).

[CONTRIBUTION FROM THE OAK RIDGE NATIONAL LABORATORY]

The Synthesis of Phenanthrene-9-C^{14} [1,2]

BY CLAIR J. COLLINS

Due to the widespread interest in cancer producing substances, it appeared that a simple method for introducing carbon-14 in reasonable yields into aromatic polynuclear hydrocarbons should be of value. Accordingly, a synthesis of phenanthrene containing carbon-14 in the 9-position (VI) which the author has designated[3] phenanthrene-9-C^{14} has been effected by means of the Wagner rearrangement[4] of 9-fluorenemethannol-10-C^{14} (V). A new synthesis of the latter compound has been developed. Fluorene (I) was converted to 9-fluorenesodium (II) by interaction with triphenylmethylsodium. Carbonation with carbon dioxide-C^{14} yielded 9-fluorenecarboxylic acid-10-C^{14} (III). Reduction of the methyl ester (IV) with lithium aluminum hydride[5] produced 9-fluorenemethanol-10-C^{14} (V).



The complete synthesis was first worked out with non-radioactive materials, and each compound in the series was purified and characterized. The series was finally effected with purification only at the phenanthrene stage. The generality of this synthetic method is now under investigation.

Acknowledgment.—The author wishes to thank Professor Weldon G. Brown, of the University of Chicago, for the design of the extraction apparatus (Fig. 2) as well as for his many suggestions during the course of this work.

Experimental

Determination of Radioactivity.—Carbon-14 determinations were carried out by measuring the ionization current of carbon dioxide-C^{14} by means of a dynamic condenser electrometer.[6,7] The wet combustion method[8] of Van Slyke, Folch and Plazin was employed to oxidize 9-fluorenecarboxylic acid-10-C^{14} and phenanthrene-9-C^{14} (1–5 mg. samples). The carbon dioxide thus formed was collected in an ionization chamber which had previously been evacuated, using nitrogen to sweep the carbon dioxide into the chamber and to fill it to atmospheric pressure. Barium carbonate-C^{14} samples were similarly analyzed after decomposition with dilute perchloric acid. The conversion of the measured ionization currents to activities in millicuries was made on the basis of data obtained in this laboratory by Dr. W. B. Leslie employing similar chambers and a barium carbonate sample of known isotopic composition.

9-Fluorenecarboxylic Acid (III).[9]—The vacuum line shown in Fig. 1 was used for this preparation. In a typical run, 100 mg. of barium carbonate was weighed into flask A which could be placed directly on the balance pan. The apparatus was then swept with nitrogen. The exhaust nitrogen was passed through Drierite, a barium hydroxide bubbler and soda-lime. Decomposition of the barium carbonate was effected by addition of 5–8 cc. of 5 *M* perchloric acid. Next, nitrogen was passed through the system at a convenient rate for fifteen minutes. The cooling mixture surrounding the Dry Ice trap was kept at −50° to −55° by adjusting the amount of Dry Ice in the $CHCl_3$–CCl_4 mixture. This trap served to collect water vapor; when cooled to Dry Ice temperature, a significant amount of carbon dioxide was retained. Carbon dioxide was frozen in the liquid nitrogen trap. After fifteen minutes the acid decomposition mixture was heated gently with a free flame to liberate the last traces of carbon dioxide. In the reaction flask (B), 3.5 cc. of a stock triphenylmethyl sodium solution, prepared from 2.0 g. of sodium, 5.0 g. of triphenylchloromethane, 40 cc. of dry ether and 40 cc. of dry benzene, by the procedure of Bachmann and Wiselogle[10] was added to 150 mg. of fluorene (m. p. 114.0–114.5°)[11] and the flask was joined to the line. The entire operation was carried out under dry nitrogen. After stirring for three minutes, by means of a magnetic stirring bar, the color changed from deep red to light orange, and the mixture was frozen in liquid nitrogen. The two traps (b, c, Fig. 1) and the reaction flask (B) were evacuated to a pressure of less than 1 mm. of mercury. The carbon dioxide was then distilled from trap c into reaction flask B by cooling the latter with liquid nitrogen, and the flask was isolated from the rest of the line. Upon warming to a

(1) This paper is based on work performed under Contract No. W-35-058-eng-71 for the Atomic Energy Project at the Oak Ridge National Laboratory.

(2) Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September 15, 1947.

(3) The carbon-14 labeled compounds described in this paper have been named by analogy to the rules set down in *Chemical Abstracts* (**39**, 5874–5875 (1945)) for deuterium and tritium. Since the prefix "deuterio" is not recommended for compounds containing deuterium, use of the term "radio" to denote the presence of carbon-14 has been avoided. Unlike deuterium nomenclature, however, the present author recommends the use of capital C in preference to lower case *c* for carbon-14 to avoid confusion with the lower case letters denoting bridgehead positions 4a, 4b, 8a, and 10a in phenanthrene. At tracer levels of C^{14} concentrations, "phenanthrene-9-C^{14}" and "phenanthrene-9,10-C^{14}_2" are indistinguishable because of the equivalence of the 9- and 10- positions. Pending the adoption of a formal convention the simpler designation has been used.

(4) Brown and Bluestein, THIS JOURNAL, **62**, 3256 (1940).

(5) Nystrom and Brown, *ibid.*, **69**, 1197 (1947); *ibid.*, **69**, 2548 (1947).

(6) Palevsky, Swank and Grenchik, *Rev. Sci. Instr.*, **18**, 298 (1947).

(7) Scherbatskoy, Gilmartin and Swift, *ibid.*, **18**, 415 (1947).

(8) Van Slyke, Folch and Plazin, *J. Biol. Chem.*, **136**, 509 (1940).

(9) Burtner and Cusic, THIS JOURNAL, **65**, 264 (1943).

(10) Bachmann and Wiselogle, *ibid.*, **58**, 1943 (1936).

(11) All melting points were determined on a Fisher–Johns melting point block.

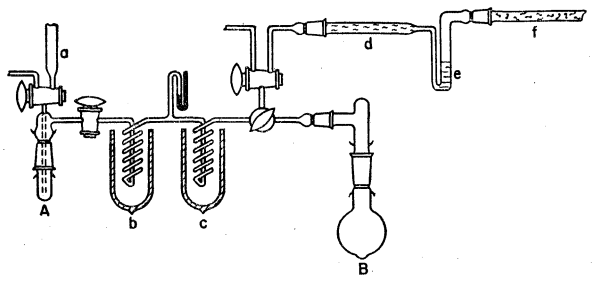


Fig. 1.—Carbonation apparatus: a, perchloric acid funnel; b, Dry Ice trap; c, liquid nitrogen trap; d, drierite; e, barium hydroxide solution; f, soda lime.

point at which the magnetic bar would just turn in the mixture, the reaction was complete, as indicated by a zero pressure in the system when the mixture was cooled to Dry Ice temperature. After admitting nitrogen, flask B was detached and 10 cc. of water was added to it. The layers were separated by means of the extraction apparatus shown in Fig. 2. The ether–benzene layer was washed twice with 5-cc. portions of water, and the combined aqueous layers were washed twice with 3-cc. portions of ether. Next, 10 cc. of 1 *N* hydrochloric acid was added to the aqueous layer, forming a white precipitate which was usually filtered directly when non-radioactive material was used. With radioactive material, however, the mixture was not filtered, but was treated with four 4-cc. portions of ether. The ether layer was washed once with 4 cc. of water, and then treated with three 4-cc. portions of saturated sodium bicarbonate solution. The bicarbonate layer, after one washing with 3 cc. of ether, was decomposed with 10 cc. of 6 *N* hydrochloric acid. Extraction with ether and concentration yielded 73–80 mg. of 9-fluorenecarboxylic acid (III); m. p. 222–226°. Consistent yields of 69–75% were obtained. The best yield was 86%.

Methyl 9-Fluorenecarboxylate (IV).—To 115.5 mg. of 9-fluorenecarboxylic acid (III) was added a chilled mixture of 5.0 cc. of methanol and 0.1 cc. of acetyl chloride. After standing at room temperature for one hour the contents of the flask were taken to dryness, yielding 120 mg. of methyl 9-fluorenecarboxylate (IV), m. p. 63.0–63.5°, 98%.

9-Fluorenemethanol (V).[12]—To 108 mg. of methyl 9-fluorenecarboxylate (IV) in 5.0 cc. of ether was added 10 cc. of 0.15 *M* lithium aluminum hydride solution (in ether). The mixture was stirred for ten minutes and then treated with 10 cc. of moist ether followed by 5.0 cc. of 6 *N* hydrochloric acid. The layers were separated, and the ether layer was washed with 5.0 cc. of water, and taken to dryness, yielding 82.4 mg. of crude alcohol melting at 80–85° (87%). One crystallization gave a product melting at 94–96°. The carbinol (7.7 mg.) was converted to 6.3 mg. (90%) of phenanthrene (VI) by the procedure of Brown and Bluestein.[4]

Phenanthrene-9-C^{14} (VI) Synthesis from Barium Carbonate-C^{14}.—The carbonation reaction was carried out as described elsewhere in this paper using 211.3 mg. of $BaC^{14}O_3$ containing 11.65 millicuries of carbon-14 per mole. Decomposition of this material produced 46.8 mg. of carbon dioxide-C^{14} (47.2 mg. theoretical) determined by direct weight in a gas weighing bulb. This was distilled into 9-fluorenesodium prepared from 300.0 mg. of fluorene and 7–8 cc. of triphenylmethylsodium solution.[10] The yield of 9-fluorenecarboxylic acid-10-C^{14} was 164.5 mg. (73%) whose activity was 11.62 millicuries carbon-14 per mole. To 122.0 mg. of this acid was added 5.0 cc. of methanol and 0.15 cc. of acetyl chloride. After standing for one hour at room temperature, the solution was concentrated in an air stream and desiccated to constant weight of 124.4 mg. over phosphorus pentoxide. This material was dissolved in 7 cc. of ether and to it was added 10 cc. of 0.16 molar lithium aluminum hydride solution. After stirring for fifteen minutes, 5 cc. of moist ether was added, followed by 5 cc. of 6 *N* hydrochloric acid. The layers were separated, the ether layer was washed with 5.0 cc. of water and taken to dryness and desiccated, yielding 114.8 mg. of an oil, which was dissolved in 10 ml. of xylene (doubly distilled over phosphorus pentoxide). To this solution was added 200–400 mg. of phosphorus pentoxide, and the mixture was heated under reflux for thirty minutes. After cooling, 5 cc. of water was added. The layers were separated and the xylene layer was washed twice with 5-cc. portions of water and concentrated and desiccated, yielding 170 mg. of an oil, which was transferred to a centrifuge tube fitted with a 19/38 female joint. This centrifuge tube was so designed that it could replace flask 1 of the extraction apparatus (Fig. 2). To this oil was added 60 mg. of picric acid and then 3.0 cc. of saturated ethanolic picric acid solution. The tube was heated with a free flame until a clear solution resulted; it was then allowed to cool. The phenanthrene picrate was separated by centrifuging, the supernatant liquid being drawn off using the extraction apparatus (Fig. 2). The picrate was decomposed with dilute aqueous sodium hydroxide solution, and extracted with ether, which was washed with water and concentrated. A repetition of this process with the solid so obtained yielded 72.5 mg. of phenanthrene-9-C^{14}, m. p. 94–95°; activity, 10.78 millicuries carbon-14 per mole. The over-all yield from barium carbonate was 51%. One crystallization from ethanol yielded white crystals melting at 96–97°. The picrate of this material melted at 141°. There was no depression of melting point when this material was mixed with an authentic sample of phenanthrene.

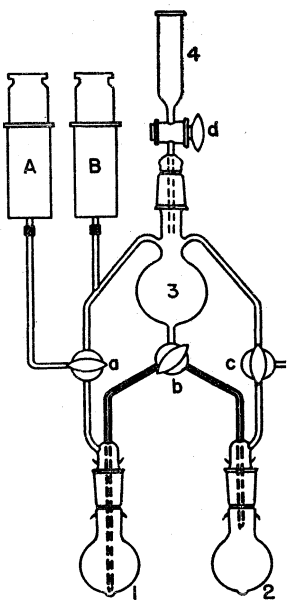


Fig. 2.—Extraction apparatus.

Extraction Procedure.—All extractions were carried out in the apparatus sketched in Fig. 2. The 50-cc. flasks 1 and 2 were interchangeable and were used in the carbonation apparatus (Fig. 1) as the reaction flask B and also in the lithium aluminum hydride reductions as the reactor vessels. This procedure prevented mechanical loss, and kept laboratory contamination with carbon-14 at a minimum. Chromatographic adsorptions were effected by replacing flask 2 (Fig. 2) with a chromatograph tube sealed to a 19/38 female glass joint.

The layers to be separated were placed in flask 1. By proper setting of the stopcocks, downward pressure on the plunger in cylinder A forced both layers into vessel 3 and also moved the plunger in cylinder B upward. Mixing was effected by pressing plunger A downward and forcing air through the two layers in 3. Solvents were added through 4, and by manipulation of stopcock b, liquid could be placed in flasks 1 and 2.

Summary

Fluorene (I) has been converted to 9-fluorenecarboxylic acid-10-C^{14} (III) by carbonation of 9-fluorenesodium (II) with carbon dioxide-C^{14}. Lithium aluminum hydride reduction of the methyl ester (IV) yielded 9-fluorenemethanol-10-

(12) The reduction of the free acid (III) proceeds very slowly, and even after twenty-four hours approximately 10% of the starting material is recovered. Further, prolonged treatment of the acid with lithium aluminum hydride in ether solution decreases the yield of carbinol.

C^{14} (V). Dehydration of V with phosphorus pentoxide was accompanied by a Wagner rearrangement to form the desired phenanthrene-9-C^{14} (VI). The over-all yields of VI, based on barium carbonate, were 50–55%.

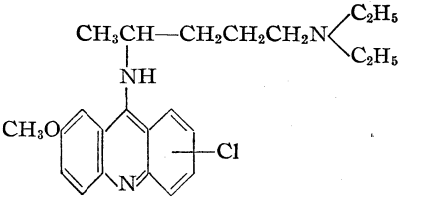
OAK RIDGE, TENNESSEE RECEIVED FEBRUARY 6, 1948

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Nuclear Isomers of Quinacrine

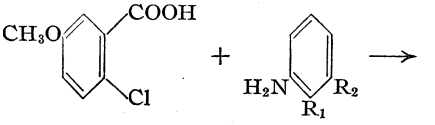
BY WILLIAM G. DAUBEN[1]

During the past few years much work has been done on the synthesis of compounds related to Quinacrine. However, of the four possible isomers of this compound which have the methoxyl

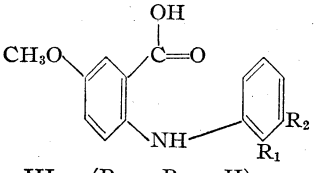


group in position two of the acridine nucleus and the chlorine atom in the opposite, nitrogen-free ring, only two have been reported. They are the 2-methoxy-6-chloro-9-substituted-aminoacridine[2] (Quinacrine) and the related 7-chloro isomer.[3] The present paper is concerned with the synthesis of the 5-chloro and the 8-chloro isomers.[4]

Following the observations of Ullmann and Kipper[5] that 2-chloro-5-methoxybenzoic acid[6] (I) can be used in the Ullmann condensation to prepare substituted N-phenylanthranilic acids (III), this compound (I) was utilized as the precursor of the desired methoxyl-substituted ring of the acridine. When the above acid (I) was allowed to react with *m*-chloroaniline (IIa) in the presence of anhydrous potassium carbonate and copper powder in boiling isoamyl alcohol, N-(3′-chlorophenyl)-5-methoxyanthranilic acid (IIIa) was formed in a yield of 19.9% and the majority of the starting acid (I) was recovered. Likewise, when acid I was allowed to react with *o*-chloroaniline (IIb), N-(2′-chlorophenyl)-5-methoxyanthranilic acid (IIIb) was isolated in a yield of only



I IIa (R_1 = H, R_2 = Cl) IIb (R_1 = Cl, R_2 = H)

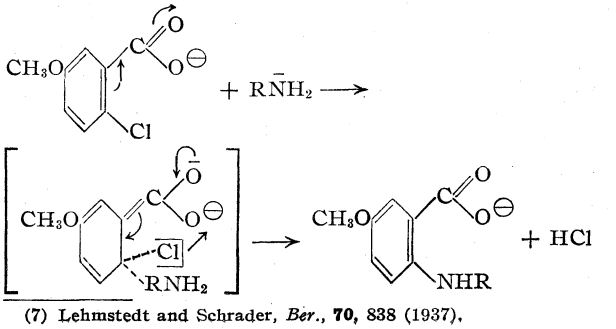


III (R_1 = R_2 = H) IIIa (R_1 = H, R_2 = Cl) IIIb (R_1 = Cl, R_2 = H)

11.4% and again the majority of the starting acid was recovered. It was found that the use of solvents with different boiling points, as *n*-butanol, *n*-pentanol, *n*-hexanol and cyclohexanol, gave still lower yields and that when the reaction was conducted in boiling nitrobenzene extensive decomposition occurred.

The small quantity of the desired materials (IIIa and IIIb) was not easily separated from the large amount of starting acid by fractional crystallization. However, this mixture was easily separated by partial acidification of a solution of their potassium salts since a substituted-anthranilic acid is a much weaker acid than a substituted benzoic acid. Crude product was precipitated when the *p*H was adjusted to seven and the starting acid was deposited from solution at a *p*H of five.

In view of the poor yields obtained in the above condensations, it is interesting to note that Ullmann and Kipper[5] have reported that the same acid (I) reacts with aniline to give N-phenyl-5-methoxyanthranilic acid (III) in a yield of 80% and that Lehmstedt and Schrader[7] have reported



(1) Present address: Department of Chemistry, University of California, Berkeley 4, California.

(2) Mauss, German Patents 553,072, 565,411.

(3) Feldman and Kopeliowitsch, *Arch. Pharm.*, **273**, 488 (1935).

(4) Since this paper was submitted for publication, Grigorovskii and Terent'eva (*J. Gen. Chem.* (*U. S. S. R.*), **17**, 517 (1947)) have reported the synthesis of the 5-chloro isomer and the attempted preparation of the 8-chloro isomer. The 2-methoxy-5,9-dichloroacridine (IV), prepared from 2,3-dichlorobenzoic acid and *p*-anisidine through the intermediate N-(4′-methoxyphenyl)-3-chloroanthranilic acid, had identical physical properties with the compound reported in this work. They, likewise, were unable to obtain a crystalline hydrochloride of the Quinacrine analog but they did obtain a solid oxalate. The 5-chloro isomer showed no anti-malarial activity. Their attempted synthesis of the 8-chloro isomer from 2,6-dichlorobenzoic acid and *p*-anisidine failed and the product isolated from the Ullmann reaction was *m*-bis-(*p*-methoxyanilino)-benzene.

(5) Ullmann and Kipper, *Ber.*, **38**, 2120 (1905).

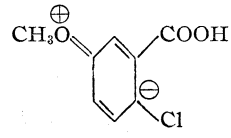
(6) Peratoner and Condorelli, *Gazz. chim. ital.*, **28**, I, 213 (1898).

(7) Lehmstedt and Schrader, *Ber.*, **70**, 838 (1937).

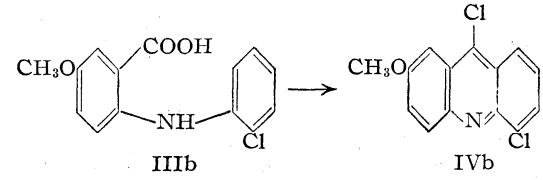
that *m*-chloroaniline (IIa) reacts with *o*-chlorobenzoic acid to give N-(3′-chlorophenyl)-anthranilic acid in 53% yield. If the mechanism of the Ullmann condensation is considered as a nucleophilic displacement of the chlorine atom by the amine, it can be seen that not only is the electrophilic strength of the *o*-chlorobenzoic acid important but also the nucleophilic strength of the reacting amine.[8] For example, Hertel and Luhrmann[9] have shown in a similar type of displacement reaction that the rate of the reaction decreases as the strength of the base decreases. From this work it would appear that the dissociation constant of the amine is a measure of its nucleophilic reactivity. This same correlation is qualitatively observed when the basic strengths[10] of the amines used in the above condensations are

Amine	$K_B \times 10^{10}$	Yield, %
Aniline	126	80
m-Chloroaniline	8.5	20
o-Chloroaniline	1.4	11

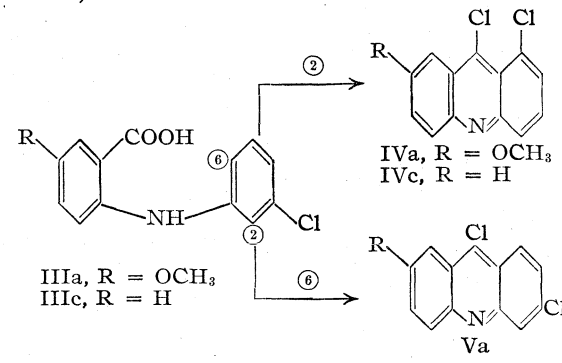
considered. Also, Tuttle[11] has shown that the presence of an electronegative group *para* to the chlorine atom of an *o*-chlorobenzoic acid greatly increases the reactivity of the chlorine toward nucleophilic displacement. In the case of 2-chloro-5-methoxybenzoic acid (I), the presence of an electropositive group, a methoxyl, in the *para* position to the chlorine atom would be expected to lessen the tendency of this chlorine atom to be displaced by a nucleophilic reagent (that is decrease the electrophilic tendency of the carbon atom holding the chlorine).



It is well-known that when a N-phenylanthranilic acid is allowed to react with phosphorus oxychloride a 9-chloroacridine is formed; that is, a ring closure and a subsequent chlorination occur. When the above anthranilic acids (IIIa and IIIb) were allowed to react with boiling phosphorus oxychloride only the corresponding 9-acridones were isolated. However, when chlorobenzene was used as a solvent and the reaction temperature was raised to 140°, good yields of the 9-chloroacridines were isolated. Starting with acid IIIb, 2-methoxy-5,9-dichloroacridine (IVb) was formed in a yield of 83.3%.



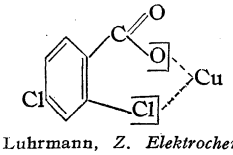
In the case of acid IIIa, two possible isomers (IVa and Va) can be formed.



Lehmstedt and Schrader[7] have studied in detail ring closures of this type. They have found in the case of N-(3-chlorophenyl)-anthranilic acid (IIIc) that reaction occurs mainly at the carbon two position to give the 8-chloro isomer (IVc). Linnell[12] also has reported similar results with compounds of this type. When acid IIIa was allowed to react with phosphorus oxychloride, only one pure dichloro compound could be obtained. After eight fractional crystallizations from benzene, 2-methoxy-8,9-dichloroacridine (IVa) was isolated in 24% yield. However, after this work was completed, Nargund and co-workers reported[13] that this same acid (IIIa) upon treatment with phosphorus oxychloride gave 2-methoxy-6,9-dichloroacridine (Va) as the only product of the reaction. These workers have published no experimental detail and no physical properties of their product so it is not possible to fully evaluate their work at this time. The 8-chloro structure was assigned to our compound IVa since it melts at 182° as compared to a melting point of 162° for the 6-chloro compound (Va), and a mixture of the two isomers melts from 145–158°. Also, the Quinacrine analog (VI) differs from Quinacrine in melting point, solubility and biological activity. The structure IVa is likewise in agreement with the results of Lehmstedt and Schrader[7] and of Linnell.[12]

The desired amino-side chain was attached to the acridine nucleus by allowing 2-methoxy-8,9-dichloroacridine (IVa) to react with 1-diethylamino-4-aminopentane in molten phenol. 2-

(8) In view of the specific reactivity of the *o*-halogen in this reaction, the role of the copper powder may be to aid in a simultaneous back and front side attack in the displacement reaction (see Swain, THIS JOURNAL, **70**, 1119 (1948)), by forming a weak, intramolecular coördinate bond between the halogen atom and the carboxylate anion.



(9) Hertel and Luhrmann, *Z. Elektrochem.*, **45**, 405 (1939); Branch and Calvin, "The Theory of Organic Chemistry," p. 426, Prentice-Hall, New York, N. Y., 1941.

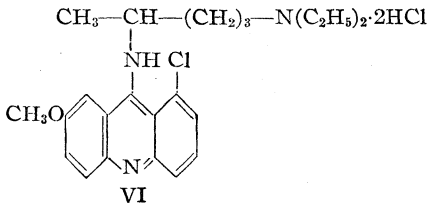
(10) Bennett, Brooks and Glasstone, *J. Chem. Soc.*, 1821 (1935).

(11) Tuttle, THIS JOURNAL, **45**, 1906 (1923).

(12) Bradbury and Linnell, *J. Chem. Soc.*, 377 (1942), and earlier papers.

(13) Shah, Kshatriga, Patel and Nargund, *J. Univ. Bombay*, Sect. A, **15**, pt. 3 (Science No. 20), 42 (1946).

Methoxy-8-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine (VI) was isolated as the dihydrochloride hydrate in a yield of 58%.



VI

When 2-methoxy-5,9-dichloroacridine (IVb) was treated in a similar manner, no crystalline amino product could be isolated. However, 2-methoxy-5-chloro-9-phenoxyacridine was obtained in 41% yield.

Dr. J. H. Bauer of the Rockefeller Foundation has investigated the antimalarial activity of the 8-chloro-isomer (VI). It was found that when it was used in 50-mg. amounts per day per 65 g. chick, it was non-toxic and had a very definite effect in prolonging the incubation period of the infection. Quinacrine, when assayed under the same conditions, was found to be effective in 8-mg. doses.

The author wishes to express his appreciation to Professor L. F. Fieser for his advice during the course of this investigation.

Experimental[14]

2-Chloro-5-methoxytoluene.[6]—2-Chloro-5-hydroxytoluene (71.5 g., 0.5 mole, m. p. 65°) was methylated in the usual manner with dimethyl sulfate (126 g., 1 mole) and 10% aqueous sodium hydroxide (200 cc.). The methyl ether distils at 77–78° (3 mm.), yield 71.5 g. (91.5%), $n^{23}D$ 1.5348.

2-Chloro-5-methoxybenzoic Acid.[6]—A mixture of 2-chloro-5-methoxytoluene (30 g., 0.192 mole), potassium permanganate (91.2 g., 0.577 mole) and water (9 liters) was refluxed, with stirring, for seven hours. The unreacted toluene compound was removed by steam distillation, the manganese dioxide filtered, and the clear, colorless filtrate acidified. The acid was obtained as white needles, yield 23.0 g. (64.3%), m. p. 172–173°. When the manganese dioxide was dissolved by bubbling-in sulfur dioxide, the same yield of acid was obtained.

N-(3'-Chlorophenyl)-5-methoxyanthranilic Acid (IIIa).—A mixture of 2-chloro-5-methoxybenzoic acid (25 g., 0.134 mole), *m*-chloroaniline (25 g., 0.196 mole), anhydrous potassium carbonate (25 g., 0.181 mole), copper powder (0.6 g.), and isoamyl alcohol (100 cc.) was heated under reflux with stirring for a period of twenty-four hours. The reaction mixture was diluted with water, the isoamyl alcohol and the unreacted amine removed by steam distillation, and the solution decolorized with Norit. The cooled filtrate then was acidified with dilute hydrochloric acid to a *p*H of 7. The yellow precipitate was removed by filtration and the filtrate was acidified to a *p*H of 5. A voluminous white precipitate of the starting acid was deposited. Upon making the latter filtrate acid to congo red, a mixture of the white solid and a brown oil was formed.

Recrystallization of the yellow precipitate from aqueous ethanol yielded N-(3-chlorophenyl)-5-methoxyanthranilic acid as yellow, feather-like needles, yield 7.4 g. (19.9%, 49.7% allowing for recovered acid), m. p. 190–191°.

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.44; H, 4.28; N, 5.30; Cl, 12.75.

The white solids upon recrystallization from aqueous ethanol gave 15 g. of starting acid. The brown sirup partially crystallized on standing and the solid which separated was starting acid. The remaining sirup was acidic but its composition was not investigated.

2-Methoxy-8,9-dichloroacridine (IVa).—The ring closure and subsequent chlorination was accomplished by heating a solution of N-(3-chlorophenyl)-5-methoxyanthranilic acid (12.6 g., 0.045 mole), phosphorus oxychloride (100 cc.), and chlorobenzene (250 cc.) at a temperature of 140° for a period of five hours. The reaction mixture was concentrated to dryness in a vacuum at 80°. The brown, sirupy residue upon the addition of dilute aqueous ammonia hardened to a yellow crystalline mass. The solid was filtered, washed with water until the washings were neutral, and then dried. The crude product was dissolved in excess dry benzene, the solution was decolorized with Norit, and the solvent was distilled until crystals began to appear. A small volume of dry benzene then was added and the solution cooled. This procedure was repeated seven times in order to obtain pure 2-methoxy-8,9-dichloroacridine. The product is light-yellow plates melting at 181–182°; the yield was 3.1 g. (24%).

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.45; H, 3.24; N, 5.40; Cl, 25.72.

2-Methoxy-6,9-dichloroacridine melts at 161–162° and a mixture of these two isomers melts from 145–158°.

The mother liquors from the above fractional crystallization on concentration deposited 4.0 g. of a yellow compound which melts over a large range and was entirely melted by 138°. When this solid was treated in the above manner no change in its composition appeared to occur.

2-Methoxy-8-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine-(VI).—1-Diethylamino-4-aminopentane (2.9 g., 0.018 mole) was added dropwise to a well-stirred mixture of 2-methoxy-8,9-dichloroacridine (3.65 g., 0.0131 mole) and phenol (18.4 g.) over a period of thirty minutes. The entire addition was conducted at steam-bath temperature. The reaction mixture was heated for an additional two hours and then diluted with warm 10% sodium hydroxide (80 cc.). A brown oil separated which floated on the alkaline solution. The entire mixture was cooled and extracted with a 1:1 mixture of benzene–ether. The extract was washed with water, dried over sodium sulfate, and the solvent was removed at reduced pressure at room temperature. The brown sirupy residue which was contaminated with a small amount of the yellow acridone was dissolved in acetone leaving the insoluble acridone. The acetone solution was acidified with dry hydrogen chloride at 0° and a small amount of the solvent was removed by means of a stream of dry air. The cooled solution set to a solid mass which yielded 5.1 g. (82.3%) of the yellow crystalline hydrochloride.

The hydrochloride was dissolved in distilled water (150 cc.) at room temperature, filtered, and the free amine generated by the addition of 50 cc. of one normal sodium hydroxide. The yellow milky solution was extracted twice with 100-cc. portions of ether, the ethereal extract dried, and the solvent removed at reduced pressure at room temperature. The brown residual oil was dissolved in 125 cc. of dry acetone; dry hydrogen chloride was added at 0°. At first, the solution became milky colored and a sirup came out of solution but upon continued addition of the gas, the sirup finally redissolved. The solution was cooled to 0° for twenty-four hours and the precipitate removed by filtration. The air-dried material melts from 135–140°. After drying at 80° at a pressure of 1 mm., the acridine melts at 197.5–199° (dec.), yield 3.75 g. (58%). Quinacrine dihydrochloride melts from 248–250°.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl\cdot H_2O$: C, 56.27; H, 6.98; N, 8.58; Cl, 21.68. Found: C, 56.40; H, 7.16; N, 8.89; Cl, 21.60.

A much less convenient method of crystallization was to dissolve the amine in dilute aqueous hydrochloric acid and

(14) All melting points are corrected. Microcombustions by Miss E. Werble.

allow the solution to stand in a vacuum desiccator over sulfuric acid at 0°. After a few days a yellow solid, identical with the above, appeared.

N-(2'-Chlorophenyl)-5-methoxyanthranilic Acid (IIIb).—A mixture of 50 g. (0.268 mole) of 2-chloro-5-methoxybenzoic acid, 50 g. (0.392 mole) of *o*-chloroaniline, 50 g. (0.362 mole) of anhydrous potassium carbonate, 1 g. of copper powder,[15] and 250 cc. of isoamyl alcohol was condensed and processed as described above. The yellow precipitate obtained by acidification to a *p*H of 7 was recrystallized twice from aqueous ethanol. The yield was 8.5 g. (11.4%, 28.5% allowing for recovered acid), m. p. 189–190°.

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.63; H, 4.32; N, 5.34; Cl, 12.92.

The white precipitate obtained at a *p*H of 5 yielded 30 g. of the starting acid. Further acidification of the mother liquor gave only a brown oil.

2-Methoxy-5,9-dichloroacridine (IVb).—The ring closure was conducted as described above employing 7.4 g. (0.027 mole) of N-(2-chlorophenyl)-5-methoxyanthranilic acid. The yield of pure product was 6.2 g. (83.8%), m. p. 157–158° (benzene).

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.55; H, 3.28; N, 4.77; Cl, 26.01.

2-Methoxy-5-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine.—The condensation was carried out and worked up as described above using 1.1 g. (0.004 mole) of 2-methoxy-5,9-dichloroacridine. Upon removal of the ether, a mixture of a yellow solid and a brown sirup was obtained. The yellow solid was removed and recrystallized from benzene. The compound was 2-methoxy-5-chloro-9-phenoxyacridine, m. p. 189–190°, yield 0.55 g. (41%).

Anal. Calcd. for $C_{20}H_{14}O_2NCl$: C, 71.53; H, 4.20; N, 4.17. Found: C, 71.42; H, 4.22; N, 4.17.

The brown sirup was processed in a manner analogous to that used for the 8-chloro isomer but no crystalline hydrochloride was obtained. Attempts to distil the product led to decomposition.

(15) When copper bronze was used as the catalyst, it was found necessary to dissolve the coating of wax and stearic acid by heating with ethanol.

Summary

2-Methoxy-8,9-dichloroacridine and 2-methoxy-5,9-dichloroacridine have been prepared. The 8-chloro isomer of Quinacrine has been prepared and its antimalarial activity determined. The 5-chloro isomer has been made but was not obtained in a crystalline form.

BERKELEY 4, CALIFORNIA RECEIVED FEBURARY 9, 1948

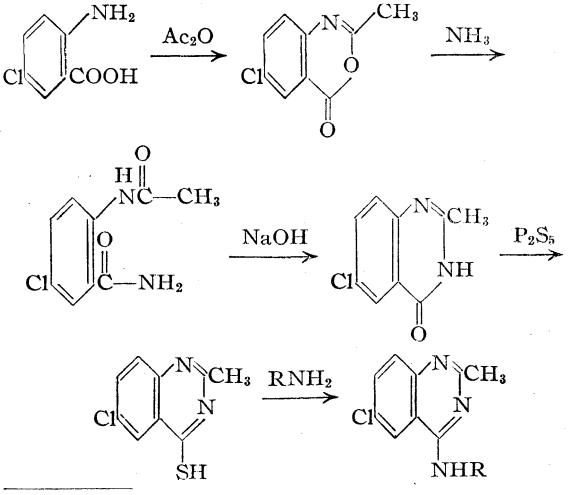
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. VI. Syntheses of Certain 2-Methyl-4-substituted Quinazolines[1]

BY ARTHUR J. TOMISEK AND BERT E. CHRISTENSEN

The study of the quinazoline compounds provides unusual interest, in view of the many novel[2] reactions and unpredictable[3] reaction products. During the course of nitration studies of 2,4-dimethylquinazoline, another unusual reaction was observed; instead of a nitro-2,4-dimethylquinazoline, the reaction product was 2-methyl-6-nitro-4-quinazolone. Even when equimolar quantities of reagents were used the nitrated quinazolone and unreacted quinazoline were the only compounds isolated from the reaction mixture, which fact indicates that the nitration of the quinazolone must have taken precedence over all other reactions. This reaction again illustrates the marked activity of a univalent substituent in the 4-position of the quinazoline nucleus.[4]

Another unpredictable reaction[5] of the quinazolines is illustrated in the chlorination of 2-methyl-4-quinazolone; in this instance benzenoid chlorination occurs along with the replacement of the 4-hydroxyl group. This makes it impossible to prepare 4-alkylaminoquinazolines with a methyl substituent in the 2-position by the usual procedures, *i. e.*, coupling of the 4-chloro derivative with desired amine. Recently Leonard and Curtin[6] have successfully employed the 4-mercaptoquinazolines in place of the usual chloro derivative as intermediates for synthesis of alkylamino compounds. This procedure has now been used to circumvent the problem of benzenoid chlorination in the preparation of 4-alkylamino-2-methylquinazolines; 2-methyl-4-quinazolone and 6-chloro-2-methyl-4-quinazolone were readily converted to the respective 4-mercaptoquinazolines by means of phos-



(1) Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 124.

(2) Leonard and Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(3) Tomisek and Christensen, THIS JOURNAL, **70**, 874 (1948).

(4) Tomisek and Christensen, *ibid.*, **67**, 2112 (1945).

(5) Dehoff, *J. prakt. Chem.*, **2**, **42**, 352 (1890); Bogert and May, THIS JOURNAL, **31**, 511 (1909).

(6) Leonard and Curtin, *J. Org. Chem.*, **11**, 349 (1946).

phorus pentasulfide in refluxing xylene. 2-Methyl-6-nitro-4-quinazolone on the other hand gave no reaction with phosphorus pentasulfide, even upon twelve hours of heating in boiling *p*-cymene. This was probably due to its solubility characteristics.

The 6-chloro-2-methyl-4-quinazolone was prepared through a series of previously unreported intermediates. For purposes of characterization small amounts of each of these intermediates were purified after each stage of the synthesis. The diagram illustrating this series of reactions is also representative of the synthesis and reaction of 2-methyl-4-quinazolone.

Experimental[7]

6-Chloro-2-methyl-4-quinazolone.—A solution consisting of 25 g. of 5-chloroanthranilic acid[8] and 75 ml. of pure acetic anhydride was refluxed one hour, then cooled to about 0° and filtered. The crystalline product (21.8 g. of crude benzoxazine) was converted to N-acetyl-5-chloroanthranilamide after standing four hours in concentrated ammonia. Ten ml. of 10% sodium hydroxide was added to the unisolated product and the mixture was heated for several minutes; then the quinazolone was brought into solution by addition of an excess of hot 10% sodium hydroxide. The basic solution was decolorized with charcoal, adjusted to *p*H 8 and filtered (5.4 g. of crude N-acetyl-5-chloroanthranilic acid was recovered from the filtrate). The product was recrystallized from alcohol, and residues from the alcoholic liquors were recrystallized (with charcoal treatment) from aqueous acetic acid. The combined quinazolone fractions, 10.45 g., m. p. 283–286°, corresponds to an over-all yield of 37%. An additional recrystallization from the acetic acid raised the m. p. to 287°.

Anal. Calcd. for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.40. Found: C, 55.30; H, 3.91; N, 14.55.

6-Chloro-2-methyl-3,1,4-benzoxaz-4-one.—A small amount of the crude benzoxazone[9] was removed at the point indicated above, decolorized and recrystallized from hot acetic anhydride solution. The colorless plates melted at 124–125°.

Anal. Calcd. for $C_9H_6NO_2Cl$: C, 55.26; H, 3.09. Found: C, 55.17; H, 2.84.

N-Acetyl-5-chloroanthranilamide.—A sample of the crude N-acetyl-5-chloroanthranilamide which occurred as an intermediate in the above synthesis of 6-chloro-2-methyl-4-quinazolone was recrystallized from alcohol to yield white crystals of m. p. 183°.

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.83; H, 4.27. Found: C, 50.88; H, 4.16.

N-Acetyl-5-chloroanthranilic Acid.—The crude N-acetyl-5-chloroanthranilic acid which occurred as a result of incomplete and/or side reaction in the above synthesis of 6-chloro-2-methyl-4-quinazolone was decolorized from hot aqueous alcohol and crystallized. The flat white needles melted at 204°. This compound is not to be confused with 5-chloroanthranilic acid (m. p. 210–212°)[10] the melting point of which in the earlier literature[11] is given as 204°.

Anal. Calcd. for $C_9H_8NO_3Cl$: C, 50.60; H, 3.77. Found: C, 50.71; H, 3.67.

2-Methyl-4-mercaptoquinazoline.—Sixteen grams (0.1 mole) of 2-methyl-4-quinazolone and 21.6 g. (0.1 mole) of phosphorus pentasulfide were mixed dry. One hundred ml. of xylene was added and mixture was refluxed two hours. The heating was interrupted at the end of the first hour to permit repulverizing of the solids in the mixture. The mixture was shaken with 100 ml. of 10% sodium hydroxide and filtered. The solid material from the filtration was thoroughly dried, then extracted with 100 ml. of hot 10% sodium hydroxide. The combined basic solutions after treatment with charcoal were precipitated with acetic acid. The solid material was removed by filtration and reprecipitated from sodium hydroxide solution.

This crude mercaptoquinazoline was recrystallized from aqueous alcohol to yield 8.55 g. (49%) of yellow needles, m. p. 217–219°. The melting point recorded for 2-methyl-4-mercaptoquinazoline as prepared from acetylanthranilic-nitrile is 218–219° (dec.).[12]

6-Chloro-2-methyl-4-mercaptoquinazoline.—The synthesis and isolation were as given for 2-methyl-4-mercaptoquinazoline. The crude 6-chloro-2-methyl-4-mercaptoquinazoline was decolorized and recrystallized from hot aqueous alcohol solution. The yield from 19.5 g. (0.1 mole) of 6-chloro-2-methyl-4-quinazoline was 11.6 g. (55%). An additional recrystallization from aqueous acetic acid gave yellow needles of m. p. (dec.) 276–278°.

Anal. Calcd. for $C_9H_7N_2SCl$: C, 51.30; H, 3.35; Cl, 16.83. Found: C, 51.53; H, 3.21; Cl, 16.78.

4-(β-Hydroxyethylamino)-2-methylquinazoline.—A mixture of 5 ml. of ethanolamine and 1.47 g. of 2-methyl-4-mercaptoquinazoline was heated for seven hours at 80°. The suspension which resulted on cooling was diluted with a small amount of water. This product was recrystallized (preferably by seeding from a previous preparation) yielding rosettes of thick, yellow needles. The product (1.5 g., 88%) was dissolved in hot dioxane, in order to remove a trace of insoluble oil. This solution was then evaporated to dryness, and the residue was recrystallized from the minimum amount of water. The pure 4-(β-hydroxyethylamino)-2-methylquinazoline crystallized from water as yellow prisms and spherulites. When dropped upon a hot melting point block the crystals appeared to melt at 164–166° resolidifying to white needles which melted (with sublimation) at 174.5–176°. Since both forms recrystallized from water to yield a mixture of highly birefringent spherulites and prisms one cannot attribute the behavior to crystal habit or to a monotropic transformation on the basis of the present information.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.83; H, 6.69; N, 20.69.

6-Chloro-4-(*p*-methoxyanilino)-2-methylquinazoline.—A mixture of 4 g. of *p*-anisidine and 1.75 g. of 6-chloro-2-methyl-4-mercaptoquinazoline was heated for six hours at 190°. The resulting dark yellow solid was triturated first with acid and then with sodium hydroxide. The solid was decolorized and recrystallized from 0.5 *N* hydrochloric acid to yield 0.59 g. of fine, yellow needles of 6-chloro-4-(*p*-methoxyanilino)-2-methylquinazoline hydrochloride. The m. p. in a capillary block preheated to 319° was 321° (dec.).

Anal. Calcd. for $C_{16}H_{15}N_3OCl_2$: C, 57.15; H, 4.50. Found: C, 57.41; H, 4.42.

Nitration of 2,4-Dimethylquinazoline.—Two and one-half grams of 2,4-dimethylquinazoline was dissolved in 20 ml. of concentrated sulfuric acid and 10 ml. of fuming nitric acid (sp. gr. 1.5) was added in one portion. In order to keep the initial temperature below 75°, it was necessary to cool the reaction mixture which was then maintained at 75° for one hour, and then poured on 200 g. of ice; tiny white needles (0.61 g.) separated on standing overnight. The liquors were neutralized to yield more product which was recrystallized from glacial acetic acid; yield 1.84 g. Several recrystallizations from glacial acetic acid and pyridine gave a product with m. p. (dec.) 302–304°, which did not depress the melting point of the 2-methyl-6-nitro-4-quinazolone prepared later by nitration of 2-methyl-4-quinazolone.

Anal. Calcd. for $C_9H_7N_3O_3$: N, 20.48. Found: N, 20.44.

(7) All melting points are corrected.

(8) Eastman Kodak Company, technical grade (blue label).

(9) Wegscheider and Faltis, *Monatsh.*, **33**, 185 (1911).

(10) Magidson and Golovchinskaya, *J. Gen. Chem.* (*USSR*), **8**, 1801 (1938).

(11) Eller and Klemm, *Ber.*, **55**, 222 (1922).

(12) Bogert, Breneman and Hand, THIS JOURNAL, **25**, 377 (1903).

Nitration of 2-Methyl-4-quinazolone.—Two and one-half grams of 2-methyl-4-quinazolone was nitrated according to the directions given for the nitration of 2,4-dimethylquinazoline. The yield of crude product was 2.8 g. The m. p. after several recrystallizations was 298–300° (dec.) Bogert and Geiger reported[13] a melting point of 299° (uncor.) for 2-methyl-6-nitro-4-quinazolone obtained by a similar nitration.

(13) Bogert and Geiger, THIS JOURNAL, **34**, 529 (1912).

Summary

4-Mercapto-2-methylquinazoline can be used as an intermediate for synthesis of 4-(β-hydroxyethylamino)-2-methylquinazoline and 6-chloro-4-(*p*-methoxyanilino)-2-methylquinazoline.

The nitration of 2,4-dimethylquinazoline yields 2-methyl-6-nitro-4-quinazolone.

CORVALLIS, OREGON RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION NO. 80 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

The Willgerodt Reaction on α-Tetralone

BY W. J. HORTON AND J. VAN DEN BERGHE[1]

The reaction of aliphatic aromatic ketones with aqueous ammonium polysulfide to produce ω-aryl aliphatic amides, first reported by Willgerodt,[2] has been shown to be applicable to olefins, acetylenes, aldehydes, alcohols and mercaptans.[3,4] It is apparent that a rearrangement is not involved.[5] This confirms Willgerodt's experiment[6] in which isovalerophenone was converted to α-methyl-γ-phenylbutyramide rather than the β-methyl-γ-phenylbutyramide expected by rearrangement. This reaction has been successfully repeated in several laboratories.[4,7,8]

The most important suggestions as to the mechanism of the reaction[4,8] have postulated a group which migrates along the chain by reversible steps, the process being terminated by irreversible changes which yield the amide. These ideas have been supported by the fact that the proposed intermediates, olefins, acetylenes, mercaptans, will yield amides if they are submitted to the conditions of the reaction. No intermediates have been isolated from the reaction mixture.

In the hope of interrupting the progression of a functional group along the aliphatic chain, we proposed to terminate the aliphatic chain of the aliphatic aromatic ketone with a second aryl group, or to use α-tetralone in the reaction[9] so that the aryl group of the ketone would also be the terminal group on the chain. We employed for convenience the modification suggested by Schwenk and Bloch[10] which avoids the use of sealed tubes.[11] The principal product of the reaction was a tertiary aromatic amine. When this was hydrolyzed using dilute sulfuric acid in a sealed tube,[12] β-naphthol was obtained and further identified by conversion to β-naphthyl methyl ether. That the amine is 4-(2-naphthyl)-morpholine was fully confirmed by independent syntheses from β-naphthol and morpholine in the presence of aqueous sodium bisulfite, and from β-naphthylamine and β,β′-dichlorodiethyl ether.[13]

The reaction of α-tetralone, morpholine and sulfur gives, in addition to the above amine, small amounts of at least one other product which has not been fully investigated.

When α- or β-naphthol replaced α-tetralone in this reaction, no amines could be found. Thus the conversion of α-tetralone to α-naphthol by means of sulfur cannot be the initial step in the reaction.

We have also investigated the behavior of morpholine and sulfur without the addition of any other material. Several reports in which the Schwenk and Bloch modification of the Willgerodt reaction was used have appeared[14,15] but products of a reaction between morpholine and sulfur have not been noted.[16] At a temperature just above that used to produce 4-(2-naphthyl)-morpholine from α-tetralone, morpholine and sulfur, the latter two components alone gave a high melting compound which resembled that isolated in the reaction of commercial diisobutylene, two styrene homologs, or certain mercaptans with morpholine and sulfur and shown to be dithiooxalodimorpholide.[15] When our product was mixed with known dithioöxalodimorpholide, no depression of the melting point was obtained. Hydrolysis of the high melting material with aqueous hydrobromic acid produced the hydrobromide of β,β′-dibromodiethylamine. It is apparent then that sulfur attacks the morpholine molecule to give hydrogen sulfide and a dithioöxalyl fragment

(1) In part from the Master's Dissertation of J. Van Den Berghe.

(2) Willgerodt, *Ber.*, **20**, 2467 (1887).

(3) For a recent review of this reaction, see Carmack and Spielman, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 83.

(4) King and McMillan, THIS JOURNAL, **68**, 525, 632 (1946).

(5) Shantz and Rittenberg, *ibid.*, **68**, 2109 (1946). Calvin, *et al.*, *ibid.*, **68**, 2117 (1946), have shown that the acid produced is not formed by the same mechanism as the amide.

(6) Willgerodt and Merck, *J. prakt. Chem.*, **80**, 192 (1909).

(7) Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940).

(8) Carmack and De Tar, *ibid.*, **68**, 2029 (1946).

(9) This is the first recorded example of a cyclic ketone in the Willgerodt reaction.

(10) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(11) Preliminary work by one of us on α-tetralone and aqueous ammonium polysulfide in a sealed tube gave crystals melting at 139–140° which contain sulfur but no nitrogen.

(12) *Cf.* Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947), who treated 1-acetamido-3,4-dimethylnaphthalene in this manner.

(13) Cretcher and Pittenger, *ibid.*, **47**, 163 (1925).

(14) Campaigne and Rutan, *ibid.*, **69**, 1211 (1947); Arnold and Rondestvedt, *ibid.*, **67**, 1265 (1945).

(15) McMillan and King, *ibid.*, **69**, 1207 (1947).

(16) Carmack has reported (ref. 8) a high melting material in the reaction of phenylacetylene with morpholine and sulfur.

which is stable when converted to dithioöxalodimorpholide.

This work is being continued in an attempt to explain the appearance of the morpholinyl group at the 2-position of the naphthalene ring when α-tetralone is used.

We are indebted to assistance from the University of Utah Research Committee. The help of Mr. C. H. Arrington is gratefully acknowledged.

Experimental[17]

4-(2-Naphthyl)-morpholine.—(a) Morpholine from Commercial Solvents Corp. was redistilled and the colorless fraction, b. p. 121.5–122° at 644 mm., was used. The α-tetralone was prepared by the methods described[18] and had a b. p. 127–137° at 13 mm. α-Tetralone prepared by air oxidation of tetralin gave similar results. A mixture of 4.0 g. (0.027 mole) of α-tetralone, 2.48 g. (0.028 mole) of morpholine and 0.86 g. (0.027 mole) of powdered sulfur was refluxed by heating the flask in an oil-bath at 128–135° for eight hours. Within the first hour, the sulfur dissolved, an odor of hydrogen sulfide was noted and the color of the solution lightened. The reaction mixture was allowed to cool to room temperature and stand overnight, whereupon it solidified. The solid was treated with a warm solution of 5 cc. of concentrated hydrochloric acid in 10 cc. of water and decanted to a filter. This treatment was repeated twice. The oil remaining undissolved was washed with water and the washings added to the acidic filtrate. The cooled filtrate was made basic with ammonia, the suspension of dark precipitate was cooled, filtered and washed with water. The dried crude amine weighed 2.87 g. Steam distillation and three recrystallizations from aqueous ethanol gave thin rods, m. p. 87–90°, reported 90°.[13]

Anal. Calcd. for $C_{14}H_{15}NO$: N, 6.57. Found: N, 6.55.

The amine was dissolved in dilute hydrochloric acid with warming and the acidity was increased to 10% by addition of concentrated hydrochloric acid. On cooling, the hydrochloride of 4-(2-naphthyl)-morpholine appeared as colorless crystals. Recrystallization first from a small volume of water and then from absolute alcohol, produced large granular crystals which melted at 211.5–215° with sudden evolution of gas at 215°.

Anal. Calcd. for $C_{14}H_{16}NOCl$: N, 5.61; neut. equiv., 250. Found: N, 5.64; neut. equiv., 250.

A solution of 0.5 g. of amine and 0.5 g. of picric acid in 25 cc. of warm ethanol gave 0.77 g. of picrate on cooling. Recrystallization from alcohol gave fine, rectangular, canary-yellow rods which melted at 152–155° (dec.).

Anal. Calcd. for $C_{20}H_{18}N_4O_8$: neut. equiv., 442. Found: neut. equiv., 438.

When α-naphthol or β-naphthol (0.027 mole) replaced α-tetralone in the above procedure, no detectable amounts of amines could be obtained from the hydrochloric acid extracts of the reaction mixture.

(b) A sample of 4-(2-naphthyl)-morpholine prepared by the reported procedure[13] melted at 84.5–87° and a mixture with the amine from (a) melted at 87–89°. A picrate was prepared which melted at 152–155° (dec.). No change in m. p. was observed when this was mixed with the picrate obtained in (a).

(c) A sealed glass tube containing 1.0 g. of β-naphthol (0.0069 mole), 1.2 g. of morpholine (0.014 mole), 0.73 g. of sodium bisulfite (0.007 mole) and 1.5 cc. of water was heated for twenty-four hours at 190–200°. Extraction of the tube contents three times with a solution of 1 cc. of alcohol in 9 cc. of 6 *N* hydrochloric acid, filtration and neutralization of the filtrate gave 1.06 g. of crude amine. On solution in dilute hydrochloric acid, filtration and neutralization, 1.03 g. of nearly colorless amine, m. p. 84–87°, was obtained. A mixture with the amine produced in (a) melted at 87–89°. Similarly, a mixture of the picrates melted without depression.

Hydrolysis of 4-(2-Naphthyl)-morpholine.—Two hundred milligrams of the amine from α-tetralone, morpholine and sulfur was sealed in a glass tube with 10 cc. of 15% sulfuric acid.[12] The tube was heated in a metal-bath at 220–240° for three hours. The crystalline contents of the tube were filtered and washed with water. The solid, dissolved in warm benzene, was washed with a solution of 0.5 cc. of hydrochloric acid in 20 cc. of water. The separated benzene solution was washed with water until neutral and the benzene evaporated. The residue partially dissolved in 10% sodium hydroxide. The filtered solution was acidified to yield a gelatinous precipitate which dissolved on warming and reappeared as colorless crystals on cooling. These melted at 114–120° and a mixture with authentic β-naphthol melted at 117–120°. A solution of 10 mg. of the crystals in 0.5 cc. of 10% sodium hydroxide and 2 cc. of water was treated with two 0.1-cc. portions of dimethyl sulfate to yield 5 mg. of β-naphthyl methyl ether, conveniently recovered by steam distillation of the reaction mixture. The β-naphthyl methyl ether was recognized by its distinctive odor, m. p. 71.5–74° alone, and when mixed with known β-naphthyl methyl ether, m. p. 71.5–73.5°.

Reaction of Morpholine and Sulfur.—A mixture of 4.3 g. (0.13 mole) of powdered sulfur and 12.4 g. of redistilled morpholine (0.14 mole) was heated in an oil-bath held at 150–158° for four hours. Use of a Hopkins-type condenser permitted gentle refluxing with only a small portion of the material becoming solid in the condenser. The warm reaction product was mixed with 50 cc. of 95% ethanol and allowed to stand at room temperature overnight. The crystals so obtained were washed with cold alcohol and weighed 1.16 g., m. p. 217–227°. A filtered solution of the compound in hot water deposited 0.45 g. of colorless flat prisms on cooling, m. p. 253.5–255°. The m. p. was not raised by subsequent recrystallization from alcohol.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S_2$: N, 10.76. Found: N, 10.76.

When mixed with dithioöxalodimorpholide prepared by the described method,[15] m. p. 254.5–256°, reported m. p. 252–253°, the mixture melted at 252.5–255°.

Hydrolysis with Hydrobromic Acid.—To 0.28 g. of the compound from morpholine and sulfur was added 10 cc. of 48% hydrobromic acid and the solution was refluxed for twelve hours. Removal of the acid at reduced pressure by warming on the water-bath left a residue which crystallized on cooling. The crystals were dissolved in 10 cc. of warm absolute alcohol, filtered and the solution concentrated. On cooling, crystals appeared which were filtered and washed with ice-cold alcohol. The material weighed 100 mg. and melted at 195–201°. Reported[19] for β,β′-dibromodiethylamine hydrobromide, m. p. 199–200°. A hot water solution of 70 mg. of the hydrobromide and 50 mg. of picric acid deposited 50 mg. of canary-yellow crystals, m. p. 125–134°. Recrystallization from a few cc. of hot water gave crystals, m. p. 132–134° with shrinking at 129°. Reported[19] for the picrate of β,β′-dibromodiethylamine, m. p. 128°.

Oxalodimorpholide.—A solution of 14.4 g. of morpholine in 50 cc. of anhydrous reagent benzene was treated with a solution of 4.2 g. of oxalyl chloride in 50 cc. of benzene. The oxalyl chloride solution was added slowly with swirling and cooling in cold water. After standing at room temperature for thirty minutes, followed by warming on the steam-bath, the cooled mixture was filtered and the filter washed with benzene. After removal of the benzene from the filtrate, the residue and the colorless salt insoluble in benzene were thoroughly extracted with warm acetone. On concentration of the acetone and cooling, 5.32 g. of short, rectangular prisms was obtained, m. p. 173–182.5°, reported 184–185°.[15] By concentration of the filtrate and addition of petroleum ether (b. p. 70–90°), 1.2 g.

(17) Melting points and boiling points are uncorrected.

(18) Martin and Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 569; Thompson, *ibid.*, Vol. 20, p. 94.

(19) Gabriel and Eschenbach, *Ber.*, **30**, 809 (1897).

was obtained, m. p. 138–176°. The first crop material was suitable for the preparation of dithioöxalodimorpholide.[15]

Summary

The reaction of α-tetralone with morpholine and sulfur yields 4-(2-naphthyl)-morpholine.

Dithioöxalodimorpholide has been isolated as a reaction product of sulfur and morpholine.

SALT LAKE CITY, UTAH RECEIVED MARCH 9, 1948

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

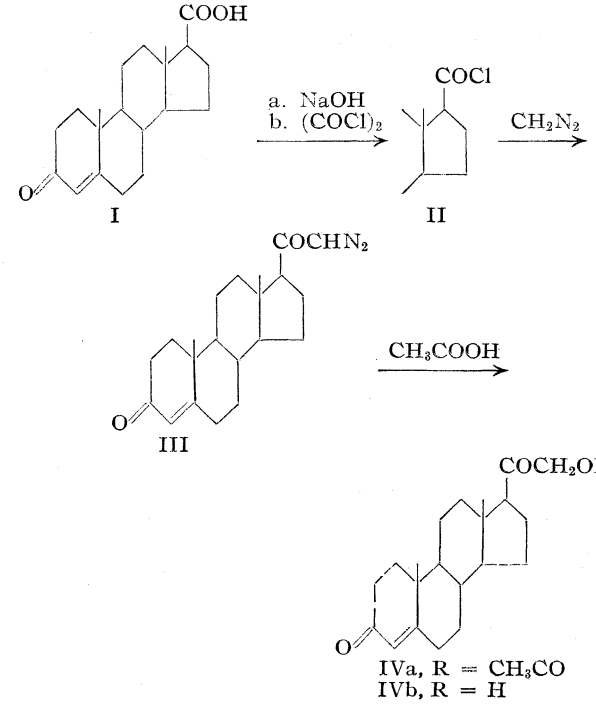
The Preparation of Desoxycorticosterone Acetate from 3-Keto-Δ^4-etiocholenic Acid

BY A. L. WILDS AND CLIFFORD H. SHUNK[1]

Desoxycorticosterone acetate (IVa) has been prepared by Reichstein and co-workers[2] from 3-acetoxy-Δ^5-etiocholenic acid by treating the acid chloride with diazomethane to form the diazoketone, followed by hydrolysis, Oppenauer oxidation of the remarkably stable diazoketone to 21-diazoprogesterone (III) and finally reaction with acetic acid. Attempts to prepare this adrenal cortical hormone from 3-keto-Δ^4-etiocholenic acid (I), thus avoiding the selective hydrolysis and oxidation of the diazoketone, have been unsatisfactory because of difficulties in preparing the acid chloride.[3,4] The α,β-unsaturated ketone grouping seems to be sensitive to reagents, such as thionyl chloride, normally used to prepare the acid chlorides. Apparently because of these difficulties, Reich and Lardon[5] developed a six-step procedure for converting 3-keto-Δ^4-steroids into the 3-acetoxy-Δ^5-derivative. This procedure was employed by von Euw and Reichstein[6] in a partial synthesis of 11-dehydrocorticosterone which necessitated reoxidation to the 3-keto-Δ^4 derivative at a later stage.

In connection with the synthesis of certain analogs of desoxycorticosterone and progesterone lacking ring C, we have developed an improved procedure for converting unsaturated keto acids of this type into the acid chlorides and diazoketones. This procedure has proved to be quite successful with 3-keto-Δ^4-etiocholenic acid (I). The critical step is the formation of the acid chloride at low temperatures (below 15°) by reaction of the sodium salt of the acid with oxalyl chloride.[7,8] After reaction with diazomethane the diazoketone III was obtained in 81% over-all yield from the acid I. By adding the diazoketone to boiling acetic acid,[9] desoxycorticosterone acetate (IVa) was obtained in 73% yield. The over-all yield is considerably higher than those reported for the earlier syntheses.

These procedures should prove of value for similar reactions with the 11-oxygenated derivatives of I.



Experimental[10]

21-Diazoprogesterone (III).—A solution of 506 mg. of 3-keto-Δ^4-etiocholenic acid[11] in 19 ml. of 0.091 *N* sodium hydroxide was frozen and evaporated to dryness (lyophilized) under reduced pressure and the residue dried at 110° (0.1 mm.) for eight hours. After cooling, 10 ml. of dry, thiophene-free benzene and 3 drops of pyridine were added; the salt was scraped from the sides of the flask, mixed thoroughly and cooled in an ice-bath before adding 2 ml. of redistilled oxalyl chloride (b. p. 60–60.5°). There was an immediate evolution of gas which stopped after a few

(1) National Research Council Predoctoral Fellow, 1946–1948.

(2) Reichstein and v. Euw, *Helv. Chim. Acta*, **23**, 136 (1940); see also Steiger and Reichstein, *ibid.*, **20**, 1164 (1937).

(3) Private communication from Dr. Lewis H. Sarett of Merck and Co., Inc., Rahway, New Jersey.

(4) Dr. Wayne Cole of The Glidden Co., Soya Products Division, Chicago, Ill., has informed us that they have obtained this acid chloride in impure form using thionyl chloride in cold ether containing a trace of pyridine.

(5) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).

(6) v. Euw and Reichstein, *ibid.*, **29**, 1913 (1946).

(7) Adams and Ulich, THIS JOURNAL, **42**, 599 (1920).

(8) Dr. Thomas L. Johnson found this to be a superior method for preparing the acid chloride of a different type of keto acid; see Wilds and T. L. Johnson, THIS JOURNAL, **70**, 1166 (1948).

(9) Dr. Warren R. Biggerstaff has found that this procedure is superior to dissolving in acetic acid before heating.

(10) All melting points are corrected.

(11) We are indebted to the Research Dept. of The Glidden Co., Soya Products Division, for this material.

seconds. The mixture was then allowed to warm to 15° for four minutes and as no further evolution of gas was noticed the solvent was evaporated under reduced pressure. Dry air was then admitted and three 1.5-ml. portions of benzene were added and evaporated, keeping the temperature below 15° at all times. Finally the acid chloride was dissolved in 5 ml. of benzene, filtered through a dry, sintered glass funnel into a cooled receiver and diluted with an equal volume of ether. The acid chloride was added slowly to a cold (−15°) ethereal solution of diazomethane (prepared from 6 g. of nitrosomethylurea[12]), maintained at −15° for one-half hour and at 0° for one-half hour, then the solvent was evaporated under reduced pressure. Trituration of the residual oil with acetone gave a total of 439 mg. (81%) of the light yellow diazoketone which decomposed at 177–178° (reported,[2] 182–184°).

Desoxycorticosterone Acetate (IVa).—To 10 ml. of boiling, purified[13] acetic acid was slowly added 163 mg. of 21-diazoprogesterone; there was immediate evolution of nitrogen and a light yellow solution resulted. After refluxing for three minutes the acetic acid was evaporated under reduced pressure and the residual oil dissolved in acetone. On cooling long needles were obtained which changed to 109 mg. of a powder upon drying at room temperature, m. p. 155–157°. A second crop of 14 mg., m. p. 153–155°, and an additional 8 mg., m. p. 146–154°, after molecular distillation of the filtrate at 160° (0.001 mm.) brought the total yield of desoxycorticosterone acetate to 73%. Recrystallization of a sample from acetone raised the m. p. to 158–159° (reported,[2] 158–159°).

Hydrolysis of the acetate by the method of Reichstein and von Euw[14] gave desoxycorticosterone; after molecular distillation at 150° (0.001 mm.) and two recrystallizations from acetone–ether, this melted at 140–142° and showed no depression when mixed with an authentic sample.

(12) The diazomethane solution was distilled, dried for two hours over potassium hydroxide pellets, and then for one hour over sodium wire before use; see Fieser and Turner, THIS JOURNAL, **69**, 2341 (1947).

(13) The acetic acid was refluxed for six hours with 5% by weight of potassium permanganate, distilled and the distillate fractionated, collecting the last fraction, b.p. 117°.

Summary

A procedure has been developed for preparing acid chlorides from α,β-unsaturated keto acids using the sodium salt and oxalyl chloride in the cold. By means of this reaction it has been possible to convert 3-keto-Δ⁴-etiocholenic acid to 21-diazoprogesterone and desoxycorticosterone acetate in good yields.

(14) Reichstein and v. Euw, *Helv. Chim. Acta*, **21**, 1181 (1938).

MADISON 6, WISCONSIN RECEIVED MARCH 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF EVANS RESEARCH AND DEVELOPMENT CORPORATION]

Esters of (Carboxymethylmercapto)-succinic Acid

BY JOHN F. MULVANEY,[1a] JAMES G. MURPHY AND RALPH L. EVANS

(Carboxymethylmercapto)-succinic acid has been prepared by Fitger,[1] by Morgan and Friedmann[2] and by Larsson.[3] Larsson gives a procedure for the preparation of the *dl*-acid in excellent yield by the interaction of maleic acid and thioglycolic acid at water-bath temperature.

During an investigation of derivatives of thioglycolic acid, we prepared esters of (carboxymethylmercapto)-succinic acid of the three types indicated in Fig. 1. No attempt was made during this work to isolate any optically active forms of these esters.

Fig. 1

Type I	Type II	Type III
SCH_2COOR	SCH_2COOH	SCH_2COOR
$CHCOOR$	$CHCOOR$	$CHCOOH$
CH_2COOR	CH_2COOR	CH_2COOH

Esters of Type I.—These were prepared in the usual manner with an acid catalyst and with toluene or benzene as water-entraining agents.

The esters were purified by fractional distillation. The octadecyl ester was crystallized from toluene, alcohol and acetone.

The properties of the esters of Type I are listed in Table I. The *n*-propyl (b. p. 125–131° at 0.1 mm.) and isopropyl (b. p. 124–129° at 0.4 mm.) esters were prepared but were not purified for analysis.

Esters of Types II and III.—Preliminary attempts to prepare esters of Type II by the addition of thioglycolic acid to alkyl maleates gave only slow and partial reaction. The isolation of fumaric acid from the reaction mixture indicated hydrolysis and isomerization. When sodium thioglycolate was used, the reaction proceeded almost to completion at room temperatures.

$$NaOOCCH_2SH + ROOCCH{=}CHCOOR \longrightarrow \begin{matrix} SCH_2COONa \\ CHCOOR \\ CH_2COOR \end{matrix} \quad (1)$$

Similarly, it was found that thioglycolic acid esters reacted more completely with sodium maleate than with maleic acid to give esters of Type III.

$$ROOCCH_2SH + NaOOCCH{=}CHCOONa \longrightarrow \begin{matrix} SCH_2COOR \\ CHCOONa \\ CH_2COONa \end{matrix} \quad (2)$$

Experimental

In general, 0.25 mole of the acid was neutralized with 15% sodium hydroxide and an alcoholic solution of the ester (0.25 mole) was added. The mixture was allowed to stand at room temperature until titration with iodine showed that the addition was almost complete.

(1) Fitger, Diss. Lund, 1924.

(1a) Present address: General Aniline Works, General Aniline and Film Corporation, Grasselli, N. J.

(2) E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).

(3) E. Larsson, *Trans. Chalmers Univ. Technol.*, **47**, 3–7 (1945).

TABLE I

ESTERS OF TYPE I

R	B. p. °C.	B. p. Mm.	$n^{25}D$	d^{25}_{25}	MD Calcd.	MD Obs.	Sulfur, % Calcd.	Sulfur, % Found
Ethyl	140–145	0.8	1.4646	1.1498	70.5	70.4	10.96	10.82
n-Butyl	161–163	0.2	1.4606	1.0517	98.2	98.6	8.54	8.92
Octadecyl	50 (melting point, uncor.)						3.43	3.43

TABLE II

Compound	Formula	M. p., °C.	Analyses, % Calculated S	Calculated Na	Found S	Found Na
(Carboxymethylmercapto)-butyl-succinate[a]	$C_{14}H_{23}O_6SNa$	148	9.37	6.72	9.51	6.49
(Carboxymethylmercapto)-benzyl-succinate[a]	$C_{20}H_{19}O_6SNa$	156–157	7.81	...	8.10	...
(Carbobutoxymethylmercapto)-succinate[b,d]	$C_{10}H_{14}O_6SNa_2$	.....	10.39	...	9.98	...
(Carboctoxymethylmercapto)-succinate[b,d]	$C_{14}H_{22}O_6SNa_2$	.....	8.80	12.62	9.01	12.50
(Carbododecoxymethylmercapto)-succinate[c,d]	$C_{18}H_{30}O_6SNa_2$	.....	7.62	...	7.32	...

[a] Purified by dissolving in methanol and precipitating with ether. [b] Purified by dissolving in methanol–water (1:1) and precipitating with acetone. [c] Purified by dissolving in water and precipitating with acetone. [d] White, waxy solids. The octyl and dodecyl compounds have surface-active properties.

The compounds prepared, all as their sodium salts, are listed in Table II.

The (carboctoxymethylmercapto) disodium succinate was converted to the free acid by acidifying an aqueous solution with hydrochloric acid. The oil that separated was dissolved in ether and washed with water. The ether then was evaporated and the oil dried in vacuum. Alkali titration gave an equivalent weight of 165 (theory 160.3) $n^{25}D$ 1.4840, d^{25}_{25} 1.146.

Acknowledgment.—The authors wish to express their appreciation to Miss Lillian Weiss and Mr. J. W. Veale for assistance in the experimental work.

Summary

1. Three tri-esters, two di-esters and three mono-esters of (carboxymethylmercapto)-succinic acid (the latter two types as sodium salts) have been prepared and some of their physical constants determined.

2. An indirect method for the preparation of certain of the mono-esters and di-esters of (carboxymethylmercapto)-succinic acid is reported.

NEW YORK, N. Y. RECEIVED FEBRUARY 28, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Mechanism for the Reaction of Dioxane Sulfotrioxide with Olefins. II. Sulfonation of Styrene

BY F. G. BORDWELL AND CHRISTIAN S. RONDESTVEDT, JR.[1]

In a continuation of the attempt to elucidate the mechanism[2] of the reaction of dioxane sulfotrioxide with olefins,[3] the sulfonation of styrene has been investigated. Styrene was chosen because of its ready availability in a pure state and because preliminary studies[4] indicated that a variety of products are formed in its sulfonation.

To ensure uniformity in the sulfonating agent and a fixed ratio of dioxane to sulfur trioxide the dioxane sulfotrioxide was prepared by adding an equimolar quantity of dioxane to a solution of sulfur trioxide in ethylene dichloride. In this way a fine suspension of dioxane sulfotrioxide was obtained.

In most of the experiments of the present investigation the sulfonation mixture, prepared at −5 to 0° by dropwise addition of a solution of styrene in ethylene dichloride to the sulfonating agent, was hydrolyzed without allowing the temperature to rise above 5°. When the aqueous layer was neutralized with sodium hydroxide, the water-soluble products were sodium 2-phenylethene-1-sulfonate[4] (I), sodium 2-phenyl-2-hydroxy-1-ethanesulfonate (II) and sodium sulfate. The identity of II was established by separation from I and sodium sulfate by fractional crystallization using alcohol–water mixtures,[5] and comparison of the S-*p*-chlorobenzylthiouronium salt[6] with an authentic sample.[7] From the ethylene dichloride layer 2,4-diphenyl-1,4-butanesultone (III) was obtained.[4,8] At higher reaction temperatures the amount of I increased at the expense of II.

(1) National Research Council Predoctoral Fellow, 1946–1947. Present address: University of Michigan, Ann Arbor, Michigan. This material was abstracted from the Ph.D. Dissertation of Christian S. Rondestvedt, Jr., October, 1947.

(2) Bordwell, Suter and Webber, THIS JOURNAL, **67**, 827 (1945).

(3) Suter and co-workers, *ibid.*, **60**, 538 (1938); **63**, 978, 1594 (1941); **65**, 507 (1943); **66**, 1105 (1944).

(4) Bordwell, Suter, Holbert and Rondestvedt, *ibid.*, **68**, 139 (1946).

(5) Kharasch, Schenk and Mayo, *ibid.*, **61**, 3092 (1939).

(6) Suter and Milne, *ibid.*, **65**, 582 (1943).

(7) We wish to thank Frank Colton for carrying out this experiment.

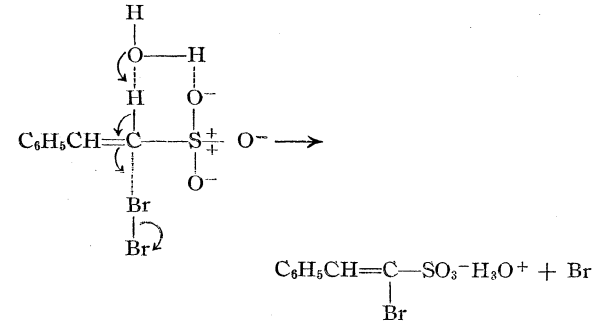
(8) This structure is assigned on the basis of unpublished results.

In order to follow conveniently the variation in the proportions of products with changing experimental conditions it was necessary to devise an analytical method for determining the relative amounts of I and II in the aqueous portions of the hydrolysis mixture. Oxidation of I with potassium permanganate has been reported to be quantitative, but not suitable for the analysis of this mixture since the presence of II interferes with the determination.[5] No reaction occurred when I was treated with hydrogen peroxide and formic acid.[9] However, titration with aqueous bromine using the bromate–bromide method was found to be rapid and quantitative. The presence of II did not affect the analytical results.

The product formed in the reaction of I with bromine water was found to be identical with that obtained in the sulfonation of β-bromostyrene with dioxane sulfotrioxide,[10] as shown by comparison of the corresponding sulfonamides. Truce[10] designated this compound as sodium 2-phenyl-1-bromoethene-1-sulfonate on the basis of its reduction to sodium 2-phenylethene-1-sulfonate under conditions similar to those used by Kohler[11] for the reduction of sodium 1-bromoethene-1-sulfonate to sodium ethene-1-sulfonate. The assigned structure[10] was substantiated in the present investigation by preparation of sodium 1-bromo-2-phenylethene-1-sulfonate from sodium 2-phenylethene-1-sulfonate in a manner comparable to Kohler's preparation of sodium 1-bromoethene-1-sulfonate by bromination of sodium ethene-1-sulfonate, and by the fact that benzaldehyde was obtained on oxidation.

It is of interest to compare the very rapid substitution reaction of sodium 2-phenylethene-1-sulfonate (I) with bromine in aqueous solution to the relatively slow addition of bromine to the double bond of 2-phenylethene-1-sulfonamide and 2-phenylethene-1-sulfonyl chloride. In acetic acid solution 2-phenylethene-1-sulfonamide decolorized an equimolar portion of bromine in about three hours (in the dark about twenty-four hours was required) to give 1,2-dibromo-2-phenyl-1-ethanesulfonamide. In the dark, carbon tetrachloride solutions of 2-phenylethene-1-sulfonyl chloride required about fifteen days for decolorization of an equimolar portion of bromine. The reaction in acetic acid was somewhat faster. When exposed to sunlight and oxygen complete decolorization in carbon tetrachloride solutions occurred in an hour. Hydrogen bromide was not evolved.

The slow rate of electrophilic addition of bromine to 2-phenylethene-1-sulfonamide and 2-phenylethene-1-sulfonyl chloride in acetic acid and carbon tetrachloride solutions is not unexpected in view of the well-known retarding effect of electron-attracting groups on the addition of bromine to olefins. The rapid attack of bromine in aqueous solution on the *alpha* carbon of the ethenesulfonate[11] and 2-phenylethene-1-sulfonate ions is undoubtedly facilitated by the negative charge on the ions. Kohler[11] showed that potassium 1,2-dibromo-1-ethanesulfonate did not undergo dehydrobromination in aqueous solutions, thus ruling out the addition of a molecule of bromine as a preliminary step in the formation of potassium 1-bromoethene-1-sulfonate in this reaction.[12] Further evidence on this point is the observation of Suter and Truce[3] that the 1-methyl-2-phenylethene-1-sulfonate ion which could react by addition but not by comparable substitution, fails to react with bromine under these conditions. A mechanism involving a molecule of water in the transition state is shown for the bromination of I.



Analysis by the isolation technique[5,7] showed that the only water-soluble products present in significant amounts in hydrolysis mixtures from sulfonations carried out below 5° were I, II and

TABLE I

SULFONATION OF STYRENE AT TEMPERATURES BELOW 5°

Expt.	Time,[a] hours	Temp., °C.	Mole per cent. of products (based on SO_3) I	II	III[b]	Na_2SO_4	% SO_3 accounted for
1	1.3[c]	0	33	48	7	8	96
	1.3[d]	0	26	55	7	8	96
2	0	0	15	72	5	5	98
3	2.25	−25	7	53	20	21	101
4	0	0	20	72	6	5	103
	1.5	2	19	74	6	4	103
	3	2	20	76	6	3	105
	4.5	2	20	74	6	4	104
	6.0	2	20	73	8	4	105
	17.5	2	21	69	9	4	103
	50	2	26	66	10	4	106

[a] Time interval from completion of addition of styrene to hydrolysis of the sulfonation mixture. [b] Yield of crude sultone. One crystallization from acetone–water usually gave a 60% recovery of reasonably pure material. [c] In this experiment the quantities were estimated by isolation of the products.[5,7] [d] The same mixture as for *c* analyzed by titration.

(9) Swern, Findley and Scanlan, THIS JOURNAL, **67**, 1786 (1945); Swern, *ibid.*, **69**, 1692 (1947).

(10) Truce, Doctoral Dissertation, Northwestern University, 1944.

(11) Kohler, *Am. Chem. J.*, **21**, 349 (1899).

(12) Ingold and Smith, *J. Chem. Soc.*, 2742 (1931), found that iodine chloride reacts with ethenesulfonic acid to give 1-iodoethene-1-sulfonic acid. Apparently they misinterpreted Kohler's work since they suggested that 2-chloro-1-iodo-1-ethanesulfonic acid was an intermediate in this reaction.

sodium sulfate. In subsequent work, therefore, I was determined by bromate–bromide titration, sulfate was determined gravimetrically and the quantity of II was taken as the difference between the total acids present and the amounts of I and sulfate determined. To complete the analysis an approximation of the quantity of III was made by evaporation of the ethylene dichloride layer and isolation of the solid product.

The results of the sulfonations carried out below 5° are summarized in Table I. Table II shows the results obtained when the sulfonation mixture was heated to 54.4° prior to hydrolysis.

TABLE II

SULFONATION OF STYRENE AT 54.4°

Time,[a] minutes	Mole per cent. of products (based on SO_3) I	II[c]	III[b]	Na_2SO_4	% SO_3 accounted for
0[d]	28	66	5	3	102
0[d]	28	64	6	4	102
12	33	58	7	3	101
15	44	45	8	3	100
23	54	36	7	2	99
33	61	31	7	1	100
48	68	27	6	1	102
72	72	25	6	0.4	101
104	74	22	5	1	102
143	74	22	5	1	102
210	74	22	4	1	101
1020	75	24	3	0.2	102

[a] Time for which sulfonation mixture was kept at 54.4°. [b] Yield of crude product. One crystallization from acetone–water gave a 60% recovery of reasonably pure material. [c] It seems probable that after a short period of heating the figures in this column also include the percentages of substances other than II (see Discussion). [d] Control taken after completion of the addition of styrene and after the reaction mixture had been allowed to stand for fifteen minutes at 10°.

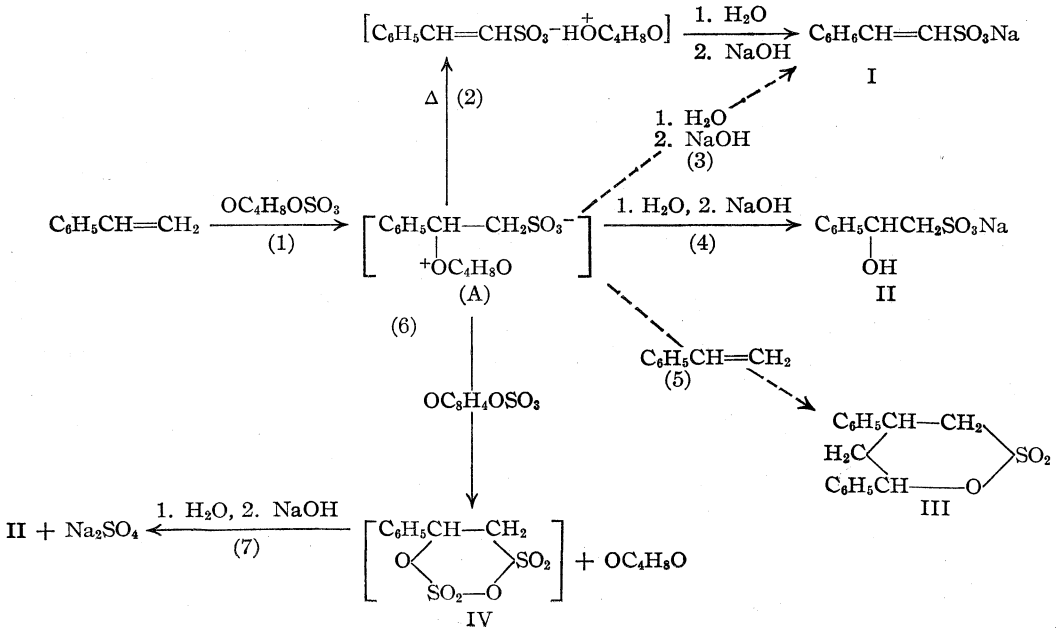
Discussion

The mode of formation previously suggested[2] for the products isolated on hydrolysis and neutralization of sulfonation mixtures obtained from the reaction of dioxane sulfotrioxide and olefins, as applied to the sulfonation of styrene, is represented on the accompanying diagram by solid-shafted arrows (reactions 1, 2, 6, 7). The arrows with broken shafts illustrate new reaction possibilities disclosed by the present investigations (reactions 3, 4, 5). Whether reactions 3, 4 and 5 are peculiar to styrene or applicable to olefins in general is yet to be determined.

At elevated temperatures I is the principal product, and reaction 2 is believed to be the primary route by which it is formed. However, at temperatures below 5° amounts of I varying from 7% to 26% were formed. Since reaction 2 is slow under these conditions (Table I), the formation of as much as 26% of I is surprising. An experiment at 2° utilizing rapid stirring and a slow addition of a more dilute solution of styrene, conditions designed to minimize local heating, resulted in 13% of I. Even at −25° (hydrolysis at 0°) 7% of I was formed. For this reason reaction 3 is tentatively suggested as an additional source of I, but this point requires further investigation.

It has been postulated[2] that the β-hydroxysulfonic acids formed on hydrolysis of these sulfonation mixtures are derived from substituted-ethionic anhydrides (reactions 6 and 7). The fact that equimolar quantities of II and sodium sulfate are not formed in the sulfonation of styrene below 5° eliminates this as the sole source of II. The bulk of II is believed to be formed by reaction 4.

Of the three species (A, III and IV) postulated as being present in the sulfonation mixture at temperatures below 5° only III has been isolated.



Isolation of alkylethionic anhydrides analogous to IV from sulfonation mixtures has been accomplished on a few occasions, but our attempts to isolate such a compound in the present investigation were unsuccessful. The presence of IV is assumed since it appears to be a logical source of the sulfuric acid obtained on hydrolysis.[13]

If (A) is the major source of II, as is suggested, it must possess surprisingly great stability since the amount of II formed on hydrolysis is not changed appreciably when the sulfonation mixture was allowed to stand at 2° for fifty hours (Table I). This stability is probably made possible by solvation with dioxane, since, in the absence of dioxane, styrene is polymerized by sulfur trioxide in ethylene dichloride solution.

If reactions 1, 5 and 6 alone are occurring below 5° prior to hydrolysis, reactions 5 and 6 should be interdependent when equimolar quantities of styrene and sulfur trioxide are used. The molar quantities of III and sulfuric acid should, therefore, be equal. This is only approximately true (Table I), but the amounts are at least of comparable magnitudes. The relatively small quantities of II and sulfuric acid obtained at −5 to 5° indicates that reaction 1 is faster under these conditions than either 5 or 6, since it does not seem likely that either of the latter is reversible. The increased quantity of sulfuric acid obtained at −25° is probably due to incompleteness of reaction 1. The resulting relative increase in the ratio of styrene to (A) leads to an increase in the proportion of III.

Previously[4] a 60% yield of practically pure I was isolated from the first three crops of the hydrolysis and neutralization products of a sulfonation carried out at temperatures above 5°. Using the analytical procedure developed for determination of I the quantity of I present in these crops was found to be 94, 98 and 96%, respectively. The residue was found to contain 56% of I, bringing the total yield of I in this experiment to 75%. A more detailed study of the formation of I at elevated temperatures has now been made (Table II). The increase in the quantity of I is explained by an acceleration of reaction 2. Under these conditions (A) should be converted completely to the dioxane salt corresponding to I, and, in time, the quantity of II should drop to low values. The minimum figure of 22% for II recorded in Table II after extended heating is probably accounted for by the formation of products other than those included in the diagram. Since II was determined only by difference the figures could represent, for example, disulfonation products.

The elimination of the proton in reaction 2 is most likely accomplished with the aid of either an extraneous dioxane molecule or the uncoördinated oxygen of the dioxane molecule incorporated in (A).[14] It was hoped that kinetic data would allow a choice between these two possibilities, but the complexity of the reaction at elevated temperatures discouraged further attempts along these lines.

(13) An alternative representation would be $C_6H_5C^+HCH_2SO_2OSO_3^-$. Other types of anhydrides may also be present.

(14) Models show that this oxygen can approach the α-hydrogen atom closely.

Acknowledgment.—We wish to thank the National Research Council for the Predoctoral Fellowship which supported this work.

Experimental[15]

Dioxane Sulfotrioxide.—The method of Suter and Evans[3] was used in some experiments, but the following method was preferred. Sulfur trioxide was distilled from an all-glass distillation apparatus containing 60% fuming sulfuric acid or "Sulfan B"[16] into dry ethylene dichloride contained in a tared flask cooled by a cold water-bath. The weight of sulfur trioxide was determined by difference to 0.05 g. An equimolar quantity of dioxane, purified by refluxing with sodium and distilling, was then added with rapid stirring. The internal temperature of the flask must be maintained below 5° in this operation to prevent charring. Since the coördination of sulfur trioxide with dioxane is very exothermic, the permissible rate of addition depends on the efficiency of cooling. For large runs it is advantageous to use a cooling bath temperature of about −40°. The reagent was obtained as fine granules.

Hydrolysis of the reagent with cold water gave 99.6% of the theoretical quantity of sulfuric acid, as determined by titration. No unsaturated material was detectable by a bromate–bromide titration.

Sulfonation of Styrene below 5° (Isolation of the Products[7]).—An equimolar quantity of styrene, dissolved in about an equal volume of ethylene dichloride, was added dropwise to dioxane sulfotrioxide suspended in ethylene dichloride. The mixture was stirred and the temperature kept below 5° (usually below 0°) during the addition. Hydrolysis was effected by pouring the reaction mixture into ice water. The ethylene dichloride layer was separated (the use of ether was helpful in overcoming the emulsions sometimes encountered) and washed; after drying, the solvent was removed at room temperature leaving crude 2,4-diphenyl-1,4-butanesultone[8] (III) as the residue. The aqueous portions were combined and neutralized with barium carbonate, and the barium sulfate was collected and determined gravimetrically. The filtrate was evaporated and three successive crops of barium sulfonates collected. A portion of the sulfonates from each crop was converted to the sodium salts by metathesis. Five grams of the sodium sulfonates from the first crop were refluxed with 50 ml. of 90% alcohol for forty-five minutes, the mixture was allowed to cool to room temperature and filtered. This process was repeated with further portions of 90% alcohol until the residue gave a negligible test for unsaturation with cold aqueous potassium permanganate solution. The residue weighed 2.0 g. and gave an 80% yield of S-*p*-chlorobenzylthiouronium 2-phenyl-2-hydroxy-1-ethanesulfonate, m. p. 179–180°, which gave no depression in melting point when mixed with an authentic sample.[6] The salt obtained by evaporating the alcohol filtrates was largely sodium 2-phenylethene-1-sulfonate (I), as shown by converting it to its S-benzylthiouronium salt[4] in 80% yield. The second and third crops were analyzed in a similar fashion. The percentages of crude I isolated from the three crops were 60, 43 and 0%, respectively. Titration of these samples by the bromate–bromide method showed 49, 36 and 2% of I. The mean values are given in Table I.

The analytical method used for subsequent sulfonations, the results of which are summarized in Table I, was similar to that described below for the analysis of the sulfonation run at 54.4°. To make certain that the determination for

(15) The microanalyses were performed by Miss Patricia Craig and Miss Margaret Hines.

(16) The γ-form of sulfur trioxide containing an inhibitor to prevent polymerization. This material was kindly furnished by the General Chemical Company, 40 Rector Street, New York, N. Y.

the experiments carried out over long periods of time was valid, the water-soluble products from a sulfonation mixture kept at 2° for fifty hours prior to hydrolysis were partially separated by the fractional crystallization technique described above. The formation of 2-phenyl-2-hydroxy-1-ethanesulfonic acid and 2-phenylethene-1-sulfonic acid as the principal products was confirmed.

Sodium 1-Bromo-2-phenylethene-1-sulfonate.—A solution of 1.05 g. (0.005 mole) of sodium 2-phenylethene-1-sulfonate was treated with bromine water until a permanent yellow color remained. The solution was evaporated to dryness on a steam-bath with the aid of a current of air. The residue, after crystallization from 90% alcohol, weighed 1.20 g. (87%).

Anal. Calcd. for $C_8H_6O_3SBrNa$: Na, 8.07; Br, 28.03. Found: Na, 8.13; Br, 27.33.

A portion was converted to the sulfonamide (m. p. 130–131°) by the procedure used by Truce,[10] and this showed no depression in melting point when mixed with a sample of his 1-bromo-2-phenylethene-1-sulfonamide, m. p. 130–131°.

1,2-Dibromo-2-phenyl-1-ethanesulfonamide.—A solution of 1.0 g. of 2-phenylethene-1-sulfonamide[4] in about 50 ml. of acetic acid was treated with an equimolar quantity of bromine, and the solution kept in sunlight for three hours. Oxygen appears to catalyze the reaction since decolorization occurs first at the surface. Concentration of the acetic acid at room temperature to about 15 ml. gave 1.0 g. (55%) of crystalline material. After two crystallizations from benzene, colorless needles, m. p. 161–162°, were obtained.

Anal. Calcd. for $C_8H_9O_2Br_2NS$: C, 27.96; H, 2.73. Found: C, 28.00; H, 2.79.

Triethylammonium bromide precipitated immediately when 0.1 g. of 1,2-dibromo-2-phenyl-1-ethanesulfonamide in a warm benzene solution was treated with excess triethylamine. Evaporation of the benzene and crystallization from water gave 1-bromo-2-phenylethene-1-sulfonamide.[10]

Sulfonation of Styrene at 54.4°.—Dioxane sulfotrioxide was prepared from 76.1 g. (0.951 mole) of sulfur trioxide, 83.7 g. (0.951 mole) of dioxane and 150 ml. of dry ethylene dichloride. A solution of 99.0 g. (0.951 mole) of styrene in 30 ml. of ethylene dichloride was added to this reagent in the course of two and one-third hours, the temperature being maintained at 5–7°. After an additional fifteen minutes at 10° two aliquots were withdrawn (by means of a 10-ml. pipet), weighed and hydrolyzed. The remaining solution was heated on the steam-bath to 55° as rapidly as possible, whereupon it was placed in a thermostat at 54.4°. Further aliquots were withdrawn at intervals. The fraction of sulfur trioxide present in each aliquot was determined from the weight of the reaction mixture and the weight of the aliquot. The aliquots were quenched immediately in ice-water, the weight of the aliquot being determined by the increase in weight of the flask holding the ice-water. Ether was added to each aliquot and the layers separated, using sodium chloride to break emulsions where necessary. After washing thoroughly the organic layer was dried and evaporated to dryness at room temperature, the weight of the residue being taken as an approximation of the quantity of 2,4-diphenyl-1,4-butanesultone[3] (III). The water layer was titrated (to phenolphthalein) with standard sodium hydroxide, then acidified and treated with 0.1 mole of barium chloride per mole of sulfur trioxide in the aliquot. The barium sulfate was determined gravimetrically (analysis reproducible to within 1% of the total sulfur trioxide). The filtrate was titrated by the bromate–bromide method to determine the amount of sodium 2-phenylethene-1-sulfonate present. The results are summarized in Table II.

Summary

1. Sulfonation of styrene at temperatures below 5° gave (after hydrolysis and neutralization) sodium 2-hydroxy-2-phenyl-1-ethanesulfonate (II) as the major product. β-Phenylethionic anhydride was ruled out as the principal precursor of II.

2. Titration with aqueous bromine using the bromate–bromide method was used to determine sodium 2-phenylethene-1-sulfonate (I) in the presence of II. A mechanism is given for the rapid reaction of I with bromine in aqueous solution.

3. The olefin–sulfur trioxide intermediate complex previously postulated[2] was useful in accounting for the various products formed in the sulfonation of styrene.

EVANSTON, ILLINOIS RECEIVED MARCH 29, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Formation of Ethers in the Preparation of Pentaerythritol

BY STANLEY WAWZONEK AND DONALD A. REES[1,2]

The preparation of pentaerythritol from acetaldehyde and formaldehyde is always accompanied by the formation of dipentaerythrityl ether.[3]

Attempts[3] to arrive at a mechanism by increasing the amount of dipentaerythrityl ether formed in this condensation proved unsuccessful. The only conclusion made was that pentaerythritol was not necessary for the formation of dipentaerythrityl ether.

One possible mechanism for the formation of dipentaerythrityl ether is outlined in the following series of reactions

$$CH_3CHO + HCHO \underset{}{\overset{OH^-}{\rightleftharpoons}} CH_2OHCH_2CHO \quad (1)$$

$$CH_2OHCH_2CHO \rightleftharpoons CH_2{=}CHCHO + H_2O \quad (2)$$

$$CH_2{=}CH{-}CHO + HOCH_2CH_2CHO \rightleftharpoons O(CH_2CH_2CHO)_2 \quad (3)$$

$$O(CH_2CH_2CHO)_2 + 6HCHO + 2OH^- \longrightarrow O(CH_2C(CH_2OH)_3)_2 + 2HCOO^- \quad (4)$$

The existence of an equilibrium between acrolein and β-hydroxypropionaldehyde in aqueous and acid solutions has already been demonstrated by Lucas.[4] Addition of an alcohol to acrolein in

(1) A. C. S. Pre-Doctoral Fellow, 1946–1947.

(2) Abstracted from a thesis by Donald A. Rees, submitted to the Graduate Faculty of the State University of Iowa in partial fulfilment of the requirements for the degree of Doctor of Philosophy, August, 1947.

(3) Friederick and Brun, *Ber.*, **63**, 2681 (1930).

(4) Lucas and Pressman, THIS JOURNAL, **64**, 1953 (1942).

the presence of alkali is the subject of a patent.[5]

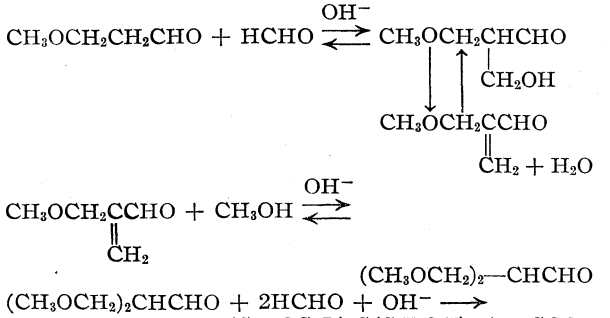
In the present investigation evidence has been obtained for the formation of ethers of pentaerythritol, by the reactions cited above, in the Tollens condensation.

The formation of pentaerythritol under the usual conditions[6] in an aqueous solution containing 50% methanol by volume gave a product which, to aid separation, was propionated. The mixture of propionates obtained was separated by distillation into pentaerythrityl tetrapropionate, the tripropionate of methylpentaerythrityl ether, and the dipropionate of dimethylpentaerythrityl ether. Identification was accomplished by saponification to pentaerythritol, methylpentaerythrityl ether and dimethylpentaerythrityl ether.

Methylpentaerythrityl ether and dimethylpentaerythrityl ether were also separated by chromatographic adsorption of their *p*-phenylazobenzoates.

The formation of methylpentaerythrityl ether indicates that acrolein is an intermediate in the formation of pentaerythritol and that it can add alcohols that may be present to form ethers. The ethers on further reaction with formaldehyde give ethers of pentaerythritol. In the present investigation methyl alcohol gave methylpentaerythrityl ether. Under the usual conditions[6] for preparing pentaerythritol, β-hydroxypropionaldehyde or products resulting from the reaction of β-hydroxypropionaldehyde and formaldehyde or even pentaerythritol can add to acrolein and give rise to dipentaerythrityl ether. The reaction of the last two with more than one molecule of acrolein would give rise to the polypentaerythrityl ethers mentioned in the patent literature.

The formation of dimethylpentaerythrityl ether is entirely consistent with the mechanism proposed. Its formation could proceed from β-methoxypropionaldehyde.



Similar reactions may be involved in the formation of some of the polypentaerythrityl ethers.

Experimental[7]

Preparation of Pentaerythritol in 50% Methanol.—To a suspension of paraformaldehyde (240 g.) in water (750 ml.) and methanol (750 ml.) containing 63 g. of acetaldehyde, there was added 53 g. of powdered quicklime in rather large portions at first in order to bring the temperature to 45° and then at a rate to maintain the temperature between 50–55°. The mixture became slightly yellow in color. After the addition was complete, stirring was continued for an additional three hours. To the resulting mixture, oxalic acid (141 g.) was added; the solid was removed by filtration and washed with two 500-ml. portions of water. The combined filtrates were evaporated under reduced pressure to dryness. The last traces of water were removed by adding 200 ml. of propionic acid and repeating the distillation under reduced pressure. The product obtained was a dark brown sirup.

Separation of the Products.—To a mixture of the sirup and propionic anhydride (780 ml.) at 0°, concentrated sulfuric acid (30 ml.) was added dropwise keeping the temperature below 4°. The resulting solution was stirred overnight at room temperature and then at 100° until solution of the sirup was complete. After two more hours at this temperature, the solution was heated under reduced pressure to remove the excess propionic anhydride, and the propionic acid formed. The liquid obtained was cooled, poured onto ice (1500 g.) and neutralized with sodium bicarbonate. Extraction with ether gave 287 g. of a deep brown colored sirup which was first rapidly distilled at 0.1 mm. from a Claisen flask. A second distillation at 4 mm. through a Vigreux column gave three distinct fractions.

Fraction	Yield, g.	B. p., °C.
I	14.5	135–148
II	52.0	165–172
III	167.4	172–197

Fraction I upon refractionation gave the dipropionate of dimethylpentaerythrityl ether, b. p. 135–138° at 6 mm., $n^{25}D$ 1.4361, d^{20} 1.057.

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.50; H, 8.75; OCH_3, 22.46. Found: C, 56.62; H, 8.67; OCH_3, 20.41.

The dipropionate of dimethylpentaerythrityl ether (5.4 g.) was refluxed with a slight excess of sodium methoxide in methanol (20 ml.) for two hours. The resulting solution was neutralized with dilute hydrochloric acid and evaporated to dryness. Extraction with chloroform gave an oil which was recrystallized from (60–70°) petroleum ether; m. p. 34–35°; yield 0.5 g. A mixture with an authentic sample[8] melted at the same temperature.

Fraction II upon refractionation gave the tripropionate of methylpentaerythrityl ether, b. p. 170–172° at 5–6 mm., $n^{25}D$ 1.4410, d^{20} 1.081.

Anal. Calcd. for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23; OCH_3, 9.75. Found: C, 56.79; H, 8.18; OCH_3, 9.03.

The tripropionate of methylpentaerythrityl ether (17 g.) was saponified in a similar manner to that used for the dipropionate of dimethylpentaerythrityl ether. The oil obtained was crystallized from chloroform; m. p. 65–67°; yield 2.3 g. A distillation at reduced pressure (2 mm.) followed by a crystallization from chloroform gave white crystals melting at 71–72°. A mixture with an authentic sample[8] melted at the same temperature.

Fraction III upon refractionation gave pentaerythrityl tetrapropionate, b. p. 184–186° at 3 mm.; m. p. 35–37°. This compound is reported in the patent literature[9] as a liquid.

Anal. Calcd. for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.45; H, 7.81.

Pentaerythrityl tetrapropionate (5.0 g.) was saponified by refluxing with sodium methoxide (0.02 g. of sodium) in dry methanol (50 ml.). Completion of the reaction was indicated by complete solution of a few drops of the reaction mixture in water. Upon cooling pentaerythritol

(5) Heyse, German Patent 554,946 [*C. A.*, **26**, 5964 (1932)].

(6) Schurink, "Organic Syntheses," Coll. Vol. I, 425 (1941).

(7) Melting points are corrected while boiling points are not.

(8) Orthner and Freyss, *Ann.*, **484**, 131 (1930).

(9) Holt, U. S. 2,031,603; *C. A.*, **30**, 2200 (1936).

crystallized from the reaction mixture. One crystallization from water gave a product (1.5 g.) melting at 259°.

Deacylation and Chromatographic Separation of Fraction I.—Fraction I (3 g.) was deacylated in a similar fashion to that used for pentaerythrityl tetrapropionate. Removal of the methanol gave a sirup which was treated in dry pyridine (50 ml.) and *p*-phenylazobenzoyl chloride[10] (3 g.). The mixture was shaken for a short time and then heated at 85° for three days. The resulting solution was shaken with water (2 ml.) for fifteen minutes and then poured onto ice (300 g.) with vigorous stirring. The resulting mixture was neutralized with sodium bicarbonate and extracted repeatedly with chloroform. The combined chloroform extracts were washed once with water and dried. Chromatographic separation was performed on a column of silicic acid 60 cm. long and 3.3 cm. in diameter. Two distinct bands were obtained. Using chloroform as the eluent, the lower band of the tri-*p*-phenylazobenzoate of methylpentaerythrityl ether was run completely through the column in order to separate the di-*p*-phenylazobenzoate of dimethylpentaerythrityl ether from the *p*-phenylazobenzoic acid. The chloroform solution of the tri-*p*-phenylazobenzoate of methylpentaerythrityl ether was concentrated to 55 ml., mixed well with ethanol (100 ml.) and allowed to stand at 0° until no more precipitate formed. The light orange crystals were filtered, washed with ethanol and recrystallized from ligroin, m. p. 190–191°.

Anal. Calcd. for $C_{45}H_{38}N_6O_7$: C, 69.77; H, 4.95; azoyl, 81.0; mol. wt., 774. Found: C, 70.08; H, 4.87; azoyl, 80.4; mol. wt. (Rast), 773, 793.

The di-*p*-phenylazobenzoate of dimethylpentaerythrityl ether was separated mechanically and removed from the silicic acid with a mixture of chloroform and ethanol. Removal of the solvent gave an orange solid which was recrystallized from ligroin, m. p. 93–94°.

Anal. Calcd. for $C_{33}H_{32}O_6N_4$: C, 68.27; H, 5.51; Found: C, 67.50; H, 5.25.

(10) Coleman, Nichols, McCloskey and Auspon, "Organic Syntheses," **25**, 87 (1945).

Summary

The Tollens condensation of acetaldehyde with formaldehyde in 50% methanol gives a mixture of pentaerythritol, methylpentaerythrityl ether and dimethylpentaerythrityl ether.

A mechanism for the formation of ethers in the preparation of pentaerythritol is proposed.

IOWA CITY, IOWA RECEIVED FEBRUARY 16, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Oxidations of Certain Polyacetyl-β-D-thioglycosides to the Corresponding Sulfones

BY WILLIAM A. BONNER AND RICHARD W. DRISKO

A single paper by Wrede and Zimmermann[1] seems to be the only report to date considering the oxidation of carbohydrate derivatives containing divalent sulfur. These investigators prepared di-tetraacetylglucosyl sulfone, di-tetraacetylgalactosyl sulfone, di-heptaacetylcellobiosyl sulfone and methyl 6-sulfo-bis-(6-desoxy-2,3,4-triacetyl-β-D-glucoside) by oxidation of the corresponding sulfides with potassium permanganate in acetic acid. Treatment of the first three of these compounds with ammonia in methanol led to the corresponding deacetylated substances. Since the chemistry of the sulfone derivatives in the sugar series has received little attention, and since no sulfones related to the simple thioglucosides have been prepared, it seemed desirable to prepare and study a few representative members of this class of compounds.

When phenyl tetraacetyl-β-D-thioglucoside was dissolved in acetic acid and treated with a slight excess of aqueous potassium permanganate, phenyl tetraacetyl-β-D-glucosyl sulfone resulted in excellent yield and purity. Phenyl triacetyl-β-D-xylosyl, phenyl triacetyl-D-arabinosyl, and ethyl tetraacetyl-β-D-glucosyl sulfones were similarly prepared. Hydrogen peroxide in acetic acid, after the method of Gilman and Beaber,[2] was also found effective in oxidizing thioglycosides to the corresponding sulfones. Phenyl, benzyl and ethyl tetraacetyl-β-D-glucosyl sulfones were prepared in good yield in this manner. It is noteworthy that when hydrogen peroxide was used as oxidant, the oxidation process was apparently attended by deacetylation of the acetylated thioglucoside despite the acetic acid solvent. This unexpected phenomenon is under further investigation at the present time.

The alkyl and aryl polyacetyl-β-D-glycosyl sulfones prepared in this study were white, nicely crystalline substances. The physical properties of the sulfones prepared in this study are contrasted with those of the corresponding parent polyacetyl-β-D-thioglycosides in Table I. It is seen that oxidation of the divalent sulfur atom in the acetylated thioglycoside to the sulfone state brings about the substantial melting point increase usually observed in converting a thioether to its sulfone.[3] Accurate correlations of the trends in the change of optical activity accompanying oxidation of the thioglycoside to its sulfone cannot be made on the basis of the data at hand, but it is apparent from Table I that such changes in rotatory power probably depend both upon the nature of the thio-aglucone and the configuration of the glycosyl residue.

By use of the calculated quantity of potassium permanganate as oxidant an attempt has been made to convert phenyl tetraacetyl-β-D-thioglucoside into phenyl tetraacetyl-β-D-glucosyl sulfoxide, a typical representative of the class intermediate

(1) Wrede and Zimmermann, *Z. physiol. Chem.*, **148**, 65 (1925).

(2) Gilman and Beaber, THIS JOURNAL, **47**, 1449 (1925).

(3) *Cf.* C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 661 ff.

TABLE I

COMPARISON OF PROPERTIES OF SEVERAL ACETYLATED THIOGLYCOSIDES WITH THE CORRESPONDING SULFONES

Compound	Acetylated thioglycoside M. p., °C.	$[\alpha]_D$, °	Acetylated sulfone M. p., °C.	$[\alpha]_D$, °
Phenyl β-D-thioglucoside	117[4]	−17.5[4,a]	189.5	−26.9[a]
Phenyl β-D-thioxyloside	78[4]	−58.9[4,a]	154.0	−86.8[a]
Phenyl D-thio-arabinoside	Sirup	+15.7[a]	147.0	+29.4[a]
Benzyl β-D-thioglucoside	98[5]	−93.1[5,b]	199.0	−48.6[b]
Ethyl β-D-thioglucoside	83–84[6]	−27.25[6,b]	154.5	−16.4[b]

[a] In chloroform solution. [b] In ethylene dichloride solution.

in oxidation state between the thioglycosides and their sulfones. Instead of isolating the desired sulfoxide, however, a mixture of the starting thioglucoside and the corresponding sulfone was obtained. It is possible that the sulfoxide, once formed, is more readily oxidized to the sulfone than is the remaining unoxidized thioglucoside oxidized to the sulfoxide.

It was found that by the action of ammoniacal methanol phenyl triacetyl-β-D-xylosyl and phenyl tetraacetyl-β-D-glucosyl sulfones could be readily deacetylated. Both deacetylation products were crystalline solids, the latter forming a hydrate. Both products rapidly reduced Benedict solution. Wrede and Zimmermann[1] similarly report reducing properties for their sulfone derivatives. The deacetylation product of the glucose derivative has been reacetylated to yield its previous acetate, and has been propionylated to give the corresponding tetrapropionate.

An initial attempt has been made to determine the ring structure of the above deacetylation products by their oxidation with periodic acid. The reaction observed, however, seems to be more complex than that usually noted[7] in the periodic acid oxidation of sugar derivatives, since the quantity of periodic acid consumed is not that predicted. Investigations into the cause of this behavior and further ring size studies are currently in progress.

Experimental Part

Phenyl Tetraacetyl-β-D-glucosyl Sulfone.—Phenyl tetraacetyl-β-D-thioglucoside (1.00 g.) was dissolved in glacial acetic acid (25 ml.). To the solution was added slowly with stirring a 5% aqueous solution of potassium permanganate containing 0.53 g. (10% excess) of the oxidant. The mixture was heated on the hot-plate for five minutes at the end of which it had begun to boil. It was cooled and treated with a saturated aqueous solution of sodium bisulfite until clear. On dilution of the clear solution with 125 ml. of water the sulfone precipitated as a white solid; yield 0.93 g. (87%), m. p. 189.5°.[8] On recrystallization from 2-propanol the m. p. was unchanged and the sample had $[\alpha]^{24}D$ −26.9° (chloroform; *c*, 1.895).

In the peroxide oxidation phenyl tetraacetyl-β-D-thioglucoside (10 g.) was dissolved in glacial acetic acid (75 ml.) and treated with 30% hydrogen peroxide (14 g., 173% excess). The mixture was refluxed for two hours, cooled, and poured into an excess of water. No precipitate formed, suggesting that the compound had undergone deacetylation during the course of oxidation. The mixture was distilled to dryness *in vacuo* and the residue treated with acetic anhydride (75 ml.) and sodium acetate (1 g.). After refluxing for one and one-half hours the acetylation mixture was poured into water to give a brown oil which solidified on rapid stirring. The crude material was filtered, dried, and weighed 7.0 g. (65%). After recrystallization from 2-propanol the m. p. was 188° and $[\alpha]^{21}D$ −27.2° (chloroform; *c*, 8.019).

Anal. Calcd. for $C_{20}H_{24}O_{11}S$: C, 50.85; H, 5.12; S, 6.80. Found: C, 50.58, 50.71; H, 5.14, 5.11; S, 6.84.

The failure to observe a precipitate on pouring the reaction mixture from the peroxide oxidation into water was interpreted as indicative of accompanying deacetylation. To test this supposition several test-tube experiments were undertaken.

Four test-tubes were charged with the following mixtures: Tube A, phenyl tetraacetyl-β-D-thioglucoside (0.50 g.) and acetic acid (8 ml.); Tube B, phenyl tetraacetyl-β-D-thioglucoside (0.50 g.), acetic acid (8 ml.) and 30% hydrogen peroxide (1.0 g.); Tube C, phenyl tetraacetyl-β-D-glucosyl sulfone (0.50 g.), acetic acid (8 ml.), and 30% hydrogen peroxide (1.0 g.); Tube D, acetic acid (8 ml.) and 30% hydrogen peroxide (1.0 g.). The tubes were placed in boiling water for two hours and cooled. Then phenyl tetraacetyl-β-D-glucosyl sulfone (0.50 g.) was dissolved in Tube D. The contents of each tube were poured into 125 ml. of water, and the four resulting mixtures placed at 0° overnight. The products were filtered, rinsed with water, and air-dried. Tube A gave unchanged thioglucoside (0.37 g., m. p. 115.5°). Tubes B, C and D gave phenyl tetraacetyl-β-D-glucosyl sulfone as follows: Tube B, (0.19 g., m. p. 180°); Tube C, (0.43 g., m. p. 187.5°); Tube D, (0.46 g., m. p. 188°). The low yield and m. p. of the product from Tube B is interpreted as due to deacetylation accompanying the oxidation of the thioglucoside.

Phenyl Triacetyl-β-D-xylosyl Sulfone.—Phenyl triacetyl-β-D-thioxyloside (1.00 g.) dissolved in acetic acid (15 ml.) was treated with potassium permanganate (0.63 g., 10% excess) dissolved in water (10 ml.). The mixture was heated for thirty minutes on the steam-bath, then cooled, clarified by addition of sufficient solid sodium bisulfite, and diluted with 1–5 ml. of ice water. There resulted 1.09 g. (99%) of crude sulfone, m. p. 151°. After three recrystallizations from 2-propanol the compound had m. p. 154° and $[\alpha]^{22}D$ −86.8° (chloroform; *c*, 1.729).

Anal. Calcd. for $C_{17}H_{20}O_9S$: C, 51.0; H, 5.04. Found: C, 51.0; H, 5.11.

Phenyl Triacetyl-D-thioarabinoside.—Acetyl bromide (27 ml., equiv. amount) was cooled to 0° in a salt–ice mixture. D-Arabinose (10 g.) (α,β-mixture) was added with mechanical stirring over a period of twenty minutes. The cold bath was removed and the mixture allowed to warm slowly. Whenever the reaction became too vigorous as evidenced by excessive evolution of hydrogen bromide the cold bath was momentarily replaced. After twenty minutes of such treatment the reaction mixture was a homogeneous, amber fluid. It was stirred at room temperature for an additional twenty-four hours, then diluted with chloroform (100 ml.). The solution was washed with ice water, cold bicarbonate solution, and ice water, then treated with calcium chloride until clear. Removal of the solvent *in vacuo* at 45–50° resulted in 15.9 g. (70%) of crude acetobromo-D-arabinose, a thick, crystalline paste.

The crude product above (15.9 g.) was dissolved in

(4) Purves, THIS JOURNAL, **51**, 3619 (1929).

(5) Schneider, Sepp and Stiehler, *Ber.*, **51**, 214 (1918).

(6) Schneider, Gille and Eisfeld, *ibid.*, **61**, 1244 (1928).

(7) Jackson in Chap. 8, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944.

(8) All melting points are corrected.

chloroform (75 ml.) and treated with ethanol (75 ml.) containing potassium hydroxide (2.63 g., one equiv.) and thiophenol (5.3 ml., 10% excess) after the manner of Purves.[3] After refluxing forty minutes the mixture was washed twice with water, once with 10% potassium hydroxide solution, again with water, then dried over sodium sulfate and decolorized by filtration through Norit and Celite. Removal of the solvent at 80° *in vacuo* left 7.8 g. (45%) of clear, amber sirup. This showed no tendency to crystallize on standing in 2-propanol, in agreement with the observation of Fletcher and Hudson.[9] The 2-propanol solution was, therefore, poured into water, the mixture extracted with ether, and the extract washed as above. The resulting sirup obtained after drying and distillation of solvent was used without further purification; $[\alpha]^{23}D$ +15.7° (chloroform; *c*, 4.583).

Anal. Calcd. for $C_{11}H_{11}O_6S(OCCH_3)_3$: acetyl, 35.1. Found:[10] acetyl, 34.5.

Phenyl Triacetyl-D-arabinosyl Sulfone.—One gram of the sirupy product above was oxidized exactly as described for the corresponding xylose derivative. The oxidation mixture was poured into water and the milky suspension extracted with ether. The extract was washed with water, bicarbonate solution and water, then dried over anhydrous sodium sulfate. Removal of the solvent left a clear sirup which, on treatment with 2-propanol, gave 0.50 g. (46%) of crude solid product, m. p. 144 to 145°. After four recrystallizations from 2-propanol the substance had m. p. 147° and $[\alpha]^{23}D$ +29.5° (chloroform; *c*, 1.290).

Anal. Calcd. for $C_{17}H_{20}O_9S$: C, 51.0; H, 5.04. Found: C, 51.2; H, 5.02.

Benzyl Tetraacetyl-β-D-glucosyl Sulfone.—Benzyl tetraacetyl-β-D-thioglucoside[4] (2.0 g.) was dissolved in acetic acid (20 ml.), and 30% hydrogen peroxide (5 g.) was added. The mixture was refluxed for two hours, the solvent evaporated under reduced pressure, and the residue acetylated with acetic anhydride (50 ml.) and sodium acetate (2 g.) as before. Isolation of the product in the previous fashion gave 1.6 g. (75%) of crude product, m. p. 196.5°. One recrystallization from 2-propanol gave the pure material, m. p. 199°, $[\alpha]^{23}D$ −44.6° (chloroform; *c*, 1.995), $[\alpha]^{22}D$ −48.6° (ethylene dichloride; *c*, 1.523).

Anal. Calcd. for $C_{13}H_{16}O_7S(OCCH_3)_4$: C, 51.8; H, 5.39; acetyl, 35.4. Found: C, 51.7; H, 5.34; acetyl, 35.7.

Ethyl Tetraacetyl-β-D-glucosyl Sulfone.—Ethyl tetraacetyl-β-D-thioglucoside[4] (5.0 g.) was refluxed for two hours in acetic acid (100 ml.) containing 30% hydrogen peroxide (18 g.). The acetic acid was distilled *in vacuo* with heating below 70°, and the residue acetylated and processed in the previous manner. There resulted 5.6 g. (103%) of crude product, m. p. 154°. After one recrystallization from 2-propanol the pure product had m. p. 154.5°, $[\alpha]^{26}D$ −15.0° (chloroform; *c*, 1.334), $[\alpha]^{22}D$ −16.4° (ethylene dichloride; *c*, 1.095).

Anal. Calcd. for $C_8H_{12}O_7S(OCCH_3)_4$: C, 45.3; H, 5.70; acetyl, 40.7. Found: C, 45.5; H, 5.83; acetyl, 40.9.

Ethyl tetraacetyl-β-D-thioglucoside (0.60 g.) was dissolved in acetic acid (25 ml.) and 5% potassium permanganate solution (8.5 g., 32% excess) added. After heating five minutes the mixture was cooled and processed as in previous permanganate oxidations. The crude product weighed 0.44 g. (68%) and had m. p. 154.5° and $[\alpha]^{23}D$ −15.5° ($CHCl_3$; *c*, 1.611).

Attempted Oxidation of Phenyl Tetraacetyl-β-D-thioglucoside to Sulfoxide.—Phenyl tetraacetyl-β-D-thioglucoside (2.00 g.) was dissolved in acetic acid (25 ml.). To this was slowly added with stirring an aqueous solution (25 ml.) containing 0.49 g. (theoretical amount for oxidation to the sulfoxide) of potassium permanganate. The solution was warmed for five minutes on the hot-plate, cooled, clarified with saturated bisulfite solution, and diluted to 125 ml. with water. The flocculent precipitate was filtered, rinsed and air-dried, m. p. 125° with preliminary softening. This was recrystallized four times from a mixture of acetone and water giving successive melting points of 145, 155, 158–160 and 162–164°. It was then recrystallized six times from 2-propanol to give successive melting points of 172–174°, 176–177°, 176–178°, 183–185°, 187–187.5° and 188°. All melting points but the last two showed preliminary softening. A mixed melting point of the final product with phenyl tetraacetyl-β-D-glucosyl sulfone showed no depression (188°). From the initial filtrate there was obtained an additional 0.18 g. of solid on further standing, m. p. 111°. On recrystallization from 2-propanol this melted at 114° and showed no mixed m. p. depression (114°) with a sample of phenyl tetraacetyl-β-D-thioglucoside of m. p. 115°.

Phenyl β-D-Xylosyl Sulfone.—Phenyl triacetyl-β-D-xylosyl sulfone (0.66 g.) was dissolved in methanol (30 ml.) which had been saturated with ammonia, and the solution permitted to stand for four days in an open beaker. The solvent evaporated to leave a white solid, m. p. 156°, dec. The product, after recrystallization from 2-propanol, readily reduced Benedict solution. The recrystallized product was extracted four times with hot ether. The remaining solid weighed 0.24 g. (53%) and had m. p. 160° dec., unchanged on further recrystallization from 2-propanol; $[\alpha]^{19}D$ was −44.8° (water; *c*, 1.137).

Anal. Calcd. for $C_{11}H_{14}O_6S$: C, 48.2; H, 5.14. Found: C, 48.2; H, 5.09.

Phenyl β-D-Glucosyl Sulfone Hydrate.—Phenyl tetraacetyl-β-D-glucosyl sulfone (2.00 g.) was covered with 100 ml. of methanol saturated with ammonia, and stirred until solution was complete. The solution stood for two days in an open beaker, after which the residual solvent was evaporated in an air stream. The tan residue was extracted four times with hot ether to leave 1.32 g. (102%) of sticky tan solid. This was dissolved in a slight excess of 2-propanol and the solution decolorized with Norit. Ligroin was added to the clear solution until slightly cloudy and on cooling in ice there resulted 0.88 g. (68%) of white crystalline solid, m. p. 90–92°. A second recrystallization raised the m. p. to 91–92°. A combustion analysis and quantitative drying in an Abderhalden pistol showed that this material contained water of hydration. Consequently, the sample was recrystallized from 2-propanol containing 10% water and ligroin, m. p. 92–93°. $[\alpha]^{26}D$ was −15.0° (water; *c*, 1.132).

Anal. Calcd. for $C_{12}H_{16}O_7S \cdot H_2O$: C, 44.7; H, 5.63. Found: C, 44.7; H, 5.73.

On reacetylation of the above sample with acetic anhydride and sodium acetate the acetylated sulfone was obtained in 87% crude yield, m. p. 188.5°, $[\alpha]^{28}D$ −26.8° (chloroform; *c*, 1.047).

An attempt was made to deacetylate phenyl tetraacetyl-β-D-glucosyl sulfone by the procedure of Bonner and Koehler[11] using potassium methylate followed by potentiometric titration with perchloric acid. The product obtained, however, did not crystallize, and proved to contain around 8% of inorganic ash. Apparently the deacetylation product retained a certain amount of potassium perchlorate which could not be separated. The sirup obtained had $[\alpha]^{22}D$ −14.3° (ethyl alcohol; *c*, 2.310), and was shown to be substantially phenyl β-D-glycosyl sulfone by the fact that it could be reacetylated to give the original starting material in 75% yield.

Phenyl Tetrapropionyl-β-D-glycosyl Sulfone.—Impure, sirupy phenyl β-D-glucosyl sulfone (0.14 g.) from the second reaction above was dissolved in pyridine (4 ml.) and treated with propionic anhydride (10 ml.). The mixture stood for two days at 0° and was thrown into ice

(9) Fletcher and Hudson, THIS JOURNAL, **69**, 1673 (1947).

(10) Since the compound in question was a sirup and incapable of further purification by convenient means, and since the sulfone prepared from this sirup gave an acceptable analysis, no attempt was made to obtain further analytical data for this compound.

(11) Bonner and Koehler, THIS JOURNAL, **70**, 314 (1948).

water. After stirring for several hours the oil was extracted into ether and the extract washed with water, 4 *N* hydrochloric acid, water, saturated bicarbonate solution, and water. After drying over sodium sulfate the solvent was distilled to yield 0.17 g. (70%) of amber sirup which could not be crystallized from 2-propanol; $[\alpha]^{19}D$ was −23.9° (chloroform; *c*, 33.3).

Anal. Calcd. for $C_{24}H_{32}O_{11}S$: C, 54.5; H, 6.10. Found: C, 55.3; H, 6.24.

Summary

1. Alkyl and aryl polyacetyl-β-D-thioglycosides have been shown to be readily oxidized to the corresponding alkyl or aryl polyacetyl-β-D-glycosyl sulfones by action of either potassium permanganate or 30% hydrogen peroxide. Partial deacetylation apparently attends the latter oxidation in acetic acid medium. A number of examples of these oxidations are given, and several members of this new class of sulfones are described.

2. Two phenyl polyacetyl-β-D-glycosyl sulfones have been deacetylated using ammoniacal methanol, and the deacetylation products have been described.

STANFORD UNIVERSITY
STANFORD, CALIFORNIA

RECEIVED JANUARY 21, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

5-Alkyl (or 5-Phenyl)-5-propoxymethylhydantoins[1]

BY HENRY R. HENZE, JOE W. MELTON[2] AND EUGENE O. FORMAN

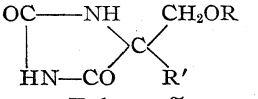
Some time ago, Henze and Rigler[3] prepared 5-ethoxymethyl-5-phenylhydantoin which later was shown to possess considerable anticonvulsant activity.[4] This behavior is in contrast to that of 5-ethyl-5-isoamyoxymethylhydantoin[3] which shows no anticonvulsant activity even in far larger doses,[4] and is, in fact, an unsatisfactory soporific. To obtain additional compounds, suitable for subsequent pharmacological testing for activity, we converted seventeen keto ethers, previously reported,[5] into the corresponding 5-alkyl (or 5-phenyl)-5-propoxymethylhydantoins. The latter have proved to be potent anticonvulsants,[4] the most active being 5-isopropoxymethyl-5-phenylhydantoin which compares favorably with 5,5-diphenylhydantoin in this respect and has merited clinical study.

Experimental

The hydantoins were obtained by warming a mixture of 1 part of keto ether, 1.1 parts of potassium cyanide and 3 parts of ammonium carbonate (U. S. P. cubes) in sufficient 50% alcohol at 58–60° for periods up to twenty-four hours. After the period of interaction, the solutions were evaporated to about half volume, acidified with hydrochloric acid and boiled to remove hydrogen cyanide. Usually, at this point, the hydantoins

TABLE I

5-ALKYL (OR 5-PHENYL)-5-PROPOXYMETHYLHYDANTOINS



—R	—R′	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_3H_7-*n*	—CH_3	85.0	42	51.60	51.39	7.58	7.51	15.05	15.38
C_3H_7-iso	—CH_3	136.5	49	51.60	51.35	7.58	7.71	15.05	15.10
C_3H_7-*n*	—CH_2CH_3	96.0	51	53.98	54.04	8.05	7.92	13.99	14.05
C_3H_7-iso	—CH_2CH_3	143.5	34	53.98	54.14	8.05	8.23	13.99	14.11
C_3H_7-*n*	—$(CH_2)_2CH_3$	113.0	54	56.05	55.91	8.47	8.30	13.08	13.32
C_3H_7-iso	—$(CH_2)_2CH_3$	166.5	66	56.05	56.08	8.47	8.76	13.08	13.38
C_3H_7-iso	—$CH(CH_3)_2$	182.0	54	56.05	56.20	8.47	8.47	13.08	13.07
C_3H_7-*n*	—$(CH_2)_3CH_3$	141.5	35	57.87	57.87	8.83	8.83	12.27	12.58
C_3H_7-iso	—$(CH_2)_3CH_3$	175.8	74	57.87	57.83	8.83	9.03	12.27	12.44
C_3H_7-iso	—$CH_2CH(CH_3)_2$	221.7	65	57.87	57.78	8.83	8.95	12.27	12.52
C_3H_7-iso	—$CH(CH_3)CH_2CH_3$	180.2	64	57.87	57.73	8.83	8.86	12.27	12.51
C_3H_7-*n*	—$(CH_2)_4CH_3$	130.0	60	59.48	59.65	9.15	9.08	11.56	11.67
C_3H_7-iso	—$(CH_2)_4CH_3$	165.4	85	59.48	59.79	9.15	9.34	11.56	11.68
C_3H_7-*n*	—$(CH_2)_2CH(CH_3)_2$	180.0	45	59.48	59.70	9.15	9.24	11.56	11.63
C_3H_7-iso	—$(CH_2)_2CH(CH_3)_2$	218.2	78	59.48	59.56	9.15	9.37	11.56	11.45
C_3H_7-*n*	—C_6H_5	133.0	75	62.89	62.67	6.50	6.33	11.28	11.42
C_3H_7-iso	—C_6H_5	162.0	78	62.89	62.89	6.50	6.34	11.28	11.52

(1) From the M. A. thesis of J. W. M. (August, 1940) and of E. O. F. (June, 1941).

(2) Present address: Department of Chemistry, Northwestern State College, Alva, Okla.

(3) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

(4) Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

(5) Henze, Duff, Matthews, Melton and Forman, THIS JOURNAL, **64**, 1222 (1942).

separated as white, crystalline solids; some, of lower m.p., separated as liquids which crystallized upon contact with ice. Recrystallization was effected in most cases by use of diluted alcohol or of a mixture of benzene and petroleum ether. The hydantoins can be dissolved in cold 10% solution of alkali and are reprecipitated unchanged upon acidification. Data for melting points and analyses are listed in Table I.

Summary

Seventeen new 5-alkyl (or 5-phenyl)-5-alkoxyalkylhydantoins have been prepared from the corresponding alkyl (or phenyl) *n*- or iso-propoxymethyl ketones. Of these, the 5-isopropoxymethyl-5-phenylhydantoin exhibits outstanding activity as an anticonvulsant.

AUSTIN, TEXAS RECEIVED APRIL 12, 1948

[CONTRIBUTION FROM THE ORGANIC DEPARTMENT OF THE ABBOTT RESEARCH LABORATORIES]

Organic Thio-antimonials in Schistosomiasis

BY LEROY W. CLEMENCE AND MARLIN T. LEFFLER[1]

Organic antimony compounds have been used for a number of years in the treatment of protozoan diseases, but with certain drawbacks such as toxicity and a high relapse rate. It was felt that oil soluble antimonials would tend to overcome these difficulties because of slower and more prolonged absorption. A series of compounds has been prepared in which each compound is either an oil or a low melting solid and is soluble in vegetable oils. The general structure is $(RS-)_3Sb$ where R is *n*-alkyl (C_8-C_{18}), aralkyl (phenylethyl or naphthylethyl), cycloalkyl (cyclohexylethyl, cyclohexylamyl, tetralylbutyl, decalylbutyl), and heteroalkyl (pyridylethyl).

The compounds were prepared by the action of antimony trichloride on the appropriate mercaptan in chloroform. They were tested in experimental schistosomiasis[2] and preliminary results indicate some promise. Further animal investigation is under way and the results will be published elsewhere.

Experimental

The procedures described below were used for the preparation of the isothiouronium bromides, mercaptans and antimony compounds. Table I gives the physical constants and analytical data of previously undescribed compounds in the two former groups; Table II gives the data on the antimony compounds.

ω-Cyclohexylamyl Bromide.[3]—To 227 g. (1.33 moles) of cyclohexylamyl alcohol[3] (prepared by hydrogenation of ethyl ω-cyclohexylvalerate[3] at 250°, 3600 lb. pressure and copper chromite catalyst; b. p. 106–107° at 3 mm., $n^{25}D$ 1.4634) cooled to −10° in a 500-cc. flask fitted with stirrer, dropping funnel and thermometer, was added dropwise, 144 g. (0.44 mole + 20% excess) of phosphorus tribromide, keeping the temperature below 0°. This

TABLE I

R—	Isothiouronium bromides Yield, %	M. p., °C.	N Analyses, % Calcd.	Found	Mercaptans Yield, %	B. p., °C.	$n^{25}D$	Analyses C Calcd.	Found	Hydrogen Calcd.	Found
β-Cyclohexylethyl-	90	115–116[a]	10.48	10.35	56	50–52.5	1.4910	66.66	67.00	11.23	11.11
ω-Cyclohexylamyl-	68	140–141[b]	9.06	8.92	87	89.5–91	1.4820	70.96	71.06	11.82	11.78
ω-(β-Tetralyl)-butyl-	89	112–113[a]	8.16	8.10	72	143	1.5569	76.36	76.19	9.09	8.89
ω-(β-Decalyl)-butyl-	56	123–124[c]	8.02	8.00	62	124[d]	1.5072	74.33	74.52	11.49	11.29

[a] Recrystallized from alcohol. [b] Recrystallized from water. [c] Recrystallized from alcohol and ether. [d] Distilled at 0.5 mm. pressure.

TABLE II

TRI-(R-MERCAPTO)-S-ANTIMONOUS ACIDS, $(R-S-)_3Sb$

R—	Anal. Sb Calcd.	Found
n-Octyl	21.9	22.14[a]
n-Decyl	19.07	18.85[a]
n-Undecyl	17.83	17.14[a]
n-Dodecyl	16.8	16.85[a,b]
n-Tetradecyl	15.05	15.40[c,d]
n-Hexadecyl	13.68	13.43[c,e]
n-Octadecyl	12.4	12.62[c,f]
β-Phenylethyl	22.85	22.9[a]
β-(1-Naphthylethyl)	17.83	17.8[a]
β-(*p*-Diisobutylphenoxyethoxy)-ethyl	11.60	11.6[a]
β-Cyclohexylethyl	22.10	21.85[a]
ω-Cyclohexylamyl	18.00	18.33[a]
ω-(β-Tetralyl)-butyl	15.63	15.52[a]
ω-(β-Decalyl)-butyl	15.22	15.30[a]
β-(2-Pyridyl)-ethyl	22.72	21.4[g]

[a] Oil. [b] Solidified on cooling, recrystallized from Skelly C, m. p. 38–40°. [c] Solid; recrystallized from Skelly C. [d] M. p. 50–51°. [e] M. p. 51–52°. [f] M. p. 58–59°. [g] Resin.

(1) Presented at the 112th meeting of the American Chemical Society, Division of Medicinal Chemistry, at New York, N. Y., September, 1947.

(2) These compounds were submitted to the Chemotherapy Center for Tropical Diseases, National Research Council, and were screened by Drs. Maxwell Schubert and Arthur DeGraff.

(3) Hiers and Adams, THIS JOURNAL, **48**, 2385 (1926); Katsnelson and Dubinin, *Compt. rend. Acad. Sci. (U. R. S. S.)*, [N. S.], **4**, 405 (1936).

addition required three hours. The reaction mixture was stirred until room temperature was reached, allowed to stand overnight, heated at 100° for several hours, then cooled and poured into 1000 cc. of ice and water with good agitation. The heavy oily layer was dissolved in ether, the ether layer washed several times with water then with sodium carbonate solution, again with water, then dried over magnesium sulfate and evaporated. On distillation in vacuum, the fraction boiling at 89.5–90.5° at 1 mm., $n^{24}D$ 1.4784, was collected; yield 271 g. (87%). *Anal.* Calcd. for $C_{11}H_{21}Br$: C, 56.65; H, 9.01. Found: C, 56.87; H, 9.14.

ω-Cyclohexylamyl Isothiouronium Bromide.—To 23.3 g. (0.1 mole) of the above bromide was added a hot, filtered solution of 7.6 g. (0.1 mole) of thiourea in 125 cc. of absolute alcohol. The mixture was refluxed for thirty-six hours, then cooled and stirred until the whole mass became a crystalline mush. The solid was filtered, washed with a little acetone and dried. The yield was 22.6 g., m. p. 138–141°. After recrystallization of this material from 250 cc. of boiling water using a small amount of norite, the yield was 20.9 g. (68%), m. p. 140–141°. *Anal.* Calcd. for $C_{12}H_{24}N_2S \cdot HBr$: N, 9.06. Found: N, 8.92.

ω-Cyclohexylamyl Mercaptan.—Seventy-eight grams (0.25 mole) of the isothiouronium compound described above was added to a solution of 50 g. (1.25 moles) of sodium hydroxide dissolved in 325 cc. of water. The mixture was heated to boiling and refluxed for ten minutes, then cooled quickly and made acid to congo red by addition of concd. hydrochloric acid. It was extracted with ether and dried over anhydrous sodium sulfate, then evaporated. The residual oil was distilled in vacuum. The main fraction boiled at 93–94.5° at 1.2 mm. It was redistilled, b. p. 89.5–91° at 1 mm., $n^{25}D$ 1.4820, yield 41 g. (87%). *Anal.* Calcd. for $C_{11}H_{22}S$: C, 70.96; H, 11.82. Found: C, 71.06; H, 11.78.

Tri-[ω-cyclohexylamylmercapto]-S-antimonous Acid.—A solution of 7.61 g. (0.033 mole) of antimony trichloride in 50 cc. of warm chloroform was filtered and added to a solution of 18.6 g. (0.1 mole) of ω-cyclohexylamyl mercaptan in 50 cc. of chloroform. The clear solution was evaporated in vacuum to remove the solvent, then placed in a vacuum desiccator over solid sodium hydroxide for forty-eight hours to remove the last traces of hydrochloric acid. A quantitative yield of almost colorless oil was obtained. It was insoluble in water, soluble in chloroform, ether, benzene and vegetable oils. *Anal.* Calcd. for $C_{33}H_{66}S_3Sb$: Sb, 17.99. Found: Sb, 18.33.

The *n*-alkyl mercaptans, except the undecyl, were obtained from the Connecticut Hard Rubber Company. This was prepared by converting undecyl alcohol to the bromide and following the above procedure. β-(*p*-Diisobutylphenoxyethoxy)-ethyl mercaptan was obtained from Rohm & Haas Company; 2-pyridylethyl mercaptan was obtained from Reilly Tar and Chemical Corporation.

The intermediates, for conversion to the remaining mercaptans by the above procedures, were obtained as follows. Phenylethyl bromide was obtained from Columbia Organic Chemicals Company. β-(1-Naphthyl)-ethyl alcohol was prepared by method of Ruzicka.[4] β-Cyclohexylethyl alcohol,[3] b. p. 78–80° at 5 mm., $n^{25}D$ 1.4629, was prepared by catalytic hydrogenation of ethyl cyclohexylacetate.

The following alcohols were previously undescribed. ω-(β-Tetralyl)-butyl alcohol was obtained by hydrogenation of ethyl ω-(β-tetralyl)-butyrate[5] at 250°, 3600 lb. pressure with copper chromite catalyst; b. p. 167° at 5 mm., $n^{25}D$ 1.5391. *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.32; H, 9.81. Found: C, 82.03; H, 9.98. ω-(β-Decalyl)-butyl alcohol was obtained by further hydrogenation of the above alcohol at 200°, 3500 lb. pressure with Raney nickel catalyst; b. p. 148–149° at 6 mm., $n^{25}D$ 1.4919. *Anal.* Calcd. for $C_{14}H_{26}O$: C, 80.00; H, 12.38. Found: C, 80.64; H, 12.33.

The bromides obtained from the alcohols were slightly impure and were converted to the corresponding isothiouronium bromides without redistillation.

An attempt was made to purify one of the antimony compounds (*n*-dodecyl-) by molecular distillation but decomposition occurred. Tri-[(β-(2-pyridyl)-ethylmercapto]-S-antimonous acid was a resinous material only slightly soluble in olive oil.

Acknowledgment.—The authors wish to thank Mr. E. F. Shelberg for the micro-analyses, Mr. R. Cox for the antimony analyses herein reported, Mr. M. Freifelder for the catalytic hydrogenations and Mr. C. Plummer for assistance in syntheses.

Summary

1. A series of thio-antimony compounds has been prepared, which are either oils or low melting solids soluble in vegetable oils.

2. Several new alcohols, isothiouronium bromides and mercaptans have been prepared.

3. The antimony compounds show some promise in experimental schistosomiasis and further investigation is being carried out.

(4) Ruzicka, *Helv. Chim. Acta*, **16**, 836 (1933).

(5) Newman and Zahm, THIS JOURNAL, **65**, 1099 (1943), described the preparation of the corresponding methyl ester.

NORTH CHICAGO, ILLINOIS RECEIVED FEBRUARY 6, 1948

[CONTRIBUTION FROM THE PROCTER AND GAMBLE COMPANY]

The Polymorphism of the Mixed Triglycerides of Palmitic and Stearic Acids

BY E. S. LUTTON, F. L. JACKSON AND O. T. QUIMBY

Introduction

The four mixed triglycerides of palmitic and stearic acid are of practical as well as academic interest. Among them are generally to be found important and frequently the predominating components of most of the highly hydrogenated fats and oils of commercial significance. These compounds, as would be expected, show many similarities in polymorphism to the single fatty acid triglycerides, but there are differences more significant than is apparent in the valuable papers of Malkin.[1,2]

The work of Clarkson and Malkin[3] on the simple triglycerides was corrected by other observers.[4,5,6] None of these later authors was in disagreement with Malkin as to number of forms and melting points. The differences from Malkin arose in association of melting points with diffraction patterns and in nomenclature. It is to be emphasized, however, that the nomenclature of the present authors[7] follows the lead of Malkin in designation of X-ray patterns, except in details particularly involving the term "beta prime." Here a form is called "beta prime" on the basis of X-ray pattern type rather than order of melting.

In view of the situation with regard to the simple triglycerides, there has been great need for reëxamination of the four important mixed glycerides of palmitic and stearic acids—namely, the symmetrical glycerides, 2-palmityldistearin (SPS) and 2-stearyldipalmitin (PSP), and the unsymmetrical glycerides, 1-palmityldistearin (PSS) and 1-stearyldipalmitin (SPP). (Theoretically the matter of optical isomerism is to be considered in connection with unsymmetrical glycerides, but it is generally felt that this is a matter of little physical significance for longer acyl groups. In this paper only such "racemic" mixtures as are prepared by ordinary synthesis are discussed.)

Experimental

The four mixed glycerides were made by established methods from the corresponding mono- or diglyceride by reaction with the proper fatty acid chloride. The mono- and diglycerides were prepared by directed rearrangement according to the method of Eckey.[8] Fatty acids were purified by distillation and by crystallization from glacial acetic acid. From the acids the corresponding chlorides were prepared by reaction with thionyl chloride and subsequent distillation. Constants for the starting materials are given in Table I along with those of the final products.

TABLE I

ANALYSES OF STARTING MATERIALS AND PRODUCTS

I. V. = iodine value, S. V. = saponification value, H. V. = hydroxyl value, % monoglyceride is by the Mehlenbacher periodic acid method.

	I. V.	S. V.		H. V.		% Mono-	Setting pt., °C.		M. p., °C.	
	Exp.	Exp.	Theory	Exp.	Theory	glyceride	Exp.	Lit.[9]	Exp.	Lit.[10,11,5,6]
Palmitic acid	0.1	220	219				62.6	62.60		
Stearic acid	.1	196	197				69.5	69.39		
1-Monopalmitin	.0	169	169.6			98.4			76.5	77
1-Monostearin	.1	156.3	156.4			101.9			81.5	81.5
1,3-Dipalmitin	.0	197.4	197.3	99	98	0.45			72.4	72.5
1,3-Distearin	.1	179.4	179.7	92	90	0.4			78.2	78
SPS		194.7	195.2						68.5	68
PSS		194.9	195.2						65.2	65
PSP		201.6	201.6						68.6	68
SPP		201.4	201.6						62.7	62.5

A typical synthesis, that of 1-palmityldistearin, is described in some detail. Twenty grams (0.061 mole) of 1-monopalmitin was dissolved in 50 g. (0.632 mole) of pyridine and 20 ml. of anhydrous chloroform. To this mixture, 41.5 g. (0.137 mole) of stearyl chloride was added slowly while the reaction vessel was cooled in an ice-bath. The mixture was then warmed on a steam-bath for six hours in order to complete the reaction. After this step, the reaction mixture was dissolved in ether and washed consecutively, twice with water, four times with 10% potassium carbonate, three times with dilute sulfuric acid and finally with water until neutral to litmus paper. The ether solution was dried over anhydrous sodium sulfate and filtered. Final purification was accomplished by four crystallizations, one from ether and three from Skellysolve B-ethyl alcohol (1:1) mixtures.

The symmetrical glycerides showed good crystallinity as compared with the chalk-like appearance of unsymmetrical compounds.

The polymorphism of the glycerides was studied by the X-ray and melting point techniques described previously.[5] Briefly flat film patterns were obtained with a regular General Electric XRD unit. The pinhole was 0.025″ and film distances were 2.5 cm. for exploratory patterns, 5.0 cm. for most short spacing determinations and 10.0 cm. for detailed short spacing and for long spacing pat-

(1) Malkin and Meara, *J. Chem. Soc.*, 103 (1939).
(2) Carter and Malkin, *ibid.*, 577 (1939).
(3) Clarkson and Malkin, *ibid.*, 666 (1934).
(4) Bailey, *et al.*, *Oil & Soap*, **22**, 10 (1945).
(5) Lutton, THIS JOURNAL, **67**, 524 (1945).
(6) Filer, *et al.*, *ibid.*, **68**, 168 (1946).
(7) Lutton, *ibid.*, **79**, 248 (1948).
(8) Eckey, U. S. Patent 2,442,534 (June 1, 1948).
(9) Francis and Piper, THIS JOURNAL, **61**, 578 (1939).
(10) Malkin, *et al.*, *J. Chem. Soc.*, 1628 (1936).
(11) Malkin, *et al.*, *ibid.*, 1409 (1937).

terns. In the case of 2-palmityldistearin, it was necessary to take 10 cm. patterns with a 0.005″ slit system for sufficient resolution of certain prominent lines.

For alpha forms three types of capillary thermal points were obtained:

Softening Point.—Sample melted, chilled two seconds at 0°, thrust into bath for observation. Softening point is half-way between the highest point of no increased translucence and the lowest point of definite increase in translucence.

Rapid Complete Melting Point.—Sample melted, cooled rapidly to minimum cloud, thrust into bath. This determination is completed as for the softening point except that complete clarity instead of increased translucence is observed.

Regular Complete Melting Point.—Sample melted, chilled, observed for complete clarity on raising the temperature 0.5° or less per minute.

Beta prime forms were obtained in three ways—from alpha by tempering near the alpha melting point, from melt just above the alpha melting point, and in one case by solvent crystallization. Thermal points were obtained as described for alpha. In the case of "regular complete melting points" samples were stored near the beta prime melting point but not long enough to produce beta.

Beta forms were obtained from beta prime by tempering near the beta prime melting point (or from alpha) and by solvent crystallization (usually Skellysolve B). Melting points were obtained by observing the sample while raising the temperature 0.5° or less per minute.

Detailed melting point and X-ray data are recorded in Tables II and III, respectively. Characterizing data compared with those for tripalmitin and tristearin are to be found in Table IV.

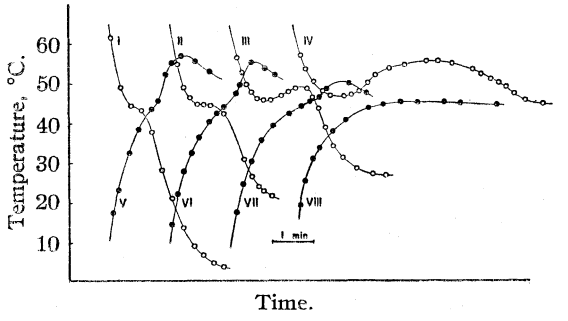


Fig. 1.—Cooling and heating curves indicating the alpha m. p. for PSP. Cooling curves—O, samples melted 100°, placed at temperature without jacket—I, 0°; II, 17°; III, 27°; IV, 44°. Heating curves—●, samples melted, chilled 10°, placed at temperature without jacket—V, 49°; VI, 47°; VII, 45°; VIII, 44°.

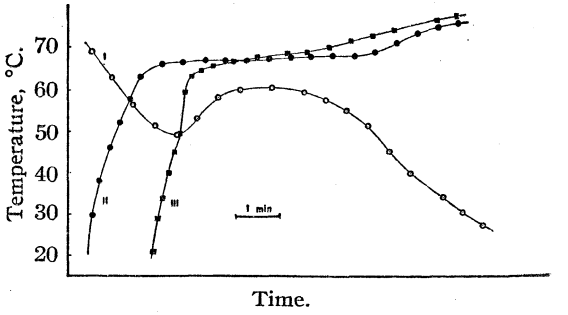


Fig. 2.—Cooling and heating curves involving beta prime for PSP, jacketed samples—I, melted, placed 0°—O; II after I, placed 80°—●; III melted, chilled 10° (no jacket), jacketed at 80°—■.

Thermal curves were run on a 1-g. sample of PSP after the manner of Clarkson and Malkin.[3] The procedure has been described previously in some detail.[12] Examples of the curves are shown in Figs. 1 and 2.

TABLE II

THERMAL DATA FOR MIXED PALMITIC–STEARIC TRIGLYCERIDES

S. P. = softening point, C. M. P. = complete m. p.

		SPS	PSS	PSP	SPP
Alpha	S. P.	50.8	49.6	46.5	46.8
	Rapid C. M. P.	51.0	50.6		47.4
	Regular C. M. P.	51.8			
Beta prime	S. P.		61.1	65.0	57.7
	Rapid C. M. P.		62.1		58.3
	Regular C. M. P.		65.0	68.6	61.7
	Solvent C. M. P.			68.6	
Beta	Regular C. M. P.	67.7	..		62.4
	Solvent C. M. P.	68.5	65.2		62.7

Discussion

These glycerides are more striking in their individuality than in their similarity. Thus one of them is quite unstable as alpha, another is relatively stable. While two are normal in being thermodynamically beta stable, one is beta prime stable and the fourth is apparently equally stable as beta prime or beta.

No vitreous (or gamma) form was found for any of these glycerides. Accordingly no more than three forms, never four, were found for each compound. For a given form of a given glyceride, *actual variation of complete melting point with extent of stabilization is common* and must be the basis for the excess "characteristic" melting points which have been previously reported.[1,2] As much as three degrees variation was observed. It was observed that long spacings were constant with such m. p. variation, while short spacings showed only differences in sharpness.

The two symmetrical glycerides offer a most interesting contrast. It is the alpha form of SPS that is unusually stable while that of PSP is so unstable that no complete melting point for it can be obtained, and the observer must be content with a softening point. Neither glyceride shows more than one form beside alpha. Most startling is the fact that, while beta is the stable form for SPS, as would be expected, beta prime is stable for PSP. The short spacing data of Malkin,[1] by the present nomenclature[7], lead to this same conclusion with regard to PSP, for the form he called beta had no 4.6 Å. spacing but only slightly modified beta prime spacings. The absence of a beta prime form for SPS is a matter of some concern especially since later work has revealed this form for the closely related homolog, 2-myristyldistearin.[13] Moreover, it is known that small amounts of impurity permit beta prime development in SPS. However, there can be no doubt that if the beta prime form exists for pure SPS it is extremely fleet-

(12) Ferguson and Lutton, THIS JOURNAL, **69**, 1445 (1947).

(13) Jackson and Lutton, unpublished.

TABLE III

DETAILED d/n VALUES FOR MIXED PALMITIC–STEARIC TRIGLYCERIDES

	SPS		PSS			PSP		SPP		
(*hkl*)	Alpha	Beta	Alpha	Beta prime	Beta	Alpha	Beta prime	Alpha	Beta prime	Beta
					Long Spacings					
001	48.9 VVS	42.75 VS	48.5 VS	44.9 VS	44.4 VS	47.0 VS	42.8 VS	47.7 VS	43.7 VS	42.0 VS
002	24.5 W	21.7 M	24.3 W–	22.3 VW–	22.7 VW	..	(21.2 VW)	24.0 VW	21.4 VW–	21.4 VW
003	16.5 S+	14.3 S+	16.1 S	15.0 S	14.8 M	15.55 M	14.22 M	14.1 S	14.5 S	14.2 S
004				11.5 VW–				11.8 VW–	11.2 W	10.6 VW–
005	9.86 W	8.66 W	9.75 W+	9.00 M	8.94 VW–	9.30 W	8.59 W	9.50 W	8.88 W	8.36 W
006	8.22 W–	7.22 W	8.13 W	7.50 M		7.75 VW	7.05 W	7.97 W	7.30 W	6.88 VW
007									6.26 VW	
008									5.45 M	
Av. d	49.2	43.1	48.5	45.1	44.7	46.65	42.75	47.6	43.8	42.1
					Short Spacings					
	4.14 VS	5.34 M	4.14 VS	4.37 M	5.34 M	4.13 VS	4.34 M	4.13 VS	4.30 VS	5.33 M
	2.40 VW	5.20 M–	2.41 VW	4.23 VS	4.90 W	2.40 VW	4.18 VS	2.40 W	4.15 S	4.61 VS
		4.57 VS		4.07 M	4.61 VS		3.99 M		3.83 VS	4.29 W
		4.44 M		3.81 S	4.28 W		3.75 S		3.13 VW	4.12 VW
		4.24 W		3.48 VW	4.07 W		3.35 VW		2.83 VW–	3.85 S
		4.12 W		3.13 W	3.87 S		3.12 VW		2.57 VW	3.67 S
		3.97 M		3.02 VW–	3.67 S		3.00 VW–			2.98 VW–
		3.81 S[a]		2.82 VW–	3.43 VW–		2.79 VW		2.29 VW	2.85 VW–
		3.72 S+[a]		2.78 VW	3.30 VW		2.58 VW–			2.58 M
		3.62 W		2.56 VW	2.84 VW		2.52 VW			2.41 W
		3.30 W–		2.40 VW–	2.58 M		2.26 VW+			2.31 W
		3.21 W		2.27 W	2.40W					2.23 VW
		2.84 VW		2.10 VW–	2.28 W					2.14 VW
		2.54 M–		1.89 VW–	2.07 W					2.07 W
		2.49 W			1.97 VW–					1.96 VW–
		2.27 W								
		2.20 VW								
		2.12 VW								
		2.06 W								
		1.93 W								
		1.85 VW								
		1.79 VW								
		1.68 VW								

[a] Resolved by 0.005″ slit, 10 cm. sample to film distance.

TABLE IV

CHARACTERISTIC THERMAL AND X-RAY DATA FOR PALMITIC-STEARIC TRIGLYCERIDES

	SSS[5,14]	SPS	PSS	PSP	SPP	PPP[5,14]
			Melting Points			
Alpha	54.9	51.8	50.6	46.5	47.4	44.7
Beta Prime	64	..	61.1–65.0	68.6	57.7–61.7	56.6
Beta	73.1	68.5	65.2	..	62.7	66.4
			X-Ray Data: Long Spacings			
Alpha	50.6	49.2	48.5	46.65	47.6	46.8
Beta Prime	46.8	..	45.1	42.75	43.8	42.3
Beta	45.15	43.1	44.7	..	42.1	40.9
			Short Spacings			
Alpha	4.14 VS	4.14 VS	4.14 VS	4.13 VS	4.14 VS	4.14 VS
Beta Prime	4.18 VS	..	4.37 VS	4.34 M	4.30 VS	4.18 VS
	3.78 S		4.23 VS	4.18 VS	4.15 S	3.78 S
			4.07 M	3.99 M	3.83 S	
			3.81 S	3.75 S		
Beta	5.24 M	5.34 M	5.34 M		5.33 M	5.24 M
		5.20 M–				
	4.61 VS	4.57 VS	4.61 VS		4.61 VS	4.61 VS
	3.84 S	3.81 S	3.87 S		3.85 S	3.84 S
	3.68 S	3.72 S+	3.67 S		3.67 S	3.68 S

ing. The beta form of SPS is characterized by the closeness of the two spacings near 3.8 Å., unresolved on ordinary patterns of 5-cm. sample to film distance.

(14) Quimby, unpublished.

Cooling and heating curves have been used often by Malkin and by others to study the polymorphism of triglycerides. Properly interpreted they can give valuable information, but there are pitfalls. Complicated relationships existing between

environment, sample and thermocouple and the imperfection of quickly formed crystals are some of the factors which can result in apparently shifting the characteristic level of thermal change. Actually one may obtain halts, bends or nicks in thermal curves at practically any temperature from the minimum to the maximum melting point of a pure triglyceride. It is necessary to confirm the significance of breaks by showing that they occur at approximately the same level with fairly wide variations in surrounding conditions.

Among the mixed glycerides discussed here only PSP has been subjected to thorough examination by thermal curves. It is particularly worthy of investigation since only two forms, instead of the previously reported four,[1] have been found. The curves, Figs. 1 and 2, while they actually support the conclusion that only two forms occur, do show how one may be led astray.

The cooling curves of Fig. 1 plainly show a thermal effect (halt, nick or minimum) at 45 to 47° in spite of large variations in cooling rate. The value is in good agreement with the alpha melting point level for PSP, Table II, and is in line with the general experience of agreement between alpha m. p. and supercooling limit for triglycerides. The heating curves of Fig. 1 also reveal this characteristic thermal point. At the inflections of these latter curves the phenomena are not simple for there are involved (1) melting of alpha, (2) transformation of alpha to beta prime and (3) beta prime crystallization from melt.

The level of beta prime melting is indicated by the heating curves of Fig. 2. Curve I, a cooling curve, shows how one may, from minima and maxima, obtain values between alpha and beta prime m. p. values, but a real significance for these values cannot be confirmed visually, nor by X-ray nor by a series of systematically varied thermal curves. Curve II of Fig. 2, following after I, shows only beta prime melting at the normal level. Curve III, run on a quickly chilled (alpha) sample, shows a slight inflection indicative of alpha melting below 50° but the main feature is beta prime melting in the neighborhood of 68°. Thus only alpha and beta prime forms were confirmed.

The differences between the unsymmetrical glycerides, while not so striking as for the symmetrical glycerides, are of equal interest. Both 1-palmityldistearin (PSS) and 1-stearyldipalmitin (SPP) show the three forms—alpha, beta prime and beta. For PSS, however, beta is obtained only from solvent. The stable form from the melt is beta prime. Accordingly, it is found on stabilization to rise in m. p. almost to the level of the beta m. p. obtained after solvent crystallization.

These four mixed glycerides may be conveniently grouped with regard to the stable form from the melt according to the nature of the acyl residue in the 2-position. This is indicated in Table V.

One must infer from the evidence here presented that many of the homologs of these glycerides which have been discussed by Malkin, *et al.*, must also in many cases have only three, perhaps only two, forms instead of four as reported. For example Malkin's own X-ray data[1] indicate that the glycerides grouped with PSP on the basis of similarity in molecular geometry (namely, 2-palmityldimyristin, 2-myristyldilaurin and 2-lauryldicaprin) must have only two forms, metastable alpha and stable beta prime.

TABLE V

STABLE FORMS FROM THE MELT

	Beta prime stable	Beta stable
Unsymmetrical	PSS	SPP
Symmetrical	PSP	SPS
Acyl in 2- position	S	P

Important differences from the evidence of Malkin, *et al.*, for these four mixed glycerides are here summarized: (1) As in the case of tristearin, no glassy forms were observed, *alpha* actually being the lowest melting form in each case. (2) The number of forms for a given glyceride in no case exceeded three and in two cases was two in contrast to Malkin's recording of four forms. (The variation in melting point here reported for a given form of a given compound seemingly is responsible for Malkin's reporting of superfluous melting points.) (3) The stable form of PSP is called beta prime (instead of beta) according to the modification of Malkin's nomenclature, which has been used in the present work. (4) Also for PSP is reported the impossibility of achieving a complete melting point for the alpha form. The observed softening point is 3° below Malkin's "melting point" value. (5) For SPS no beta prime form is here reported and beta has a characterizing feature; this is the closeness of the two smaller main short spacings so that they are unresolved on an ordinary 5 cm.–0.025″ pinhole pattern (Malkin's values for these spacings are farther apart). (6) Differences in long spacing data are best discussed in relation to Table VI.

TABLE VI

COMPARISON WITH MALKIN'S LONG SPACINGS

(LJQ) are data of Lutton, Jackson and Quimby.
(M) are data of Malkin and co-workers

	SPS			PSP		
	α	β′	β	α	β′	β
(LJQ)	49.2	..	43.1	46.65	42.75	..
(M)	50.5	47.5	44.2	50.2	44.7	43.2

	PSS			SPP		
	α	β′	β	α	β′	β
(LJQ)	48.5	45.1	44.7	47.6	43.8	42.1
(M)	48.8	44.7	46.5	47.8	43.9	42.5

In several cases agreement is within experimental error; in a few instances differences are of the order of 1.0 Å. Serious differences are a 3.55 Å. difference for the alpha form of PSP, a 1.8 Å. difference for the beta form of PSS and difference as to the existence of a beta value for PSP. It is presumed that Malkin's value reported for beta

prime PSP is not correct but that his value for "beta" is the true beta prime long spacing value. Malkin's beta prime value for a pure SPS is tentatively questioned on the basis of the present authors' failure to obtain such a form.

Acknowledgment.—The authors wish to express their appreciation for permission from the Procter & Gamble Co. to publish the portions of this investigation which are of general interest, and to the members of this laboratory who have assisted in the experimental work and have given advice in the preparation of the manuscript.

Summary

As compared with the great similarity in polymorphic behavior of the single fatty acid saturated triglycerides, the mixed palmitic–stearic triglycerides show a remarkable individuality. Many of the conclusions here reached with regard to their behavior are at variance with those of Malkin and co-workers.

The symmetrical isomers show a high degree of crystallinity; the unsymmetrical compounds are microcrystalline. All four compounds exhibit a lowest melting alpha form—unusually stable in the case of 2-palmityldistearin and unusually labile in the case of 2-stearyldipalmitin.

Occurrence of forms other than alpha can be briefly tabulated:

Glyceride	Forms beside *alpha*
2-Palmityldistearin	Only beta
2-Stearyldipalmitin	Only beta prime
1-Palmityldistearin	Only beta prime from melt, beta from solvent (beta prime and beta equally stable)
1-Stearyldipalmitin	Beta prime and beta (beta stable)

A given form of a given glyceride may vary several degrees in melting point depending on its degree of stabilization. This variation may account for the fact that previous workers have reported more characteristic thermal points for a given glyceride than can be substantiated by X-ray diffraction patterns.

IVORYDALE, OHIO RECEIVED FEBRUARY 6, 1948

[CONTRIBUTION FROM THE PROCTER & GAMBLE CO.]

The Polymorphism of 1-Monostearin and 1-Monopalmitin

BY E. S. LUTTON AND F. L. JACKSON

Introduction

The polymorphism of the compounds 1-monocaprylin through 1-monostearin has been studied by Rewadikar and Watson[1] by means of capillary melting point methods but without the help of X-ray diffraction data. Malkin and co-workers,[2,3,4] using X-ray diffraction and thermal techniques, have studied the polymorphism of saturated 1-mono-, 1,3-di- and triglycerides. However, further work has led to corrections and new interpretations in the field of triglycerides.[5,6,7] Similarly, re-examination of the 1-monoglycerides, specifically 1-monostearin and 1-monopalmitin, as reported in the present paper has shed new light on the polymorphic behavior of this class of compounds.

As in the case of the triglycerides[6] every effort has been made to maintain the nomenclature introduced by Malkin.[3] However, the discovery of four polymorphic forms (here called subalpha, alpha, beta prime and beta) instead of three for the 1-monoglycerides and the fact that subalpha and beta prime have very similar X-ray patterns required some revision and refinement of Malkin's basis for nomenclature. A particular complication is the subalpha form, a distinct form accounting for the reversible thermal effects reported by Malkin on cooling alpha and subsequent reheating.

The basis for monoglyceride nomenclature may be summarized as follows.

Subalpha has a single strong short spacing line at 4.15 Å., other medium lines at 3.9, 3.75 and 3.55 Å. This form undergoes a reversible transformation to alpha and therefore has no m. p.

Alpha has a single strong short spacing line at 4.15 Å. with other weak short spacing lines. This form has the lowest complete m. p. Triglyceride alpha similarly has a single strong short spacing line at 4.15 Å. and is the lowest melting form.

Beta prime has a strong short spacing line at 4.15 Å., and a 3.65 Å. medium line which is the strongest one between 4.2 and 2.6 Å. This form has an intermediate complete m. p. Triglyceride beta prime has strong spacings at 4.2 and 3.8 Å., and is normally the intermediate melting form.

Beta has a strong short spacing line at 4.55 Å. and is the highest melting form. Triglyceride beta has a strong line at 4.6 Å. and is generally the highest melting form.

It is apparent from the preceding paragraphs that the bases for nomenclature are similar for the mono- and triglycerides.

Experimental

The monoglycerides were prepared according to the

(1) Rewadikar and Watson, *J. Indian Inst. Sci.*, **13**, A, 128 (1930).
(2) Clarkson and Malkin, *J. Chem. Soc.*, 666 (1934).
(3) Malkin and Shurbagy, *ibid.*, 1628 (1936).
(4) Malkin, Shurbagy and Meara, *ibid.*, 1409 (1937).
(5) Bailey, *et al.*, *Oil & Soap*, **22**, 10 (1945).
(6) Lutton, THIS JOURNAL, **67**, 524 (1945).
(7) Filer, *et al.*, *ibid.*, **68**, 168 (1946).

directed rearrangement method of Eckey.[8] Monostearin was prepared from a mix of 35% completely hydrogenated linseed oil and 65% linseed oil, to which was added 15–20% of dry glycerol and 0.5% NaOMe (a catalyst suspended in xylene). The mixture was agitated for forty-eight hours each at 60, 49 and 38°, during which time the crude monostearin precipitated in increasing amounts. An excess of glacial acetic acid was added to kill the catalyst, the mix was water-washed to remove sodium acetate, and the final purification accomplished by six crystallizations from Skelly B–ethyl alcohol mixtures.

Monopalmitin was prepared similarly from cottonseed oil stearine plus 15–20% of glycerol and 0.5% NaOMe catalyst. (The stearine was the precipitate from a partially crystallized oil and contained 30–35% combined palmitic acid.) The temperature cycle used here was 38, 32 and 27°.

The degree of purity of the monoglycerides is indicated by the analyses in Table I.

TABLE I

ANALYSES OF MONOGLYCERIDES

I. V. = iodine value, S. V. = saponification value, % monoglyceride by the periodic acid method.[9]

	Experimental				Theory			Lit.[3]
Glyceride	I. V.	S. V.	% Monoglyceride	C. m. p., °C.	I. V.	S. V.	% Monoglyceride	C. m. p. °C.
1-Monostearin	0.0	156.2	104.5	81.5	0.0	156.4	100.0	81.5
1-Monopalmitin	.0	169.0	101.9	77.0	.0	169.6	100.0	77.0

The samples were examined by X-ray diffraction, thermal methods and by dilatometry. The techniques of X-ray diffraction and thermal examination have been described elsewhere.[6,10]

The X-ray specimens were prepared in three ways: (1) melted samples were drawn into Pyrex glass capillaries and tempered in various ways depending on the polymorphic form desired, (2) powdered crystalline samples were made into 0.5 mm. thick disk-shaped pellets which were X-rayed perpendicularly to the flat side of the disk, and in addition (3) powdered samples were made into 1-cm. rods of 0.5 mm. diameter after the manner of Piper.[3] The rods were mounted vertically in the path of the X-ray beam. They gave excellent long and short spacing X-ray lines on the same film, while the disk-shaped pellets yielded very poor long spacings presumably due to orientation of the hydrocarbon chains perpendicularly to the face of the disk.

Thermal examination was accomplished with samples in capillary tubes. Beta prime and beta melting points were obtained by ordinary complete melting point determination with a rise in bath temperature of 0.5° per minute. Alpha melting points were obtained by thrusting capillaries into a bath of definite temperature. The alpha m. p. was the point halfway between the maximum temperature for remaining solid (indicated by any cloudiness, however faint) and the minimum temperature for complete clarity. These two temperatures were usually less than 0.2° apart.

The dilatometer procedure was without special features. A one-gram sample was placed in a glass bulb and the bulb joined to the dilatometer capillary by an interchangeable joint. The sample was melted, the dilatometer evacuated and the sample then frozen. At this point the dilatometer was completely filled by running mercury into the evacuated space and onto the sample.[11] The mercury content was adjusted by setting the sample at a temperature about 10° above the melting temperature. After the desired sample treatment, dilatometer readings (distance of the mercury meniscus from the top of the dilatometer) were taken at successive temperatures. The dilatometer was particularly helpful in studying the alpha–subalpha relationships.

The alpha form was obtained by rapid cooling of the melt. As in the case of triglycerides, its melting point represents the approximate supercooling limit. Alpha has a low temperature limit of existence at which it transforms reversibly to subalpha, so that at room temperature both monostearin and monopalmitin exist in the subalpha rather than the alpha form.

The beta prime form was obtained by fairly rapid crystallization from dilute (1:300) ether or Skellysolve B solutions. It was not obtained from a melt nor by tempering alpha. By a similar procedure Chen and Daubert[12] obtained metastable forms of triacid triglycerides.

Relatively slow crystallizations from solvents (50–50 mixtures of alcohol and Skellysolve B) gave beta. This form was not obtained by direct crystallization from the melt without seeding, but was obtained by transformation of alpha or beta prime.

Results

The thermal points are recorded in Table II in comparison with the data of Malkin. The two sets of values are in reasonable agreement except that no second transition point was observed below the alpha m. p. as reported by Malkin for monostearin.

TABLE II

THERMAL POINTS, °C.

(LJ), Data of Lutton and Jackson; (MS), data of Malkin and Shurbagy

	(LJ)				(MS)			
	Subalpha Transformation Pt.[a]	Alpha M. p.	Beta prime M. p.	Beta M. p.	Subalpha Transformation Pt.	Alpha M. p.	Beta prime M. p.	Beta M. p.
1-Monostearin	49	74	78	81.5	42 and 47.5	74	79	81.5
1-Monopalmitin	39	66.9	74.6	77.0	34	66.5	74	77.0

[a] Determined by microscope (and approximately by dilatometer).

Detailed X-ray data are shown in Table III with average long spacing values which are compared with those of Malkin[3] and Filer.[7] Long spacing agreement is reasonably good except in the case of the alpha form for monostearin. The present value is 8 Å. short of that reported by Malkin. Characteristic short spacing data are shown in Table IV in comparison with those of Malkin and Filer. For the beta form, agreement is better in certain respects with Filer's data, but some of Filer's strong lines were not confirmed. It is uncertain whether Malkin's so-called beta prime data should properly be regarded as pertaining to beta prime or subalpha. From the reported spacings and description of procedure no decision can be made.

Dilatometer results for the alpha $\rightleftarrows$ subalpha reversible change are shown in Fig. 1.

Discussion

While in most features of behavior the monoglycerides were found to correspond to the beha-

(8) Eckey, U. S. Patent 2,442,534 (June 1, 1948).

(9) Pohle, Mehlenbacher and Cook, *Oil & Soap*, **22**, 115 (1945).

(10) Nordsieck, Rosevear and Ferguson, *J. Chem. Phys.*, **16**, 175 (1948).

(11) McBain and Field, *J. Phys. Chem.*, **37**, 675 (1933).

(12) Chen and Daubert, THIS JOURNAL, **67**, 1256 (1945).

TABLE III

X-RAY SPACINGS, IN Å. OBTAINED WITH Cu RADIATION, $\gamma_{K\alpha} = 1.54$ Å.

(*hkl*)	1-Monostearin				1-Monopalmitin			
	Subalpha	Alpha	Beta prime	Beta	Subalpha	Alpha	Beta prime	Beta
				Long Spacings (LJ)				
001	49.7 VS	50.7 VS	49.7 VS	50.0 VS	45.0 VS	45.1 VS	45.0 VS	45.5 VS
002	25.5 W	25.0 M	25.2 W	25.0 W	22.8 M	22.8 W		23.0 VW
003	16.9 W	16.7 S	16.8 W	16.6 M	15.3 M	15.15 M	15.1 W	15.25 S
004	12.7 W	12.5 M	12.6 W	12.5 M	11.4 M	11.4 M	11.3 VW	11.4 S
005								
006	8.42 VW	8.38 M	8.40 VW	8.34 M	7.53 M	7.60 W		7.60 M
007	7.17 VW	7.18 M			6.55 W			6.47 W
008				6.27 VW				
009				5.63 W		5.10 W		5.06 M
Av. d	50.3	50.2	50.1	50.1	45.5	45.6	45.25	45.6
(MS) d	50.0?	58.3	50.0?	50.0	45.8?		45.8?	45.8
(FSDL) d				49.9				45.7
				Short Spacings (LJ)				
(LJ)				4.88 W			5.00 VW	4.87 VW
	4.13 VS	4.64 W	4.15 VS	4.54 VS	4.14 VS	4.65 W	4.15 VS	4.55 S
	3.92 M	4.18 VS	3.89 VW	4.36 VS	3.92 M+	4.18 VS	3.85 VW−	4.37 S
	3.75 M	3.82 W	3.61 M	4.13 W	3.74 M+	3.99 VW	3.69 W	4.13 W
	3.58 M	2.47 VW	3.30 VW	3.85 VS	3.54 M+	3.80 W	3.29 W+	3.86 S
	3.28 W		2.91 VW	3.74 W	3.29 W	2.46 VW−	2.78 VW	3.74 W
	3.10 VW		2.79 VW	3.64 VW	2.92 VW		2.52 M	3.50 M
	2.94 VW		2.52 M	3.54 W+	2.78 VW		2.25 VW	3.29 M
	2.81 VW		2.25 VW	3.43 VW	2.54 W			3.08 M
	2.52 M		2.22 W	3.30 VW	2.50 W			2.67 VW
	2.42 VW			3.12 M	2.41 VW			2.54 VW
	2.32 W			2.97 VW	2.33 W			2.47 M
	2.23 W				2.21 W			2.23 VW
	2.09 W			2.45 M	2.08 W			2.14 VW
								2.06 VW−

(FSDL), Data of Filer and co-workers

TABLE IV

CHARACTERISTIC SHORT SPACINGS IN Å. FOR MONOGLYCERIDES (COMPARISON WITH PREVIOUS DATA)

	Subalpha	Alpha	Beta prime	Beta
(LJ)	4.14 VS	4.64 W	4.15 VS	4.55 S+
	3.92 M	4.18 VS	3.87 VW	4.37 S+
	3.75 M	3.99 VW	3.65 W+	3.86 S+
	3.56 M	3.81 W	3.30 W−	3.74 W
(MS)	4.24 VS?	4.2 VS	4.24 VS?	4.65 VS
	3.86 M?		3.86 M?	3.94 S

	1-Monostearin Beta	1-Monopalmitin Beta
(FSDL)	4.74 W	4.73 VS
	4.55 VS	4.55 VS
	4.37 S	4.37 VS
		4.27 VS
		3.94 VS
	3.84 VS	3.84 VS
	3.74 W	3.74 S
	3.52 S	

vior described by Malkin, there were departures of considerable significance particularly in the case of alpha and subalpha forms.

Alpha and Subalpha.—Alpha, in the correspondence of its melting point to the supercooling limit and by the value of its one strong short spacing (4.18 Å.), resembles the alpha form

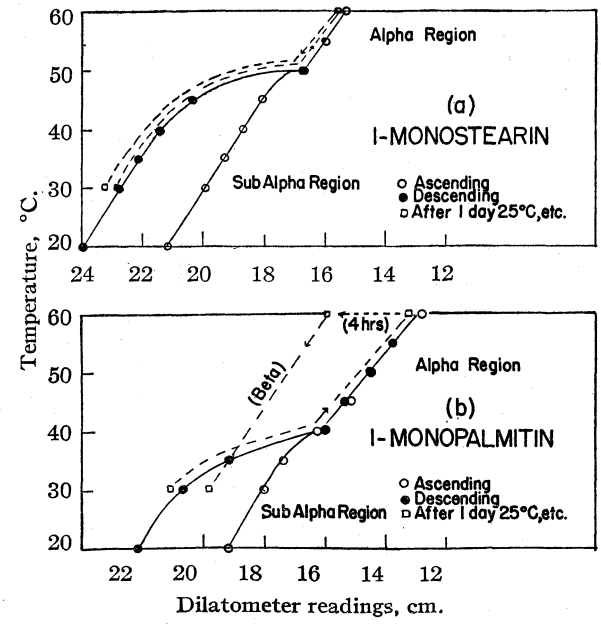


Fig. 1.—Dilatometer curves of reversible alpha to subalpha transformation.

of triglycerides. There are important differences, however. Weak short spacings on both sides of 4.18 Å. evidence certain unidentified complexities of structure not found for triglycerides. Of greater interest are the long spacing values. Double chain length structures are indicated, but the values are 8 Å. short of that to be expected for completely extended untilted molecules, 58 Å. for monostearin. (A value of this magnitude, reported by Malkin, was not confirmed.) Alpha, beta prime and beta values are very nearly equal and the simplest conclusion is that they each indicate titled molecules. A tilted alpha, supposedly of hexagonal cross-sectional type, would be contrary to previous experience and preconceptions.

The alpha form goes reversibly to a form, here called subalpha, at a temperature about 25° below the alpha melting point. The reversibility was completely established, in the present study by successive X-ray exposures above, below and above the transition point to give respectively alpha, subalpha and alpha patterns. This transition point was actually located by Malkin, with the help of thermal curves, but he did not describe a clearcut association of change in diffraction pattern with thermal effect. He said that alpha "is stable only very near its melting point," but it is actually reasonably stable clear down to the transition point. He speaks of the form below the transition point as an "intermediate form" somewhat akin to a "glass" and without "a regular crystalline lattice," but *subalpha* is actually a highly ordered structure, apparently considerably more ordered than *alpha* which is itself of a fair degree of crystallinity.

The alpha $\rightleftarrows$ subalpha change is readily followed also by the dilatometer and microscope.[13]

If a dilatometer sample is melted and chilled quickly to 20°, then heated in steps to 60° and cooled stepwise to 20°, curves such as those shown in Fig. 1 are obtained. The solid ascending curves show a small break at about 49° for 1-monostearin and 39° for 1-monopalmitin. The solid descending curves show greatly accentuated contractions in the same temperature regions indicating that the subalpha form is decidedly more dense than it was initially. The order of contraction in the alpha $\rightarrow$ subalpha change is about 0.04 specific volume units.

After the ascending and descending curves were run the dilatometers stood overnight at room temperature and then were read at 30°, heated directly to 60°, allowed to attain a constant reading, and cooled to 30°. The points obtained are joined by broken lines on Fig. 1 and the time sequence is indicated by arrows. The data show that the descending alpha to subalpha path is essentially duplicated for 1-monostearin. However, 1-monopalmitin transformed to beta in four hours at 60°. Cooling 1-monopalmitin beta to 30° revealed a lower density for this form than for subalpha—a fact which was substantiated for other samples of 1-monopalmitin as well as for 1-monostearin after long stabilization. Preliminary specific volume data for 1-monopalmitin at 30.0 are 0.937 for subalpha, 0.983 for alpha (extrapolated from 0.996 at 60.0°) and 0.949 for beta. Final data will be reported later.

The large density difference between slowly and rapidly chilled subalpha is puzzling, especially in view of the great similarity in X-ray patterns for the two states. The difference may be due to vacuoles or perhaps to a less complete stabilization and less perfect alinement of chains or crystallites in the chilled sample. (Comparable variations in density have been observed, but not yet reported, for triglycerides and in those cases have been found to be associated with observable variations in melting point.)

With the microscope the transformation of alpha to subalpha is revealed quite sharply by the appearance of many little shrinkage cracks as the temperature is lowered to a level just below the point of transformation. These cracks are almost completely "healed" by raising the temperature and holding it just above the transformation point.

It is believed that Malkin was concerned, at least part of the time, with subalpha when he used the term beta prime. Especially in the case of his recent publication[14] containing data on monoelaidin it is apparent that the so-called beta prime form conforms much more closely, in X-ray spacing, to the subalpha values than to the beta prime values here reported for monopalmitin and monostearin. Malkin's beta prime m. ps. are not accounted for by this line of thought, however.

No evidence was obtained by the various techniques employed in this study for the lower of the monostearin transformation points reported by Malkin. It is the higher value that was confirmed and that corresponds to the alpha $\rightarrow$ subalpha change.

Some indication of the stability of the alpha (and subalpha) forms is given by the observation that monopalmitin subalpha persists about thirty days at room temperature as compared with more than one hundred twenty days for monostearin. This is comparable to the room temperature stabilities of the alpha forms of the corresponding triglycerides. A difference in high temperature alpha stability between mono- and triglycerides appears on running complete melting points on alpha (subalpha) forms at a heating rate of 0.5 per minute. Monopalmitin and monostearin give approximately their respective alpha m. p.s but the triglycerides transform during heating to give approximately their beta m. p.s.

Beta Prime.—Despite considerable effort to obtain the beta prime form from the melt or from alpha, it was actually obtained only by rapid crystallization of dilute ether or Skellysolve B so-

(13) Microscopic observations by Dr. Don G. Kolp of this laboratory.

(14) Malkin and Carter, *J. Chem. Soc.*, 554 (1947).

lutions. Crystals, while well defined, were small. As has been indicated, the beta prime X-ray pattern is somewhat similar to that of subalpha. The distinguishing features are indicated in Table IV, a summary table of characteristic values. In brief, the chief difference is that beta prime lacks the two medium strength lines shown by subalpha for the region between 4.15 Å. and 3.65 Å.

Beta.—The beta form is obtained by slow crystallization from solvent or by transformation of alpha and beta prime forms. It was not obtained directly from the melt. The crystals from solvent are relatively large platelets with a beautiful gloss. Beta is the only truly stable crystalline form.

Acknowledgment.—The authors are grateful to the members of this Laboratory who have given valued advice and experimental assistance.

Summary

While largely confirming the work of Malkin, a reëxamination of the polymorphic behavior of 1-monostearin and 1-monopalmitin has resulted in new information which differs in important aspects from earlier findings.

These monoglycerides have four forms—subalpha, alpha, beta prime and beta. The last three have melting points increasing in the order named. Beta alone is thermodynamically stable. Beta prime has been obtained only from solvent. There is a reversible alpha–subalpha transformation about 25° below the alpha m. p. but above room temperature. All forms for a given monoglyceride have very nearly the same long spacing and appear to be tilted double-chain-length structures. The forms are readily distinguished by means of short spacings except for subalpha and beta prime, which, in spite of notable differences in thermal behavior, show only minor differences in diffraction pattern.

IVORYDALE, OHIO RECEIVED MARCH 4, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

Kinetics of the Reaction between Ethylene Chlorohydrin and Hydroxyl or Alkoxyl Ions in Mixed Solvents[1,2]

BY JOHN ED STEVENS,[3] C. LAW MCCABE AND J. C. WARNER

Previous investigations of the reaction between ethylene chlorohydrin and hydroxyl ion have established the following facts concerning the reaction. It is clearly second order,[4,5,6] the rate being proportional to the concentration of chlorohydrin and to the concentration of hydroxyl ion, and the side reaction with water at temperatures in the vicinity of 30° is so slow[7] that it may be neglected. There is no significant back reaction in alkaline solution[8] and the product with water as the solvent is ethylene oxide and not ethylene glycol.[9] There is a very small negative kinetic salt effect in water and in water–ethanol mixtures.[6] More recently, Porret,[10] who apparently was unaware of the work of Winstrom and Warner,[6] has reported the results of an investigation which duplicates their kinetic studies in water as solvent. His velocity constants, activation energy and kinetic salt effects are in excellent agreement with those reported by Winstrom and Warner. Porret[11] has also determined equilibrium constants for the reaction in the temperature range 0 to 50°. These results confirm the view that no correction for the back reaction needs to be made in alkaline solutions.

It was the purpose of the present investigation to study the kinetics of this reaction in a number of water–non-aqueous solvent mixtures down to low dielectric constants for the mixtures, *i. e.*, to high concentrations of the non-aqueous solvents.

Experimental

Materials and Procedure.—Previously described[6] methods for the purification of materials and the preparation of reagents were used with only minor modifications. Temperature variations in thermostats were followed by means of Beckman thermometers and absolute temperatures were established within 0.01° by use of a N.B.S. platinum resistance thermometer. The thermostat operated at 30 ± 0.005° was of the conventional type, and the one operated at 15 ± 0.01° was also of the conventional type, but was placed inside a large insulated container through which air, cooled by ice, was circulated to maintain the environment at 10 to 12°. Experiments at 0 ± 0.005° were carried out in large Dewar flasks filled with washed cracked ice and distilled water.

Standard solutions of sodium ethoxide and sodium methoxide were prepared by treating metallic sodium with the corresponding anhydrous alcohol, determining the concentration by titration and then diluting to the desired strength with the anhydrous alcohol.

Since the reaction proceeds with a decrease in hydroxyl or alkoxyl ion concentration and a corresponding increase in

(1) Abstracted from a dissertation submitted by John Ed Stevens to the Carnegie Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Science.

(2) Presented before the Physical and Inorganic Division at the Detroit meeting of the American Chemical Society, April, 1943.

(3) Present address: Shell Development Company, Emeryville, Calif.

(4) Evans, *Z. physik. Chem.*, **7**, 335 (1891).

(5) Smith, *ibid.*, **81**, 339 (1912); **A152**, 153 (1931).

(6) Winstrom and Warner, THIS JOURNAL, **61**, 1205 (1939).

(7) Radulescu and Muresanu, *Bull. Soc. Sci. Cluj. Roumanie*, **7**, 128 (1932).

(8) Brönsted, Kilpatrick and Kilpatrick, THIS JOURNAL, **51**, 428 (1929).

(9) British Patents 286,850 (Feb. 8, 1927); 292,066 (Jan. 11, 1927). Ushakov and Mikhailov, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 249 (1937).

(10) Porret, *Helv. Chim. Acta*, **24**, 80E (1941).

(11) Porret, *Helv. Chim. Acta*, **27**, 1321 (1944).

chloride ion concentration, it is obvious that the reaction may be followed by withdrawing samples at suitable time intervals, delivering them into an excess of standard acid to stop the reaction, and titrating for either excess acid or chloride. In each new solvent mixture, it was always established that these two methods of following the reaction gave results which were in agreement within the experimental error; thereafter the acid–base titration (rosolic acid indicator) was used in a majority of the experiments.

In most experiments, equal starting concentrations of ethylene chlorohydrin and carbonate-free hydroxide (or alkoxide) were used and the velocity constant was obtained from the slope of the best straight line obtained by plotting $1/c$ against time.

Kinetic Results.—Velocity constants were determined in 1,4-dioxane–water, methanol–water, ethanol–water, isopropanol–water and *t*-butanol–water mixtures at 30°. Rates were also determined at 0 and 15° in the first three of the above solvent mixtures.

Velocity constants in ethanol–water mixtures are given in Table I. The rate in 100% ethanol was determined by using sodium ethoxide and ethylene chlorohydrin as reactants in anhydrous alcohol. Table II gives the velocity constants in methanol–water and 1,4-dioxane–water mixtures including the rate constant for the reaction of sodium methoxide with ethylene chlorohydrin in 100% methanol. Table III reports the velocity constants obtained at 30° in isopropanol–water and in *t*-butanol–water mixtures. In Fig. 1, velocity constants as a function of dielectric constant[11a] at 30° are summarized for all of the solvent mixtures.

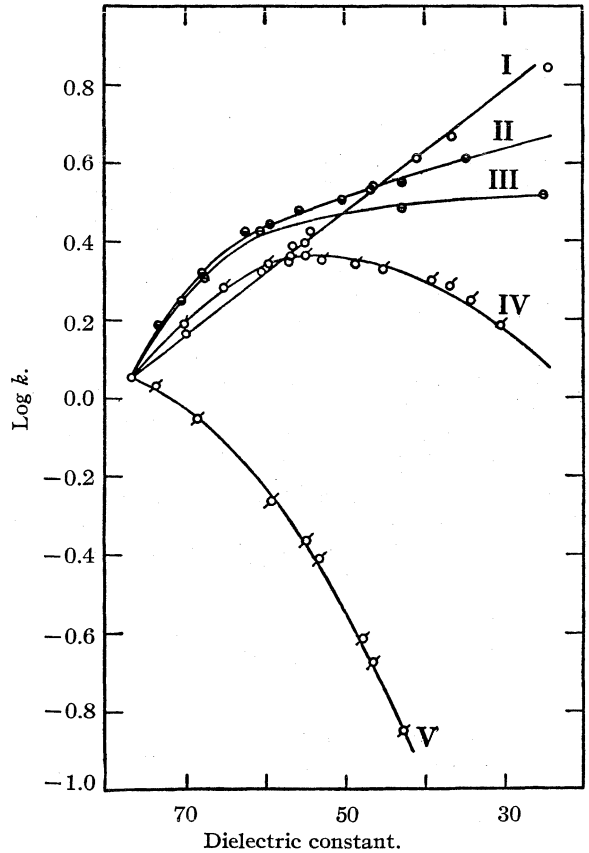


Fig. 1.—All at 30°: I, dioxane–water; II, isopropanol–water; III, *t*-butanol–water; IV, ethanol–water; V, methanol–water.

(11a) Akerlof, THIS JOURNAL, **54**, 4125 (1932); Akerlof and Short, *ibid.*, **58**, 1242 (1936).

TABLE I

SUMMARY OF RESULTS IN ETHANOL–WATER MIXTURES

Wt. % ethanol	Dielectric constant	k (min.$^{-1}$)	Wt. % ethanol	Dielectric constant	k (min.$^{-1}$)
	At 30°			At 15°	
0.0	76.7	1.13	0.0	82.2	0.166
11.9	70.0	1.56	9.6	76.7	.710
20.6	65.0	1.93	20.6	70.0	.284
30.0	59.5	2.23	28.8	65.0	.349
34.3	57.0	2.27	37.6	59.4	.376
37.6	55.0	2.33	44.8	55.0	.359
40.9	53.0	2.28	54.9	48.9	.323
48.4	48.7	2.21	61.7	45.0	.302
54.9	45.0	2.17		At 0°	
65.8	39.0	2.04	0.0	88.4	.0186
69.7	36.9	1.95	18.6	76.7	.0307
75.0	34.2	1.81	20.6	75.4	.0325
83.7	30.1	1.53	36.6	65.0	.0450
100.0	23.5	0.95	37.7	64.3	.0460
			52.1	55.0	.0387
			54.9	53.2	.0378
			68.6	45.0	.0290

TABLE II

SUMMARY OF RESULTS IN METHANOL–WATER AND 1,4-DIOXANE–WATER MIXTURES

	In methanol–water			In 1,4-dioxane–water		
Temp., °C.	Wt. % methanol	Dielectric constant	k (min.$^{-1}$)	Wt. % dioxane	Dielectric constant	k (min.$^{-1}$)
30	0.0	76.7	1.13	0.0	76.7	1.13
	7.0	73.7	1.08	7.6	70.0	1.50
	18.0	68.4	0.878	18.6	60.4	2.11
	37.9	59.0	.545	22.9	56.7	2.32
	46.6	55.0	.429	23.1	56.5	2.46
	50.5	53.2	.388	24.9	55.0	2.48
	61.5	47.8	.241	25.8	54.2	2.66
	64.7	46.3	.214	34.3	46.7	3.41
	72.6	42.4	.144	34.6	46.0	3.47
	84.7	37.5	.0702	41.0	40.8	4.15
	92.8	33.5	.0450	46.0	36.6	4.74
	100.0	30.7	.0225	61.2	24.1	7.08
				71.4	16.2	8.43
15	0.0	82.3	.169	0.0	82.2	0.166
	12.0	76.7	.123	6.2	76.7	.204
	54.9	55.0	.0343	29.7	55.0	.470
				34.3	51.1	.578
0	0.0	88.4	.0186	0.0	88.4	.0186
	22.8	76.7	.00864	12.3	76.7	.0297
	64.6	65.0	.00198	34.3	55.0	.0772

Reaction Product in Mixed Solvents.—Previous investigators[9] have stated that ethylene oxide is the product of the reaction of ethylene chlorohydrin with hydroxyl ion in aqueous solution. This has been confirmed by our investigations. We considered it necessary, however, to establish the nature of the reaction product in our water-non-aqueous solvent mixtures and in anhydrous ethanol and anhydrous methanol. The possible products would seem to be ethylene glycol, ethylene oxide or (in alcoholic solutions) an hydroxy ether of the Cellosolve type. Any attempt to separate ethylene oxide from the glycol and the hydroxy ether by distillation is complicated by the hydrolysis of the oxide to glycol which is quite rapid at temperatures as high as 80°. Our evidence was obtained by

TABLE III

SUMMARY OF RESULTS IN ISOPROPANOL–WATER AND *t*-BUTANOL–WATER MIXTURES AT 30°

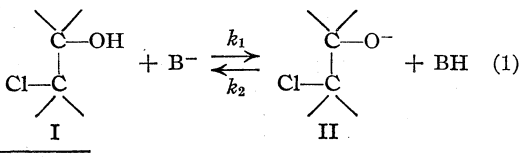
In isopropanol–water			In *t*-butanol–water		
Wt. % isopropanol	Dielectric constant	k (min.$^{-1}$)	Wt. % butanol	Dielectric constant	k (min.$^{-1}$)
0.0	76.7	1.13	0.0	76.7	1.13
5.0	73.2	1.55	10.4	67.9	2.05
8.6	70.6	1.81	18.8	60.6	2.66
11.4	67.9	2.11	39.8	42.7	3.08
20.4	62.2	2.66	63.2	24.7	3.47
24.7	59.2	2.81			
29.7	56.7	3.02			
37.4	50.2	3.23			
48.0	42.8	3.60			
59.2	34.9	4.10			
70.3	27.6	4.68			

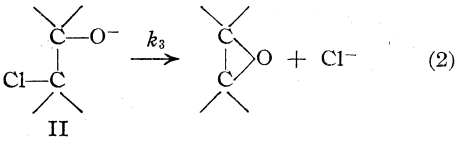
adaptation of Lubatti's method[12] for determining ethylene oxide in gas mixtures: To samples which had reacted to completion, standard solutions of hydrochloric acid and calcium chloride were added in such amounts that a slight excess of acid and 30 g. of chloride ion per 100 ml. were present. Under these conditions ethylene oxide is converted back to ethylene chlorohydrin and an equivalent of acid is consumed. The rate of this reversal in acid solution has been studied.[8] Similar experiments with known solutions of glycol and hydroxy ether showed that no acid was consumed by these substances. That glycol does not react with acid under these conditions is supported by other investigators.[13] Although the method did not yield results of the desired precision and reproducibility, and has since been greatly improved, the acid consumed in various experiments was between 90 and 105% of the amount calculated assuming ethylene oxide was the only product of reaction. It seems safe to say, therefore, that ethylene oxide was the principal product in all of the solvent mixtures used in this investigation as well as in water, in anhydrous methanol and in anhydrous ethanol.

Discussion

The fact that ethylene oxide is the product obtained in all of the experiments performed in this investigation indicates that the second order reaction between ethylene chlorohydrin and hydroxyl ion, alkoxyl ion or mixtures of the two reactants cannot proceed by the usual displacement type of mechanism. Furthermore, the data obtained in methanol–water and in ethanol–water mixtures is unusual and cannot be explained on a basis of the expected influence of the dielectric constant of the solvent upon the reaction rate.

Mechanism.—It seems possible to give a qualitative explanation of all the facts which have been observed by assuming the mechanism suggested by Winstein and Lucas,[14,15] namely



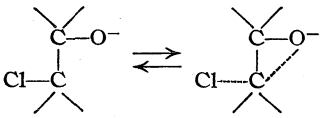


If Step 1 is an equilibrium step for which the equilibrium constant is K and Step 2, in which the anion goes through the activated state to form ethylene oxide with a rate constant k_3, is slow, then

$$\frac{-d[B^-]}{dt} = \frac{d[Cl^-]}{dt} = \frac{k_3K}{[BH]}[CH_2Cl—CH_2OH][B^-]\frac{\gamma_I^0\gamma_{B^-}}{\gamma_{BH}^0\gamma_{II}} \quad (3)$$

where k (observed) $= k_3K/[BH]$, when B^- is the base conjugate to a pure solvent BH. It is obvious that according to this mechanism the rate of reaction should be proportional to the concentration of the chlorohydrin and to the concentration of the anion base (OH^-, CH_3O^- or $C_2H_4O^-$). Furthermore the mechanism accounts for the negligible kinetic salt effect. (As a first approximation,[15a] ionic strength would have little influence on the value of the activity coefficient quotient in Eq. 3).

Influence of Dielectric Constant of Solvent.—One would expect the dielectric constant of the medium to have little effect on the equilibrium (Step 1) because the electrostatic contribution to the free energy of reaction would be small. On the other hand, the conversion of the anion into the activated complex



is quite like the formation of the activated complex in the bimolecular displacement of halide from alkyl halides by hydroxyl ion; there is a distribution of charge and one would expect an increase in rate as the dielectric constant of the medium is decreased.[16] The expected effect is observed in 1,4-dioxane–water mixtures, but it seems obvious that some factor other than dielectric constant has an important influence in the alcohol–water mixtures, especially in methanol–water and ethanol–water.

Influence of Acid–Base Level of Solvent.—If one postulates that ethanol is a stronger acid than water and that methanol is a still stronger acid than ethanol, then hydroxyl ion will be leveled somewhat in these mixed solvents by the reaction $OH^- + ROH \rightleftarrows RO^- + H_2O$. The extent of the reaction, and hence the reduction in the base level of the medium will depend upon the

(12) Lubatti, *J. Soc. Chem. Ind.*, **51**, 361T (1932).

(13) Norris, Watt and Thomas, THIS JOURNAL, **38**, 1079 (1916).

(14) Winstein and Lucas, *ibid.*, **61**, 1576 (1939).

(15) This mechanism for the reaction of chlorohydrins with strong bases has received further confirmation in the recent work of Kadesch, *ibid.*, **68**, 46 (1946).

(15a) La Mer, *Chem. Rev.*, **10**, 179 (1932); *J. Franklin Inst.*, **225**, 709 (1938).

(16) Hughes, *Trans. Faraday Soc.*, **37**, 609 (1941); Hughes and Ingold, *ibid.*, **37**, 666 (1941); Harned and Samaras, THIS JOURNAL, **54**, 15 (1932); Scatchard, *Chem. Rev.*, **10**, 236 (1932).

acid strength of ROH and the ratio [ROH]/[H_2O] in the solvent mixture. The extent to which the carbanion is formed in the equilibrium step of the process (Step 1) undoubtedly depends upon the base level of the system, and a decrease in basicity would, therefore, cause a decrease in rate. It is tentatively suggested that in methanol–water mixtures, the influence of methanol in decreasing the basicity over the entire range of composition is sufficient to more than compensate for the expected increase in rate due to decreasing dielectric constant. It seems logical to assume that ethanol is a weaker acid than methanol and hence has less influence on the basicity. We may assume, at low ethanol concentrations, that the dielectric constant effect is predominant, but that at the higher concentrations the decreased basicity brings about a decrease in rate, thereby accounting for the observed maximum in the rate constants as a function of ethanol composition. The fact that rate constants in the alcohol–water mixtures extrapolate smoothly to the rate constants for reaction with alkoxyl ion in the anhydrous alcohols supports this explanation. Accurate information on acid-base levels in ethanol–water and methanol–water mixtures is sorely needed and is being sought in this laboratory.

Summary

1. The rate of reaction of ethylene chlorohydrin with hydroxyl ion (or with alkoxyl ion) has been measured in 1,4-dioxane–water, methanol–water, ethanol–water, isopropanol–water and *t*-butanol–water mixtures at 30° up to high concentrations of the non-aqueous solvent. Measurements in anhydrous ethanol and methanol are included. For the first three solvent mixtures, rate measurements were also made at 0 and 15°.

2. In methanol–water mixtures, the reaction rate decreased continuously with increase in methanol concentration. With the addition of ethanol to water, the rate at first increased, reached a maximum value at about 38% ethanol (30°), and then decreased at higher ethanol concentrations. In the other solvent mixtures, the rate increased with a decrease in dielectric constant over the entire range of solvent composition.

3. It has been established that ethylene oxide is the principal reaction product in all of the solvents used, including anhydrous ethanol and anhydrous methanol.

4. The Winstein–Lucas mechanism which postulates an initial equilibrium step in which a proton is removed from the chlorohydrin to form an anion, followed by an intramolecular displacement of chloride by the negatively charged oxygen, is consistent with (a) the bimolecular character of the reaction, (b) the absence of an appreciable kinetic salt effect, (c) the formation of ethylene oxide as the principal product, and (d) the increase in rate with decrease in dielectric constant is the principal factor influencing the rate. This mechanism is also capable of giving a qualitative explanation of the unusual results obtained in methanol–water and ethanol–water mixtures by taking into account the possible influence of the acid–base level in these solvents upon the initial equilibrium step.

PITTSBURGH 13, PENNSYLVANIA

RECEIVED FEBRUARY 5, 1948

[CONTRIBUTION FROM BELL TELEPHONE LABORATORIES, INC.]

Measurements on the Absorption of Microwaves. III. Losses of Camphor Dissolved in Cyclohexane

BY D. H. WHIFFEN[1]

The general outline of the type of absorption of electromagnetic radiation of about a centimeter wave length by mobile liquids and solutions has already been established.[2,3] Before investigating some of the details or exceptional systems, it was thought profitable to measure one system carefully; such a system may also be useful for comparing various methods of measurement.

Solutions of camphor in cyclohexane seem to have several advantages for this purpose. Firstly, the use of solutions makes a large range of loss tangents available according to the concentration employed. Secondly, cyclohexane is easily purified so as to give an almost negligible loss; this is in contrast to benzene which is difficult to keep dry. Thirdly, camphor was chosen because of its large dipole moment, its rigidity, its high solubility, the ease of purification by sublimation, and because preliminary experiments had indicated that its solutions in cyclohexane obeyed the Debye loss curve[4] with a relaxation time of 7×10^{-12} sec., which corresponds to a maximum loss at 1.3 cm. wave length.

Experimental

Cavities.—The loss tangents were obtained from the Q of a cavity resonator completely filled with the test liquid. The details of the resonator used at 3.3 cm. are shown in Fig. 1. This is a cylindrical cavity which can be resonant in the $H_{1,1,2}$ mode[5] when filled with a liquid

(1) Present address: St. John's College, Oxford, England.

(2) Whiffen and Thompson, *Trans. Faraday Soc.*, **42A**, 114 and 122 (1946).

(3) Jackson and Powles, *ibid.*, **42A**, 101 (1946).

(4) Debye, "Polar Molecules," Chemical Catalog Co., Reinhold Publ. Corp., New York, N. Y., Chap. V.

(5) Lamont, "Waveguides," Methuen, New York, N. Y.

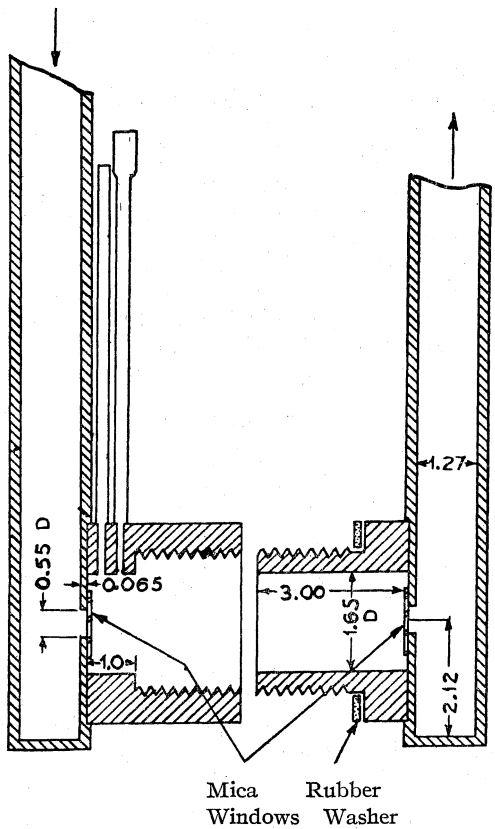


Fig. 1.—3.3-Cm. wave length resonant cavity; dimensions in cm.

of dielectric constant about 2.0 at a frequency near 9,500 Mc./sec. The liquid is contained by two very thin mica windows which are stuck with seccotine over the coupling holes, which are located centrally in each end-plate. The central barrel is in two parts so that the windows could be fixed in position and the cavity can be thoroughly cleaned. When assembled the two parts meet in a butt-joint and this is located one quarter of the way along the barrel, where there is a node in the longitudinal wall currents. The whole is silver-plated and when screwed up the end guides are kept parallel thus ensuring coupling into and out of the same member of the degenerate $H_{1,1,2}$ modes. Since the cavity is not resonant at a convenient wave length when filled with air, the Q due to the wall resistance and the coupling losses must be found with the help of a lossless liquid or by calculation. In this instance the observed Q when filled with the best sample of cyclohexane was 4,050 and the theoretical Q is 7,100, whence the maximum loss tangent of the cyclohexane is 0.00011, which is the difference in the reciprocal Q's; this figure is only a maximum since it has usually been observed[6,7] that the Q's of air filled cavities are lower than the theoretical values calculated from the direct current resistivities of the walls. For work with solutions it is the reciprocal Q of the cavity filled with solvent which must be subtracted from that of the cavity filled with solution to obtain the loss due to the solute molecules, and so the solvent and the resistance losses need not be separated.

The cavity used at 1.3 cm. is essentially a scale model of that already described and has a barrel length of 2.29 cm. and diameter of 0.63 cm. The $H_{1,1,3}$ mode is used and when filled with cyclohexane it has a Q of 2,500; the theoretical Q is 3,800 so that the loss tangent of the cyclohexane is less than 0.00014 at room temperature and 1.3 cm. wave length.

The cavities are immersed in a thermostat whose temperature is held constant to better than 0.1° and the rubber washer indicated in the diagram serves to keep the thermostat liquid from the inside of the cavity.

Q Measurements.—The wave guide bench arrangement is shown in Fig. 2. The signal oscillator is stabilized in frequency by comparison of its output with a cavity resonator, any difference in frequency causing an error voltage to be fed back to the reflector of the oscillator (723A at 3.3 cm.) and also to the thermal tuning grid in the case of the oscillator used at 1.3 cm. (2K50). The error voltage is obtained by a modification of the first Pound[8] circuit or else by a rather different arrangement due to Dr. Townes[9] which involves a very small frequency modulation of the oscillator. The output powers of both the signal and the beat oscillators are monitored with a crystal detector and a microammeter. Superheterodyne detection is employed, the beat oscillator being swept through a small frequency range. The detecting crystal is connected through a calibrated carbon attenuator to a 60 Mc./sec. amplifier and thence to a detecting system whose output meter shows a signal dependent on the peak input during the sweep. The meter is used as a null instrument and the power calibration rests in the attenuator for the 60 Mc./sec. signal.

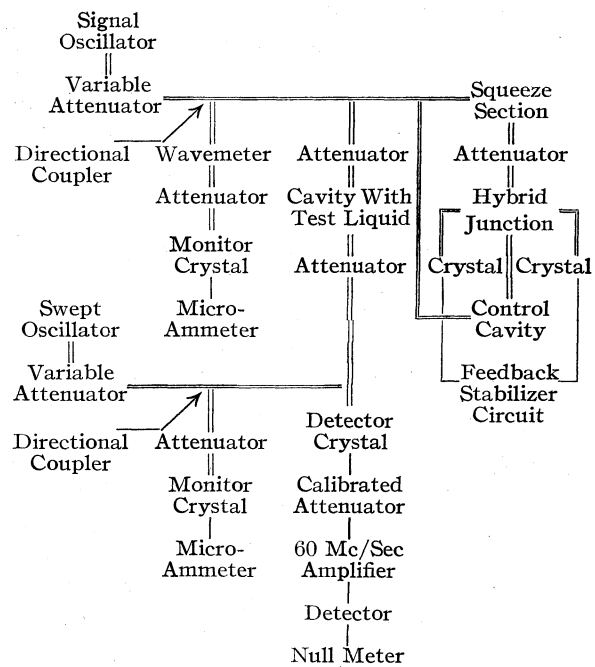


Fig. 2.—Arrangement of the wave-guide bench.

Measurements of the Q are made by observing first the maximum transmission of the cavity and the frequency at which this occurs; then 3 db., or other convenient amount, of attenuation are removed and the frequency of the signal oscillator readjusted so that the output from the cavity is reduced to its former value. From the difference between this frequency and that at the corresponding point on the other side of the maximum the Q can be calculated from the usual formula for a resonance curve

$$Q = f/\delta f(P_{\max.}/P - 1)^{1/2}$$

where f is the frequency, δf the total frequency difference

(6) Horner, Taylor, Dunsmuir, Lamb and Jackson, *J. Inst. Elect. Engrs.*, **93**, 53 (Part III 1946).

(7) Bleaney, Loubser and Penrose, *Proc. Phys. Soc.*, **59**, 185 (1947).

(8) Pound, *Rev. Sci. Instruments*, **17**, 490 (1946).

(9) To be published.

and $P_{max.}$ and P are the power transmissions at the peak and at the points of observation of δf. The frequency meter at 1.3 cm. is an $H_{0,1,n}$ cylindrical resonator which has been calibrated against the ammonia spectrum[10,11] while that used at 3.3 cm. is a coaxial line meter checked against a substandard which derives its calibration from quartz crystals. In the measurement of the Q there is a scatter of experimental values corresponding to a probable error of 3% in each reading; several determinations are made on each Q which reduces this error, but there may also be systematic errors due to the small frequency sensitivity of the directional couplers and the monitor crystals so that the results can only be trusted to 5%.

Measurements at 10 cm.—Measurements at 10 cm. wave length are made using a coaxial line after the method of von Hippel and his co-workers.[12] The test liquid at the end of a short-circuited coaxial line has its surface in contact with a quarter wave length plug of Teflon (polyfluorethylene) of negligible loss; the liquid is introduced from a pipe through the reflecting end of the line. The plug is located so as to leave one quarter wave length of liquid at room temperature. However uncertainty in its expansion leads to some uncertainty in the length of the liquid filling at other temperatures, and the observed losses at the higher temperatures may be too low on this account.

Materials.—The cyclohexane was a commercial product dried and purified by shaking with active silica gel. The *dl*-camphor was a commercial resublimed product.

The solutions for the measurements at 3.3 and 1.3 cm. ranged in concentration up to 2.5 g./liter, whereas the smaller loss and the less sensitive technique at 10 cm. wave length necessitated solutions up to 25 g./liter. The density[13] of pure cyclohexane was used to correct for the change of volume concentration with temperature.

Results and Discussion

The losses due to a solute are best expressed as the molecular loss tangent, that is Loss tangent/C where C is the concentration in g. moles/liter; this name and concentration unit have been chosen to be in keeping with general usage in other fields of chemistry. In no case was there any indication of a departure from a linear dependence of loss with concentration. This is shown for the losses at 3.3 cm. in Fig. 3.

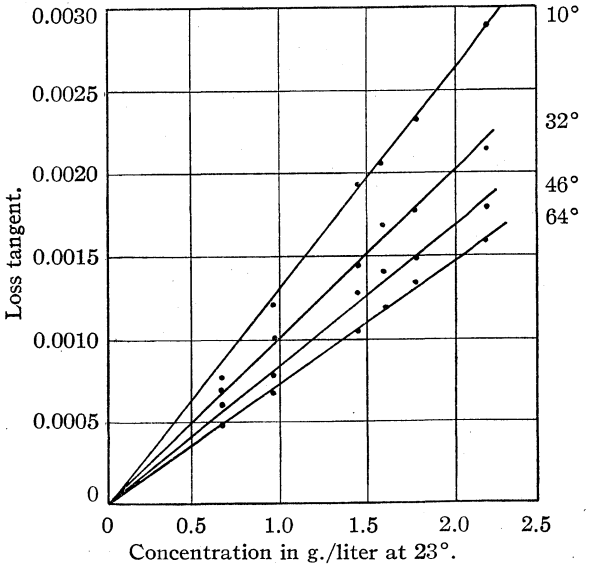


Fig. 3.—Loss of camphor in cyclohexane at 3.3 cm.

The experimental results are summarized in Table I which gives the observed molecular loss tangents; in each case the value is taken from the slope of a graph covering the concentration range. No explanation is offered for the smaller loss at 29° compared to the neighboring temperatures at 1.3 cm. wave length; the reduction is scarcely more than the estimated experimental errors.

TABLE I

1.3 cm. 24,000–23,500 Mc./sec.		3.3 cm. 9500–9250 Mc./sec.		10.0 cm. 3000 Mc./sec.	
T, °C.	Loss	T, °C.	Loss	T, °C.	Loss
10	0.246	10	0.194	12	0.064
29	.226	32	.156	25	.056
46	.235	46	.135	37	.047
62	.202	64	.118	51	.037
				66	.030

For comparison at a common temperature the losses at 10, 30, 50 and 70° were obtained by interpolation and slight extrapolation. These were compared with the Debye loss expression used in the form[2]

$$\text{Loss} = \frac{(\epsilon + 2)^2}{\epsilon} \frac{4\pi N\mu^2}{27kT} \frac{\omega\tau}{1 + \omega^2\tau^2}$$

ϵ, the dielectric constant of the solvent is 2.0 and μ, the dipole moment of camphor, was taken as 3.00 D; Sidgwick's table[14] gives range from 2.94–3.05 D. ω is the angular frequency and τ, the time of relaxation, is the only unknown quantity. The values of this parameter which best fit the results, together with the experimental losses and the calculated losses using these times, are given in Table II. This table shows agreement between

TABLE II

Temp., °C.	Time of relaxation, sec.	Losses at 1.3 cm. exp.	1.3 cm. calcd.	3.3 cm. exp.	3.3 cm. calcd.	10 cm. exp.	10 cm. calcd.
10	7.4×10^{-12}	0.246	0.255	0.194	0.190	0.066	0.067
30	6.2×10^{-12}	.228	.235	.159	.155	.052	.053
50	5.3×10^{-12}	.230	.220	.131	.129	.039	.045
70	4.5×10^{-12}	.193	.200	.111	.105	.029	.036

the experimental and calculated losses within 5% except for the higher temperature results at 10 cm. wave length and a special experimental error, which would lead to low experimental values here, has been mentioned above.

Measurements are at too few frequencies for a claim to be made that the Debye expression with one relaxation time is undoubtedly the proper form for describing the loss, but the agreement is such that it can be said that single relaxation times, one for each temperature, do give a reasonable description of the system. In particular the recipro-

(10) Strandberg, Kyhl, Wentink and Hillger, *Phys. Rev.*, **71**, 326 (1947).

(11) Coles and Good, *ibid.*, **71**, 383 (1947).

(12) Hippel, Jelatis and Westphal, "Measurements of Dielectric Constant and Loss in Coaxial Waveguides," report from Massachusetts Institute of Technology, 1943.

(13) "International Critical Tables."

(14) *Trans. Faraday Soc.*, **30**, 1934.

cals of these times describe the rate of rotation and the temperature dependance of this rate may be expressed as an activation energy. Figure 4 shows a graph of $\log\tau$ against $1/T$ and the slope of this line is equivalent to an activation energy, E_τ, of 1.7 kcal. if the time of relaxation is expressed by

$$\tau = Ae^{-E_\tau/RT}$$

This value may be compared with that of 1.7 kcal. for the similar activation energy for the rotation of camphor in *n*-heptane,[2] and also with the value of 2.3 kcal. for the corresponding activation energy for the viscosity of cyclohexane[13] over the range 15–30°. Further the interpolated value for the relaxation time at 20° which is 6.8×10^{-12} sec. in cyclohexane is very close to the value 6.5×10^{-12} sec. for camphor in *n*-heptane[2] but these values are by no means proportional to the macroscopic viscosity coefficients which are 0.96 and 0.41 cpoise, respectively.[13]

Acknowledgments.—The author wishes to thank Prof. P. Debye for his interest in the work and Dr. C. H. Townes for many invaluable discussions and suggestions. He also wishes to thank the Commonwealth Fund for the award of a Fellowship and the Bell Telephone Laboratories for granting the use of their facilities so freely during its tenure.

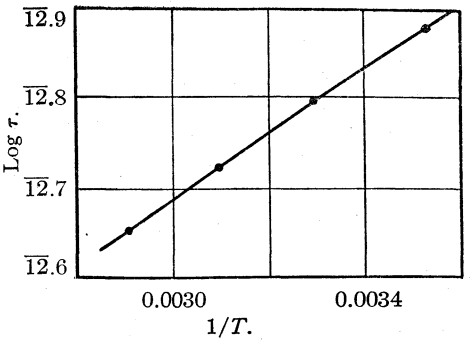


Fig. 4.—Graph of $\log_{10}\tau$ against $1/T$; slope equivalent to 1.7 kcal. energy of activation.

Summary

A description of the measurement of the dielectric loss of liquids at microwave frequencies using a completely filled cavity resonator is given. Solutions of camphor in cyclohexane have been measured over the range 10–70° at three wave lengths, 1.3, 3.3 and 10 cm. The observed losses can be well explained by a single Debye loss curve; the relaxation time is 6.8×10^{-12} sec. at 20° and the temperature coefficient corresponds to an activation energy of 1.7 kcal.

MURRAY HILL, NEW JERSEY

RECEIVED FEBRUARY 20, 1948

[CONTRIBUTION FROM THE UNIVERSITY OF MINNESOTA AND CORNELL UNIVERSITY]

Potentiometric Investigation of Tripyrophosphatomanganic(III) Acid

BY JAMES I. WATTERS AND I. M. KOLTHOFF

Evidence presented in a previous paper[1] indicated that the violet complex ion of manganese (III) and pyrophosphoric acid is a chelate ring complex anion having essentially the formula $Mn(H_2P_2O_7)_3^{-3}$. The ionic weight was estimated by application of Jander's expression[2] to the polarographically determined diffusion coefficients, and the hydrogen content of the complex was deduced from *p*H, ionic charge, and theoretical considerations. An investigation of the oxidation potential of the manganese(II)–manganese(III) couple in acidic pyrophosphate solutions along with the various factors influencing it is described in the present paper.

A new potentiometric procedure for determining manganese by titrating the trivalent complex with standard iron(II) sulfate solution is also described. Volumetric procedures in which the trivalent complex is titrated with iron(II) sulfate and the end-point detected with diphenylamine sulfonate as indicator, as well as amperometrically, will be described in subsequent papers. On the basis of the present studies,[3] Lingane and Karplus[4] have developed a potentiometric method for determining manganese in which manganese(II) is titrated to the violet manganese(III) pyrophosphate complex with standard permanganate solution. Their titration curves substantiate the authors' results.

Theoretical

In the experimental part it is shown that the potential at a platinum electrode of the complex manganic(III)–manganous(II) system is reversible, and that both complexes are mononuclear. It has been mentioned that the trivalent manganese complex contains three pyrophosphate radicals.[1] The hydrogen content of the pyrophosphate ions, either in the form of complex ions or simple ions, is a function of the *p*H of the solution. The number of associated hydrogen ions in the various ions at a particular *p*H, will be indicated by x, y and z. The number of pyrophosphate radicals in the manganese(II) complex will be indicated by m to illustrate the method of its evalua-

(1) I. M. Kolthoff and J. I. Watters, *Ind. Eng. Chem., Anal. Ed.*, **15**, 8 (1943).

(2) G. Jander and H. Spandau, *Z. physik. Chem.*, **A185**, 325 (1939).

(3) J. I. Watters, Ph.D. Thesis, University of Minnesota, 1943.

(4) J. J. Lingane and Robert Karplus, *Ind. Eng. Chem., Anal. Ed.*, **18**, 191 (1946).

tion. The following equation for the electrode reaction can be written

$$Mn(H_xP_2O_7)_m^{-(4m-mx-2)} + (3-m)H_yP_2O_7^{-(4-y)} \rightleftharpoons Mn(H_zP_2O_7)_3^{-(9-3z)} + (mx+3y-my-3z)H^+ + e \quad (1)$$

The equation for the oxidation potential of this system at 25° in terms of activities can be written as

$$E = E_0^c + 0.0591 \log a\mathrm{Mn^{III}C}/a\mathrm{Mn^{II}C} - (3-m)\ 0.0591 \log aH_yP_2O_7^{-(4-y)} + (mx+3y-my-3z)\ 0.0591 \log aH^+ \quad (2)$$

Upon converting hydrogen ion activity to paH and other activities to concentrations, this equation becomes

$$E = E_0^c + 0.0591 \log (f_1/f_2f_3) + 0.0591 \log (\mathrm{Mn^{III}C})/(\mathrm{Mn^{II}C}) - (3-m)\ 0.0591 \log (H_yP_2O_7^{-(4-y)}) - (mx+3y-my-3z)\ 0.0591 pa\mathrm{H} \quad (3)$$

In these equations $Mn^{III}C$ and $Mn^{II}C$ indicate the two complex ions, a denotes molar activity, and f_1 the molar activity coefficient of $Mn^{III}C$, f_2 that of $Mn^{II}C$ and f_3 that of $H_yP_2O_7^{-(4-y)}$ and parentheses indicate molar concentration. E_0^c indicates the standard potential for the reaction.

If only the concentration ratio of the two manganese complexes is varied, the potential change ΔE at 25° at constant p_aH and ionic strength can be expressed as follows

$$\Delta E_{2-1} = 0.0591\ \Delta \log (\mathrm{Mn^{III}C})/(\mathrm{Mn^{II}C})_{2-1} \quad (4)$$

By means of this equation it is possible to establish that the complexes are mononuclear and that a one-electron change occurs.

The effect on the potential resulting from variations of only the total pyrophosphate concentration can be expressed as

$$\Delta E_{2-1} = (m-3)\ 0.0591\ \Delta \log (H_yP_2O_7^{-(4-y)})_{2-1} \quad (5)$$

By simple calculations involving the ionization constants of pyrophosphoric acid it can be shown that, at constant ionic strength and paH, the concentrations of all species of pyrophosphates are proportional to the total pyrophosphate concentration. Accordingly, equation (5) can be converted to the following form

$$\Delta E_{2-1} = (m-3) \times 0.0591\ \Delta \log (C_s)_{2-1} \quad (6)$$

C_s denoting the total pyrophosphate concentration. From this equation, it is possible to determine m, the number of pyrophosphate ions associated with each manganese(II) ion by determining the change in potential, E, as a function of the total pyrophosphate concentration.

The effect of varying the paH is given by the equation

$$\Delta E_{2-1} = (3z+my-3y-mx)\ 0.0591 \Delta pa\mathrm{H}_{2-1} \quad (7)$$

Certain complications enter in the evaluation of x, y and z. Obviously pyrophosphate ions and both complex ions in various degrees of association with hydrogen ion enter the reaction or are in equilibrium with reacting forms. The observed coefficient of paH (eq. 7) will be a weighted average for the several reactions which may occur. An equation for a predominant reaction in a given paH range might be written. In this case, the concentration of the uncomplexed pyrophosphate ion could be evaluated since the ionization constants of pyrophosphoric acid are known. However values of the hydrogen ionization constants of the two complex acids are unknown. Accordingly, the actual concentrations of complex ions of any given degree of dissociation for which the electrode reaction might be written cannot be solved even though the total concentrations of manganese (III) and manganese(II) are known. Recourse to a sufficiently high paH to be certain that one complex contains no associated hydrogen ions is denied because in alkaline solutions the complex manganese(III) ion disproportionates to produce manganese dioxide. Likewise, the complexes are too strongly acidic to assume quantitative association during a variation in paH in fairly strong acidic solutions. The latter behavior is to be anticipated because positive nuclear ions enhance the acidity of acids in the complex. Pyrophosphoric acid complexed with either manganese(II) or manganese(III) is a stronger acid than the simple pyrophosphoric acid, and the manganese (III) should be more acidic than the manganese (II) complex.

The value of z in fairly strong acid solutions has been shown[1] to be close to 2 corresponding to 6 hydrogen ions in the manganese (III) complex. However, the evidence did not preclude the possible association of one or possibly two additional hydrogen ions or the dissociation of several more hydrogen ions depending on the exact pH with a corresponding effect on the potential. It follows that only differences in the acidities of the two complexes can be found on the basis of equation (7).

Experimental

Apparatus.—The potential measurements were made in a 100-ml. tall form lipless beaker with a bright platinum indicator electrode and a saturated calomel reference electrode. The beaker was equipped with a no. 11 rubber stopper with holes to receive electrodes, buret, a stirrer, and a tube for admitting purified nitrogen. Unless otherwise indicated, oxygen-free nitrogen was bubbled through the solution for fifteen minutes to remove oxygen. A temperature of 25 ± 0.1° was maintained by means of a thermostatically controlled water-bath. In a few titration experiments the temperature of the bath was changed to 26°, which was room temperature.

A Leeds and Northrup Student's potentiometer was used on conjunction with a Leeds and Northrup portable enclosed lamp and scale galvanometer. The paH measurements were made by means of a Beckman glass electrode pH meter.

Reagents.—Analytical reagents were employed. A stock solution of 0.1 M manganese(II) sulfate in 0.01 N sulfuric acid was used.[1] Standard 0.1 N iron(II) sulfate solution having a pH of about 1.6 was prepared by dissolving approximately 40 g. of Mohr salt in water, adding 2 ml. of sulfuric acid (1:1) and diluting to one liter. This solution, which was oxidized only slowly by air, was standardized daily just before being used. Standard 0.01 N iron(II) sulfate solution was prepared by dilution

of 0.1 *N* solution with sulfuric acid (1:100). Sodium and potassium pyrophosphate[1] were both used as a source of pyrophosphate. The *p*H of the pyrophosphate solutions was adjusted to the desired value with either sulfuric or nitric acid.

Procedure.—The manganese(III) complex was prepared from the manganese(II) complex, in 0.4 *M* pyrophosphate having a *p*H of about 2, by shaking with lead dioxide and then filtering according to the procedure described in a previous paper.[1] The solution was stirred mechanically during potential measurements.

Results and Discussion

Equations (4) through (7) were tested by means of various experiments designed to permit the observation of potential changes resulting from carefully controlled variations.

Effect of the Manganese(III) to Manganese (II) Ratio.—Experimentally, equation (4) was tested by measuring the potential of solutions prepared by mixing varying proportions of the air-free oxidized and unoxidized portions of a solution, 10 millimolar in manganese ion, 0.4 *M* in sodium pyrophosphate, and 2.40 in *pa*H. The potentials in Table I are plotted as a function of log $(Mn^{III}C)/(Mn^{II}C)$ in line c, Fig. 1. The points fall on a straight line which has a slope of 0.0598 v., in good agreement with the theoretical value of 0.0593 volt for a one-electron transfer at 26°.

TABLE I

RELATION BETWEEN POTENTIAL AND RATIO $(Mn^{III})/(Mn^{II})$

$\text{Log}_{10}\frac{(Mn^{III})}{(Mn^{II})}$	*E* (S. C. E.), volts
1.69897	0.8456
1.39794	.8288
1.09691	.8116
0.69897	.7877
.39794	.7697
.22185	.7592
.09691	.7523
.00000	.7463
− .22185	.7327
− .39794	.7220
− .69897	.7042
−1.09691	.6800
−1.39794	.6612
−1.97634	.6323

Another experiment was performed by observing the effect on the potential resulting from changes in total manganese concentration while the ratio of the oxidized to reduced form remained constant. A solution 5 millimolar in both the manganese(III) and the manganese(II) complexes, 0.4 *M* in sodium pyrophosphate and 2.40 in *p*H, was diluted ten times with a solution 10 millimolar in sodium sulfate instead of manganese sulfate, 0.4 *M* in sodium pyrophosphate and 2.40 in *p*H. Upon dilution the potential retained a constant value of 0.7463 v. (S.C.E.). From these experiments it follows that the electrode behaves in a reversible manner for a one-electron transfer with respect to the two manganese complex ions, and that both the oxidized and reduced forms of the complex ions must contain only one manganese atom. This conclusion has further support in the fact that potentiometric titrations discussed later show that the oxidation states differ by unity.

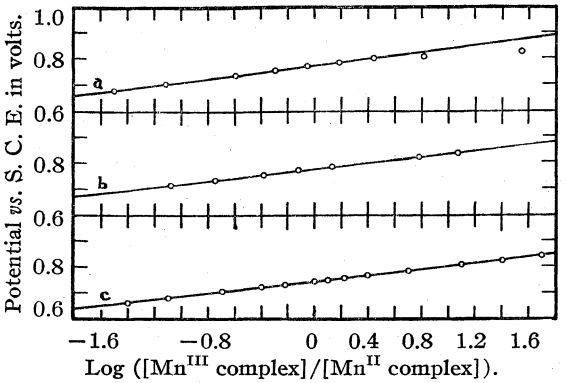


Fig. 1.—Line a, data obtained from the titration curve of 0.001 *M* manganese (III) complex with iron (II); line b, data from titration curve of 0.01 *M* manganese (III) complex; line c, data obtained from Table I.

Effect of the Pyrophosphate Concentration.—Equation (6) was tested experimentally by varying the total concentration of pyrophosphate from 0.4 to 0.04 *M* keeping the ionic strength and the *pa*H constant. In the following experiments the *pa*H was 2.06. The ionic strength of the system which was 0.4 *M* in sodium pyrophosphate was calculated to be 1.83. The solution containing 0.04 *M* pyrophosphate was made 1.83 *M* in potassium nitrate in order to have the same ionic strength as the 0.4 *M* pyrophosphate solution. The various solutions were 0.5 millimolar both in manganese(II) and manganese (III). The average value of the oxidation potential (*vs.* S.C.E.) of the solution 0.04 *M* in pyrophosphate was found to be 0.8278 ± 0.001 v. and of the solution 0.4 *M* in pyrophosphate 0.7670 ± 0.001 v. After correcting for the amount of pyrophosphate combined with manganese, the potential change was found to be 60.8 ± 2.0 mv. for a change in the pyrophosphate concentration from 0.3975 to 0.0375 *M*. Substituting these values in equation (6) yields 2.00 for the value of *m*.

In order to establish that *m* remained constant throughout the dilution, another experiment was performed in which the pyrophosphate concentration was varied continuously. To a solution 5 millimolar in both manganese(II) and manganese (III) and 0.4 *M* in sodium pyrophosphate, was added 1.83 *M* potassium nitrate solution. The *pa*H was kept constant at 1.58 by adding small amounts of nitric acid. The results are given in Table II. They show that in the concentration range of pyrophosphate used a value of $m = 2$ satisfies the experimental data.

From polarographic experiments[1] it was concluded that the manganese(III) complex contains three pyrophosphates. This relation of two to

TABLE II

THE INFLUENCE OF PYROPHOSPHATE CONCENTRATION ON THE POTENTIAL

Dilution V/V_0	Potential *vs.* S. C. E., mv.	$\frac{\Delta E}{\Delta \log Cs}$, mv.
1.0	824.7	
1.5	834.7	56.8
2.0	839.6	49.5
3.0	850.3	53.7
7.5	874.6	57.2
10.0	884.3	59.6

three in the number of chelate complexing ions has been observed repeatedly in complexes of di- and trivalent elements of the first transition series. An analogous behavior of the iron(III) oxalate–iron(II) oxalate couple was observed by Schaper[5] and verified by Lingane.[6]

Effect of Hydrogen Ion Concentration.—Since the value of m has been found to be two, equation (7) becomes

$$\Delta E_{z-1} = (3z - 2x - y)\, 0.0591\, \Delta paH_{z-1} = -w\, 0.0591\, \Delta paH_{z-1} \quad (8)$$

Experimentally, this equation was tested by measuring the potential as the *pa*H was varied by adding concentrated nitric acid or ammonium hydroxide dropwise to a solution 5 millimolar in both manganese(II) and manganese(III) complexes and 0.4 M in sodium pyrophosphate. The effect of changing the *pa*H in this solution is shown in Table III and Fig. 2. The value of w corresponds to the number of hydrogen ions involved in the reaction if the activity coefficient of the hydrogen ions remains constant with variations in the acidity. Each value given for w is the average obtained with reference to the preceding and succeeding data. In solutions having a *pa*H smaller than 3, the solution was rich violet in color. As the *pa*H approached 7, the color of the complex became increasingly amber. When the *pa*H exceeded 7 appreciably, a precipitate formed due to disproportionation of the amber-colored complex

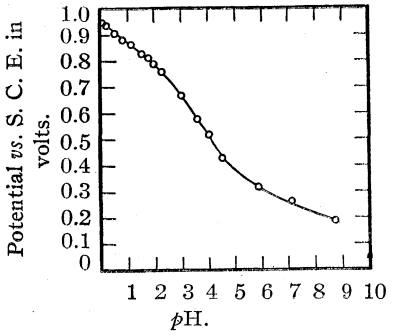


Fig. 2.—Change of potential with *pa*H in mixture 0.005 M in both manganese(II) and manganese(III) complexes and 0.4 M in sodium pyrophosphate.

(5) C. Schaper, *Z. physik. Chem.*, **72**, 315 (1910).

(6) J. J. Lingane and H. Kerlinger, *Ind. Eng. Chem., Anal. Ed.*, **13**, 77 (1941).

TABLE III

EFFECT OF p_aH ON THE POTENTIAL

*pa*H	Potential vs. S. C. E., mv.	w	Color
0.05	946.2	..	Rich violet
.19	934.5	1.51	Rich violet
.52	903.5	1.51	Rich violet
.80	879.6	1.21	Rich violet
1.12	861.1	1.23	Rich violet
1.52	826.0	1.31	Rich violet
1.76	812.4	1.54	Rich violet
1.97	788.7	1.80	Rich violet
2.27	758.4	1.90	Rich violet
2.99	668.0	2.33	Rich violet
3.59	578.0	2.44	Violet (less intense)
4.02	518.5	2.64	Violet (trace of amber)
4.54	428.2	2.61	Amber violet
5.85	318.4	1.03	Brown amber
7.11	262.3	0.77	Brown turbid
8.72	187.0	..	More turbid

to form manganese dioxide and manganese (II) ion.

At a *pa*H approaching zero w became approximately 1.5. In the lower limit of this *pa*H range, y can be assigned approximately the value 4 since the pyrophosphoric acid is largely associated. Assigning the value of 2 to z on the basis of polarographic data[1] leads to a calculated value of approximately 2 for x, indicating that both the manganese(II) and the manganese(III) complexes are definitely more acidic than pyrophosphoric acid. The following equation may accordingly be written for the predominant equilibrium in strongly acidic solutions.

$$Mn(H_2P_2O_7)_2^{-2} + H_4P_2O_7 \rightleftharpoons Mn(H_2P_2O_7)_3^{-3}\ (\text{violet}) + 2H^+ + e \quad (9)$$

In the *pa*H range of 0 to 3, there is a large variation in the extent of association of hydrogen ions with pyrophosphoric acid. This factor alone accounts for the major portion of the change of w. Accordingly if there is any decrease in the value of z in this range, there is also a compensating decrease in the value of x.

In the *pa*H range of 3 to 6, pyrophosphoric acid is largely present as $H_2P_2O_7^{-2}$. Furthermore, the degree of association of pyrophosphoric acid does not change rapidly in this range and does not contribute appreciably to the value of w. In the lower half of this range the observed value of w is about 2.5. This value should be zero if both complex ions contained dihydrogen pyrophosphate ions. It is evident that the manganese(III) complex must contain fewer hydrogen ions than the manganese(II) complex. Accordingly z is unity or zero. This decrease in the value of z is accompanied by a change in the color of the manganese (III) complex from violet to amber.

In the *pa*H range of 6.7 to 9.4, the ion $HP_2O_7^{-3}$ preponderates in pyrophosphate solutions. The more acidic complex ions undoubtedly contain

simple pyrophosphate ions. Assigning the value zero to x and z, yields a value of unity for w which is approximately the value observed. The main reaction in this *pa*H range is

$$Mn(P_2O_7)_2^{-6} + HP_2O_7^{-3} \rightleftharpoons Mn(P_2O_7)_3^{-9} + H^+ + e \quad (10)$$

Cartledge and Ericks[7] in a study of the oxalate complexes of manganese(III) observed a red complex, $Mn(C_2O_4)_3^{-3}$, which changed to a brown complex, $Mn(C_2O_4)_2(H_2O)_2^{-1}$, when the concentration of excess oxalate ion was decreased by dilution. The color change in the manganese(III) pyrophosphate complex cannot be due to an analogous displacement of pyrophosphate ions by water molecules because a one-hundred fold dilution of the violet complex with water at a *pa*H of 2 caused no change of color from violet to amber, but a change of the *pa*H to 2.4 caused a definite change in color. Furthermore a large excess of the complex-forming pyrophosphate ions is present in solutions containing the amber-colored complex.

On the basis of these considerations it appears that the manganese(III) complex is rich violet in color when an average of two hydrogen ions are associated with complexed pyrophosphate ion and it is amber in color when one or no hydrogen ion is associated with each pyrophosphate.

Potentiometric Titrations.—Titrations 1 and 2 in which 75 ml. of 1 millimolar manganese(III) complex was titrated with 10.06 millinormal iron (II)sulfate, with air present and with dissolved air removed, yielded curves (a) and (b) in Fig. 3. Titration 3 was performed with a ten-fold increase in the concentration of both the manganese(III) complex and the iron(II) sulfate in the presence of dissolved air. This titration curve was practically identical with curve b in Fig. 3.

In blank determinations performed in the same manner as the titrations, 0.07 ml. of 0.01006 N iron(II) sulfate was added before a potential change was observed. This blank correction due to a trace of oxidizing agent, probably very finely divided lead dioxide, was applied in all calculations. The calculated molarities of the manganic complex in the three titrations, assuming a one electron change, were 1.0013, 1.0010, and 9.972 millimolar corresponding to errors of +0.13, +0.10 and −0.28%, respectively. The large potential break and the accuracy which is better than 0.3% in the presence or absence of dissolved air, indicate the excellence of the potentiometric titration from a practical viewpoint.

Effect of Oxygen.—Although dissolved oxygen had no noticeable effect on the results of the titration, some of the potentials, especially in the more dilute solutions, were influenced by its presence. Before the end-point the corresponding potentials in all three titrations were in good agreement. However, beyond the end-point, the presence of dissolved oxygen influenced the potential in the solutions which were only one millimolar in manganese complex because of air oxidation of the ferrous iron.

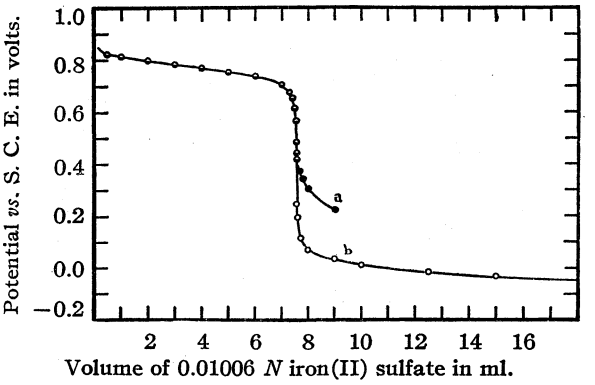


Fig. 3.—Potentiometric titration curve of 0.001 M manganese (III) complex with iron (II); a, dissolved air not removed; b, dissolved air removed.

Since the changes in *pa*H and volume during the titrations were small, the potential change before the end-point was due largely to changes in the ratio of the concentrations of the two complex manganese ions. This permitted a convenient confirmatory test of equation (4). Upon plotting the potential *versus* log $(Mn^{III}C)/(Mn^{II}C)$ for titrations 2 and 3, the lines a and b in Fig. 1 were obtained. Straight lines with slopes of 0.059 v. were found in both cases. Considering the small effect due to dilution and a small *p*H change the average value of the potential of 0.776 v. at the midpoint in the titrations agreed satisfactorily with the formal potential of 0.767 v. of the couple at various concentrations in a solution 0.4 M in sodium pyrophosphate having the same *pa*H, namely, 2.06.

Similar calculations involving the iron(III) and iron(II) pyrophosphate complexes which determine the potential beyond the end-point yielded a slope of 0.059 v. and a potential of 0.033 v. (S.C.E.) for this couple in a solution containing equal concentration of the two complex ions at a *pa*H of 2.06. It follows that both of the manganese and both of the iron complexes are mononuclear and that both undergo one-electron changes.

The potential at the endpoint should be one-half the sum of the above potentials of the two couples at *pa*H of 2.06, namely, 0.405 v. (S.C.E.). The value of 0.410 v. (S.C.E.) calculated by the method of second derivatives from titration b (Fig. 3) is in satisfactory agreement with the theoretical.

The Standard Potential.—The potential of a solution equimolar in the manganese(III) and manganese(II) complexes, in a solution 0.4 M in sodium pyrophosphate and having a *pa*H of 2.06 is +0.767 ± 0.003 v. *versus* the saturated calomel electrode or +1.013 ± 0.003 v. *versus* the

(7) G. H. Cartledge and W. P. Ericks, THIS JOURNAL, **58**, 2065 (1936).

standard hydrogen electrode at 25°. Extrapolating to a *pa*H of zero and a pyrophosphate concentration of unity on the basis of experimental data previously presented yields a value of +1.15 v. as the "formal" oxidation potential for the reaction in equation (9) at 25°. Strictly speaking this potential is not the formal potential, since the hydrogen ion activity and not its concentration was extrapolated to zero. Nor is it the standard potential since the concentrations and not activities of the complex ions and pyrophosphoric acid are used. As the activity coefficients are not known, the standard potential cannot be solved but is probably close to 1.15 v.

Although the data will not permit an accurate evaluation of the instability constants, an approximation may be made of their ratios. On the basis of the standard potential of 1.51 v. for the aqueous manganese(III)/manganese(II) couple determined by Grube and Huberich,[8,9] the following relation between the instability constants K_{III} for tri-dihydrogen pyrophosphatomanganate(III) complex and K_{II} for di-dihydrogen pyrophosphatomanganate(II) is obtained

$$1.15 \text{ v.} = 1.51 + 0.0591 \log \frac{a_{Mn^{+3}}}{a_{Mn^{+2}}} =$$

$$1.51 \text{ v.} + 0.0591 \log \frac{K_{III} a_{Mn^{III}C} \, a_{H_4P_2O_7^{-3}}}{K_{II} a_{Mn^{II}C} \, a_{H_4P_2O_7^{-2}}} \text{ volts} \qquad (11)$$

Since the standard potential is calculated for all substances in the last term at unit activity the following relation is obtained

$$K_{III} = 10^{-6} K_{II} \ (ca.) \qquad (12)$$

(8) G. Grube and K. Huberich, *Z. Elektrochem.*, **29**, 17 (1923).

(9) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Inc., New York, N. Y., 1938, pp. 221.

Summary

The couple tripyrophosphatomanganic(III) acid/dipyrophosphatomanganic(II) acid was shown to behave reversibly at a platinum electrode. The influence of the total pyrophosphate concentration, ratio of manganese(III)/manganese(II) concentrations, and *pa*H were studied. At a *pa*H near zero, the equilibrium was shown to be essentially

$$Mn(H_2P_2O_7)_2^{-2} + H_4P_2O_7 \rightleftarrows Mn(H_2P_2O_7)_3^{-3} \text{ (violet)} + 2H^+ + e \qquad (9)$$

The potential of a platinum electrode in a solution containing equal concentrations of manganese (II) and manganese(III) in a solution 0.4 *M* in pyrophosphate having a *pa*H of 2.06 is +1.013 ± 0.003 v. *versus* the standard hydrogen electrode. The standard potential for the reaction indicated in equation (9) is E_0 = (*ca.*) −1.15 v. (Lewis and Randall convention).

As the *pa*H approaches 7, the manganese(III) complex becomes increasingly brown amber in color, due to the ionization of additional hydrogen ions from the complex. In an alkaline solution, the manganese(III) complex is unstable disproportionating to form manganese dioxide and manganese(II) ion.

A new method for determining manganese by means of a potentiometric titration of tripyrophosphatomanganic acid with iron(II) sulfate is described.

MINNEAPOLIS, MINNESOTA RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION FROM THE PHILADELPHIA QUARTZ CO.]

The Effect of Sodium Silicates on the Absorption Spectra of Some Dyes

BY R. C. MERRILL, R. W. SPENCER AND R. GETTY

That certain dyes change color in the presence of various colloids has long been known. Familiar examples are the variation in color of a biological stain depending on the nature of the stainable substrate, which P. Ehrlich called metachromasy, and the protein error of indicators. Micellar solutions of colloidal electrolytes, such as cetyl pyridinium chloride[1] and long chain sulfonates and sulfates[2,3] change the color of pinacyanol chloride and other dyes.[4,5] This paper reports the effects of another group of colloidal electrolytes, the sodium silicates, on the absorption spectra of the dyes, pinacyanol chloride, toluidine blue O, Rhodamine 6G, and the sodium salt of 2,6-dichlorobenzenone indophenol.

(1) S. E. Sheppard and A. L. Geddes, *J. Chem. Phys.*, **13**, 63 (1945).

(2) M. L. Corrin, H. B. Klevens and W. D. Harkins, *ibid.*, **14**, 480 (1946).

(3) M. L. Corrin and W. D. Harkins, THIS JOURNAL, **69**, 679 (1947).

(4) G. S. Hartly, *Trans. Faraday Soc.*, **30**, 444 (1934).

(5) J. E. Smith and H. L. Jones, *J. Phys. Chem.*, **38**, 243 (1934).

Experimental

All of the sodium silicates used were commercial products of the Philadelphia Quartz Co. Their composition is summarized in Table I. The sodium metasilicate pentahydrate was in the form of pure white free flowing crystals which have a melting point of 72.2°. The "E" and "Star" silicates are clear, transparent, aqueous solutions and the "S" is an opalescent solution. The sodium oxide content is determined by titration with standardized hydrochloric acid to the methyl orange end-point. Silica

TABLE I

COMPOSITION OF SODIUM SILICATES

Name	Formula	M. W.	Na_2O, %	SiO_2, %
Metso crystals	$Na_2SiO_3 \cdot 5H_2O$	122	29.1	28.2
Star	$Na_2O \cdot 2.6SiO_2$	217	10.5	26.3
E	$Na_2O \cdot 3.3SiO_2$	262	8.6	27.7
S	$Na_2O \cdot 4.0SiO_2$	305	6.3	24.6

TABLE II

THE INTENSITIES OF BAND MAXIMA IN 2×10^{-5} MOLAR SOLUTIONS OF PINACYANOL CHLORIDE

Solvent	pH	α Band $\lambda(m\mu)$	α Band $\epsilon m \times 10^4$	α' Band $\lambda(m\mu)$	α' Band $\epsilon m \times 10^4$	β Band $\lambda(m\mu)$	β Band $\epsilon m \times 10^4$	γ Band $\lambda(m\mu)$	γ Band $\epsilon m \times 10^4$
H_2O	5.92	599	5.94	...	..	546	7.33	...	..
0.020 M NaOH	12.24	599	5.65	630	1.84	546	5.03	490	2.08
.020 M Na_2SiO_3	12.23	599	3.90	630	2.36	556	2.73	486	2.34
.020 M $Na_2O \cdot 2.6SiO_2$	11.02	593	3.49	630	2.24	...	..	492	3.65
.020 M $Na_2O \cdot 4.0SiO_2$	10.83	584	2.62	630	1.25	...	..	502	3.64
2×10^{-5} M $Na_2O \cdot 3.3SiO_2$	6.78	599	5.87	...	..	546	6.88	...	..
2×10^{-4} M $Na_2O \cdot 3.3SiO_2$	9.17	599	3.07	...	..	~550	2.72	490	1.20
2×10^{-3} M $Na_2O \cdot 3.3SiO_2$	10.20	584	2.48	630	1.37	...	..	488	2.41
6×10^{-3} M $Na_2O \cdot 3.3SiO_2$	10.40	582	3.45	630	1.69	...	..	492	3.46
2×10^{-2} M $Na_2O \cdot 3.3SiO_2$	10.85	587	3.47	630	1.98	...	..	493	3.92

is determined gravimetrically. The sodium hydroxide was J. T. Baker analyzed C.P. grade.

The dyes were all commercial products and used without further purification. The pinacyanol chloride and sodium salt of 2,6-dichlorobenzenoneindophenol were purchased from the Eastman Kodak Co. Rhodamine 6G (C.I. No. 752) was obtained from the National Aniline division of the Allied Chemical and Dye Corp. The toludine blue O was the certified dye stain sold by the Coleman and Bell Co. which contained 66% dye. The molar concentrations of the solutions are given on the basis of actual dye content, assuming that the first three dyes were pure. The pH of the dye solution was determined with a Beckman pH meter.

The absorption curves were obtained with a General Electric Co. recording spectrophotometer. From the transmission curves thus obtained the molar extinction coefficients, ϵ_m, were calculated at 10 mμ intervals and at maxima and minima from the equation $\log_{10} I_0/I = \epsilon_m Cd$ where C is the molar concentration of the dye, d the width of the cell (0.50 cm.), and I_0 and I the intensity of the incident and transmitted light. All the absorption curves were obtained at room temperature (around 22–23°).

Results

The absorption spectra of 2×10^{-5} M pinacyanol chloride in water and in 0.02 M solutions of sodium hydroxide, sodium metasilicate and silicates with silica to alkali (Na_2O) ratios of 2.6 and 4.0 are shown in Fig. 1. The effect of four concentrations, including 0.02 M, of the 3.3 ratio silicate on the absorption spectra of 2×10^{-5} M dye is illustrated in Fig. 2. Table II gives the intensities of the band maxima for these solutions. All solutions were diluted fivefold immediately prior to being placed in the spectrophotometer after

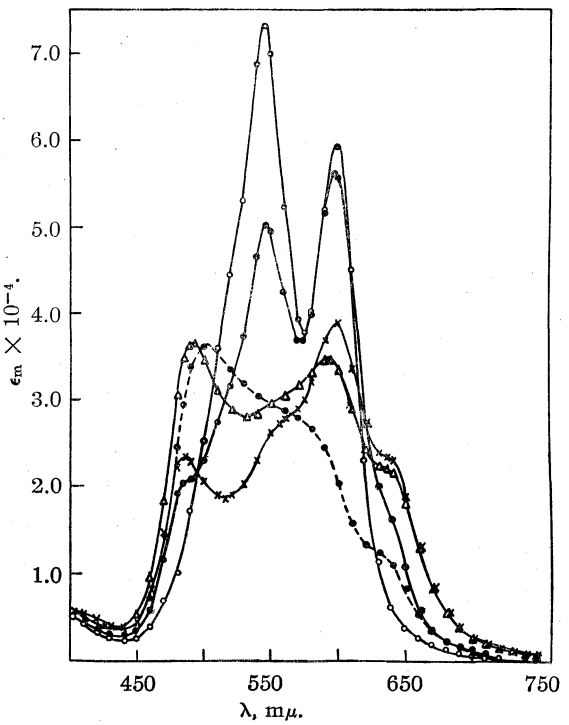


Fig. 1.—Molar extinction coefficients of 2×10^{-5} M pinacyanol chloride: O—O in H_2O, ●—● in 0.02 M NaOH; ×—× in 0.02 M Na_2SiO_3, △—△ in 0.02 M $Na_2O \cdot 2.6\ SiO_2$, ●···● in 0.02 M $Na_2O \cdot 4.0\ SiO_2$.

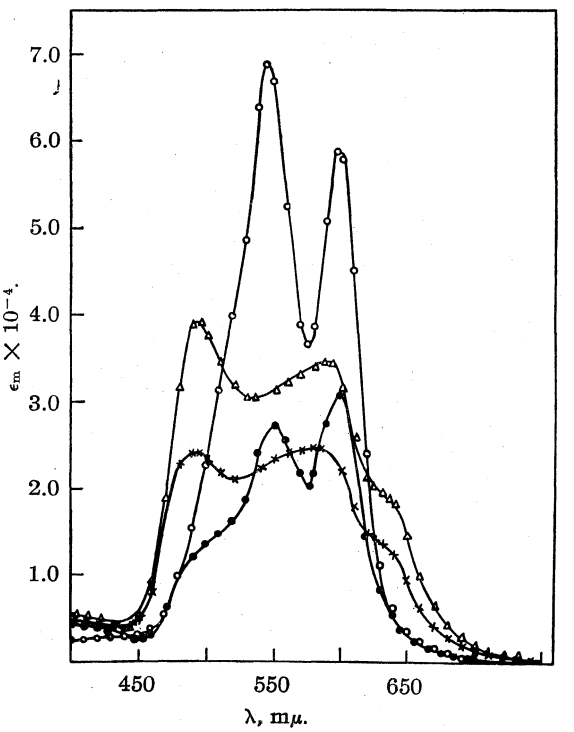


Fig. 2.—Molar extinction coefficients of 2×10^{-5} M pinacyanol chloride in varying concentrations of $Na_2O \cdot 3.3$ SiO_2: O—O 2×10^{-5} M, ●—● 2×10^{-4} M, ×—× 2×10^{-3} M, △—△ 2×10^{-2} M.

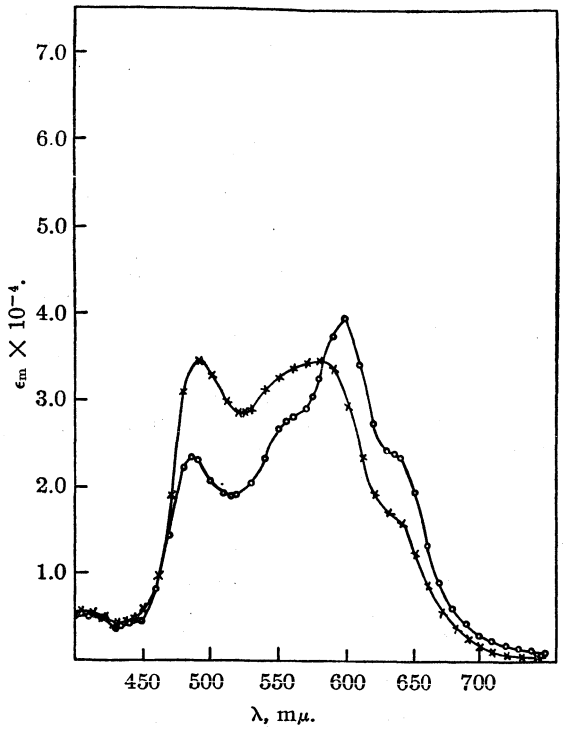


Fig. 3.—Molar extinction coefficients of 2×10^{-5} M pinacyanol chloride in Na_2SiO_3 and $Na_2O \cdot 3.3\ SiO_2$ solutions containing the same amount of SiO_2: O—O 0.02 M Na_2SiO_3, ×—× 0.006 M $Na_2O \cdot 3.3\ SiO_2$.

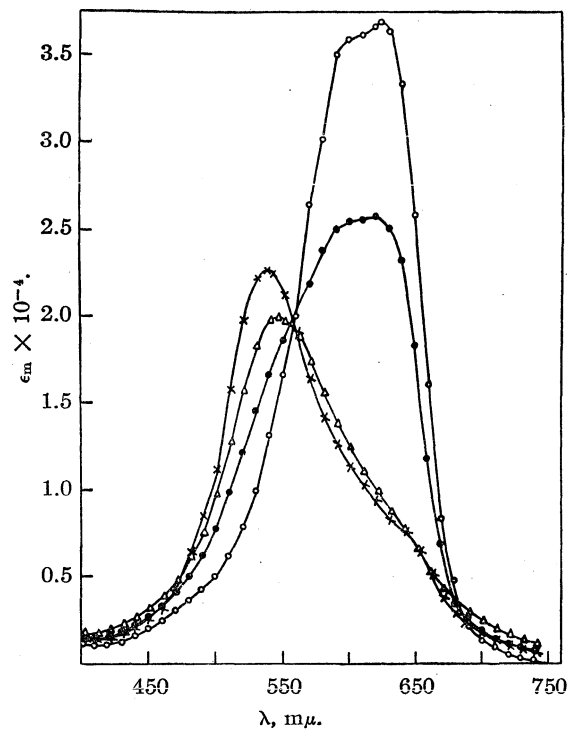


Fig. 4.—Molar extinction coefficients of 2.5×10^{-5} M toluidine blue O in water and varying concentrations of $Na_2O \cdot 3.3SiO_2$: O—O in H_2O, ●—● in 5×10^{-4} M $Na_2O \cdot 3.3SiO_2$, △—△ in 5×10^{-3} M $Na_2O \cdot 3.3SiO_2$, ×—× in 5×10^{-2} M $Na_2O \cdot 3.3SiO_2$.

having stood about fifteen hours at the higher concentration. Our absorption curve for pinacyanol chloride in water is in excellent agreement with that expected by interpolation from the curves given by Sheppard[6] for different concentrations of dye.

The effect on the dye's absorption spectrum of increasing the silica to alkali ratio of the 0.02 M silicates is to decrease greatly the intensity of the α band at about 595 mμ, and even more that of the β band at 546 mμ. New bands, α' at 630 mμ and γ at about 490 mμ, appear in the metasilicate solution. The intensity of the γ band is about 50% greater in solutions of the higher ratio silicates whereas that of the α' band becomes progressively less with increasing silica to alkali ratio. The effect of increasing the concentration of the 3.3 ratio silicate parallels that of increasing the silica to alkali ratio at a given concentration in that the intensity of the α band is greatly decreased and that of the β band even more. Their effects differ in that the intensities of both the α' band, which becomes apparent in a 2×10^{-3} M silicate solution, and the γ band, first being evident in a 2×10^{-4} M silicate, increase progressively with increase in concentration. Both the α and β bands appear to have a minimum intensity at a silicate concentration about 2×10^{-3} M. The visual color of the dye solutions changes from blue to purple as the silica to alkali ratio or the silicate concentration is increased.

The differences in the absorption spectra of 2×10^{-5} M pinacyanol chloride in 0.020 M sodium metasilicate and 0.006 M 3.3 ratio silicate (Fig. 3) both of which contain the same amount of silica, show clearly that the silica is in a different form in the two solutions.

The differences in the absorption spectra of 2.5×10^{-5} M toluidine blue 0 in 0.01 M sodium metasilicate and varying concentrations of the 3.3 ratio silicate as compared with that in water (Figs. 4 and 5) are similar to those observed in solutions of the polymeric sodium "hexametaphosphate"[7] and agar.[8] Results with this dye suggest that the addition of small amounts of colloidal electrolytes greatly decreases the intensity of the two only partially resolved bands, α at 624 mμ and β (which at this concentration in water occurs at 600 mμ), and gradually decreases the wave length at which the β band maxima occurs. At higher concentrations the intensity of the band at around 540 mμ increases, and in "hexametaphosphate" solutions[7] goes through a maximum. The effects of the silicates on the intensities of the band maxima of 2.5×10^{-5} M toluidine blue 0 solutions are summarized in Table III. The dye

(6) S. E. Sheppard, *Rev. Mod. Physics*, **14**, 303 (1942).

(7) J. M. Wiame, THIS JOURNAL, **69**, 3146 (1947).

(8) L. Michaelis and S. Granick, *ibid.*, **67**, 1212 (1945).

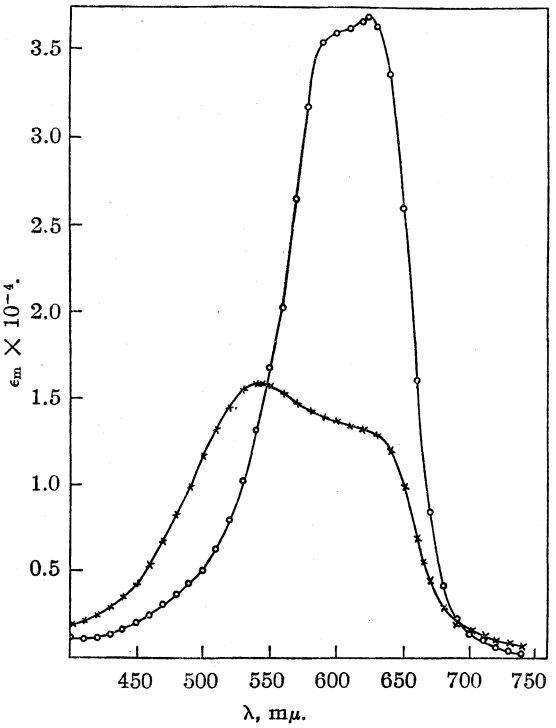


Fig. 5.—Molar extinction coefficients of 2.5×10^{-5} *M* toluidine blue O: O—O in H_2O, ×—× in 0.01 *M* Na_2SiO_3.

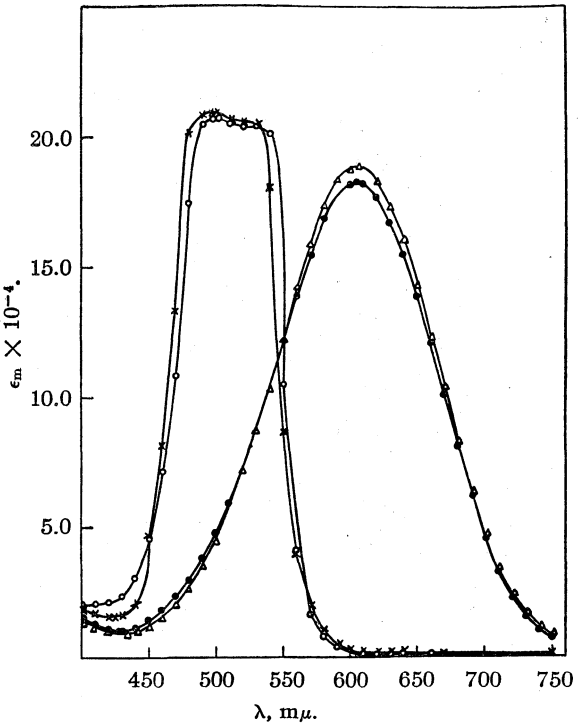


Fig. 6.—Molar extinction coefficients of 1×10^{-4} Rhodamine 6G and 1×10^{-4} *M* sodium 2,6-dichlorobenzenone indophenol: Rhodamine 6G O—O in H_2O, ×—× in 0.01 *M* $Na_2O{\cdot}3.3SiO_2$; sodium 2,6-dichlorobenzenone indophenol ●—● in H_2O, △—△ in 0.01 *M* $Na_2O{\cdot}3.3SiO_2$.

appears blue in water and in the 5.0×10^{-4} *M* 3.3 ratio silicate solution, but is purple at all other silicate concentrations studied.

TABLE III

THE INTENSITIES OF BAND MAXIMA IN 2.5×10^{-5} MOLAR SOLUTIONS OF TOLUIDINE BLUE O

Solvent	*p*H	α Band λ (mμ)	α Band $\epsilon_m \times 10^4$	β Band λ (mμ)	β Band $\epsilon_m \times 10^4$
H_2O	6.53	624	3.69	600	3.59
5.0×10^{-4} *M* $Na_2O{\cdot}3.3SiO_2$	9.49	622	2.57	600	2.54
1.0×10^{-3} *M* $Na_2O{\cdot}3.3SiO_2$	9.91	...	..	546[a]	1.98
5.0×10^{-3} *M* $Na_2O{\cdot}3.3SiO_2$	10.11	...	..	546[a]	2.00
5.0×10^{-2} *M* $Na_2O{\cdot}3.3SiO_2$[b]	11.12	...	..	538[a]	2.27
1.0×10^{-1} *M* Na_2SiO_3	11.96	624	1.31	5.44	1.58

[a] May be new band. [b] There is an indication of a new band at around 640 mμ at this silicate concentration.

Figure 6 shows the absorption spectra of 1×10^{-4} *M* Rhodamine 6G and 1×10^{-4} *M* sodium 2,6-dichlorobenzenone indophenol in water and in 0.010 *M* solutions of $Na_2O{\cdot}3.3SiO_2$. The addition of this concentration of silicate appears to shift by about 6 mμ toward shorter wave lengths, the band (or unresolved bands) of Rhodamine 6G occurring from about 460 to 540 mμ. The water spectrum is probably somewhat complicated by the dye's fluorescence. Rhodamine 6G is orange and fluorescent in water and red and non-fluorescent in micellar solutions of anionic detergents and in solutions of various silicates including the metasilicate.

A 1×10^{-4} *M* solution of sodium 2,6-dichlorobenzenone indophenol has a single band maximum in the visible occurring at 605 mμ with a molar extinction coefficient of 18.2×10^4. The addition of 0.010 *M* $Na_2O{\cdot}3.3SiO_2$ to this dye produces practically no change in the color of the solution but *increases* the intensity maximum 3%. Unlike other dyes used in this investigation, the dye ion in this case has the same charge as the silicate ions and micelles.

Discussion

The reduction in intensity of the α and β bands of solutions of pinacyanol chloride and toluidine blue O of as much as 50% by silicate solutions as dilute as 2×10^{-4} *M* is much larger than that observed for ordinary electrolytes. For example, the height of the main band of methylene blue in water is decreased only 5% when the solution is made 1*M* in potassium chloride and somewhat less with 1*M* potassium nitrate.[9] Lewis, *et al.*,[9] suggest that salts increase the formation in aqueous solution of a colorless form of the dye produced by simultaneous, reversible addition of hydrogen and hydroxyl ions. It appears that this suggestion does not explain the large reductions due to colloidal electrolytes, especially since, as Lewis states, one must also assume polymerization of the colorless substance in order to explain effects

(9) G. N. Lewis, O. Goldschmid, T. T. Magel and J. Bigeleisen, THIS JOURNAL, **65** 1150 (1943).

as large as 5%. A more likely explanation (*cf.* ref. 10) is that the dye and colloidal electrolyte interact in such a manner as to restrict free rotation of some part of the molecule involved in the electronic transitions giving rise to the bands. This decreases the number of fully extended planar ions suitably oriented per unit time to the electric vector of the light rays.

Probably sorption of colloidal particles is involved but the interaction is at least partially electrostatic for effects plainly visible to the eye occur only when the charges on the dye ion and colloidal particles are opposite in sign. Precipitation or flocculation occurs rapidly at dye and silicate concentrations greater than those reported in Tables II and III; the higher concentrations in these tables precipitated after standing a day or two.

The addition of silicates alters the relative intensities of the α and β band maxima of pinacyanol chloride. Thus, the ratio of the maximum molar extinction coefficients of the α to β band is 0.81 in water, 0.85 in 2×10^{-5} M $Na_2O \cdot 3.3SiO_2$ and 1.13 in 2×10^{-4} M $Na_2O \cdot 3.3SiO_2$. Some investigators regard the α band as characteristic of the monomer dye ion, the β band as peculiar to a dimer, and the γ band peculiar to high polymers.[11,12,13,14] Since these bands are generally apparent in organic solvents where there is no evidence of dimerization or polymerization it appears more likely that the β and γ bands are not new bands peculiar to dimers or polymers, but are vibrationally coupled transitions proper to the monomeric ions which are, however, enhanced in the dimer or polymer.[10] Because electrolytes generally increase the extent of formation of associated ions in aqueous systems, it would be expected that, if the first hypothesis is true, the ratio of the intensities of the α to β bands would decrease on the addition of electrolytes. That the opposite effect occurs on the addition of both sodium hydroxide and silicates is evidence that the bands are not peculiar to dimers or polymers. That the relative intensity of the α and β bands of thionine is not affected by the addition of a chloride[14] is a further indication.

(10) S. E. Sheppard and A. L. Geddes, THIS JOURNAL, **66**, 2003 (1944).

(11) G. Scheibe, *Kolloid Z.*, **82**, 1 (1938).

(12) W. L. Lewschin, *Acta Physicochim. U. R. S. S.*, **1**, 685 (1934).

(13) H. O. Dickinson, *Trans. Faraday Soc.*, **43**, 486 (1947).

(14) E. Rabinowitch and L. F. Epstein, THIS JOURNAL, **63**, 69 (1941).

Silicates also produce a shift in the wave length at which the band maxima appear and causes new bands to become evident thus producing a visual change in the colors of the solutions. The color change of toluidine blue in agar solutions is attributed to the adsorption of molecular aggregates of dye larger than the dimer by agar.[8] In "hexametaphosphate" solutions the color change has been attributed to a linear complex polymer produced by each dye ion reacting with a phosphate group.[7] The color change of dyes in soap solutions is attributed to preferential solubilization of one form of dye from the equilibrium mixture by the soap micelle.[3] Since silicates do not solubilize water-insoluble dyes and still produce comparable color changes, it is evident that the intimate type of interaction producing solubilization is not necessary to give a change in color. A reasonable explanation is that these color changes are also due to sorption at the surface of the colloidal silica particle and/or chemical combination of the dye cation with the negative ionic groups of the colloid. The change in the wave length at maximum intensity of the various bands with concentration indicates that the complexes responsible for their appearance vary in composition.

Summary

The addition of various sodium silicates to a pinacyanol chloride solution changes the absorption spectra by decreasing the intensity of the α and β bands to different extents, and by forming new α' and γ bands. The visual color change is from blue to purple. Their addition to a solution of toluidine blue 0 reduces the intensity of the absorption band and shifts the band maxima from 620 mμ to about 540 mμ, causing a visual change from blue to purple. Silicates shifted the band maxima of Rhodamine 6G about 6 mμ toward the violet but did not alter the intensity by more than 2%. This dye was orange and fluorescent in water and red and non-fluorescent in silicate solutions. Silicates had little effect on the absorption spectra of the sodium 2,6-dichlorobenzenone indophenol. The silicates used had the molecular formulas Na_2SiO_3, $Na_2O \cdot 2.6SiO_2$, $Na_2O \cdot 3.3SiO_2$ and $Na_2O \cdot 4.0SiO_2$. Their effects are attributed to sorption and electrostatic interaction of the dye ion with the silicate ions and micelles.

RECEIVED FEBRUARY 11, 1948

[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES]

Studies of the Fischer–Tropsch Synthesis. IV. Properties of Reduced Cobalt Catalysts[1]

BY ROBERT B. ANDERSON,[2] W. KEITH HALL,[2] AND L. J. E. HOFER[2]

A number of catalysts of easily reducible metals are prepared by precipitation of their oxides or carbonates, followed by reduction in hydrogen to the metal. Since most precipitated oxides or carbonates sinter excessively on reduction, with decreases in both surface area and bulk volume, promoters and carriers are added to minimize these effects. This paper describes such changes for cobalt–thoria–kieselguhr and cobalt–thoria–magnesia–kieselguhr Fischer–Tropsch catalysts and similar preparations with one or more of the components omitted. Also included are carbon monoxide chemisorption and X-ray diffraction studies.

Properties of these catalysts in the unreduced state[3] and of the kieselguhrs used as carriers,[4] and the characteristics of these catalysts in the synthesis[5,6] have been reported previously. It was shown that the surface areas of the cobalt–basic carbonate-promoter complex[7] were only slightly increased by additions of promoters and, or, carriers. However the kieselguhr increased the bulk volume of the catalyst; the bulk volume of granular catalysts containing kieselguhr varied directly with the bulk volume of the kieselguhr. It was also shown that the cobalt basic carbonate was deposited chiefly in the pores of the kieselguhr that were larger than 5 microns in diameter.

Hofer and Peebles[8,9] have reported X-ray diffraction studies of some of this series of catalysts after reduction, carburization and use in the synthesis. McCartney and Anderson[10] have reported electron micrograph and adsorption studies of changes of a pure cobalt oxide powder upon reduction. In a subsequent section of this paper, the results are compared with those of Emmett and Brunauer[11] on reduced iron synthetic ammonia catalysts. Surface–area studies of iron Fischer–Tropsch catalysts, now in progress, will be reported in a later paper.

Experimental

The catalysts studied were cobalt–thoria–kieselguhr (100:18:100) catalyst designated by 108B, a series of cobalt–thoria–magnesia–kieselguhr (100:6:12:200) designated as 89 and preparations similar to the 89-series with one or more components omitted. The methods of preparing these catalysts have been reported in previous papers.[3,5,12] Hofer and Peebles[8] have described the preparation of the cobalt oxide powder used in this work. For reduction, adsorption and density studies, the catalysts were placed in an adsorption vessel with a special four-way stopcock which permitted hydrogen to be flowed over the catalyst during reduction.[13] To facilitate filling and removal of catalysts without change in volume of the vessel, the charge tube as shown previously was extended to the level of the stopcock and closed with a ground-glass joint. After filling of the adsorption vessel a close-fitting glass rod was inserted into the charge tube to minimize the dead space. Adsorption and reduction studies were made in a small vessel which held about one gram of catalyst, and density determinations were made in a larger vessel holding about ten grams. Helium and mercury densities were made on the same reduced sample. In all cases, the reduced catalysts were handled in a manner which precluded exposure to air.

The hydrogen for the reduction was passed over hot copper and through anhydrous magnesium perchlorate to remove traces of oxygen and water vapor. The adsorption vessel was heated in a horizontal position to avoid heating the stopcock and ground joint. The small resistance furnace used to heat the samples was controlled automatically to $\pm 3°$.

Before reduction the samples were evacuated at 100° for one hour to remove adsorbed vapors and to minimize the effect of differences in drying of the samples. The weights of samples after this treatment were used in computing surface areas, and except for the data in Table III the areas of reduced catalysts were expressed per gram of unreduced catalyst. The reduction procedure was to heat the catalyst rapidly to reduction temperature, 360 or 400°, in a slow stream of nitrogen. Since the cobalt was present as a basic carbonate, about 65% of the total weight loss on reduction occurred during this treatment. When the reduction temperature was reached, hydrogen at a space velocity[14] of 6000 was passed over the catalyst for two hours. Then the catalyst was evacuated at the reduction temperature to a vacuum of less than 10^{-3} mm. to remove chemisorbed hydrogen.

Adsorption isotherms were determined by conventional volumetric methods.[15] The gases used were of high purity, containing considerably less than 0.1% of oxygen. Before starting the carbon monoxide isotherms, the samples were

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Physical Chemists, Bureau of Mines, Central Experiment Station, Pittsburgh, Pa.

(3) Anderson, Hall, Hewlett and Seligman, THIS JOURNAL, **69**, 3114 (1947).

(4) Anderson, McCartney, Hall and Hofer, *Ind. Eng. Chem.*, **39**, 1618 (1947).

(5) Anderson, Krieg, Seligman and O'Neill, *ibid.*, **39**, 1548 (1947).

(6) Anderson, Krieg, Seligman and Tarn, *ibid.*, in press.

(7) The area of the cobalt-promoter complex was calculated with the following equations which assume the area of kieselguhr to be additive, $A_{complex} = A_{catalyst} - f_{KG}A_{KG}$, where $A_{complex}$, $A_{catalyst}$ and A_{KG} are the area of the complex and catalyst per gram of unreduced catalyst and the area of kieselguhr per gram respectively and f_{KG} is the weight fraction of kieselguhr in the unreduced catalyst. The area of complex per gram of complex in the unreduced catalyst was obtained by dividing $A_{complex}$ by $1 - f_{KG}$. It should be mentioned that the area of the kieselguhr did not change appreciably when subjected to the usual reduction procedures.

(8) Hofer and Peebles, THIS JOURNAL, **69**, 893 (1947).

(9) Hofer and Peebles, *ibid.*, **69**, 2497 (1947).

(10) McCartney and Anderson, *J. Appl. Phys.*, **18**, 902 (1947).

(11) This work is summarized in Brunauer and Emmett, THIS JOURNAL, **62**, 1733 (1940).

(12) Storch, *et al.*, Bureau of Mines Technical Paper 709; Synthetic Liquid Fuels Process. Hydrogenation of carbon monoxide. Part I, in press.

(13) Anderson, *Ind. Eng. Chem., Anal. Ed.*, **18**, 156 (1946).

(14) Volumes of hydrogen (S. T. P.) per volume of catalyst space per hour.

(15) Emmett, "Advances in Colloid Science," ed. by Kraemer, Vol. I, Interscience Publishers, New York, N. Y., 1942, pp. 1–36.

TABLE I

SURFACE AREAS OF UNREDUCED AND REDUCED COBALT FISCHER-TROPSCH CATALYSTS

Catalyst	Form[a]	Kiesel-guhr[b]	Method of reduction[c] Temp., °C.	Hours	% Wt. loss	Surface areas of catalysts, sq. m. Unreduced Total per gram	Unreduced Complex per gram of complex	Reduced Total[d] per gram	Reduced Complex[e] per gram of complex	Ratio of area of complex after to before reduction
Co:ThO_2:MgO:Kg = 100:6:12:200										
89H	P	H. S. C.	400	2	19.8	67.2	127.2	41.9	83.8	0.620
89J	P	F. C.	400	2	17.4	85.5	155.4	62.0	99.6	.640
89K	P	Port.	400	2	19.7	88.8	160.3	62.7	105.5	.651
89K	G	Port.	400	2	17.7	101.1	185.0	62.2	104.5	.580
89U	P	Germ.	400	2	19.3	86.2	157.5	37.8	59.6	.374
89V	P	D-911	400	2	20.4	77.6	126.0	50.2	70.1	.550
89BB	P	JM-II	400	2	18.9	66.2	121.5	46.2	84.6	.690
89FF	P	FCX	400	2	16.7	102.9	177.5	80.2	133.2	.751
Co:ThO_2:KG = 100:18:100										
108B	P	F. C.	360	2	24.4	71.6	96.2	32.4	50.0	.390
Co:ThO_2:MgO = 100:6:12	G	None	400	2	37.7	154.8	154.8	52.8	52.8	.341
Co:ThO_2 = 100:6	G	None	400	2	38.7	171.0	171.0	14.6	14.6	.085
Co:MgO[f] = 100:12	G	None	400	2	41.6	142.6	142.6	35.2	35.2	.247
Co:MgO[g] = 100:8	G	None	400	2	42.0	129.6	129.6	18.3	18.3	.141
Co:Kg = 100:200	G	F. C.	400	2	21.1	75.6	124.7	18.3	14.2	.109
Co:Kg = 100:200	G	H. S. C.	400	2	21.2	77.2	152.4	6.87	12.0	.078
Cobalt basic carbonate	G	None	400	2	44.2	126.2	126.2	2.5	2.5	.020
Cobalt oxide powder	[h]	None	250	24	30.2	67.0	67.0	3.2	3.2	.048

[a] G = granules, broken filter cake; P = pellets (1.6 mm. long by 3.2 mm. diameter). [b] H. S. C. = Johns Manville Hyflo Super-Cel, F. C. = Johns Manville Filter-Cel, Port. = Portuguese kieselguhr, D-911 = Dicalite 911, JM-II = Johns Manville II, FCX = acid extracted Filter-Cel. For a complete description of these samples see references 4 and 6. [c] All reductions except cobalt oxide powder were made with hydrogen at space velocities per hour of 6000. Cobalt oxide powder was reduced in hydrogen at a space velocity of 100. [d] Per gram of unreduced catalyst. [e] Per gram of complex in unreduced catalyst. [f] Contains powdered magnesia. [g] Contains precipitated magnesia. [h] A fine powder.

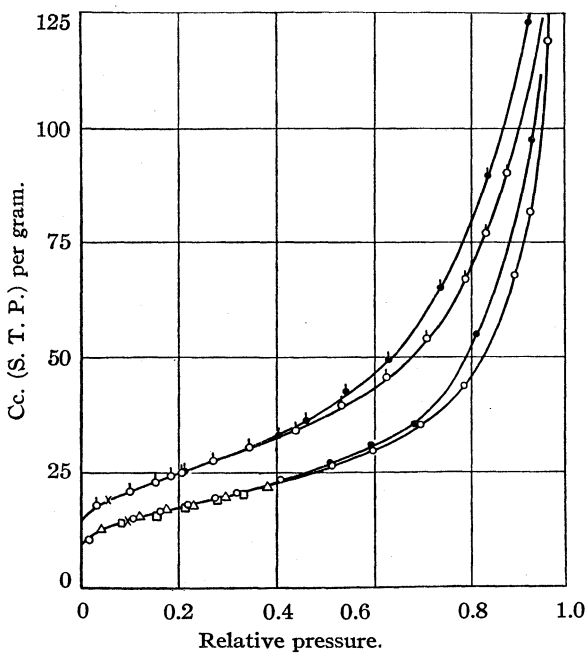


Fig. 1.—Adsorption of nitrogen at −195° on unreduced and reduced cobalt catalyst 89J, where Ó represents the unreduced catalyst and O, □ and △ represent different samples of reduced catalyst. Desorption points are solid, and the volume of gas corresponding to a monolayer is represented by X.

cooled in helium at −195° to ensure temperature equilibration. Surface areas were computed from the simple B. E. T. equation[16] with the cross-sectional area of the nitrogen molecule taken as 16.2 sq. Å. The methods of determining helium and mercury densities have been described previously.[3,4]

The samples used in X-ray diffraction analysis were reduced, using the same conditions as those above. They were opened under petroleum ether and stored for a few days under this liquid. The samples, wet with petroleum ether, were ground to a paste, mixed with collodion and partly extruded from a section of stainless steel tubing. This technique is described by Barrett.[17] The tubing was 19 gage 0.7 mm. inside diameter. The specimens were mounted in a Debye–Scherrer powder camera of 71.62 mm. inside diameter. FeK_α radiation from a sealed-off X-ray tube equipped with beryllium windows with manganese dioxide filters was used. The tube was operated at 30 kv. and 7 ma.

Experimental Results

Surface-area data for unreduced and reduced catalysts and similar preparations are given in Table I. Also included are areas for the cobalt–promoter complex[7] computed by assuming the area of the kieselguhr to be additive. Since part of the surface area of the kieselguhr may be covered or blocked by the cobalt–promoter complex, this area of complex must be considered as the lower limit of its actual value. Nitrogen isotherms at −195° of pelleted catalyst 89J before and after reduction are given in Fig. 1.

(16) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(17) Barrett, "Structure of Metals," McGraw-Hill Book Co., Inc., New York, N. Y., 1943, p. 118.

TABLE II

CHANGES IN SURFACE AREA DURING HEATING AND REDUCTION

(All data per gram of original unreduced catalyst or complex)

Catalyst	Original catalyst Area sq. m./g.	Original catalyst Area of complex per gram complex	Heated catalyst[a] Area sq. m./g.	Heated catalyst[a] Area of complex per gram complex	Evacuated catalyst[a] Area sq. m./g.	Evacuated catalyst[a] Area of complex per gram complex	Reduced catalyst[a] Area sq. m./g.	Reduced catalyst[a] Area of complex per gram complex
Co:ThO_2:MgO:KG = 100:6:12:200, 89J	85.5	155.4	65.5	108.9	67.0	109.8	62.0	99.6
Co:ThO_2:MgO = 100:6:12	154.8	154.8	68.3	68.3	61.1	61.1	52.8	52.8
Co:Kg[b] = 100:200	75.6	124.7	37.1	52.4	35.5	49.2	18.3	14.2
Cobalt basic carbonate	126.2	126.2	24.2	24.2	21.6	21.6	2.5	2.5

[a] Area of catalyst and complex per gram of catalyst and per gram of complex in the original unreduced catalyst respectively. [b] Contains Filter-Cel.

TABLE III

MERCURY AND HELIUM DENSITIES OF UNREDUCED AND REDUCED COBALT CATALYSTS

Catalyst	Form[a]	Unreduced catalysts: Densities Hg	Densities He	Pore volume cc./g.	Area sq. m./g.	$\bar{d}$,[b] Å.	Reduced catalysts: Densities Hg	Densities He[c]	Pore[d] volume cc./g.	Area[d] sq. m./g.	$\bar{d}$,[b] Å.	Mercury volumes per gram of unreduced catalyst, cc.: Before reduction	After reduction
Co:ThO_2:MgO:KG = 100:6:12:200													
89H	P	1.20	2.74	0.47	67.2	280	0.993	3.10	0.68	51.8	527	0.833	0.816
89J	P	0.974	2.76	0.66	88.7	297	0.780	3.07	0.95	76.6	500	1.026	1.037
89K	P	1.20	2.77	0.47	88.8	212	1.045	3.08	0.63	77.4	327	0.833	0.768
89K	G	0.611	2.77	1.28	101.1	506	0.537	3.13	1.54	76.8	804	1.635	1.530
89U	P	1.10	2.80	0.55	86.2	255	0.901	3.08	0.79	46.7	672	0.909	0.896
89FF	P	1.295	[e]	0.41	102.9	160	1.138	3.03	0.55	99.0	222	0.772	0.712
Co:ThO_2:KG = 100:18:100													
108B	P	1.13	3.08	0.56	71.6	313	0.905	3.69	0.73	42.3	693	0.885	0.836
Co:ThO_2:MgO = 100:6:12	G	0.781	3.62	1.00	154.8	259	1.057	6.72	0.80	84.1	379	1.280	0.593
Co:KG = 100:200	G	0.457	2.71	1.75	75.6	926	0.378	3.00	2.31	22.8	4060	2.189	2.082
Cobalt basic carbonate	G	0.925	3.81	0.82	126.1	293	4.476[f]	9.00	0.112	4.2	1070	1.081	0.125

[a] P = pellets (1.6 mm. long by 3.2 mm. diameter); G = granules, broken filter cake. [b] Average pore diameters computed from $\bar{d} = 4V/A$, where V is the pore volume and A the surface area per gram. [c] Helium densities calculated from compositions of reduced catalysts: 89-type, 3.12; 108B, 3.69; Co:ThO_2:MgO = 100:6:12, 7.79; Co:Kg = 100:200, 3.06; and cobalt basic carbonate, 8.9. [d] Pore volumes and surface areas per gram of reduced catalyst. [e] Not determined, assumed to be 2.77. [f] This sample wet by mercury.

TABLE IV

CHEMISORPTION OF CARBON MONOXIDE ON REDUCED COBALT FISCHER–TROPSCH CATALYSTS

All data per gram of unreduced catalyst

Catalyst	Form[a]	V_m cc.	V_{CO},[b] cc.	Complex per gram of complex: V_m, cc.	Complex per gram of complex: V_{CO}, cc.	$\frac{V_{CO}}{V_{m\text{-complex}}}$	Co atoms[c] in surface, %
Co:ThO_2:MgO:KG = 100:6:12:200	P	9.58	4.40	18.72	8.80	0.470	72.3
89J	P	14.15	3.10	23.92	6.20	.259	39.9
89K	P	14.31	3.80	24.80	7.60	.306	47.1
89K	G	14.19	4.00	24.40	8.00	.328	50.4
89U	P	8.64	2.17	13.98	4.34	.311	47.9
89V	P	11.48	3.80	16.48	7.60	.461	71.0
Co:ThO_2:KG = 100:18:100							
108B	P	7.40	2.56	11.42	2.84	.448	69.0
Co:ThO_2:MgO = 100:6:12	G	12.06	6.90	12.06	6.90	.572	88.0
Co:ThO_2 = 100:6	G	3.33	1.95	3.33	1.95	.586	90.2
Co:MgO[d] = 100:12	G	8.03	3.70	8.03	3.70	.461	71.0
Co:MgO[e] = 100:8	G	4.17	2.17	4.17	2.17	.520	80.0
Co:KG[f] = 100:200	G	4.18	0.85	3.28	1.70	.518	79.7
Cobalt basic carbonate	G	0.58	0.36	0.58	0.36	.632	97.2
Cobalt oxide powder		0.73	0.73	0.48	0.48	.648	99.7

[a] G = granules, broken filter cake; P = pellets. [b] V_{CO} computed from the difference the total carbon monoxide isotherms and the physical nitrogen at equal relative pressures. [c] $V_{CO}/V_{m\text{-complex}}$ divided by 0.65, the value of $V_{CO}/V_{m\text{-complex}}$ for cobalt metal. [d] Powdered magnesia. [e] Precipitated magnesia. [f] Filter-Cel.

Data for changes in surface area during a one-hour treatment with nitrogen at 400° and in a subsequent evacuation at 400° for sixteen hours are presented in Table II. Data for helium and mercury densities (the latter determined at 1 atmosphere), pore volumes,[18] and average pore diameters, $\bar{d}$, computed from the equation for open end cylindrical pores[19] $\bar{d} = 4V/A$, where V is the pore volume and A the surface area, are given in Table III. In Table IV data for the chemisorption of carbon monoxide are presented and compared with the volume of nitrogen required to form a physical monolayer. In Fig. 2 are typical carbon monoxide and nitrogen isotherms at −195° for reduced catalysts. In Table V are given X-ray diffraction data for catalysts and similar preparations.

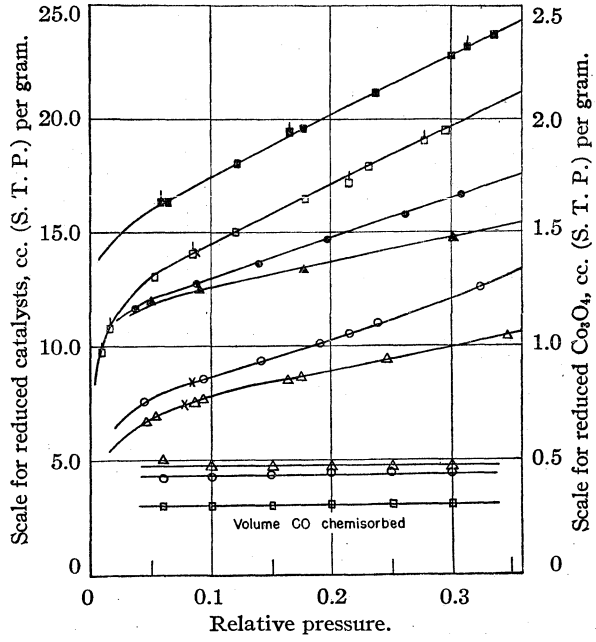


Fig. 2.—Sorption of nitrogen and carbon monoxide at −195° on reduced pelleted catalysts 89H and 89J and reduced cobalt oxide powder where open points represent nitrogen and solid points represent carbon monoxide isotherms. Points of reduced 89H are given by ○, two samples of reduced 89J by □ and ⊡, and the reduced cobalt oxide by △. The volumes of chemisorbed carbon monoxide are given in lower part of the graph.

Changes of Surface Area on Reduction

In Fig. 1 the circles, squares and triangles of the isotherm of the reduced catalyst indicate the reproducibility of isotherms of three different reductions of pelleted catalyst 89J. Isotherms of both unreduced and reduced catalysts showed hysteresis at relative pressures greater than 0.4. The hysteresis loop in the range of relative pressures of 0.4 to 0.7 was considerably smaller for the reduced catalyst than for the unreduced, the hysteresis of the isotherm of the reduced catalyst being only slightly greater than that of the isotherm of the kieselguhr that it contained. This may indicate enlargement or removal of some of the pores of diameters less than 50 Å., since hysteresis in this range is usually related to the presence of small pores.

The data in Table I show that the surface areas of all of the catalysts studied decreased on reduction. The areas of the cobalt-promoter complex[7] of the catalysts containing both promoters and carriers decreased to 37.4 to 75% of the area of the complex of the unreduced catalysts. The area of catalysts with promoter but no kieselguhr decreased to 8.5 to 34.1% of the unreduced areas. The areas of the complex of preparations containing kieselguhr but no promoters decreased to 7.8 to 10.9% of the unreduced areas, and the area of the preparation with neither promoter nor carriers decreased to 2.0% of the unreduced area. Thus it is observed that catalysts of the 89 type were most resistant to sintering upon reduction. Catalysts with calcined and flux-calcined kieselguhrs, 89BB and 89H, respectively, did not sinter any more

TABLE V

X-RAY DIFFRACTION DATA

Preparation	Diffuseness[a]	X-Ray reflections: Face-centered cubic I[b]	hkl	d/n, Å.[b]	Hexagonal close-packed I	hkil	d/n, Å.
Cobalt basic carbonate (unsupported)	B	S	111	2.04	w	$10\bar{1}0$	2.15
		M	200	1.76	w	$10\bar{1}1$	1.91
		S	220	1.25			
		S	311	1.06			
Cobalt basic carbonate (on Filter Cel)	C	vS	111	2.04	w	$10\bar{1}0$	2.14
		M	220	1.25			
		M	311	1.06			
Co: ThO_2 (100: 6) (unsupported)	C	S	111	2.04	w	$10\bar{1}0$	2.15
		M	220	1.25			
		M	311	1.06			
Co: MgO (100: 8) (unsupported)	C	vS	111	2.02			
		w	200	1.76			
		M	220	1.25			
		S	311	1.06			
Co: MgO (100: 12) (unsupported)	D	vS	111	2.02			
		w	200	1.77			
		M	220	1.25			
		M	311	1.06			
Co: MgO: ThO_2 (100: 12: 6) (unsupported)	D	M	111	2.02			
		vw	200	1.76			
		w	220	1.24			
		w	311	1.06			
89J Co: ThO: MgO: Filter Cel (100: 6: 12: 200)	D	M	111	2.02			
		w	220	1.25			
		w	311	1.06			
89H Co: ThO_2: MgO: Hyflo Super-Cel (100: 6: 12: 200)	D	M	111	2.00			
		w	220	1.24			
		w	311	1.06			
108B Co: ThO_2: Filter-Cel (100: 18: 100)	D	M	111	2.04			
		M	220	1.25			
		M	311	1.06			

[a] B = diffuse; C = more diffuse; D = very diffuse. [b] vS = very strong; S = strong; M = medium; w = weak; vw = very weak.

(18) The volume of pores with openings smaller than 5 microns in diameter (pores not filled by mercury at atmospheric pressure) computed from the difference of the reciprocals of the mercury and helium densities.

(19) Emmett and DeWitt, THIS JOURNAL, 65, 1253 (1943).

than catalysts prepared from natural kieselguhrs. However, since the areas of these catalysts in the unreduced state were less than those of catalysts with the natural kieselguhrs, the areas of reduced catalysts 89H and BB were less than the rest of the 89 series. Of the individual promoters, magnesia added as a powder appears to be the most effective and thoria the least. However, the data for the preparations with powdered magnesia may be misleading, since the magnesia itself has a high area which is probably not appreciably decreased in the preparation or reduction[20] and thus may increase the total area. Consistent with this, the volume of chemisorbed carbon monoxide per unit surface area (Table IV) was less for preparations with powdered magnesia than for the other samples. Thoria was not very effective in preventing sintering in either the cobalt–thoria preparation or in catalyst 108B. Kieselguhr appears to be nearly as effective as the thoria, the natural kieselguhrs being only slightly more effective than flux-calcined Hyflo Super-Cel.

The surface areas of unreduced catalysts[3] as granules (broken filter cake) was 10 to 15% greater than those of corresponding pelleted catalysts. Here, the explanation was given that the decrease in area on pelleting was due to compression of some of the particles of the cobalt-promoter complex so that nitrogen molecules could not penetrate the spaces between them. After reduction granular catalyst 89K had the same area as reduced pelleted 89K. This is consistent with the previous hypothesis since reduction could cause enlargement of pores so that all of the surface would be accessible.

The data in Table II show the changes in surface area upon heating or evacuations at 400° and during the reduction. The area of the cobalt basic carbonate decreased considerably upon both heating and reduction. The area of the catalyst with kieselguhr but no promoters likewise decreased sizably both on heating and reduction, but not as greatly as the cobalt basic carbonate. The area of the promoted preparation without kieselguhr decreased sizably on heating but only slightly on reduction. The area of the catalysts with both promoters and carriers decreased less in both steps than other preparations, the greatest decrease occurring in the heating step. Thus the kieselguhr appeared to be somewhat effective in preventing sintering of the surface during the heating step and less effective during the reduction. The promoters were about as effective in preventing sintering in the heating step as the kieselguhr, but very effective in inhibiting sintering during reduction. The catalysts containing both promoters and carriers which combine both of the protective actions sinter least in both of the steps.

Changes in Densities and Pore Volumes on Reduction

In Table III the mercury densities determined at 1 atmosphere (under these conditions mercury should penetrate only pores larger than 5 microns in diameter[21]) show that preparations containing kieselguhr did not change in volume as measured by mercury on reduction, whereas the volume of mercury displaced by preparations without kieselguhr decreased considerably. This is shown in the last two columns of Table III. This agrees with the role of the kieselguhr postulated previously[3] —that the kieselguhr acts as a "brush-pile" which defines the volume of the catalyst particle.

It was found that the mercury wet the reduced cobalt basic carbonate (pure cobalt metal) to some extent, which, of course, invalidates the usual interpretation of mercury densities; however, this was the only sample upon which this phenomenon was observed. Presumably, the presence of promoters or kieselguhr prevents such wetting. Should this occur to a slight extent on all of the reduced catalysts, the general picture of the changes in volume on reduction would not be altered, since the changes in volume are easily observed visually.

The helium densities were less accurate than the mercury densities due to the small volume of helium displaced by the reduced catalysts. However, repeated determinations on the same sample usually agreed within 3%. With exception of the low helium density observed with the reduced cobalt–thoria–magnesium oxide preparation, for which we have no explanation except possibly incomplete reduction, the observed densities differed no more than 4% from those computed from the catalyst composition, assuming no solution or compound formation of the catalyst components.

The pore volumes of all the catalysts containing kieselguhr increased on reduction, but those of preparations without this carrier decreased. Average pore diameters were computed by the equation of Emmett and DeWitt[19] for cylindrical open-end pores. Since the decreases in surface area were always greater than decreases in pore volume, the average pore diameters always increased on reduction.

Reduction was accompanied by a decrease in surface area and in some cases by a decrease in bulk volume. With unpromoted and unsupported cobalt, large changes occurred in both. When cobalt atoms are formed by reduction, they must be able to migrate until they find stable sites in the lattice of the already reduced metal. In fact, in the reduction of the cobalt oxide powder (Table I) for twenty-four hours at 250° hexagonal aggregates or possibly crystals of cobalt several microns in diameter were formed.[10]

Kieselguhr provides a framework which prevents the decrease in bulk volume on reduction and at the same time inhibits sintering of the surface. The cobalt–promoter complex probably shrinks about the kieselguhr particles, thus inhibiting the growth of large crystallites of cobalt.

The promoters, which at least in the case of

(20) Zettlemoyer and Walker, *Ind. Eng. Chem.*, **39**, 69 (1947).

(21) Ritter and Drake, *Ind. Eng. Chem., Anal. Ed.*, **17**, 782 (1945).

thoria and precipitated magnesia are thoroughly mixed with the cobalt basic carbonate, have a more intimate role than the kieselguhr. In the change from the basic carbonate to cobalt metal, the volume of the part containing the cobalt decreases several-fold. The cobalt atoms possibly retreat from the surface, leaving a matrix of the relatively unchanged promoter which inhibits migration of atoms and growth of large crystallites.

Chemisorption of Carbon Monoxide on Reduced Catalysts

In the research of Emmett and Brunauer[11,22] the chemisorption of carbon monoxide at −195° was taken as an indication of the extent of iron present on the surface of the iron catalysts. Figure 2 shows typical isotherms of carbon monoxide and nitrogen at −195° on reduced cobalt catalysts and cobalt oxide powder plotted on a relative pressure basis. Since the physical properties of carbon monoxide and nitrogen including molecular size are nearly identical, the nitrogen isotherm was taken equal to the physical carbon monoxide isotherm. The difference of the carbon monoxide (physical plus chemisorption) and nitrogen isotherms at equal relative pressures was taken as the volume of chemisorbed carbon monoxide. The constancy of these differences as shown in Fig. 2 demonstrates the correctness of this assumption. Emmett and Brunauer[11,22] found that the ratio of the amount of chemisorbed carbon monoxide to the physically held monolayer, as determined by the B.E.T. method[16] on pure iron, was 1.10 to 1.18, while on two nickel preparations Emmett and Skau[23] observed ratios of 0.92 and 1.78. Ratios slightly larger than one, such as observed on pure iron catalysts, may be explained by assuming the chemisorbed molecules to be more densely packed in the chemisorbed layer than in the physically held one. On reduced cobalt oxide powder and cobalt basic carbonate the ratios of chemisorbed carbon monoxide to the monolayer of physically held nitrogen were only 0.65. The reasons for these differences of these ratios for pure iron and cobalt are not known. However, Emmett[24] found that with highly sintered iron preparations this ratio was less than 1. The two pure cobalt preparations described in the present paper may be regarded as highly sintered.

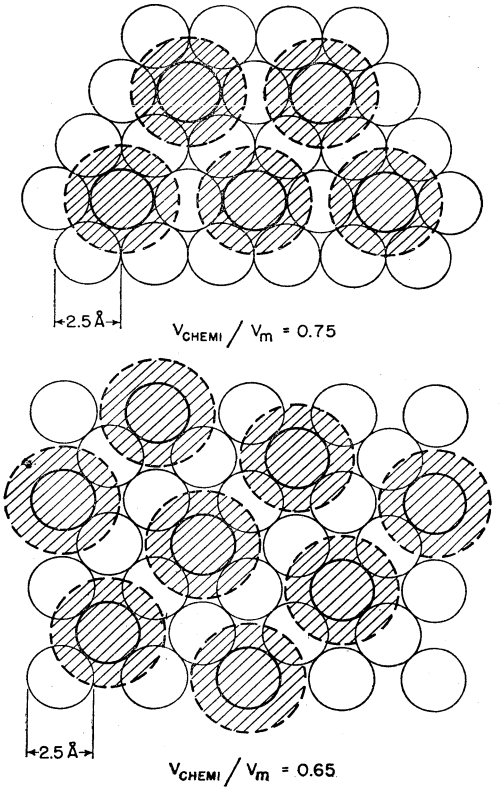


Fig. 3.—A representation of the manner that carbon monoxide may chemisorb on a cobalt surface. The upper drawing represents the closest packed faces of α- or β-cobalt, and the lower drawing the 100 faces of β-cobalt. Chemisorbed carbon monoxide molecules (the sectioned, dotted circles) are assumed to attach to the centers of cobalt atoms. The diameters of these circles give a cross sectional area of 16.2 sq. Å. per molecule in a close packed monolayer.

An explanation which is probably greatly oversimplified may be given from the geometry of possible cobalt surfaces. Two of the possible crystal faces of α- and β-cobalt are shown in Fig. 3. If chemisorbed molecules are assumed to attach to the centers of the cobalt atoms, the size of the molecule will prevent adsorption on adjacent cobalt atoms. The resulting ratios of chemisorbed to physically held molecules will be 0.65 and 0.75 for the faces shown, which are near the ratios observed for cobalt metal in the reduced cobalt oxide powder and cobalt basic carbonate.

For the reduced cobalt–thoria–magnesia kieselguhr catalysts the ratios of chemisorbed carbon monoxide to the V_m value for the complex varied from 0.259 to 0.470, and for the cobalt–thoria–kieselguhr catalyst this ratio was 0.448. The ratios of chemisorbed carbon monoxide to the nitrogen–monolayer for cobalt–promoter and cobalt–kieselguhr preparations varied from 0.461 to 0.586. Cobalt–thoria preparations had higher ratios than those of cobalt–magnesia.

The ratio of chemisorbed to physically held molecules divided by the ratio for pure cobalt metal, 0.65, may not be an accurate indication of the extent of cobalt atoms in the catalyst surface, since, as shown in Fig. 3, all of the atoms adjacent to the cobalt atom adsorbing the carbon monoxide could be replaced by promoters without changing the ratio. In any case, the data of Table IV indicate that the surface of the catalyst with both pro-

(22) Emmett and Brunauer, THIS JOURNAL, **57**, 1754 (1935); **59**, 310, 1553 (1937).

(23) Emmett and Skau, *ibid.*, **65**, 1029 (1943).

(24) Emmett, private communication.

moter and carrier must be covered to at least 30% by substances other than cobalt.

X-Ray Diffraction Patterns of Reduced Cobalt Catalysts

The diffraction patterns of this series of preparations in the reduced state show the effect of promoters (thoria and magnesia) and the support (kieselguhr) on crystallite size. The background due to scattering from the amorphous constituents of the catalysts, particularly thoria and kieselguhr, makes exact evaluation of line broadening difficult; nevertheless the trends are unmistakable. Reduced cobalt basic carbonate gave the sharpest diffraction pattern, but some line broadening corresponding to crystallites about 800 Å. diameter was observed. The most diffuse patterns were obtained from 108B, Co:MgO (100:12), Co:ThO_2:MgO (100:6:12), 89J and 89H. The line broadening of this group corresponded roughly to crystallites of 100–300 Å. The preparations Co:ThO_2 (100:6), Co:Filter-Cel (100:200), and Co:MgO (100:8) gave line broadening corresponding to crystallites 300–600 Å. diameter. These results are in general agreement with surface area measurements.

The diffraction patterns of many of these preparations lack expected reflections. This has been previously noted[9] in connection with fully promoted and supported catalysts. The diffraction pattern of the reduced cobalt basic carbonate contained relatively strong 111, 200, 220, and 311 lines of face-centered cubic cobalt as well as faint $10\bar{1}0$ and $10\bar{1}1$ lines of hexagonal close-packed cobalt; such a pattern would normally be expected of a mixture of a relatively large amount of f.c.c. cobalt and a small amount of h.c.p. cobalt. With increasing amounts of promoter and support the 200-f.c.c. line and the $10\bar{1}0$- and $10\bar{1}1$-h.c.p. lines tend to disappear; in a fully promoted and supported catalyst, such as 89J and 108B, the 200-f.c.c. and $10\bar{1}0$- and $10\bar{1}1$-h.c.p. lines cannot even be identified with certainty. It is interesting to note that the persistent lines 111, 220, and 311 of f.c.c. correspond to 0002, $11\bar{2}0$, and $11\bar{2}2$ of h.c.p., respectively, in interplanar spacing. Among the partly promoted or supported preparations, those containing magnesia produced a weak but unmistakable 200-f.c.c. reflection, whereas neither the $10\bar{1}0$- or the $10\bar{1}1$-h.c.p. lines could be positively identified. The converse is true of those partly promoted or supported preparations containing no magnesia. A theoretical discussion of this phenomenon will be published shortly.

Discussion

Promoters may have two functions: first, that of maintaining or increasing the extent of the surface and, second, that of providing a surface of the proper physical or chemical nature. In some cases a single promoter may perform both of these functions and in other cases only one of them. Russell and Taylor[25] showed that thoria as a promoter in nickel catalysts performed both of these functions. The surface area as estimated by the chemisorption of hydrogen and carbon dioxide was increased 20 to 40%, while the activity for hydrogenation of carbon dioxide to methane increased nine fold. Similarly, thoria in cobalt–thoria–kieselguhr catalysts may accomplish both of these functions. Alkali in precipitated- or fused-iron Fischer–Tropsch catalysts appears to alter the distribution of products but does not increase the surface area or activity appreciably. In doubly promoted (alumina–potassium oxide) synthetic ammonia catalysts, alumina is an effective structural promoter and potassium oxide is assumed to alter the chemical nature of the surface to inhibit formation of imide and amide groups on the surface.[11] The studies of Emmett and Brunauer[11] and others demonstrate these effects. The data in the present paper show chiefly the effect of promoters and carriers in maintaining surface area, but the X-ray diffraction and chemisorption data give some information as to the nature of the surface.

The chemisorption studies indicate that a sizable fraction of promoter was present on the catalyst surface. In addition to greater surface areas and surface stability of the promoted catalysts, the relatively isolated metal atoms or groups of atoms at the surface may have greater activity than that of crystallites of unpromoted metals.

The X-ray diffraction data were in qualitative agreement with surface–area measurements, but in addition revealed that the cobalt metal in promoted and supported catalysts had an anomalous crystal structure. The presence of the promoters and the support favored this anomalous structure. It should be noted that X-ray diffraction studies reveal the average structure of the crystallites of cobalt and not just the surface.

It has been suggested that kieselguhr as a carrier in cobalt and nickel catalysts produces the proper degree of dispersion of the active metal and gives the desired porosity.[26] The data in this paper demonstrate the manner in which these effects are accomplished. Kieselguhr provided a framework about which the metal oxide complex shrank when reduced to the metal. Kieselguhr also provided a system of large, accessible pores and appeared to prevent excessive decrease in the area of the metal. It should be noted that in our catalysts the cobalt–promoter complex was deposited chiefly in the pores of the kieselguhr that were larger than 5 microns.[3]

Upon reduction, the bulk volume of the catalyst containing kieselguhr remained unchanged, whereas the bulk volume of the unsupported catalyst decreased several fold. Kieselguhr as a carrier is important if the reaction is highly exothermic, as in the Fischer–Tropsch synthesis, or

(25) Russell and Taylor, *J. Phys. Chem.*, **29**, 1325 (1925).

(26) Hall, Craxford and Gall, "Interogation of O. Roelen," British Intelligence Objectives Sub-Committee, 1945.

if the catalyst is reduced in the reactor. If the reaction is highly exothermic, the heat produced by a dense, unsupported catalyst may exceed the capacity of the reactor to remove the heat of reaction, and the catalyst may overheat. This is possibly the reason for the great improvement in life of cobalt and nickel Fischer–Tropsch catalysts when kieselguhr was used as a carrier.[27] Pichler[28] has stated that industrial development of the synthesis in Germany appeared possible only after the introduction of kieselguhr as a carrier for cobalt catalysts. If the catalyst is to be reduced in the converter, the large decrease in bulk volume on reduction of unsupported catalysts will cause a large amount of reactor space to be wasted.

Ries[29] and Visser and DeLange[30] have shown that unreduced catalysts of cobalt and nickel, respectively, precipitated in the presence of kieselguhr have considerably higher surface areas per gram of active metal than the unsupported catalyst. Visser and DeLange have shown the formation of hydrosilicate bonds between the nickel and kieselguhr. With our catalysts the presence of kieselguhr does not greatly increase the area of the unreduced catalyst, and there is very little evidence to indicate any reaction of cobalt with the kieselguhr. In fact, in the standard methods of preparing the cobalt catalysts these effects are minimized by keeping the time of contact of the reacting solutions with the kieselguhr as short as possible.

Craxford[31] studied the rates of carbiding, hydrogenation of carbide and synthesis on cobalt–thoria–kieselguhr (100:18:100) catalysts and on similar preparations with thoria or kieselguhr or both omitted. The rate of hydrogenation of ethylene was taken as an indication of the surface area, and since these rates were of the same magnitude, it was assumed that the surface areas were about equal. Hence, Craxford concluded that thoria and kieselguhr do not act primarily by increasing the available cobalt area, but as specific promoters for formation and reduction of carbide.

The data presented in the present paper indicate that the differences in both total surface area (Table I) and area of cobalt (Table IV) are quite large. The volume of chemisorbed carbon monoxide per gram of complex varied roughly in the same manner as Craxford's activities for carbide formation and reduction and for the synthesis. The uncertainties of this comparison are large because: (a) in some cases the catalysts compared did not have the same composition, and (b) the methods of catalyst preparation may have been considerably different. However, we believe that this comparison shows the activities of Craxford's catalysts to be strongly a function of surface area.

Acknowledgment.—The authors are pleased to acknowledge the assistance of Norma Golumbic and Harlan Hewlett in catalyst preparation, Raymond Hahn for some of the density measurements, and W. C. Peebles for X-ray diffraction studies.

Summary

1. Reduced cobalt–thoria–magnesia–kieselguhr and cobalt–thoria–kieselguhr catalysts and similar preparations with one or more of the components omitted have been studied by nitrogen surface areas and carbon monoxide chemisorptions at −195°, mercury and helium densities, and X-ray diffraction.

2. The promoters were found to prevent excessive decreases in surface area on reduction.

3. Kieselguhr as a carrier was somewhat effective in preventing the decrease of surface area on reduction, but its most important function was to prevent the decrease in bulk volume of the catalyst on reduction.

4. The carbon monoxide chemisorption studies showed that an appreciable fraction of the surface was occupied by promoter.

5. The X-ray diffraction data were in qualitative agreement with the surface-area determinations, but in addition indicated that the cobalt in supported and promoted catalysts had an anomalous structure.

PITTSBURGH 13, PENNSYLVANIA

RECEIVED JANUARY 30, 1948

(27) Fischer and Koch, *Brennstoff Chem.*, **13**, 61 (1932); Fischer and Meyer, *ibid.*, **12**, 225 (1931).

(28) Pichler, "Synthesis of Hydrocarbons from Carbon Monoxide and Hydrogen," to be published by Hobart Publishing Co., Washington, D. C.

(29) Ries, *J. Chem. Phys.*, **14**, 465 (1946); also *Ind. Eng. Chem.*, **37**, 310 (1945); and THIS JOURNAL, **67**, 1242 (1945).

(30) Visser and DeLange, *De Ingenieur*, **58**, 24 (1946); DeLange, private communication.

(31) Craxford, *Trans. Faraday Soc.*, **42**, 580 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Transference Numbers and Hydration of Some Quaternary Ammonium Salts[1]

BY CECIL H. HALE[2] AND THOMAS DE VRIES

It is a generally accepted fact that ions in aqueous solution are hydrated to some extent. The degree of hydration depends, amongst other factors, upon the nature and size of the ion. Von Hevesy[3] has shown that nearly all univalent organic ions are so large and the strength of the electric field surrounding them so weak that hydration should not occur. If organic ions are not hydrated, the electrolytic transfer of water in solutions of tetraalkylammonium salts should show a transfer of water to the anode equivalent to the amount of water carried by the anions alone or, more probably, the results should show a trend of less hydration for the larger organic cations. In this research, the electrolytic transfer of water in solutions of tetramethyl-, tetraethyl-, tetra-*n*-propyl-, and tetra-*n*-butylammonium iodides was studied. Maltose was used as the non-electrolyte because it has a high optical rotation and its concentration can be measured very accurately by means of a polarimeter. Some experiments were also made in which acetone and ethyl acetate were the reference substances. The well-known Nernst method as developed by Washburn[4] was used in this investigation.

Apparatus and Experimental

The transference apparatus shown in Fig. 1 is a modification of the one described by MacInnes and Dole.[5] It was constructed of Pyrex glass tubing of 19 mm. internal diameter. The stopcocks which separated the anode and cathode compartments were hollow and open at each end to permit the circulation of water through them when the apparatus was in the constant temperature bath. The apparatus consisted of two sections, connected by a spherical joint to allow the anode and cathode compartments to be weighed. The total length of 130 cm. contained 10 bends, spaced to reduce convection and diffusion during electrolysis. For analysis the solution in the apparatus was divided into five portions. The approximate volumes of the different compartments were: cathode, 115 ml.; anode, 150 ml.; cathode middle, 40 ml.; anode middle, 40 ml.; middle, 90 ml. There was never any appreciable variation in the concentrations of the three middle compartments, which proved the effectiveness of the design of the apparatus in the prevention of diffusion and convection.

The electrodes were made of silver and silver iodide, deposited electrolytically on 18-gage platinum wire.

Silver coulometers were used to measure the current. The silver nitrate solutions from the platinum crucibles were filtered through sintered glass crucibles to prevent the loss of deposited silver. One coulometer was connected to each electrode in order to detect any electrical leaks. It was necessary to coat the glass joints with picein wax to prevent such leaks.

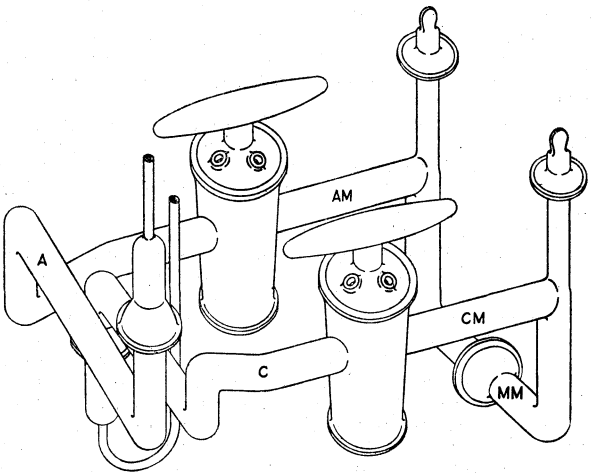


Fig. 1.—Transference apparatus: A, anode compartment; AM, anode middle; MM, middle middle; CM, cathode middle; C, cathode compartment.

The polarimeter was a Schmidt and Haensch instrument which could be read to ±0.01 degree of rotation. Light of wave length 5893 Å. was obtained from a tungsten bulb by means of a monochromator. A four decimeter tube was used.

Electrolysis experiments were carried out in a thermostat maintained at 25 ± 0.02°.

Quaternary ammonium iodides were prepared from alkyl iodides and the corresponding tertiary amines. The compounds were purified by repeated recrystallizations from ethyl acetate to which a small amount of ethanol had been added.

The silver cyanide solution for silver plating the electrodes was prepared by the dissolution of 46 g. of silver nitrate, 70 g. of potassium cyanide, 31.5 g. of sodium carbonate and 0.5 g. of sodium thiosulfate in one liter of distilled water.

The maltose used was Merck, "purified" grade. Electrical conductivity measurements showed it to be free from electrolytes.

In the transference experiments, the electrolysis was allowed to continue for about forty-eight hours. A potential of about 50 volts was necessary to obtain the desired current of about 5 milliamperes. At the end of the electrolysis, the stopcocks were closed and the anode middle, cathode middle and middle solutions were transferred by means of a pipet to weight burets. The apparatus was then removed from the bath and the two sections separated, cleaned and dried, the stopcocks remaining closed. The two sections were first weighed before the solutions were transferred to weight burets.

Analysis.—The quaternary ammonium salt solutions were titrated with 0.05 *M* silver nitrate at about 50°. The end-point was determined potentiometrically using a Garman and Droz[6] titrimeter. Weight burets were used in all the titrations.

The concentration of the maltose in grams per 100 ml. in the solutions were found from the equation $0.1923\alpha - 0.010$, where α is the optical rotation. This relation was established by measuring the rotation of solutions of known concentration. The presence of the quaternary

(1) Presented before the Physical and Inorganic Division at the 113th meeting of the American Chemical Society, Chicago, Ill., April 19–22, 1948.

(2) Abstract of the Ph.D. dissertation of C. H. Hale whose present address is Esso Laboratories, Baton Rouge, La.

(3) G. von Hevesy, *Z. Elektrochem.*, **27**, 77 (1921).

(4) E. W. Washburn, THIS JOURNAL, **31**, 322 (1909).

(5) D. A. MacInnes and M. Dole, *ibid.*, **53**, 1357 (1931).

(6) R. L. Garman and M. E. Droz, *Ind. Eng. Chem., Anal. Ed.*, **11**, 398 (1939).

ammonium iodides was found to have no measurable effect on the optical rotation of the solution.

Acetone determinations were made by a method based on the formation of iodoform.[7] The deviation of triplicate determination was 0.1%.

Ethyl acetate was determined by hydrolysis in alkaline solution. A measured excess of carbonate-free 0.35 *N* sodium hydroxide solution was added to a weighed sample and refluxed for forty-five minutes, and back titrated with 0.1 *N* sulfuric acid. With a correction from blank determinations the deviation of triplicate determinations was 0.05%.

The transference numbers of sodium and potassium iodide were determined to test the apparatus and the techniques. The values obtained at the anode and the cathode agreed well with each other and with the values in the literature to within 0.001.

The quaternary ammonium iodides invariably gave a much larger value for the cation transference number at the anode than at the cathode. A typical set of values are presented in Table I. The deposit on the anode did not have the appearance of pure silver iodide, but was white and somewhat flocculent. Further, the transference numbers calculated from the analysis of the anode solutions did not agree in successive experiments. These facts indicated that formation of solid solutions of the quaternary ammonium iodide with silver iodide. A solution of tetramethylammonium iodide was electrolyzed in a small beaker with no attempt made to separate the solutions at the silver-silver iodide electrodes. The final solution was analyzed for iodide ion concentration and it was found that approximately one mole of tetramethylammonium iodide had disappeared for every four moles of silver iodide deposited at the anode. The transference numbers obtained from measurements of anode solutions were recalculated on the assumption that solid solutions of the quaternary ammonium iodide and silver iodide were formed in the ratio of one to four. The values were in approximate agreement with those obtained at the cathode. In every case, the ratio necessary to give complete agreement was between one to three and one to five.

TABLE I

TRANSFERENCE NUMBER OF TETRAETHYLAMMONIUM IODIDE

Experiment no.	15	16
Initial concn., mole/kg.	0.1013	0.1013
Final concn., anode soln.	0.0888	0.0864
Final concn., cathode soln.	0.1094	0.1113
Final concn., anode middle	0.1010	0.1012
Final concn., cathode middle	0.1011	0.1011
Wt. of anode soln., g.	144.695	144.467
Wt. of cathode soln., g.	115.370	115.107
Wt. of Ag in coulometers, g.	0.4352	0.5477
t_c at anode	0.467	0.437
t_c at cathode	0.236	0.237

The transference numbers of the quaternary ammonium iodides were first measured with no reference substance added and these results are presented in Table II. The concentrations of the salts were about 0.1 *M* except in the case of the tetra-*n*-butylammonium iodide where, because of limited solubility, it was necessary to use about 0.07 *M* solutions. Several attempts to electrolyze solutions of the tetrabutylammonium salt were unsuccessful because of the formation of hydrogen at the cathode. This difficulty was overcome by the use of a silver bromide electrode for the cathode.

Hydration of Ions.—The electrolytic transfer of water in solutions of the quaternary ammonium iodides was measured with maltose as the reference non-electrolyte. The results of a typical experiment with 0.1 *M* solutions of tetraethylammonium iodide are given in detail in Table III. The results with tetramethyl- and tetra-*n*-propylammonium iodides are included in Table IV, which also shows the values found with the other reference substances. Experiments in which tetra-*n*-butylammonium iodide and maltose were used were unsuccessful because of the formation of crystals at the cathode and slight gassing at the anode.

TABLE II

TRANSFERENCE NUMBERS OF QUATERNARY AMMONIUM IODIDES

Salt	Cation transference number	
Tetramethylammonium iodide	0.321	0.323
Tetraethylammonium iodide	.236	.237
Tetra-*n*-propylammonium iodide	.179	.171
Tetra-*n*-butylammonium iodide	.106	.103

TABLE III

HYDRATION OF TETRAETHYLAMMONIUM IODIDE, MALTOSE AS REFERENCE SUBSTANCE

	23		24	
Experiment no.	Salt[a]	Maltose[b]	Salt[a]	Maltose[b]
Initial concn.	0.0949	3.268	0.0949	3.271
Final concn., anode soln.	.0758	3.280	.0823	3.284
Final concn., cathode soln.	.1110	3.238	.1090	3.249
Final concn., anode middle	.0949	...	.0949	...
Final concn., cathode middle	.0949	...	.0949	...
Final concn., middle middle	.0949	3.267	.0948	3.276
Density of initial soln., g./ml.	1.0166		1.0169	
Density of final anode soln.	1.0154		1.0159	
Density of final cathode soln.	1.0177		1.0177	
Density of final middle middle	1.0164		1.0169	
Wt. of anode soln., g.	151.321		150.589	
Wt. of cathode soln., g.	116.745		116.528	
Wt. of Ag in coulometers, g.	0.7916		0.7419	
t_c at cathode	0.263		0.245	
Moles H_2O transferred to cathode per faraday	4.9		4.9	

[a] Concentration expressed as moles per kg. of solution. [b] Concentration expressed as g. per 100 ml. of solution.

TABLE IV

SUMMARY OF HYDRATION MEASUREMENTS

	Moles H_2O transferred to cathode per faraday		
Salt	Maltose	Ethyl acetate	Acetone
$(CH_3)_4NI$	3.9	20	6.4
	4.4		5.7
$(C_2H_5)_4NI$	4.9	20	...
	4.9		
$(C_3H_7)_4NI$	3.9	..	...
	3.2		
$(C_4H_9)_4NI$	...	35	...

Acetone and ethyl acetate also were used as reference non-electrolytes. Two experiments were made with 0.1 *M* tetramethylammonium iodide which contained 0.1% acetone. The limited accuracy of the analytical method for determining acetone casts some doubt on the values of the actual amount of water transported. However, the results confirmed at least qualitatively those obtained with maltose, and a transfer of water toward the cathode apparently occurred in each case. Acetone could not be used as a reference non-electrolyte with solutions of the other quaternary ammonium iodides because the addition of iodine, involved in the determination, formed precipitates with the higher salts.

(7) M. B. Jacobs, "The Analytical Chemistry of Industrial Poisons, Hazards and Solvents," Interscience Publishers, Inc., New York, N. Y., 1941, p. 535.

Ethyl acetate was used as the reference substance in the electrolysis of tetramethyl-, tetraethyl- and tetrabutylammonium iodide. In each case water was apparently transferred toward the cathode, as was the case with maltose. These results are included in Table IV.

The transfer of water toward the cathode during the hydrolysis indicates that the cation is more highly hydrated than the anion, which is contrary to the prediction that large organic ions should not be hydrated. A plausible explanation of this failure to follow prediction is that the changes in concentration of the reference substance are not only caused by the transfer of water but also by the transfer of the non-electrolyte to the anode. The assumption that the reference substance is carried along with the iodide ion is substantiated by the fact that the anion transference number is decreased by the addition of non-electrolyte. The effects of the non-electrolytes on the cation transference numbers are shown in Table V.

TABLE V

EFFECTS OF NON-ELECTROLYTE ON CATION TRANSFERENCE NUMBERS

Salt	Cation transference number: Nothing added	Maltose added	EtOAc added
$(CH_3)_4NI$	0.322	0.340	0.356
$(C_2H_5)_4NI$	.237	.254	.278
$(C_3H_7)_4NI$	.175	.153	...
$(C_4H_9)_4NI$	.105	...	.110

The association of non-electrolytes with ions in solution has been suggested by Fisher and Koval.[8] They found that sucrose, acetone and urea reduced the transference number of the hydrogen ion in solutions of sulfuric acid and concluded that complex ions of the type, $H_3O^+ \cdot$non-electrolyte, exist. Longsworth[9] recently used the moving boundary method to measure water transport in solutions of alkali chlorides with various reference non-electrolytes. He also concluded that the reference substances were not electrically inert and therefore not stationary during the electrolysis.

If one assumes that neither the iodide ion nor the quaternary ammonium ion is hydrated, that is, that the water molecules are stationary, then the amount of reference non-electrolyte carried along by the iodide can be calculated. The results for such a calculation are presented in Table VI based on the data obtained with maltose, ethyl acetate and acetone. Only about one per cent. of the iodide ions need to be associated with an equivalent amount of maltose to explain the experimental results. One might also assume that the iodide ion but not the quaternary ammonium ion is hydrated and calculate the amount of reference substance associated with the iodide ion. In Table VII are given the results of such a calculation for maltose when the iodide ion is arbitrarily assigned hydration values of five and of ten molecules of water.

TABLE VI

AMOUNT OF REFERENCE SUBSTANCE ASSOCIATED WITH IODIDE IONS ASSUMING WATER STATIONARY

Salt	Moles of non-electrolyte per mole of iodide ions: Maltose	Ethyl acetate	Acetone
$(CH_3)_4NI$	0.011	0.10	0.029
	.012		.029
$(C_2H_5)_4NI$	.011	.12	...
	.008		
$(C_3H_7)_4NI$	.008	..	...
	.006		
$(C_4H_9)_4NI$	...	.09	...

TABLE VII

AMOUNT OF MALTOSE ASSOCIATED WITH IODIDE IONS HYDRATION VALUES OF IODIDE ION ASSUMED

Salt	Mole of maltose per mole of iodide ion: I^-	$I^- \cdot 5H_2O$	$I^- \cdot 10H_2O$
$(CH_3)_4NI$	0.011	0.020	0.028
	.012	.020	.029
$(C_2H_5)_4NI$	.011	.019	.028
	.008	.017	.025
$(C_3H_7)_4NI$	.008	.015	.023
	.006	.016	.024

Summary

The transference numbers of 0.1 *M* solutions of tetramethyl-, tetraethyl-, tetra-*n*-propyl- and tetra-*n*-butylammonium iodide have been measured. The cation transference numbers were found to decrease as the size of the cation increased.

The electrolytic transport of water was measured in solutions of the same quaternary ammonium iodides with maltose, acetone and ethyl acetate as reference non-electrolytes. The results indicated that the reference substances were associated with a small fraction of the iodide ions and could not serve to determine the degree of hydration of the ions.

WEST LAFAYETTE, INDIANA RECEIVED MARCH 1, 1948

(8) P. Z. Fisher and T. E. Koval, *Univ. état Kiev. Bull. sci., rec. chim.*, No. 4, 137 (1939).

(9) L. G. Longsworth, THIS JOURNAL, **69**, 1288 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Quantum Yields of the Photochemical Reduction of Ceric Ions by Water and Evidence for the Dimerization of Ceric Ions

BY LAWRENCE J. HEIDT AND MAYNARD E. SMITH[1]

Water solutions containing ceric perchlorate and perchloric acid evolve oxygen when they absorb ultraviolet light and the ceric is reduced to cerous perchlorate.[2]

Baur[2a] and Weiss and Porret[2b] studied the photochemical reaction in the full light of a quartz mercury arc lamp. Weiss and Porret obtained maximum gross quantum yields of the order of one-tenth in solutions one-tenth molar in ceric perchlorate and one molar in perchloric acid. Their quantum yields decreased as the cerous perchlorate accumulated.

We have measured the quantum yields of the reaction when the solutions are irradiated with monochromatic light of λ 254 mμ. The light intensity, I, and the concentrations of cerous, c_3, and ceric, c_4, perchlorates were varied many fold. The perchloric acid concentration, c_2, was held at 1.03 ± 0.03 M and the ionic strength, μ, at 1.1 ± 0.1, all at 23 ± 3°.

Solutions of ceric perchlorate in perchloric acid are thermally unstable at 25°. The equilibrium ratio c_4/c_3 is about 10^{-8} in molar perchloric acid in equilibrium with the atmosphere (p_{O_2} = 0.2 atm.), but the rate of the thermal reduction of the ceric perchlorate by water is extremely slow. In one of our stock solutions which was 5.3 M in perchloric acid and was kept in the dark at 25 ± 3°, c_4 decreased from 1.36 to 1.20 M in eleven months while c_3 increased from 0.32 M.

Materials.—The chemical reagents were of analytical reagent grade or were prepared from material of this quality. The water was chloride-free distilled water.

Stock solutions of ceric and cerous perchlorates were prepared from a sample of snow white granular ceric oxide, 98.5% pure CeO_2, which was supplied by the Rohm and Haas Chemical Co., Philadelphia, Pa.

The ceric oxide could not be converted directly into ceric perchlorate even when dispersed as a fine hydrous oxide in 72% perchloric acid at room temperature or at 100° for periods of several months.

The ceric perchlorate was finally prepared by reducing the ceric oxide to cerous ions by bromide in perchloric acid. The bromine and excess bromide were removed by boiling. The cerous ions were then oxidized electrolytically to the ceric state. The experimental details follow.

Forty grams of the granular ceric oxide and 80 g. of sodium bromide were added to 275 ml. of 72% perchloric acid. The mixture was simmered for two hours under an appropriate hood. The hot solution was filtered by suction through a sintered glass filter. The filtrate was boiled down to half its initial volume; on cooling a colorless solid separated which was removed by decantation and filtering as above. The colorless filtrate, stock solution C, contained 1.68 moles of cerous perchlorate and 5.3 moles of perchloric acid per liter of solution. It contained no material oxidizable by ceric sulfate.

The stock solution B of ceric perchlorate was made by electrolyzing 63 ml. of solution C in a Pyrex beaker. The cylindrical electrodes were of platinum gauze of the type used for copper determinations. They were placed coaxially in the beaker and the smaller electrode was rotated rapidly to stir the solution. The beaker was surrounded by running tap water. The current density was kept for eleven hours at roughly 0.1 amp. per sq. in. of the anode surface. The solution then contained 1.36 moles of ceric perchlorate, 0.32 mole of cerous perchlorate and 5.3 moles of perchloric acid per liter of solution. The concentration of sodium perchlorate in solutions B and C was less than 10/3 the total cerium concentration. About 9.26 moles of sodium perchlorate dissolve in a liter of water solution at 25° and the density of the solution is 1.678 g. per ml.

Analytical Procedures.—The methods of analysis were entirely volumetric. The primary standard of oxidimetry was U. S. Bureau of Standards Sample 40b of sodium oxalate. The primary standard of acidimetry was potassium acid phthalate.

The cerous, ceric and acid concentrations were determined by essentially the same procedures used by M. S. Sherrill, C. B. King and R. C. Spooner.[3] Several modifications require mention. In determining c_4, 2 ml. of concd. sulfuric acid were added to each 5 ml. sample analyzed and the resulting solution after mixing was either titrated immediately or heated in boiling water for five minutes. Five or ten drops (0.25 or 0.50 ml.) of 0.0043 M orthophenanthroline indicator were used to identify the end-point in each analysis. The titrations were carried out with ferrous sulfate or ferrocyanide solutions. End-points were reproduced at best to $\pm 10^{-7}$ mole of ceric ion. This was accomplished by using similar test-tubes for all the titrations and viewing the solutions end on against a white illuminated background.

The actinometer solutions of uranyl oxalate were titrated at 80° with permanganate solution after adding 2 ml. of 4 N sulfuric acid per 10 ml. of the oxalate sample. End-points were determined to $\pm 10^{-8}$ mole of oxalate by means of the differential electrometric method previously developed.[4] Care was taken to minimize even local excesses of the permanganate until the end-point was reached.

Absorption spectra of the solutions were mapped out by means of a Hilger sector photometer backed by a quartz spectrograph. The cerous solutions were colorless, the ceric solutions ranged from colorless in the case of the most dilute solutions to amber in the case of the most concentrated solutions.

Extinction coefficients, ϵ, were measured in the region of λ, 254 mμ by means of a Beckman ultraviolet spectrophotometer. Values of ϵ were calculated by means of the equation $\epsilon = (1/cd) \log_{10} (I_0/I)$ when c is the concentration of the solute in moles per liter of solution, I_0 and I are the intensities of the light beams after traversing equal depths, d in cm., of the solvent and solution, respectively. Water, perchloric acid and sodium perchlorate absorbed a negligible amount of light of λ, 254 mμ in the cerous and ceric solutions over the range of concentrations and depths

(1) The part of this article concerned with the experimental study of the effect of cerous perchlorate upon the reaction is taken from the thesis submitted by Maynard E. Smith in September, 1946, to the Department of Chemistry of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Master of Science.

(2) (a) E. Baur, *Z. physik. Chem.*, **63**, 683 (1908), was the first to identify oxygen as the gaseous product of the reaction. This was ater confirmed by (b) J. Weiss and D. Porret, *Nature*, **139**, 1019 (1937).

(3) M. S. Sherrill, C. B. King and R. C. Spooner, THIS JOURNAL, **65**, 170 (1943).

(4) L. J. Heidt, *ibid.*, **61**, 3455 (1939).

TABLE I

EXTINCTION COEFFICIENTS, ϵ, OF CEROUS AND CERIC PERCHLORATES IN 1.03 ± 0.03 *M* PERCHLORIC ACID AT 23 ± 3°

c_4	c_3	c_4/c_3	ϵ at λ, 253	254	255 mμ
0	0.00007 to 0.03	0	ϵ_3, 760 ± 70	750 ± 70	740 ± 70
0.0006 to 0.0094		2.5	ϵ_4, 1750 ± 90	1710 ± 95	1670 ± 90
0.0007 to 0.0043		.78	ϵ_4, 1740 ± 110	1680 ± 120	1610 ± 80
0.0024		.42	ϵ_4, 1790 ± 20	1750 ± 20	1660 ± 20
0.0009 to 0.0023		.22	ϵ_4, 1765 ± 85	1700 ± 20	1540 ± 60

The average value of ϵ_4 is 1730 and of ϵ_3 is 750.

employed. The solutions obeyed Beer's law, *i. e.*, $\epsilon c = \epsilon_3 c_3 + \epsilon_4 c_4$ within the limits given in Table I.

Quantum yields were determined for monochromatic light of λ 254 mμ. The apparatus has been described.[5] It has been shown[5] that the light of λ 185 mμ produced by the lamp is completely (more than 99.99%) absorbed between the lamp and the reaction vessel by the two-cm. layer of running tap water and the cylindrical clear fused quartz filter containing a one-cm. layer of chlorine gas at one atm. A one-cm. layer of glacial acetic acid produced the same results.

Two sets of transparent fused quartz cylindrical reaction vessels were employed. In one set the cells had diameters of 1.3 cm and each held 11 ml. when filled to the neck. In the other set the diameters ranged from 2.4 to 2.8 cm. and each held 42 ml. when filled to the neck. The transmission of light of λ 254 mμ by the cell walls of all the reaction vessels was the same within 1%. The stirrers were made of transparent fused quartz ribbon and were rotated on the axes of the cells.

Concentrations of cerous and ceric perchlorates were limited to those that absorbed over 90% of the light of λ 254 mμ incident on the solutions before the light reached the stirrer. Less than 1% of this light emerged from any reaction cell.

Light fluxes incident upon the solutions were measured with the uranyl oxalate actinometer first standardized by W. G. Leighton and G. S. Forbes.[6] The actinometer solution for the 11 ml. cells contained 0.0017 mole of uranyl oxalate and 0.0040 mole of oxalic acid per liter of solution, and for the 42 ml. cells it was half this strength.

Light fluxes were determined at the beginning, middle and end of each day of work or more often if the light flux was believed to be varying more than 5%. The duration of each photolysis was measured to the nearest second. Up to 20% of the oxalate and 16% of the ceric concentrations were destroyed by photolysis.

The photochemical data are given in terms of the quantum yield, ϕ, of the reaction, *i. e.*, the moles of ceric perchlorate reduced to cerous perchlorate per mole of light quanta absorbed only by the ceric perchlorate. The pertinent data are given in Table II. $\phi_{gross} = V\Delta c_4/E$, $\phi = \phi_{gross}(1730\ c_4 + 750\ c_3)/1730\ c_4$, $\phi^* = \phi_{gross}(1730\ c_4 + 750\ c_3)/750\ c_3$. V is the volume in liters of the solution irradiated, Δc_4 is the change in the molar concentration of the ceric perchlorate produced by the irradiation, and E is the fraction of an einstein (6×10^{23} quanta) of light of λ, 254 mμ absorbed by the solution irradiated. The starred values refer to cerous instead of ceric perchlorate.

The values given in Table II for c_3, c_4 and the perchloric acid concentration are the average values during photolysis. The symbol c_4^0 refers to the value of concentration of ceric perchlorate in the unphotolyzed sample. The number in parentheses following the gross quantum yield indicates the number of expts upon which the values in that row are based. The column headed 10^6 E/min. gives the average light flux of λ 254 mμ incident upon the solutions irradiated; in all cases except expt. 1, this value also equals the light flux absorbed by the solution.

In expt. 1, the irradiation of the perchloric acid produced no detectable substances which either oxidized ferrocyanide or reduced permanganate in dilute sulfuric acid.

In two sets of experiments with a solution like that used in expt. 5, ϕ gross remained constant within 4% when the light intensity was changed 1/3.7 by dimming the lamp by means of a variac in the lamp circuit.

Two different methods were employed to change the concentration of cerous perchlorate. In expts. 11 and 14, appropriate amounts of the ceric perchlorate solution in which c_4/c_3 was about three were reduced with hydrogen peroxide free of preservative until c_4 equalled about 0.012. In all the other expts. appropriate amounts of the ceric and cerous stock solutions B and C were mixed. Both methods produced the same results.

The effect of cerous perchlorate upon the reaction is shown in Fig. 1. A decrease in the quantum yield, ϕ, is seen to be produced by an increase in the concentration of cerous perchlorate, *i. e.*, a decrease in the ratio of ceric to cerous perchlorate when other variables are held constant. Cerous perchlorate absorbs ultraviolet light of λ 254 mμ but since ϕ is based upon the light of this wave length absorbed only by the ceric perchlorate, the value of ϕ would have remained unchanged if the cerous perchlorate acted only as an inner filter. The line passing through the data is based on the hypothesis that the cerous perchlorate deactivates the photon activated ceric ions.

The line in Fig. 1 was determined by a plot of $1/\phi$ *vs.* c_3. The data on such a plot fall on a straight line within the limits of error. The line

(5) L. J. Heidt, *Science*, **90**, 472 (1939).

(6) (a) W. G. Leighton and G. S. Forbes, THIS JOURNAL, **52**, 3139 (1930); see also (b) L. J. Heidt, *J. Phys. Chem.*, **40**, 624 (1942).

TABLE II

GROSS AND NET QUANTUM YIELDS AT 23 ± 3° FOR THE PHOTOLYSIS OF CERIC AND CEROUS PERCHLORATES IN 1.03 ± 0.03 *M* PERCHLORIC ACID AT IONIC STRENGTHS OF 1.1 ± 0.2, BY LIGHT OF λ 254 mμ

Expt.	c_3	c_4	c_4/c_3	Cell vol., l.	Min.	Δ_{c_4}/c_4^0	$10^6 E$/min.	ϕgross	ϕ
1	0.00000	0.00000	0.00000	0.011	1020	0.00000	5.9	0.00000(2)	0.0000
2	.00045	.00123	2.72	.042	9.0	.162	25.6	.040 (2)	.0464
3	.00102	.00234	2.30	.042	8.0	.125	26.4	.062 (2)	.0736
4	.00207	.00465	2.25	.042	6.0	.0794	28.4	.095 (2)	.113
5	.00358	.00987	2.76	.042	3.3	.0655	71.3	.118 (3)	.136
6	.00357	.01088	3.04	.011	15.0	.0795	6.01	.110 (2)	.125
7	.00285	.0106	3.72	.011	15.5	.129	8.07	.128 (4)	.143
8	.00696	.01638	2.35	.011	25.0	.0595	3.62	.122 (2)	.145
9	.00637	.01105	1.73	.011	15.0	.0627	5.7	.092 (2)	.115
10	.00655	.01088	1.66	.011	20.0	.0887	6.6	.084 (2)	.106
11	.0135	.0113	0.835	.042	9.0	.025	29.3	.046 (2)	.070
12	.01502	.01113	.74	.011	15.0	.0505	10.1	.042 (2)	.066
13	.0340	.0112	.33	.011	30.0	.0212	7.1	.0124 (2)	.0287
14	.0540	.0120	.222	.042	15.0	.01335	36.1	.0125 (2)	.0369
15	.00238	.00012	.0050	.011	815	.0096*	11.2	.00029(2)	.00029*
16	.0098	.000196	.0020	.011	1033	.0093*	10.9	.00038(2)	.00038*
17	.0394	.000401	.0012	.011	1307	.00202*	10.4	.00065(1)	.00065*
18	.0792	.000244	.000307	.011	1295	.000613*	12.1	.00034(2)	.00034*

intercepts the $1/\phi$ axis at 5 ± 0.2 and has a slope, $(1/\phi)/c_3$, of 670 ± 50; hence $1/\phi = 5 + 670\ c_3$ and $\phi = 1/(5 + 670\ c_3)$ for these data.

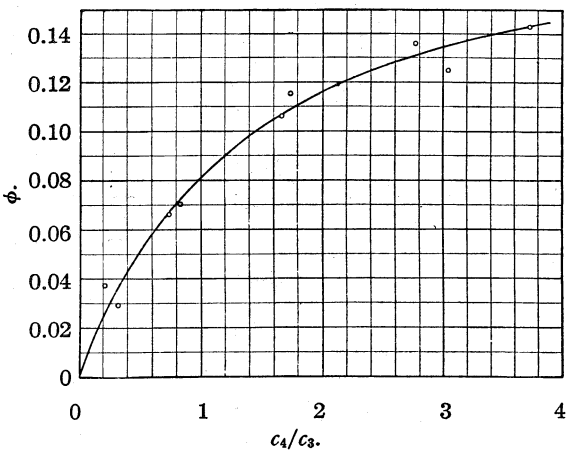


Fig. 1.—c_2 = 1.03 ± 0.003, c_4 = 0.0110 ± 0.00045, μ = 1.2 ± 0.1.

The possibility that the changes in ϕ are produced by changes in the light flux absorbed by the ceric perchlorate is eliminated by the finding noted above that ϕ did not change when the light intensity was changed several-fold while other variables were held constant.

There remains, however, the possibility that the quantum yields, ϕ, are decreased by cerous ions because the light absorbed by them causes them to be oxidized to ceric ions. The data in expts. 15, 16, 17 and 18 show that this reaction does occur and that the quantum yield, ϕ^*, of the reaction is about 0.001 in 0.06 molar cerous perchlorate. This value of ϕ^* is, however, less than 1% of the total decrease of 0.12 produced in ϕ by this concentration of cerous perchlorate in 0.011 molar ceric perchlorate, so the main effect of the cerous ion is to deactivate ceric ions. The decrease of 0.12 in ϕ is obtained from Fig. 1 where ϕ drops from 0.15 to 0.03 when c_4/c_3 decreases from 4 to 0.2 while the concentration of ceric perchlorate remains at 0.011 molar.

The photochemical oxidation of cerous to ceric perchlorate in expts. 15, 16, 17 and 18 was made evident by the orange color of ceric sulfate produced in the photolyzed but not in the unphotolyzed solutions when they were treated with concentrated sulfuric acid in the course of the analysis of them for ceric ions. The intensity of the orange color which developed in the solutions was directly proportional to the amount of ferrous ion required to bleach them. We did not test for hydrogen produced by the photoxidation of the cerous ions, but it is worth noting that when $\epsilon_3 c_3 \phi^* = \epsilon_4 c_4 \phi$, the amounts of cerous and ceric perchlorates in the solution being irradiated would remain unchanged while water was being broken down into oxygen and hydrogen.

Figure 2 shows that an increase in the net quantum yield ϕ accompanies an increase in c_4. The increase occurs in spite of an accompanying increase in c_3 since in the case of these data c_4/c_3 is nearly constant at 2.8. It is not caused by the increase in the concentration of photon activated ceric perchlorate because ϕ was found not to depend upon the light intensity. The line passing through the data is based on the hypothesis that only light absorbed by ceric dimers produces the measured reaction. The dependence of ϕ upon c_4 and c_3 is then given by the equation $\phi = y/(a + bc_3)$ where y is the fraction of the ceric ions dimerized and a and b are constants. $y/(1 - y)^2 = 2K_p c_4$ where K_p is a constant under the prevailing conditions. The last equation for ϕ is repre-

TABLE III

MOLAL POTENTIALS E_1^0 AT 25° FOR THE REACTION $CeOH^{+3} + {}^1/_2H_2 = Ce^{+3} + H_2O$

Calculated from the data of Sherrill, King and Spooner at a perchloric acid concentration of 0.8 M. The values of $^*E_1^0$ have allowed for the dimerization of ceric ions. The symbols are explained in the text.

c_2	10^3c_4	c_4/c_3	$10^3\ {}^0c'_m$	$10^3\ c'_m$	E	E_f^0	E_1^0	$^*E_1^0$
0.8024	8.436	5.4531	4.827	2.884	1.73219	1.68301	1.7023	1.7155
.8036	6.572	1.9312	3.763	2.549	1.70970	1.68721	1.7072	1.7167
.8038	5.698	1.3351	3.263	2.319	1.70110	1.68810	1.7080	1.7168
.8048	3.968	0.6626	2.273	1.742	1.68456	1.68958	1.7095	1.7163
.8075					Extr.	1.6930	1.7128	

sented by the line in Fig. 2 when K_p equals 50, and a/y and b/y equal 5 and 670, respectively, from the data in Fig. 1.

The value of K_p was estimated by the method of successive approximations. This involved evaluating c_4 for various values of y and K_p. Next, a and b were evaluated for the values of y at $c_4 = 0.011$. Then ϕ was calculated for the values of c_4 covered by the data. Values of K_p equal to 50 ± 10 fit the data within the limits of error, but when K_p is set equal to 100 or 25 the calculated values of ϕ fall well outside the limits of error especially at the lower values of c_4.

A value of 50 for K_p gives a value of 0.398 for y at c_4 equal to 0.011 and the corresponding values of a and b are 2 and 270, respectively.

The tendency of the observed values of ϕ to fall above the line in Fig. 2 at the highest concentrations of ceric perchlorate suggests that photosensitive trimers and higher polymers of ceric ions are also formed in these solutions.

The nature of ceric monomers in perchloric acid has been postulated by Professor M. S. Sherrill[3] based on e. m. f. data on these solutions. The formulas postulated are $CeOH^{+3}$ and $Ce(OH)_2^{+2}$. The equilibrium constant for the reaction $CeOH^{+3} + H_2O = Ce(OH)_2^{+3} + H^+$ was found to be 0.6. A slight extension of this idea suggests that the formulas of the dimers are Ce–O–Ce^{+6}, HOCe–O–$CeOH^{+4}$ and Ce–O–$CeOH^{+5}$. The formation of the dimers would be expected to take place by splitting out water from the hydroxyls attached to separate ceric monomers. The same kind of reaction would also produce trimers and higher polymers involving the $Ce(OH)_2^{+2}$ ion.

The formation of ceric dimers in ceric perchlorate solutions is also supported by the e. m. f. measurements of M. S. Sherrill, C. B. King and R. C. Spooner.[3] The solutions in their Run III are nearest in composition to our solutions; the main difference is that their perchloric acid concentration, c_2, was 0.8 compared to 1.03 M in our work.

The e. m. f. measurements were made on the cell H_2, $HClO_4$ at c_1/c_2, c_3, c_4 Pt. This cell can be thought of as two cells connected in series, namely, cell I, H_2, c_1/c_2, H_2, and cell II, H_2, c_2/c_9, c_3, c_4 Pt. The first of these cells has a liquid junction potential $E_L = (2T_{H^+} - 1)\ 0.05915 \log (c_1\gamma_1/c_2\gamma_2)$ or very nearly $E_L = (0.6744)\ 0.05915 \log (c_1/c_2) = 0.03989 \log (c_1/c_2)$ as calculated by S. K. S. The observed e. m. f. values, E, were corrected to hydrogen at 1 atm. and 25°. Table III gives the data for their Run III.

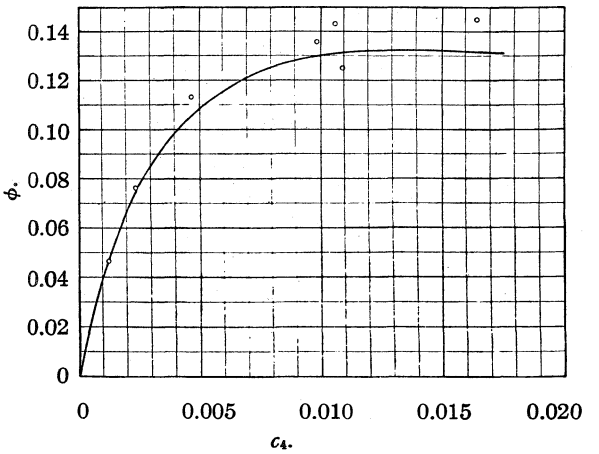


Fig. 2.—$c_2 = 1.03 \pm 0.3$, $c_4/c_3 = 2.80 \pm 0.26$, $\mu = 1.1 \pm 0.1$.

The formal potential E_f^0 ($= E - 0.05915 \log (c_4/c_1c_3) - E_L$) includes the liquid junction potential E_L' produced by c_3 and c_4 in c_2 of Cell II and in addition a term involving the activity coefficients of the various species in the solutions.

Constant values of 1.7134 ± 0.0004 volts were obtained by S. K. S. for the molal potential E_1^0 of the reaction $CeOH^{+3} + {}^1/_2H_2 = Ce^{+3} + H_2O$ when c_2 is between 0.54 and 1.6 M and $c_4 = {}^0c'_m + {}^0c''_m$, ${}^0c''_m/{}^0c'_m = 0.6/c_2$ and $E_1^0 = E_f^0$(extr.) + $0.05915 \log (c_4/c_2{}^0c'_m)$. The symbols ${}^0c'_m$ and ${}^0c''_m$ represent the concentrations of $CeOH^{+3}$ and $Ce(OH)_2^{+2}$, respectively, when there is no dimerization. The symbol E_f^0(extr.) represents the value obtained for E_f^0 when extrapolated to $c_4/(c_3 + c_4)$ equal to zero. The value of E_1^0 calculated from E_f^0 at any actual value of c_4 is always less than the value calculated from E_f^0 (extr.), and it increases as c_4 decreases as shown in Table III. This trend is eliminated when allowance is made for the dimerization of ceric ions. The values of E_1^0 corrected for this effect are the $^*E_1^0$ values in Table III.

$$^*E_1^0 = E_f^0 + 0.05915 \log (c_4/c_2c'_m)$$

TABLE IV

THE VALUES OF $*E_1^0$ FOR THE SEPARATE E. M. F. RUNS MADE BY SHERRILL, KING AND SPOONER. THE AVERAGE VALUE OF $*E_1^0$ IS 1.7174; IT IS 1.7169 WHEN RUN V IS OMITTED

Run	Expts.	c_2	c_4	$*E_1^0$
V	6	0.1973 ± 0.0018	0.0010 to 0.0093	1.72074 ± 0.00085
IV	5	.4787 ± .0016	.0010 to .0086	1.71793 ± .00072
VII	2	.5325 ± .0015	.0032 to .0072	1.71853 ± .00057
VIII	4	.5347 ± .0011	.0009 to .0055	1.71584 ± .00041
III	4	.8036 ± .0007	.0040 to .0084	1.71633 ± .00043
IX	3	1.2977 ± .0007	.0010 to .0045	1.71530 ± .00038
II	2	1.6304 ± .0007	.0032 to .0048	1.71664 ± .00024
I	2	2.3841 ± .0014	.0048 to .0066	1.71751 ± .00026

where

$$c_4 = c'_m + c''_m + 2c_p$$
$$c'_m + c''_m = \sqrt{c_p/50}, \text{ and}$$
$$c'_m/c''_m = 0.6/c_2$$

The values of $*E_1^0$ for the separate runs in the order of increasing acid strength, c_2, are given in Table IV.

The average value of $*E_1^0$ for Run V is significantly higher than the other values and the ionic strength, μ, is the lowest (μ equals 0.26 compared to 0.5 to 2.4 in the other runs). An increase in the value of $*E_1^0$ would be produced if the activity of $CeOH^{+3}$ decreased with μ. This can be seen by comparing the values of E_1^0 and $*E_1^0$ in Table III. The higher values of $*E_1^0$ in Table III are associated with the lower values of the activity of the $CeOH^{+3}$ which resulted from the correction for the dimerization. A decrease in μ favors the hydrolysis of $CeOH^{+3}$ but it also favors a decrease in the dimerization. The two effects thus tend to cancel each other and this is supported by the lack of any trend in the values of $*E_1^0$ in Table IV with changes in μ between 0.5 and 2.4.

Empirically, the values of $*E_1^0$ depend linearly upon the logarithm of $(c_2 + 3c_3 + 4c_4)/c_2$, as is shown in Fig. 3. The equation for the line in the Fig. is $*E_1^0 = (1.71545 \pm 0.00026) + (0.06185 \pm 0.00594) \log [(c_2 + 3c_3 + 4c_4)/c_2]$. The probable deviation of any value of $*E_1^0$ from the line is 0.00082.

The molal oxidation potential E_1^0 of the electrode reaction (1) $CeOH^{+3} + H^+ + E^- = Ce^{+3} + H_2O$ obtained by the above method is 1.7155 instead of 1.7134 volts obtained from E^0_f(extr.).

The molal oxidation potentials of the other

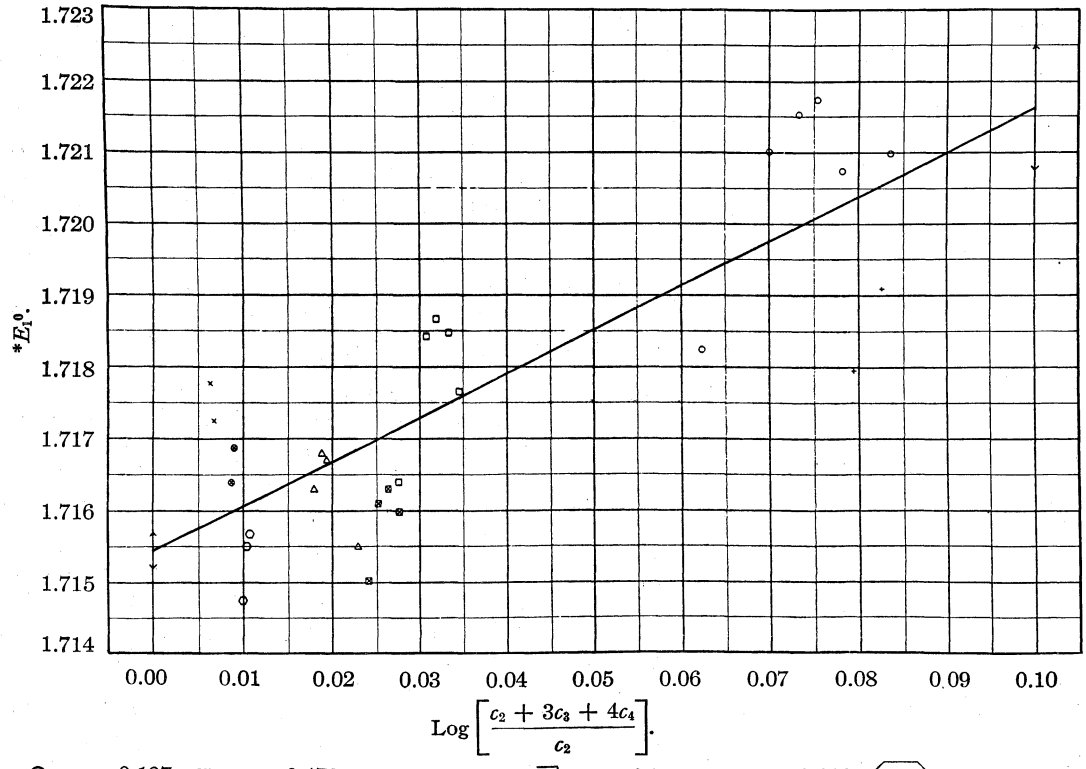


Fig. 3.—○, $c_2 = 0.197$; □, $c_2 = 0.479$; +, $c_2 = 0.532$; ⊠, $c_2 = 0.535$; △, $c_2 = 0.803$; ⬭, $c_2 = 1.297$; ⊗, $c_2 = 1.630$; ×, $c_2 = 2.384$.

TABLE V

CONCENTRATIONS OF THE VARIOUS CERIC SPECIES PRESENT AT 25° OVER THE RANGE OF CONCENTRATIONS COVERED BY THE QUANTUM YIELD MEASUREMENTS

$c_2 = 1.03$; $c_p/c_m^2 = y/(1-y)^2 2c_4 = 50$; $c'_m = (CeOH^{+3}) = c_m/(1 + 0.6/c_2) = c_m/1.583$; $c''_m = (Ce(OH)_2^{+2}) = c_m - c'_m$; $c_{1p} = (Ce—O—Ce^{+6}) = 50(c'_m)^2$; $c_{2p} = (HOCe—O—Ce—OH^{+4}) = 50(c''_m)^2$; $c_{1,2p} = (Ce—O—Ce—OH^{+5}) = 100 c'_m c''_m$

c_4	y	$10^3 c_p$	$10^3 c_m$	$10^3 c'_m$	$10^3 c''_m$	$10^5 c_{1p}$	$10^5 c_{2p}$	$10^5 c_{1,2p}$
0.000102	0.010	0.00051	0.101	0.0638	0.0372	0.020	0.00692	0.024
.00101	.085	0.043	0.924	0.583	0.341	1.7	0.58	1.99
.0102	.385	1.96	6.23	3.94	2.29	78	26	91
.0149	.450	3.35	8.20	5.18	3.02	134	46	156

electrode reactions on the above basis are:

(2) $Ce(OH)_2^{+2} + 2H^+ + E^- = Ce^{+++} + 2H_2O$; $E_2^0 = 1.7286$ volts

(1p) $0.5\ Ce—O—Ce^{+6} + H^+ + E^- = Ce^{+++} + 0.5\ H_2O$; $E_{1p}^0 = 1.6652$ volts

(2p) $0.5\ HO—Ce—O—Ce—OH^{+4} + 2H^+ + E^- = Ce^{+++} + 1.5\ H_2O$; $E_{2p}^0 = 1.6783$ volts

(1,2p) $0.5\ Ce—O—CeOH^{+1} + 1.5H^+ + E^- = Ce^{+++} + H_2O$; $E^0_{(1,2p)} = 1.6628$ volts

$$E_2^0 = E_1^0 - 0.05915 \log 0.6$$
$$E_{1p}^0 = E_1^0 - 0.05915 \log \sqrt{K_{1p}}$$
$$E_{2p}^0 = E_2^0 - 0.05915 \log \sqrt{K_{2p}}$$
$$E_{1,2p}^0 = (E_1^0 + E_2^0)/2 - 0.05915 \log \sqrt{K_{1,2p}}$$
$$K_{1p} = K_{2p} = K_{1,2p}/2 = 50$$

within the limits of error of either the quantum yield measurements or the e. m. f. data.

The compositions of the ceric perchlorate solutions over the range covered by the quantum yield measurements are given in Table V.

The following reactions in addition to the equilibria given above account for the quantum yields.

K_p $\quad 2c_m = c_p$

k_I $\quad c_p + h\nu = c_p^*$

k_1 $\quad c_p^* + H_2O = 2c_3 + 2H^+ + {}^1/_2O_2$

k_2 $\quad c_p^* + c_3 = c_p + c_3$

k_3 $\quad c_p^* + S = c_p + c_3$

c_m is the concentration of all the ceric monomers
c_p is the concentration of all the ceric dimers
S is any substance except c_3; the solutions do not fluoresce
k_1, k_2, and k_3 are the rate constants for the corresponding reactions

The reactions give a maximum quantum yield of two and the following equation for ϕ

$$\phi = 2yk_1/(k_1 + k_3S + k_2c_3)$$

or

$$\phi = y/(a + bc_3) \text{ at constant ionic strength}$$
$$a = (k_1 + k_3S)/2k_1 = 2.0$$
$$b = k_2/2k_1 = 270$$

Thus the deactivation of the photon-activated ceric dimer by cerous ions is $2 \times 55.5 \times 2.70$ or 30,000 times more efficient at 25° than the reduction of the dimer by water. The remainder of the environment, however, reacts with the photon-activated dimer little more efficiently ($k_3S/k'_1 \cdot (H_2O) = 3$) than the measured photochemical reaction.

Our initial interest in the photochemistry of the ceric perchlorate system was to learn something about the way in which water is photochemically oxidized to oxygen since this oxidation is a fundamental step in the photosynthetic process in living organisms. The work above shows that light absorbed by ceric monomers has a negligible effect upon the reaction. This implies that divalent oxygen is not photochemically oxidized unless the photon activated ceric unit can absorb two electrons from the oxygen. There is no evidence for the intermediate formation of peroxide in the photochemical oxidation of divalent oxygen either in the present research or when the photon activated unit is the persulfate anion,[7] $S_2O_8^=$. In the latter case all tests for the photochemical formation of hydrogen peroxide along with the oxygen were negative although hydrogen peroxide is made thermally from persulfates.

Summary

1. Photolysis of ceric perchlorate in perchloric acid has been measured quantitatively in ultraviolet monochromatic light of λ 254 mμ.

2. Net quantum yields, ϕ, based on the light absorbed by the ceric perchlorate depend on the concentrations of cerous, c_3, and ceric perchlorates. The dependence is given by the equation $\phi = y/(a + bc_3)$ where y is the fraction of ceric ions dimerized and a and b are constants. ϕ does not depend upon the light intensity, and is negligible for ceric monomers.

3. The dimerization of ceric ions is also supported by e. m. f. measurements on solutions of cerous and ceric perchlorates in perchloric acid, but it is not revealed by measurements of the extinction coefficients of the solutions in the region of λ 254 mμ.

4. The molal oxidation potentials of the various cerium species are calculated.

5. Cerous ions were found to be photochemically oxidized to ceric ions.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 24, 1948

(7) L. J. Heidt, *J. Chem. Phys.*, **10**, 297 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Near Ultraviolet Absorption Spectra of Monosubstituted Benzenes: the Effect of Certain Meta Directing Groups[1]

BY W. F. HAMNER AND F. A. MATSEN

The effect of electron donating (*i.e.*, ortho-para directing) groups on the near ultraviolet absorption spectra of monosubstituted benzenes has been extensively investigated[2,3] and the following trends established: the greater the extent of migration into the ring the longer the wave length of the O–O band, the higher the intensity of the spectrum as a whole and of the substitution subspectrum (A, A + C, etc.)[4b] relative to the benzene subspectrum (A + B, A + B + C, etc.).[4a]

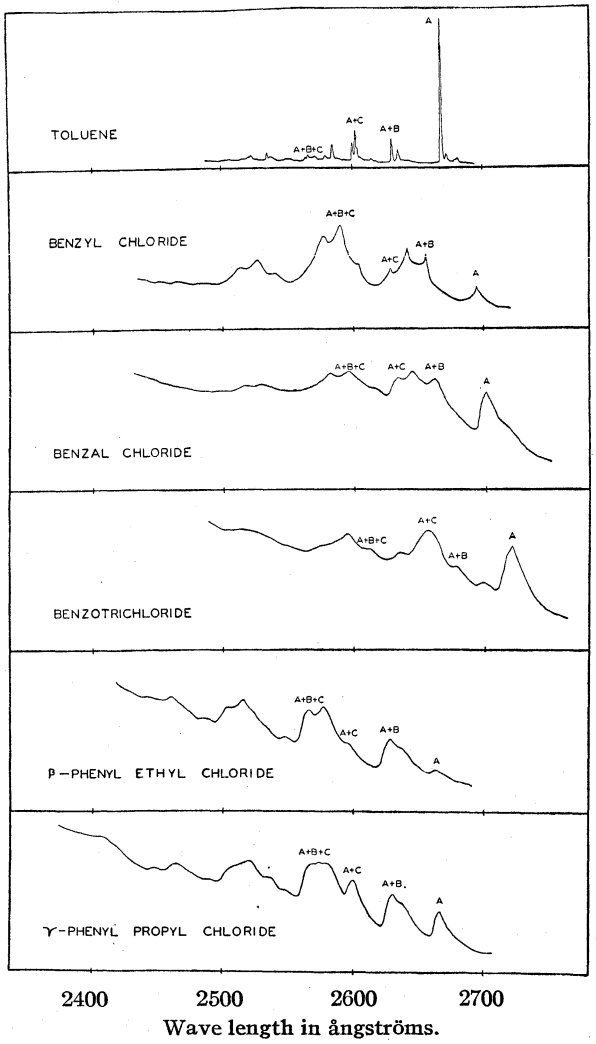


Fig. 1.—Microphotometer tracings of the vapor spectra of chloroalkyl substituted benzenes; intensity scale varies from compound to compound.

It was of interest therefore to investigate the spectra of electron attracting (*i.e.*, meta-directing) groups. According to the data of Flurscheim and Holmes[5] the per cent. meta compound formed upon nitration is as follows: toluene, 4.4; benzyl chloride, 11.6; benzal chloride, 32.8–33.3; benzotrichloride, 48.3–48.6. This is attributed to the increasing migration of electrons out of the ring due to the progressive replacement of the hydrogen atoms by strongly electronegative chlorine atoms. This series presents a gradual transition from ortho-para toward meta direction.

Experimental

The benzyl chloride, benzal chloride and benzotrichloride were donated by the Hooker Electrochemical Company, the β-phenylethyl chloride and γ-phenylpropyl chloride were Eastman Kodak Co. white label grade; the compounds were subjected to vacuum distillation or recrystallization to insure purity. The refractive indices of the fractions used are:

Compound	Temp., °C.	n_D
$C_6H_5CH_2Cl$	17.4	1.5391
$C_6H_5CHCl_2$	19.4, 20.0	1.55155, 1.55121
$C_6H_5—CCl_3$	19.2, 20.0	1.55841, 1.55806
$C_6H_5—CH_2CH_2Cl$	20.0	1.52760
$C_6H_5—CH_2CH_2CH_2Cl$	20.0	1.52237

The spectra of the vapor were photographed in the first order of a three-meter 15,000 line per inch, Eagle mounted grating spectrograph using a 2.5 kva hydrogen discharge tube. The cells were all-quartz connected by a side-arm to a reservoir which contained the sample, the temperature of which controlled the vapor pressure in the cell. The plates were scanned on a Leeds and Northrup microphotometer and the wave lengths determined by comparison with standard iron lines.

The solution spectra were obtained in cyclohexane solution with a Beckman quartz spectrophotometer.

Results

Microphotometer tracings of the vapor spectra are given in Fig. 1 along with that for toluene. The intensities of the spectra are not comparable since conditions were chosen to give maximum contrast. The chloroalkylbenzene spectra are more diffuse than that of toluene which appears to be due to the broadening of the rotational structure and to the interaction of a dissociative electronic level.

From Fig. 1 it will be seen that the substituent subspectrum becomes relatively more important as the number of chlorine atoms on the α atom of

(1) Presented at the 112th meeting of the American Chemical Society New York, N. Y., September 15–19, 1947.

(2) A. L. Sklar, *Rev. Modern Phys.*, **14**, 232 (1942).

(3) F. A. Matsen, W. W. Robertson and R. L. Chouke, *Chem. Rev.*, **41**, 273 (1947).

(4) (a) The benzene subspectrum consists of bands containing the 500 cm.$^{-1}$ (B) the mode which makes the benzene spectrum allowed. (b) The substitution subspectrum consists of the additional bands which appear in substituted benzenes: 0 − 0(A), 0 + 900 (A + B) etc.

(5) Flurscheim and Holmes, *J. Chem. Soc.*, 1607 (1928).

the substituent is increased and as the chlorine atom is substituted successively β, γ and α.

The wave lengths, the relative intensities and assignments in terms of excited state fundamentals for the band maxima are given in Table I. These spectra, due to their diffuseness, exhibit only a few of the fundamentals and combination bands exhibited by more discrete spectra.[6] For β-phenylethyl chloride and γ-phenylpropyl chloride the 700 cm.$^{-1}$ fundamental is lost on the shoulder of the stronger 900 cm.$^{-1}$ fundamental but does appear in combinations. The wave numbers of the zero–zero bands lie in the following order: β-phenylethyl chloride > γ-phenylpropyl chloride > toluene > benzyl chloride > benzal chloride > benzotrichloride.

The solution data[7] are given in Fig. 2. The spectra of β-phenylethyl and γ-phenylpropyl chloride lie so close to toluene that they were not included on the graph. The order of the intensities of absorptions are in the order benzotrichloride > benzal chloride > benzyl chloride $\cong$ toluene > γ-phenylpropyl chloride > β-phenylethyl chloride.

TABLE I

WAVE LENGTHS, RELATIVE INTENSITIES, AND PROBABLE ASSIGNMENTS OF MAXIMA

Å.	Cm.$^{-1}$	Relative intensity	Probable assignment
		Benzyl chloride	
2694	37,110	MS	0 − 0
2655	37,650	S	0 + 540
2641	37,860	S	0 + 750
2628	38,040	M	0 + 930
2604	38,390	W	0 + 540 + 750
2589	38,620	VS	0 + 2 × 750; 0 + 540 + 930
2577	38,790	S	0 + 750 + 930
2540	39,360	W	
2526	39,570	W	
2515	39,760	W	
		Benzal chloride	
2701	37,020	VS	0 − 0
2661	37,570	MS	0 + 550
2644	37,810	MS	0 + 790
2634	37,950	S	0 + 930
2617	38,200	VW	
2596	38,510	M	0 + 550 + 930
2582	38,720	M	0 + 790 + 930
2522	39,640	M	
		Benzotrichloride	
2721	36,740	VS	0 − 0
2629	37,040	W	0 + 300
2678	37,340	VW	0 + 600
2656	37,640	S	0 + 900
2635	37,940	W	0 + 300 + 900
2613	38,250	W	0 + 600 + 900
2595	38,520	W	0 + 2 × 900
		Phenylethyl chloride	
2662	37,560	W	0 − 0
2628	38,040	S	0 + 480
2595	38,520	W	0 + 960
2576	38,810	VS	0 + (730) + 480
2564	38,980	VS	0 + 480 + 960
2547	39,250	W	0 + (730) + 960
2514	39,760	MS	
2487	40,190	W	
2461	40,630	W	
		Phenylpropyl chloride	
2664	37,530	MS	0 − 0
2638	38,040	S	0 + 510
2598	38,480	MS	0 + 950
2578	38,780	VS	0 + (740) + 510
2564	38,980	VS	0 + 510 + 950
2535	39,440	W	0 + 2 × 950
2516	39,730	M	
2416	40,600	M	
2405	41,560	W	

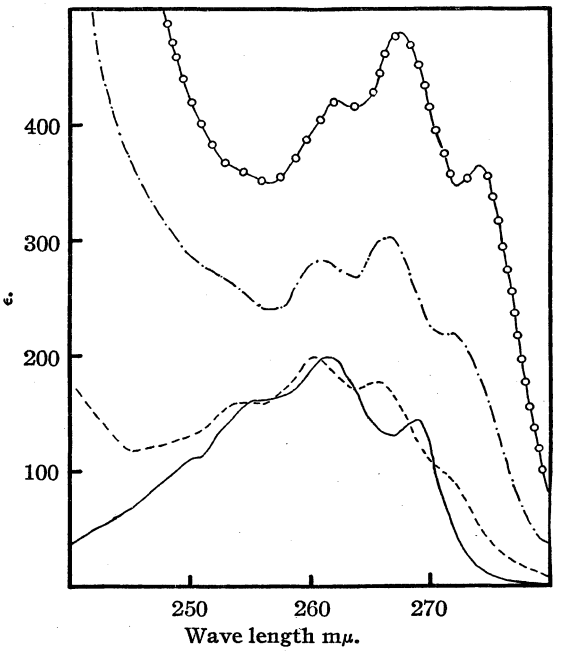


Fig. 2.—Ultraviolet absorption spectra in solutions of cyclohexane: —, toluene; ---, benzyl chloride; -·-·-, benzal chloride; -o-o-o, benzotrichloride.

Conclusions

The migration of electrons out of the ring has qualitatively the same effect on the spectra as the migration into the ring.

The intensities of absorption and the importance of the substitution subspectrum are functions of the transition probability which is very low for benzene due to the hexagonal symmetry of the electron distribution. It has been proposed by Sklar[2] that the hexagonal symmetry is distorted by migration of electrons into the ring due to the substitution of ortho–para directing groups. This research shows that the distortion is also accom-

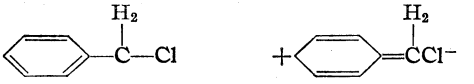
(6) See footnote 3 for particular references.

(7) See also L. J. Anderson and S. L. Linden, THIS JOURNAL, **69**, 2091 (1947).

plished by the migration of electrons out of the ring. Very qualitatively it appears that the migration in for toluene is of the same order as the migration out for benzyl chloride.

The position of the zero–zero bands is a function of the difference of zero point energies in the ground and excited state and the height of the excited state above the ground state. The former is influenced by the mass of the substituent and appears to become smaller as the mass of the substituent increases.[3]

The height of the excited above the ground state may be discussed from the point of view of resonance between valence structures or of molecular orbitals. From the former, there is resonance involving structures like the following



which will lower the excited state relative to the ground state. The substitution of more chlorine atoms produces more ionic structures with a resultant increased lowering of the excited state. From the molecular orbital point of view the withdrawal of electrons by the electronegative chlorine atoms tends to leave vacant a p orbital on the carbon atom. The molecule then possesses seven

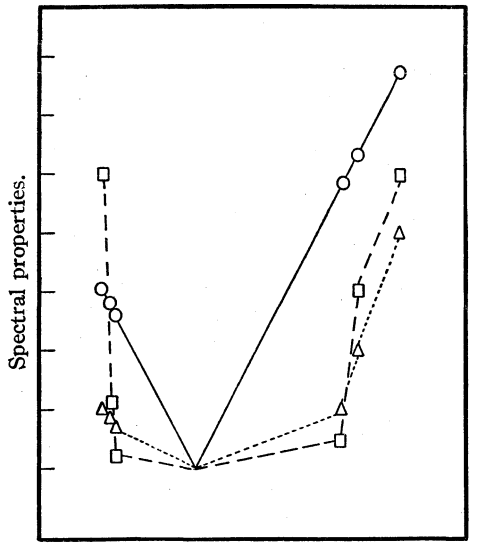
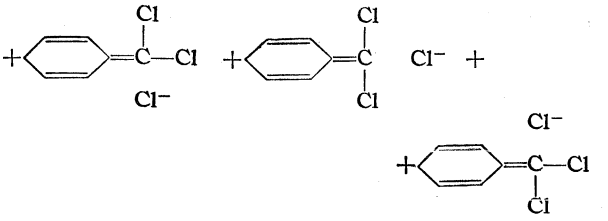


Fig. 3.—Spectral properties and postulated electron migration: The position of the zero–zero bands (O), the estimated intensity of the spectrum compared to that of benzene (△), and the estimated ratio of intensity of the substitution subspectrum to intensity of the benzene subspectrum (□) are plotted as ordinates. From left to right the points correspond to compounds toluene, γ-phenylpropyl chloride, β-phenylethyl chloride, benzyl chloride, benzal chloride and benzotrichloride. The abscissa is a scale of electron migration so chosen as to make the points (O) fall on straight lines.



interacting p orbitals in which six π electrons move. This system may be compared to aniline and phenol which also possess seven interacting orbitals; however, eight electrons move in these orbitals. The seven orbital–six electron system may be shown to be more stable and to possess a relatively lower-lying excited state than a six-orbital–six electron system accounting for the observed spectral shifts.

The substitution of chlorine for hydrogen atoms reduces hyperconjugation, the principal mechanism by which the methyl group sends electrons into the ring. The direction of migration is reversed on the replacement of one hydrogen atom by a chlorine as may be seen by Fig. 3.

From left to right along the abscissa of Fig. 3 there is progression from migration into the ring to migration out of the ring. At some point there must be zero migration. Since the right side goes up continuously it seems necessary to locate the zero migration point between toluene and benzyl chloride; that is the direction of migration is reversed by the replacement of one hydrogen atom by a chlorine atom. This is substantiated by the spectrum of β-phenylethyl chloride which has a weaker substitution spectrum, a lower intensity and a zero–zero band which lies farther from the visible than either toluene or benzyl chloride. Thus the shift of the chlorine atom from an α- to a β-carbon atom reduces its effect enough to place β-phenylethyl chloride near the minimum of the curve in Fig. 3. In γ-phenylpropyl chloride the effect of the chloride is so reduced that the hyperconjugation with the ring becomes predominating which places the compound up on the left branch of the curve.

Assuming that in benzyl chloride the migration is out of the ring, the problem is raised as to why the per cent. meta formed is not higher than the 11.6% reported. If the substituent had no effect, 40 per cent. meta should be formed; if the substituent withdrew electrons a still higher per cent. meta should be formed. Several suggestions present themselves: (1) there is a permanent positive inductive (non-resonance) effect associated with carbon which will always be ortho–para directing, (2) there are polarizing effects in the substitution reaction of the kind discussed by Pauling and Wheland[8] which are not detected spectroscopically.

Summary

1. The spectra of benzyl, benzal, benzotri-,

(8) Wheland, THIS JOURNAL, 64, 900 (1942); Pauling and Wheland, *ibid.*, 57, 2086 (1935).

β-phenylethyl and γ-phenylpropyl chloride have been obtained in the vapor phase and in cyclohexane solution.

2. A theoretical discussion of the results is given.

AUSTIN, TEXAS RECEIVED JANUARY 14, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Relation between the Absorption Spectra and the Chemical Constitution of Dyes. XX. Induced Non-Coplanarity in Symmetrical Benzidine Dyes[1]

BY ROBERT J. MORRIS[2] AND WALLACE R. BRODE[2]

In an earlier paper in this series[3] an investigation was made on the separation of chromophores in disazo dyes by the introduction of insulating methylene, ethenylene and ethylene groups. This study was made on both symmetrical and unsymmetrical disazo dyes and from the data obtained it was shown that when two chromophores were separated by one or two methylene groups, the chromophores function almost as though they were in separate molecules. However, the frequency of each chromophore was slightly diminished by the presence of the other. This was considered due either to the mutual influence of the two chromophores or to added molecular weight. The closer the separated chromophores approached each other when directly connected, the greater their mutual effect. When the azo chromophores were connected by a well-defined conjugate system, each chromophore strongly influenced the electronic excitation of the other.

The observed shift of the principal absorption band to lower frequency caused by an increase in molecular weight of the compound was, however, of a low order of magnitude compared with the shift caused by the conjugation of chromophoric systems.

In azo dye structures, the conditions effecting the coplanarity of the dye molecule would also be expected to have considerable effect on their absorption spectra. As early as 1923, Ley and Rincke[4] made comparisons of the absorption spectra of planar *trans*-stilbene with *trans*-α-methylstilbene. Interpretation of their results indicated that the methyl group in the latter crowds an ortho hydrogen of the more remote benzene ring. Planarity was therefore inhibited, as was, in consequence, the resonance interaction between the two benzene rings. The unsubstituted benzidine nucleus has been shown to exhibit some steric inhibition to complete coplanarity because of the bond angles and distances involved in its structure.[5] Moyer and Adams[6] have shown that the compound 3,3′-diaminodimesityl, because of the steric effects of the methyl groups in the 2,2′,6,6′-positions, was definitely non-coplanar. It was further predicted that the characteristic effect of the conjugation of the biphenyl molecule on the absorption spectra would vanish for compounds possessing this inhibited structure. This hypothesis was supported by observations conducted by Pickett.[7] In this investigation it was shown that the absorption spectra of bimesityl was almost identical with that of mesitylene but differed significantly from biphenyl. Other examples of the effect of 2,2′-substitution on the absorption spectra of the biphenyl molecule have been recorded by Rodebush.[8] Jones[9] has also presented data and a general review on steric hindrance of resonance.

Experimental

The dyes prepared for this study were synthesized from intermediates of known purity by standard procedures for diazotization and coupling. The cresols used were available in grades of acceptable purity. Benzidine, 3,3′-dimethylbenzidine and 3,3′-dimethoxybenzidine obtained from Eastman Kodak Company were analyzed and shown to be of acceptable purity. The 2,2′-dimethyl[10] and 2,2′,6,6′[11]-tetramethyl benzidine derivatives were synthesized and purified before use.

All the dyes prepared were purified by repeated recrystallization from dilute acetic acid until a constant purity resulted. The analysis for the purity of all dye samples was accomplished by the use of a standardized titanium trichloride solution.

Absorption measurements were made by the use of a Beckman quartz spectrophotometer. The properly diluted samples were introduced into 1.00-cm. fused silica cells and their absorption spectra determined using the corresponding solvent as a reference solution. Readings were generally taken at 10 mμ intervals, although in some places determinations were made at closer intervals to increase the accuracy of the measurements. A dilution to 0.000015 *M* served for obtaining the complete absorption spectra of all the dyes measured. In neutral solu-

(1) Presented before the Organic Chemistry Division at the New York meeting of the American Chemical Society, September 17, 1947.

(2) Present address, (R. J. M.) Department of Chemistry, University of Nevada, Reno, Nevada; (W. R. B.) National Bureau of Standards, Washington 25, D. C.

(3) W. R. Brode and J. D. Piper, THIS JOURNAL, **57**, 135 (1935); **63**, 1502 (1941).

(4) H. Ley and F. Rincke, *Ber.*, **56**, 771 (1923).

(5) J. M. Robertson and I. Woodward, *Proc. Roy. Soc.* (*London*), **A142**, 333 (1933).

(6) W. W. Moyer and R. Adams, THIS JOURNAL, **51**, 630 (1929).

(7) L. W. Pickett, G. F. Walter and H. France, *ibid.*, **58**, 2296 (1936).

(8) B. Williamson and W. H. Rodebush, *ibid.*, **63**, 3018 (1941).

(9) L. A. Jones, *Chem. Reviews*, **32**, 1 (1943); *ibid.*, **63**, 1658 (1941); **67**, 2127 (1945).

(10) P. Jacobsen, *Ber.*, **28**, 2541 (1895).

(11) R. B. Carlin, THIS JOURNAL, **67**, 928 (1945).

tion this concentration was attained by the proper dilution of a 0.00006 *M* alcoholic solution (referred to as the stock solution) of the dye by use of additional 95% ethanol. For measurements in basic media, the final concentration of 0.000015 *M* was attained by dilution of the 0.00006 *M* stock with aqueous sodium hydroxide. Determinations in concentrated acid media were made by dilution of the stock solution to 0.000015 *M* with 12 *N* hydrochloric acid (concd. HCl). Absorption data on the dyes, after correction for salt and inert non-absorbing material as indicated by the analytical data, were recorded with molecular extinction as ordinates and frequency (fresnel) as abscissa. (fresnel = vibrations per sec. $\times 10^{-12}$ = wave number per cm. $\times$ speed of light in cm. per second, *i. e.*, $1/\lambda = \nu' = \nu/c$ where λ = wave length, ν' = wave number, ν = frequency and c = speed of light.) Molecular extinction (ϵ) is defined as $k \times$ molecular weight where k is the specific extinction. $k = E/cd$; where E = extinction, c = concn. in g. per l. and d = cell length in cm.

Discussion of Results

The curves obtained for these azo dyes show definite changes in the absorption spectra as a non-coplanar condition becomes established for the benzidine nucleus. This is evident by the shift of the absorption to higher frequencies with the establishment of these conditions. Such a shift is contrary to the expected change with the increasing molecular weight. Although a partial restriction to complete molecular conjugation has been previously reported for the diphenyl molecule because of the interference of the hydrogen atoms in the 2,2′,6,6′-positions, it is believed that the unsubstituted benzidine dyes possessing this structure show considerable conjugation through the 1,1′-bond. This was demonstrated by the distinct change in the absorption bands of these dyes when the relatively large, unreactive methyl groups are introduced in the 2,2′- and 2,2′,6,6′-positions on the benzidine nucleus. Figures 1, 2 and 3 show the definite shift in the absorption band with these molecular changes. The marked change in the absorption observed is undoubtedly

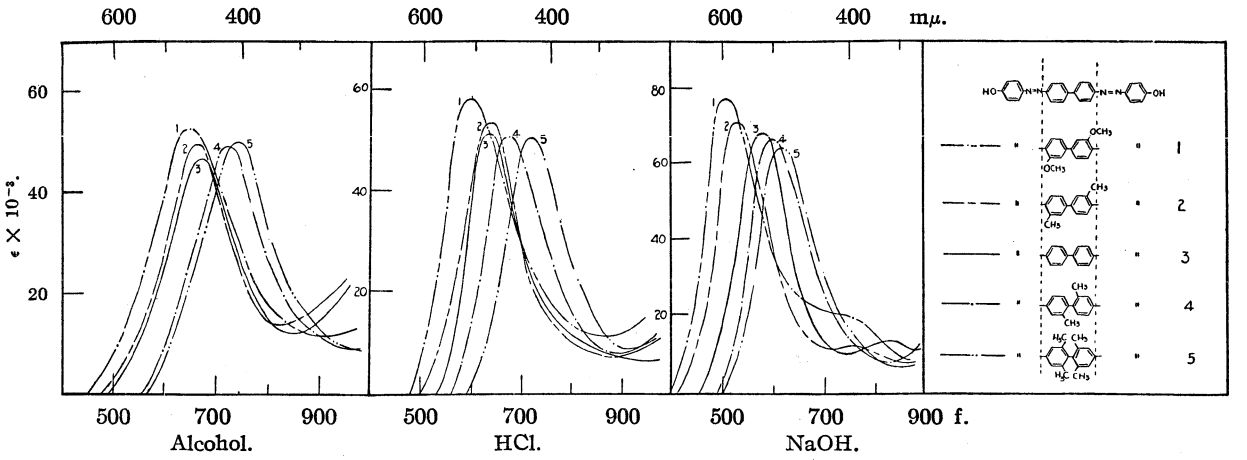


Fig. 1.—The absorption spectra recorded for the dyes prepared by tetrazotization and coupling benzidine and the indicated substituted benzidines with phenol. The absorption spectra from left to right were taken in 95% ethanol, 3% sodium hydroxide and concentrated hydrochloric acid.

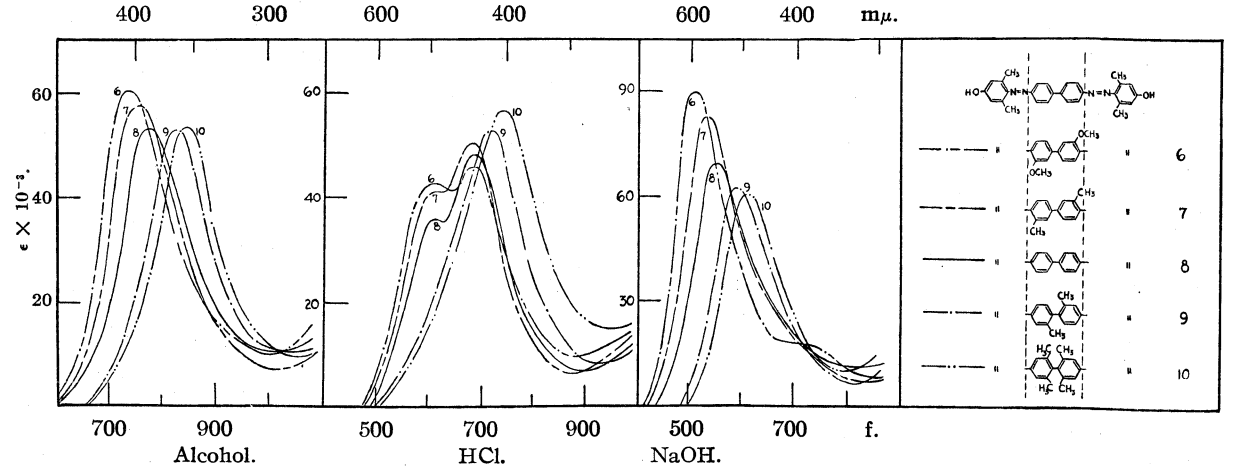


Fig. 2.—The absorption spectra recorded for the dyes prepared by tetrazotization and coupling benzidine and the indicated substituted benzidines with *p*-xylenol. The absorption spectra from left to right were taken in 95% ethanol, 3% sodium hydroxide and concentrated hydrochloric acid.

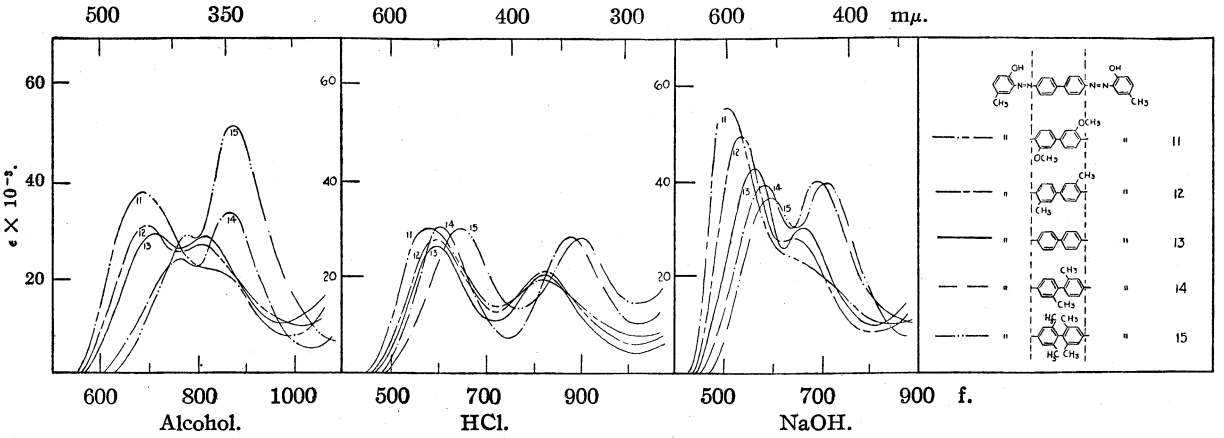
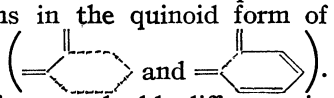


Fig. 3.—The absorption spectra recorded for the dyes prepared by tetrazotization and coupling benzidine and the indicated substituted benzidines with *p*-cresol. The absorption spectra from left to right were taken in 95% ethanol, 3% sodium hydroxide and concentrated hydrochloric acid.

caused by the establishment of more exaggerated non-planar conditions for the half-structures involved. The Fig. 1 shows a typical series of curves using phenol as the coupling constituent; similar types of curves were also obtained when ortho cresol and meta cresol were coupled, except for a very slight displacement to lower frequency due to the additional weight. In Fig. 2, a change in the general absorption curves of the dyes derived from *p*-xylenol was evident in the basic media. This is probably due to the increased difficulty that such dyes would encounter in establishing a quinoid structure due to the interference of the large groups ortho to the azo chromophores. In Fig. 3, the double band formation evident throughout the absorption for these compounds may be ascribed to the two possible chromophoric paths in the quinoid form of phenylazo-*p*-cresol  This would result in a resolvable difference in the absorption for each conjugate system. Figures 3 and 5 illustrate this tendency. These ortho-coupled compounds do not appear at first to bear the simple relationship between the various substituted members as that shown by the para-coupled members. However, when the average of the frequencies of the component parts of the ortho-coupled bands are taken and compared with the frequency changes observed for the para-coupled bands, it will be noted that a similar relationship exists.[12]

Complete insulation of the two chromophores present in these disazo molecules was not accomplished by 2,2′-dimethyl substitution. So pronounced was this insulation for the 2,2′,6,6′-tetramethylbenzidine structure, however, that the absorption spectra exhibited by these dyes not only closely resembled the spectra for a suitable concentration of a corresponding half structure, but also was almost identical with the absorption of a molecule of like structural type in which the insulation at the 1,1′-bond was accomplished by the insertion of a methylene or ethylene link. In Fig. 4 an example of these similarities may be noted. This similarity serves to further indicate the pronounced restriction to complete molecular conjugation through the 1,1′-bond, when a definite non-coplanarity for the two half structures is present.

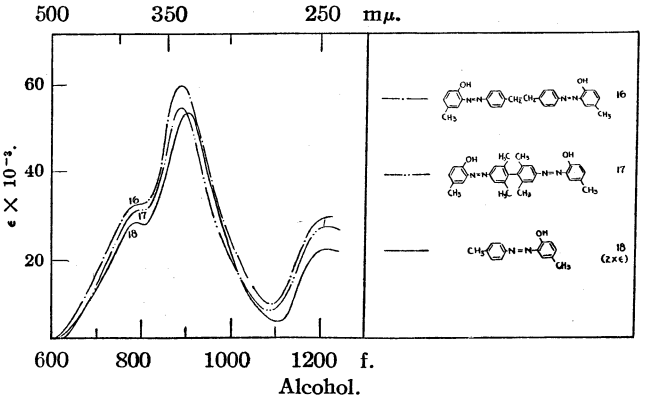


Fig. 4.—Comparison data are presented for the absorption spectra in alcohol solution of two disazo dyes showing restriction to molecular conjugation and a monoazo dye of suitable construction to most nearly represent a half-structure for these molecules.

Absorption spectra taken in acidic and basic media again illustrate the decisive effects of non-coplanarity. With the establishment of more polar conditions for the molecule, either by the use of a solvent that favors the quinoid form for these structures or by introducing the more polar methoxy groups into the 3,3′-position on the benzidine nucleus, even the partial restriction evident for the unsubstituted benzidine nucleus was greatly reduced. This is shown by the marked shift of the

(12) W. R. Brode, "Major Instruments of Science and their Applications to Chemistry" (Vol. 4 of "Frontiers in Chemistry"), Interscience Pub., New York, N. Y., 1945, p. 115.

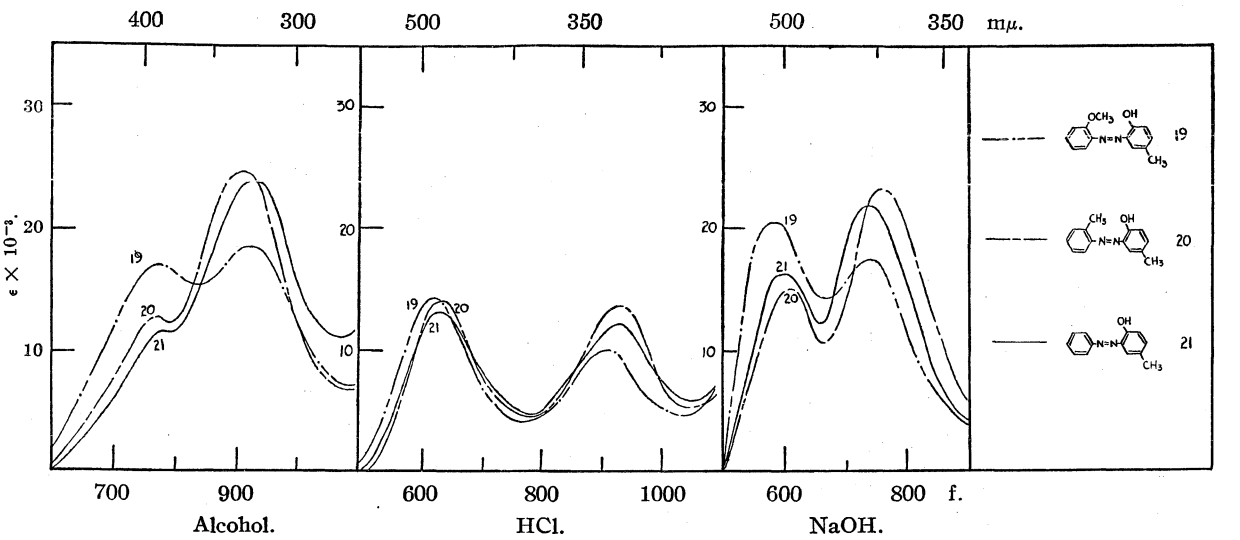


Fig. 5.—The absorption spectra recorded for the monoazo dye phenylazo-*p*-cresol and its derivatives. The absorption spectra from left to right were taken in 95% ethanol, 3% sodium hydroxide and concentrated hydrochloric acid.

absorption to lower frequency attendant with a distinctive increase in the molecular extinction for the molecules altered in the aforementioned ways. The establishment of these more coplanar conditions was most evident in the changes in the absorption spectra recorded for the benzidine dyes as illustrated in Figs. 1, 2 and 3. However, even the more simple monoazo dyes revealed these tendencies as indicated in the Fig. 5. The study of the steric effects in symmetrical dyestuffs as reported in this paper has been extended to unsymmetrical disazo dyes and to trisazo dyes and will be reported in a separate discussion.[13]

Summary

A spectrophotometric study has been made on twenty-five symmetrical benzidine dyes and the absorption spectra for fifteen of these structures have been reproduced as recorded in neutral, acidic and basic media. An absorption study of phenyl-azo-*p*-cresol dye and its methyl and methoxy derivatives was made. The absorption spectra exhibited by the insulated disazo structures caused by non-coplanarity was compared with a corresponding half structure as well as a similar molecule in which the insulation was derived from the insertion of an ethylene link. These data indicate that compounds with restricted rotation differ markedly in their absorption spectra from those capable of free rotation. The partial conjugation present in these dyes is aided by the establishment of a more coplanar configuration for the benzidine nucleus. This molecular conjugation is progressively inhibited by the introduction of the relatively large, unreactive methyl groups in the 2,2′- and 6,6′-positions on the benzidine nucleus. For the dyes prepared from the tetramethyl substituted nucleus, the insulation to molecular conjugation at the 1,1′-bond appears almost complete.

(13) W. R. Brode and R. J. Morris, *J. Org. Chem.*, **13**, 200 (1948).

COLUMBUS, OHIO RECEIVED SEPTEMBER 4, 1947

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Copolymerization. V. Relative Monomer Addition Rates in Vinyl Copolymerization

BY REID G. FORDYCE, EARL C. CHAPIN AND GEORGE E. HAM

Until the recent publication by Alfrey and Price[1] it has been necessary to refer relative monomer reactivity ratios to the particular two-component system investigated. These authors, however, have indicated that it may be possible by means of two constants, Q and e, to characterize the relative rates of copolymerization of any vinyl monomer with any other vinyl monomer whose Q and e parameters are known. Utilizing the experimental study of Lewis, Mayo and Hulse,[2] Q and e values were assigned to styrene, methyl methacrylate, acrylonitrile and vinylidene chloride which appeared to account satisfactorily for their behavior in copolymerization. Because of the practical and theoretical usefulness of this general approach to the problem of copolymerization, it appeared desirable to test the validity of their relationships[1] for a number of additional systems. It is the purpose of this communication to present additional data on relative monomer addition rates and to examine these results, along with previously published values, in the light of the Alfrey and Price equations.

In this work, the four base monomers cited above were used as reference points to calculate the Q and e values for new monomers. The Q and e values reported for any monomer are based on copolymerization rate data of that monomer with at least two other monomers. To obtain cross checks of this kind, it was necessary to supplement published results with a study of the following systems: vinyl acetate–acrylonitrile, vinyl acetate–methacrylonitrile, α-methylstyrene–acrylonitrile, α-methylstyrene–methacrylonitrile and styrene–methacrylonitrile.

In determining monomer–polymer composition curves for the above systems, polymerizations were allowed to proceed to low conversions (mainly $< 4\%$) and the initial copolymer formed was isolated, purified and analyzed in duplicate by the micro-Dumas method.

The relationships of Alfrey and Price[1] were used to derive simplified forms of the copolymer equations involving n components. Copolymer compositions were calculated by substituting the Q and e values reported in these equations, and a comparison of the predicted composition with the composition determined by analysis was made.

Results and Discussion

The shapes of the monomer–polymer composition curves for the systems vinyl acetate–acrylonitrile, vinyl acetate–methacrylonitrile, α-methylstyrene–acrylonitrile, α-methylstyrene–methacrylonitrile and styrene–methacrylonitrile are shown in Fig. 1. These curves are based on data obtained from mass copolymerizations, interrupted at low conversions. Table I summarizes the polymerization conditions and the analytical results of the experiments.

TABLE I

Monomer, mole % acrylonitrile	Time at polymerization temp., hr.	Wt. % conversion	Nitrogen analyses, % I	Nitrogen analyses, % II	Copolymer, mole % acrylonitrile[a]
Vinyl Acetate–Acrylonitrile copolymerizations					
Mass polymerization at 60°, 0.1% Bz_2O_2					
12.18	4.0	0.5	14.37	14.51	67.8
17.86	4.25	0.9	17.86	17.88	79.2
52.0	4.5	1.2	21.00	21.36	88.9
70.8	5.0	0.4	22.12	22.19	92.5
93.6	8.0	1.2	24.90	25.10	98.8
100.0	...	...	25.50	25.58	96.8[b]
Vinyl Acetate–Methacrylonitrile Copolymerizations					
Mass polymerization at 70°, 0.05% Bz_2O_2					
12.47	24	1.0	13.44	13.62	73.0
24.35	25.5	0.2	15.51	15.74	82.1
46.2	10.5	0.2	17.38	17.52	90.0
82.8	10.5	0.3	19.26	19.29	99
100.0	...	...	19.90	19.98	95.5[b]
α-Methylstyrene–Acrylonitrile Copolymerizations					
Mass polymerization at 75°, 0.05% Bz_2O_2					
9.1	23	3.0	5.34	5.22	36.7
22.8	23	2.4	6.35	6.41	42.5
36.0	23	1.6	7.14	6.77	45.4
42.4	15	4.0	7.90	7.83	49.8
53.0	15	3.5	8.63	8.54	53.0
84.0	15	2.3	9.82	9.52	57.4
94.0	15	2.6	11.74	11.98	65.9
α-Methylstyrene–Methacrylonitrile Copolymerizations					
Mass polymerization at 80°, 0.10% Bz_2O_2					
7.05	6	<1.0	4.34	4.27	32.6
25.5	6	<1.0	6.10	6.19	43.8
44.0	6	<1.0	7.68	7.76	52.6
63.0	6	2.4	9.54	9.46	61.5
85.0	6	4.6	12.09	12.29	73.4
Styrene–Methacrylonitrile Copolymerizations					
Mass polymerization at 80°, 0.1% Bz_2O_2					
6.5	9	1.0	2.59	2.75	19.2
25.2	9	2.0	5.66	5.89	38.7
54.3	3	1.6	8.21	8.16	52
84.6	11	1.8	11.98	11.84	69.7

[a] Corrected for incomplete nitrogen evolution. [b] Not corrected.

It was found that the micro-Dumas method of nitrogen analysis gave only 96.8 and 95.5% of the theoretical nitrogen content for polyacrylonitrile or polymethacrylonitrile, respectively. For this reason the nitrogen analyses obtained on the above

(1) Alfrey and Price, *J. Polymer Science*, **2**, 101 (1947).
(2) Lewis, Mayo and Hulse, THIS JOURNAL, **67**, 1701 (1945).

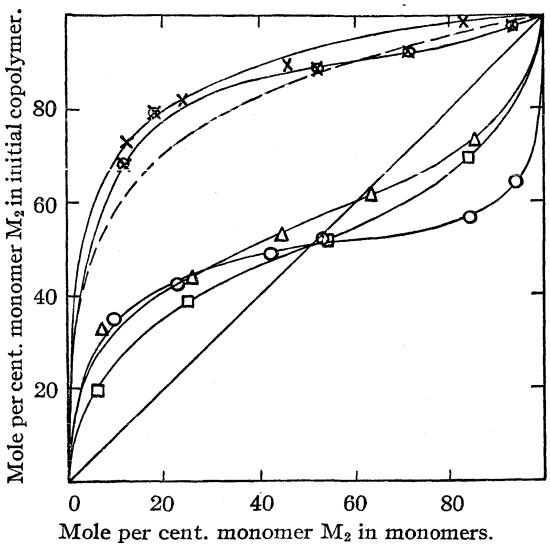


Fig. 1.—Monomer–polymer composition curves: ⊗, vinyl acetate–acrylonitrile (experimental); ---, vinyl acetate–acrylonitrile (theoretical $r_1 = 0.02$, $r_2 = 6$); ⊠, vinyl acetate–methacrylonitrile; O, α-methylstyrene–acrylonitrile; △, α-methylstyrene–methacrylonitrile; □, styrene–methacrylonitrile.

systems were corrected by assuming that any acrylonitrile or methacrylonitrile in a copolymer would evolve a proportionate amount of nitrogen.

Monomer reactivity ratios for these systems were determined by varying their values in the differential copolymer equation[3,4] until a good curve through the experimental points was obtained. This was possible in every case except the vinyl acetate–acrylonitrile system. Here some divergence between the experimental points and the theoretical curve exists as shown in Fig. 1. The relative reactivity ratios[5] for these systems were determined:

	r_1	r_2
Vinyl acetate–acrylonitrile	0.02 ± 0.02	6 ± 2
Vinyl acetate–methacrylonitrile	.01 ± .01	12 ± 2
α-Methylstyrene–acrylonitrile	.1 ± .02	0.06 ± 0.02
α-Methylstyrene–methacrylonitrile	.12 ± .02	.35 ± .02
Styrene–methacrylonitrile	.25 ± .02	.25 ± .02

In connection with the above data it is interesting to note that whereas α-methylstyrene readily forms copolymers containing more than 50 mole per cent. combined α-methylstyrene, we have been unable to polymerize it alone by a free radical mechanism.

The following relationships of Price and Alfrey[1] were employed for assigning Q and e values

$$r_1 = \frac{Q_1}{Q_2} e^{-e_1(e_1-e_2)} \quad (1)$$

$$r_2 = \frac{Q_2}{Q_1} e^{e_2(e_1-e_2)} = \frac{Q_2}{Q_1} e^{-e_2(e_2-e_1)} \quad (2)$$

Owing to the nature of the equations and to the inherent inaccuracies of the values of r_1 and r_2, the Q and e values for a given monomer varied somewhat depending on the system chosen for calculation. Consequently, the values reported represent only a fit to the data available. Undoubtedly, these values will have to be modified as more information becomes available.

The sequence of calculations used for determining Q and e values has a bearing on the results. From published data and data presented here, Q and e values were calculated from the systems indicated.

	Q	e	System
Methyl acrylate	0.34	0.38	Styrene–methyl acrylate[6]
Methacrylonitrile	.77	0.67	Styrene–methacrylonitrile
α-Methylstyrene	.59	−1.26	α-Methylstyrene–acrylonitrile
α-Methylstyrene	.67	−1.11	α-Methylstyrene–methacrylonitrile
Vinyl acetate	.013	−0.45	Vinyl acetate–acrylonitrile
Vinyl acetate	.024	−0.78	Vinyl acetate–methacrylonitrile
Vinyl chloride	.027	−0.22	Vinyl chloride–acrylonitrile[7]
Vinyl chloride	.03	−0.16	Vinyl chloride–methylacrylate[7]

The values of Q and e for methyl acrylate and for methacrylonitrile were not modified. The average of the two values obtained for α-methylstyrene, vinyl acetate and vinyl chloride was taken. The Q and e parameters determined in this manner are summarized, including those previously published[1]

	Q	e
Styrene	1.00	−1.0
Methyl methacrylate	0.64	0
Acrylonitrile	.34	1.0
Vinylidene chloride	.16	0
Vinyl chloride	.028	−0.19
Methyl acrylate	.34	+0.38
Vinyl acetate	.018	−0.61
α-Methylstyrene	.63	−1.18
Methacrylonitrile	.77	+0.67

The degree of agreement between calculated relative rates of polymerization and the values determined experimentally has been fully described by Price and Alfrey for the four reference monomers. A similar comparison for the monomers reported here is

	r_1 Calcd.	r_1 Obsd.	r_2 Calcd.	r_2 Obsd.
Vinyl chloride[a]–acrylonitrile	0.065	0.074[7]	3.7	3.7
Vinyl chloride[a]–methyl acrylate	0.074	0.083[7]	9.8	9.0
Vinyl chloride–styrene	0.046	0.067[7]	16	35
Vinyl chloride–vinyl acetate	1.7	1.8[8]	0.5	0.6

(3) Mayo and Lewis, THIS JOURNAL, **66**, 1594 (1944).

(4) Alfrey and Goldfinger, *J. Chem. Phys.*, **12**, 205 (1945).

(5) The values correspond to the r_1 and r_2 nomenclature of Alfrey, Mayo and Wall, *J. Polymer Science*, **1**, 581 (1946).

(6) Alfrey, Merz and Mark, *J. Polymer Research*, **1**, 37 (1946).

(7) Chapin, Ham and Fordyce, THIS JOURNAL, **69**, 538–542 (1948).

(8) From a paper by T. Alfrey, Jr., presented at the American Chemical Society Meeting, Atlantic City, N. J., April 8–12, 1946.

Styrene–methyl acrylate[a]	1.3	1.3[6]		0.20	0.20
Styrene–vinyl acetate	41.5	50		0.021	.02
Styrene–methacrylonitrile[a]	0.25	0.25		0.25	0.25
Vinyl acetate[a]–acrylonitrile	.02	.02 ± 0.02		3.4	6 ± 2
Vinyl acetate[a]–methacrylonitrile	.011	.01 ± .01		18	12 ± 2
α-Methylstyrene[a]–acrylonitrile	.14	.1 ± .02		0.06	0.06 ± 0.02
α-Methylstyrene[a]–methacrylonitrile	.09	.12 ± .02		0.35	0.35 ± .02

[a] The data which either were used directly or were used to calculate average Q and e values for the designated monomer. The results of greatest interest, however, are those systems which are not marked, since these data represent the cross checks on the validity of predictions based on the Price–Alfrey relationships.

An examination of the above reveals, first, that in no case has the predicted shape of the monomer–polymer composition curve, with respect to the azeotrope line, been in error. When the curve predicted from the above Q and e values lay above or below the azeotrope line, experimental data have been in agreement with the prediction. Unpublished results on a number of other vinyl copolymer systems studied at these laboratories have not as yet revealed a single exception to this.

Considering the assumptions and uncertainties involved in the derivation of the Alfrey–Price equations, as well as the experimental error involved in many of the rate function parameters, quantitative agreement is surprisingly good. Certain discrepancies shown above are not as significant as they appear. For example, in the system styrene–vinyl chloride the monomer–polymer composition curves drawn from the calculated and from the observed r_1, r_2 values actually lie quite close to each other in spite of the fact that superficial inspection of the figures indicates a serious divergence. It is concluded on the basis of available data that the Alfrey–Price relationship, when regarded as an empirical tool for predicting copolymerization behavior, is of the utmost utility qualitatively, and forecasts good values for the relative rates of copolymerization for comonomers whose Q and e values are known.

The data also verify certain generalizations implicit in the Alfrey–Price relationships. Monomer–polymer curves which cross the azeotrope line occur principally when comonomers with similar Q values but with e values of opposite sign are copolymerized. The above data for the acrylonitriles with the styrenes exemplify this. The copolymerization of comonomers with widely different Q values gives curves which deviate widely from the azeotrope line. The systems styrene–vinyl chloride and vinyl acetate–acrylonitrile show this clearly.

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]^2Q_1^2e^{-e_1^2} + [M_1][M_2]Q_1Q_2e^{-e_1e_2} + \cdots + [M_1][M_n]Q_1Q_ne^{-e_1e_n}}{[M_2]^2Q_2^2e^{-e_2^2} + [M_1][M_2]Q_1Q_2e^{-e_1e_2} + \cdots + [M_2][M]_nQ_2Q_ne^{-e_2e_n}}$$

$$\frac{d[M_1]}{d[M_n]} = \frac{[M_1]^2Q_1^2e^{-e_1^2} + [M_1][M_2]Q_1Q_2e^{-e_1e_2} \cdots + [M_1][M_n]Q_1Q_ne^{-e_1e_n}}{[M_n]^2Q^2{}_ne^{-e_n^2} + [M_1][M_n]Q_1Q_ne^{-e_1e_2} \cdots + [M_n][M_{n-1}]Q_nQ_{n-1}e^{-e_ne_{n-1}}}$$

The concepts of Price and Alfrey can be used to transform the equations for relative monomer addition rates into simpler forms requiring much less time for calculations. The simplification is particularly useful for systems containing three or more monomers. For the general case of n monomers substitution in the derivation of Walling and Briggs[9] gives $n - 1$ simultaneous equations.

It is of interest that these copolymer equations exist in a form which clearly shows the individual steps involved in the propagation reaction, *i.e.*, the sum of all the terms in the numerator or denominator represent the sum of all possible propagation reactions resulting in addition of the given monomer to the growing chain.

The Q and e values given above have been substituted in these equations to predict interpolymer compositions for systems containing more than two monomers. These values were then compared with the results obtained. The following is typical of the agreement obtained between calculated and analytical values

	Initial[a] monomer composition	Predicted[a] polymer composition	Polymer[a] composition by analysis
Styrene	32.0	65.7	67.1[7]
Acrylonitrile	48.8	33.7	32.5
Vinyl chloride	19.2	0.6	0.4
Styrene	30.2	70.5	70.4[7]
Acrylonitrile	15.4	26.4	26.2
Vinyl chloride	54.4	3.1	3.4
Styrene	60	75.5	76.1[7]
Methyl acrylate	20	23.4	22.8
Vinyl chloride	20	1.1	1.1
Styrene	25.21	41.5	40.7[10]
Methyl methacrylate	25.48	27.4	25.5
Acrylonitrile	25.40	24.7	25.8
Vinylidene chloride	23.91	6.4	8.0

[a] Data for the three-component systems are expressed as weight per cent., those for the four-component system are expressed as mole per cent.

Agreement between calculated and observed values, as shown above, is further support for the general validity of the Alfrey–Price relationships. The agreement obtained also lends weight to the approximate correctness of the Q and e values reported.

Experimental

Vinyl Acetate Monomer.—Redistilled Niacet Chemical Co. material was taken for all experiments.

Styrene monomer was the redistilled product of Monsanto Chemical Co.

Acrylonitrile was the redistilled product of American Cyanamid Chemical Co.

Methacrylonitrile was redistilled Shell Development Co. product.

α-Methylstyrene.—Redistilled Dow Chemical Co. product was used.

Benzoyl Peroxide.—The product of the Lucidol Corp. was used as received.

(9) Walling and Briggs, THIS JOURNAL **67**, 1774 (1945).

Mass Copolymerization.—The method for determining monomer–polymer composition curves for the five systems reported was essentially the same in each case. Solutions comprising 100 g. of total monomers were prepared by adding appropriate amounts of monomer, comonomer and benzoyl peroxide to 4-oz. French square bottles. The concentrations employed are given in Table I. Air above the monomers was swept out with nitrogen and a metal cap screwed tightly on the bottle mouth. Copolymerizations were carried out in an air oven regulated to ±1° within the polymerization temperature given in Table I. Polymerization at that temperature was continued until a slight increase in viscosity was observed or, in the case of copolymer samples high in combined nitrile, until a small amount of insoluble copolymer had precipitated from the comonomer solution. The reaction was then poured into 3000 ml. of stirred denatured ethanol (2B) at room temperature and the bottle rinsed with ethanol. In the case of vinyl acetate copolymers, hexane was used in place of ethanol throughout. The mixture was boiled to complete the coagulation and filtered. Final purification was effected by similar treatment with two fresh 1500-ml. portions of denatured ethanol. After drying in an evaporating dish for forty-eight hours in a circulating air oven at 60°, the copolymer was analyzed in duplicate for nitrogen by the micro-Dumas method. Analytical data and conversion values are summarized in Table I.

Summary

Monomer–polymer composition curves for the systems vinyl acetate–acrylonitrile, vinyl acetate–methacrylonitrile, α-methylstyrene–acrylonitrile, α-methylstyrene–methacrylonitrile and styrene–methacrylonitrile are reported. These data, along with previously published copolymerization rates, were used to check the validity of predictions based on the Price–Alfrey relationships. Excellent qualitative and good quantitative agreement was found for the systems studied.

Values for the Q and e parameters for five additional monomers are suggested, and simplified forms for copolymer equations involving any number of components are presented.

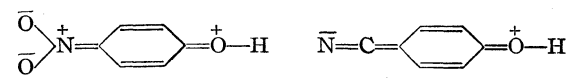
DAYTON 7, OHIO RECEIVED NOVEMBER 15, 1947

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Steric Inhibition of Resonance. III.[1] Acid Strengths of Some Nitro- and Cyanophenols

BY G. W. WHELAND, R. M. BROWNELL[2] AND E. C. MAYO

The acid strength of a phenol is greatly increased by the introduction of a nitro group para to the hydroxyl group. In most instances, in fact, the ionization constant of a *p*-nitrophenol is approximately a thousand times as large as is that of the corresponding unnitrated phenol; in other words, a para nitro group usually decreases the pK_a of a phenol by about 3 units. This greater acidity of the nitrophenol has been attributed[3,4] in part to an electrostatic interaction between the ionizable proton and the dipole moment of the nitro group; and in part also to resonance with a relatively unstable quinoid structure (such as I). Moreover, the effect produced by a para *cyano* group upon the acid strength of a phenol is qualitatively the same as (but usually rather smaller than) that produced by a para nitro group. Again, the observed increase in acid strength can be attributed[3] in part to an electrostatic interaction, since the dipole moment of the para cyano group (like that of the para nitro group) is directed so that its positive end points toward the aromatic ring, and hence toward the ionizable proton; and in part also to resonance with an unstable quinoid structure (such as II).



I II

Although both the electrostatic and the resonance effects should therefore increase the acid strengths of the nitro- and cyanophenols, there is no *a priori* way for the estimation of either their absolute or their relative magnitudes. Data now in the literature suggest, however, that the two effects are fairly large and of comparable magnitude. Thus, calculations by Westheimer[3] have led to the conclusion that the electrostatic effect alone should decrease the pK_a of *p*-nitrophenol (with respect to that of phenol itself) by approximately 1.25 units; hence, it may be inferred that the resonance effect must be responsible for the observed further decrease of approximately 1.6 units (*cf.* Table I, below). Similarly, Westheimer's calculations show that, with *p*-cyanophenol, the electrostatic effect alone should decrease the pK_a by approximately 1.30 units; hence, it can likewise be inferred that the resonance effect must here be responsible for the observed further decrease of approximately 0.75 unit (*cf.* Table I, below).

The experiments reported in this paper were performed in order to obtain additional evidence either for or against the belief that the electrostatic and the resonance effects are about equally responsible for the relatively great acid strengths

(1) For the second paper of this series, see Spitzer and Wheland, THIS JOURNAL, **62**, 2995 (1940).

(2) A portion of this paper is an abstract of a thesis presented by R. M. Brownell to the faculty of the Division of the Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Master of Science, March, 1943. Though here published for the first time, this portion of the work has already been briefly discussed in a book by one of us (Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 185).

(3) Westheimer, THIS JOURNAL, **61**, 1977 (1939).

(4) Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, p. 205.

TABLE I

VALUES OF pK_a AT 25°

Compound	I (E. C. M.)[a]	II (R. M. B.)[a]
Phenol[b]	9.99[c]	...
3,5-Dimethylphenol	10.18	10.09[c]
2,6-Dimethylphenol	10.58	10.60[d]
p-Nitrophenol[b]	7.16	7.21[d]
3,5-Dimethyl-4-nitrophenol	8.25[f]	8.24[e]
2,6-Dimethyl-4-nitrophenol	7.22[d,e,f]	7.16[d,e,g]
p-Cyanophenol[b]	7.95[c]	...
3,5-Dimethyl-4-cyanophenol	8.21[f]	...
2,6-Dimethyl-4-cyanophenol	8.27[f]	...

[a] Since these two sets of data were obtained at quite different times, by different investigators, and hence, possibly, under somewhat different circumstances, both sets are merely recorded separately, without any attempt to average corresponding values. [b] *Cf.* Landolt–Börnstein, "Physikalisch-chemische Tabellen"; "International Critical Tables." [c] Average of four determinations. [d] Average of three determinations. [e] Average deviation, 0.02. [f] Mixtures warmed to effect solution. [g] Samples dissolved by complete neutralization with calcium hydroxide and resulting solutions back-titrated, to approximately two-thirds neutralization, with standard hydrochloric acid.

of *p*-nitro- and *p*-cyanophenols. If the resonance with the quinoid structure (such as I or II) is prevented from occurring, only the electrostatic interaction remains; hence, from the observed acid strength of the compound in question, the magnitude of the electrostatic effect alone can be directly estimated. If the resonance effect is important, such an "inhibition" of the resonance should, therefore, lead to a significant decrease in acid strength, and so to a significant increase in the value of pK_a. Now, with a *nitro*phenol, the quinoid resonance (of the type stated) is largely, if not entirely, inhibited[5] when there is a methyl group in each of the two positions ortho to the nitro group; for, under such circumstances, the nitro group cannot lie in the plane defined by the benzene ring, but must instead be twisted out of that plane by a rotation about the carbon–nitrogen bond. With a *cyano*phenol, on the other hand, the quinoid resonance can*not* be thus inhibited[1]; for, since the cyano group is linear, it cannot be twisted out of the plane of the ring by any sort of rotation.

The foregoing considerations lead to the conclusion that, if resonance is an important factor in increasing the acid strengths of the *p*-nitro- and *p*-cyanophenols, the pK_a of a *p*-nitrophenol should be appreciably increased by the introduction of two methyl groups in the positions *ortho* to the nitro group; but that that of a *p*-cyanophenol should not be greatly affected by a corresponding substitution. Since, however, methyl substituents *directly* influence the acid strengths of phenols, even in the absence of nitro or cyano groups, a complete analysis of the problem requires that the pK_a's of several phenols besides the ones mentioned be also measured.

The data obtained in this investigation are listed in Table I. As expected, methyl groups ortho to the nitro group markedly decrease the acid strength of the phenol, whereas methyl groups ortho to the cyano group have comparatively little effect. The prediction, based on the assumption that the quinoid resonance increases the acid strengths of the *p*-nitro- and *p*-cyanophenols, is therefore confirmed. Methyl groups ortho to the *hydroxyl* group slightly decrease the acid strength, presumably because of either a direct electrostatic effect or a direct resonance (hyperconjugation) effect, or of both.

From a comparison of the data given in Table I for 3,5-dimethylphenol and for 3,5-dimethyl-4-nitrophenol, it appears that the electrostatic effect of the nitro group decreases the pK_a of the latter compound by about 1.9 units. The discrepancy between this value and the one calculated by Westheimer (1.25 units) may be explained by the assumption either that the quinoid resonance in 3,5-dimethyl-4-nitrophenol is only partially inhibited, or that the methyl groups increase the electrostatic interaction between the nitro group and the proton by decreasing the effective dielectric constant of the medium.[3] That the second of these two factors (just mentioned) really exists, and is important, is suggested by the fact that the decrease in acid strength produced by methyl groups ortho to the hydroxyl group is much smaller in 2,6-dimethyl-4-nitrophenol and in 2,6-dimethyl-4-cyanophenol than it is in 2,6-dimethylphenol, even though, in neither of the first two compounds, could the methyl groups in any way affect the resonance.

Experimental

Method and Apparatus

The pK_a values reported were measured potentiometrically. A typical cell contained an aqueous solution of the desired phenol, which had been partially neutralized by standard calcium hydroxide; a Corning 015 glass electrode with an inner reference electrode[6]; and a saturated calomel electrode. The design of the calomel electrode assembly (Leeds and Northrup Company, Cat. No. 7724) was such that the liquid junction was formed through a ground glass joint at the end of the salt bridge. The cell was immersed in an oil thermostat maintained at 25 ± 0.5°. The values of the e. m. f. were measured to the nearest 0.2 mv. by means of a Leeds and Northrup vacuum tube electrometer.

The phenol concentrations in the solutions measured ranged from 0.0015 to 0.0088 *M* and were determined by the solubilities of the respective phenols, by the degrees of neutralization intended, and by the normalities of the calcium hydroxide solutions to be used. In general, the concentration of phenol was such that not less than 9 or 10 ml. of calcium hydroxide solution would be required per 100 ml. of final solution. Calcium hydroxide was

(5) (a) Birtles and Hampson, *J. Chem. Soc.*, 10 (1937); (b) Ingham and Hampson, *ibid.*, 981 (1939); (c) Wheland and Danish, THIS JOURNAL, **62**, 1125 (1940); (d) Spitzer and Whelan, *ibid.*, **62**, 2995 (1940); (e) Westheimer and Metcalf, *ibid.*, **63**, 1339 (1941).

(6) The glass electrodes used in obtaining one set of data (II (R. M. B.), Table I) were made by Mr. John D. Farr and contained silver–silver chloride inner reference electrodes. The one used for the other set of measurements (I (E. C. M.), Table I) was a commercial product, purchased from the Central Scientific Company; the inner reference electrode was unspecified and unobservable.

chosen as the base because of the low error attending the positive ion of this substance in measurements with glass electrodes.[7] The concentrations of the calcium hydroxide solutions used varied between 0.00770 and 0.01940 *N*. The ionic strength of the final solution was always well under 0.01.

The glass electrode was standardized daily by measuring the e. m. f. of a cell containing a Sörensen borate–hydrochloric acid buffer with a *p*H of 8.25 (interpolated) at 25°.[8] The *p*H of each phenol solution was calculated in the usual way[9] from the corresponding e. m. f. and the appropriate value of the e. m. f. given by the buffer solution. From the *p*H value thus obtained, the pK_a of the phenol was computed.[10] The pK_a's were corrected for the ionic strength effect by means of the Debye–Hückel limiting law,[11] and for the hydrolysis of the salt with use of the assumption that the concentrations of hydrogen and hydroxide ion were equal to the respective activities, as determined by the measured *p*H.

Unless otherwise noted in Table I, each pK_a value reported is the average of at least five independent determinations, with an average deviation of not more than 0.01 *pK* unit. The measurements of column II (R. M. B.) were made on phenol solutions, each of which was approximately half neutralized with calcium hydroxide; those of column I (E. C. M.), on the other hand, were made on solutions which varied in degree of neutralization as widely as was permitted by the solubilities of the particular phenols concerned. If, in a measurement, there was any question whether an error had been made, the value obtained was not included in the average even if it were reasonable. Three values were rejected on statistical grounds.[12]

With the cyanophenols, it was necessary to consider the possibility that the cyano groups might be hydrolyzed during the preparation of the solutions studied. The belief that no significant hydrolysis occurred is supported by the following evidence: (1) Nitriles of comparable molecular weight are, in general, not appreciably hydrolyzed under the conditions here employed. More specifically, Thiele and Eichwede[13] have stated that 2,6-dimethyl-4-cyanophenol is not hydrolyzed when it is boiled with dilute aqueous acids or bases; and, although the hydrolysis of 3,5-dimethyl-4-cyanophenol, itself, is not mentioned in the literature, a number of comparable compounds,[14] such as 2,6-dimethylbenzonitrile[15] and 2,4,6-trimethylbenzonitrile[16] in particular, have been reported to be stable toward alkalies. Moreover, 3,5-dimethyl-4-cyanophenol was found in this present study to be apparently unaffected when it was warmed with alkaline aqueous hydrogen peroxide. (2) Calculations indicate that appreciable hydrolysis of a cyanophenol to a product of significantly different acid strength would probably be evidenced by a systematic variation, exceeding experimental deviations, in the pK_a values calculated for that compound over the range of degrees of neutralization concerned. No such systematic variations were observed. (3) The excellent agreement between individual results, which was obtained for each of the cyanophenols studied, was independent, not only of the degree of neutralization, but also of the age of a solution and of the length of time during which it was warmed. (4) The three cyanophenols investigated, when recovered from representative solutions by acidification and extraction with ethyl acetate, showed no marked change in melting point. (5) With the use of Nessler reagent, the amount of ammonia produced was shown, in typical instances, to be less than 0.5% of that corresponding to complete hydrolysis.

(7) Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, chap. 7.

(8) Sörensen, *Biochem. Z.*, **21**, 131 (1909); Walbum, *ibid.*, **107**, 219 (1920).

(9) See p. 296 of ref. 7.

(10) (a) Cohn, THIS JOURNAL, **49**, 173 (1927); (b) Cohn, Heyroth and Menkin, *ibid.*, **50**, 696 (1928); (c) MacInnes, Belcher and Shedlovsky, *ibid.*, **60**, 1094 (1938).

(11) See ref. 10a.

(12) Pierce and Haenisch, "Quantitative Analysis," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 43.

(13) Thiele and Eichwede, *Ann.*, **311**, 363 (1900).

(14) For a general discussion of the hydrolysis of such compounds, see Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, p. 39.

(15) Berger and Olivier, *Rec. trav. chim.*, **46**, 600 (1927).

(16) Grignard, Bellet and Courtot, *Ann. chim.*, [9] **4**, 28 (1915); Küster and Stallberg, *Ann.*, **278**, 207 (1894).

Materials

The temperatures reported below are uncorrected. They were taken, unless otherwise indicated, on a thermometer calibrated against one standardized by the Bureau of Standards, or on the latter itself.

Phenol.—Mallinckrodt Analytical Reagent grade was distilled; a portion of the large amount that boiled, according to a non-standardized thermometer, constantly at 177.0° was reserved for use and stored in a vacuum desiccator in the presence of phosphorus pentoxide.

3,5-Dimethylphenol.—Eastman Kodak Co. best grade was recrystallized from light petroleum ether; m. p. (R. M. B.) 62.8–63.3°, m. p. (E. C. M.) 62.5–63.0°.[17]

2,6-Dimethylphenol.—2,6-Dimethylphenol, prepared from Eastman Kodak Co. *m*-2-xylidine through the diazonium salt, was recrystallized from light petroleum ether; m. p. (R. M. B.), on non-standardized thermometer, 48°, m. p. (E. C. M.) 44.7–45.6°.

***p*-Nitrophenol.**—Eastman best grade was recrystallized from carbon tetrachloride; m. p. (R. M. B.) 112.6–113.0°, m. p. (E. C. M.) 113.2–113.7° and 113.0–113.5°.

3,5-Dimethyl-4-nitrophenol.—3,5-Dimethyl-4-nitrophenol, prepared by the nitration of 3,5-dimethylphenol, was isolated by the codistillation procedure used by Rassow and Schultzky[18] for *p*-nitrophenol. This procedure employs a high-boiling petroleum fraction; an "ink oil" obtained from the Martin Driscoll Company, Chicago, was found to have approximately the correct boiling range, *viz.*, 265–280° (760 mm.). This method was found to give much more satisfactory yields than the usual procedures for isolating the *para* isomer; m. p. (R. M. B.) 107.1–107.6°, m. p. (E. C. M.), after recrystallization from carbon tetrachloride, 107.6–108.3°.

2,6-Dimethyl-4-nitrophenol.—2,6-Dimethyl-4-nitrophenol, obtained by condensation of the sodium salt of nitromalonaldehyde with diethyl ketone, as described by Jones and Kenner,[19] was purified by several decolorizations with Norite or Nuchar and recrystallizations from various solvents, of which the most efficacious was carbon tetrachloride. Because of the evident instability of this compound at temperatures near its melting point, the melting point of any sample varied markedly with the duration of heating; the best melting points obtained for the two portions used for measurement were, respectively: m. p. (R. M. B.) 170.5–170.6°, m. p. (E. C. M.), on non-standardized thermometer, 169.6–169.7°.

***p*-Cyanophenol.**—*p*-Cyanophenol, prepared from *p*-aminophenol by a Sandmeyer reaction, was decolorized with Norite and recrystallized from carbon tetrachloride; m. p. 112.0–112.4°.

3,5-Dimethyl-4-cyanophenol.—3,5-Dimethyl-4-cyanophenol was prepared by a stepwise procedure from 3,5-dimethylphenol. The 3,5-dimethylphenol was converted, by means of a Gattermann reaction, to 2,6-dimethyl-4-hydroxybenzaldehyde and the oxime of this aldehyde was dehydrated with acetic anhydride, as described by v. Auwers and co-workers,[20] to the desired cyano-xylenol. It was found that the yield of 2,6-dimethyl-4-acetoxybenzonitrile, the intermediate involved in the dehydration

(17) Kester (*Ind. Eng. Chem.*, **24**, 770 (1932)) states that although melting points of 64, 64.5 and 68° have been reported, 63.2° was the highest melting point obtained in his laboratory.

(18) Rassow and Schultzky, *Angew. Chem.*, **44**, 669 (1931).

(19) Jones and Kenner, *J. Chem. Soc.*, 1842 (1931).

(20) v. Auwers, Mürbe, Saurwein, Deines and Schornstein, *Fortschr. Chem. Physik physik. Chem.*, **18**, no. 2, 5 (1924).

process, could be greatly improved through purification of this compound by vacuum distillation rather than by recrystallization from water. The crude 3,5-dimethyl-4-cyanophenol was recrystallized from benzene; it formed glistening, white scales; m. p., on non-standardized thermometer, 177.5–177.7°.

Because of reports[19,21] that 3,5-dimethyl-4-cyanophenol crystallizes from benzene in small needles and melts at about 175°, the identity of this compound was confirmed by analysis.[22]

Anal. Calcd. for C_9H_9ON: C, 73.38; H, 6.16; N, 9.52. Found: C, 73.55; H, 6.38; N, 9.46.

2,6-Dimethyl-4-cyanophenol.—2,6-Dimethyl-4-cyanophenol was prepared from mesitol by the method of Thiele and Eichwede[13] and recrystallized from medium-boiling petroleum ether; m. p. 124.0–124.4°.

(21) Houben and Fischer, *Ber.*, **66**, 339 (1933).

(22) The carbon–hydrogen analysis was made by Mr. James G. Burt.

Summary

1. The pK_a's of the following compounds have been determined at 25°: 3,5-dimethylphenol, 2,6-dimethylphenol, 3,5-dimethyl-4-nitrophenol, 2,6-dimethyl-4-nitrophenol, 3,5-dimethyl-4-cyanophenol, 2,6-dimethyl-4-cyanophenol.
2. The pK_a's at 25° have been redetermined for the following compounds: phenol, *p*-nitrophenol, *p*-cyanophenol.
3. The results provide evidence that the total effect produced by a para nitro or para cyano group on the acid strength of phenol is due about equally to an electrostatic interaction and to resonance.

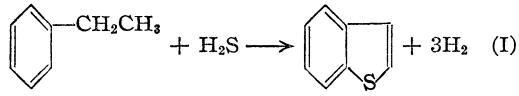
CHICAGO, ILLINOIS RECEIVED APRIL 5, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

Catalytic Synthesis of Thianaphthene from Ethylbenzene

BY CORWIN HANSCH AND FRED HAWTHORNE

In a recent paper, Moore and Greensfelder[1] published the procedure for a new synthesis of thianaphthene from styrene and hydrogen sulfide. While this procedure is an excellent one for the preparation of thianaphthene itself, it would not be as convenient for the preparation of substituted thianaphthenes because of the lack of availability of the proper styrenes as starting materials. Thus, it seemed that the dehydrogenation of an alkylbenzene in the presence of hydrogen sulfide might be accomplished over a single catalyst with formation of the thianaphthene in one step according to Equation I.



(I)

The present paper reports the results of such an attempt.

Experimental

All experiments were carried out in a Pyrex catalyst tube in a continuous flow system. The apparatus used was similar to that described by Hoog, Verheus and Zuiderweg.[2]

The hydrogen sulfide used in this work was commercial grade used directly from the cylinder. Eastman Kodak Co. white label ethylbenzene was distilled before using.

Catalyst Preparations. I. Chromium on Aluminum Oxide.—To a boiling solution of 36.4 g. of chromic anhydride in 400 ml. of distilled water was added 200 g. of ALORCO alumina,[3] Grade H40, Type R2200, 8–14 mesh. The mixture was dried at 100°.

II. Chromium and Nickel on Aluminum Oxide.—Chromic anhydride (7.6 g.) and 12.5 g. of $Ni(NO_3)_2 \cdot 6H_2O$ were dissolved in 50 cc. of water and the solution brought to boiling. To this solution was added 50 g. of activated alumina with vigorous stirring. The mixture was then dried in an oven at 100°.

For the preparation of thianaphthene, the straight chromium catalyst[4] was reduced *in situ* with a slow stream of hydrogen, for one hour at the temperature at which dehydrogenation was to be made, then a stream of hydrogen sulfide passed over the catalyst for fifteen to twenty minutes at the same temperature. Ethylbenzene was then introduced at a uniform rate. A space velocity ratio of about 9:1 of hydrogen sulfide and ethylbenzene was found to give the highest conversion. Most of the liquid products were separated in a Liebig condenser. A small amount of liquid entrained in the large volume of hydrogen sulfide and hydrogen was separated by passing the gases through a U-tube filled with glass wool and cooled in an ice-bath. Using this technique, it was possible to obtain excellent material balances in all runs. The thianaphthene was isolated by distillation and identified by a comparison of it and its picrate with that of a sample prepared by a known procedure.[5]

Discussion

Table I shows the effect of temperature and space velocity on the conversion of ethylbenzene to thianaphthene.

TABLE I

The space velocity of hydrogen sulfide in all runs was 1400 cc./cc./hr.

Catalyst	Temp., °C.	Space velocity,[a] ethylbenzene cc./cc./hr.	% Conversion to thianaphthene
I	550	160	9.3
I	575	160	18.5
I	575	260	13.2
II	575	160	17.0
II	610	245	13.2
II	625	160	18.5

[a] Calculated as cc. of vapor at S.T.P.

The above runs were made for periods of four hours. It was observed that, although the rate of dehydrogenation (as estimated by hydrogen evolution) was more rapid

(1) THIS JOURNAL, **69**, 2008 (1947).

(2) Hoog, Verheus and Zuiderweg, *Trans. Faraday Soc.*, **35**, 995 (1939).

(3) This type of alumina was used exclusively in the research and was supplied through the courtesy of the Aluminum Ore Company.

(4) The nickel–chromium catalysts were reduced for two hours.

(5) Hansch and Lindwall, *J. Org. Chem.*, **10**, 381 (1945).

at temperatures of 600° and above, the activity of the catalyst decreased much more rapidly than at the optimum temperature 575°. Very little difference in activity or life of the two catalysts reported in this paper was noted. Several other catalysts of different ratios of chromium and nickel were prepared; they also showed very little difference in activity. With space velocity ratio of 4:1 of hydrogen sulfide to ethylbenzene, only low yields (~5%) of thianaphthene were obtained.

Preliminary results with other alkylbenzenes indicate that the reaction may be general, however, the yields do not appear to be as good as in the case of ethylbenzene.

Acknowledgment.—The authors are very much indebted to the Research Corporation for a Frederick Gardner Cottrell grant-in-aid which supported this research.

Summary

Thianaphthene has been prepared in 18.5% conversion from hydrogen sulfide and ethylbenzene using a chromia on alumina catalyst at 575°.

CLAREMONT, CALIF. RECEIVED MARCH 27, 1948

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, NO. 1178]

The Purification and Properties of Antibody against *p*-Azophenylarsonic Acid and Molecular Weight Studies from Light Scattering Data

BY DAN H. CAMBPELL, ROBERT H. BLAKER AND ARTHUR B. PARDEE[1a]

It is becoming increasingly evident that many fundamental problems dealing with the structure and behavior of antibody molecules must be studied with purified antibody preparations in solution of known composition rather than in complex solutions such as serum. Methods which are devised for the isolation and purification of antibodies on a practical scale are hence of considerable interest and importance. The following report describes a method for the isolation and purification of antibody against *p*-azophenylarsonic acid in which the antibody is removed from the antiserum by specific precipitation with a polyhaptenic dye and recovered from a solution of the dissociated antigen–antibody complex.

The recovery of antibodies from specific antigen–antibody complexes has been accomplished by a variety of methods.[1b] Perhaps the best known is the one described by Heidelberger and Kendall[2] and Heidelberger and Kabat,[3] in which 15% sodium chloride solutions were used to produce a shift in the antigen–antibody ratio of specific precipitates of SSS or of intact Pneumococcus and antipneumococcus serums favoring the liberation of antibody. Liu and Wu[4] were able to obtain as good if not better yields of antibody preparations by acid dissociation of similar antigen–antibody complexes at about *p*H 4.0 with subsequent isolation of antibody by salt precipitation or removal of antigen by centrifugation if bacterial cells were used. Recently, a report has been made by Haurowitz, *et al.*,[5] which describes the isolation and purification of antibody against *p*-aminobenzylamine, anthranilic, arsanilic, and sulfanilic acids by the use of methods somewhat similar to those used by us in the present investigation. The principal difference was their use of an acid-insoluble conjugated protein for a precipitating antigen. Our own investigations of a number of antigen–antibody systems have indicated that, in general, acid dissociation is the method of choice, at least for the systems involving ovalbumin, polysaccharide, and arsanilic acid antigens. The last of these is a particularly good system since simple polyhaptenic dye antigens can be used for specific precipitating agents. The physical properties of such antigens are so different from those of the antibody proteins that the dissociated complexes can usually be separated into the antigen and antibody components without difficulty. Certain dye antigens have the added advantage that they have a low solubility under acid conditions and hence upon dissociation of the antigen–antibody precipitate the antibody dissolves and the antigen remains behind as an insoluble acid.

Purification of Antibody.—Several methods were studied for the dissociation of antibody from antigen–antibody complexes and its subsequent recovery from the dissociated mixture. For example, treatment of precipitates by alkali at *p*H 9.0–10.0 resulted in considerable dissociation, as evidenced by solution of the precipitates, but the yields of antigen-free protein were low because of the high solubility of the antigen and its tendency to remain attached to the protein. Furthermore, some denaturation of antibody protein always occurred and the purity of antibody as based on the ratio of specifically precipitable protein to total protein usually gave values of only 10 to 20%. Another method which was used with some success was dissociation of dye–antigen complexes with a simple hapten such as arsanilic acid and subsequent dialysis against the hapten until the solution was free of the dye antigen. This

(1a) Present address, McArdle Laboratory, University of Wisconsin, Madison, Wisconsin.

(1b) Dan H. Campbell and Frank Lanni, "The Amino Acids and Proteins," edited by D. M. Greenberg, Chapt. XII, "Immunology of Proteins," Thomas Publishing Co., in press.

(2) M. Heidelberger and F. E. Kendall, *J. Expil. Med.*, **64**, 161 (1936).

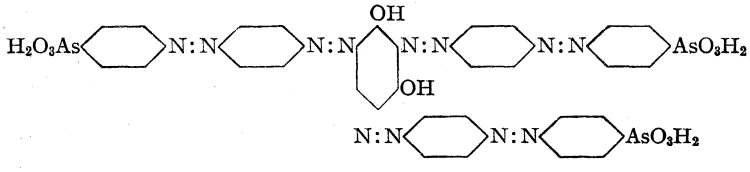
(3) M. Heidelberger and E. A. Kabat, *ibid.*, **67**, 181 (1938).

(4) S. C. Liu and H. Wu, *Proc. Soc. Expil. Biol. Med.*, **41**, 144 (1939).

(5) F. Haurowitz, Sh. Tekman, Miervet Bilen and Paula Schwerin, *Biochem. J.*, **41**, 305 (1947).

method was limited to precipitating antigens of sufficiently small molecular size to permit diffusion through the dialysis membrane. Such antigens are rather inefficient precipitating agents, and considerable time was required to dialyze away first the dye antigen and then the arsanilic acid. The method of choice in most instances and the one used for the antibody preparation in the present study was (1) the use of a good precipitating dye antigen, (2) dissociation of the antigen–antibody complex with arsanilic acid and then acidification to about *p*H 3.5, and (3) precipitation of the dissociated antibody with salt. The purified antibody used in study of physical properties was a pool obtained by mixing several purified preparations, but all were made by essentially the same method.

Serums from a number of rabbits which had been immunized over a period of many months with sheep serum-*p*-azophenylarsonic acid were pooled and a preliminary precipitation titration was made in order to determine the antigen–antibody ratio for optimum precipitation as well as to obtain an approximate idea of the antibody concentration. The antigen used for all preparations was a trisubstituted resorcinol dye having the following structure



The antigen solutions was adjusted to *p*H 8.0 and dilutions were made which varied by a factor of 2 from 1:1000 to 1:256,000, and these were added in 0.5 ml. volumes to tubes containing 0.5 ml. of a 1:4 or 1:5 dilution of the pooled antiserum at *p*H 8.0. The mixtures were allowed to react for about two hours at room temperature and forty-eight hours at 4°. The precipitates were then washed with 1.0% sodium chloride solution and analyzed for protein by the Folin–Ciocalteu method as modified by Pressman.[6] Most of the pooled sera gave maximum precipitation in slight antigen excess with antigen dilutions around 1:40,000 under the above conditions, and antibody protein values of from about 6 mg./ml. of serum to as high as 15 mg./ml. For precipitation of antibody from an 850-ml. batch of pooled serum which showed a preliminary titration maximum for antibody precipitation of 1:10,000 (1:40,000/1:4) was adjusted to *p*H 8.0 with 0.5 *M* sodium hydroxide, diluted with one volume of saline, and mixed with an equal volume of 1:20,000 antigen solution. After several hours at room temperature and about seventy-two hours at 4° about half of the supernatant was siphoned off and the remainder centrifuged and the precipitate washed free of soluble dye and protein with 1.0% sodium chloride at room temperature. The insoluble antigen–antibody complex was usually dissociated first with sodium arsanilate and was then acidified. Although acid dissociation alone was fairly successful it was found that hapten dissociation facilitated separation and gave higher yields. Thus the precipitate was first suspended in 25 to 50 ml. of 10% sodium arsanilate at *p*H 8.0–8.5 and the mixture carefully stirred until no further solution was evident. This required from two to four hours and usually resulted in a solution with only faint turbidity. When precipitates were allowed to develop over a period of longer than seventy-two hours the dissociation with haptens required much longer time and in a few extreme instances were not complete at twelve hours. The antigen–antibody–hapten solution was then quickly adjusted to *p*H 3.2 and again carefully stirred for about one hour at room temperature. At this *p*H most of the dye antigen became insoluble and the antibody protein remained in solution. A small amount of antibody usually remained with the insoluble dye and arsanilic acid but practically all was recovered in one washing with saline and was added to the original acid extract. The small amount of antibody which remained with the insoluble dye was easily recovered by washing. The antibody was precipitated by addition of a saturated sodium chloride solution in a final concentration of 4.0 *M*. Traces of dye which remained soluble in the acid solution were removed by the careful fractional precipitation with salt solution. The dye being relatively insoluble precipitated with much less salt than was required for antibody globulin. In such instances, 10–20% of the antibody would precipitate with the dye but could be recovered by further fractional precipitation with salt at *p*H 3.2. The final salt precipitated antibody was then re-

TABLE I

DATA ON THE PURIFICATION OF ANTIBODY FROM RABBIT ANTI-SHEEP SERUM-*p*-AZOPHENYLARSONIC ACID

Volume of pooled serum, ml.	Type of antigen	Maximum[c] antibody pptd., mg./ml.	Total protein recovered,[d] mg.	Yield, %	Purity[e]
25	R^1_3[a]	14.81	368	97	98
850	R^1_3	6.27	4487	84	87
230	R^1_3	14.81	3390	99	96
400	R^1_3	9.05	3158	87	93
750	XXX[b]	8.68	4100	63	71
100	XXX	8.68	685	79	83

[a] The trisubstituted resorcinol dye described in text. [b] A chromotropic acid derivative containing two azophenyl-azo-arsonic acid groups. These antibody preparations were not used in the present study. [c] Subsequent experiments with the purified antibody indicated that less precipitate was obtained in the presence of serum proteins, hence these values may represent only relative amounts of antibody. [d] Protein based on microkjeldahl analysis. [e] Purity = specific precipitable protein/total protein in solution.

(6) David Pressman, *Ind. Eng. Chem., Anal. Ed.*, **15**, 357 (1943).

suspended in 0.9% saline and dialyzed against saline until the *p*H became practically neutral.

Representative values for several batches of pooled serum are given in Table I. It will be seen that the preparations obtained by use of the trisubstituted dye antigen were better than those obtained by use of a chromotropic acid derivative. This was due largely to the fact that the latter antigen showed an appreciable solubility at *p*H 3.5 and hence tended to complex with the soluble protein. Serums with lower titers always gave smaller yields.

Electrophoretic Pattern.—Electrophoretic studies of the purified preparations in the Tiselius apparatus indicated a very high degree of homogeneity. The experiments were made with approximately 1.0% protein solutions in 0.15 *M* sodium chloride plus 0.04 *M* phosphate buffer at *p*H 7.2. The current used was approximately 15 ma. and the pattern allowed to develop for two to three hours. The electrophoretic mobility was very similar to that of the gamma globulin fraction of serum.

Molecular Weight Determination. (a) From Osmotic Pressure.—The molecular weight determinations by osmotic pressure were made with simple osmometers of the static rise type with a Visking cellophane bag used for the membrane. The protein concentration was 2.0% in 0.15 *M* sodium chloride and 0.04 *M* phosphate buffer at *p*H 7.3. The values obtained varied from 136,000 to 144,000, as compared to the currently accepted values of 158,000. The slightly lower values were probably a reflection of the *p*H at which the determinations were made.

(b) From Light Scattering Data.—Measurements of the turbidity, refractive index, and depolarization of a protein solution can, under certain conditions, be used to calculate the molecular weight of the dissolved protein. The theoretical bases of these calculations are due principally to Rayleigh,[7] Von Smoluchowski,[8] Einstein,[9] Raman,[10] and Debye.[11]

If the dissolved particles are small compared with the wave length of light the following equation gives a relation between the turbidity of the solution, its concentration, refractive index, depolarization, and the molecular weight of the solute.

$$h = \left\{ \frac{32\pi^3 n^2 \left(\frac{\partial n}{\partial c}\right)^2 c}{\lambda^4 N_0 \left(1/M + \frac{2Bc}{RT}\right)} \right\} \left(\frac{6 + 3\rho}{6 - 7\rho}\right) \qquad (1)$$

where

h is the extinction coefficient due to scattering
n is the refractive index of the solution
c is the concentration
$\partial n/\partial c$ is the refractive index increment of the solute
λ is the wave length of the incident light
N_0 is Avogadro's number
M is the molecular weight of the solute
B is a constant which describes the deviation of the system from van't Hoff's law
R is the gas constant
T is the absolute temperature
ρ is the depolarization of the scattered light.

In practice it is difficult to measure h accurately so instead the amount of light which is scattered at an angle of 90° to the incident beam is measured. For solutions of particles which are small compared with the wave length of light the angular distribution of intensity of scattered light obeys a $(1 + \cos^2\theta)$ relation where θ is the angle between the direction of the incident beam and the scattered beam. The relation between h, I_0, the intensity of the original beam and i, the intensity of the light scattered at 90° to the incident beam, is

$$h = \frac{16\pi}{3} i/I_0 \qquad (2)$$

The direct measurement of the quantity, i/I_0, is a time consuming task so that routine measurements in this Laboratory are made by comparing the light scattered from a solution with that scattered from a sealed tube of purified carbon disulfide. Various investigators have reported values of i/I_0 for carbon disulfide and in addition the value has been redetermined in this Laboratory.[12] The value of i/I_0 for carbon disulfide which has been used in this investigation is $4.4 \cdot 10^{-5}$ for light of the wave length of 5461 Å.

The instrument which was used for the measurement of the scattered light is one which was designed and built in this Laboratory. A slightly convergent beam of monochromatic light from a mercury arc (GE-AH-4) is passed up through the bottom of a cylindrical glass cell. The light which is scattered in directions near 90° to the incident beam is focused on a 931-A electron multiplier phototube. A small fraction of the incident beam is reflected to another phototube and the outputs of the two tubes are balanced against one another by means of a potentiometer arrangement. A constant voltage transformer reduces fluctuations in the mercury arc and in the supply of a voltage regulator and rectifier which provides a source of high potential for the plates of the phototubes.

A diaphragm arrangement is installed in the path of the scattered beam which permits sections of polaroid film with known orientations to be switched in and out of the light path. This device gives a convenient way of measuring the depolarization of the scattered light.

The refractive index increment is measured with a differential refractometer similar in design to one which has been described in the literature.[13,14]

(7) Lord Rayleigh, *Phil Mag.*, **12**, 81 (1881).
(8) M. Von Smoluchowski, *Ann. Physik*, **25**, 205 (1908).
(9) A. Einstein, *ibid.*, **33**, 1275 (1910).
(10) C. V. Raman, *Indian J. Phys.*, **2**, 1 (1927).
(11) P. Debye, *J. Applied Phys.*, **15**, 338 (1944).

(12) A more complete description of the light scattering apparatus and technique which have been developed in this Laboratory will soon be published.
(13) D. Rau and W. Roseveare, *Ind. Eng. Chem., Anal. Ed.*, **8**, 72 (1936).
(14) P. Debye, *J. Applied Phys.*, **17**, 392 (1946).

Four solutions of the protein were made with a dilute salt solution (0.15 *M* sodium chloride) and were dialyzed against the same solution for two weeks at 4°. The *p*H of the protein solution at the end of the dialysis was 7.5. The solutions were then centrifuged for twenty minutes in a field 32,000 times that of gravity to remove any suspended dust, placed in a scattering cell, and the intensity of the scattered light compared with that scattered from carbon disulfide for a wave length of 5461 Å. Depolarization measurements were made. The refractive index increment was computed from the difference between the refractive indices of the solution and the solvent. Two of the solutions were slightly colored. Optical density measurements were made on these solutions with a spectrophotometer at the wave length used so that the magnitude of the scattering could be corrected for the true absorption. Concentrations were determined as described in the previous section.

The molecular weight of the dissolved protein is given by

$$M = \frac{\lambda^4 N_0}{2\pi^2 n^2 \left(\frac{\partial n}{\partial c}\right)^2 (c/i/ics_2)_{c\to 0}(I_0/ics_2)} \qquad (3)$$

which follows from (1) and (2)

$c/i/ics_2$ is the concentration of the solution divided by the ratio of the intensity of the light scattered from the solution to that scattered from carbon disulfide. This quantity is corrected for the depolarization of the scattered light and is extrapolated to zero concentration.

A plot of $c/i/ics_2$ *vs.* c is given in Fig. 1. The refractive index increment of this protein is 0.171. The depolarization of the solution is 0.032 and apparently is independent of concentration.

The value of the molecular weight which is calculated from light scattering measurements, 158,000 ± 10,000 compares favorably with previously published data from sedimentation and osmotic pressure studies.

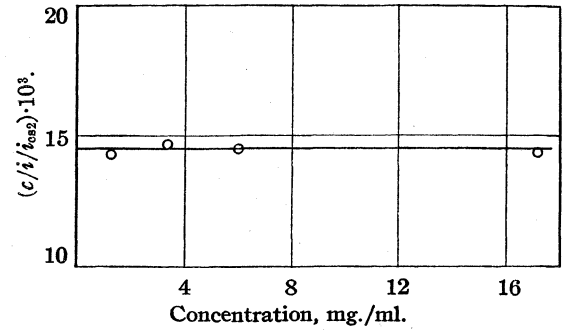


Fig. 1.—Light scattering data for purified rabbit antibody.

There is evidence, however, that the turbidity, depolarization, and refractive index of a protein solution change somewhat with *p*H and perhaps with salt content.[15,16] Not enough work has yet been done to understand how these changes should be taken into account when a value of the molecular weight is to be calculated.

We wish to express our thanks to Professor R. M. Badger and Dr. Stanley Swingle for their suggestions and assistance.

This work was supported in part by a Grant from the Rockefeller Foundation.

Summary

Methods are described for the isolation and purification of rabbit antibody against *p*-azophenylarsonic acid. The purified preparations were electrophoretically homogeneous and similar to gamma globulin.

Molecular weight studies from osmotic pressure and light scattering data gave values of approximately 140,000 and 158,000, respectively.

(15) Unpublished work on solutions of human serum albumin, human serum globulin, and blood group A-Specific substance.

(16) S. Armstrong and others, THIS JOURNAL, **69**, 1747 (1947).

PASADENA, CALIF. RECEIVED FEBRUARY 6, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

The Inhibition of Microbiological Growth by Allylglycine, Methallylglycine and Crotylglycine[1,2]

BY KARL DITTMER, HARLAN L. GOERING,[3] IRVING GOODMAN AND STANLEY J. CRISTOL

The interchange of an aromatic sulfide for a vinylene group in thiamin,[4] nicotinic acid[5] and phenylalanine[6] has led to the formation of specific metabolite antagonists. Because of these effects and because of the theoretical basis for the similarity of the vinylene group (—CH=CH—) and a divalent sulfur atom (—S—),[7] it has been possible to assume that substituting a sulfur for a vinylene group or *vice versa* may be the basis for the preparation of one type of specific metabolite antagonist.[8,9,10]

Since all of these examples are of aromatic com-

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) This paper, which is Number 1 of the Unsaturated Amino Acid Series, was presented in part at the 111th meeting of the American Chemical Society at Atlantic City, April, 1947.

(3) American Cyanamid Company Fellow.

(4) Woolley and White, *J. Exp. Med.*, **78**, 489 (1943).

(5) Erlenmeyer, Block and Kiefer, *Helv. Chim. Acta*, **25**, 1066 (1942).

(6) Dittmer, Ellis, McKennis and du Vigneaud, *J. Biol. Chem.*, **164**, 761 (1946).

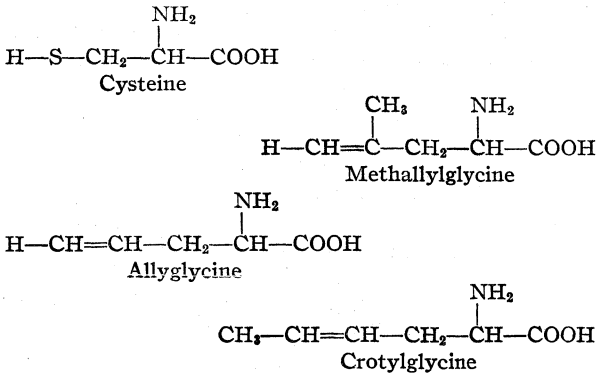
(7) Neuhaus, *Die Chemie*, **57**, 33 (1944).

(8) Wagner-Jauregg, *Naturwissenschaften*, **31**, 335 (1943).

(9) Woolley, *Physiol. Rev.*, **27**, 308 (1947).

(10) Roblin, *Chem. Rev.*, **38**, 255 (1946).

pounds, it seemed desirable to determine whether similar changes in aliphatic compounds containing sulfur or vinylene groups would likewise result in the formation of antagonists. To test this we chose to make the vinylene analogs of the sulfur-containing amino acids. In this paper we wish to report on the growth-inhibitory properties of the vinylene analogs of cysteine, allylglycine and the two closely related unsaturated amino acids methallylglycine and crotylglycine. The structural relationships of these unsaturated amino acids to cysteine are illustrated by the following chemical formulas. The position of the double bond in these compounds is inferred from their syntheses.



We have determined the amounts of these unsaturated amino acids required to inhibit the growth of three strains of *Escherichia coli* and strain 139 of *Saccharomyces cerevisiae*. The effects of various amino acids and vitamins on the toxicity of these unsaturated amino acids are now being investigated.

Experimental

Preparation of Unsaturated Amino Acids.—The syntheses of the unsaturated amino acids by procedures similar to those reported by Albertson[11] will be described in a separate paper.[12] The starting materials were allyl chloride, methallyl chloride and crotyl chloride from which were obtained *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine, respectively.

Inhibition of Growth of *Escherichia coli*.—Three strains of *E. coli* were used in this study; one was an unidentified strain[13] which will be referred to as strain N; the second is listed by the American Type Culture Collection as number 9723; and the third was kindly supplied by Dr. William Shive; it will be referred to as strain T. For these tests the organisms were grown for sixteen hours in the synthetic medium described by MacLeod.[14] Best results were obtained when the medium was prepared daily and the *p*H carefully adjusted to 7.3. Six and five-tenths milliliters of medium was added to the various addenda dissolved in a volume of 1.0 ml. in the assay tubes (20 × 150-mm.). The tubes were capped by aluminum caps and autoclaved for five minutes at 15 pounds pressure and then inoculated with 1 drop of a pure *E. coli* suspension. The inoculum was prepared and handled as described previously,[6] except that during these experiments each culture was washed once with sterile saline before it was diluted for the inoculum.

The effects of increasing amounts of *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine on the growth of three strains of *E. coli* are illustrated by the curves plotted in Figs. 1, 2 and 3, respectively. The amounts of each

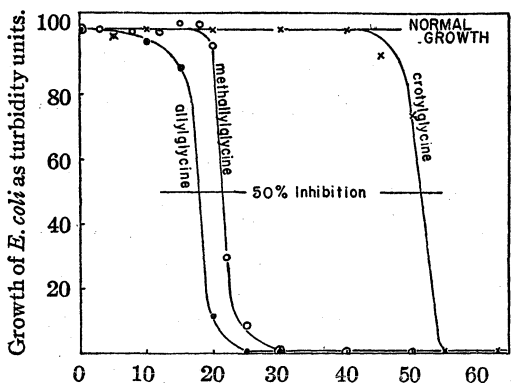


Fig. 1.—The inhibition of the growth of *E. coli*, unidentified strain N, by *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine.

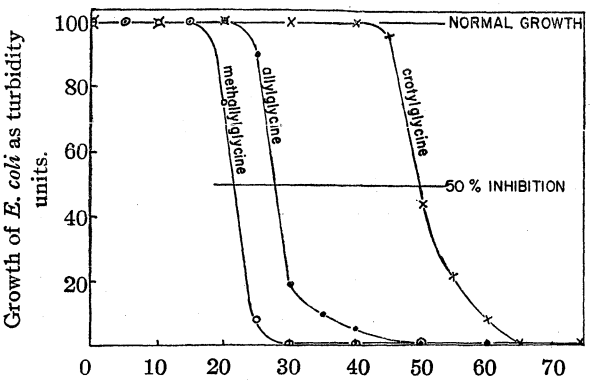


Fig. 2.—The inhibition of the growth of *E. coli*, ATCC 9723, by *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine.

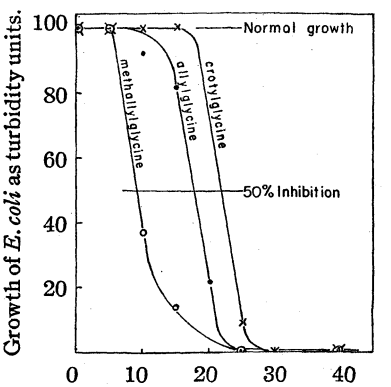


Fig. 3.—The inhibition of the growth of *E. coli*, unidentified strain T, by *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine.

(11) Albertson, THIS JOURNAL, **68**, 450 (1946).

(12) Goering, Cristol and Dittmer, *ibid.*, in press.

(13) This culture of *E. coli* was originally obtained from Professor James Neill of the Department of Bacteriology, Cornell University Medical College, and is the same as that used in the work previously reported.[6]

(14) MacLeod, *J. Exp. Med.*, **72**, 217 (1940).

inhibitor required to reduce the growth of each strain to 50% of normal and to complete inhibition are tabulated in Table I. The data of Table I represent the averages obtained from a large number of determinations. From these data and the curves of Figs. 1, 2 and 3, it can be seen that allylglycine and methallylglycine have very similar inhibitory activity, but crotylglycine is less active for all three strains of *E. coli*.

TABLE I

DATA ILLUSTRATING THE RELATIVE EFFECTIVENESS OF THREE UNSATURATED AMINO ACIDS AS MICROBIAL GROWTH INHIBITORS

Microörganism	Amounts of unsaturated amino acid required[a] per 7.5 ml. of medium: *dl*-Allylglycine γ	*dl*-Methallylglycine γ	*dl*-Crotylglycine γ
E. coli, strain N			
for 50% Inhibition[a]	16[b]	22	50
for 100% Inhibition[a]	20–40	25–40	50–80
E. coli, strain 9723			
for 50% Inhibition	27	20	50
for 100% Inhibition	30–50	25–40	50–70
E. coli, strain T			
for 50% Inhibition	17	10	23
for 100% Inhibition	20–30	15–25	30–40
S. cerevisiae, strain 139			
for 50% Inhibition	6	55–100	700–1000
for 100% Inhibition	50	>1 mg.	>4 mg.

[a] The amounts required for complete inhibition vary much more than the amounts required for 50% inhibition. The values for 50% inhibition are averages while the range of amounts required for 100% inhibition are given. [b] For a short period of time during these tests, between 30 and 50γ were required for 50% inhibition of normal growth.

Allyl chloride, allyl alcohol and allylurea were tested at a concentration of 1 mg. per 7.5 ml. of medium and were found to be either completely inactive or only slightly inhibitory.

Inhibition of the Growth of *Saccharomyces cerevisiae*.—The technique followed in the yeast growth experiments was similar to that described previously.[6] The medium employed was that used by Snell, Eakin and Williams[15] except for the level of aspartic acid, which was increased to 2 g. per 10 liters of medium.

The effects of increasing amounts of *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine on the growth of *S. cerevisiae* are shown in Fig. 4. The amounts of the inhibitors required to produce 50 and 100% inhibition of normal growth are also listed in Table I. From the curves of Fig. 4 and the data of Table I it is evident that of the three unsaturated amino acids, allylglycine is by far the best yeast growth inhibitor and crotylglycine is the poorest.

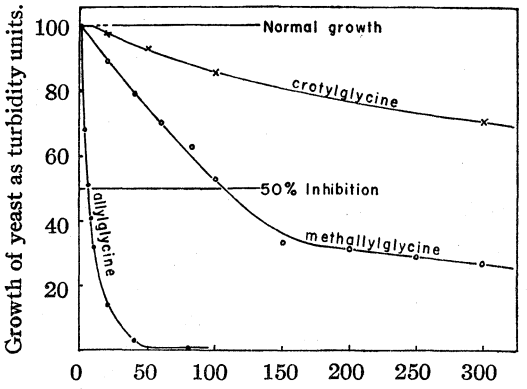


Fig. 4.—The inhibition of the growth of *S. cerevisiae*, strain 139, by *dl*-allylglycine, *dl*-methallylglycine and *dl*-crotylglycine.

Acknowledgment.—The authors are greatly indebted for the very excellent assistance received from Mrs. Charmion McMillan, Mrs. Hester P. McNulty and Mrs. Virginia Janda. The authors also wish to thank Mr. V. C. Irvine and Mr. W. S. Thornhill of the Shell Chemical Corporation for generous supplies of allyl chloride and methallyl chloride.

Summary

As possible antagonists for cysteine three unsaturated alpha amino acids, allylglycine, methallylglycine and crotylglycine, were tested for their growth inhibition of three strains of *Escherichia coli* and strain 139 of *Saccharomyces cerevisiae*. Allylglycine and methallylglycine were almost equally effective inhibitors of *E. coli*, producing complete inhibition of growth for sixteen hours in very small concentrations. Crotylglycine was less active on the growth of all three strains of *E. coli*. For *S. cerevisiae*, allylglycine was the most effective inhibitor of the three unsaturated amino acids and crotylglycine showed only low inhibitory action.

BOULDER, COLORADO RECEIVED FEBRUARY 18, 1948

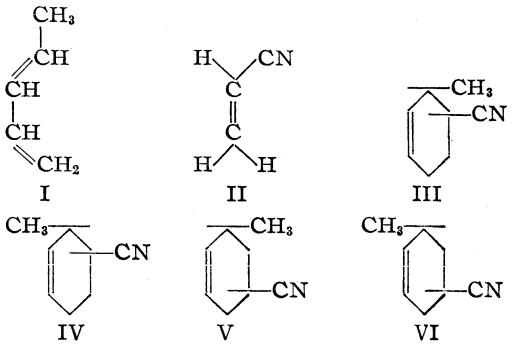
(15) Snell, Eakin and Williams, THIS JOURNAL, **62**, 175 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

The Condensation of Piperylene with Acrylonitrile and Methyl Acrylate

BY JOHN S. MEEK AND JAMES W. RAGSDALE

When a diene such as piperylene (I) which possesses only one plane of symmetry undergoes the Diels–Alder reaction with an unsymmetrically substituted dienophile such as acrylonitrile (II) then possibly four different racemic nitriles might be formed. In this case these are *cis*- (III) and *trans*-1,2,5,6-tetrahydro-*ortho*-tolunitrile (IV) and *cis*- (V) and *trans*-1,2,3,6-tetrahydro-*meta*-tolunitrile (VI). The possibility of the formation of

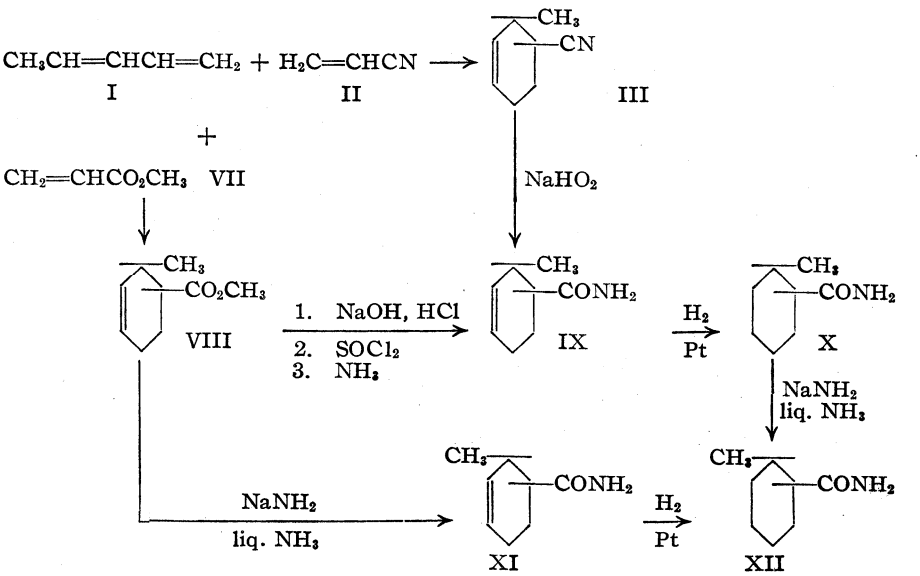


such isomers was recognized by Lehmann and Paasche.[1] However, in only a few cases have the adducts been identified as ortho or meta isomers and in no case has it been definitely proven whether these were *cis* or *trans* in nature. Lehmann and Paasche condensed acrolein with 4-*p*-xylyl-1,3-pentadiene and assigned to the resulting adduct the structure of an ortho isomer in which the aldehyde group and the *p*-xylyl group were *trans* to each other.[1] Their proof of structure was inconclusive and their adduct was not converted to any known compound.

Recently it was found that the adduct of acrylonitrile and piperylene was a mixture of an ortho and a meta isomer and that the ortho isomer was roughly seven times as abundant as the meta isomer in the mixture.[2] Therefore, this reaction was chosen in an effort to learn if these isomers were *cis* or *trans* in nature, and at the same time it was planned to study the previously unreported condensation of piperylene and methyl acrylate (VII).

Methyl acrylate was found to condense readily with piperylene to give a 65% yield of an adduct (VIII). Dehydrogenation of VIII and subsequent hydrolysis produced *o*-toluic acid. No *m*-toluic acid was isolated. Saponification of VIII, conversion to the acid chloride, and treatment with ammonia gave a solid amide (IX). This upon hydrogenation gave the known *cis*-hexahydro-*o*-toluamide (X).[3] The over-all yield from the crude adduct to IX was 57%, showing that the majority of the adduct was the *cis*–ortho isomer VIII.

In an attempt to get a better conversion of VIII to IX, ammonolysis was tried. None appeared to take place with alcoholic ammonia solutions. The use of liquid ammonia with ammonium chloride was next tried,[4] but no identifiable product could be obtained. The use of sodium amide in liquid ammonia gave a small yield of a compound (XI) which was identified as *trans*-1,2,5,6-tetrahydro-*o*-toluamide by hydrogenation to the known *trans*-hexahydro-*o*-toluamide (XII).[3] A subsequent experiment showed that under similar conditions the *cis* amide was converted to the *trans* isomer.



The crude adduct of piperylene and acrylonitrile was treated with sodium hydroxide and hydrogen peroxide in alcohol. An 85% yield of IX was obtained and thus the majority of the adduct was shown to be III. Attempts to isolate an amide

(1) Lehmann and Paasche, *Ber.*, **68**, 1146 (1935).

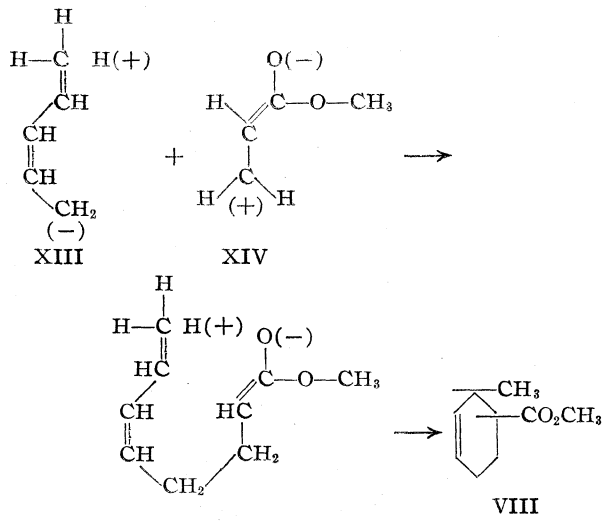
(2) Frank, Emmick and Johnson, THIS JOURNAL, **69**, 2313 (1947).

(3) Skita, *Ann.*, **431**, 1 (1923); v. Auwers, *J. prakt. Chem.*, [2] **124**, 209 (1930).

(4) Fellinger and Audrieth, THIS JOURNAL, **60**, 579 (1938).

derived from either IV, V or VI have failed so far although it has been shown that V or VI if not both must be present in the reaction mixture.[2]

From these two examples it appears that piperylene condenses with a negatively substituted unsymmetrical ethylene to give chiefly the *cis*-ortho isomer. This is what one would expect on the basis of resonance and inductive effects in the compounds studied. For in piperylene it has been shown that the inductive and hyperconjugative effect of the methyl group causes a negative charge to reside on the terminal carbon atom[5] (XIII). In methyl acrylate, as well as many other negatively substituted ethylenes, the β-carbon atom is positive when compared to the α-carbon atom due to mesomeric effects (XIV). Thus the molecules may line up as pictured below to form the ortho isomer, the negative end of one being attracted by the positive end of the other. In the piperylene molecule (XIII) hyperconjugation of the methyl group results in its having a positive charge. This charge attracts it to the negative charge on the carbonyl group resulting from resonance, and thus a *cis* configuration results.



XIII XIV

VIII

The formation of the meta isomer in the case above would require the positive end of the dienophile to join with the positive end of the diene which would need a higher energy of activation than that required for the formation of the ortho isomer.

Experimental

The piperylene, methyl acrylate and acrylonitrile used in these experiments were Eastman Kodak Company practical grade, and they were used without further purification. About 70% of the piperylene was the *trans* isomer.

Adduct of Piperylene with Methyl Acrylate (VIII).—A mixture of 57 g. (0.67 mole) of methyl acrylate, 45.5 g. (0.67 mole) of piperylene and 0.1 g. of hydroquinone were placed in a Parr hydrogenation bomb under 1200 pounds of hydrogen pressure and heated for six hours at 200°. The hydrogen was used to test for leaks in the apparatus, and also in the hope that it would cut down peroxide formation and the diffusion of the piperylene which might result in polymerization taking place around the valves of the bomb head. No such polymerization was encountered and the use of the bomb avoided the dangers of sealed glass tubes and permitted the use of larger amounts of materials. The product was distilled through a short Vigreux column and 67.4 g. (65%) of adduct was obtained, b. p. 180–205° (627 mm.). A small portion was redistilled and the fraction boiling at 181–183° (622 mm.), $n^{20}D$ 1.432 was taken for analysis.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.13; H, 9.15. Found: C, 70.28; H, 8.98.

The adduct was dehydrogenated by heating under reflux with a 25% palladium on charcoal catalyst. Saponification of the resulting oil and acidification gave *o*-toluic acid. This was identified by means of a mixed melting point with an authentic sample and by preparing the *p*-bromophenacyl ester derivative.

Adduct of Piperylene with Acrylonitrile (III).—A mixture of 38.5 g. (0.72 mole) of acrylonitrile, 58 g. (0.85 mole) of piperylene and a trace of hydroquinone and iodine were placed in the bomb as in the above procedure and were heated at 130° for eight hours. Distillation of the resulting product gave 18.7 g. of crude piperylene, 18.4 g. of acrylonitrile, and 47.6 g. (54%) of crude adduct. Frank, Emmick and Johnson[2] have reported a 56% yield when equivalent amounts of *trans*-piperylene and acrylonitrile were heated for twenty-four hours on a steam-bath. Fractionation of our adduct through a column possessing 12 theoretical plates failed to separate the position isomers shown to be present but not isolated by those authors. The adduct boiled at 190–191° (620 mm.), $n^{20}D$ 1.4710.[6]

***cis*-1,2,5,6-Tetrahydro-*o*-toluamide (IX).**—To a solution of 2.1 g. of VIII in 15 ml. of methanol was added a solution of 1.6 g. of potassium hydroxide in 3 ml. of water. The mixture was allowed to stand in the cold for forty hours. This was then acidified with hydrochloric acid and extracted with ether. This extract was then warmed to remove the ether and any methanol present, and the residual oil was heated with 6 g. of thionyl chloride for thirty minutes. The acid chloride was poured into ice-cold concentrated ammonium hydroxide and the resulting solid was isolated by means of filtration and washed with water. Recrystallization from hot water gave 1.1 g. (58%) of amide, m. p. 143°.

This same amide was prepared from the adduct of acrylonitrile and piperylene by the action of alkaline hydrogen peroxide using the procedure given for converting *o*-tolunitrile to the amide[7] with 18.1 g. (0.15 mole) of the adduct being used. A yield of 16.1 g. (85%) of the amide was obtained, m. p. 140–142°. Recrystallization from 10% methanol gave crystals melting at 143° as before and a mixed melting point of the two was not depressed.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.02; H, 9.41; N, 10.06. Found: C, 69.1; H, 9.20; N, 10.13.

Methyl *cis*-Hexahydro-*o*-toluate.—Hydrogenation of a small quantity of VIII showed that about 2% more than the theoretical amount of hydrogen was absorbed at room conditions with Adams catalyst being used. Hydrogenation of 20 g. (0.13 mole) of VIII in 40 ml. of methanol with 50 mg. of platinum oxide was carried out. The platinum was removed by means of filtration and the filtrate was distilled through a short Vigreux column. The main fraction boiled at 181–183° (623 mm.) and weighed 15.2 g. (75%); $n^{20}D$ 1.432; d^{24} 0.956.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.46.

***cis*-Hexahydro-*o*-toluamide (X).**—The 15.2 g. of hydrogenated ester prepared above were allowed to stand

(5) Hannay and Smyth, *ibid.*, **65**, 1931 (1943).

(6) We are indebted to Mr. Robert C. Ronald for this fractionation.

(7) Noller, "Organic Syntheses," Col. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 586.

almost two days with 6 g. of sodium hydroxide in aqueous ethanol. The mixture was acidified with hydrochloric acid and then ether extracted. Fractional distillation gave 10 g. (72%) of *cis*-hexahydro-*o*-toluic acid, b. p. 119–121° (9 mm.), $n^{20}D$ 1.4572; reported,[8] b. p. 122–123° (10 mm.), $n^{20}D$ 1.458. A small amount of the acid was heated with thionyl chloride, the excess reagent was removed by distillation and the acid chloride was poured into ice-cold ammonium hydroxide. The amide obtained was recrystallized twice from a methanol–water mixture and melted sharply at 149.5°; reported[8] m. p. 151–153°.

Twelve grams of IX prepared from the adduct of acrylonitrile was placed in 135 ml. of methanol with 50 mg. of Adams catalyst and hydrogenated at room conditions. The platinum was removed by filtration and the filtrate was evaporated to dryness and gave 11.3 g. (93%) of crude amide, m. p. 149°. Treatment with charcoal in a 10% methanol solution gave a product melting sharply at 150°. A mixed melting point with the hexahydroamide prepared from VIII as reported previously showed no depression.

Attempted Ammonolyses of VIII.—All attempts to prepare IX by the action of ammonia on VIII failed. Treatment of VIII with aqueous ammonia or anhydrous ammonia in absolute ethanol with heating failed to give any solid product. Finally the procedure of Fellinger and Audrieth[4] was tried. A solution of 4.8 g. of VIII and 2 g. of ammonium chloride in 120 ml. of liquid ammonia was placed in a 500 ml. Parr bomb and heated at 80–100° for twenty-four hours. The ammonia was allowed to evaporate and the residue was dissolved in 10% methanol and treated with charcoal. After removing the charcoal by filtration and the methanol by evaporation, chilling the solution resulted in the formation of white crystals, 0.1 g. (5%), m. p. 120–122°. Hydrogenation of 52.6 mg. of the substance with 10 mg. of Adams catalyst absorbed slightly more than the theoretical amount of hydrogen which would have been taken up by a tetrahydrotoluamide. Recrystallization of the hydrogenated product gave a white solid, m. p. 141.5°. This does not correspond to the melting point of 155–156° reported for the only known form of hexahydro-*m*-toluamide,[9] and save for an analysis of the hydrogenated material these compounds were not investigated further.

Anal. Calcd. for $C_8H_{15}NO$: N, 9.91. Found: N, 9.70.

***trans*-1,2,5,6-Tetrahydro-*o*-toluamide (X).**—To 120 ml. of liquid ammonia were added 2 g. of sodium hydride and 4.8 g. of VIII. The mixture was heated as before in a Parr bomb, and then the ammonia was allowed to evaporate. The resulting powder was dissolved in water, neutralized with hydrochloric acid, and then ether extracted. Evaporation of the ether gave a gum which was dried on a porous plate and then treated with charcoal and recrystallized from 10% methanol; yield, 0.1 g. (5%), m. p. 166°.

Anal. Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.75.

***trans*-Hexahydro-*o*-toluamide (XII).**—Twenty-six milligrams of XI was hydrogenated with Adams catalyst in methanol. Slightly more than the theoretical amount of hydrogen was absorbed. Evaporation of the methanol following removal of the catalyst gave a product melting at 178°. Recrystallization from hot water raised the melting point to 180°, reported m. p. for *trans*-hexahydro-*o*-toluamide is 180–181°.[3-8]

Two grams of *cis*-hexahydro-*o*-toluamide, 2 g. of sodium hydride and 100 ml. of liquid ammonia were heated under pressure at 90° for two hours. The material was worked up as in the preparation of XI and 0.3 g. (15%) of amide, m. p. 180°, was obtained. A mixed melting point with the product obtained by hydrogenating XI was not depressed. When 2 g. of X, 2 g. of sodium hydride and 100 ml. of liquid ammonia were allowed to stand together for several hours while the ammonia gradually evaporated, no *trans* amide was obtained.

Acknowledgment.—This work has been supported in part by a grant-in-aid from the Council of Research and Creative Work of the University of Colorado. The sodium hydride used in this work was a gift of the Electrochemical Division of E. I. du Pont de Nemours, Inc., and the thionyl chloride was a gift of the Hooker Electrochemical Company.

Summary

The condensation of piperylene with two negatively unsymmetrically substituted ethylenes, acrylonitrile and methyl acrylate, in the Diels–Alder reaction has been found to give in both cases chiefly the *cis*-ortho isomer. This is in agreement with predictions based upon electronic theories.

BOULDER, COLORADO RECEIVED FEBRUARY 20, 1948

(8) Zelinsky, *Ber.*, **41**, 2676 (1908).

(9) Markownikoff, *J. prakt. Chem.*, [2] **49**, 64 (1894).

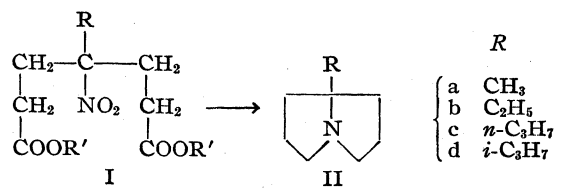
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines. II. Basicities of 8-Alkylpyrrolizidines[1]

BY NELSON J. LEONARD AND KARL M. BECK[2]

The 8-alkylpyrrolizidines (II) offer an excellent opportunity for the detection of F-strain[3] in a bicyclic amine system, and the method of synthesis of 8-methylpyrrolizidine (IIa) reported from this Laboratory[1] shows promise of general application. Therefore, the preparation of homologous 8-alkylpyrrolizidines has been investigated so that the relative basicities of the products could be determined.

A favorable yield of 8-methylpyrrolizidine (IIa) had previously been realized in the hydrogenation of diethyl γ-methyl-γ-nitropimelate (Ia) in ethanol over copper chromite at 250–350 atm. and 275°.[1] In extending the method to 8-*n*-propyl-

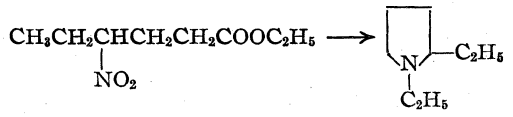


(1) For the first article in the series, see Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).

(2) Present address: Abbott Laboratories, North Chicago, Illinois.

(3) Brown, THIS JOURNAL, **67**, 374 (1945).

pyrrolizidine (IIc) and 8-isopropylpyrrolizidine (IId), it was found advantageous to employ dioxane as the solvent.[4] The reaction time in dioxane was one-third that required in ethanol. Yields between 60 and 65% were realized. 8-Ethylpyrrolizidine (IIb) was obtained in comparable yield by the one-step catalytic reduction of the condensation product of 1-nitropropane with two moles of ethyl acrylate (Ib). When the condensation product of 1-nitropropane with one mole of ethyl acrylate (III) was hydrogenated in ethanol over copper chromite at 200–300 atm. and 250°, 1,2-diethylpyrrolidine (IV) was obtained in 50% yield. Catalytic hydrogenation gave about the



III IV

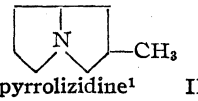
same yield of IV whether the reduction was carried out in one step or by the two-step process with platinum oxide at low pressure followed by copper chromite at high pressure.[1] That N-alkylation occurred is not surprising, since Adkins[5] has cited the N-ethylation of primary and secondary amines with ethanol solvent above 150°, and Barr and Cook[6] have observed N-alkylation in the preparation of certain piperidines by catalytic hydrogenation over copper chromite in methyl, ethyl and butyl alcohols. N-Methylation did not proceed readily in the pyrrolidine series, for when III was hydrogenated in methanol over copper chromite at 200–300 atm. and 250°, none of the expected 1-methyl-2-ethylpyrrolidine could be isolated.

The precursors (Ic,d) of 8-*n*-propyl-and 8-isopropyl-pyrrolizidine were prepared conveniently by the general method of Bruson,[7] through the condensation of methyl acrylate with 1-nitrobutane and 1-nitro-2-methylpropane in the presence of benzyltrimethylammonium hydroxide. Seventy to eighty per cent. of the nitroparaffins was accounted for in the form of condensation products when about 0.07 mole of benzyltrimethylammonium hydroxide was employed per mole of nitroparaffin. From 1-nitrobutane were obtained dimethyl γ-*n*-propyl-γ-nitropimelate (Ic) and methyl γ-nitroheptanoate; from 1-nitro-2-methylpropane, dimethyl γ-isopropyl-γ-nitropimelate (Id) and methyl γ-nitroisoheptanoate. The condensation of nitroisobutane with methyl acrylate gave a predominant yield of the isoheptanoate and only 10% of the pimelate derivative. In further reaction of the methyl γ-nitroisoheptanoate with another mole of methyl acrylate to give dimethyl γ-isopropyl-γ-nitropimelate, diethylamine[8] was found to be superior to benzyltrimethylammonium hydroxide as the condensing agent.

The reduction of the γ-nitropimelate esters furnished a series of alkylpyrrolizidines, for which it was desired to determine the basicity values. The high pK_H value (11.48) for heliotridane, or optically active 1-methylpyrrolizidine, as measured by Adams, Carmack and Mahan,[9] suggested that the fusion of two five-membered rings through a common C–N bond placed the electron pair of the nitrogen in an exposed or sterically freed position. Determination of the *p*H at half neutralization for other alkylpyrrolizidines would indicate whether the unusually high figure for heliotridane was inherent in the pyrrolizidine nucleus. None of our observed pK_H values for alkylpyrrolizidines (see Table I) was in the range of the figure for heliotridane; all exhibited basicity of a much lower order, yet higher than that for analogous acyclic tertiary amines. The higher basicity of cyclic, as compared with acyclic ethers and amines has been ascribed by Brown to B-strain[3] in the acyclic molecules.[10] F-strain[3,11] in the pyrrolizidines should increase with increasing size of the 8-alkyl group attached to the pyrrolizidine nucleus, because the apparent *cis* fusion of the two rings necessitates the protrusion of the 8-alkyl group toward the face of the nitrogen atom. This may be seen by comparing the accompanying photographs of models of the 8-methyl (Fig. 1), 8-ethyl (Fig. 2), 8-isopropyl (Fig. 4), and 8-*n*-propyl (Fig. 3) compounds. The pK_H values determined

TABLE I

BASICITY OF 8-ALKYLPYRROLIZIDINES AND RELATED COMPOUNDS

Compound	Formula	pK_H	BF_3 adduct	Picrate m. p., °C.
2-Methylpyrrolizidine[12]		10.49	....	169–170
8-Methylpyrrolizidine[1]	IIa	10.69	Solid	281
8-Ethylpyrrolizidine[1]	IIb	10.67	Solid	238
8-Isopropylpyrrolizidine	IId	10.70	Solid	228–229
8-*n*-Propylpyrrolizidine	IIc	10.61	None	156–157
1,2-Diethylpyrrolidine	IV	10.02	Liquid	120–121

(4) An amide is the probable last intermediate[1] in the over-all reduction process, and Adkins ("Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 95, 112) has recommended the use of dioxane as a solvent for the catalytic reduction of amides.

(5) Adkins, *ibid.*, p. 26.

(6) Barr and Cook, *J. Chem. Soc.*, 438 (1945).

(7) Bruson, U. S. Patent 2,342,119 (Feb. 22, 1944); U. S. Patent 2,390,918 (Dec. 11, 1945).

(8) Kloetzel, THIS JOURNAL, **69**, 2271 (1947), has demonstrated the efficacy of diethylamine as a catalyst for the addition of nitroparaffins to α,β-unsaturated ketones.

(9) Adams, Carmack and Mahan, *ibid.*, **64**, 2593 (1942).

(10) Examples include the following relations in basicity: tetrahydrofuran > dimethyl ether, relative to boron trifluoride [Brown and Adams, *ibid.*, **64**, 2557 (1942)]; pyrrolidine > dimethylamine, relative to trimethylboron [Brown and Taylor, *ibid.*, **69**, 1332 (1947)]; quinuclidine > triethylamine, relative to trimethylboron [Brown, Symposium on the Mechanisms of Organic Reactions, Notre Dame, Indiana, September, 1946].

(11) Examples include the following relations in basicity: pyridine > 2,6-lutidine, relative to boron trifluoride [Brown, Schlesinger and Cardon, *ibid.*, **64**, 325 (1942)]; pyridine > 2-picoline, relative to trimethylboron [Brown and Barbaras, *ibid.*, **69**, 1137 (1947)].

(12) Clemo and Melrose, *J. Chem. Soc.*, 424 (1942).

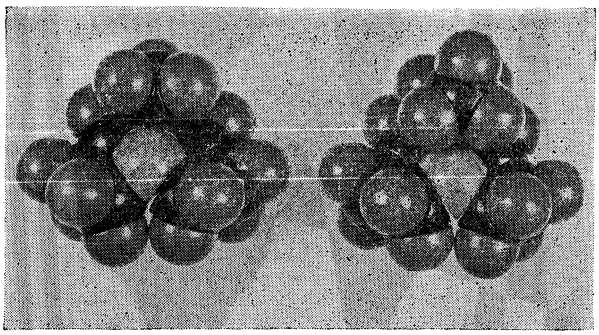


Fig. 1.

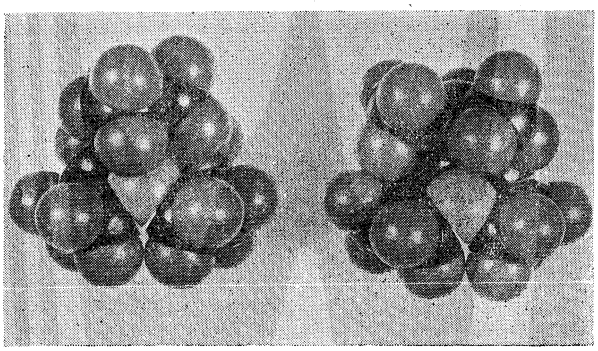


Fig. 2.

Fig. 3.

Fig. 4.

in 50% aqueous methanol for the series of 8-alkylpyrrolizidines are indicated in Table I, as corrected to 25° and accurate within ±0.01 *p*H unit. In the homologous series of 8-alkylpyrrolizidines, the pK_H values decrease in the order: 8-methyl > 8-ethyl > 8-*n*-propyl, corresponding to the increase in steric hindrance of the 8-alkyl group. The steric effect outweighs the positive inductive effect (+I) of the alkyl group introduced since, in consideration of the polar effect alone, the order of basicities would be the reverse of the observed order. The proximate pK_H values for 8-isopropyl- and 8-methylpyrrolizidine indicate that in IId the increased positive inductive effect of the isopropyl group and the increased steric effect (similar to that in IIb) are about equal in their counteracting influences. The basicity value for 8-methylpyrrolizidine is greater by 0.20 *p*H unit than that for 2-methylpyrrolizidine. This is probably due to the inductive effect of the methyl group, which is only one carbon removed from the nitrogen in the 8-methylpyrrolizidine. A comparison of the effect on basicity of the introduction of a methyl group into the 2- and 8-positions of pyrrolizidine with that of the introduction of a methyl group into the corresponding positions of 1-ethylpiperidine[13] indicates close analogy between the two systems. Thus, the basicity value for 1-ethyl-2-methylpiperidine is greater by 0.22 *p*H unit than that for 1-*n*-propylpiperidine. The basicity value for 1,2-diethylpyrrolidine (IV, Table I) is much lower than that for the pyrrolizidines, a fact which illustrates that the bicyclic bases (five-membered rings) are stronger than analogous monocyclic bases (five-membered ring) with the same number of carbon atoms and the same mode of attachment.

The acid in these determinations of basicity was the proton, since the pK_H values were determined by half-neutralization of the amine with dilute hydrochloric acid. It is apparent from Brown's work[3,10,11] that a bulkier acid, such as boron trifluoride or trimethylboron, would amplify the steric effect of the 8-alkyl substituent on the basicity of the pyrrolizidine nucleus. The results of passing boron trifluoride through the liquid amines are summarized in Table I. Solid adducts of boron trifluoride were formed immediately with IIa, b and d, and a distillable liquid adduct, b.p. 253° (755 mm.), was obtained with IV. No solid product was obtained with IIc, and if any adduct was formed, it was highly unstable since IIc could be distilled from the reaction mixture. Thus the greater F-strain in 8-*n*-propylpyrrolizidine revealed in the reaction with a protonic acid is indicated more strikingly in the reaction with boron trifluoride. An interesting but possibly fortuitous correlation between pK_H values and picrate melting points has also been included in Table I.

Experimental[14]

Methyl γ-Nitroheptanoate and Dimethyl γ-*n*-Propyl-γ-nitropimelate (Ic).—The esters were made from 1-nitrobutane[15] essentially by the procedure described by Bruson[7] for the condensation of 1-nitropropane with methyl acrylate, with the exception that three times the recommended amount of Triton B was employed. The methyl γ-nitroheptanoate was obtained in 51% yield as a colorless liquid, b. p. 102° (2 mm.); $n^{20}D$ 1.4388.

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.18; H, 7.97; N, 7.64.

The dimethyl γ-*n*-propyl-γ-nitropimelate was obtained in 36% yield as a yellow-green oil, b. p. 157° (1 mm.); $n^{20}D$ 1.4612; d^{20}_4 1.133.

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09; *MR*D, 66.57. Found: C, 53.07; H, 7.74; N, 5.29; *MR*D, 66.63.

Methyl γ-Nitroisoheptanoate and Dimethyl γ-Isopropyl-γ-nitropimelate (Id).—Using the same procedure, 75.7 g. (0.734 mole) of 1-nitro-2-methylpropane (nitroisobutane)[16] was caused to condense with 130 g. (1.5 moles) of methyl acrylate in the presence of 30 g. of Triton B. The methyl γ-nitroisoheptanoate was obtained as a colorless liquid, b. p. 102° (2 mm.); $n^{20}D$ 1.4397; d^{20}_4 1.115; yield, 82.5 g. (59.3%).

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.08; H, 7.92; N, 7.48.

The dimethyl γ-isopropyl-γ-nitropimelate was obtained as a green oil, b. p. 168° (2 mm.); d^{20}_4 1.138; yield, 19.1 g. (9.5%).

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 54.09; H, 7.68; N, 4.58.

(13) Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

(14) Melting points and boiling points have not been corrected for stem immersion. We gratefully acknowledge the assistance of Donald L. Felley and Gradus L. Shoemaker.

(15) We are indebted to Dr. Robert F. Taylor, Commercial Solvents Corporation, for this material.

(16) Made by the method of Shaw, *Bull. roy. acad. Belg.*, [3] **34**, 1019 (1897), modified by the use of ether solvent in the reaction mixture.

The condensation of 79 g. of methyl γ-nitroisoheptanoate with 40 g. of methyl acrylate in the presence of 30 ml. of *t*-butyl alcohol and 25 g. of Triton B produced 23 g. (20%) of Id, and 69% of the isoheptanoate was recovered. The condensation of 54.2 g. of methyl γ-nitroisoheptanoate with 40 g. of methyl acrylate in the presence of 30 ml. of *t*-butyl alcohol and 30 g. of diethylamine produced 32.5 g. (41%) of dimethyl γ-isopropyl-γ-nitropimelate, and again most of the unreacted monobasic ester was recovered.

1,2-Diethylpyrrolidine (IV)

One-Step Reduction.—A solution of 38 g. (0.2 mole) of ethyl γ-nitrocaproate[7] (b. p. 93° (1 mm.), $n^{20}D$ 1.4358) in 100 ml. of ethanol was reduced with hydrogen in the presence of 20 g. of copper chromite at 250° and 300–350 atm. An exothermic reaction began when the temperature reached 125°, and the theoretical amount of hydrogen was absorbed after five hours at 250°. The catalyst was removed by filtration, 200 ml. of benzene was added, and the benzene–ethanol–water azeotrope was removed at 63–65° followed by solvent at 78–80°. The 1,2-diethylpyrrolidine was collected at 140–141° (750 mm.); $n^{20}D$ 1.4372; d^{20}_4 0.8098; yield 11.2 g. (44%). The analysis and physical properties of the tertiary amine and the analysis of its picrate were consistent with the structure assigned to this product.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01; MR_D, 41.06. Found: C, 75.79; H, 13.72; N, 10.96; MR_D 41.18.

When the same procedure was followed using methanol as the solvent, a high-boiling liquid was obtained, b. p. 230–233° (750 mm.); $n^{20}D$ 1.4535; d^{20}_4 0.9804, the identity of which has not been established.

Anal. Found: C, 62.63; H, 11.25.

Two-Step Reduction.—A solution of 56 g. (0.31 mole) of ethyl γ-nitrocaproate in 125 ml. of ethanol was reduced with hydrogen in the presence of 1 g. of platinum oxide catalyst at 2–4 atm. and 25°. After seven days the theoretical amount of hydrogen for reduction of the nitro group had been absorbed, and the catalyst was removed by filtration. The filtrate was reduced further at 250° and 300 atm. with hydrogen in the presence of 20 g. of copper chromite. After five hours the theoretical amount of hydrogen had been absorbed. Twenty grams (50%) of 1,2-diethylpyrrolidine was isolated in the same manner as in the more convenient one-step hydrogenation of ethyl γ-nitrocaproate in ethanol.

1,2-Diethylpyrrolidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 120–121°. The melting point of a mixture with picric acid was depressed.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: N, 15.72. Found: N, 15.86.

8-*n*-Propylpyrrolizidine (IIc) and 8-Isopropylpyrrolizidine (IId).—Method and yield are similar for these compounds and for IIb, starting with the appropriate γ-alkyl-γ-nitropimelic ester. The synthesis of IId serves as an example. A solution of 46 g. (0.167 mole) of dimethyl γ-isopropyl-γ-nitropimelate (Id) in 90 ml. of purified dioxane was hydrogenated at 250–260° and 200–350 atm. in a high-pressure bomb. Rocking was begun when the temperature in the bomb reached 100°. After fifteen minutes at 125° sufficient hydrogen had been absorbed to reduce the nitro group, and rocking was discontinued until the temperature reached 260°. After seven hours, the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was fractionated at atmospheric pressure. The colorless, basic fraction distilling at 187–193° (745 mm.) was collected and purified by redistillation; yield, 16.5 g. (64.4%).

8-*n*-Propylpyrrolizidine: b. p. 192° (745 mm.); $n^{20}D$ 1.4632; d^{20}_4 0.8918.

8-Isopropylpyrrolizidine: b. p. 191° (745 mm.); $n^{20}D$ 1.4692; d^{20}_4 0.8899.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.45; N, 9.14; MR_D, 48.10. Found (IIc): C, 77.99; H, 12.66; N, 8.57; MR_D, 47.35. Found (IId): C, 77.73; H, 12.40; N, 8.52; MR_D, 47.98.

8-*n*-Propylpyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed brilliant yellow needles, m. p. 156–157°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.54; H, 5.75; N, 14.73.

8-Isopropylpyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed brilliant yellow needles which melted, with decomposition, at 228–229°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.10; H, 5.80; N, 14.57.

Determination of Basicity Constants.—The pK_H values were determined by dissolving a weighed portion of freshly distilled amine, calculated to require 15–20 ml. of 0.12 *N* hydrochloric acid, in 90 ml. of aqueous methanol calculated to be about 50% methanol at the end of the neutralization. The amount of 0.1200 *N* hydrochloric acid necessary to react with exactly half of the amine present was then added, and the solution was allowed to stand for twenty minutes. The *p*H of the solution was then measured using a Beckmann model G (laboratory model) *p*H meter with a high *p*H glass electrode (designed for *p*H measurements from 9 to 14). Duplicate or triplicate measurements were made in each case, and the pK_H values were corrected to 25°.[17] The method was checked to determine its accuracy. The pK_H value for one of the amines was determined at one-half the amine concentration used in the series. The identical value observed indicated that activities were not an influential factor in the determination. Also, the *p*H values at one-third and two-thirds neutralization of one of the amines were measured, and the pK_H was calculated by use of the equation $pK_H = pH \pm \log 2$. The identity of the values thus obtained with the *p*H at one-half neutralization was substantial proof that the half-neutralization point was actually being determined by the general procedure employed. The pK_H values are considered accurate within ±0.01 *p*H unit.

Summary

1. The preparation of pyrrolizidines by the one-step catalytic reduction of γ-nitropimelic esters has been extended to the synthesis of 8-*n*-propyl- and 8-isopropyl-pyrrolizidine.

2. Comparison of the pK_H values of 2-methyl-, 8-methyl-, 8-ethyl-, 8-*n*-propyl- and 8-isopropyl-pyrrolizidine have shown that the basicity of the pyrrolizidine is decreased as the length of the 8-alkyl group is increased.

URBANA, ILLINOIS RECEIVED FEBRUARY 26, 1948

(17) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND THE LILLY RESEARCH LABORATORIES]

The Action of Alkali on Chloral-quinaldine

BY R. B. WOODWARD AND EDMUND C. KORNFELD

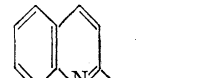
By treatment of chloral-quinaldine (I) with alcoholic sodium hydroxide, Einhorn[1] obtained β-(2-quinolyl)-acrylic acid (II), and a *bright orange* sodium salt, $C_{12}H_{10}O_2NNa\cdot 3H_2O$, which was formulated as a derivative of the hydroxyacid (III).

I

II

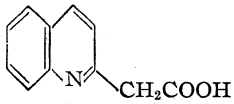
The salt was supposed to have been transformed by oxidation in turn to quinoline-2-acetaldehyde (IV) and quinoline-2-acetic acid (V). Borsche[2]

III

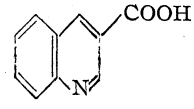


IV

noted that the properties of the acid obtained by oxidation were inconsistent with the formulation as (V), and was able to demonstrate that the substance was quinoline-3-carboxylic acid (VI), but did not challenge the expressions for the anterior substances.

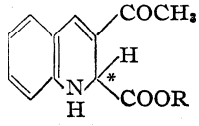


V

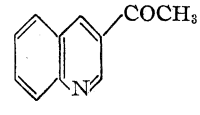


VI

In this communication it is shown that the orange sodium derivative is in fact a salt of 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid (VII, R = H).

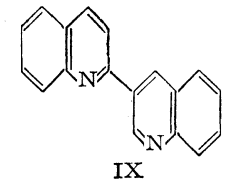


VII

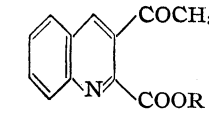


VIII

We were able to demonstrate first, by direct comparison, that the carbonyl derivative obtained on oxidation, and formulated by Einhorn as (IV), is 3-acetyl-quinoline[3] (VIII). The (erroneous) proof of the structure (IV) rested on the conversion of the substance, by condensation with *o*-aminobenzaldehyde, to 3-(2-quinolyl)-quinoline (IX); it is interesting to note that 3-acetylquinoline gives the same product (IX) in that reaction.[4] The orange salt, and the ethyl ester (VII, R = Et), m. p. 110.5–111.5°, obtained from it, were



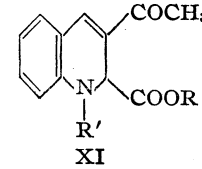
IX



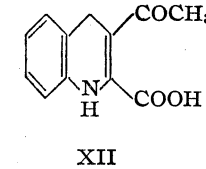
X

oxidized by potassium permanganate in aqueous pyridine to 3-acetylquinoline-2-carboxylic acid[3] (X, R = H) and the corresponding ester[3] (X, R = Et), respectively.

Further, the methyl ester (VII, R = Me) was transformed by benzoyl chloride in pyridine to an N-benzoyl derivative (XI, R = Me, R′ = C_6H_4-CO—), m. p. 140–141°, while the ethyl ester (VII, R = Et) gave with acetic anhydride the N-acetyl derivative (XI, R = Et, R′ = CH_3CO—), m. p. 130–131°. These facts necessitate the formulation of the original acid as (VII, R = H) or XII. An unequivocal decision in favor of (VII,



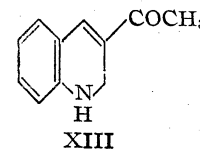
XI



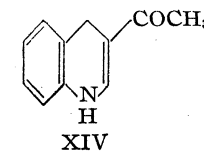
XII

R = H) was made possible through the isolation, through resolution by brucine, of an optically active sodium salt, $[\alpha]^{28}D$ −430°. Of the two possibilities, only VII possesses an asymmetric carbon atom (starred).

We turn now to a consideration of certain remarkable properties of the orange acid (VII, R = H). When this substance is pyrolyzed, 3-acetylquinoline and a *product*, $C_{11}H_{11}ON$, are formed. The latter was isolated by previous investigators,[1,2] but was not identified. We have found that the substance is oxidized by aqueous permanganate to 3-acetylquinoline, and that in turn, it may be resynthesized by the hydrogenation of the latter substance in the presence of Raney nickel. Since the compound is colorless, the expression (XIII) is excluded, and it seems probable that the structure (XIV) represents the



XIII



XIV

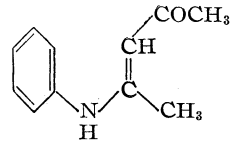
compound correctly. This conclusion is supported by the close similarity of the ultraviolet absorption spectrum of the substance (Fig. 1) to that of acetylacetone anil (XIVa) which contains the

(1) Einhorn, *Ber.*, **19**, 904 (1886); *cf.* also Einhorn and Sherman, *Ann.*, **287**, 38 (1895).

(2) Borsche and Manteuffel, *ibid.*, **526**, 22 (1936).

(3) Koller, *Monatsh.*, **52**, 59 (1929).

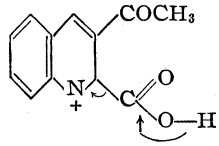
(4) Koller and Ruppersberg, *ibid.*, **58**, 238 (1931).



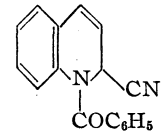
XIVa

same chromophore as XIV. The failure of the hydrogenation to proceed beyond the dihydro-stage, as well as the lack of carbonyl reactivity in (XIV) may be attributed to the interaction, through the double bond, between the imino and the carbonyl groups. The formation of (XIV) from (VII, R = H) takes place by decarboxylation, with simultaneous wandering of a double bond; it is worthy of note that not infrequently the decarboxylation of β,γ-unsaturated acids takes place with movement of the double bond to the α,β-position.[5]

Another interesting transformation of the orange acid is its spontaneous air oxidation. When the acid is exposed to air, the color gradually fades, and changes from orange to buff. The conversion is remarkably accelerated by light, and the sole product is 3-acetylquinoline. No 3-acetylquinoline-2-carboxylic acid (X, R = H) can be isolated and, further, the latter acid is stable under the conditions of the experiment. It is clear that (X, R = H) cannot be an intermediate in the change and that another intermediate, more subsceptible to decarboxylation, must be involved. We suggest that the withdrawal of two electrons and a proton (probably in stages) from (VII, R = H) gives an intermediate (XV) in which the environment of the carboxyl group is favorable to the ready loss of carbon dioxide, with the electronic shift shown (XV, arrows); the



XV



XVI

change thus becomes fully analogous to the decarboxylation of β-keto-acids, β-bromo-acids, and other acids containing properly situated electron-accepting centers. A similar mechanism must be operative in the aqueous permanganate oxidation of (VII) since, again, 3-acetylquinoline is the sole product, and (X, R = H) is stable under the conditions of the experiment (presence of permanganate *and* manganese dioxide).

The behavior of the N-benzoyl derivative (XI, R = Me, R′ = C_6H_5CO—) on acid hydrolysis presents an interesting contrast to that of N-benzoyl-2-cyano-1,2-dihydroquinoline (XVI).[6] While the latter undergoes a remarkable cleavage to benzaldehyde and quinoline-2-carboxylic acid

(5) *Cf.* Wallach, *Ann.*, **365**, 258 (1909). The change is also formally similar to that which accompanies the decarboxylation of β-keto-acids.

(6) Reissert, *Ber.*, **38**, 1610 (1905).

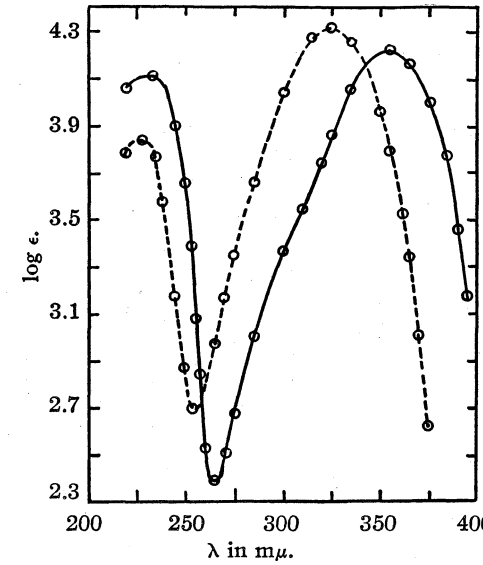
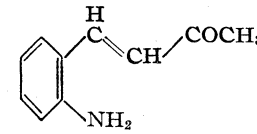


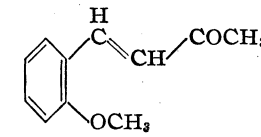
Fig. 1.— ----, Acetylacetone anil; —, 3-acetyl-1,4-dihydroquinoline.

(the reaction forms the basis of a general method for the preparation of aldehydes from acids), (XI, R = Me, R′ = C_6H_5CO—), under the same conditions, gave only the corresponding *acid* (XI, R = H, R′ = C_6H_5CO—), m. p. 198° (dec.) on more vigorous treatment, benzoic acid was split off, but in no instance could benzaldehyde be detected.

The color of the compound (VII) and its derivatives is consonant with the structure now assigned to it. It was, in fact, this property which revealed at once that the previous structure (III) could not be correct, since from the point of view of light absorption III is simply a 2-alkylquinoline, and consequently colorless. On the other hand (VII) possesses the absorbing system of *o*-aminobenzalacetone (XVII); unfortunately, the

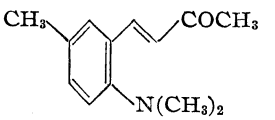


XVII

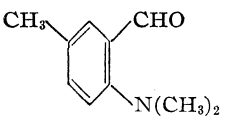


XVIII

latter substance does not appear to be capable of existence, in consequence of its ready conversion to quinaldine. However, there can be no doubt that it (and VII) should be colored. The corresponding methoxy compound (XVIII), for example, is bright orange. We have obtained absorption data which provide further support for these views. In view of the non-existence of (XVII), we had hoped to examine the spectrum of 2 - dimethylamino - 5 - methylbenzalacetone (XIX); the methyl group is (to a good approximation) irrelevant to the spectral discussion, and its presence offers preparative advantages (*vide infra*). It might be doubted that the spectrum of (XIX) and that of (VII) would be directly com-



XIX



XX

parable, in view of the considerable bulk of the N-methyl groups, which might force the dimethylamino group, or the adjacent side chain out of the plane, with consequent resonance damping; in any case, remarkably, and possibly for steric reasons, we were unable under any conditions to bring about the condensation of 2-dimethylamino-4-methylbenzaldehyde (XX) with acetone. On the other hand, we did determine the ultraviolet absorption spectrum of the aldehyde (XX) (Fig. 2), of *p*-dimethylaminobenzaldehyde (XXI) (Fig. 2)

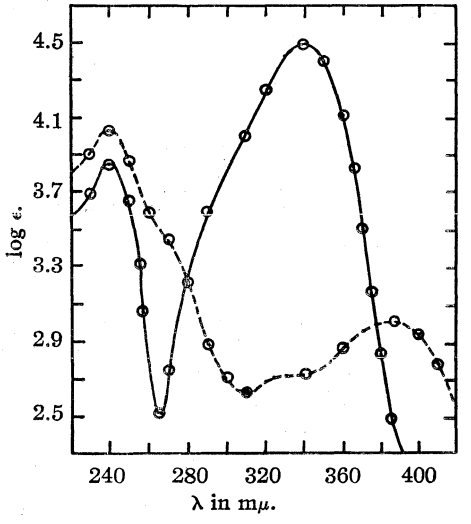


Fig. 2.— —*p*-Dimethylaminobenzaldehyde; ---, 2-dimethylamino-5-methylbenzaldehyde.

and *p*-dimethylaminobenzalacetone (XXII) (Fig. 3). It may be expected that the differences between the spectra of the *p*-substituted aldehyde and its condensation product will be reflected in the comparison of the spectrum of (XX) with that (Fig. 4) of the orange compound and its derivatives. The fact that this is the case provides confirmation of our view of the constitution of these substances; in the change XXI → XXII, a short wave length band (240 mμ) is displaced to 250 mμ (Δ = 10 mμ) and a long wave length band (338 mμ) moves to 385 mμ (Δ = 47 mμ). Correspondingly, in comparing (XX) with (VII), a shift of a short wave length band (240 mμ) to 250 mμ (Δ = 10 mμ), and of a long wave length band (370 mμ) to 415 mμ (Δ = 45 mμ) is observed. In the latter case, a third band, discernible only as a shoulder (~270 mμ) in the spectrum of (XX) appears as a well-defined maximum at 320 mμ in that of (VII). Furthermore, the relative intensities of the various bands, which differ markedly in the *ortho* as compared with the *para* series, are in each case comparable within the series. The greater complexity

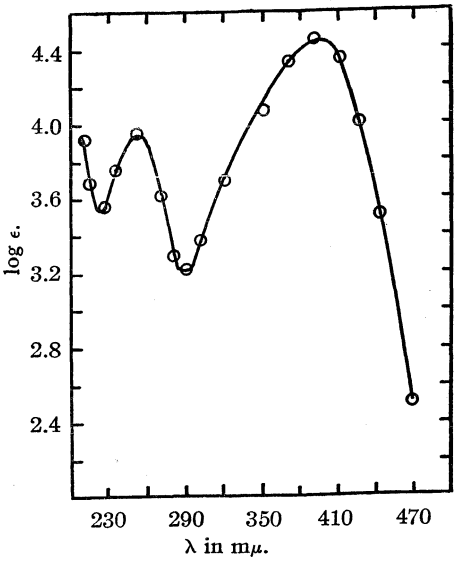


Fig. 3.—*p*-Dimethylaminobenzalacetone.

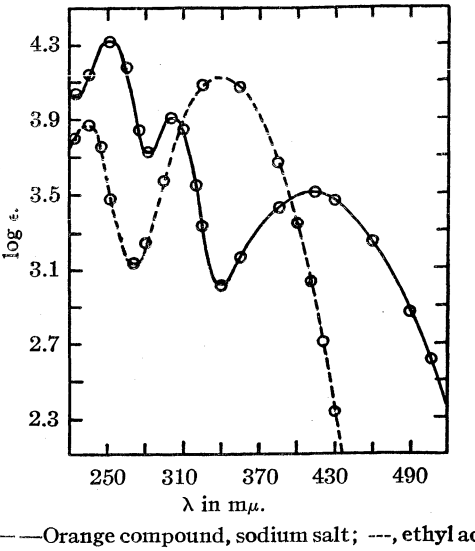
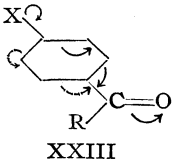
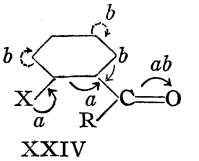


Fig. 4.— —Orange compound, sodium salt; ---, ethyl acetopyruvate-anil.

of the spectra of the *ortho* as compared with the *para* compounds is another example of a general effect[7] which probably has its origin in the greater symmetry of the latter; thus, while the available oscillatory paths in (XXIII) are indistinguishable, in (XXIV), two distinct oscillations of different



XXIII

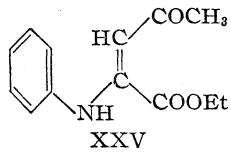


XXIV

length (*a* or *b*) may be envisaged, whose excitations should involve different energies and, corre-

(7) *Cf.* Dede and Rosenberg, *Ber.*, **67**, 147 (1934); Morton and Stubbs, *J. Chem. Soc.*, 1347 (1940); Blout and Gofstein, THIS JOURNAL, **67**, 15 (1945).

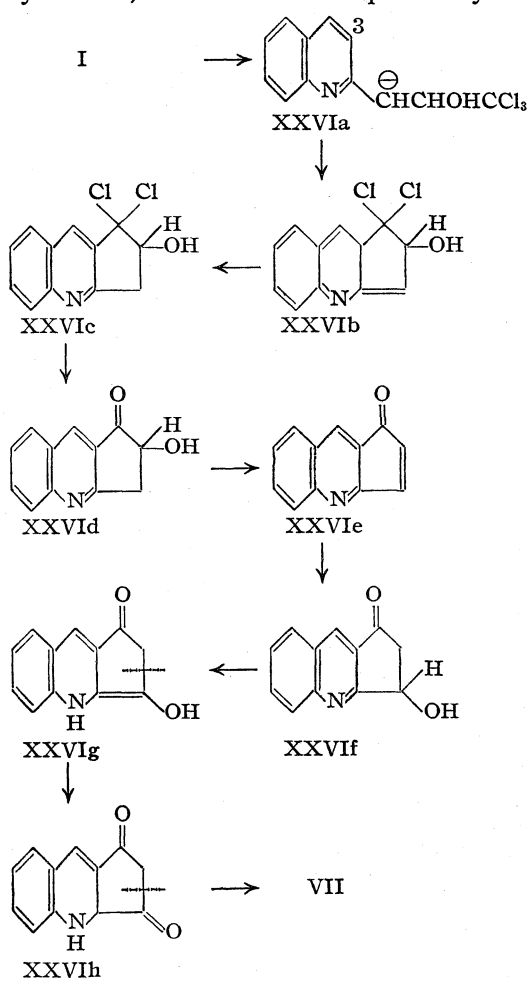
spondingly, different absorption bands. A final spectrographic check on our structural conclusions is provided by the absorption spectrum (Fig. 4) of (XXV), which contains the absorbing system



XXV

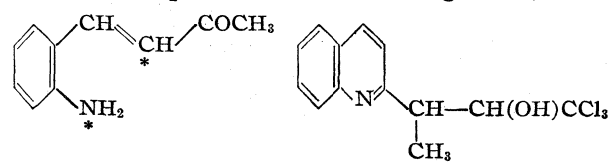
of (XII). It is clear that this spectrum bears no resemblance to those of the orange acid and its esters, and that consequently the expression (XII) is excluded for these substances.

There remains only a consideration of the mechanism of the remarkable change, I → VII. The following mechanistic scheme is a reasonable one; it is intended as an outline only, and in particular, the sequence of steps, and the exact nature of the various intermediates may be varied considerably. Thus, the removal of a proton by base



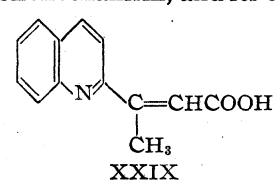
XXVIa XXVIc XXVIb XXVId XXVIe XXVIg XXVIf XXVIh VII

gives XXVIa, in which the availability of electrons at C.3 permits attack on the trichloromethyl group, with loss of halide ion and cyclization. The α,γ shift (XXVIb → XXVIc) with aromatization, and the hydrolysis of the remaining chlorine atoms are unexceptional. The loss of water (XXVId → XXVIc) is permissible in view of the β-position of the hydroxyl group with respect to the quinoline nucleus and its subsequent readdition in the opposite sense (XXVIe → XXVIf) is characteristic of α,β-unsaturated carbonyl compounds. The change XXVIf → XXVIg is reminiscent of the familiar α-methylpyridine–α-pyridone methide equilibrium, which in this case is rendered irreversible by the ketonization, XXVIg → XXVIh. Normal cleavage of the β-diketone (XXVIh) then leads to VII. Complicated as the suggested sequence is, it is difficult to conceive of a simpler series to account for so deep-seated a change. We have considered one other possibility, namely, that in effect the chloral-quinaldine (I) breaks down to give *o*-aminobenzalacetone (XXVII) and chloral, or equivalents of these fragments; sub-



XXVII XXVIII

sequent re-condensation of the aldehyde group of chloral at the starred positions, followed by hydrolysis could lead to (VII). It will be noted that a prerequisite for the mechanism outlined above is the presence of *two* hydrogen atoms on the carbon α to the quinoline nucleus. On the other hand, the second mechanism possesses no such feature. Consequently, the chloral-α-ethylquinoline condensation product (XXVIII) should undergo an analogous rearrangement to 3-propionyl-1,2-dihydroquinoline-2-carboxylic acid, if the second mechanism is operative, but no such change is possible in the event that the alternative sequence is correct. We have prepared XXVIII and observed that it is smoothly converted by alcoholic sodium hydroxide to β-(α-quinolyl)-crotonic acid (XXIX); no evidence of the formation of a rearrangement product analogous to (VII) could be obtained. Consequently, we reject the cleavage–recondensation mechanism, and its equivalents.

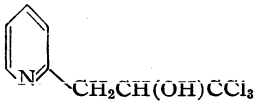


XXIX

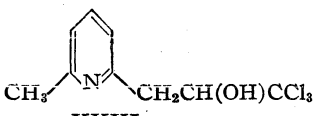
In conclusion, we may point out that we have prepared the chloral condensation products XXX,[8] XXXI,[9] XXXII[10] and XXXIII[11] and subjected them to the conditions which bring about the change I → VII. In none of these cases

(8) Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939).
(9) Einhorn and Gilbody, *Ber.*, **26**, 1414 (1893).
(10) Koenigs and Menzel, *ibid.*, **37**, 1330 (1904).
(11) Clemo and Hoggarth, *J. Chem. Soc.*, 1241 (1939).

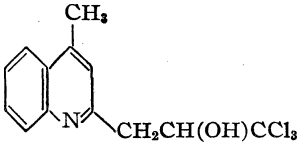
have we observed any reaction other than the normal conversion to the corresponding substituted acrylic acid.



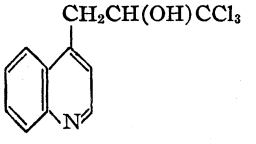
XXX



XXXI



XXXII



XXXIII

Experimental

Chloralquinaldine (I).—The method of Bachman[12] was used. It was found to be essential that the initial exothermic reaction be moderated so that the temperature did not exceed 100°. Dark-colored by-products were formed if the mixture was allowed to overheat; yield, 71%, m. p. 145–146°.

Sodium Salt of 2-Carboxy-3-acetyl-1,2-dihydroquinoline (VII, R = Na).—This product was obtained in 35–45% yield by the method of Einhorn.[1] The free acid, m. p. 123–125° (dec.), was obtained by neutralizing a concentrated aqueous solution of the sodium salt with hydrochloric acid.

The acid was resolved in the following way: the orange sodium salt (32.8 g., 0.112 mole) and brucine sulfate (56 g.) were dissolved together in 500 ml. of hot water. The product which separated slowly from the cooled solution was collected and recrystallized twice from water, with considerable loss. The salt was then decomposed by taking up in 50 ml. of water and adding a solution containing 1.8 g. of sodium hydroxide. Brucine was removed by three extractions with chloroform. The aqueous layer was cooled, and the *l*-sodium salt which separated was recrystallized from dilute ethanol, m. p. 187–191°; $[\alpha]^{28}D$ −430° (l = 2 dcm, C = 0.5 g./100 ml. H_2O). A sample for analysis was dried at 125°.

Anal. Calcd. for $C_{12}H_{10}O_3NNa$: C, 60.25; H, 4.21; N, 5.86. Found: C, 60.33; H, 4.51; N, 5.61.

2-Carbethoxy-3-acetyl-1,2-dihydroquinoline (VII, R = Et).—The sodium salt trihydrate of 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid (4.0 g.) was suspended in 40 ml. of absolute ethanol, the solution was immersed in ice, and saturated with dry hydrogen chloride. After twelve hours the solvent was removed *in vacuo*, the residue was stirred with ice and water and neutralized with sodium bicarbonate. After addition of cold 10% sodium hydroxide (25 ml.) the product was removed, washed with water and dried; yield, 2.16 g. (65%). Recrystallized from dilute ethanol, it formed bright-yellow needles, m. p. 110.5–111.5°. *Anal.* Calcd. for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16. Found: C, 68.63; H, 5.75.

The ester was obtained in like yield by direct esterification of the free acid (VII, R = H). The corresponding **methyl ester (VII, R = Me)** was obtained in a similar manner. After repeated recrystallization from dilute methanol, it formed golden-yellow prisms, m. p. 140–141°. It is undoubtedly identical with the ester, m. p. 145°, obtained by Borsche[2] from the acid and diazomethane. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67. Found: C, 67.22; H, 5.21.

N-Benzoyl-2-carbomethoxy-3-acetyl-1,2-dihydroquinoline (XI, R = Me, R′ = C_6H_5CO—).—The above methyl ester (VII, R = Me, 0.95 g.) and benzoyl chloride (0.62 g.) were dissolved in 10 ml. of dry pyridine. After standing several days the solvent was removed *in vacuo* and the residue was made alkaline with dilute sodium bicarbonate solution. The product which oiled out was washed by decantation with water and recrystallized from methanol; yield, 0.4 g., pale yellow crystals, m. p. 140–141°. *Anal.* Calcd. for $C_{20}H_{17}O_4N$: C, 71.63; H, 5.11. Found: C, 71.84; H, 4.87.

When this benzoyl derivative (0.1 g.) was allowed to stand for two days with 1 ml. of concentrated hydrochloric acid, addition of water gave the crystalline free *acid* (XI, R = H; R′ = C_6H_5CO—) which was recrystallized from dioxane; m. p. 198–199° (dec.). *Anal.* Calcd. for $C_{19}H_{15}O_4N$: C, 71.02; H, 4.71. Found: C, 70.33; H, 4.89.

More drastic hydrolysis of the N-benzoyl ester (XI, R = Me, R′ = C_6H_5CO—) with concentrated hydrochloric acid at 100° gave benzoic acid in 55% yield and an unidentified oil. No benzaldehyde could be detected.

2-Carbethoxy-1,3-diacetyl-1,2-dihydroquinoline (XI, R = Et, R′ = CH_3CO—).—2-Carbethoxy-3-acetyl-1,2-dihydroquinoline (VII, R = Et, 0.6 g.) was dissolved in 2 ml. of pyridine and 3 ml. of acetic anhydride; the solution was warmed on the steam-bath for three hours. The excess solvents were removed *in vacuo* and ice-water was added to the residue. The oil soon solidified and was collected, washed and recrystallized from ethanol; yield of pale-yellow prisms, 50%; m. p. 131–132°. *Anal.* Calcd. for $C_{16}H_{12}O_4N$: C, 66.88; H, 5.96. Found: C, 67.32; H, 5.69.

3-Acetylquinoline (VIII).—This ketone was prepared by permanganate oxidation of the sodium salt (VII, R = Na) according to Borsche and Manteuffel[2] (yield, 85%), by chromic acid oxidation (A) of the salt or by the action of light and air on the free acid (VII, R = H) (B).

(A) The sodium salt (VII, R = Na, 5 g.) was dissolved in a mixture of 150 ml. of glacial acetic acid and 100 ml. of water. Concentrated sulfuric acid (2 ml.) was added followed by a solution of 1.85 g. of potassium dichromate in 30 ml. of water. The solution which turned green was concentrated *in vacuo* and the residue was made alkaline with ammonium hydroxide. The solution of the residue in ethanol was filtered and evaporated *in vacuo*. The residue was crystallized twice from water. It then had m. p. 96–98° and mixed with a sample from the permanganate oxidation of (VII, R = Na) or with an authentic sample of 3-acetylquinoline (see below) melted at 96–99°.

(B) A sample of the orange acid (VII, R = H) was allowed to stand in air for eleven days with frequent stirring of the crystals. The bright orange color gradually faded and finally a buff-colored crystalline solid remained. The decomposition was markedly favored by sunlight; exposure in thin layers was best. The product was stirred with 10% sodium bicarbonate solution, removed by filtration and washed with water. Recrystallization from water gave 3-acetylquinoline, m. p. 96–98°. From the sodium bicarbonate solution a small further quantity of 3-acetylquinoline, but no 3-acetylquinoline-2-carboxylic acid was obtained.

For comparison authentic samples of 3-acetylquinoline (VIII), m. p. 97–99°, 3-acetylquinoline-2-carboxylic acid (X, R = H), m. p. 142–143° (dec.), and the corresponding ethyl ester (X, R = Et), m. p. 93–94.5°, were prepared by the condensation of *o*-aminobenzaldehyde (Raney nickel reduction of *o*-nitrobenzaldehyde[13]) with ethyl acetopyruvate followed by hydrolysis and decarboxylation, according to Koller.[3]

Oxidation of (VII, R = Na) and (VII, R = Et) with Permanganate in Aqueous Pyridine.—While permanganate oxidation of (VII, R = Na) according to Borsche's procedure gives only 3-acetylquinoline, careful oxidation in aqueous pyridine gives some 3-acetylquinoline-2-carboxylic acid:

One hundredth of a mole (2.96 g.) of the sodium salt was suspended in 140 ml. of pyridine. A solution of 1.2 g. in potassium permanganate in 140 ml. of warm pyridine was then added. Little evidence of reaction was noted until 50 ml. of water was added. After a few minutes the pre-

(12) Alberts and Bachman, THIS JOURNAL, 57, 1284 (1935).

(13) Ruggli and Schmid, *Helv. Chim. Acta*, 18, 1235 (1935).

cipitated manganese dioxide was removed and the filtrate was concentrated to a very small volume. Addition of a little sodium acetate caused the crude acid to separate (m. p. 120° (dec.)). The product was stirred with 2 ml. of 10% sodium bicarbonate and the mixture was filtered to remove 3-acetylquinoline. The filtrate was first acidified with hydrochloric acid and further concentrated *in vacuo*. The pure acid, m. p. 141–142° (dec.), separated as white needles from the cooled solution. The mixed melting point with authentic 3-acetylquinoline-2-carboxylic acid, m. p. 142–143° (dec.) (see above), was likewise 141–142° (dec.).

The ethyl ester (VII, R = Et) (2.0 g.) was dissolved in 200 ml. of pyridine and 200 ml. of water. The solution was cooled in ice to 2°. Potassium permanganate (1.4 g.) in 80 ml. of pyridine and 80 ml. of water was added dropwise, with stirring and cooling in ice. After the addition which took about twenty minutes the solution was warmed to room temperature and the manganese dioxide was removed. The filtrate was treated with 0.75 ml. of concd. hydrochloric acid and concentrated *in vacuo* to a very small volume. The residue which crystallized was suspended in a little ice water and was filtered and washed with water; yield, 50%. Recrystallization from ethanol gave white needles, m. p. 93–94°, mixed with an authentic sample (see above) of (X, R = Et), m. m. p. 93–94.5°.

Stability of (X, R = H) under Conditions of Aqueous Permanganate Oxidation.—A solution containing 5 ml. of 1% potassium permanganate, 0.5 ml. of 10% sodium bicarbonate and 4 ml. of water was cooled in ice and 5 ml. of 1% sodium bisulfite was added. 3-Acetylquinoline-2-carboxylic acid (0.1 g.) was added and the solution was heated to boiling. Manganese dioxide was removed and the filtrate was concentrated *in vacuo*. Acidification with one drop of concd. hydrochloric acid yielded the unchanged acid, m. p. 142–143° (dec.).

3-Acetyl-1,4-dihydroquinoline (XIV). (a) **By Pyrolysis of (VII, R = H).**—3-Acetyl-1,2-dihydroquinoline-2-carboxylic acid (8.1 g.) was placed in a 200-ml. round-bottom flask and heated in a metal-bath for twenty minutes at 180–190°. (Nitrogen was bubbled through the flask during the pyrolysis.) The resultant red oil was cooled and taken up in ethanol. From the cooled solution colorless plates separated which after recrystallization from dilute ethanol melted at 177–181°.

(b) **By Catalytic Hydrogenation of 3-Acetylquinoline.**—One gram of the ketone was hydrogenated at atmospheric pressure in 100 ml. of absolute ethanol using about 2 g. of Raney nickel catalyst. The theoretical volume of hydrogen was absorbed in two hours. The catalyst was removed and the filtrate concentrated *in vacuo* to *ca.* 15 ml. From the cooled solution the product (XIV) separated in 40% yield, m. p. 174–180°.

Permanganate Oxidation of 3-Acetyl-1,4-dihydroquinoline (XIV).—A sample of the dihydro-compound (XIV) (200 mg.) was dissolved in a hot mixture of 50 ml. of water and 10 ml. of acetone. A solution of 122 mg. of potassium permanganate in 10 ml. of water was then added dropwise and with shaking in the course of ten minutes. The resulting mixture was reheated to boiling, filtered and the filtrate concentrated *in vacuo* to about 10 ml. The product crystallized on cooling and was recrystallized from water; yield, 50%; m. p. 97–98°; mixed with authentic 3-acetylquinoline, m. m. p. 98–99°.

α-Anilinoacetopyruvic Ester (XXV).—One tenth of a mole each of aniline and ethyl acetopyruvate were mixed with 40 ml. of ether. After three days the ether was evaporated and the product distilled twice *in vacuo;* yield, 65%; b. p. 170–171° (8 mm.). *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48. Found: C, 67.22; H, 6.38. The corresponding *o*-toluidino ester was prepared similarly from *o*-toluidine and ethyl acetopyruvate; yield, 57%, b. p. 154–155° (3 mm.). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93. Found: C, 68.07; H, 6.40.

2-Dimethylamino-5-methylbenzaldehyde (XX).—2-Dimethylamino-5-methylbenzyl alcohol was prepared by the method of von Braun and Kruber[14] in 45% yield, b. p. 125–127° (8 mm.). Oxidation to the aldehyde was carried out by the modified Oppenauer procedure of Woodward, Wendler and Brutschy.[15]

Potassium (20 g.) was dissolved in 400 ml. of *t*-butanol and the excess alcohol was removed completely *in vacuo*. To the dry potassium *t*-butoxide was added 33 g. of 2-dimethylamino-5-methylbenzyl alcohol, 2 liters of dry benzene and 260 g. of dry benzophenone. The mixture was refluxed in an atmosphere of nitrogen for twenty-three hours, after which it was extracted with dilute hydrochloric acid (150 ml. concd. acid and 500 ml. of water). The acid extract was made alkaline with sodium hydroxide and the product was extracted with 300 ml. of ether in three portions. The ether was removed and the residue was fractionated through a 30-cm. Podbielniak column. About 35% of dimethyl-*p*-toluidine (b. p. 90–97° (12–15 mm.)) and 40% of the bright-yellow desired aldehyde, b. p. 138–142° (16 mm.), were obtained.

The *p*-nitrophenylhydrazone, prepared in hot ethanol containing a few drops of glacial acetic acid, crystallized from ethanol in deep red-orange prisms, m. p. 185–186°. *Anal.* Calcd. for $C_{16}H_{18}O_2N_4$: C, 64.41; H, 6.08. Found: C, 64.50; H, 5.69.

The azine was prepared by allowing a solution of 0.7 g. of the aldehyde, 2.5 ml. of ethanol, 2.0 ml. of water and 0.1 g. of hydrazine hydrate to stand at room temperature for twenty-four hours. It crystallized from ethanol in lemon-yellow elongated plates, m. p. 147–148°. *Anal.* Calcd. for $C_{20}H_{26}N_4$: C, 74.49; H, 8.13. Found: C, 74.83; H, 7.92. In several attempts to effect condensation of the aldehyde with acetone, the starting material was recovered unchanged.

2-Ethylquinoline.—This compound was prepared by a method similar to that used by Ziegler[16] in the preparation of 2-butylquinoline.

Lithium metal (28 g.) was pounded into a thin sheet and the sheet was cut with scissors into small pieces, which were added quickly to 1200 ml. of dry ether. The mixture was stirred and cooled in ice while 200 g. of ethyl bromide was added dropwise during thirty minutes. The addition was conducted at such a rate that a steady reflux of the ether was maintained. Quinoline (200 ml.) was then added dropwise during fifteen minutes with stirring and cooling in ice. Unreacted lithium was then skimmed off and water was added cautiously with stirring to the mixture. The ether layer was separated, washed with water and dried over sodium sulfate. After the solvent was evaporated the residue of crude 1,2-dihydro-2-ethylquinoline was dissolved in 500 ml. of nitrobenzene. The mixture was heated slowly to 200° and was kept at that temperature five minutes. The solution was cooled, diluted with ether and the bases were extracted with dilute hydrochloric acid containing 175 ml. of the concd. acid. The acid extract was made alkaline with sodium hydroxide, and the product was taken up in ether. The ether extract was dried over potassium hydroxide after which the solvent was distilled. The residue was fractionated carefully *in vacuo*, and the 2-ethylquinoline was obtained as a yellow oil, b. p. 125–130° (15 mm.); yield 30%. The picrate was prepared, m. p. 147–149°. Doebner[17] reports a melting point of 148°.

Chloral-2-ethylquinoline (XXVIII).—To 58 g. of ethylquinoline was added 40 ml. of pyridine and 54.5 g. of chloral. The mixture was heated on a steam-bath for one and one-half hours. During the early part of the heating period, the reaction was exothermic, and the temperature was kept below 105° by periodic cooling. The product was then poured into water and was washed several times with water by decantation. Addition of a little ethanol caused the product to crystallize slowly. The adduct was filtered and washed with cold alcohol to remove dark-colored impurities, yield, 57%. A sample was recrystallized for analysis from methanol; m. p. 117–118°. *Anal.*

(14) von Braun and Kruber, *Ber.*, **45**, 2980 (1912).

(15) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945).

(16) Ziegler, *Ann.*, **485**, 182 (1931).

(17) Doebner, *ibid.*, **242**, 272 (1887).

Calcd. for $C_{13}H_{12}ONCl_3$: C, 51.26; H, 3.97. Found: C, 51.02; H, 4.11.

Hydrolysis of Chloral-2-ethylquinoline.—This hydrolysis was conducted using the same molar proportions and conditions as those used for chloral-quinaldine.

Five hundredths of a mole of the adduct was warmed with 67 ml. of ethanol, and 56 ml. of water was added slowly. The mixture was heated to boiling, and to it was added, as quickly as the vigorous ebullition would permit, a solution of 11.7 g. of sodium hydroxide in 37 ml. of water. After the reaction had subsided the solution was kept hot for five minutes and 100 ml. of hot ethanol was added. After the mixture had cooled overnight, no crystalline product had separated, so the solvents were removed *in vacuo*, and the residue was dissolved in water. The product was precipitated with 11 ml. of concd. hydrochloric acid and 5 ml. of acetic acid: yield, 79%, m. p. 190–195° (dec.). Recrystallization from dilute dioxane gave the colorless β-2-quinolylcrotonic acid, m. p. 204–206° (dec.).

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.22; H, 5.20. Found: C, 72.85; H, 5.18.

Summary

The action of alcoholic sodium hydroxide on chloral-quinaldine gives 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid.

CAMBRIDGE 38, MASS. RECEIVED OCTOBER 6, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Reaction of Benzophenone β-Naphthil with Phenylmagnesium Bromide and with Phenyllithium

BY HENRY GILMAN AND JOHN MORTON

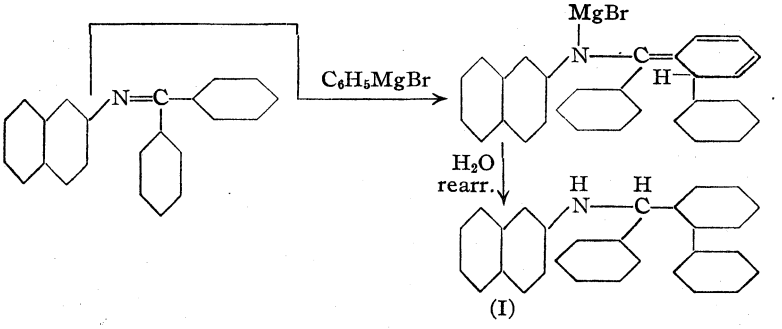
The forced reaction of phenylmagnesium bromide with benzophenone anil was reported earlier from this Laboratory.[1] It was found that the Grignard reagent undergoes a lateral-nuclear 1,4 addition to the conjugated system consisting of the anil linkage and an unsaturated linkage of one benzohydrylidene phenyl group to produce, after hydrolysis and a hydrogen shift, *o*-phenylbenzohydrylaniline. Similar lateral-nuclear additions, in which Grignard reagents add 1,4 to ketones whose carbonyl groups are conjugated with unsaturated linkages in aromatic nuclei, have since been described[2]; also, it has been demonstrated that benzalquinaldine adds phenylmagnesium bromide in a lateral-nuclear sense.[3]

Further work in this Laboratory[4] established that phenyllithium adds to benzophenone anil at the anil linkage only, yielding triphenylmethylaniline. This reaction proceeds at the temperature of refluxing ether, whereas phenylmagnesium bromide has no detectable effect upon the anil at this temperature.

The present study of the reaction of benzophenone β-naphthil with phenylmagnesium bromide and with phenyllithium, has been carried out to discover whether the substitution of an N-β-naphthyl group for the N-phenyl group of benzophenone anil could affect the course of reaction with either of the organometallic compounds, and particularly whether any addition involving the naphthyl group itself could be observed.

We find that the naphthil behaves quite similarly to the anil with respect to both organometallic compounds. With phenylmagnesium bromide at the temperature of refluxing ether, no reaction occurs; when ether–toluene is used and the temperature is raised to 90–100°, a compound melting at 185–186° and having a nitrogen content corresponding to that of *o*-phenylbenzohydryl-β-naphthylamine (I) is obtained in pure yields as high as 71%. Like the similarly substituted aniline described earlier,[1] this substance yields 9-phenylfluorene when refluxed with alcoholic hydrochloric acid.

The compound melting at 185–186° has been shown to be identical with the product of the forced reaction between *o*-biphenylylmagnesium iodide and benzal-β-naphthylamine, and was thus identified as (I). The reaction leading to the formation of compound (I) from the naphthil is shown.



(I)

We find that phenyllithium, on the other hand, reacts with the naphthil at the temperature of refluxing ether to produce a compound which melts at 185° but which gives a large depression of melting point when mixed with (I). The product from the RLi reaction proved to be identical with the product of the condensation of triphenylcarbinol with β-naphthylamine in glacial acetic acid. The

(1) Gilman, Kirby and Kinney, THIS JOURNAL, **51**, 2252 (1929).

(2) Kohler and Nygaard, *ibid.*, **52**, 4128 (1930); Allen and Overbaugh, *ibid.*, **57**, 1322 (1935); Koelsch and Rosenwald, *ibid.*, **59**, 2166 (1938); Lutz and Reveley, *ibid.*, **63**, 3178 (1941); Geissman and Morris, *ibid.*, **66**, 716 (1944); Fuson, McKusick and Spangler, *ibid.*, **67**, 597 (1945); Koelsch and Rosenwald, *J. Org. Chem.*, **3**, 462 (1938); Koelsch and Anthes, *ibid.*, **6**, 558 (1941); Fuson, Kaiser and Speck, *ibid.*, **6**, 845 (1941); Fuson, Armstrong and Speck, *ibid.*, **7**, 297 (1942).

(3) Hoffman, Farlow and Fuson, THIS JOURNAL, **55**, 2000 (1933).

(4) Gilman and Kirby, *ibid.*, **55**, 1625 (1933).

product, then, must be triphenylmethyl-β-naphthylamine (II), and its formation from the naphthil must proceed as follows

$$\beta\text{-}(C_{10}H_7)N{=}C(C_6H_5)_2 \xrightarrow{C_6H_5Li} \beta\text{-}(C_{10}H_7)NLi{-}C(C_6H_5)_3 \xrightarrow{H_2O} \beta\text{-}(C_{10}H_7)NH{-}C(C_6H_5)_3 \quad (II)$$

The pure yield is 72.5%.

Experimental

Preparation of Benzophenone β-Naphthil.—The preparation of this compound given by Reddelien[5] was modified as follows: 143 g. (0.56 mole) of benzophenone anil was heated with 148 g. (1.03 mole) β-naphthylamine in a flask equipped with a downward condenser and evacuated to 20 mm. Heat was applied with a strong, direct Bunsen flame. After a considerable quantity of aniline had distilled over, solid β-naphthylamine began to appear in the receiver, whereupon the heating was stopped. The reaction mixture solidified on cooling. Two recrystallizations of this solid from absolute ethanol gave 110 g. (64%) of greenish crystals melting at 96–97°.

Reaction of Phenylmagnesium Bromide with Benzophenone β-Naphthil.—Two-tenths mole of phenylmagnesium bromide in ether was added to 15.5 g. (0.05 mole) of benzophenone β-naphthil in toluene. There was no observable reaction during the addition. The solution was partly freed of ether by raising the temperature to 90–100°, and was stirred for ten hours at the elevated temperature. The mixture was then cooled and hydrolyzed with iced ammoniacal ammonium chloride, and the ether–toluene layer was separated and steam-distilled. The light-colored residue weighed 14–16 g. (71–82%) and generally melted between 175 and 180°. Solution of this material in boiling ethanol–toluene and subsequent extended cooling yielded 10.5–14 g. (51–71%) of pure white powder melting at 185–186°. In one case, there appeared a small amount (approx. 0.5 g.) of a resinous material which separated from the alcohol–toluene some weeks after all the amine had crystallized. The composition of this substance has not as yet been determined.

Anal. Calcd. for $C_{29}H_{23}N$: N, 3.62. Found: N, 3.45, 3.87.

Cleavage of o-Phenylbenzohydryl-β-naphthylamine and of Triphenylmethyl-β-naphthylamine.—One gram of (I) was refluxed for seventeen hours in a mixture of 10 cc. of concentrated hydrochloric acid and 30 cc. of 95% ethanol. The solution was evaporated and the solid residue treated with dilute hydrochloric acid to remove amines. The remaining solid was recrystallized from 95% ethanol to give 0.21 g. (34%) of 9-phenylfluorene, and β-naphthylamine. Triphenylmethyl-β-naphthylamine (1 g.) cleaved under the same conditions to give 0.33 g. (53%) of triphenylmethane, and β-naphthylamine. The identities of the cleavage products were established by comparison with authentic specimens.

Reaction of o-Biphenylylmagnesium Iodide with Benzal-β-naphthylamine.—Thirty grams (0.1 mole) of *o*-iodobiphenyl[1] in dry ether was added to 5 g. (0.2 atom) of magnesium turnings. Activated copper–magnesium alloy[6] was used to start the reaction, which proceeded smoothly with the formation of 0.074 mole (74%) of Grignard reagent. The resulting solution was added to a solution of 17.1 g. (0.074 mole) of benzal-β-naphthylamine[7] in toluene. Ether was distilled off until the temperature reached 90°, and the solution was stirred at this temperature for eight hours. The mixture was hydrolyzed with dilute hydrochloric acid, and the toluene layer was separated and steam-distilled. The tarry residue from this process was dissolved in hot ethanol–toluene, and this solution, after lengthy cooling, deposited 2.5 g. (8.8%) of salmon-colored crystals melting at 182–184°. Another recrystallization from the same solvent yielded 2.0 g. (7%) of almost colorless crystals melting at 185–186°. This melting point is not depressed by mixture with the compound obtained from benzophenone β-naphthil and phenylmagnesium bromide.

Reaction of Benzophenone β-Naphthil with Phenyllithium.—Twenty-three grams (0.075 mole) of the naphthil in ether was treated with 0.08 mole of phenyllithium in ether. Gentle spontaneous refluxing occurred as the solutions were mixed. After being stirred for six hours at reflux, the solution was hydrolyzed with water. Just prior to hydrolysis, the solution gave a positive Color Test I.[8] The ethereal layer was separated, washed with water, and steam-distilled. Twenty-four grams (84%) of greenish-white residue melting at 176–178° was obtained. This was recrystallized from ethanol–toluene to give 21 g. (72.5%) of white crystals melting at 185–186° but giving a large depression of this melting point when mixed with (I).

Anal. Calcd. for $C_{29}H_{23}N$: N, 3.62. Found: N, 3.50.

Condensation of β-Naphthylamine with Triphenylcarbinol.—In this reaction, modeled after the synthesis of the similarly substituted aniline given by Baeyer and Villiger,[9] 5 g. of triphenylcarbinol and 10 g. of β-naphthylamine were refluxed for one-half hour in glacial acetic acid. The solution was cooled and diluted with water, whereupon a white precipitate appeared. This was filtered off and washed with 95% ethanol, leaving a powdery residue which, when recrystallized from watered acetone, weighed 0.1 g. (1.3%) and melted at 185–186°. A mixed melting point with the material from the phenyllithium reaction showed no depression.

Summary

Benzophenone β-naphthil undergoes a lateral-nuclear 1,4 addition with phenylmagnesium bromide under forced conditions, yielding *o*-phenylbenzohydryl-β-naphthylamine. The same naphthil undergoes 1,2 addition with phenyllithium under mild conditions, to yield triphenylmethyl-β-naphthylamine.

AMES, IOWA RECEIVED APRIL 3, 1948

(5) Reddelien, *Ber.*, **54**, 3121 (1921).

(6) Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

(7) Claisen, *Ann.*, **237**, 273 (1887).

(8) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

(9) Baeyer and Villiger, *Ber.*, **35**, 3016 (1902).

[CONTRIBUTION FROM THE KNIGHT CHEMICAL LABORATORY, UNIVERSITY OF AKRON]

The Reaction of α,β-Dichloropropionaldehyde with a Number of Grignard Reagents

BY VAUGHN W. FLOUTZ

The research project here reported was undertaken to determine the behavior of representative Grignard reagents with α,β-dichloropropionaldehyde. Studies have shown that chloral and α,α,β-trichlorobutyraldehyde, commonly called butyl chloral, react normally with arylmagnesium halides, but abnormally with certain other Grignard reagents to give a primary alcohol by reduction of the aldehyde and an unsaturated hydrocarbon by oxidation of the Grignard reagent.[1,2] Unlike chloral and butyl chloral, α,β-dichloropropionaldehyde carries one chlorine atom on the alpha carbon rather than a maximum number. It was found that the reaction proceeds normally with phenylmagnesium bromide and gives a good yield of secondary alcohol. α,β-Dichloropropionaldehyde reacts with *n*-hexylmagnesium bromide, cyclohexylmagnesium bromide and β-phenylethylmagnesium bromide to give the secondary alcohols of normal addition in a smaller yield. In each case there is formed in addition to the secondary alcohol 2,3-dichloropropanol-1 (glycerol 2,3-dichlorohydrin) by the reduction of some of the aldehyde, and an unsaturated hydrocarbon by oxidation of some of the Grignard reagent. In the case of benzylmagnesium chloride no secondary alcohol was detected; the only reaction product identified was dibenzyl. It has been found that both chloral and butyl chloral exhibit this same behavior with benzylmagnesium chloride.[2]

Experimental[3]

α,β-Dichloropropionaldehyde and Phenylmagnesium Bromide.—In the preparation of this Grignard reagent, and also those subsequently considered, a 1-liter, three-necked flask, fitted with a mercury-seal stirrer, dropping funnel and condenser was employed. A 0.25 gram-atom portion of magnesium turnings was placed in the flask and covered with 250 ml. of anhydrous ether, and the reagent was formed by adding 0.25 mole of the halide dissolved in an equal volume of dry ether. The reagent was cooled and the aldehyde, dissolved in a like volume of dry ether, was added at a rate such that there was no refluxing of the ether. The product was poured slowly into a mixture of ice and water, and the resulting mixture was cleared by the addition of 5% aqueous acetic acid. The ether layer was removed, washed in turn with sodium bicarbonate solution, saturated sodium bisulfite solution, and water, and then dried over anhydrous sodium sulfate.

The ether solution from the reaction of α,β-dichloropropionaldehyde and phenylmagnesium bromide was subjected to distillation to remove the ether. The distillation was then continued under reduced pressure in an atmosphere of nitrogen to obtain the secondary alcohol 2,3-dichloro-1-phenylpropanol-1.

α,β-Dichloropropionaldehyde and *n*-Hexylmagnesium Bromide, Cyclohexylmagnesium Bromide and β-Phenylethylmagnesium Bromide.—The ether solution of the products from the reaction of the aldehyde with *n*-hexylmagnesium bromide was subjected to distillation to remove the ether and the hexene-1 formed in the reaction. The ether and larger portion of the hexene-1 were distilled by use of a hot water-bath; following this the residue was heated in an oil-bath to a bath temperature of 120°, and this additional distillate was added to the first portion. To determine more accurately the amount of hexene-1 produced, the hydrocarbon was converted into 1,2-dibromohexane; this was accomplished by treating the distillate in subdued light with a slight excess of bromine. The residue from the removal of ether and hexene-1 was distilled under diminished pressure to obtain the primary alcohol 2,3-dichloropropanol-1, and the secondary alcohol 1,2-dichlorononanol-3. The primary alcohol was further identified through its oxidation with fuming nitric acid to produce α,β-dichloropropionic acid.[4]

The reaction mixture from the cyclohexylmagnesium bromide, treated in a similar way, gave cyclohexene, determined as the dibromide, the primary alcohol and 2,3-dichloro-1-cyclohexylpropanol-1. That from β-phenylethylmagnesium bromide yielded styrene, determined as the dibromide, the primary alcohol and 1,2-dichloro-5-phenylpentanol-3.

α,β-Dichloropropionaldehyde and Benzylmagnesium Chloride.—The ether solution of the reaction products was distilled to remove the ether. The residual liquid on standing overnight deposited a considerable amount of non-crystalline solid. This substance had the characteristics of a polymerized material or a condensation product from the aldehyde, and was not identified. The liquid remaining from the removal of this solid was distilled under reduced pressure in an atmosphere of nitrogen. The only product isolated from the distillate was dibenzyl.

TABLE I

REACTION PRODUCTS

	Secondary alcohol											Dibromo addition product		Primary alcohol $CH_2ClCHCl-CH_2OH$	
						Analyses, %									
		Yield,		B. p.,		Calculated			Found						
RMgBr	Formula	G.	%	°C.	Mm.	C	H	Cl	C	H	Cl	G.	%	G.	%
C_6H_5MgBr[a]	$C_9H_{10}OCl_2$	35	68.3	150–151	10	52.71	4.92	34.58	52.39	4.89	34.36	..	..	...	..
$C_6H_{13}MgBr$[b]	$C_9H_{18}OCl_2$	19.5	36.6	139–141	12	50.71	8.51	33.27	50.41	8.61	33.32	10	16.4	6.5	20.2
$C_6H_{11}MgBr$[c]	$C_9H_{16}OCl_2$	13.5	25.6	144–146	12	51.20	7.64	33.59	51.30	7.66	33.50	14	23.1	8	24.8
$C_6H_5(CH_2)_2$-MgBr[d]	$C_{11}H_{14}OCl_2$	28.5	49	155–158	4	56.67	6.05	30.42	56.92	6.10	30.21	8	12.1	4	12.4

[a,b,c,d] In addition 1 g. of diphenyl, 3 g. of *n*-dodecane, 3 g. of dicyclohexyl and 1.5 g. of 1,4-diphenylbutane, respectively, were isolated.

(1) Floutz, THIS JOURNAL, **67**, 1615 (1945).

(2) Floutz, *ibid.*, **68**, 2490 (1946).

(3) A portion of the α,β-dichloropropionaldehyde was furnished through the courtesy of the Shell Development Company. That used in the initial studies was synthesized by the low temperature addition of chlorine to acrolein, according to the literature.

(4) Yarnell and Wallis, *J. Org. Chem.*, **4**, 270–283 (1939).

No secondary alcohol was detected; the larger part of the liquid began to decompose and carbonize at a bath temperature of 180° and pressure of 4 mm. An average of results from two runs gave amorphous solid, 12.5 g.; dibenzyl, 6.3 g.; tarry, carbonaceous residue, 14.5 g.

Table I provides essential data. Yields in each case are averages from two runs.

Summary

1. The reaction of α,β-dichloropropionaldehyde with phenylmagnesium bromide, *n*-hexylmagnesium bromide, cyclohexylmagnesium bromide, β-phenylethylmagnesium bromide and benzylmagnesium chloride has been studied.

2. The new secondary alcohols 2,3-dichloro-1-phenylpropanol-1, 1,2-dichlorononanol-3, 2,3-dichloro-1-cyclohexylpropanol-1 and 1,2-dichloro-5-phenylpentanol-3 have been prepared via the Grignard reaction.

AKRON, OHIO RECEIVED MARCH 17, 1948

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1162]

Cyclobutane Derivatives. IV. Ziegler Bromination[1a] of Methylenecyclobutane[1b,2]

BY EDWIN R. BUCHMAN AND DAVID R. HOWTON

In connection with another investigation,[3] we have studied the reaction,[1a] under a variety of conditions, between N-bromosuccinimide (NBS) and methylenecyclobutane (I). It was found that, although NBS reacted with I faster in the usually employed carbon tetrachloride[1a] than in benzene,[4] higher yields of allylic bromides, C_5H_7Br, were obtained in the latter solvent; in both cases the addition of small amounts of dibenzoyl peroxide[5] proved advantageous. A typical experiment carried out in benzene and with added peroxide gave the following products[6]: a C_5H_7Br fraction (14%), methylenecyclobutane dibromide[7] (56%), N-phenylsuccinimide[9] (15%) and succinimide (66%). In carbon tetrachloride and without added peroxide another minor product was encountered, apparently formed by direct 1:1 addition[8] of NBS to I.

The C_5H_7Br mixture (II + III) was investigated as indicated on the diagram. II and III were separated by virtue of the great difference in the rates at which they react with trimethylamine in benzene at room temperature. III reacted in a few minutes to precipitate the corresponding[10] allylic quaternary ammonium bromide (V) while the complete conversion of II to IV required several weeks; the relative amounts of IV and V isolated indicate a II:III ratio in the C_5H_7Br fraction of about 15:1.

The structure[11] of V (and indirectly that of IV) was established by relating it to the known[13] saturated quaternary bromide (IX). In this connection the applicability of a recently described[12] two-step reduction method was investigated. The addition of bromine to V yielded a single dibromo bromide to which structure VII must be assigned since on catalytic hydrogenation it was converted to a bromide identified (by comparison with an authentic sample[13]) as IX. However, the bromination of IV gave not only compound VI isomeric with VII (and yielding on reduction VIII isomeric with IX) but also, by a novel rearrangement, a nearly equal amount of bromide VII identical with the material originating from V.

A structure proof based on reactions not accompanied by possible rearrangements was achieved

(1) (a) *Cf.* Ziegler, Späth, Schaaf, Schumann and Winkelmann' *Ann.*, **551**, 80 (1942); (b) *cf.* Ziegler bromination of ketene dimer' Blomquist and Baldwin, THIS JOURNAL, **70**, 29 (1948).

(2) Presented before the Pacific Division of the American Association for the Advancement of Science at the San Diego Meeting, June, 1947.

(3) See Paper V of this Series, to be published.

(4) *Cf.* Ettlinger and Fieser, *J. Biol. Chem.*, **164**, 451 (1946).

(5) *Cf.* Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(6) Yields based on NBS.

(7) Földi[8] obtained saturated dibromides from reactions of N-bromo-N-methylbenzenesulfonamide with certain olefins. In this Laboratory it has been found that I and cyclobutene,[3] which react slowly with NBS, give dibromides as major products (yield apparently independent of added peroxide but dependent on nature of solvent, see Experimental), while cyclohexene,[9] which reacts rapidly, gives only a small amount of dibromide.

The mechanism of formation of the dibromides remains obscure. Földi's unsubstantiated explanation that substituted derivatives of ethylenediamine and substituted dibromides are formed in equivalent amount obviously cannot apply in the present case. The possibility that hydrogen bromide (which would combine with NBS to make free bromine available, *cf.* Meystre, Ehmann, Neher and Miescher, *Helv. Chim. Acta*, **28**, 1252 (1945); Wieland and Miescher, *ibid.*, **30**, 1876 (1947); Barnes, THIS JOURNAL, **70**, 145 (1948)) is formed during the slow reaction is unsupported by experimental evidence; brominated reaction products from I appear to be stable and no loss of hydrogen bromide was noted during the Ziegler reaction or during the working-up procedure.

Cf. Buckles, Organic Division Abstracts, April, 1948, page 36L.

(8) *Cf.*. Földi, *Ber.*, **63**, 2257 (1930); Lichoscherstow, *et al.*, *Chem. Zentr.*, **109**, I, 3330 (1938); **110**, II, 66 (1939); **111**, I. 3246 (1940); **111**, II, 198 (1940); Kharasch and Priestly, THIS JOURNAL, **61**, 3425 (1939); Fosdick, Fancher and Urbach, *ibid.*, **68**, 840 (1946); ref. 1a.

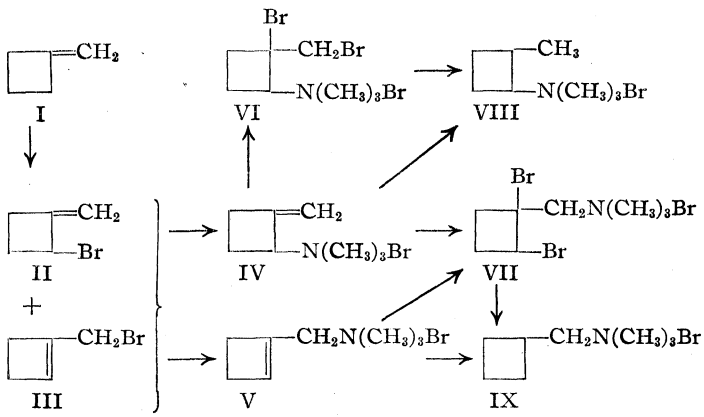
(9) *Cf.* Howton, THIS JOURNAL, **69**, 2060 (1947).

(10) The precipitated fractions are quite pure; we assume that III is the precursor of V and II of IV.

(11) As a possible aid in assigning structures to such compounds, it may be noted that there appears to be a degree of correspondence in m. p.'s between allylic quaternary picrates and the related saturated picrates, *e. g.*, picrates corresponding to V and IX melt at 127 and 117°, respectively, while for the IV–VIII pair the values are 215 and 245°; Howton[12] gives: 2-cyclohexenyltrimethylammonium picrate, m. p. 130°, and cyclohexyltrimethylammonium picrate, m. p. 125°; allyltrimethylammonium picrate, m. p. 220°, and *n*-propyltrimethylammonium picrate, m. p. 200°.

(12) Howton, THIS JOURNAL, **69**, 2555 (1947).

(13) (a) v. Braun, Fussgänger and Kuhn, *Ann.*, **445**, 201 (1925); see also (b) Demjanow and Dojarenko, *Ber.*, **55**, 2727 (1922); *Chem. Zentr.*, **94**, III, 746 (1923).



by the direct catalytic reduction of IV and of V. From V, IX was obtained, while IV gave a relatively good yield[14] of VIII identical with the reduction product from VI; this synthesis of VIII incidentally confirms the formulas assigned to both VI and VIII.

This research was aided by a grant from the Research Corporation; the authors wish also to express their thanks to Dr. Saul Winstein and to Dr. Martin G. Ettlinger for helpful discussions.

Experimental[15]

Ziegler Bromination of I.—A two-liter three-necked flask was charged with 178 g. (1.0 mole) of NBS,[1a] 2.42 g. (0.01 mole) of dibenzoyl peroxide, 71.0 g. (1.044 mole) of I[16] and 740 ml. of thiophene-free benzene (dried over sodium); the flask was equipped with a mercury-sealed Hershberg stirrer, a water-cooled reflux condenser topped by another containing Dry Ice, and a thermometer dipping into the reaction mixture. The stirred mixture was maintained at 75–80° (gentle reflux) by means of a heating mantle. From time to time the reaction mixture was cooled to about 40° and a drop of liquid was removed and tested with aqueous potassium iodide for the presence of NBS; after six and one-half hours the test was negative. After standing overnight at room temperature, 57.9 g. of crystalline solid (A) was filtered from the brown mixture; 11.6 g. of I was recovered from the filtrate by distillation at atmospheric pressure, using a 30-cm. helix-packed column. Most of the benzene was then removed through the same column at 200 mm. On standing overnight, 19.7 g. of solid (B) crystallized from the residue. The filtrate from B was then distilled rather rapidly through a 9-cm. helix-packed column with efficient condensation (Dry-Ice trap) of the distillate, first at 70 mm. and then at 30 mm. until all of the allylic bromides had been removed. The resulting distillate was refractionated through the same column giving 21.6 g. (14.6%[6]) of a mixture of II and III, b. p. 55.2–56.7° at 70 mm. This material rapidly decolorized potassium permanganate in acetone solution, slowly decolorized bromine in carbon tetrachloride, gave an immediate precipitate with alcoholic silver nitrate and slowly darkened on standing at room temperature exposed to light.

Anal.[17] Calcd. for C_5H_7Br: C, 40.84; H, 4.80; Br, 54.36. Found: C, 40.83; H, 5.11; Br, 54.78.

The residual oil from the rapid initial distillation of the C_5H_7Br fraction deposited 12.1 g. of crystalline material (C) on standing; this was filtered off and the filtrate combined with a small amount of oil left from the final fractionation of the C_5H_7Br distillate and distilled at 3 mm., giving 65.1 g. (56.2%[6]) of I dibromide, pale yellow subtly lachrymatory oil, b. p. 43–50°, $n^{25}D$ 1.532,[17] d^{25}_4 1.801[17]; this material[18] decolorized permanganate in acetone rapidly and formed a precipitate soon after mixing with a benzene solution of dimethylamine.

Removal of I dibromide from the reaction mixture left 43.8 g. of dark brown, very viscous oil which deposited 1.8 g. of crystalline material (D) after standing several months. Careful examination of the four crops of crystalline material showed A to be substantially pure succinimide, B and D to be N-phenylsuccinimide[9] and C to be a mixture of these two substances; total yield[6] of the first 66%, of the latter 15%. A fractional distillation *in vacuo* was carried out on the 42 g. of residual oil; small additional amounts of succinimide and of N-phenylsuccinimide were obtained but no other homogeneous product was isolated.

Reactions of this type gave consistently approximately the yields of bromination products indicated above; a bromination in benzene but without added peroxide required eleven and one-half hours and yielded[6] 9.1% of allylic bromides and 57.1% of the dibromide. In carbon tetrachloride the results were less consistent; figures[6] are given for two representative runs; 8.8% of allylic bromides and 52.8% of dibromide (two and one-half hours, 1.6 mole % peroxide), 5.6% of bromides and 34.1% of dibromide (three and one-half hours, no peroxide added). In *n*-heptane with 1.6 mole % peroxide the reaction appeared complete after two hours; 6.0% of monobromides and 24.3%[6] of dibromide were isolated from the gummy reaction mixture. Using excess of I as solvent and with added peroxide, no appreciable bromination took place even after twenty hours of refluxing.

From an experiment carried out in carbon tetrachloride (no added peroxide), it was found possible to isolate a small amount of a slightly colored, very viscous oil, b. p. 79° at 0.25 mm., which gave analytical figures close to those calculated for the adduct of I and NBS; it was difficult to completely free this oil from succinimide by distillation.

Anal. Calcd. for $C_9H_{12}BrNO_2$: C, 43.92; H, 4.92; N, 5.69. Found: C, 44.46; H, 5.31; N, 6.16.

(2-Methylenecyclobutyl)-trimethylammonium Bromide (IV) and (1-Cyclobutenylmethyl)-trimethylammonium Bromide (V).—The above mixture of II and III (21.6 g.) was treated in a centrifuge bottle with 63 g. (slight excess) of an 18% solution of trimethylamine in C. P. benzene. A voluminous crystalline precipitate (V) formed immediately; after standing for fifteen minutes at room temperature, this product was separated by centrifugation, washed with benzene and dried *in vacuo*, yield 1.4 g. (4.6%). Crude V, m. p. 162.5° (prior sintering), was found to be extremely hygroscopic (in other experiments V was obtained as an oil); it decolorized permanganate[19] rapidly and was characterized by conversion

(14) Whereas V behaved normally[12] on reduction, giving trimethylamine as a major reaction product, IV yielded somewhat better than 50% of VIII. Seemingly IV does not possess a fully effective allylic double bond.

(15) All melting points are corrected. Microanalyses by Dr. G. Oppenheimer and G. A. Swinehart of this Institute.

(16) B. p. 40.0–42.3°; preparation, see Shand, Schomaker and Fischer, THIS JOURNAL, 66, 636 (1944); a portion of the material used in this research was prepared by Mr. J. R. Fischer.

(17) These figures were obtained from a sample prepared in a similar fashion from a Ziegler bromination carried out in carbon tetrachloride.

(18) An authentic sample of I dibromide, b. p. 41–45° at 2.2 mm., $n^{24}D$ 1.537, decolorized permanganate and gave with dimethylamine the same series of reaction products (to be described in another connection).

(19) The behavior of quaternary bromides and picrates toward potassium permanganate in acetone or acetone–water solution was investigated. The unsaturated bromides IV and V as well as the corre-

to the quaternary picrate,[19,20] large dark yellow striated blades from ethanol–acetonitrile, m. p. 126.6–127.1° (analysis see below).

A small amount of material (0.4 g.) which deposited in the next seventy-five minutes was shown (by conversion to the picrate[20]) to be predominantly IV. After the benzene solution had stood tightly stoppered for two weeks longer, a dense network of colorless needles had formed which was centrifuged off (16.2 g. of IV); two months later another crop (4.6 g.) was collected; total yield of crystalline IV, 70%. A small amount of oily material (crude IV) subsequently separated from the benzene solution and there remained a certain amount of bromine-containing benzene-soluble material which apparently did not react with trimethylamine.

Fractional crystallization of the IV obtained above and examination of the mother liquors (by conversion to the picrate[20]) failed to disclose the presence of any appreciable amount of V. IV[19] formed hygroscopic sparse clusters of colorless rods from acetone–ethanol, m. p. 229° dec.

Anal. Calcd. for $C_8H_{16}BrN$: C, 46.61; H, 7.82; N, 6.80. Found: C, 47.17; H, 8.07; N, 6.60.

The picrate[19,20] corresponding to IV crystallized from ethanol in long yellow feathers, m. p. 215–217° dec.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found (IV picrate): C, 47.51; H, 5.41; N, 15.85. Found (V picrate): C, 47.47; H, 5.36; N, 15.59.

Bromination of IV.—A solution of 1.41 g. of IV (as obtained from the benzene–trimethylamine solution) in 5 ml. of chloroform was treated with 1.10 g. (one molecular equivalent) of bromine; the resulting two-liquid-phase mixture was tightly stoppered and allowed to stand at room temperature for ten days. The crop of clustered jagged crystals (VI) which had emerged from the pale orange solution was freed of mother liquors by rinsing with chloroform and dried, m. p. 203.5° dec., yield 1.02 g. (41%). A sample was recrystallized from ethanol–water, colorless truncated dog-tooth-like crystals, some arranged in rows to form long, irregular blades, m. p. 195.5° dec.[21] (analysis below).

The mother liquors and washings from this crop of VI were freed of solvent and rapidly diluted with acetone, giving a voluminous white crystalline precipitate of crude VII weighing 0.93 g. (37%), m. p. *ca.* 168°. This was recrystallized by dissolving in a small amount of warm methanol and rapidly diluting with acetone, broad colorless plates with bluntly pointed terminations, m. p. 163–164° dec.[21]

Anal. Calcd. for $C_8H_{16}Br_2N$: C, 26.25; H, 4.41; N, 3.83. Found (VI): C, 26.19; H, 4.85; N, 3.74. Found (VII): C, 26.77; H, 4.64; N, 3.77.

Another bromination of IV (procedure similar to that used for bromination of V, see below) gave a 33% yield of VI and a 27% yield of VII (isolated as the picrate). VII obtained in this manner and the corresponding picrate were compared (mixed m. p.'s gave no depression) with material from bromination of V. VII from bromination of IV was also converted (see below) to IX and its picrate (mixed m. p.'s).

The quaternary picrate corresponding to VI was recrystallized from ethanol–water, yellow rhombic plates, some with striations parallel to all four edges of the rhombs, others growing to a point in such a way as to form stubby triangular prisms, m. p. 173°.[21] The picrate corresponding to VII, orange-yellow bars or granules from ethanol–water, melted at 172°.[21] A mixture of the two isomeric picrates gave a difficultly-detectable depression of the melting point.

Anal. Calcd. for $C_{14}H_{18}Br_2N_4O_7$: C, 32.70; H, 3.53. Found (VI picrate): C, 32.80; H, 3.55. Found (VII picrate): C, 32.99; H, 3.60.

Bromination of V.—A solution of 1.09 g. of crude crystalline V in 4 ml. of chloroform was treated dropwise with bromine until a heavy oil separated out; the mixture was then diluted with benzene and treated with more bromine until the color of the latter persisted in the benzene epiphase. The heavy oil was then thoroughly washed with benzene, taken up in 25 ml. of ethanol and slowly freed of solvent on the steam-bath; the residual clear tan sirup was taken up in 10 ml. of acetone and placed in an ice-box overnight, giving rise to 0.65 g. of VII, compact rosettes, crude m. p. 170° dec. Mother liquors yielded an additional 0.24 g. of VII, crude m. p. 169° dec. and 0.57 g. of crude VII picrate[22] (total yield of VII, 66.5%).

(2-Methylcyclobutyl)-trimethylammonium Bromide (VIII).—Recrystallized IV (0.90 g.) was added to a suspension of pre-reduced palladium-on-barium-sulfate catalyst[12] (2.25 g.) in 25 ml. of water and the mixture was shaken with hydrogen at room temperature and atmospheric pressure. After nineteen hours the absorption rate was negligible and 155.8 ml. of hydrogen had been absorbed (theory for one mole-equivalent, 112 ml.). The catalyst was centrifuged off, the solution was treated with sodium hydroxide in slight excess and the liberated trimethylamine was removed on the steam-bath *in vacuo*. Then, after neutralization with hydrobromic acid, the solution was evaporated to dryness. The residue was extracted with chloroform and the extracts were freed of solvent and treated with acetone; in this way three crops of crude VIII were obtained totaling 0.41 g. (45%) and from the mother liquors 0.11 g. of VIII picrate (total yield of VIII, 52%). VIII picrate made from this crude VIII did not depress the m. p. of a like picrate obtained from VI (see below).

Catalytic reduction[12] of VI gave a theoretical yield of crude VIII; after recrystallization from acetone–methanol, it formed colorless plates of various rectangular shapes, m. p. 270° dec.

Anal. Calcd. for $C_8H_{18}BrN$: C, 46.16; H, 8.71; N, 6.73. Found: C, 46.04; H, 8.97; N, 6.10.

The corresponding picrate formed bundles of yellow needles from ethanol, m. p. 244.6–244.8°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66. Found: C, 47.24; H, 5.81.

(Cyclobutylmethyl)-trimethylammonium Bromide (IX).—Reduction[23] of cyclobutyl cyanide[24] in ethanol–12 *N* hydrochloric acid using a palladium-on-Norit catalyst gave cyclobutylmethylamine hydrochloride, characteristic colorless flakes from acetone–ethanol, m. p. 235.5°. This hydrochloride (1.54 g.) was methylated in the usual way[13b] with methyl iodide and potassium hydroxide in methanol. After removal of solvent the product was separated by continuous extraction with chloroform, yield of crude (cyclobutylmethyl)-trimethylammonium iodide nearly quantitative (3.18 g.); recrystallization from acetone–ethanol gave glistening colorless needles, m. p. 205.6–206.5°.

Anal. Calcd. for $C_8H_{18}IN$: C, 37.66; H, 7.11; N, 5.49. Found: C, 37.80; H, 6.96; N, 5.48.

The iodide was converted to the base with silver oxide and this after neutralization with hydrobromic acid gave

sponding picrates decolorized permanganate rapidly while VI, VII, VIII and IX and their picrates did not. The stability of VI is of interest since I dibromide reacts readily with permanganate under these conditions, see ref. 18.

(20) See ref. 12, footnote 5.

(21) Melting point bath heated slowly; m. p. varies considerably with rate of heating.

(22) Mother liquors from this picrate gave 0.45 g. of material m. p. below 95°, from which, after several recrystallizations, a homogeneous substance was obtained, sparsely-clustered thin rectangular slats from ethanol–acetonitrile, m. p. 142.5–143.2°, halogen-free, unsaturated to permanganate. This may be (2-methyl-2-butenyl)-trimethylammonium picrate derived from 2-methylbutene-1 originally present (see footnote 8 of ref. 16) as an impurity in I.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.25; H, 5.73; N, 15.75.

(23) *Cf.* Hartung, THIS JOURNAL, **50**, 3370 (1928).

(24) B. p. 147–148° (747 mm.), prepared in 62% yield according to Freund and Gudeman, *Ber.*, **21**, 2697 (1888).

IX, beautiful sparse clusters of colorless triangular prisms from acetone–methanol, m. p. 220–221° (lit.[13a] m. p. 214°). Another sample of IX (from reduction of VII) exhibited dimorphism; on seeding a supercooled solution of the material in acetone–methanol, colorless needles were rapidly deposited which changed into massive granules, the interconversion being complete in about three hours at 0°. These granules melted at 219.6–220.2°, resolidified on withdrawing from the bath, then melted at 226°; a sample mixed with authentic IX showed the same behavior.

Anal. Calcd. for $C_8H_{18}BrN$: C, 46.16; H, 8.71; N, 6.73. Found: C, 45.75; H, 8.77; N, 6.39.

The above salts gave the corresponding picrate, bright yellow-orange dendrites from ethanol, m. p. 116.5–117.1°.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.40; H, 5.75; N, 15.50.

The halides with excess of aqueous sodium picrate gave a picrate–sodium picrate double salt,[20] fine yellow needles from ethanol, m. p. 164.4–164.7° (prior sintering).

Anal. Calcd. for $C_{14}H_{20}N_4O_7 \cdot C_6H_2N_3NaO_7 \cdot 0.5H_2O$: C, 38.97; H, 3.76; N, 15.91; Na, 3.73. Found: C, 38.83; H, 4.04; N, 16.26; Na, 3.39.

Catalytic reduction[12] of VII gave in good yield IX (mixed m. p. with authentic IX) which was converted to the picrate (mixed m. p.). A very small yield of IX (isolated as the picrate–sodium picrate double salt, mixed m. p. and analysis) resulted from the reduction[12] of crude V using a palladium-on-Norit catalyst; trimethylamine hydrobromide constituted the major reaction product.

Summary

The Ziegler bromination of methylenecyclobutane has been studied. The major bromination product is the olefin dibromide and under the best conditions found (in benzene and with added peroxide) the yield of allylic bromides is 14%.

The allylic bromides were investigated by conversion to the allylic trimethylammonium bromides, the structures of which were established.

PASADENA 4, CALIFORNIA RECEIVED MARCH 15, 1948

[CONTRIBUTION FROM THE COATES LABORATORIES OF LOUISIANA STATE UNIVERSITY]

Analysis of the Vibrations of Benzene Derivatives. I. The Class A_1 Carbon Vibrations of Toluene

BY A. R. CHOPPIN AND C. H. SMITH[1,2]

The assignment of experimentally observed vibrational frequencies of aromatic molecules to definite modes of vibration has encountered difficulties, chief of which has been the large number of vibrations belonging to each symmetry class. Only for the highly symmetrical benzene molecule has it been possible to make assignments with confidence.

For toluene, the assignments have been more speculative. The polarization measurements in the Raman spectrum made by Cabannes and Rousset[3] and by Cleveland[4] have been of importance in identifying the totally symmetric vibrational frequencies. However, the number of observed polarized lines is less than the theoretical number of totally symmetric vibrations, even if toluene is assigned C_{2v} symmetry. Teets and Andrews[5] constructed a mechanical model of toluene, and found certain correlations between its vibrational frequencies and those observed in the Raman spectrum of toluene. Pitzer and Scott,[6] reasoning by analogy with benzene, assigned a frequency and vibrational form to each of the fundamental vibrations of the toluene molecule. However, except for the 1003 cm.$^{-1}$ frequency, they did not analyze the changes that occur in the vibrational forms on going from benzene to toluene. Ginsburg, Robertson and Matsen[7] have analyzed the near-ultraviolet absorption spectrum of toluene vapor and made a considerable number of frequency assignments.

Recently, the authors[8] have developed an interpretation of the ultraviolet absorption spectrum of toluene which differs from that of Ginsburg, Robertson and Matsen in that the 623 cm.$^{-1}$ frequency (in the ground state) is assigned to Class A_1 instead of Class B_1. Furthermore, the authors have proposed certain approximate vibrational forms for the Class A_1 carbon vibrations of toluene. These forms were based upon analogies with benzene and upon frequency changes taking place upon the substitution of deuterium for the various hydrogens of toluene. They differ in some cases from the forms assigned by Pitzer and Scott,[6] and from the forms observed in the mechanical model.[5]

In an attempt to settle these differences in the assignment of the frequencies and modes of vibration of toluene, the mathematical analysis presented in this article was made.

Calculations

In order to simplify the mathematical analysis, the carbon and hydrogen vibrations are treated as distinct uncoupled sets. This follows a previous qualitative treatment of the benzene vibrations.[9] For the purpose of the calculation of the carbon vibrations, it is assumed that each hydrogen is

(1) American Chemical Society Post-doctoral Research Fellow at Louisiana State University.

(2) The authors are indebted to Newton Grant for checking some of the calculations.

(3) Cabannes and Rousset, *Ann. phys.*, **19**, 229 (1933).

(4) Cleveland, *J. Chem. Phys.*, **13**, 101 (1945).

(5) Teets and Andrews, *J. Chem. Phys.*, **3**, 175 (1935).

(6) Pitzer and Scott, THIS JOURNAL, **65**, 803 (1943).

(7) Ginsburg, Robertson and Matsen, *J. Chem. Phys.*, **14**, 511 (1946).

(8) Choppin and Smith, THIS JOURNAL, **70**, 577 (1948).

(9) Angus, Bailey, Hale, Ingold, Leckie, Raisin, Thompson and Wilson, *J. Chem. Soc.*, 971 (1936).

TABLE I

NORMAL COÖRDINATES FOR THE CLASS A_1 CARBON VIBRATIONS OF TOLUENE

Comparing with Figure 1, the upward direction of the vertical component and the outward direction of the horizontal component are given positive signs.

Normal coördinate	ξ_1	ξ_2	ξ_3	ξ_4	ξ_5	ξ_6
Calcd. freq. (cm.$^{-1}$)	497	779	965	1156	1380	1704
Me-group motion	1.00	1.00	0.12	−0.61	0.36	−0.21
C-1 motion	0.52	−0.20	−0.10	1.00	−1.00	1.00
C-2 motion (total)	0.36	0.80	0.95	0.90	0.22	1.06
C-2 (horiz. comp.)	−0.31	0.74	−0.78	−0.78	−0.22	0.40
C-2 (vert. comp.)	−0.17	−0.30	−0.56	0.44	0.02	−0.99
Angle C-2 with horiz.	29°	22°	36°	29°	4°	68°
C-3 motion (total)	0.41	1.11	0.06	1.26	0.57	0.90
C-3 (horiz. comp.)	−0.28	1.00	0.04	1.25	0.27	0.20
C-3 (vert. comp.)	−0.30	−0.49	0.04	−0.22	0.50	0.88
Angle C-3 with horiz.	47°	26°	40°	10°	60°	77°
C-4 motion	−0.70	0.61	1.00	−0.66	−0.52	−0.46
% of V due to K_1	23	26	1	16	27	6
% of V due to K_2	8	37	51	48	63	82
% of V due to $K\alpha$	69	37	48	36	10	12

condensed into the nucleus of the carbon atom to which it is attached, forming a "molecule" containing seven mass-points. The methyl group has a relative mass of 15, the carbon in position one a mass of 12, and each of the other carbons a mass of 13. The "molecule" belongs to point-group C_{2v}. It has 15 normal vibrations, six belonging to Class A_1 (totally symmetric), one belonging to Class A_2 (symmetric only with respect to the two-fold axis), five belonging to Class B_1 (symmetric only with respect to the molecular plane), and three belonging to Class B_2 (symmetric only with respect to the plane of symmetry perpendicular to the molecular plane). When the secular equation is expressed in terms of symmetry coördinates,[10] it can be factored into four separate equations, one for each symmetry class. The Class A_1 vibrations may be set up in a sixth-order determinant. The calculations of this article use a valence-force potential system with the following force constants: 4.50×10^5 dynes per cm.,[11] valence-stretching constant for the single bond; 7.58×10^5 dynes per cm.,[12] valence-stretching constant for the aromatic bonds; 0.65×10^5 dynes per cm.,[12] force constant for the bending of the aromatic –C–C–C– angle in the plane of the ring. The single bond force constant was calculated by Stitt from an analysis of the ethane molecule. This particular value does not include interaction between the hydrogens of ethane. It was used since Pitzer and Scott[6] found that the methyl group of toluene has essentially free rotation. The aromatic bond force constants were calculated by Lord and Andrews from the benzene molecule. The aromatic bond distances in toluene were assumed to be the same as in benzene; it is not necessary to use any actual values.

The six roots of the Class A_1 factor of the secular equation are as follows: 497, 779, 965, 1156, 1380 and 1704 cm.$^{-1}$. The normal coördinates are given in Table I and in Fig. 1.

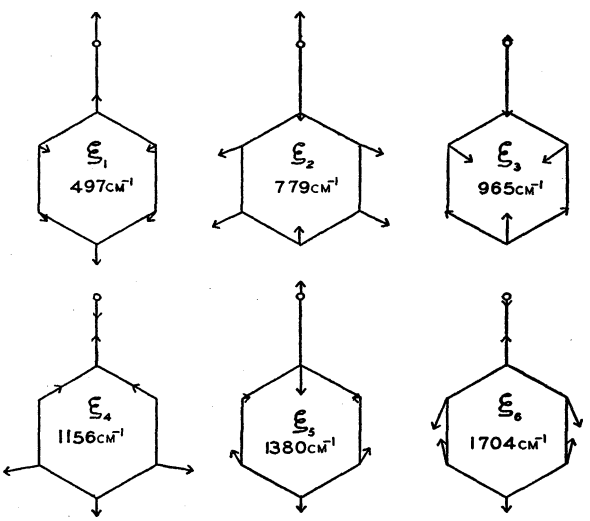


Fig. 1.—Calculated frequencies and normal coördinates for the Class A_1 carbon vibrations of toluene.

Discussion

Comparison with Spectral Frequencies.—Theoretically, all of the Class A_1 carbon vibrations should be active in the Raman spectrum (giving polarized lines) and in infrared and ultraviolet absorption. Possible correlations between calculated and observed frequencies of toluene are shown in Table II.

The frequency changes taking place when deuterium is placed on the toluene molecule[8] are of value in checking the vibrational forms. If deuterium is placed upon a carbon atom which is vibrating with a large amplitude, there will be a greater decrease in frequency than would be the

(10) Howard and Wilson, *J. Chem. Phys.*, **2**, 630 (1934).
(11) Stitt, *ibid.*, **7**, 297 (1939).
(12) Lord and Andrews, *J. Phys. Chem.*, **41**, 149 (1937).

TABLE II

COMPARISON OF CALCULATED FREQUENCIES OF TOLUENE WITH OBSERVED VALUES

Frequencies are given in cm.$^{-1}$

Calculated	Raman[13,14] (Pol.)[4]	Ultraviolet[7,8]	Infrared[15]
497	520 (0.44)	520	521
779	786 (0.03)	787	786
965	1003 (0.13)	1003	1003
	1029 (0.11)	..	1030
1156	1209 (0.29)	1210	1211
1380	1379 (0.46)	..	1379
			1460
			1497
1704	..	..	1736
			1802

case if the deuterium were placed upon a carbon atom vibrating with a small amplitude.

The calculated 497 cm.$^{-1}$ frequency correlates with the polarized 520 cm.$^{-1}$ Raman line. The frequency changes upon deuteration check with the calculated normal coördinate, ξ_1, except for the meta carbon atom.

No calculated frequency lies near the observed 623 cm.$^{-1}$ line. It must be concluded that this frequency *does not* correspond to a Class A_1 carbon vibration. This is in agreement with the observation that this line is depolarized in the Raman spectrum. It disagrees with the authors' previous assignment.[8]

The calculated 779 cm.$^{-1}$ frequency correlates with the polarized 786 cm.$^{-1}$ Raman line. The frequency changes upon deuteration check with the calculated form, ξ_2, except for toluene-2-*d* in the ground state.

From Raman data alone, the calculated 965 cm.$^{-1}$ frequency could belong to either the 1003 or the 1029 cm.$^{-1}$ Raman line. However, the 1029 cm.$^{-1}$ frequency was not observed in ultraviolet absorption. This gives rise to the assumption that the 1029 cm.$^{-1}$ Raman line belongs to a Class A_1 hydrogen-bending vibration. This idea is supported by the observation of a line, which has been assigned to a Class A_1 hydrogen-bending vibration, at 1031.0 cm.$^{-1}$ in the Raman spectrum of benzene-*d*.[16] The observed 1003 cm.$^{-1}$ line must correspond with the 965 cm.$^{-1}$ calculated frequency (ξ_3). In the ground state, frequency changes upon deuteration check, with form ξ_3 in every case. This coördinate, where the motion is chiefly confined to the 2, 4 and 6 positions, strikingly confirms the form deduced by Pitzer and Scott[6] from a consideration of the spectra of benzene and the methyl benzenes. In ultraviolet absorption, two strong frequencies were observed in the excited state in this spectral region (933 and 966 cm.$^{-1}$ for toluene). One possible explanation is that the hydrogen-bending vibration, observed at 1029 cm.$^{-1}$ in the Raman spectrum, is coupled in with the carbon vibrations in the excited state, even though it does not appear in the ultraviolet absorption for the ground state. A more probable explanation lies in assigning one of these excited state lines to a carbon vibration of another symmetry class. It is to be noted that, for the excited state, the group of frequencies in the deuterated toluenes, beginning with 966 cm.$^{-1}$ for toluene itself, check with the form of the normal coördinate ξ_3.

The calculated 1156 cm.$^{-1}$ frequency corresponds with the observed 1209 cm.$^{-1}$ polarized Raman line. The observed frequencies of the deuterated toluenes are not in particularly good agreement with the form ξ_4.

The calculated 1380 cm.$^{-1}$ frequency is near the 1379 cm.$^{-1}$ polarized Raman line. However, this frequency was not observed in ultraviolet absorption; it differs from other correlated frequencies in that the calculated value is not lower than the observed value. This makes its correlation questionable, especially since Pitzer and Scott[6] correlated the 1379 cm.$^{-1}$ Raman line with the symmetric hydrogen-bending motion within the methyl group. Cabannes and Rousset[3] observed a polarized Raman line at 1483 cm.$^{-1}$ and Pitzer and Scott[6] assigned this line to a Class A_1 vibration. However, neither Howlett[13] nor Kohlrausch and Wittek[14] observed a Raman line at 1483 cm.$^{-1}$, raising doubt as to its actual existence. Several infrared bands have been observed in the region[15]; possibly one of them may correspond to the calculated form ξ_5. Apparently, ξ_5 is not active in either the Raman spectrum or near-ultraviolet absorption.

The calculated 1704 cm.$^{-1}$ frequency is far removed from the 1603 cm.$^{-1}$ line which Pitzer and Scott[6] assigned to a Class A_1 vibration, and no Raman lines have been observed near the calculated value. Possibly, one of the frequencies observed in the infrared may correspond to form ξ_6. Apparently, ξ_6 is inactive in both the Raman and ultraviolet spectra.

Comparison with the Vibrations of Mechanical Models.—Teets and Andrews[5] constructed a mechanical model of the toluene molecule and observed its vibrational forms and frequencies. Unfortunately for comparison with the calculated frequencies, they used the centric formula of benzene as the basis for their model. This resulted in relatively high frequencies for those vibrations involving bending of the ring.

Trenkler[17] constructed mechanical models for mono-substituted benzene, using the resonating benzene formula as the basis for his model. One of the models had a mass distribution somewhat similar to that found in toluene. The actual form

(13) Howlett, *Can. J. Res.*, **5**, 472 (1931).

(14) Kohlrausch and Wittek, *Monatsh.*, **74**, 1 (1941).

(15) American Petroleum Institute Research Project 44 at the National Bureau of Standards. Catalog of Infrared Spectrograms. Serial Numbers 308 and 480, toluene (liquid), contributed by the U. S. Naval Research Laboratory, Washington, D. C.

(16) Bailey, Gordon, Hale, Herzfeld, Ingold and Poole, *J. Chem. Soc.*, 299 (1946).

(17) Trenkler, *Physik. Z.*, **37**, 338 (1936).

of the vibrations of these models has been given by Kohlrausch.[18] The agreement between the calculated forms and frequencies and those observed in the model is not bad, except that Trenkler's form ω_3 has more motion in the meta carbon atoms than does form ξ_3, and its frequency is completely out of line with both calculated and observed values.

Summary

The approximate vibrational forms and frequencies of the Class A_1 carbon vibrations of toluene have been calculated, using a simplified valence-force potential system and force constants from benzene and ethane. The calculated vibrations have been compared with spectral frequencies and with the vibrations of mechanical models. The results have been interpreted so as to *indicate* the following:

1. The observed 623 cm.$^{-1}$ frequency of toluene *does not* belong to a Class A_1 carbon vibration.
2. The 520, 786, 1003 and 1210 cm.$^{-1}$ observed frequencies of toluene belong to Class A_1 carbon vibrations.
3. The 1029 and 1379 cm.$^{-1}$ frequencies of toluene belong to symmetric hydrogen-bending vibrations.
4. Two of the Class A_1 carbon vibrations of toluene are not active in either the Raman or the near-ultraviolet absorption spectra.

(18) Kohlrausch, *Physik. Z.*, **37**, 58 (1936).

BATON ROUGE, LA. RECEIVED MARCH 16, 1948

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

Fluorination of Thiophosphorylethoxydichloride[1]

BY HAROLD SIMMONS BOOTH, DONALD RAY MARTIN[2] AND FRED E. KENDALL[3]

Inasmuch as thiophosphoryl trichloride has been stepwise fluorinated in this Laboratory[4] to give thiophosphoryl chlorofluorides and trifluoride, it was of interest to study the effect of substituting an ethoxy group for a chlorine atom upon the fluorination reaction. Therefore, the fluorination of thiophosphorylethoxydichloride by the Swarts reaction was undertaken.

Experimental

Preparation and Purification of Thiophosphorylethoxydichloride.—The thiophosphorylethoxydichloride was prepared by a modification of the directions given by Pishchimuka[5] from thiophosphoryl trichloride and dried, redistilled absolute ethyl alcohol. The thiophosphoryl trichloride was a C. P. (chemically pure) grade obtained from the Victor Chemical Company which was then fractionally distilled.

Two hundred grams of thiophosphoryl trichloride was placed in a three-necked flask fitted with a stirrer, drying tube and a separatory funnel containing 100 g. of absolute ethyl alcohol. The alcohol was added dropwise over a period of two to three hours, care being exercised that the temperature of the reactor did not exceed 10°[6] thus reducing the yield. The crude thiophosphorylethoxydichloride was fractionated once under a pressure of 70 mm. and 4 times under a pressure of 25 mm. in a Raschig ring-packed electrically heated column to give a 70% yield of the purified product.

Fluorination of Thiophosphorylethoxydichloride.—The method and apparatus used for the stepwise fluorination, using the Swarts reaction,[7] was the same as that described elsewhere,[8,9] except that, owing to the high boiling points of the products, an air-cooled condenser was substituted for the usual water-cooled condenser. In order to obtain the chlorofluoride, the fluorination products were removed with an automatic stopcock set to maintain a pressure of 20–30 mm. in the generator. The temperature of the generator must be at, or below, 50° to prevent decomposition of thiophosphorylethoxydichloride and thiophosphorylethoxychlorofluoride. In exploratory fluorination reactions, it was observed that simple addition of antimony trifluoride to thiophosphorylethoxydichloride in a flask, open to the atmosphere through a drying tube, produced about the same results providing the temperature of the reactor was kept below 50°. Little or no reaction was observed when the fluorination was attempted without antimony pentachloride as the catalyst.

Purification of Thiophosphorylethoxydifluoride.—The fluorination products were fractionally distilled in a modified Dufton column as described by Booth and Bozarth.[10] The best coolant for the column head was water, cooled by ice and salt. Samples, from separate generations, were collected by distillation at two different operating pressures, namely, 60 and 100 mm., and found to be identical. The tailings in the still pot had such a low vapor pressure that their distillation in this type of fractionating column was not possible.

Purification of this compound was first attempted with the heated column used to purify the starting material. The distillation was attempted at atmospheric pressure with the receiver open to the atmosphere through a drying tube. However, a reaction of a volatile product with the atmosphere outside the drying tube was observed so this method of purification was abandoned.

Purification of Thiophosphorylethoxychlorofluoride.—The tailings of the above distillations were placed in the heated column used for the purification of thiophosphorylethoxydichloride and were fractionally distilled at pressures of 25 and 70 mm. These samples were found to be

(1) From a thesis presented by Fred E. Kendall to the Graduate School of Western Reserve University, February, 1943, in partial fulfillment of the requirements for the degree of Doctor of Philosophy and based upon work done in connection with a research project sponsored by the Naval Research Laboratory, Office of Research and Inventions, U. S. Navy Department. Publication delayed for security reasons.

(2) Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(3) Present address: The Master Builders Co., Cleveland, Ohio.

(4) H. S. Booth and M. C. Cassidy, THIS JOURNAL, **62**, 2369–2372 (1940).

(5) P. S. Pishchimuka, *Ber.*, **41**, 3854–3859 (1908); *J. Russ. Phys. Chem. Soc.*, **44**, 1406–1554 (1912).

(6) E. Clemmensen, U. S. Patent 1,945,183, Jan. 30, 1934 (to Monsanto Chemical Co.).

(7) F. Swarts, *Acad. roy. Belg.*, **24**, 309 (1892).

(8) H. S. Booth and C. F. Swinehart, THIS JOURNAL, **54**, 4751–4753 (1932).

(9) H. S. Booth and A. R. Bozarth, *ibid.*, **61**, 2927–2934 (1939).

(10) H. S. Booth and A. R. Bozarth, *Ind. Eng. Chem.*, **29**, 470–475 (1937).

identical. After the removal of the thiophosphorylethoxychlorofluoride, there remained in the still pot a heavy, viscous residue which did not lend itself to subsequent distillation inasmuch as it apparently polymerized at the temperature required to cause vaporization. This material was seemingly resistant to water and organic solvents, but was readily attacked by nitric acid. A similar product forms in the preparation of thiophosphorylethoxydichloride as first observed by Pishchimuka.[5]

Analyses.—The samples weighed in approximately 1-ml. sealed glass ampoules[11] were hydrolyzed in a calculated excess of a 0.5 *N* solution of sodium hydroxide. The hydrolyses were rapid for thiophosphorylethoxydifluoride and thiophosphorylethoxychlorofluoride, but slower for thiophosphorylethoxydichloride. Usually the hydrolytic reactions were allowed to proceed overnight before the samples were treated with hydrogen peroxide to oxidize the sulfide to sulfate. After insurance of the complete removal of excess peroxide, the chlorine was determined by the Volhard method,[11] the sulfur as sulfate gravimetrically[12,13] and the phosphorus volumetrically by precipitating it as ammonium phosphomolybdate which was then dissolved in an excess of 0.25 *N* sodium hydroxide and back-titrated with standardized nitric acid to the phenolphthalein end-point.[12,14,15] Separate samples were hydrolyzed, as described above, and the alcohol fractionally distilled into a tared receiver. The weight of distillate and its density at 25° were used to determine the percentage of ethoxy group present.[16] Fluorine was obtained by difference. A summary of the analyses is contained in Table I.

TABLE I

$C_2H_5OPSX^1X^2$

All compounds are soluble in alcohol, acetone, ether and carbon tetrachloride, but insoluble in water

X^1X^2 are		Cl Cl	Cl F	F F
B. p., °C., 20 mm.		52.0	26.2	78.4[d]
F. p., °C.		−78.4 ± 0.5	−178 ± 1.0	−124 ± 0.5
Vapor pressure constants[a]	*A*	−2108.1	−1984.7	−1700
	B	7.7846	7.9320	7.7174
Variation[b]	Av. ±	0.4	0.7	1.1
	Max.	+1.5	+2.5	−2.7
Liquid d^0_4		1.4395	1.3828	1.3019
Heat of vaporization, cal.		9647	9082	7779
Corrosion,[c] 10^4 in./month		5.66	1.18	1.26
Percentage compositions, %	Sulfur Calcd.	17.91	19.72	21.94
	Sulfur Found	17.76 17.87	19.65 19.70	22.02 22.07
	Phosphorus Calcd.	17.32	19.06	21.20
	Phosphorus Found	17.12 17.18	18.90 18.98	20.97 21.01
	Chlorine Calcd.	39.62	21.80	...
	Chlorine Found	39.58 39.65	21.65 21.70	... ..
	C_2H_5O Calcd.	23.80	27.69	30.84
	C_2H_5O Found	23.50 23.68	27.44 27.50	30.33 30.60

[a] Constants in the equation $\log p$ (mm.) $= (A/T) + B$. [b] Variation in vapor pressure in mm. [c] Corrosion $= C = 43.9W/ASt$. [d] At 760 mm. pressure.

Determination of Physical Constants (see Table I).—The freezing points of separately generated and fractionally distilled samples of these compounds were determined as described by Booth and Martin.[17] In the determination of the freezing points of the dichloride and the difluoride, supercooling was observed to the extent of 12.6 and 10.5°, respectively. The freezing point of thiophosphorylethoxychlorofluoride was difficult to obtain due to a tendency toward glass formation. Further cooling of the glass produced a crystalline product which gave a very short, but reproducible, break in the cooling curve. The transformation from the glass to the crystalline solid was accompanied by a crackling noise and frequently the freezing point cell was broken. Attempts to obtain a melting point were unsuccessful.

Liquid densities were determined at 0° using the method of Booth and Hermann.[18] Qualitative solubility tests were made by adding each compound dropwise to comparable volumes of solvents and allowing the components to stand in contact with each other without stirring for thirty minutes. Except for water, complete miscibility with the solvent was observed immediately upon contact.

The vapor pressures were determined by the static method of Booth, Elsey and Burchfield.[19] The equations in Table I are derived from the original vapor pressure data.

Discussion

Thiophosphorylethoxydichloride was described by Pischimuka[5] as being an oily, clear liquid, possessing a peculiar odor. The liquid density and the boiling point reported by Pischimuka[5] are in poor agreement with the values reported in this study which may be due to impurities in the product obtained by Pischimuka due to reactions described by Cloez[20] and Chevrier.[21] The determination of the vapor pressure of this compound was not possible above 90° because it decomposes into a more volatile constituent. In air and in water, thiophosphorylethoxydichloride shows no tendency to hydrolyze. Small amounts of the liquid have no vesicant action upon the hands. No corrosion was observed when the vapors were in contact with mercury and only slight corrosion was measured[22] when steel was kept in contact with the liquid for eighty-four hours at 0° (see Table I).

Thiophosphorylethoxychlorofluoride is a clear liquid with an odor similar to, but sharper than, thiophosphorylethoxydichloride. Upon exposure to air, dense grayish-white clouds of smoke appear which are attributed to oxidation rather than hydrolysis, inasmuch as no reaction was observed when the liquid was placed in water although it did react readily with a 0.5 *N* solution of sodium hydroxide. A similar reaction occurs to a greater extent when the difluoride is exposed to the atmosphere. The chlorofluoride in the gaseous state apparently does not attack mercury and its corrosion of steel, as would be expected, is less than that of the dichloride which is very slight as shown in Table I.

Thiophosphorylethoxydifluoride is a clear, highly refractive liquid, having an odor similar to that of the dichloride and chlorofluoride. Voluminous clouds of a grayish-white reaction product are liberated when the difluoride is allowed to mix with the atmosphere. As with the chlorofluoride,

(11) H. S. Booth and W. D. Stillwell, THIS JOURNAL, **56**, 1531–1535 (1934).

(12) W. W. Scott, "Standard Methods of Chemical Analysis," Vol. I, 5th ed., D. Van Nostrand Co., Inc., New York, N. Y., 1938.

(13) S. Popoff and E. W. Neuman, *Ind. Eng. Chem., Anal. Ed.*, **2**, 45–54 (1930).

(14) N. H. Furman and H. M. State, *ibid.*, **8**, 420–423 (1936).

(15) W. M. McNabb, THIS JOURNAL, **49**, 891–896 (1927).

(16) O. v. Lupin, *Z. anal. Chem.*, **97**, 210–220 (1934).

(17) H. S. Booth and D. R. Martin, THIS JOURNAL, **64**, 2198–2205 (1942).

(18) H. S. Booth and C. V. Hermann, *ibid.*, **58**, 63–66 (1936).

(19) H. S. Booth, H. M. Elsey and P. E. Burchfield, *ibid.*, **57**, 2064–2065 (1935).

(20) S. Cloez, *Compt. rend.*, **24**, 388–389 (1847).

(21) Chevrier, *ibid.*, **68**, 924–927 (1869); *Z. Chem.*, 413 (1869).

(22) J. H. Perry, "Chemical Engineers' Handbook," 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 2095.

the reaction is believed to be one of oxidation inasmuch as the liquid does not appear to react with water. The fumes have an odor similar to that of ozone. As with the other compounds, little or no reaction with mercury or steel was observed (see Table I).

As expected, the substitution of fluorine for chlorine increases the stability of the compounds in this series. In the determination of the vapor pressures it was observed that the dichloride decomposes around 90°, and the chlorofluoride around 100° whereas the difluoride was observed to be stable up to its normal boiling point, 78.4°.

Although the equations for the vapor pressure of the dichloride and chlorofluoride are reliable only up to around 100°, calculation of the boiling points of these compounds under 760 mm. pressure gives values of 157 and 120°, respectively. Once again the Swarts rule for regular lowering of the boiling point of a compound by substitution of a fluorine atom is valid. One fluorine atom lowers the boiling point from 157 to 120° (Δ = 37°) and the second fluorine substitution cause the boiling point to drop to 78.4° (Δ = 42°).

Acknowledgment.—This investigation was carried out under the sponsorship of the Naval Research Laboratory. We are deeply indebted to members of the staff of the Chemical Division for valuable suggestions and encouragement during its progress.

Summary

Thiophosphorylethoxydichloride was prepared from thiophosphoryltrichloride and ethanol, purified and certain of its physical and chemical properties observed. Upon fluorination, by means of the Swarts reaction with antimony pentachloride as catalyst, thiophosphorylethoxychlorofluoride and thiophosphorylethoxydifluoride were obtained. These new compounds were purified and some of their physical and chemical properties studied.

The properties determined for the above compounds include freezing point, vapor pressure, boiling point, heat of vaporization, Trouton constant, liquid density, solubilities, corrosion tests, and hydrolysis.

CLEVELAND, OHIO RECEIVED MARCH 15, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Polarographic Characteristics of +2 and +3 Vanadium. I. Polarography in Non-complexing Solutions[1]

BY JAMES J. LINGANE AND LOUIS MEITES[2]

Previous papers[3,4] from this Laboratory have discussed the polarography of the +2 and +3 states of vanadium in solutions of dilute acids and of oxalates. In these media the V(II)–V(III) couple is thermodynamically reversible at the dropping electrode. The investigation described in this and a following paper was undertaken to extend the information concerning solutions of these ions and of their complexes. The polarographic characteristics of +2 and +3 vanadium have been studied in a wide variety of media, including dilute acids and alkalies, phosphate, acetate, pyridine, and carbonate buffers, and solutions of the halides, thiocyanate, cyanide, thiosulfate, pyrophosphate, borate, benzoate, phthalate, salicylate, tartrate and citrate. This paper discusses only the cases in which no complex ions are formed. The experimental technique was essentially the same as that used in previous studies.[3,4]

Data and Discussion

We have found the half-wave potential for the reduction of vanadic to vanadous ion in 1 *N* sulfuric, hydrochloric, or perchloric acid to be -0.508 ± 0.002 v. *vs.* the saturated calomel electrode, which agrees very well with the standard potential of the couple reported by Jones and Colvin.[5] Zeltzer's determination of this constant[6] actually corresponds to the half-wave potential of +4 vanadium[3]; his solutions appear to have been quantitatively air-oxidized.

As the concentration of free acid is decreased, the wave becomes somewhat irreversible and shifts to more negative potentials. In 0.002 *N* acid the half-wave potential is −0.59 v. A second small wave at about −0.95 v. develops as the acid concentration is decreased. This wave is due to reduction of the hydrolysis product $V(OH)^{++}$, whose polarographic characteristics are discussed below.

We previously found the anodic half-wave potential of vanadous ion in 1 *N* sulfuric acid to be −0.50 v.,[3] and the corresponding (anodic) diffusion current constant to be -1.74 ± 0.01.[4] Since this constant is much larger than that found for vanadic ion, 1.41 ± 0.01, it follows that aquovanadous ion must be much smaller than aquovanadic ion. The half-wave potential of this anodic wave is not measurably affected by replacing the sulfuric acid with hydrochloric or perchloric acid.

(1) This paper is based on a thesis submitted by Louis Meites to the Graduate Faculty of Harvard University in partial fulfilment of the requirements for the degree of Doctor of Philosophy in February, 1947.

(2) Present address: Department of Chemistry, Princeton University, Princeton, N. J.

(3) J. J. Lingane, THIS JOURNAL, **67**, 182 (1945).

(4) J. J. Lingane and L. Meites, *ibid.*, **69**, 1021 (1947).

(5) G. Jones and J. H. Colvin, *ibid.*, **66**, 1563 (1944).

(6) S. Zeltzer, *Coll. Czechoslov. Chem. Commun.*, **4**, 319 (1932).

Vanadic ion in 1 *N* acid solutions shows no anodic wave, nor is vanadous ion oxidized beyond the +3 state in these solutions.

Polarograms of +3 vanadium in unbuffered potassium chloride solutions consist of several very irreversible waves, whose total height decreases as hydrous vanadic oxide precipitates. Since several species are clearly involved, the over-all half-wave potentials are meaningless.

Polarograms of +3 vanadium in acetic acid–sodium acetate buffers (1 *M* total acetate) are presented in Fig. 1. These polarograms consist of two cathodic waves whose relative heights are a function of *p*H. Thus, at *p*H 4.1 the over-all diffusion current constant is 2.21 times that of the first wave alone, at *p*H 5.4 the ratio is 2.44, and at *p*H 6.3 it is 2.72. The individual diffusion current constants have been determined only in the buffer of *p*H 5.4, where they are, respectively, 0.57 ± 0.01 and 1.39 ± 0.01. The total diffusion current constant is so close to that found for a one-electron reduction of +3 vanadium in 1 *N* sulfuric acid that the reduction in these acetate media must proceed only to the +2 state and the doublet waves must be attributed to two different molecular species of +3 vanadium in sluggish equilibrium.

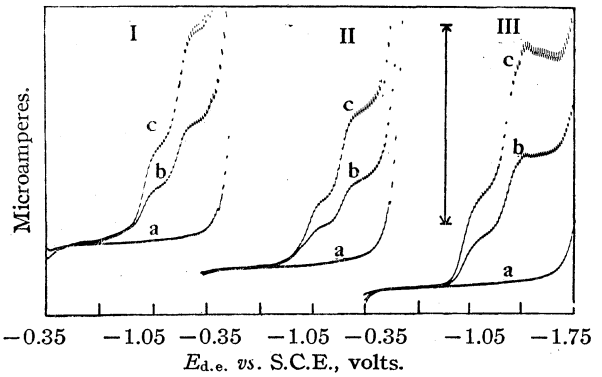


Fig. 1.—Polarograms of (a) 0, (b) 1.83, and (c) 3.44 millimolar +3 vanadium in acetic acid–sodium acetate buffers (1 *M* total acetate) of *p*H (I) 4.10, (II) 5.40, and (III) 6.30. The height of the arrow corresponds to six microamperes.

These species are most probably $V(OH)^{++}$ and VO^{+} formed by hydrolytic dissociation of the aquovanadic ion

$$V^{+++} + H_2O = V(OH)^{++} + H^{+} \quad (1)$$
$$V(OH)^{++} = VO^{+} + H^{+} \quad (2)$$

Since the relative height of the first wave decreases with increasing *p*H, this wave corresponds to reduction of $V(OH)^{+}$ and the second wave results from reduction of the more hydrolyzed species VO^{+}. It is not possible to compute the exact relative concentrations of the two species in the body of the solution from the relative wave heights. At potentials on the first wave the equilibrium in reaction 2 *tends* to shift to the left as $V(OH)^{++}$ is removed by the electrode reaction, and consequently the relative height of the first wave *tends* to be larger than corresponds to the true relative concentration of $V(OH)^{++}$ in the body of the solution. In an acetate buffer of *p*H 5.4 the ratio of the second to first wave heights is 1.44, from which we conclude that the $(VO^{+})/V(OH)^{+}$ ratio in the body of the solution is equal to or greater than 1.44. This is consistent with the data for the hydrolysis of vanadic ion given by Jones and Ray.[7]

The half-wave potential of the first wave in acetate buffers is −0.970 v. at *p*H 4.1, −0.978 v. at *p*H 5.4, and −1.008 v. at *p*H 6.3. Corresponding values for the second wave are, *seriatim*, −1.232, −1.245 and −1.300 v. Since both waves are somewhat irreversible, little thermodynamic significance can be attached to the magnitude of either rate of shift. However, the fact that a given *p*H change causes approximately twice as great a shift of the half-wave potential of the second wave as the first is in agreement with the expected relative effect of hydrogen ion if the electrode reactions are, respectively

$$V(OH)^{++} + H^{+} + e = V^{++} + H_2O \text{ and}$$
$$VO^{+} + 2H^{+} + e = V^{++} + H_2O$$

In an acetic acid–sodium acetate buffer of *p*H 5.4, +2 vanadium yields a double anodic wave as shown in Fig. 2. The first wave has a half-wave potential of −0.886 v. and a diffusion current constant of −1.090 ± 0.007. The half-wave potential of the second wave is −0.106 v. and its diffusion current constant is −3.36 ± 0.06. The

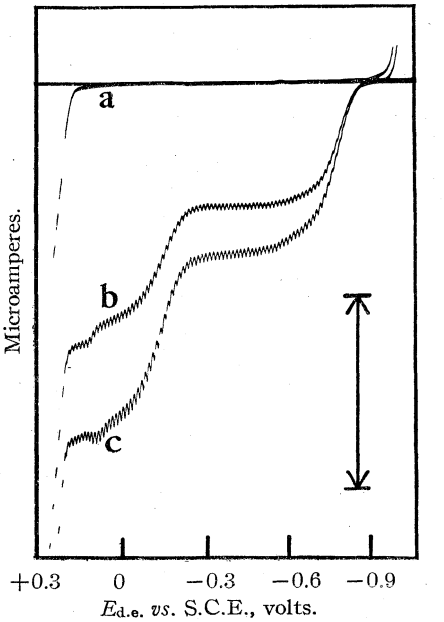


Fig. 2.—Polarograms of (a) 0, (b) 2.83, and (c) 3.96 millimolar +2 vanadium in an acetic acid–sodium acetate buffer (1 *M* total acetate) of *p*H 5.40. The height of the arrow corresponds to ten microamperes.

(7) G. Jones and W. A. Ray, THIS JOURNAL, **66**, 1571 (1944).

ratio of the diffusion current constants, 3.08, indicates that the waves are due to successive 1- and 3-electron oxidations of the +2 vanadium to the +3 and + 5 states. Plots of $-E_{d.e.}$ against log $(i/i_d - i)$ have slopes of −73 and −54 mv. (according to the common sign convention, this slope is negative for an anodic wave) instead of the −59.1 and −29.6 expected[4] for reversible −1 and −2 electron oxidations. Therefore neither stage of the oxidation proceeds strictly reversibly, and the $V^{+3} \rightarrow V^{+5}$ stage is less reversible than the $V^{+2} \rightarrow V^{+3}$ step.

Hydrous vanadic oxide is quantitatively precipitated on addition of solutions of +3 vanadium to a supporting electrolyte containing 1 *M* sodium hydroxide and 0.08 *M* sodium sulfite, and polarograms made immediately after the solutions are composited show no anodic or cathodic wave. However, even though the solutions are protected against air-oxidation by both hydrogen and sulfite, a double anodic wave at about −0.46 and −0.38 v. soon develops and rapidly increases in height as the solution ages. We have succeeded in keeping solutions of very powerful reducing agents (*e. g.*, vanadous oxalate[4]) for hours without measurable air-oxidation, and hence it appears that alkaline suspensions of vanadic hydroxide are actually thermodynamically metastable. Since +5 vanadium gives no anodic wave whatever, and +4 vanadium in this medium gives only a single anodic wave at −0.432 v.,[3,8] the reaction which takes place probably produces two hypovanadite ions at approximately equal concentrations and in slow equilibrium with each other.

Curves I in Fig. 3 are polarograms of +3 vanadium in weakly acid (*p*H about 3) 1 *M* potassium fluoride. No wave due to reduction of the vanadium is observed; the wave which appears in the residual current curve is probably due to an impurity in the potassium fluoride used. A colorless precipitate, possibly of $K_2VF_5 \cdot H_2O$,[9] is formed in these mixtures. This is the most insoluble salt of + 3 vanadium encountered in the whole of the present work.

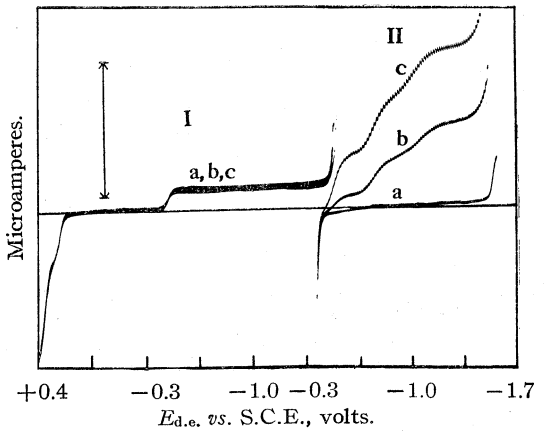


Fig. 3.—Polarograms of (a) 0, (b) 1.83, and (c) 3.44 millimolar +3 vanadium in (I) 1 *M* potassium fluoride and (II) 1 *M* potassium iodide. The height of the arrow corresponds to ten microamperes.

Solutions of +2 vanadium in the same medium (Curves I, Fig. 4) give three approximately equal anodic waves, with half-wave potentials of −0.701, −0.15, and +0.21 v. The first wave, which has a diffusion current constant of −1.96 ± 0.01, corresponds to oxidation to the +3 state. The other waves, which are too ill-defined for accurate measurement, must therefore represent oxidation to the +4 and +5 states. The vanadous–vanadic fluoride couple in this medium is very irreversible: the slope of the plot of $-E_{d.e.}$ against log $(i/i_d - i)$ is −166 mv., instead of the −59.1 mv. expected[4] for a reversible one-electron oxidation.

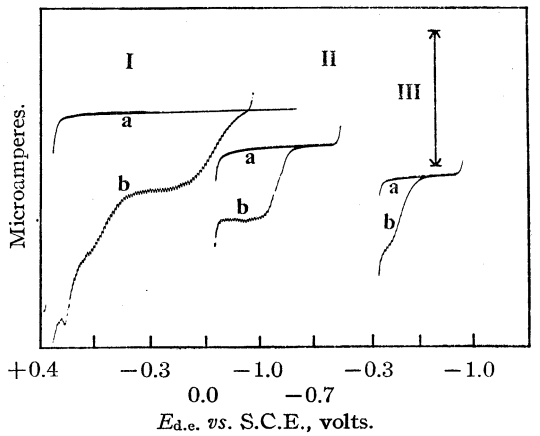


Fig. 4.—Polarograms of (I) (a) 0 and (b) 2.03 millimolar +2 vanadium in 1 *M* potassium fluoride, (II) (a) 0 and (b) 1.55 millimolar +2 vanadium in 1 *M* potassium bromide, and (III) (a) 0 and (b) 1.47 millimolar +2 vanadium in 1 *M* potassium iodide. The height of the arrow corresponds to ten microamperes.

In a 1 *M* potassium bromide solution (Curves II, Fig. 4), +2 vanadium gives a single well-defined anodic wave whose half-wave potential is −0.495 v. The magnitude of the corresponding diffusion current constant, −2.03 ± 0.03, indicates that the oxidation proceeds only to the +3 state. Plots of $-E_{d.e.}$ against log $(i/i_d - i)$ have slopes of −74 mv., and this small irreversibility appears to be the cause of the deviation from the reversible half-wave potential of the vanadous–vanadic couple.

Solutions of +3 vanadium in 1 *M* potassium bromide give a double cathodic wave (Fig. 5) with half-wave potentials at −0.43 and −0.87 v. Both waves are well-defined, but the ratio of their diffusion current constants varies with the *p*H: at *p*H 6 the diffusion current constant for the total second wave is 3.3 times that of the first wave alone, at *p*H 4.7 the ratio is 1.75, and at *p*H 4 it is 1.46. Below *p*H 4 the over-all diffusion current

(8) J. J. Lingane and L. Meites, *Anal. Chem.*, **19**, 159 (1947).

(9) E. Petersen, *J. prakt. Chem.*, [2] **40**, 48 (1889).

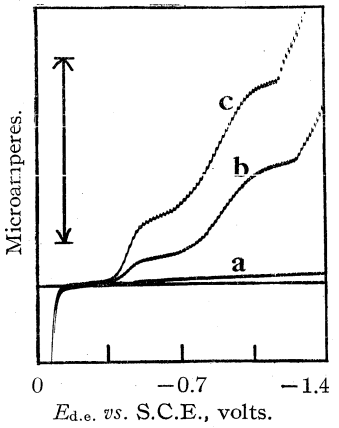


Fig. 5.—Polarograms of (a) 0, (b) 1.83, and (c) 3.44 millimolar +3 vanadium in 1 *M* potassium bromide, *p*H 2.5. The height of the arrow corresponds to ten microamperes.

constant is 1.940 ± 0.009, while that of the first wave alone is 1.419 ± 0.005, and the ratio is 1.37 ± 0.01. Since the over-all constant is close to that which corresponds to a one-electron oxidation of +2 vanadium in the same medium, it follows that the reduction of +3 vanadium must also involve only one electron, and consequently that the waves are due to the reduction of two species in sluggish equilibrium. Since both waves are irreversible (the slopes of plots of $E_{d.e.}$ against log $(i/i_d - i)$ are 74 and 170 mv., respectively), polarographic identifications of these species are impossible.

Only one ill-defined anodic wave is observed with solutions of +2 vanadium in 1 *M* potassium iodide (Curves III, Fig. 4). This wave has a half-wave potential of −0.49 v. and a diffusion current constant of −2.275 ± 0.03; it represents oxidation to the +3 state.

Solutions of +3 vanadium in 1 *M* potassium iodide show a triple cathodic wave (Curves II, Fig. 3) at a *p*H of about 2.5. The half-wave potentials of these waves are −0.46, −0.71 and −0.98 v. At *p*H values between 2 and 3 the total diffusion current constants of the second and third waves are 0.792 ± 0.003 and 2.75 ± 0.02, and the fact that the latter figure is fairly close to the value found for a one-electron oxidation of +2 vanadium leads to the conclusion that the sum of all three waves represents reduction only to the +2 state.

Table I contains data on the variation of the half-wave potentials of +3 vanadium with *p*H and potassium iodide concentration. These data were assembled from polarograms of which Fig. 6 is representative.

The half-wave potentials of the two waves given by +3 vanadium in an iodide-free acetate buffer of *p*H 5.0, calculated by interpolation in the data quoted previously, are −0.98 and −1.24 v. These figures are in good agreement with those observed in the presence of 1 *M* iodide; the small

TABLE I

HALF-WAVE POTENTIALS OF +3 VANADIUM AT VARYING *p*H AND POTASSIUM IODIDE CONCENTRATION

The figures represent the half-wave potentials, in volts, referred to the saturated calomel electrode.

KI, molar	*p*H → 1.8	2.5	4.0[a]	5.0[a]	6.0[a]	13[b]
0.10	....	....	.....	−1.03	.....	N. R.[c]
				−1.28		
0.33	....	....	.....	−1.01	.....	N. R.
				−1.26		
1.00	−0.49	−0.47	−0.978	−1.018	−1.038	N. R.
	−0.97	−0.71	−1.183	−1.256	−1.283	
		−0.98				

[a] Acetic acid–sodium acetate buffer (1 *M* total acetate). [b] 0.1 *M* sodium hydroxide. [c] N. R.: not reducible, hydrous vanadic oxide quantitatively precipitated.

differences are probably not significant. Therefore, according to our earlier interpretation of this same double wave, the wave at −1.0 v. must be due to reduction of $V(OH)^{++}$ and the wave at −1.2 v. to the reduction of VO^+. As would be predicted from this, the relative height of the first wave decreases with increasing *p*H and increasing hydrolysis, and the effect of *p*H on the half-wave potential of the second wave is about twice as great as on that of the first wave. Then the second wave at *p*H 1.8 must also be due to reduction of $V(OH)^{++}$, while the first, since it is at the same potential as the wave given by +3 vanadium in 1 *N* acid solutions, must be due to reduction of the simple vanadic ion. The wave at −0.71 v., which appears only when the *p*H is close to 2.5, is difficult to explain. It may be due either to a hydroxy-iodo complex of vanadic ion or to a compound such as $HV(SO_4)_2$,[10] but there is no definite evidence to confirm either supposition.

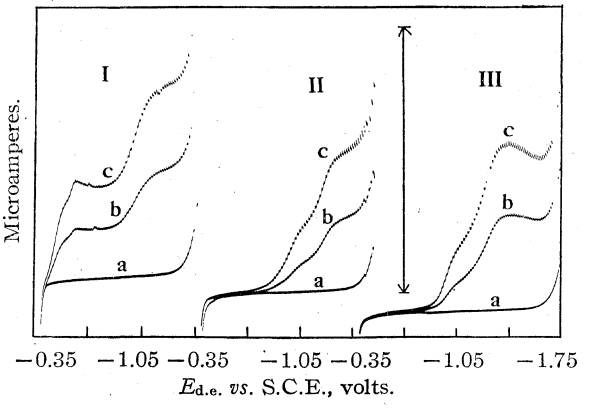


Fig. 6.—Polarograms of (a) 0, (b) 1.83, and (c) 3.44 millimolar +3 vanadium in 1 *M* potassium iodide, *p*H (I) 1.8 (0.02 *N* sulfuric acid), (II) 4.0, and (III) 5.5. The solutions of (II) and (III) contained acetic acid–sodium acetate buffers (1 *M* total acetate). The height of the arrow corresponds to twenty microamperes.

Summary

1. Acidic solutions of +3 vanadium are shown to contain, in addition to simple vanadic ion,

(10) H. T. S. Britton and G. Welford, *J. Chem. Soc.*, 761 (1940).

V^{+++}, its hydrolysis products $V(OH)^{++}$ and VO^{+}.

2. Data are presented on the ionic states and polarographic characteristics of +2 and +3 vanadium in solutions of dilute acids and alkalies, acetate buffers, and of the various halide ions.

CAMBRIDGE, MASS. RECEIVED JANUARY 23, 1948

[CONTRIBUTION NO. 221 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

Free Radical-initiated Reaction of Ethylene with Carbon Tetrachloride

BY R. M. JOYCE, W. E. HANFORD[1] AND J. HARMON

This paper describes the free radical-initiated polymerization of ethylene in the presence of the chain transfer agent, carbon tetrachloride. Because of the simplicity of the products formed from ethylene as a polymerizing monomer, and because carbon tetrachloride is a very efficient chain transfer agent for ethylene, it has been possible to isolate and establish the structures of the products of this chain transfer polymerization reaction. In addition, a qualitative study of the variation of chain length of the products with reaction conditions has been made.

The presence of chlorine in polystyrene prepared in carbon tetrachloride has been observed by several investigators,[2] and Price[3] has advanced the hypothesis that these polymers contained Cl and CCl_3 end-groups. Kharasch[4] has reported the addition of carbon tetrachloride to octene-1 to produce 1,1,1,3-tetrachlorononane, initiated by free radicals from diacyl peroxides. More recently, Kharasch[5] has described the addition of carbon tetrachloride to ethylene at low pressures to obtain a compound believed to be 1,1,1,3-tetrachloropropane. Evidence presented in this paper establishes that this structure is correct.

We have investigated the benzoyl peroxide-initiated reaction of ethylene with carbon tetrachloride over the pressure range 50–15000 lb./sq. in., and have shown that the reaction gives a series of compounds of the formula $Cl(CH_2CH_2)_nCCl_3$. When this reaction is carried out at an ethylene pressure of 1500 lb./sq. in., the major portion of the product comprises the first four members of this series. These compounds have been separated by fractional distillation, and their properties are given in Table I.

TABLE I

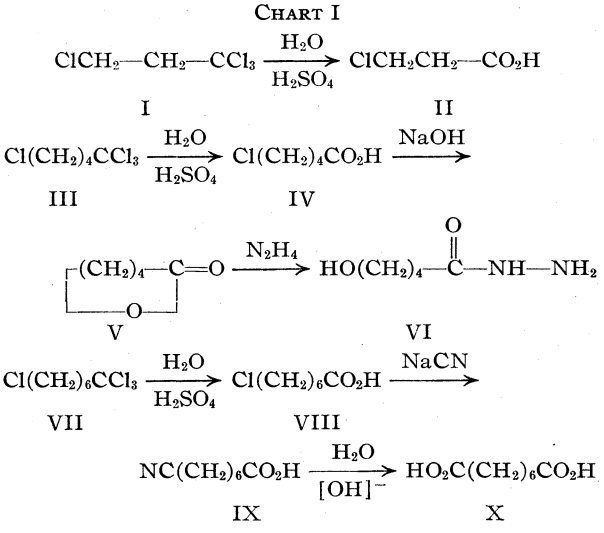
PROPERTIES OF $Cl(CH_2CH_2)_nCCl_3$

n	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4
1	159	760[a]	1.4794[a]	1.4463
	59	24		
2	112	24	1.4859	1.3416
3	143	24	1.4824	1.2535
4	168	20	1.4804	1.1943

[a] Kharasch[5] reported b. p. 155°, $n^{20}D$ 1.4825.

The structures of the first three compounds were established by the reactions shown in Chart I, beginning with the hydrolysis of the CCl_3 group to a carboxylic acid with sulfuric acid and water.[6]

CHART I



Under these conditions the tetrachloropropane (I) gave β-chloropropionic acid (II) melting at 40–42°. The tetrachloropentane (III) gave 5-chlorovaleric acid (IV). This was readily converted to δ-valerolactone (V), b. p. 124° (30 mm.), by treatment with aqueous or alcoholic alkali. Reaction of the lactone with hydrazine gave the known hydrazide of 5-hydroxyvaleric acid (VI) melting at 105–107°. The tetrachloroheptane (VII) gave 7-chloroheptanoic acid (VIII). The structure of this acid was proved by reaction with sodium cyanide followed by hydrolysis to suberic acid (X). Similar hydrolysis of the tetrachlorononane gave a chlorononanoic acid which is believed to be the 9-chloro compound. The properties of these chloro acids are shown in Table II.

The reaction of ethylene with carbon tetrachloride has been run at pressures ranging from 50 to 15000 lb./sq. in. The reaction rate increases

(1) Present address: M. W. Kellogg Company, 225 Broadway, New York 7, New York.

(2) (a) Suess, Pilch and Rudorfer, *Z. physik. Chem.*, **A179**, 361 (1937); **A181**, 81 (1937); (b) Breitenbach, Springer and Abrahamczik, *Oesterr. Chem. Ztg.*, **41**, 182 (1938); (c) Springer, *Kautschuk*, **14**, 212 (1938); (d) Breitenbach and Maschin, *Z. physik. Chem.*, **A187**, 175 (1940).

(3) Price, *Ann. N. Y. Acad. Sci.*, **44**, 351 (*cf.* p. 366) (1943).

(4) Kharasch, Jensen and Urry, *Science*, **102**, 128 (1945).

(5) Kharasch, Jensen and Urry, THIS JOURNAL, **69**, 1100 (1947).

(6) Joyce, U. S. Patent 2,298,430.

TABLE II

PROPERTIES OF $Cl(CH_2)_mCO_2H$

m	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4
4	122–124	8	1.4525	1.1667
6	136–137	5	1.4550	1.0916
8	164–166	7.5	1.4588 (27.5°)	....

markedly with pressure and, unless careful control is maintained, particularly with respect to dissipation of the heat of reaction, violently explosive reactions may occur.[7]

In this connection it is important to provide efficient agitation. The use of a diluent is desirable if the reaction is to be carried out on a scale greater than 500–1000 ml. reactor volume, except at pressures below about 150 lb./sq. in. A diluent is definitely advisable on any scale when the reaction is run above about 1000 lb./sq. in. The most effective diluent for moderating the reaction is water, presumably because of its inertness under reaction conditions and its high specific heat. We have carried out the reaction with a charge comprising 100 g. each of water and carbon tetrachloride and 0.23 g. of benzoyl peroxide in a 400-ml. reactor at 12000 lb./sq. in. It should not be inferred, however, that these conditions are necessarily safe, particularly if the agitation is inefficient. An explosion is a definite possibility should this reaction be attempted on a larger scale, or with a higher ratio of benzoyl peroxide to carbon tetrachloride.

When benzoyl peroxide is employed as initiator, the reaction proceeds smoothly in the temperature range 90–120°. A small amount of benzoyl peroxide suffices to initiate the reaction and it has been our practice not to employ more than 0.003 molecular equivalent of this peroxide based on carbon tetrachloride. As little as 0.0007 molecular equivalent has been used successfully. Within these ranges of benzoyl peroxide concentration, and employing a charge comprising 210 g. of carbon tetrachloride and 35 g. of water at 1400 lb./sq. in. ethylene pressure, we have obtained yields of 300–370 g. of reaction product per gram of benzoyl peroxide. The yields are somewhat lower at lower pressures. The exclusion of oxygen from the reaction mixture is desirable.

The proportions of the individual tetrachloroalkanes in the reaction product depend on the concentration of ethylene relative to that of carbon tetrachloride. This concentration can be changed by varying the ethylene pressure. Moreover, at a given pressure, dilution of the carbon tetrachloride with a solvent for ethylene which is relatively inert as a chain transfer agent, such as an aliphatic hydrocarbon, also serves to increase the concentration of ethylene relative to carbon tetrachloride. The variations in chain length of the products formed under various reaction conditions are shown in Table III.

(7) (a) Bolt, *Chem. Eng. News*, **25**, 1866 (1947); (b) Joyce, *ibid.*, **25**, 1866 (1947).

TABLE III

VARIATION IN CHAIN LENGTH OF $Cl(CH_2CH_2)_nCCl_3$ WITH REACTION CONDITIONS

Ethylene pressure, lb./sq. in.	$Cl(CH_2CH_2)_nCCl_3$ Wt. per cent. of total product $n = 1$	$n = 2$	$n = 3$	$n = 4$	$n > 5$
50	77	23	..	..	..
80– 150	62.6	32.0	5.4	..	..
1200–1400	9.5	59.4	22.6	6.5	2.0
1500–1700	3.7	46.7	28.1	13.1	8.4
4000	1.0	24.1	24.5	21.8	28.6
1200–1400[a]	5.7	46.4	28.1	15.3	4.5
1200–1400[b]	1.8	24.0	25.9	21.7	26.6

[a] Organic phase comprised 96 g. of carbon tetrachloride and 59.5 g. of 2,2,4-trimethylpentane. [b] Organic phase comprised 54 g. of carbon tetrachloride and 87.5 g. of 2,2,4-trimethylpentane.

The concept of chain transfer in a free radical polymerization was first proposed by Flory.[8] The following mechanism, by which the tetrachloroalkanes are believed to be formed from ethylene and carbon tetrachloride, has been proposed by others[3,5] for this type of reaction. The establishment of the structures of these tetrachloroalkanes and our failure to isolate compounds of other structures from this reaction support this mechanism.

$$R\cdot + CCl_4 \longrightarrow RCl + \cdot CCl_3 \quad (1)$$

$$\cdot CCl_3 + C_2H_4 \longrightarrow Cl_3CCH_2CH_2\cdot \quad (2)$$

$$Cl_3CCH_2CH_2\cdot + nC_2H_4 \longrightarrow Cl_3C(CH_2CH_2)\cdot_{n+1} \quad (3)$$

$$Cl_3C(CH_2CH_2)\cdot_{n+1} + CCl_4 \longrightarrow Cl_3C(CH_2CH_2)_{n+1}Cl + \cdot CCl_3 \quad (4)$$

$$2\cdot CCl_3 \longrightarrow Cl_3CCCl_3 \quad (5)$$

The initiating radical R· is derived from benzoyl peroxide. It would be expected to be the phenyl radical, since the decomposition of benzoyl peroxide in carbon tetrachloride has been shown to produce chlorobenzene in considerable quantity.[9] However, chlorobenzene has not been isolated as a by-product in this reaction, benzoic acid being the only aromatic compound obtained.

Definite evidence that the $\cdot CCl_3$ radical propagates the chain cycle is provided by the isolation of hexachloroethane from the reaction mixture. During the fractional distillation of the product from a run involving 5.5 kg. of carbon tetrachloride, several grams of hexachloroethane distilled between the C_3 and C_5 cuts.

The above mechanism appears to be the only one operating in this reaction. Careful fractional distillation of the products has failed to reveal the presence of any other types of compounds, such as $Cl(CH_2CH_2)_nCl$ or $Cl_3C(CH_2CH_2)_nCCl_3$. The formation of the former type would require a mechanism in which an initiating free radical reacted with carbon tetrachloride as follows

$$R\cdot + CCl_4 \longrightarrow RCCl_3 + \cdot Cl \quad (6)$$

This type of free radical reaction is much less probable than reaction 1.[10] Compounds of the type

(8) Flory, THIS JOURNAL, **59**, 241 (1937).

(9) Böeseken and Gelissen, *Rec. trav. chim.*, **43**, 869 (1924).

(10) Waters, "Chemistry of Free Radicals," Clarendon Press, Oxford, 1946, p. 130.

$Cl_3C(CH_2CH_2)_nCCl_3$ could be formed by a chain termination reaction involving the combination of two growing radicals such as those produced in equations (2) and (3). However, the termination reaction (4) evidently predominates so that these compounds are not formed to any significant extent.

Experimental

Small-Scale Reaction of Ethylene with Carbon Tetrachloride.—A stainless steel-lined tubular pressure reactor having an internal volume of about 350 ml. and equipped with a thermocouple well and gas inlet was charged with 210 g. (1.36 moles) of freshly distilled carbon tetrachloride, 35 g. of water, and 0.47 g. (0.00194 mole) of benzoyl peroxide ("Lucidol"). The reactor was evacuated, pressured to 500 lb./sq. in. with ethylene, and placed horizontally in a shaking box equipped with a heater. When the temperature of the reaction mixture had been raised to 70°, the pressure was increased to 1400 lb./sq. in. by injection of ethylene, and the heating was continued. The reaction mixture was maintained at 95°, and the pressure in the range 1200–1400 lb./sq. in. by injection of additional ethylene as required, for five hours. The reaction product was then removed from the cooled reactor, separated from the water, and dried over anhydrous magnesium sulfate. After removal of the unreacted carbon tetrachloride by distillation, a preliminary fractional distillation gave the following results

Cut	B. p., °C.	Mm.	Weight, g.	Weight per cent.
C_3	<90	12	11.7	7.2
C_5	90–115	11	97.0	59.7
C_7	115–145	11	36.0	22.2
C_9	145–175	11	12.5	7.7
$>C_9$	Residue		5.0	3.2

The pure compounds can be obtained from these cuts by redistillation (*cf.* Table I).

Large-Scale Reaction of Ethylene with Carbon Tetrachloride.—A horizontal stainless steel autoclave having a capacity of 12.5 l., equipped with a horizontal agitator, a thermocouple well, gas inlet, and rupture disc assembly, was charged with 4420 g. of carbon tetrachloride (28.7 moles), 4420 g. of water, and 10 g. (0.0414 mole) of benzoyl peroxide. The reactor was purged twice by pressuring with ethylene to 300 lb./sq. in. and venting. The reactor was then pressured to 510 lb./sq. in. with ethylene and heated with stirring. When the temperature reached 85° the pressure was increased to 1500 lb./sq. in. by injection of additional ethylene from a storage vessel. A rapid reaction set in when the temperature reached 95° and the temperature rose to 139° in about five minutes, the pressure remaining constant at 1600 lb./sq. in. during this period. The reactor was cooled slowly to 100°, maintaining the pressure in the range 1500–1700 lb./sq. in. by injection of additional ethylene as required. The lack of further pressure drop when the temperature was maintained at 100° indicated that the reaction had ceased and the mixture was cooled and discharged.

The water was separated from the organic phase and the latter was washed with 10% sodium carbonate solution and twice with water. It was then dried over anhydrous magnesium sulfate. The carbon tetrachloride was removed from the product in a stripping still and careful fractional distillation of the residue gave the following results:

Cut	Weight, g.[a]	Weight % of total	Molecular equivalents of carbon tetrachloride
C_3	126	3.7	0.69
C_5	1580	46.6	7.53
C_7	951	28.1	4.00
C_9	444	13.1	1.67
$>C_9$	285	8.5	0.95[b]
Total	3386	100.0	14.84

[a] These figures do not include small amounts of intermediate cuts and a few grams of hexachloroethane distilling between the C_3 and C_5 cuts. [b] Analysis of the residue indicated the composition $Cl(CH_2)_{10.5}CCl_3$.

Of the carbon tetrachloride charged, 1565 g. was recovered, leaving 2855 g., 18.54 moles, to account for. The yield of isolated compounds based on carbon tetrachloride was (14.84/18.54) × 100 = 80.0 per cent.

Structure of 1,1,1,3-Tetrachloropropane.—A mixture of 25 g. of 1,1,1,3-tetrachloropropane, 100 g. of 96% sulfuric acid, and 1 g. of water was stirred vigorously while heating on a steam-bath for one and one-half hours. At the end of this time, the evolution of hydrogen chloride had ceased and a dark, homogeneous solution resulted. The solution was cooled, poured onto 300 g. of ice, and extracted continuously with ether overnight. The ether solution was dried over magnesium sulfate, filtered, and distilled to obtain 9 g. (55% of the theoretical) of *beta*-chloropropionic acid boiling at 110° (20 mm.) and melting at 40–42°.

Structure of 1,1,1,5-Tetrachloropentane.—A mixture of 1260 g. of 1,1,1,5-tetrachloropentane and 1500 g. of 96% sulfuric acid was stirred vigorously and heated to 90–95° on a steam-bath. A vigorous evolution of hydrogen chloride set in. A solution of 180 g. of water and 330 g. of concentrated sulfuric acid was then added under the surface of the reaction mixture over a period of one hour. After maintaining the heating and stirring for an additional hour, the reaction mixture was cooled and poured onto 2500 g. of cracked ice. The crude separated acid was extracted with three 500-cc. portions of carbon tetrachloride. The combined carbon tetrachloride solutions were washed well with water and the carbon tetrachloride was then removed in a stripping still. The resulting product was purified by distillation through a precision still, and there was obtained 639 g. (78% of theoretical) of 5-chlorovaleric acid boiling at 128–131° (11 mm.).

A solution of sodium hydroxide in methanol (406 ml., 2.0 *N*) was placed in a 1-liter 3-necked flask equipped with a stirrer, thermometer and dropping funnel. The solution was cooled to 10–15° and a solution of 111 g. of 5-chlorovaleric acid in 150 ml. of methanol was added, maintaining the temperature below 15°. The resulting solution was made neutral to phenolphthalein by adding methanolic sodium hydroxide solution, and was refluxed with stirring for two hours. It was then cooled and filtered. The methanol was removed from the filtrate in a stripping still and the residue distilled through a precision column, yielding 63 g. (77.5% of the theoretical) of δ-valerolactone boiling at 92° (8 mm.), $n^{26}D$ 1.4550.

One-half gram of the lactone was heated on a steam-bath with 2 ml. of 85% aqueous hydrazine for one hour and then evaporated under reduced pressure. The resulting hydrazide of 5-hydroxyvaleric acid solidified and was recrystallized from ethanol, melting point 105–107°.

Structure of 1,1,1,7-Tetrachloroheptane.—One gram of 1,1,1,7-tetrachloroheptane was stirred vigorously with 10 ml. of concentrated sulfuric acid on a steam-bath for one and one-half hours. The mixture was cooled, poured on ice, extracted with ether, and the ether solution dried over magnesium sulfate. Half of the solution was evaporated, the residue neutralized with sodium hydroxide and treated with *p*-phenylphenacyl bromide. There was obtained the *p*-phenylphenacyl ester of 7-chloroheptanoic acid, melting at 73–75°.

Anal. Calcd. for $C_{20}H_{23}O_2Cl$: Cl, 10.72. Found: Cl, 10.83.

The second portion of the ether solution was evaporated and the residue neutralized with *N*/3 sodium hydroxide. Two-tenths gram of sodium cyanide was added to the solution and the mixture was refluxed for five hours. One and one-half grams of potassium hydroxide was then

added and the solution refluxed for six hours; ammonia was evolved during this operation. The resulting solution was cooled and acidified to congo red with hydrochloric acid. The precipitated suberic acid was collected on a filter and recrystallized from water, m. p. 138–140°; neut. eq., 86.4. There was no depression of the melting point when mixed with an authentic sample of suberic acid.

Hydrolysis of 1,1,1,9-Tetrachlorononane.—A mixture of 500 g. of concentrated sulfuric acid and 15 g. of water was heated to 95° with stirring on a steam-bath, and 133 g. (0.5 mole) of 1,1,1,9-tetrachlorononane was dropped in over a period of one hour. Stirring and heating were continued for three hours. The solution was then cooled, poured on 1200 g. of cracked ice, and extracted with two 100-ml. portions of carbon tetrachloride. The extract was dried over magnesium sulfate and distilled to obtain 55 g. (57% of the theoretical) of a chloro acid, presumably 9-chlorononanoic acid, boiling at 163.5–167° (7.5 mm.); $n^{36}D$ 1.4540; calcd. for $C_9H_{17}O_2Cl$: neut. eq., 192.5; found: neut. eq., 192.8.

Summary

The benzoyl peroxide-initiated reaction of ethylene with carbon tetrachloride gives a series of compounds having the general formula $Cl(CH_2CH_2)_nCCl_3$. When the reaction is carried out at 1500 lb./sq. in. the product is comprised principally of these compounds in which n has the values 1–4. The effect of reaction conditions on the proportions of individual members of this series in the reaction product is described.

Wilmington, Del. Received September 25, 1947

[Contribution from the Department of Chemistry, University of Delaware]

I. The Peroxide-Catalyzed Chlorination of Trimethylchlorosilane and *t*-Butyl Chloride[1]

By J. J. McBride, Jr., and H. C. Beachell

Trimethylchlorosilane has been chlorinated directly by Krieble and Elliot, a mixture of chlorination products being obtained.[2] Chlorination by sulfuryl chloride in the presence of benzoyl peroxide has been applied to various aliphatic hydrocarbons[3] and to certain organosilicon compounds.[4,5] This method of chlorination, however, has not been applied to trimethylchlorosilane, nor to its carbon analog, *t*-butyl chloride, previous to this work. The results are of interest in furnishing further information on the deactivation effect of the $-SiCl$ group on an alpha methyl group. (Sommer and Whitmore report that, like methylchloroform, methyltrichlorosilane cannot be chlorinated in this way.[4]) The chlorination of *t*-butyl chloride by the same method affords a means of comparing the relative effect of a silicon atom and a carbon atom in this reaction

Trimethylchlorosilane.—Refluxing an equimolar mixture of trimethylchlorosilane and sulfuryl chloride in the presence of benzoyl peroxide for several hours gave no detectable amount of chlorination product. When the experiment was repeated, however, using chlorobenzene as an inert diluent to increase the reflux temperature, a 38% yield of chloromethyldimethylchlorosilane was obtained after four hours. The yield of product was increased to 52% by adding the sulfuryl chloride dropwise to the refluxing mixture of trimethylchlorosilane and chlorobenzene. Density and refractive index have been determined for chloromethyldimethylchlorosilane. These are new physical constants for this compound.

In the majority of cases of fractionation of the reaction mixture, it was found that when almost all the chloromethyldimethylchlorosilane had been distilled off and there was a high concentration of higher boiling material left, *i. e.*, chlorobenzene and residue, the temperature dropped abruptly from 116° to about 71° where equilibrium was attained. The boiling point of dimethyldichlorosilane is given as 70°.[6] The identity of the material was established by determination of density, which is given in the literature[6] and by analysis for hydrolyzable chlorine. The presence of dimethyldichlorosilane may be due to disproportionation of chloromethyldimethylchlorosilane at a temperature above its boiling point or to the pyrolysis of unidentified polymeric by-products. No evidence for the presence of higher chlorinated products has been found, and other experimental evidence indicates that the reaction is limited to the introduction of a single chlorine under the conditions of the experiments.

The molar refraction for chloromethyldimethylchlorosilane was calculated by the Lorentz and Lorenz formula using the values obtained for density and refractive index. A value of 34.41 was obtained. This is in excellent agreement with the value of 34.70 obtained by addition of the atomic refraction equivalents. (The value used for silicon is that given by Whitmore for silicon in trimethylchlorosilane.[7])

***t*-Butyl Chloride.**—The chlorination of *t*-butyl chloride was carried out under the same conditions as that of trimethylchlorosilane. When an

(1) Abstracted from a thesis by J. J. McBride, Jr., submitted to the faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science.

(2) Krieble and Elliot, This Journal, **67**, 1810 (1945).

(3) Kharasch and Brown, *ibid.*, **62**, 925 (1940).

(4) Sommer and Whitmore, *ibid.*, **68**, 485–487 (1946).

(5) Sommer, Dorfman, Goldberg and Whitmore, *ibid.*, **68**, 488–489 (1946).

(6) Rochow, "Chemistry of the Silicones," John Wiley and Sons, New York, N. Y., 1946.

(7) Whitmore, *et al.*, This Journal, **68**, 475 (1946).

equimolar mixture of *t*-butyl chloride and sulfuryl chloride in the presence of benzoyl peroxide was refluxed with chlorobenzene, a 46% yield of 1,2-dichloro-2-methylpropane (b. p. 107–108°) was obtained after three hours. When the sulfuryl chloride was added dropwise to the refluxing mixture, a 59% yield of the chlorination product was obtained after three and one-quarter hours.

Experimental

Trimethylchlorosilane.—The trimethylchlorosilane used in this work was purchased from the Dow–Corning Corporation and redistilled, taking the fraction boiling at 57–58° at 760 mm. The boiling point is given as 57.6°.[5]

Chloromethyldimethylchlorosilane.—(a) 100 g. (0.92 mole) of trimethylchlorosilane, 124.2 g. (0.92 mole) of sulfuryl chloride, 0.5 g. of benzoyl peroxide and 200 ml. (220 g.) of chlorobenzene were placed in a 500-ml. round-bottomed flask fitted with a 30-inch reflux condenser surmounted with a cold finger, the inside dimensions of which were 3.5 × 25 cm. This was filled with a salt–ice mixture. Ground glass joints were used throughout. The evolved gases were passed through a drying tube of indicating Drierite into two 1-liter Florence flasks, the first a trap, and the second containing water so that the flow of gas could be observed. The flask was heated with a Glas-Col mantle. The mixture was refluxed vigorously. Gas was evolved at a fairly rapid rate and a gentle reflux was maintained from the cold finger. After three hours the evolution of gas had nearly stopped. The reaction mixture was fractionated in a Whitmore–Fenske total condensation, partial take-off column of about twenty theoretical plates. Twenty-eight grams of unreacted trimethylchlorosilane was recovered and 36 g. of chloromethyldimethylchlorosilane (b. p. 115–117°) obtained before the temperature dropped to 70°. Four grams was obtained between 70 and 131°. Two hundred and seventeen grams of chlorobenzene was recovered and 34 g. of a dark viscous liquid remained in the still pot. The yield based on unrecovered starting material was 38%.

(b) A 500-ml. 3-necked flask was fitted with a 250-ml. dropping funnel, a mercury-sealed stirrer and the reflux system described above. Fifty-four grams (0.5 mole) of trimethylchlorosilane, 0.5 g. of benzoyl peroxide and 108 ml. (119 g.) of chlorobenzene were placed in the reaction flask. The flask was heated as before. When the mixture was refluxing vigorously, sulfuryl chloride was added slowly with stirring over a period of four hours. The mixture was refluxed for two hours more until gas was no longer evolved. Fractionation of the product gave 22 g. of unreacted trimethylchlorosilane, 22 g. of chloromethyldimethylchlorosilane and 107 g. of chlorobenzene. Seventeen grams of tarry residue remained. The yield in this case was 52%.

(c) The chloromethyldimethylchlorosilane obtained in these experiments was redistilled and the middle cut, b. p. 115.2–116° at 762 mm. taken for analysis and determination of physical constants; $n^{20}D$ 1.4360; d^{20}_4 1.0865; M_D calcd. 34.70; M_D obs. 34.41. *Anal.* Calcd. for $(CH_3)_2Si(Cl)CH_2Cl$: hydrolyzable Cl, 24.79. Found: Cl, 24.42.

Dimethyldichlorosilane.—A 2.5-g. 71–73° fraction collected in one of the distillations was examined. The following constants were found: d^{20}_4 1.0637; $n^{28}D$ 1.4002; M_D calcd. 29.42; M_D obs. 30.09. Rochow gives the density as 1.062 at 20°.[6]

1,2-Dichloro-2-methyl-propane.—Fifty grams (0.39 mole) of *t*-butyl chloride (b. p. 51.0–51.5°), 53.1 g. (0.39 mole) of sulfuryl chloride, 0.5 g. of benzoyl peroxide, and 100 ml. (110 g.) of chlorobenzene were refluxed as in (a). Reaction was practically complete in three hours. The product was fractionated in a Whitmore–Fenske column of about twenty theoretical plates. There was obtained 10.3 g. of unreacted *t*-butyl chloride, 25.2 g. of 1,2-dichloro-2-methylpropane (b. p. 107.1–108.0°, $n^{28}D$ 1.4316), 101 g. of chlorobenzene and 13 g. of dark, oily residue. This is a yield of 46.3%.

The reaction was repeated as in (b) using 100 g. (0.79 mole) of *t*-butyl chloride, 106.2 g. (0.79 mole) of sulfuryl chloride, 0.5 g. of benzoyl peroxide and 200 ml. (220 g.) of chlorobenzene. Evolution of gas was rapid from the start. Reaction was complete in three hours. Fractionation of the product gave 28.5 g. of unreacted *t*-butyl chloride and 58.5 g. of 1,2-dichloro-2-methylpropane, b. p. 107–108°, $n^{25}D$ 1.4323. This is a yield of 59%.

Discussion

It appears that *t*-butyl chloride is chlorinated more readily by sulfuryl chloride than is trimethylchlorosilane. This is in accord with the action of the silicon atom as an electron sink.[8]

The deactivating effect on an α-methyl group of a chlorine attached to carbon is evident since the yields of monochlorinated product from *t*-butyl chloride are not nearly so high as those obtained with other types of hydrocarbons and chlorinated hydrocarbons.[3,9]

Summary

Trimethylchlorosilane has been chlorinated by the use of sulfuryl chloride and benzoyl peroxide in the presence of chlorobenzene (as an inert diluent to increase the reaction temperature), to give chloromethyldimethylchlorosilane.

Two new physical constants, density and refractive index, have been determined for chloromethyldimethylchlorosilane. These are: d^{20}_4 1.0865; $n^{20}D$ 1.4360.

t-Butyl chloride has been chlorinated under the same conditions to give 1,2-dichloro-2-methylpropane.

NEWARK, DELAWARE RECEIVED FEBRUARY 26, 1948

(8) Whitmore and Sommer, THIS JOURNAL, **61**, 481 (1939).

(9) Kharasch and Brown, *ibid.*, **61**, 2142 (1939).

[FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Further Studies of the Action of Pancreatic Amylase: Extent of Hydrolysis of Starch[1]

BY ROSLYN B. ALFIN[2] AND M. L. CALDWELL

Although pancreatic amylase has been known and studied for many years, remarkably little quantitative information is available concerning its action. A survey of the literature shows contradictory statements about the extent of the hydrolysis of starches by this amylase[3-10] and uncertainty about the products formed or the order of their appearance.[3,4,10-16]

The present report is a summary of part of a detailed study of the action of highly purified pancreatic amylase[17] carried out under conditions which have been found to favor its activity and to protect it from inactivation.[18] Information of this kind is important to a better understanding both of the amylase and of the chemical nature of starch.

Experimental

Preparations of highly purified pancreatic amylase were obtained from pancreatin[19] by a modification of the method of Sherman, Caldwell and Adams.[17] They showed no evidence of maltase activity in the concentrations used in this work.

The hydrolyses of starch were carried out at 40° and the reaction mixtures were adjusted to *p*H 7.2 in the presence of 0.01 *M* phosphate (sodium) and 0.02 *M* chloride (sodium), conditions which had been shown to protect this amylase from inactivation and to favor its activity.[16] The amylase preparations, also, were dissolved in 0.01 *M* phosphate, 0.02 *M* chloride at *p*H 7.2 at 0° and used as promptly as possible.[18]

The substrates included whole potato starch, a straight chain component of corn starch[20] and Lintner's soluble potato starch. The latter was included for comparative purposes as it has been the most widely used substrate for the laboratory study of amylase action. The starches were washed repeatedly with distilled and with redistilled water and air dried.

In experiments designed to study the extent of the hydrolysis of starch, concentrations of the amylase were chosen so that the reactions would proceed rapidly and be practically complete before contamination by yeasts and bacteria might be expected appreciably to influence the results. Phemerol[23] and toluene were added to hydrolysis mixtures which were allowed to react for more than five hours. Neither of these reagents was found to influence the activity of the amylase nor the reducing values of the reaction mixtures in the concentrations used.

The reducing values of the reaction mixtures were converted to their equivalents of maltose and usually are given in terms of the percentage yield of the maltose which could be obtained theoretically from the substrate. Usually, the reducing values were determined by iodometric titration[24] although a ferricyanide ceric sulfate method[25] also was used.

Results

Extent of Hydrolysis of Starch.—The average data given in Fig. 1 are typical of the results obtained when different concentrations of pancreatic amylase reacted with soluble potato starch, whole potato starch or with the linear fraction from corn starch.[26,27] They show that the extent of the hydrolysis of these substrates by pancreatic amylase depends in each case within wide limits upon the concentration of amylase used. Similar results have since been obtained with corn starch[28] and with waxy maize starch.[29] With each substrate the hydrolysis curves show a change from a rapid to a slow phase of the reaction, typical of many other enzyme reactions but, here, the reaction curves tend to flatten at higher values as the concentration of amylase is increased. With different concentrations of pancreatic amylase, there was no evidence of a common limit in the extent of the hydrolysis of any of these substrates such as has been reported for this amylase[6,7,8,10] or as is observed when different concentrations of beta amylase act on starch or on its branched-chain components.[30] These results illustrate an important difference between the action of pancreatic amylase and that of beta-amylase. They also cast doubt upon the rather common practice[6,7,8] of assuming a limit in the hydrolysis of starch by

(1) The authors wish to thank the Corn Industries Research Foundation for generous grants in aid of this investigation.

(2) The data reported here are taken from a dissertation submitted by Roslyn B. Alfin in partial fulfillment of the requirements for the degree Doctor of Philosophy in Chemistry under the Faculty of Pure Science of Columbia University.

(3) Kuhn, *Ann.*, **443**, 1 (1925).

(4) Freeman and Hopkins, *Biochem. J.*, **30**, 442 (1936).

(5) Freeman and Hopkins, *ibid.*, **30**, 451 (1936).

(6) Willstätter, Waldschmidt-Leitz and Hesse, *Z. physiol. Chem.*, **126**, 143 (1923).

(7) Blom, Bak and Braae, *ibid.*, **250**, 104 (1937).

(8) von Euler and Svanberg, *Ber.*, **56**, 1749 (1923).

(9) Pringsheim and Liebowitz, *ibid.*, **59**, 991 (1926).

(10) Hopkins, *Adv. in Enz.*, **6**, 389 (1946).

(11) Freeman and Hopkins, *Biochem. J.*, **30**, 446 (1936).

(12) Myrbäck, Örtenblad and Ahlborg, *Biochem. Z.*, **307**, 49 (1940).

(13) Örtenblad and Myrbäck, *ibid.*, **307**, 123 (1941).

(14) Myrbäck, *ibid.*, **307**, 132 (1941).

(15) Myrbäck, *ibid.*, **307**, 140 (1941).

(16) Sherman and Punnett, THIS JOURNAL, **38**, 1877 (1916).

(17) Sherman, Caldwell and Adams, *J. Biol. Chem.*, **88**, 295 (1930).

(18) Sherman, Caldwell and Adams, THIS JOURNAL, **50**, 2529, 2535, 2538 (1928).

(19) Parke Davis and Company, pancreatin from swine.

(20) The linear fraction from corn starch was kindly furnished by Dr. T. J. Schoch. It was hydrolyzed completely to fermentable sugar by beta amylase and corresponded to 94% crystalline "amylose"[21] by potentiometric titration.[22]

(21) Kerr and Severson, THIS JOURNAL, **65**, 193 (1943).

(22) Bates, French and Rundle, *ibid.*, **65**, 142 (1943).

(23) Phemerol is *p-t*-octyl-phenoxy-ethoxy-ethyl-dimethyl-benzyl-ammonium chloride.

(24) Caldwell, Doebbeling and Manian, *Ind. Eng. Chem., Anal. Ed.*, **8**, 181 (1936).

(25) Hassid, *ibid.*, **8**, 138 (1936).

(26) Meyer, Brentano and Bernfeld, *Helv. Chim. Acta*, **23**, 845 (1940).

(27) Schoch, THIS JOURNAL, **64**, 2957 (1942).

(28) Caldwell and Daly, unpublished.

(29) Caldwell and Mindell, unpublished.

(30) Caldwell and Adams, "Am. Assoc. Cer. Chem., Monograph Series," Vol. I, Chapter II (1946).

pancreatic amylase at 75% theoretical maltose when solutions of unknown amylase concentrations are being compared and evaluated.

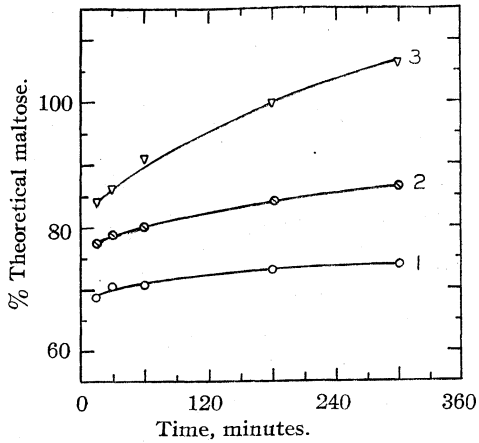


Fig. 1.—Influence of amylase concentration upon the extent of the hydrolysis of Lintner soluble potato starch by purified maltase-free pancreatic amylase: amylase preparation, mg. per 1000 mg. starch: Curve 1, 1 mg.; Curve 2, 8 mg.; Curve 3, 32 mg.; optimal conditions.[18]

Study of Hydrolysis Mixtures at Stages of Very Slow Action.—It was found repeatedly that the introduction of additional amylase into reaction mixtures which had reached stages of very slow rates of change resulted in further increases in their reducing values and, as would be expected, that larger increases in reducing value followed the use of larger additions of amylase. It is evident that products capable of further hydrolysis by the enzyme remained in reaction mixtures which had reached stages of very slow rates of change.

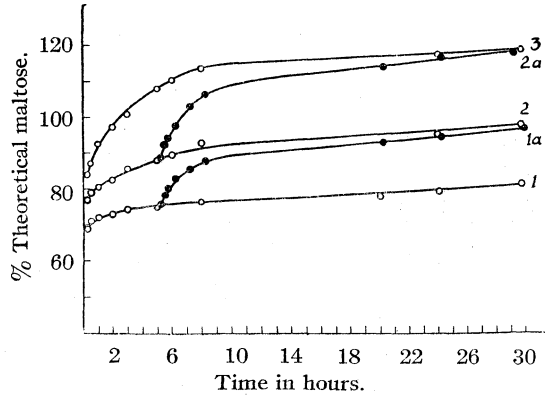


Fig. 2.—Extent of hydrolysis by additional pancreatic amylase of hydrolysis mixtures which had reached stages of very slow rates of change: Curve 1, 1 mg. amylase preparation per 1000 mg. starch; Curve 2, 8 mg.; Curve 3, 32 mg.; Curve 1a, addition of amylase to reaction 1 to bring amylase concentration equal to that in reaction 2; Curve 2a, addition of amylase to reaction 2 to bring amylase concentration equal to that in reaction mixture, 3; optimal conditions.[18]

Moreover, the data summarized in Fig. 2 show that the extent of hydrolysis attained was practically the same, as judged by the theoretical maltose calculated from the reducing values, whether a given concentration of amylase was added at the start of the reaction or in part after the reaction had reached the stage of slow action. The data given in Fig. 2 are strictly comparable as the reaction mixtures which had reached stages of very slow action were divided and one portion was treated with additional amylase while the other was continued at 40° as before.

Similarly, the data summarized in Fig. 3 show that the amylase had not been inactivated irreversibly to any appreciable extent in reaction mixtures which had reached stages of very slow rates of change. Additional substrate, introduced into such reaction mixtures, was hydrolyzed to an extent which was very similar to that attained in comparable reaction mixtures which had contained initially an equivalent concentration of amylase and ratio of amylase to substrate. It should be pointed out that the conditions of these experiments were chosen to protect the amylase from inactivation.[18]

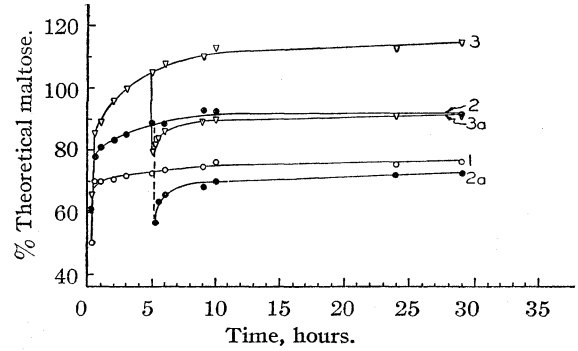


Fig. 3.—Hydrolysis of additional substrate by pancreatic amylase in starch hydrolyzates which had reached stages of very slow rates of change: Curve 1, 1 mg. amylase preparation per 1000 mg. starch; Curve 2, 8 mg.; Curve 3, 32 mg.; Curve 2a, part of reaction mixture of Curve 2 diluted with substrate to give amylase concentration equal to that in reaction mixture of Curve 1; Curve 3a, part of reaction mixture of Curve 3 diluted with substrate to bring amylase concentration equal to that in reaction mixture of Curve 2; optimal conditions.[18]

These findings, that the per cent. of theoretical maltose, calculated from the reducing values of the reaction mixtures, is practically the same under a number of different conditions, does not mean necessarily that the same products are formed from the starch in these different reaction mixtures. This point will be considered more fully elsewhere.[31]

Removal of Products by Dialysis.—The results so far reported suggested the possibility that under favorable conditions the hydrolysis of starch by pancreatic amylase continues until

(31) Alfin and Caldwell, unpublished.

equilibrium is established and that this equilibrium is upset by the addition either of more amylase or of more substrate. The slowing down of enzyme reactions has often been attributed to reaction with or equilibrium between the enzyme and its substrate or between the enzyme and the products of its action.

These possibilities were studied by the use of efficient dialysis to remove the readily dialyzable products during the hydrolyses. Starch–amylase mixtures were prepared and divided into two portions. One of these was allowed to react as usual in a flask held at 40° and was examined at intervals for reducing value. The other portion was placed in small dialyzing bags[32] and dialyzed at 40° against a buffer solution of the same electrolyte concentration and *p*H value as the substrate. The bags held approximately 5-ml. portions. They were kept in rapid motion during the dialysis and the outside solution, which was used in portions equal to four times the total volume of the hydrolysis mixture being dialyzed, was replaced ten to twenty times during a five-hour dialysis. At intervals during the reaction, one or two of the dialysis bags were removed and the contents measured for volume and examined for reducing value and for total solids. At intervals, the outside solution, also, was concentrated and examined for reducing value. Typical data for comparable hydrolyses conducted with and without dialysis are summarized in Tables I and II.

TABLE I

INFLUENCE OF DIALYSIS DURING HYDROLYSIS UPON THE EXTENT OF THE HYDROLYSIS OF LINTNER'S SOLUBLE POTATO STARCH BY PANCREATIC AMYLASE

Reaction[a] time, min.		Theoretical maltose: Hydrolysis accompanied by dialysis,[b] % Inside	Outside	Total	Hydrolysis without dialysis, %
A	300	12.4	56.3	68.7	68.8
		11.0	57.8	68.8	
B	300	Not measurable	70.8	70.8	71.7
C	300	Not measurable	66.4	66.4	69.7
D	360	Not measurable	74.3	74.3	72.6
E	360	6.5	75.8	82.3	82.9
F	600	2.8	82.2	85.0	83.5

[a] Lintner's Soluble Potato Starch: 1%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2. Hydrolyses at 40°; amylase preparation, 1 mg. per 1000 mg. starch. [b] Dialyzed during the hydrolysis against 0.01 *M* phosphate; 0.02 *M* chloride at *p*H 7.2.

The data summarized in Table I show remarkably good agreement between the per cent. of theoretical maltose calculated from the reducing values of comparable dialyzed and undialyzed hydrolysis mixtures of soluble potato starch and pancreatic amylase. These data lead to the conclusion that the slowing down of the reaction in the hydrolysis of starch by pancreatic amylase cannot be explained by assuming reaction with or equilibrium between the amylase and maltose or glucose or other readily dialyzable products of the reaction. If this were the case, the removal of such products would be expected to increase the extent of the hydrolysis of the dialyzed reaction mixtures.

(32) Cellophane tubing purchased from the Visking Corporation was used to make the bags.

TABLE II

INFLUENCE OF DIALYSIS DURING HYDROLYSIS UPON THE EXTENT OF THE HYDROLYSIS OF POTATO STARCH BY PURIFIED PANCREATIC AMYLASE

Reaction[a] time, minutes		Theoretical maltose: Hydrolysis accompanied by dialysis,[b] % Inside	Outside	Total	Hydrolysis without dialysis, %	Diff., %
A	60	31.1	37.4	68.5	70.9	2.4
B	180	6.9	65.2	72.1	75.5	3.4
C	360	Not measurable	66.7	66.7	73.7	7.0
D	360	1.24	70.7	71.9	78.5	6.6
E	360	1.04	70.7	71.7	79.8	8.1
F	360	1.08	75.1	76.2	85.8	9.6
G	600	0.4	69.1	69.5	79.9	10.4
H	600	0.4	72.5	72.9	86.4	13.5
I	600	0.4	74.5	74.9	88.1	13.2

[a] Potato starch, 1%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2; hydrolyses at 40°. Amylase preparation, 1 mg. per 1000 mg. of starch. [b] Dialyzed during hydrolysis against 0.01 *M* phosphate; 0.02 *M* chloride at *p*H 7.2.

When whole potato starch was used as the substrate (Table II) instead of Lintner soluble starch (Table I), there was not such good agreement in the per cent. of theoretical maltose calculated from the reducing values of comparable dialyzed and undialyzed hydrolysis mixtures. However, as the values for the undialyzed hydrolysis mixtures were consistently higher than those for the dialyzed hydrolysis mixtures, these data, also, lead to the conclusion that inter-reaction with or equilibrium between readily dialyzable products and amylase does not explain the slowing down of the reaction between pancreatic amylase and starch.

The reducing products formed from Lintner soluble potato starch hydrolyzed with and without dialysis were differentiated into fermentable sugars (maltose and glucose) and non-fermentable reducing products by a modification of the method of Somogyi.[33] The data summarized in Table III show that when the hydrolysis was accompanied by dialysis, reducing products capable of further hydrolysis by the amylase escaped hydrolysis, presumably by being dialyzed away. In this comparison again, the total reducing values of dialyzed and of undialyzed hydrolysis mixtures were very similar even though the products responsible for that total reducing action were quite different.

When the initial concentrations of amylase were not too large, the addition of amylase to dialyzed hydrolysis mixtures which had reached stages of very slow rates of change resulted in small but measurable increases in their reducing values. These results showed the presence in the dialyzed

(33) Somogyi, *J. Biol. Chem.*, **119**, 741 (1937).

TABLE III

INFLUENCE OF DIALYSIS DURING THE HYDROLYSIS UPON THE PRODUCTS FORMED FROM LINTNER'S SOLUBLE POTATO STARCH BY PURIFIED MALTASE-FREE PANCREATIC AMYLASE

Hydrolyses[a]	Time, hours	Reducing values calculated as per cent. theoretical maltose: Total			reducing dextrins[b]			maltose and glucose[b]		
		Inside	Outside	Total	Inside	Outside	Total	Inside	Outside	Total
Dialyzed	6	1.4	80.0	81.4	1.4	32.8	34.2	0	47.2	47.2
Undialyzed	6			82.9			24.3			58.6

[a] Lintner Soluble Potato Starch, 1%; 0.01 *M* phosphate, 0.02 *M* chloride, *p*H 7.2; amylase preparation, 1 mg. per 1000 mg. starch. One-half of reaction mixture was dialyzed during the hydrolysis against 0.01 *M* phosphate, 0.02 *M* chloride, *p*H 7.2. Hydrolysis and dialysis at 40°. [b] Determined by selective fermentation with washed baker's yeast; dextrins by difference.

hydrolysis mixtures of products capable of further hydrolysis by the amylase.

Similarly, the addition of substrate to dialyzed hydrolysis mixtures which had reached stages of very slow action resulted in extensive hydrolysis of the added substrate. The typical data given in Table IV show that a second portion of substrate was hydrolyzed in five hours to a similar extent (66.2% theoretical maltose) as the original portion of the substrate (69.7% theoretical maltose). It is evident that there had been no significant irreversible loss or inactivation of pancreatic amylase in the dialyzing hydrolysis mixtures under the conditions of these experiments.

TABLE IV

EVIDENCE FOR THE PRESENCE OF PANCREATIC AMYLASE AFTER HYDROLYSIS OF LINTNER'S SOLUBLE STARCH ACCOMPANIED BY DIALYSIS

Reaction[a] time, minutes	Theoretical maltose, %
A. Original Hydrolysis with Dialysis	
300	69.7
B. Hydrolysis of Fresh Substrate by Amylase Remaining in an Equal Volume of A (above)	
15	49.8
30	56.8
60	60.8
120	65.6
300	66.2
1200	68.6

[a] Lintner Soluble Potato Starch: 1%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2; 40°. Amylase preparation, 1 mg. per 1000 mg. starch.

On the other hand, marked inactivation of the amylase (86 to 87%) occurred when portions of the same solutions of purified pancreatic amylase were dialyzed for five hours at 40° under the same conditions, but in the absence of substrate, against a buffer solution of the same electrolyte concentration and *p*H value. These results give experimental evidence for the suggestion often advanced that the amylase unites with its substrate, in this case with the larger less readily dialyzable products of the hydrolysis of starch, and thus is protected from appreciable irreversible inactivation or from appreciable loss due to dialysis.

The loss of pancreatic amylase activity which occurs during dialysis of its aqueous solutions has not yet been reversed[17,34] by uniting the dialyzed solution with its dialyzate as has been possible under suitable conditions with certain enzymes which contain dialyzable prosthetic groups.

The data reported here indicate that the slowing down of the reaction in the hydrolysis of starch by pancreatic amylase is due to the replacement of the original substrate by products for which the amylase has less affinity. These dextrins are hydrolyzed only slowly by pancreatic amylase and are present in relatively low concentrations. Under the conditions of these experiments, the slowing down of the reactions is not due to irreversible inactivation of the amylase nor, as is often reported,[10] to action with or equilibrium between the more readily dialyzable products of the hydrolysis and the amylase. However, there is evidence of union between the amylase and the less readily dialyzable products of the hydrolysis of starch. These products are being investigated.

Examination of Preparations of Purified Pancreatic Amylase for Traces of Maltase, Phosphorylase and Phosphatase Activities.—No evidence of *maltase* activity was found in composite samples of the preparations of purified pancreatic amylase even when the highest concentrations used in this work were held for twenty-four hours with 1% maltose under the conditions used for the hydrolysis of starch. This failure to find maltase activity furnishes conclusive evidence that the results reported here were not influenced to any significant extent by traces of maltase activity.

Similarly, no evidence of *phosphorylase*[35,36] or of *phosphatase*[37] activity was found in relatively high concentrations of the preparations of purified pancreatic amylase.

Examination of Preparations of Purified Pancreatic Amylase for Traces of Other Carbohydrases.—The preparations of purified pancreatic amylase were also examined for traces of carbohydrases other than amylase by attempts to cause the selective inactivation of amylase activity, on the one hand, and of other carbohydrase (glucosidase, or dextrinase) activities on the other. Amylase activity refers here to the increase in the reducing value (mg. maltose) per unit weight of amylase preparation in the early stages of hydrolysis of 1% starch or to the

(34) Meyer, Fischer and Bernfeld, *Helv. Chim. Acta*, **30**, 64 (1947); *Arch. Biochem.*, **14**, 149 (1947).

(35) Green and Stumpf, *J. Biol. Chem.*, **142**, 355 (1942).

(36) Allen, *Biochem. J.*, **34**, 858 (1940).

(37) Prebluda and McCollum, *J. Biol. Chem.* **127**, 495 (1939).

disappearance of starch[38] per unit weight of amylase preparation when these measurements were made in thirty minutes at 40° under specified conditions.[18] "Glucosidase" activity refers to the increase in the reducing value (calculated as mg. maltose) per unit weight of amylase preparation in two hours when the substrates were hydrolysis mixtures of starch and pancreatic amylase which had reached stages of very slow change but which still contained products capable of further hydrolysis by additional amylase preparation.

TABLE V

A SUMMARY OF ATTEMPTS TO CAUSE THE SELECTIVE INACTIVATION OF AMYLASE AND OF "GLUCOSIDASE" ACTIVITIES OF PURIFIED PANCREATIC AMYLASE PREPARATIONS

Treatment of amylase solution	Amylase activities Saccharogenic[a]	Amyloclastic[b]	"Glucosidase" activity[c]
A. Amylase Solution Held at 50° for Five Minutes			
Unheated[d]	100	100	100
Heated[e]	17	17	10
Unheated[f]	100	100	100
Heated[g]	54	50	50
B. Amylase Solution Held at Unfavorably High Hydrogen-Ion Activities			
Untreated[d]	100	100	100
Acid-treated[h]	61	59	67
C. Influence of calcium ions at 50°			
Heated with Ca^{++}[i]	100	100	100
Heated without Ca^{++}[j]	36	40	29
D. Influence of calcium ions at unfavorable hydrogen-ion activities			
Held with Ca^{++}[k]	100	100	100
Held without Ca^{++}[l]	69	71	57
E. Influence of HNO_2			
Held at *p*H 4.8 and 0°[m]	100	100	100
The same plus nitrite[n]	55	59	47

[a] Saccharogenic activity: mg. of "maltose" formed in thirty minutes at 40° per mg. amylase preparation acting on 1% soluble potato starch under specified conditions.[18] [b] Amyloclastic activity: mg. of soluble potato starch hydrolyzed per mg. amylase preparation in thirty minutes at 40° under specified conditions to products which give a clear red color with iodine. [c] "Glucosidase" activity: increase in mg. "maltose" per mg. added amylase preparation when amylase is added at stage of very slow rate of action to a potato starch-amylase reaction mixture and allowed to react for two hours. [d] Amylase solution: 25 mg. of amylase preparation in 100 ml. solution (0.02 *M* sodium chloride, 0.01 *M* phosphate, at *p*H 7.2). Held at 0° until examined for activity. [e] A portion of amylase solution of *d* held at 50° for five minutes before being examined for activity. [f] and *g* Same as *d* and *e* but the dry purified amylase preparation had been stored in the refrigerator for several weeks. [h] Same as *d* but held at *p*H 4.5 or at *p*H 4.6 or at *p*H 5.0 at 0° for five, ten or fifteen minutes before being adjusted to *p*H 7.2 and measured for amylase activity (average values). [i] Amylase solution: 25 mg. of amylase preparation in 100 ml. solution (0.02 *M* sodium chloride, 0.02 *M* calcium chloride, at *p*H 7.2) held at 50° for five minutes. [j] Same as *i* but without calcium chloride. [k] Amylase solution: 25 mg. of amylase preparation in 100 ml. solution (0.02 *M* sodium chloride, 0.02 *M* calcium chloride), held at 0° at *p*H 4.0, *p*H 4.5, or at *p*H 5.0 for five or ten minutes before being adjusted to *p*H 7.2 and measured for amylase activity. [l] The same as *k* but containing no calcium chloride. [m] Amylase preparation dissolved in 0.25 *M* sodium acetate, 0.01 *M* sodium phosphate and 0.02 *M* sodium chloride at *p*H 4.8 held at 0° for fifteen minutes before being adjusted to *p*H 7.2 and measured for amylase activity. [n] Same as *m* but with addition of 1.0 *M* sodium nitrite. All data are averages of several determinations.

(38) Hydrolysis of starch to products which give a clear red color with iodine.

All determinations of amylase and of "glucosidase" activities in any given series of measurements were kept strictly comparable. Amylase solutions were prepared and divided into two portions. After one had been treated to cause partial inactivation of the amylase, both portions were examined side by side, with portions of each of the two substrates, for amylase and for "glucosidase" activities.

The conditions chosen for the partial inactivation of the amylase were based upon the results of much previous work in this laboratory with similar purified preparations[17,39,40] and on preliminary experiments.

The data summarized in Table V (A and B) show that there was appreciable loss of "glucosidase" as well as of amylase activity when aqueous solutions of purified pancreatic amylase were partially inactivated at 50° or at unfavorably high hydrogen-ion activities.

Kneen[41] has shown that calcium ions protect malt α-amylase from inactivation when its aqueous solutions are held at unfavorable temperatures or at unfavorably high hydrogen-ion activities. The data summarized in Table V (C and D) show that both the amylase and the "glucosidase" activities of purified pancreatic amylase were protected by calcium ions from inactivation in aqueous solutions held at 50° or at unfavorably high hydrogen-ion activities.

In 1942, Little and Caldwell[39,40] showed that the amylase activity of pancreatic amylase depends upon the presence of free primary amino groups in the protein molecule. Any treatment which caused the loss of primary amino nitrogen caused a corresponding loss of amylase activity. The data summarized in Table V (E) show that "glucosidase" as well as amylase activity was decreased when solutions of purified pancreatic amylase were treated with nitrous acid under conditions which caused the rapid loss of primary amino groups. In these experiments the influence of the unfavorably high hydrogen-ion activities was taken into consideration. Aliquots of the amylase solution adjusted to *p*H 4.8, and 0.25 *M* acetate, 0.01 *M* phosphate and 0.02 *M* chloride were held at 0° for the specified length of time in the absence of and in the presence of 1.0 *M* nitrite. The solutions were then adjusted to *p*H 7.2 with phosphate and compared with an untreated control solution for amylase and for "glucosidase" ac-

(39) Little and Caldwell, *J. Biol. Chem.*, **142**, 585 (1942).

(40) Little and Caldwell, *ibid.*, **147**, 229 (1943).

(41) Keen, Sandstedt and Hollenbeck, *Cereal Chem.*, **20**, 399 (1943).

tivities. The excess nitrite was removed by treatment with sulfamic acid before reducing values were determined.

The data summarized in Table V fail to give any evidence by selective inactivation for the presence of a second carbohydrase in addition to amylase in the preparations of purified pancreatic amylase used here. The differences obtained in the inactivation studies of "glucosidase" activities were small and undue emphasis cannot be placed on comparisons of inactivation percentages when different activities, obtained by different types of measurements, are involved. However, the results as a whole give the same trend for the inactivation of "glucosidase" and of amylase activities and appear to justify the conclusion that the properties of pancreatic amylase observed in this investigation are not influenced to any important extent by the presence of contaminating carbohydrases.

Summary and Conclusions

A study of the action of highly purified pancreatic amylase shows that the extent of the hydrolysis of unfractionated potato starch, Lintner soluble starch and of the linear fraction from corn starch depends in each case upon the concentration of amylase. Relatively very high concentrations of the amylase gave no evidence of a limit in the hydrolysis of starch by pancreatic amylase such as is observed with β-amylase.

The reaction curves showed a rapid phase of reaction followed by a phase of very slow rate of change but the extent of the hydrolysis attained was dependent within wide limits upon the concentration of amylase. Under the conditions of these experiments the slowing down of the reactions was not due to any appreciable inactivation of the amylase nor to inter-reaction with or equilibrium between amylase and maltose, glucose or other readily dialyzable products of hydrolysis.

Evidence is presented which shows that the slowing down of the hydrolysis is due to relatively low concentrations of products which the amylase hydrolyzes slowly, for which it has low affinity.

Data are presented which show that the results obtained here are not influenced to any appreciable extent by the presence of maltase or of other carbohydrases.

NEW YORK 27, N. Y. RECEIVED[42] APRIL 21, 1948

(42) Original manuscript received May 7, 1947.

[CONTRIBUTION FROM PHILLIPS PETROLEUM COMPANY, RESEARCH DEPARTMENT]

Butylation of Benzene during Propylation in the Presence of Isobutane. Ratio of Reactivities of Benzene and Isobutane

BY FRANCIS E. CONDON AND MARYAN P. MATUSZAK

In an experiment originally designed to determine the ratio of the rates of alkylation of benzene and isobutane, a mixture of these two hydrocarbons was subjected to alkylation with propylene in the presence of hydrofluoric acid as catalyst. It was found that, besides isopropylation of benzene, considerable *t*-butylation occurred. The formation of *t*-butylbenzene may be taken as an indication of the intermediate formation of *t*-butyl carbonium ions, which must have been derived from isobutane in accordance with the following considerations.

According to the ionic mechanism of catalytic alkylation of a hydrocarbon, the initial step is formation of a carbonium ion[1]; for example

$$H^+ + C_3H_6 \longrightarrow i\text{-}C_3H_7^+ \qquad (1)$$

When the alkylatable hydrocarbon is an isoparaffin like isobutane, the various subsequent steps may be generalized as reactions in which a carbonium ion, however formed, produces another carbonium ion, either by acquiring hydrogen with its bonding electrons from isobutane, thereby producing also a paraffin

$$i\text{-}C_3H_7^+ + i\text{-}C_4H_{10} \xrightarrow{k} t\text{-}C_4H_9^+ + C_3H_8 \qquad (2)$$

or by uniting with an olefin, which may have been introduced as such, or may have been formed by the reverse of a reaction like 1

$$i\text{-}C_3H_7^+ + i\text{-}C_4H_8 \longrightarrow C_7H_{15}^+ \qquad (3)$$

The new carbonium ions formed by such reactions undergo similar reactions; in addition, some of them undergo preliminary rearrangement, thereby accounting for the multiplicity of products from isoparaffin alkylation.[2]

In the aforementioned experiment, substantially no alkylation of isobutane occurred, in spite of a 50-fold molecular excess of isobutane over benzene. Consequently, it was not possible to deduce, from the composition of the alkylation product, a numerical value for the ratio of the rate of alkylation of benzene to the rate of alkylation of isobutane. There was deduced, however, an approximate numerical value for the ratio of the reactivity of benzene with isopropyl carbonium ion to the reactivity of isobutane with this ion. This deduction was possible because the isopropylation of benzene

$$i\text{-}C_3H_7^+ + C_6H_6 \xrightarrow{k'} i\text{-}C_3H_7C_6H_5 + H^+ \qquad (4)$$

(1) Price and Ciskowski, THIS JOURNAL, **60**, 2499 (1938).

(2) (a) Bartlett, Condon and Schneider, *ibid.*, **66**, 1531 (1944); (b) see also Schmerling, *ibid.*, **68**, 275 (1946); Ciapetta, *Ind. Eng. Chem.*, **37**, 1210 (1945).

was competitive with reaction 2, which must have been substantially the only precursor to the *t*-butylation of benzene, inasmuch as the benzene was reacting with all carbonium ions so rapidly that reaction 3 was negligible. On the assumption that all *t*-butyl carbonium ions reacted with benzene immediately after formation by reaction 2, the ratio of the rate of reaction 4 to the rate of reaction 2 must have equalled the ratio of the number of isopropyl groups, *a*, to the number of *t*-butyl groups, *b*; that is

$$\text{Rate 4/Rate 2} = k'(i\text{-}C_3H_7^+)(C_6H_6)/k(i\text{-}C_3H_7^+)(i\text{-}C_4H_{10}) = a/b$$

Consequently

$$k'/k = a(i\text{-}C_4H_{10})/b(C_6H_6)$$

The value of a/b, obtained from the composition of the product, was 7.1. The value of $(i\text{-}C_4H_{10})/(C_6H_6)$ was taken as 49, the mol ratio of isobutane to benzene in the feed, on the approximation that alkylated benzene is alkylated at the same rate as benzene. These values gave $k'/k = 350$. That is, benzene was approximately 350 times as reactive as isobutane.

TABLE I

BUTYLATION OF BENZENE DURING HYDROFLUORIC ACID-CATALYZED ALKYLATION OF 2 MOLE PER CENT. BENZENE IN ISOBUTANE WITH PROPYLENE

		Part 1	Part 2
Temperature, °C.		35–38	35–38
Average contact time, min.		8.0	9.3
HF initially charged, kg.		1.4	
HF added during run, kg.		0.3	0.3
Initial acidity, wt. % HF[a]		98.4	93.0
Final acidity, wt. % HF[a]		93.0	93.3
Feed composition, wt. % (mole %)	Propane	0.5	0.5 (0.6)
	Isobutane	95.17	93.48 (93.4)
	n-Butane	1.7	1.7 (1.7)
	Benzene	2.63	2.58 (1.9)
	Propylene	...	1.74 (2.4)
Hydrocarbon charged, kg.		23.7	23.8
Hydrocarbon effluent, kg.		22.4	21.6
Effluent composition, wt. %	Propane	0.4	0.6
	Isobutane	96.6	95.0
	n-Butane	0.9	0.9
	Alkylate[b]	2.10	3.50
Alkylate[b] composition, wt. % (mole %)			
Paraffins		0.4	1.4 (1.7)
Benzene		96.6	20.1 (31.7)
Isopropylbenzene		0.0	29.3 (29.9)
t-Butylbenzene		0.0	6.3 (5.8)
m-Diisopropylbenzene[c]		0.0	14.8 (11.2)
p-Diisopropylbenzene		0.0	12.5 (9.5)
m-*t*-Butylisopropylbenzene		0.0	3.6 (2.5)
p-*t*-Butylisopropylbenzene		0.0	3.4 (2.4)
Residue		3.0[d]	8.6 (5.3)

[a] By titration of 1 g. with 1 *N* potassium hydroxide (phenolphthalein). [b] Including unreacted benzene. [c] In view of recently reported findings of Melpolder, Woodbridge and Headington, THIS JOURNAL, **70**, 935 (1948), the *m*-diisopropylbenzene (b. p. 203.18°) may have included some *o*- (b. p. 203.75°). [d] B. p. above 270°.

Experimental Part

Materials.—The isobutane and the propylene were products of Phillips Petroleum Company. They were analyzed by fractionation in a Podbielniak Heligrid low-temperature column. C. P. benzene was used.

Anhydrous hydrofluoric acid from the Harshaw Chemical Company was used.

Equipment and Procedure.—The experiment was of the continuous type, with recycling of the acid. The hydrocarbon feed was blended in a 94-liter (25-gal.) steel cylinder, from which it was displaced by pumping water in through a tube which led to the bottom. From the cylinder the feed passed through a silica-gel drier into the reactor. Surging of the feed was minimized by an electrically heated surge tank attached to the feed line after the drier. The reactor[3] was a 1470-ml. steel vessel having a 6.3-cm. (2.5-in.) turbo-mixer, turning about 1725 r. p. m. The reactor was surrounded by a stirred water-bath. Temperature in the reactor was measured by a thermocouple. Acid-to-hydrocarbon volume ratio in the reactor was maintained near unity by occasional additions of fresh acid. This ratio was determined by withdrawing several ml. of the mixture through an eduction tube into a graduated test-tube immersed in a Dry Ice-bath and measuring the volumes of the hydrocarbon and acid layers. From the reactor the mixture passed to a 1440-ml. inclined separator, from which the acid layer was recycled to the reactor by gravity through a U-shaped trap which prevented passage of the reaction mixture into the acid-return line. The pressure in the system was maintained at 10 atm. by a Hanlon-Waters air-operated motor valve, controlled by a Taylor "Fulscope" controller, located on the effluent line from the settler. The hydrocarbon effluent was collected in tared 57-liter (15-gal.) steel cylinders.

The data for the experiment are in Table I. In part 1, half of an isobutane–benzene mixture was used, without propylene, to equilibrate the silica-gel drier and the catalyst and to test the isobutane for any possible presence

TABLE II

PROPERTIES OF FRACTIONS OF PRODUCT FROM HYDROFLUORIC ACID-CATALYZED ALKYLATION OF 2 MOLE PER CENT. OF BENZENE IN ISOBUTANE WITH PROPYLENE

Fraction	Wt., g.	Boiling range, °C. (740 mm.)	d^{20}_4	$n^{20}D$	Mol. wt.[a]
		Part 1			
11	79.8	80.0– 80.0	0.875	1.4977	...
12	360.1	80.0– 80.0	0.880	1.5006	...
13	5.4	80.0–270	....	....	...
Res.	13.3	Above 270	....	....	...
		Part 2			
21	80.9	73.3– 79.7	0.859	1.4874	...
22	78.7	79.7– 80.0	.881	1.4997	...
23	19.4	80.0–152.2	.8599	1.4882	...
24	195.3	152.2–152.9	.8616	1.4902	118
25	19.6	152.9–166.7	.8621	1.4905	121
26	42.4	166.7–176.3	.8662	1.4920	142
27	90.7	176.3–203.3	.8580	1.4890	159
28	42.1	203.3–210.5	.8580	1.4894	151
29	63.0	210.5–212.2	.8573	1.4890	158
30	19.3	212.2–214.1	.8581	1.4888	159
31	17.1	214.1–220.3	.8594	1.4891	171
32	25.8	220.3–230.1	.8618	1.4910	169
33	29.4	230.1–237.9	.8578	1.4890	198
34	35.3	Residue	....	....	...

[a] By lowering of the freezing point of benzene.

(3) See "Hydrofluoric Acid Alkylation," Phillips Petroleum Co., Bartlesville, Oklahoma, 1946, p. 2, Fig. 1.

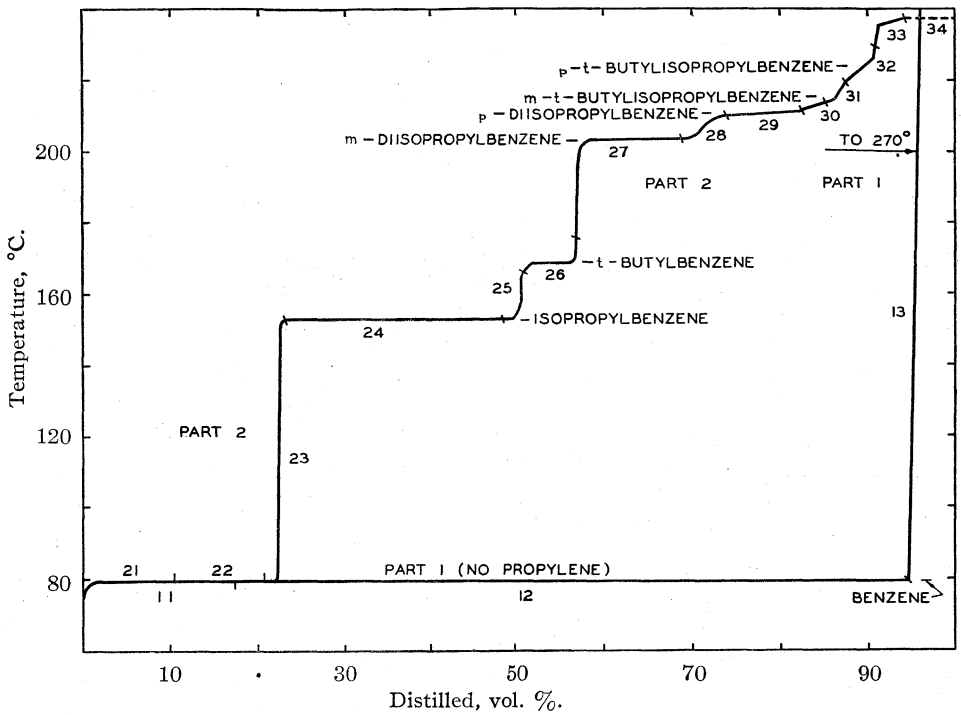


Fig. 1.—Fractionation of product from HF alkylation of 2 mole % benzene in isobutane with propylene (numbers designate fractions).

of isobutylene as an impurity. In part 2, the other half of the isobutane-benzene mixture, after being mixed with the propylene, was used; the first 0.5 kg. of hydrocarbon effluent was discarded, inasmuch as it represented flushing of the system.

The hydrocarbon effluent was partly debutanized in a 3-m. (10-ft.) Monel column, 3.17 cm. (1.25 in.) in diameter, packed with 6.35-mm. (0.25-in.) carbon Raschig rings. The debutanization was completed in a 1.5-m. (5-ft.) vacuum-jacketed glass column, 12.7 mm. (0.5 in.) in diameter, packed with 2.4-mm. ($^3/_{32}$-in.) wire helices. All overhead material was combined and was analyzed by low-temperature Podbielniak fractionation.

Product boiling above 25° was fractionated in a Podbielniak Heligrid vacuum-jacketed column. To a 20-g. residue from fractionation of the product from part 1, 18 g. of cetane (b. p. 290°) was added as a "chaser," and distillation was continued from an ordinary distilling flask.

From the fractionation curves shown in Fig. 1, from the properties of the fractions in Table II, and from the results of preparation of solid derivatives described in Table III, the product compositions reported in Table I were computed.

Preparation of Derivatives (Table III).—*p-t*-Butylacetanilide was prepared according to Ipatieff and Schmerling.[4] Benzoic acid and *m*- and *p-t*-butylbenzoic acids were obtained by oxidizing 1-cc. (0.85-g.) samples with 8.5 g. of chromium trioxide in 30 cc. of boiling glacial acetic acid for one hour. Iso- and terephthalic acids were obtained from fractions 27 and 29 by oxidizing 3-cc. (2.5-g.) samples with 200 cc. of boiling dilute nitric acid (1:3). They were esterified with methanol, in the presence of a little sulfuric acid.

TABLE III

DERIVATIVES OF FRACTIONS OF PRODUCT FROM HYDROFLUORIC ACID-CATALYZED ALKYLATION OF 2 MOLE PER CENT. BENZENE IN ISOBUTANE WITH PROPYLENE

Fraction	Derivative	Yield, %	Neut. equiv.	M. p., °C. Obsd. (uncorr.)	M. p., °C. Beilstein	Beilstein reference
26	*p-t*-Butylacetanilide	20	...	168.5–170	170	XII, 1167
24	Benzoic acid	30	...	121 –123	121	IX, 96
27	Dimethyl isophthalate	25	...	62 – 64	67–68	IX, 834
29	Dimethyl terephthalate	25	...	138 –139.5	140	IX, 843
30	*m-t*-Butylbenzoic acid	3	184	125 –128	127	IX, 560
31	*m-t*-Butylbenzoic acid	5	183	117 –123	127	IX, 560
32	*p-t*-Butylbenzoic acid	2	186	161.5–164	164	IX, 560

Acknowledgments.—Mr. G. T. Leatherman assisted with the experiment; Miss Alicia Perez determined molecular weights; and Phillips Petroleum Company kindly granted permission to publish the data.

Summary

A 2 mole per cent. mixture of benzene in isobutane was subjected to hydrofluoric acid-catalyzed alkylation with propylene. The principal

(4) Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937).

reaction was isopropylation of benzene. Substantially no alkylation of isobutane occurred; however, isobutane reacted, yielding *t*-butylbenzene and *m*- and *p*-*t*-butylisopropylbenzenes. The composition of the product showed that benzene reacted approximately 350 times as readily as isobutane.

BARTLESVILLE, OKLA. RECEIVED JULY 19, 1947

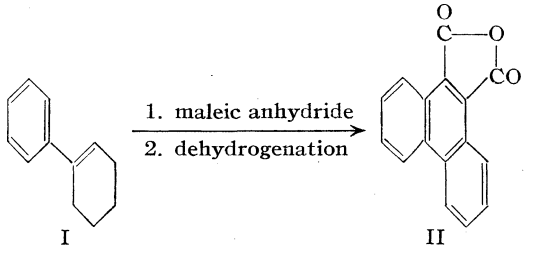
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Condensation of Phenylcycloalkenes with Maleic Anhydride. I. Synthesis of 7-Methoxy-3,4-benzphenanthrene

BY JACOB SZMUSZKOVICZ[1] AND EDWARD J. MODEST

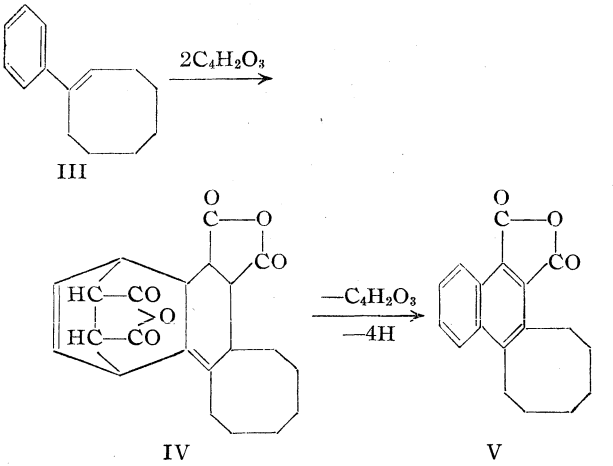
Additions to diene systems in which one double bond is in a benzene ring and the second in an alicyclic ring have not hitherto been reported.[2] The 1,2-double bond in naphthalene in conjugation with the double bond of an olefinic system,[3] with that in cyclopentene[4] or in cyclohexene,[5] is sufficiently reactive to participate in the Diels–Alder condensation. Styrene itself forms copolymers with dienophiles, but some derivatives of styrene form normal adducts.[6,7]

We now have found that 1-phenylcyclohexene-1 (I) adds maleic anhydride at 220° with formation of an amorphous adduct, which can be dehydrogenated to phenanthrene-9,10-dicarboxylic acid anhydride (II); the over-all yield is 25%. Other investigators have prepared this aromatic anhydride from bicyclohexenyl (17% yield)[8]; from phenanthrene, sodium, and carbon dioxide (25.7% yield)[9]; and from diphenyl-2-carboxylic acid (42% yield).[10]



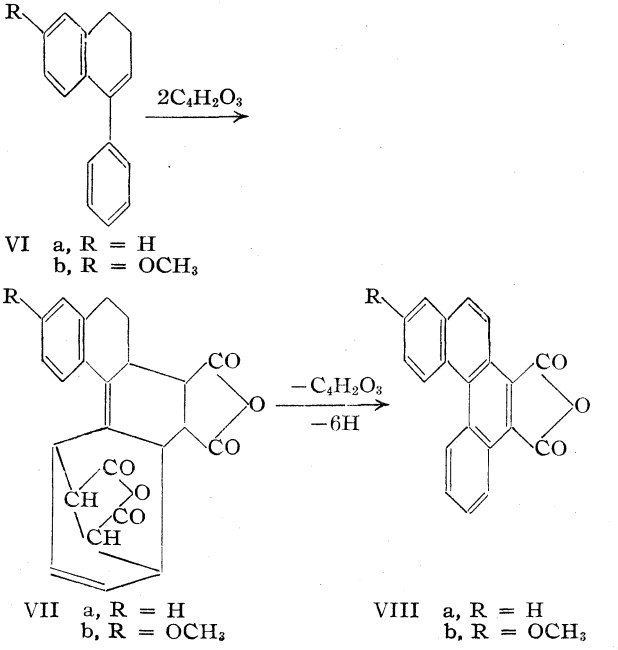
I II

1-Phenylcycloöctene-1 (III) reacts with maleic anhydride at steam-bath temperature. The product, obtained in quantitative yield, is the bis-adduct (IV), which upon dehydrogenation with sulfur yields 1,2-cycloöctanonaphthalene-3,4-dicarboxylic acid anhydride (V).



III IV V

1-Phenyl-3,4-dihydronaphthalene (VIa) and 1-phenyl-6-methoxy-3,4-dihydronaphthalene (VIb) react with maleic anhydride; the bis-adducts VIIa and VIIb are formed. The yields vary with the reaction temperature employed, from moderate at 95° to quantitative at 160°.



VI a, R = H
b, R = OCH_3

VII a, R = H
b, R = OCH_3

VIII a, R = H
b, R = OCH_3

(1) On leave of absence from the Weizmann Institute of Science, Rehovoth, Palestine.

(2) Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, New York, N. Y., in press.

(3) Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).

(4) Bachmann and Kloetzel, THIS JOURNAL, **60**, 2204 (1938).

(5) F. Bergmann and Szmuszkovicz, *ibid.*, **69**, 1367 (1947).

(6) Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).

(7) Wagner-Jauregg, *Ann.*, **491**, 1 (1931).

(8) C. Weizmann, E. Bergmann and Berlin, THIS JOURNAL, **60**, 1331 (1938).

(9) Jeanes and Adams, *ibid.*, **59**, 2608 (1937); U. S. Patent 2,231,787 [*C. A.*, **35**, 3268 (1941)].

(10) Schönberg and Warren, *J. Chem. Soc.*, 1838 (1939); compare Geissman and Tess, THIS JOURNAL, **62**, 514 (1940).

Upon treatment with sulfur VIIa and VIIb are aromatized to the anhydrides VIIIa and VIIIb in 100 and 68.5% yields, respectively.

Decarboxylation of VIIIa with barium hydroxide and copper bronze affords 3,4-benzphenanthrene in 70% yield (compare ref. 5). Decarboxylation of VIIIb gives the hitherto unknown 7-methoxy-3,4-benzphenanthrene (63.7% yield).

These reactions thus constitute an efficient synthesis of 3,4-benzphenanthrene in three steps and provide a route to various substituted benzphenanthrenes. Comparable additions to systems containing the thiophene ring will be reported shortly.

Acknowledgment.—The authors wish to express their thanks to Prof. L. F. Fieser for his generous support of this investigation and to Mrs. Mary Fieser for her advice and assistance in preparing the manuscript.

Experimental[11]

Phenanthrene-9,10-dicarboxylic Acid Anhydride, II.—1-Phenylcyclohexene-1[12] (1 g.) was heated with maleic anhydride (2 g.) at 220° for three hours. The brown viscous mass was cooled, dissolved in warm acetic acid, and precipitated with water. The light brown substance, obtained in quantitative yield, softens at 105° and melts completely at 160°. This crude material (1.7 g.) was heated with 850 mg. of sulfur for twenty minutes at 230–250°. The anhydride II was sublimed at 240–270° (0.005 mm.), 390 mg., 25%. On crystallization from acetic anhydride it forms yellow rods melting at 316–317°.

Anal. Calcd. for $C_{16}H_8O_3$: C, 77.42; H, 3.25. Found: C, 77.00; H, 3.25.

1,2-Cycloöctanonaphthalene-3,4-dicarboxylic Acid Anhydride, V.—1-Phenylcycloöctene-1[13] (1 g.) was heated with maleic anhydride (2 g.) on the steam-bath for twenty-four hours. The brown oil was decanted from the well-formed prisms, which were washed with acetic acid and methanol; m. p. 249–250°.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.09; H, 5.80. Found: C, 68.74; H, 5.43.

The oil was dissolved in acetic acid and precipitated with water. This crude material could be purified by crystallization from dilute dioxane. The over-all yield was quantitative.

Dehydrogenation of the adduct (284 mg.) was carried out with sulfur (70 mg.) at 220–240° for fifteen minutes. The crude product sublimed at 220–240° (0.001 mm.); the yellow sublimate (150 mg., 53.5%), after crystallization from acetic acid, was obtained as yellow plates, m. p. 175–176°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.08; H, 5.63.

3,4-Benzphenanthrene.—A mixture of 1-phenyl-3,4-dihydronaphthalene[14] (1 g.) and maleic anhydride (2.5 g.) was heated on the steam-bath for twenty hours. The brown oil was dissolved in acetic acid; scratching induced crystallization. The white precipitate was filtered and washed with methanol (300 mg., 14.8%), m. p. 315–316°. Crystallized from acetic acid, it forms clusters of leaflets, m. p. 315–316° (dec.). The analysis conforms to that of the tetracarboxylic acid monoanhydride of VIIa.

Anal. Calcd. for $C_{24}H_{20}O_7$: C, 68.56; H, 4.80. Found: C, 68.43; H, 5.05.

If the mixture of starting materials was heated for twenty hours at 150–160°, 1.5 g. of the bis-adduct was obtained, m. p. 315–316°. An additional 500 mg. of white material melting at 160–170° (probably the tetracarboxylic acid) resulted from addition of water to the filtrate. The yield was quantitative.

Dehydrogenation of the adduct (200 mg.) was conducted with large excess of sulfur (75 mg.) at 270–290° for nine minutes. The excess sulfur is necessary in this case to lower the initial temperature and to prevent carbonization; The product (VIIIa) sublimed at 230–245° (0.001 mm.). m. p. 249–251°. It crystallized from acetic anhydride in the form of elongated yellow needles melting at 257–258°.[5] The yield was quantitative.

Anal. Calcd. for $C_{20}H_{10}O_3$: C, 80.53; H, 3.38. Found: C, 80.53; H, 3.38.

The same aromatic anhydride resulted from the dehydrogenation of the tetracarboxylic acid mentioned above.

The aromatic anhydride (VIIIa) (0.7 g.) was finely ground with 4 g. of crystalline barium hydroxide and 1.4 g. of copper bronze and the mixture was heated in a tube. The reaction started at 300°; water-pump suction was applied and heating was continued to 350°. The oily distillate solidified on treatment with methanol (375 mg., 70%). This material, crystallized from ethanol, m. p. 68°, was identical with 3,4-benzphenanthrene (mixed m. p. determination).

7-Methoxy-3,4-benzphenanthrene.—The addition of maleic anhydride to 1-phenyl-6-methoxy-3,4-dihydronaphthalene[15] was carried out as in the preceding case. The bis-adduct (VIIb) was obtained in 49% yield at 95° and in quantitative yield at 150–160°. It crystallized from the reaction mixture in the form of white prisms, m. p. 348–349° (dec.).

Anal. Calcd. for $C_{25}H_{20}O_7$: C, 69.44; H, 4.66. Found: C, 69.39; H, 4.81.

A mixture of VIIb (1.75 g.) and sulfur (0.49 g.) was heated to 307°. A violent reaction ensued and heating was continued at 270–280° for twenty minutes. Sublimation at 230–300° (0.001 mm.) yielded 0.91 g. (68.5%) of yellow material VIIIb, m. p. 220–225°, which crystallized from acetic anhydride as yellow needles, m. p. 233–234°.

Anal. Calcd. for $C_{21}H_{12}O_4$: C, 76.82; H, 3.69. Found: C, 76.90; H, 3.50.

Decarboxylation, carried out as before, led to a yellow oil (63.7% yield), which solidified on treatment with methanol and which crystallized from the same solvent in the form of colorless plates, m. p. 90–91°. The analysis conforms to that of 7-methoxy-3,4-benzphenanthrene.

Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.28; H, 5.59.

The picrate formed in ethanol and crystallized from the same solvent as elongated red needles, m. p. 120–121°.

Anal. Calcd. for $C_{25}H_{17}O_8N_3$: C, 61.60; H, 3.52. Found: C, 61.39; H, 3.27.

Summary

1. Four compounds of the phenylcycloalkene series have been successfully condensed with maleic anhydride.

2. An efficient synthesis of 3,4-benzphenanthrene has been developed.

3. Preparation of 7-methoxy-3,4-benzphenanthrene is described.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 9, 1948

(11) All melting points are corrected.

(12) Auwers and Trepmann, *Ber.*, **48**, 1216 (1915).

(13) Fieser and Szmuszkovicz, THIS JOURNAL, submitted for publication.

(14) Weiss and Woidich, *Monatsh.*, **46**, 453 (1925).

(15) F. Bergmann and Szmuszkovicz, THIS JOURNAL, **69**, 1773 (1947).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE AND THE DEPARTMENT OF CHEMISTRY OF UNIVERSITY OF DELAWARE]

Anomalous Oxidation of Some Secondary Alcohols Containing an α-Neo Carbon[1]

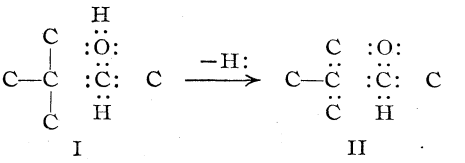
BY WILLIAM A. MOSHER AND FRANK C. WHITMORE

The oxidation of secondary alcohols with such reagents as chromic anhydride in acetic acid solution generally gives good yields of the corresponding ketones. In connection with the preparation of methyl *t*-amyl ketone for use in the synthesis of 2,3,4-trimethylhexane[2] an unexpected product was isolated. The oxidation of methyl-*t*-amylcarbinol with chromic anhydride in acetic acid, containing about 20% water, gave 7% *t*-amyl alcohol in addition to the desired ketone. The same reaction with methyl-*t*-butylcarbinol gave 6% *t*-butyl alcohol, and isopropyl-*t*-amylcarbinol gave 7% *t*-amyl alcohol.

Although this preliminary work is not sufficiently comprehensive to permit any generalization as to this type of reaction, the indications are that complete substitution on the carbon *alpha* to the hydroxyl-bearing carbon leads to unusual behavior on oxidation with chromic anhydride. Probably other alcohols with a lower degree of substitution behave in a similar manner, but greater susceptibility of the alcohols which might be formed to oxidative attack prevents their isolation. It is believed that the complete elucidation of the formation of the tertiary alcohols in this unexpected oxidation may well be the key to all oxidative carbon-to-carbon single bond ruptures in oxygenated organic compounds in polar solvents. Related studies are now under way.

From the standpoint of mechanism, the first question is whether the tertiary alcohols are formed from the carbinol or from the ketone formed in the oxidation. The oxidation of pinacolone with dichromate and acid has been studied by Friedel and Silva[3] and by Butlerow[4] who found that trimethylacetic acid was formed. We have repeated this oxidation using chromic anhydride as employed in the above alcohol oxidations. While the oxidation of the alcohols is rapid at 30° no oxidation of the pinacolone is apparent until temperatures close to 100° are reached. Only trimethylacetic acid could be isolated although any *t*-butyl alcohol which might have been formed would probably have been further oxidized. The great difference in ease of oxidation of ketones and carbinols, which is well known, points to a different mechanism and favors the belief that the fission to the tertiary alcohols occurs in the carbinol rather than in the ketone.

The following tentative mechanism for the cleavage exemplified with pinacolone, is suggested. The oxidizing agent abstracts a hydrogen with an electron pair (a hydride ion) from the hydroxyl group. Certainly the hydrogen of the hydroxyl is the most polar hydrogen in the molecule so that the energetics would favor approach of the oxidizing agent. The great difficulty with which ethers are oxidized by reagents, other than oxygen, is also in harmony.



I II

The intermediate ion II, which would be expected to show many carbonium ion type reactions, can be stabilized intramolecularly in two ways. First, a proton may be expelled followed by rearrangement of an electron pair to create a carbonyl group. This process is apparently the chief one because of the high yields of ketone obtained. The second possibility depends on the fact that the electronically deficient oxygen atom exerts a powerful attraction for the electron pair joining the *t*-butyl group to the oxygenated carbon atom, while the *t*-butyl has a low attraction for these same electrons.[5] The configuration here, R_3C-C-O^+, is analogous to that found by Whitmore and Stahly to be critical for the acid catalyzed depolymerization of branched olefins,[6] R_3C-C-C^+. If this electron pair is appropriated by the oxygen, rupture of the molecule occurs to form a tertiary carbonium ion and a molecule of aldehyde. Both stabilization processes are summarized in Fig. 1. We have made the assumption that the normal product of the reaction, the ketone, and the abnormal product, the tertiary alcohol, have come from a common intermediate. There is no direct evidence for this, and later work may possibly show that two independent mechanisms are involved.

The carbonium ion formed in the cleavage may react with water: $(CH_3)_3C^+ + HOH \rightleftarrows (CH_3)_3COH + H^+$. Reaction with acetic acid to give *t*-butyl acetate might also take place, but such esters are hydrolyzed very readily in acidic solutions.[7] At higher temperatures olefin would be expected through the expulsion of a proton from the tertiary carbonium ion and this has been found to be the case.[8] The experimental conditions used in

(1) Presented in part before the Organic Division, American Chemical Society, New York, N. Y., September, 1944.

(2) Whitmore, Organic Division, American Chemical Society, Cleveland, April, 1944.

(3) Friedel and Silva, *Compt. rend.*, **76**, 230 (1873); *Ber.*, **6**, 146, 826 (1873); *Bull. Soc. Chim.*, [2] **19**, 193 (1873).

(4) Butlerow, *Ann.*, **170**, 168 (1873).

(5) Whitmore and Bernstein, THIS JOURNAL, **60**, 2626 (1938).

(6) Whitmore and Stahly, *ibid.*, **55**, 4153 (1933); **68**, 281 (1946).

(7) Cohen and Schneider, *ibid.*, **63**, 3382 (1941).

(8) N. C. Cook, The Pennsylvania State College, private communication.

this work would oxidize any aldehyde which might be formed. Aldehydes have been isolated under modified conditions, however, and the description of that work will be published later.

This work has been supported in part by a Frederick Gardner Cottrell grant from the Research Corporation, which is gratefully acknowledged.

Experimental

Materials.—Methyl-*t*-amylcarbinol was prepared from *t*-amylmagnesium chloride and acetaldehyde, methyl-*t*-butylcarbinol from *t*-butylmagnesium chloride and acetaldehyde and isopropyl-*t*-amylcarbinol from isopropylmagnesium bromide and dimethylethylacetyl chloride, employing the usual procedures. All products were fractionated through columns of 12–15 theoretical plates. One sample of methyl-*t*-butylcarbinol was prepared by the catalytic reduction of pinacolone prepared from acetone. Further details will be published with the original investigation.[2]

Oxidation of Alcohols.—All oxidations were carried out in the following manner, exemplified with methyl-*t*-amylcarbinol. In a 3-necked 3-liter flask 336 g. of methyl-*t*-amylcarbinol (2.9 moles, $n^{20}D$ 1.4300) was dissolved in 150 ml. of glacial acetic acid. The flask was equipped with a stirrer, dropping funnel, and thermometer. Two moles (200 g.) of chromic anhydride was dissolved in 100 ml. of water and 250 ml. of glacial acetic added when solution in the water was complete. The chromic anhydride solution was added dropwise to the carbinol over a period of eight hours with the temperature below 30° at all times. The product was diluted with 2 liters of water and the ketone layer separated and washed with bicarbonate solution and then water. The water layer from the reaction was steam-distilled after the addition of 20 ml. of ethyl alcohol to react with any unused oxidant. The oil layer from the steam distillate was combined with the main portion after washing as before. The crude ketone was dried over potassium carbonate which also served to remove any acids present. The dry product was fractionated through a column equivalent to 15 theoretical plates.

Identification of Products.—From each oxidation early distillation cuts were obtained with physical properties corresponding to *t*-amyl or *t*-butyl alcohol. It was the characteristic odor of these cuts which prompted further study. These suspected cuts were treated with concentrated hydrochloric acid and the chlorides obtained, after checking density and index of refraction, were converted to the Grignard reagents, and these reacted with phenyl isocyanate to give, respectively, *t*-amylacetanilide, m. p. and mixed m. p. 105–106°, and *t*-butylacetanilide, m. p. and mixed m. p. 132°. The tertiary alcohol cuts from methyl-*t*-butyl-, methyl-*t*-amyl-, and isopropyl-*t*-amylcarbinols were, respectively, 6, 7 and 7%. The yields of ketone obtained were 70–75%. Three separate oxidations

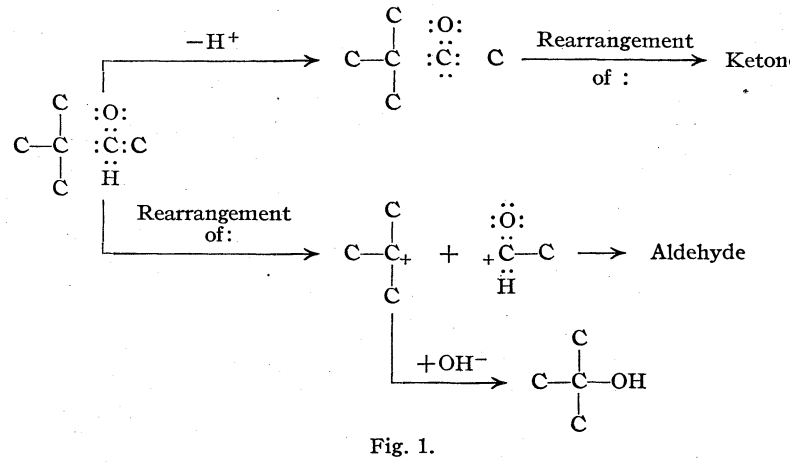


Fig. 1.

were made with methyl-*t*-amylcarbinol and two with methyl-*t*-butylcarbinol; the results were identical. The yield of *t*-butyl alcohol from methyl-*t*-butylcarbinol prepared from pinacolone was the same as the yield from the product made through the Grignard reaction.

Oxidation of Pinacolone.—Pinacolone was prepared according to "Organic Syntheses."[9] Oxidation was carried out as in the case of methyl-*t*-amylcarbinol above. Oxidation did not take place at 50 or 80°, but did proceed at 100°. After five hours the reaction mixture was diluted and steam distilled. Basic reagents were avoided. Fractionation gave 75% trimethylacetic acid (b. p. 164° (760 mm.), anilide m. p. and mixed m. p. 129°) and 18% unreacted ketone. No tertiary butyl alcohol was detected.

Summary

1. Oxidation of methyl-*t*-amylcarbinol and isopropyl-*t*-amylcarbinol with chromic anhydride in acetic acid gives in both cases 7% *t*-amyl alcohol. Similarly methyl-*t*-butylcarbinol gives 6% *t*-butyl alcohol.

2. These tertiary alcohols are formed from the carbinols as the oxidation of pinacolone does not take place under similar conditions and under more drastic conditions yields trimethylacetic acid.

3. A mechanism involving the removal of a hydride ion from the hydroxyl group to give an intermediate ion with an electronically deficient oxygen is proposed. The tertiary alcohols are obtained by rearrangement of an electron pair without the attached group, while ketones, the principal products, are obtained by expulsion of proton from the intermediate.

NEWARK, DELAWARE RECEIVED JANUARY 5, 1948

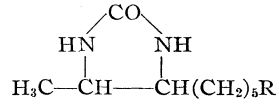
(9) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., pp. 459, 462.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN–LA ROCHE, INC.]

The Synthesis and Biological Activity of 4-Methyl-5-(ε-sulfoamyl)-2-imidazolidone, a Sulfonic Acid Analog of Desthiobiotin

BY ROBERT DUSCHINSKY AND SAUL H. RUBIN

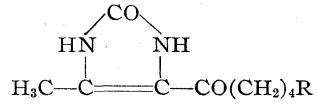
Replacement of carbonyl by sulfonyl groups in metabolites sometimes results in substances of antagonistic biological behavior.[1] In this respect the study of a sulfonic acid analog (I, R = SO_3H)



I

of desthiobiotin (I, R = CO_2H) appeared of interest. The substance was therefore synthesized and tested microbiologically.[2]

The general methods involved in the synthesis have been described previously.[3] 4-Methyl-2-imidazolone and δ-bromovaleryl chloride were submitted to a Friedel-Crafts condensation. The bromoketone obtained (II, R = Br) was converted



II

into the sodium sulfonate (II, R = SO_3Na) which was reduced catalytically to give the sodium salt of 4-methyl-5-(δ-sulfoamyl)-2-imidazolidone (I, R = SO_3Na). As in the completely analogous step in the synthesis of desthiobiotin,[3] two moles of hydrogen corresponding to the reduction of the keto group were absorbed rapidly, while the third mole corresponding to the hydrogenation of the double bond was taken up much more slowly. In view of the similarities of method and behavior, it is assumed that, as in the desthiobiotin synthesis, *cis*-addition at the double bond takes place.

The growth-promoting or growth-inhibiting properties of the compound for *Saccharomyces cerevisiae* 139 and *Lactobacillus casei* were tested by methods which have been previously reported.[4]

The sulfo compound did not support growth in biotin-free media. For *S. cerevisiae* it proved to be an antibiotin at a molar inhibition ratio of about 300,000. When *d,l*-O-heterobiotin was substituted for biotin in the medium, the ratio was found to be 17,000. This result presents additional evidence for the reported greater resistance of biotin toward inhibitors as compared to its oxygen analog.[5] When *d,l*-desthiobiotin was substituted for biotin, the growth of *S. cerevisiae* was inhibited at a molar ratio of 40,000. With *L. casei* no inhibition of growth was noticed at a molar ratio of more than 5,000,000 in media supplemented with *d*-biotin or *d,l*-O-heterobiotin.

Experimental[6]

4-Methyl-5-(δ-bromovaleryl)-2-imidazolone (II, R = Br).—δ-Bromovaleric acid was prepared in good yield by the procedure of Hunsdiecker and Hunsdiecker[7] by the reaction of methyl silver adipate with bromine and saponification of the resulting ester with a mixture of acetic and hydrobromic acids. The product was converted into the acid chloride[8] by means of thionyl chloride. The δ-bromovaleryl chloride (26.7 g.) was added to a suspension of 13.1 g. of 4-methyl-2-imidazolone[3] in 130 cc. of nitrobenzene. Aluminum chloride(44 g.) was added gradually with continuous stirring and occasional cooling. After heating the mixture for four and one-half hours in a bath at 60°, the evolved hydrochloric gas being driven off with a slow stream of nitrogen, it was poured on 200 g. of ice. Stirring and addition of 200 cc. of ether produced crystals, which were washed well with water and ether. The yield was 16.2 g. (43%), m. p. 199–201° (dec.). Recrystallization from 95% ethanol gave rectangular plates melting at 206–207° (dec.).

Anal. Calcd. for $C_9H_{13}O_2N_2Br$: C, 41.39; H, 5.02; Br, 30.61. Found: C, 41.92; H, 5.20; Br, 30.33.

Sodium Salt of 4-Methyl-5-(δ-sulfovaleryl)-2-imidazolone (II, R = SO_3Na).—A mixture of 2.61 g. of the bromoketone, 1.38 g. (1.1 moles) of sodium sulfite and 8.5 cc. of water was refluxed for two hours. The solution was evaporated to dryness and the residue boiled with 22 cc. of water and 140 cc. of ethanol; some insoluble material was separated by filtration. Upon cooling, crystals deposited which were washed bromine-free with ethanol. The yield was 2.1 g. (74%) of prismatic needles which, after recrystallization from aqueous 80% ethanol, melted in an evacuated capillary tube at 332–334° (dec.).

Anal. Calcd. for $C_9H_{13}O_5N_2SNa$: C, 38.02; H, 4.61; Na, 8.09. Found: C, 38.17; H, 4.45; Na, 8.29.

Sodium Salt of 4-Methyl-5-(ε-sulfoamyl)-2-imidazolidone (I, R = SO_3Na).—The foregoing imidazolone (1.68 g.) was hydrogenated at room temperature and atmospheric pressure with 1 g. of prehydrogenated Adams platinum catalyst in 15 cc. of acetic acid. Two moles of hydrogen were taken up in one hour, a third mole overnight, whereby the material, initially in suspension, passed into solution. After separation of the catalyst, the solution was evaporated to a sirup, which was rendered free of acetic acid by evaporation with methanol. The final residue was dissolved in 25 cc. of hot methanol. Addition of 25 cc. of dry ether and cooling produced 1.09 g. of crystals (68%). The substance was recrystallized for analysis by dissolving in methanol and adding ether. It did not show a distinct melting point.

Anal. Calcd. for $C_9H_{17}O_4N_2SNa$: C, 39.64; H, 6.29;

(1) Roblin, *Chem. Rev.*, **38**, 377 (1946).

(2) We had accomplished the present work when Hofmann, Bridgwater and Axelrod, THIS JOURNAL, **69**, 1550 (1947), reported the synthesis of a sulfonic acid analog of oxybiotin.

(3) Duschinsky and Dolan, *ibid.*, **67**, 2079 (1945).

(4) Rubin, Drekter and Moyer, *Proc. Soc. Exp. Biol. Med.*, **58**, 352 (1945); Rubin, Flower, Rosen and Drekter, *Arch. Biochem.*, **8**, 79 (1945).

(5) Axelrod, De Woody and Hofmann, *J. Biol. Chem.*, **163**, 771 (1946); Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, **69**, 191 (1947).

(6) Melting points were determined with an uncalibrated set of Anschütz thermometers.

(7) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 296 (1942).

(8) Merchant, Wickert and Marvel, THIS JOURNAL, **49**, 1830 (1927).

S, 11.78; Na, 8.45. Found: C, 39.06, 39.30; H, 6.06, 5.74; S, 11.38; Na, 8.22.

Acknowledgment.—The authors are indebted to Dr. Al Steyermark for the microanalyses and to Mr. Jacob Scheiner for the microbiological assays.

Summary

A sulfonic acid analog of desthiobiotin was synthesized. The compound showed inhibitory activity toward *S. cerevisiae*, which was more pronounced against *d,l*-O-heterobiotin and *d,l*-desthiobiotin than *d*-biotin. The compound had no effect on *L. casei*.

NUTLEY, NEW JERSEY RECEIVED MARCH 1, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

The Reaction of Some Radioactive Mustard-type Vesicants with Purified Proteins[1]

BY JOHN L. WOOD,[2] JULIAN R. RACHELE, CARL M. STEVENS,[3] FREDERICK H. CARPENTER AND VINCENT DU VIGNEAUD

In a collaborative attack on the problem of the mechanism of action of mustard-type vesicants, we had undertaken to study the reaction of vesicants with proteins. A study of the reactions of a large number of amino acids with vesicants has already been described.[4] The second phase of our work was the study of the interaction of vesicants with certain well characterized, highly purified proteins. Preliminary experiments indicated that treatment of certain proteins with relatively large amounts of vesicant resulted in a chemical reaction. The reaction products differed from the original proteins in physical properties and had a higher sulfur content. These observations supplemented earlier evidence[5] of chemical reactions between vesicants and proteins and indicated the desirability of a detailed study.

Kistiakowsky, Moritz, Henriques and co-workers[6] had already demonstrated that an extremely small amount of mustard gas (H) is bound in the tissue at the site of a burn produced by a minimum amount of H. At the same time, all indications were that the vesicants were capable of reacting with a large number of different types of groups presumably present in proteins. Reactions at the site of the burn must involve only a small percentage of these groups and possibly only certain types. It was, therefore, of particular interest to study the reaction of H-type vesicants with proteins *in vitro* at correspondingly low ratios of vesicant to protein in an effort to determine the most reactive groups under these conditions. It was decided to utilize the radioactive tracer technique in approaching this question.

(1) The work described in this paper was carried out under Contract OEMsr-144 between the Office of Scientific Research and Development and Cornell University Medical College, and is described in Progress Reports to the National Defense Research Committee, January, 1942, to November, 1943.

(2) Present address: School of Biological Sciences, The University of Tennessee, Memphis, Tenn.

(3) Present address: Department of Chemistry, State College of Washington, Pullman, Wash.

(4) du Vigneaud, Stevens, McDuffie, Wood and McKennis, THIS JOURNAL, **70**, 1620 (1948).

(5) (a) Berenblum and Wormall, *Biochem. J.*, **33**, 75 (1939); (b) unpublished British Reports: Berenblum (1940), Pirie (1941), Peters (1941).

(6) Progress Reports to NDRC Section B4C (1942).

Benzyl β-chloroethyl sulfide (benzyl-H*) and *n*-butyl β-chloroethyl sulfide (butyl-H*), containing S^{35} of 87-day half-life,[7] were synthesized from benzyl mercaptan* and butyl mercaptan*, respectively. The general scheme for the synthesis of the vesicants is shown

$$RMgX \xrightarrow{S^*} RS^*MgX \xrightarrow[H^+]{HOH} RS^*H \xrightarrow[ClCH_2CH_2OH]{NaOH}$$

$$RS^*CH_2CH_2OH \xrightarrow{HCl} RS^*CH_2CH_2Cl$$

A number of syntheses of these compounds containing isotopic sulfur have already been described.[8] The procedure employed by us in this investigation contains technical features which facilitated the handling of the small amounts of materials involved, and is, therefore, presented in some of its details.

The estimations of radioactivity were carried out essentially by the method of Henriques and coworkers.[9] The radioactivity of the sulfur in the vesicants used to treat the proteins was sufficient to allow the detection of as little as 5×10^{-6} mg. of benzyl-H* or butyl-H* residues per milligram of protein sulfur in the protein derivative or its hydrolysis products.

The proteins utilized were crystalline insulin, crystalline pepsin and crystalline tobacco mosaic virus.

Insulin.—Insulin was selected for study particularly because of its unique physiological activity, and because a large amount of chemical data on the molecule is available. Furthermore, it has no known organic constituents other than amino acids.

Insulin was treated with benzyl-H* or butyl-H* in amounts ranging from 0.25 to 4.0 mg. of vesicant per 100 mg. of protein. This resulted in insulin-vesicant* preparations containing from 0.3 to

(7) An asterisk (*) is used to indicate the presence of radiosulfur in a compound.

(8) Tarver and Schmidt, *J. Biol. Chem.*, **146**, 69 (1942); Seligman, Rutenburg and Banks, *J. Clin. Investigation*, **22**, 275 (1943); Kilmer and du Vigneaud, *J. Biol. Chem.*, **154**, 247 (1944).

(9) Henriques, Kistiakowsky, Margnetti and Schneider, *Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946).

5.3 vesicant residues[10] per molecule of insulin, as shown by the data of Table I (Preparations 1–9). It may be pointed out that the amount of vesicant which combined with the protein depended upon the amount of vesicant applied. In fact, despite the sixteenfold variation in the amount of vesicant applied, the per cent. of the applied vesicant which combined with the insulin was approximately constant (*ca.* 50%).

Using a method which is essentially that employed by Scott[11] for the crystallization of insulin, it was possible to obtain from an insulin-benzyl-H* preparation crystals of the alkylated protein. After recrystallization, this product contained an average of 1.1 vesicant residues per molecule of protein. It is of interest that the product, when tested in rabbits, displayed considerable hypoglycemic activity.

Pepsin.—Crystalline pepsin was dissolved in 0.05 *M* borate buffer (*p*H 7.4) at a concentration of 20 mg./cc. and treated with benzyl-H*. From the data of Table I (Preparation 10), it can be seen that pepsin combined with approximately 35% of the vesicant.

Tobacco Mosaic Virus Protein.—The early reports of Berenblum[5b] on the susceptibility of nucleoproteins to precipitation by mustard gas indicated the desirability of studying the nature of the reaction of vesicants with nucleoproteins.[12] As a protein for study, we selected tobacco mosaic virus (TMV). This material contains 6% of nucleic acid. The protein has a unique amino acid composition, being devoid of histidine as well as methionine, and possessing a small content of cysteine, which, however, is not detectable chemically except after denaturation.[13] Furthermore, the intact protein has a unique and readily measurable biological activity which might be of help in characterizing the changes brought about by vesicant treatment.

Treatment of TMV with various amounts of benzyl-H* or butyl-H* (Table I, Preparations 11–14) resulted in the attachment of 25–40% of the applied vesicant to the TMV. Because of the enormous molecular weight of the virus, even the lowest level of vesicant applied (0.25 mg./100 mg. of TMV) resulted in the substitution of approximately 260 vesicant residues per virus molecule.

Through the kindness of Dr. W. M. Stanley and Dr. L. O. Kunkel, we were able to obtain tests of the biological activity of Preparations 11 and 13.

The determination of the virus activity was carried out on 34 half-leaves of *N. glutinosa*, and the samples were inoculated at a concentration of 10^{-5} g./cc. As a control, buffered solutions of a sample of virus and a sample of benzyl-H* were stirred separately and then combined and dialyzed. This control sample was found to be as active as the original virus and was used as the standard. Preparation 11 possessed 93% of the activity of the control sample, while Preparation 13 showed 52% of the activity of the control.

From these results, it may be concluded that Preparation 11 was not appreciably inactivated, while Preparation 13 had only about half of the activity of the control. These samples contained, respectively, 1500 and 3200 vesicant residues per virus molecule. Apparently, then, treatment leading to the addition of approximately 1500 vesicant residues to reactive groups of the protein caused no appreciable inactivation, while treatment resulting in the substitution of an additional 1700 groups caused 50% inactivation.

Preparation 11 was also tested for the production of mutants. Each of 225 plants was inoculated with material from a different lesion produced in *N. glutinosa* by the control sample of virus, and each of 225 more plants with material from a different lesion produced by benzyl-H*-treated virus. Of the plants inoculated with the control virus, 196 became diseased, and 4 of these were atypical, resulting apparently from mutants. Of the plants inoculated with the vesicant-treated virus, 174 became diseased, and 5 of these appeared atypical. Thus, the vesicant treatment which resulted in the substitution of approximately 1500 vesicant residues caused neither inactivation nor mutation of the virus to an extent detectable by the tests employed.

Experimental

Benzyl β-Chloroethyl Sulfide (Benzyl-H*) Containing Radiosulfur.—Barium sulfate*[14] was reduced to barium sulfide* by a procedure similar to those which have already been described.[15] Dried barium sulfate* (116 mg.) was spread in a thin layer on a platinum boat and placed in a Vycor tube. The air was expelled by a stream of hydrogen and the Vycor tube was heated at 900–1000° for two hours and then allowed to cool, a slow stream of hydrogen being maintained throughout the reduction. The issuing gases were bubbled through an absorption train consisting of 6 cc. of 0.5 *N* sodium hydroxide in a small test-tube and 1 cc. in a second tube.

The boat containing the barium sulfide* was placed along with 5 mg. of zinc dust in a 125-cc. ₹ 24/40 Erlenmeyer flask equipped with a separatory funnel and a delivery tube. The delivery tube was attached to the sodium hydroxide absorption train used with the reduction of the barium sulfate* and the apparatus was swept with oxygen-free nitrogen. Twenty cubic centimeters of 6 *N* phosphoric acid, which had been boiled with about 5 mg. of zinc dust to expel air and cooled somewhat, was placed in the separatory funnel. This acid was dropped onto the barium sulfide* at such a rate as to produce a slow evolution of hydrogen sulfide*, which was absorbed in the

(10) These values represent a statistical average of the number of vesicant residues per molecule in the particular preparation, and are not intended to indicate that every molecule contains this number of residues.

(11) Scott, *Biochem. J.*, **28**, 1592 (1934).

(12) For other studies of reactions of vesicants with nucleoproteins, see Banks, Boursnell, Francis, Hopwood and Wormall, *Biochem. J.*, **40**, 745 (1946); Young and Campbell, *Can. J. Research*, **25B**, 37 (1947).

(13) Stanley and Lauffer, *Science*, **89**, 345 (1939); Ross, *J. Biol. Chem.*, **136**, 119 (1940).

(14) Samples of barium sulfate containing radiosulfur were kindly supplied by Dr. M. Kamen and Dr. F. C. Henriques, Jr.

(15) Cooley, Yost and McMillan, THIS JOURNAL, **61**, 2970 (1939); Boursnell, Francis and Wormall, *Biochem. J.*, **40**, 743 (1946); Henriques and Margnetti, *Ind. Eng. Chem., Anal. Ed.*, **18**, 476 (1946).

sodium hydroxide scrubbers. When all the acid had been added, the reaction mixture was warmed slowly to its boiling point, allowed to cool in a stream of nitrogen and swept with nitrogen for one hour.

Fifteen cubic centimeters of 0.1 *N* iodine in potassium iodide and 1 cc. of concentrated hydrochloric acid were placed in a 50-cc. centrifuge cone. The 6 cc. of sodium sulfide* solution from the first scrubber was introduced at the bottom of the solution by means of a long slender pipet. The 1 cc. of solution from the second scrubber was used to wash the first and the washings were added to the iodine solution. The scrubbers were washed further with small portions of water until a nitroprusside or lead acetate test for the sulfhydryl group on the washings was negative. The portion of the transfer pipet coated with sulfur* was then broken off and placed in the iodine solution. After fifteen minutes the excess iodine was destroyed with a few drops of a freshly prepared solution of stannous chloride in 5 *N* hydrochloric acid. When the resulting suspension was allowed to stand overnight, the free sulfur* coagulated and was then collected by centrifugation. The precipitate was washed with water by centrifugation and decantation.

Ten cubic centimeters of purified *m*-xylene was added and the sulfur* was dissolved by boiling the mixture cautiously. The xylene solution was transferred to a 15-cc. centrifuge cone, washed first with a few cc. of the acid stannous chloride solution to remove traces of iodine and then with water. The traces of water in the xylene solution were removed by azeotropic distillation. The xylene solution was transferred to a 50-cc. centrifuge cone with xylene, evaporated to a volume of 5 cc. and cooled to room temperature under nitrogen. Five cubic centimeters of a 0.4 *N* solution of benzylmagnesium bromide in benzene was added. The tube was stoppered and allowed to stand overnight at room temperature.

The resulting suspension of benzylmercaptomagnesium bromide* was centrifuged and the excess Grignard solution was decanted. The solid was washed 3 times with 5-cc. portions of petroleum ether (b. p. 35°) by centrifugation and decantation. It was then suspended in petroleum ether (5 cc.) and cooled in an ice-bath under nitrogen. (A nitrogen atmosphere was maintained as long as benzyl mercaptan* was present.) One cubic centimeter of 5 *N* hydrochloric acid was added and the mixture was shaken until free of solids. The acid layer was separated by means of a pipet. The petroleum ether layer containing the benzyl mercaptan* was washed with two 1-cc. portions of water and the washings were added to the acid layer. The combined aqueous layers were extracted with 1-cc. portions of peroxide-free ether until the nitroprusside test for the sulfhydryl group was negative. The combined ether extracts were added to the petroleum ether layer. Then 1 cc. of an ether solution containing 36 mg. of ethylene chlorohydrin and 1 cc. of 1 *N* sodium hydroxide were added. The two layers were thoroughly mixed by bubbling the alkali through the organic layer with the aid of a pipet. The mixture was heated gently in a hot water-bath until the organic solvents had evaporated. If the aqueous solution was not alkaline or not free of mercaptan, additional alkali or additional ethylene chlorohydrin or both were added and warming was continued until all the mercaptan had reacted.

The benzyl β-hydroxyethyl sulfide* was extracted with one 5-cc., one 3-cc. and three 1-cc. portions of ether. In a 15-cc. centrifuge tube, the combined ether extracts were washed with 1 cc. of water. The ether solution was transferred to a Carius tube which was heated on a water-bath to remove the ether. The last traces of ether were removed by attachment to a water pump. Two cubic centimeters of petroleum ether and 3 cc. of concentrated hydrochloric acid were added to the residue. The tube was cooled, sealed and shaken at 65–70° for twenty-four hours; 2 cc. of petroleum ether was added and the petroleum ether layer was separated. The acid layer was extracted with three 2-cc. portions of petroleum ether. The combined petroleum ether solutions were concentrated at −40° and 10^{-3} mm. Toward the end of the concentration, crystals generally appeared. The last traces of petroleum ether were removed at 0° (10^{-3} mm.). If the product on melting was not perfectly colorless, it was distilled at 10^{-3} mm. and 40° onto a cold finger which was cooled to *ca.* −70° with a Dry Ice–cellosolve mixture. The apparatus was so arranged that after completion of the distillation the colorless product dropped into a cup. The product adhering to the cold finger was rinsed into a cup with 2 cc. of petroleum ether and this solution was transferred to a small weighing tube. The tube was connected to a distilling apparatus and cooled to −70°. The benzyl β-chloroethyl sulfide* crystallized and the petroleum ether was removed *in vacuo* at gradually rising temperatures up to 10°. The yield was 70–72 mg. (75–77%).

Anal. Calcd. for $C_9H_{11}ClS$: Cl, 19.0. Found: Cl, 18.9.

Butyl β-Chloroethyl Sulfide (Butyl-H*) Containing Radiosulfur.—Barium sulfate* (116 mg.) was converted to sulfur* and the sulfur* was dissolved in xylene in the manner described previously. To the dried, cooled solution in a 50-cc. centrifuge cone was added 40 cc. of a 0.6 *N* solution of *n*-butylmagnesium bromide in benzene. After three to four hours the tube was filled with petroleum ether (b. p. 50–60°) and the mixture was centrifuged. The supernatant liquid was decanted into a 100-cc. centrifuge tube. The residue of butylmercaptomagnesium bromide* was stirred with 25 cc. of petroleum ether and centrifuged. This supernatant liquid was added to the solution in the 100-cc. centrifuge tube and the volume was increased to 100 cc. with petroleum ether, whereupon an additional amount of precipitate was obtained. This was collected and added to the main residue. The combined precipitates were washed with 25 cc. of petroleum ether by centrifugation.

The butylmercaptomagnesium bromide* was suspended in a few cc. of petroleum ether, cooled in an ice-bath under nitrogen and treated with 2 cc. of 5 *N* hydrochloric acid. The mixture was transferred to a 30-cc. glass-stoppered flask with a little petroleum ether. The flask was shaken violently until the magnesium salts had dissolved. The hydrochloric acid was separated and the petroleum ether layer was washed with 2 cc. of water. The combined aqueous solutions were extracted with small portions of petroleum ether until a test for the sulfhydryl group was negative. To the combined petroleum ether layers in the 30-cc. flask were added 1 cc. of water containing 40 mg. of ethylene chlorohydrin and 1 cc. of 1 *N* sodium hydroxide.

The flask was shaken at room temperature for three to four hours until all the mercaptan had reacted. The aqueous layer was separated and the organic layer was washed with 2 cc. of water. The combined aqueous layers were extracted repeatedly with 1-cc. portions of petroleum ether. The combined petroleum ether layers were centrifuged and then were passed through an 8 × 50 mm. column of Permutit (Permutit according to Prof. Otto Folin, Eimer and Amend No. 901194). The product was then eluted with 25 cc. of dry benzene. The benzene solution was concentrated at room temperature under reduced pressure (water pump). The residue was distilled at 0° and 10^{-3} mm. onto a cold finger at −70°. The butyl β-hydroxyethyl sulfide* was transferred to a Carius tube with 2 cc. of petroleum ether, and 3 cc. of concentrated hydrochloric acid was added. The tube was sealed and shaken for twenty-four hours at 65°. The butyl β-chloroethyl sulfide* was then isolated in the manner described for the benzyl analog except that in this case the temperature was not raised above −40° (10^{-3} mm.) for removal of the last traces of petroleum ether. The product was usually analytically pure without distillation. The yield of butyl β-chloroethyl sulfide* was 33–46 mg. (44–62%).

Anal. Calcd. for $C_6H_{13}ClS$: Cl, 23.2. Found: Cl, 23.1.

Treatment of Insulin with Vesicants*.—Crystalline zinc insulin (500 mg.) was dissolved in 10 cc. of water by the slow addition of 4.5 cc. of 0.1 *N* hydrochloric acid. Five

cubic centimeters of 0.25 *M* borate buffer (*p*H 7.4) was added, followed by the dropwise addition with stirring of 5.5 cc. of 0.1 *N* sodium hydroxide. The final solution had a *p*H of 7.4.

Procedure A.—Samples (0.25–4.0 mg.) of benzyl-H* or butyl-H* were added to 5-cc. aliquots of the protein solution and the mixtures were stirred gently for twelve to twenty-four hours. The stirring was carried out in such a way as to disperse the vesicant in fine droplets throughout the protein solutions with minimal disturbance of the surface of the solutions. The reaction mixtures were then extracted with peroxide-free ether or were dialyzed against running water. Either treatment was found to remove practically all of the radiosulfur-containing material not precipitated by trichloroacetic acid. This procedure was used for Preparations 1–7 (Table I).

TABLE I

VESICANT*-TREATED PROTEINS

Prepn.	Protein	Vesicant*	Mg. ves. applied / 100 mg. protein	% Applied vesicant attached to protein	*M* Vesicant / *M* Protein[a]
1	Insulin	Benzyl-H*	0.25	55	0.3
2	Insulin	Benzyl-H*	2.0	55	2.4
3	Insulin	Benzyl-H*	4.0	50	4.3
4	Insulin	Benzyl-H*	4.0	50	4.3
5	Insulin	Benzyl-H*	2.0	55	2.4
6	Insulin	Butyl-H*	4.0	50	5.3
7	Insulin	Butyl-H*	0.25	55	0.4
8	Insulin	Butyl-H*	2.1	40	2.2
9	Insulin	Butyl-H*	1.6	50	2.1
10	Pepsin	Benzyl-H*	2.0	35	1.3
11	TMV	Benzyl-H*	2.0	35	1500
12	TMV	Butyl-H*	0.25[b]	40	260
13	TMV	Benzyl-H*	6.0	25	3200
14	TMV	Benzyl-H*	2.0	40	1700

[a] These ratios are calculated on the basis of the following molecular weights: insulin, 40,000; pepsin, 35,000; tobacco mosaic virus, 40,000,000. [b] In this experiment, the concentration of the protein solution was 40 mg./cc.; in all other experiments it was approximately 20 mg./cc.

Procedure B.—In this procedure, dilute, ethanolic solutions of the vesicant* (1.6–2.1 mg.) were added portionwise with stirring over a period of several hours to 5-cc. aliquots of the protein solution. The solutions were then dialyzed. Preparations 8 and 9 (Table I) were obtained in this manner.

Crystallization of Benzyl-H*-treated Insulin.—Preparation 5, after dialysis against running water for twenty-four hours, was transferred to a 25-cc. volumetric flask; 1 cc. of 0.1 *N* hydrochloric acid was added and the volume was adjusted to 25 cc. by addition of water. A 6-cc. aliquot of this solution (containing 24 mg. of vesicant*-treated insulin) was added to a solution consisting of 10.5 cc. of 0.67 *M* phosphate buffer (*p*H 7.15), 5 cc. of water and 0.84 cc. of 1 *N* hydrochloric acid. One cubic centimeter of zinc acetate solution (2.5 mg. of zinc), 2.1 cc. of acetone and 0.6 cc. of 1 *N* ammonium hydroxide were added. The *p*H of the solution was then adjusted to 6.2 with 0.1 *N* hydrochloric acid, and it was allowed to stand at 5° for twelve hours and at room temperature for twenty-four hours. The yield of crystalline material was 12 mg.; from a control experiment with untreated insulin, 16 mg. of crystals was obtained. The recoveries were thus 50 and 66%, respectively, of the total protein. The radioactivity of the vesicant*-treated protein indicated that it contained 1.5 benzyl-H* residues per molecule of insulin.

For recrystallization, 9 mg. of the crystals was dissolved in 1 cc. of 0.05 *N* hydrochloric acid. A small residue was removed by centrifugation. To the solution was added a slightly warmed mixture of 7.5 cc. of water, 7.5 cc. of phosphate buffer (*p*H 7.15) and 1.5 cc. of acetone. The mixture was centrifuged and the supernatant liquid was decanted. The *p*H of the supernatant was lowered from 7.1 to 6.1 by addition of 1 *N* hydrochloric acid and the solution was allowed to stand overnight at room temperature. A small amount of crystalline precipitate formed. This was collected, washed with water and then with absolute alcohol, and dried. The yield was approximately 2 mg. The radioactivity of this recrystallized sample indicated the presence of 1.1 benzyl-H* residues per molecule of insulin. The specific activity was thus 73% of that of the once-recrystallized material.

Treatment of Tobacco Mosaic Virus (TMV) with Vesicants*.—Preparations 11, 13 and 14 (Table I) were obtained by treatment of solutions of TMV (20 mg./cc.) in 0.05 *M* borate buffer (*p*H 7.5) with benzyl-H* (0.4–1.2 mg./cc. of protein solution) under conditions similar to Procedure A for insulin.

For Preparation 12, 1 g. of TMV was dissolved in 25 cc. of 0.25 *M* borate buffer (*p*H 7.5). To this solution, 1 cc. of an ethanolic solution of butyl-H* (2.5 mg.) was added in ten portions over a period of six hours with continuous stirring. The solution was then dialyzed against running water for twenty-four hours.

Acknowledgment.—The authors wish to thank Dr. G. H. A. Clowes for crystalline insulin, Dr. R. M. Herriott for crystalline pepsin, and Dr. W. M. Stanley for crystalline tobacco mosaic virus. They also wish to thank Mr. Roscoe C. Funk, Jr., for the microanalyses and for assistance with the radioactivity measurements. The authors would also like to take this opportunity to express their appreciation to Dr. Mary Elizabeth Wright for invaluable aid in the preparation of this manuscript.

Summary

A method is described for the synthesis of the mustard-type vesicants, benzyl β-chloroethyl sulfide (benzyl-H) and *n*-butyl β-chloroethyl sulfide (butyl-H), containing radiosulfur. Studies were made of the reaction of these radioactive vesicants with three highly purified proteins: insulin, pepsin and tobacco mosaic virus.

NEW YORK, N. Y. RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Chemical Studies on Vesicant-treated Proteins[1]

BY FREDERICK H. CARPENTER, JOHN L. WOOD,[2] CARL M. STEVENS[3] AND VINCENT DU VIGNEAUD

In a preceding paper[4] we have described the treatment of certain crystalline proteins (insulin, pepsin and tobacco mosaic virus (TMV)) with benzyl β-chloroethyl sulfide (benzyl-H*) and *n*-butyl β-chloroethyl sulfide (butyl-H*) containing radiosulfur.[5] The present report describes studies made on these vesicant*-treated proteins with the object of determining the nature of the attachment of some of the substituting groups.

The work of other investigators[6] on the nature of the linkages formed by the action *in vivo* of mustard gas on tissues had shown that a large percentage of the vesicant residues could be split from these tissues by alkali or heat. There was also evidence from the work of another Laboratory[7] that a large proportion of the vesicant residues bound to certain proteins by vesicant treatment *in vitro* could be removed by the action of alkali.

It was of interest to study in more detail the alkali lability of the linkages formed by the treatment of proteins with vesicant. For this purpose we used the vesicant*-treated protein preparations described previously,[4] which contained relatively minute amounts of vesicant* residues and were in this respect comparable to the tissue preparations.

A study was made of the effect of *p*H and temperature upon the rate of liberation of vesicant residues from two preparations of butyl-H*-treated insulin. These preparations contained 2.2 and 2.1 vesicant* residues[8] per mole of protein. The results are summarized in Table I and Fig. 1. Treatment with relatively strong alkali (Table I) liberated in a few minutes about 65% of the radiosulfur-containing residues in a form soluble in trichloroacetic acid; continued treatment up to fifty-two hours liberated very little more radiosulfur-containing material. Treatment with alkali under milder conditions (Fig. 1) demonstrated that the rate of liberation of radiosulfur-containing residues from butyl-H*-treated insulin was a function of both the *p*H and the temperature. At *p*H 9.5 (30°) and 11 (0°, 30°), the radioactive material was liberated initially at a rapid rate which decreased to a fairly constant value.

TABLE I

EFFECT OF ALKALI ON BUTYL-H*-TREATED INSULIN

Time, hr.	Radiosulfur liberated, % 1.2 *N* NaOH at 0°	0.1 *N* NaOH at 27°
0.25	65	57
0.75	64	67
3.00	67	71
5.00	68	71
52.00	75	75

The nature of the radiosulfur-containing residues split from vesicant*-treated insulin by alkali was also investigated. When the trichloroacetic acid solutions of the alkali-labile vesicant* residues from the above experiments were extracted with petroleum ether, the major portion of the radiosulfur-containing material was found to be in the organic solvent. These experiments were not carried further, but in similar experiments on benzyl-H*-treated insulin it was shown that, after treatment of the protein preparation with alkali, the portion of the radioactive material which could be extracted into ether consisted almost entirely of benzyl β-hydroxyethyl sulfide*. Identification of the compound* was accomplished through application of the "washing-out" technique. A known amount of non-radioactive benzyl β-hydroxyethyl sulfide was added to the ether extract as a carrier and the solution was treated with α-naphthyl isocyanate. The resulting urethan derivative was purified by successive recrystallizations to constant radioactivity. From the amount of radioactivity in this purified derivative, the amount of benzyl β-hydroxyethyl sulfide* present in the ether extract could be calculated.

A considerable proportion (30–50%) of the radiosulfur-containing residues could be split in an ether-extractable form from vesicant*-treated insulin by heating at 150° in neutral solution. Here again evidence was obtained that the residues consisted almost entirely of the hydroxy compounds ($RS^*CH_2CH_2OH$, R = C_4H_9— or $C_6H_5CH_2$—).

With benzyl-H*-treated pepsin (Preparation 10[4]), 95% of the radiosulfur-containing material could be extracted into ether after autoclaving the pepsin preparation at 150° for five hours, while

(1) The work described in this paper was carried out under Contract OEMsr-144 between the Office of Scientific Research and Development and Cornell University Medical College and is described in Progress Reports to the National Defense Research Committee, December, 1942, to January, 1944.

(2) Present address: School of Biological Sciences, The University of Tennessee, Memphis, Tenn.

(3) Present address: Department of Chemistry, State College of Washington, Pullman, Wash.

(4) Wood, Rachele, Stevens, Carpenter and du Vigneaud, THIS JOURNAL, **70**, 2547 (1948).

(5) An asterisk (*) is used to indicate the presence of radiosulfur (S^{35} of 87-day half-life) in a compound.

(6) Ball, *et al.*, Informal Progress Report to NDRC Section B4C, August 19, 1942; Moritz, Henriques, *et al.*, Informal Progress Report to Division 9:5:1, NDRC, November 10, 1943.

(7) Northrop, *et al.*, Informal Progress Reports to NDRC Section B4C, June, 1942, to September, 1942; for the published results of this work, see Herriott, Anson and Northrop, *J. Gen. Physiol.*, **30**, 185 (1946).

(8) These values represent a statistical average of the number of vesicant residues per molecule in the particular preparation, and are not intended to indicate that every molecule contains this number of residues.

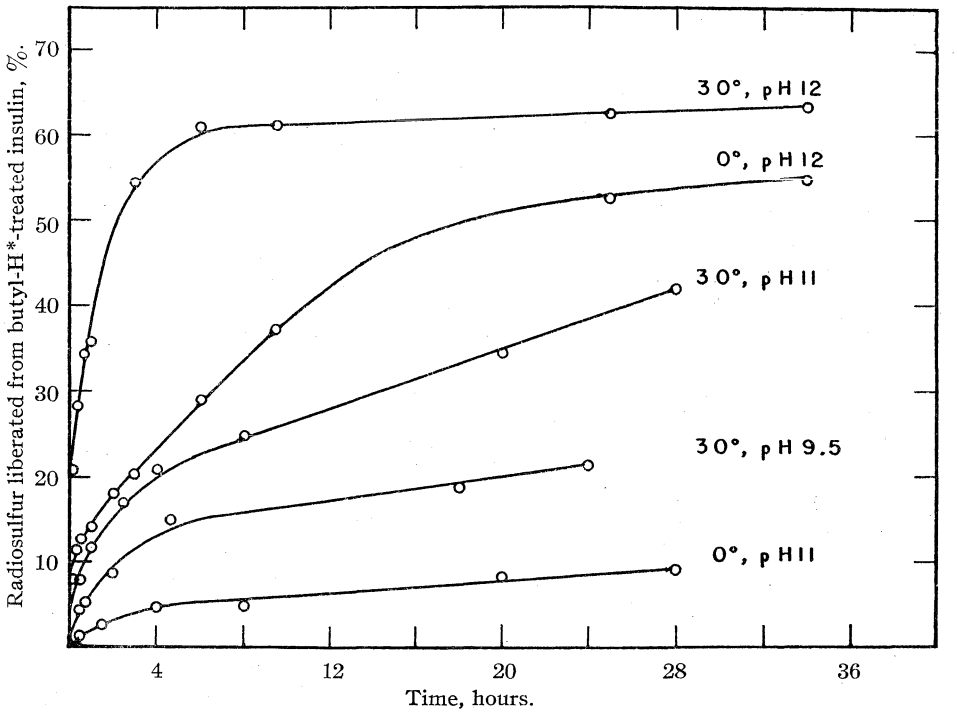


Fig. 1.—The liberation of radiosulfur-containing material, in a form not precipitated by trichloroacetic acid, from butyl-H*-treated insulin at various temperatures and *p*H levels.

70% of the vesicant* residues was liberated by treatment at *p*H 11 for three days.

We were interested in investigating vesicant*-treated TMV to determine what proportion, if any, of the vesicant residues was attached to the nucleic acid moiety. The nucleic acid which was separated from butyl-H*-treated TMV (Preparation 12[4]) was found to contain 5% of the radioactivity of the original TMV preparation. When it is recalled that TMV contains only 6% nucleic acid, it can be seen that the nucleic acid has "competed" quite effectively with the protein for the vesicant. In addition, it was noted that in the case of the nucleic acid moiety a smaller proportion of the vesicant* residues was attached through alkali-labile linkages than in the case of the protein moiety. Alkali treatment of the nucleic acid moiety liberated about 33% of the vesicant* residues, while similar treatment of the protein moiety resulted in the liberation of 86% of the vesicant* residues.

Experimental

Cleavage of Vesicant* Residues from Butyl-H*-treated Insulin Preparations by Treatment with Alkali.—In the general procedure employed, 1 volume of the appropriate buffer was mixed with 1 or in some cases 2 volumes of a dialyzed solution of a butyl-H*-treated insulin preparation.[4] The final concentration of insulin varied from 4 to 12 mg. per cc. The buffer and insulin solutions were brought to the same temperature before being mixed, and this temperature was maintained throughout the reaction. At noted time intervals after mixing, 1 cc. of the reaction mixture was withdrawn and delivered into 1 cc. of a 10% solution of trichloroacetic acid in 0.06 *N* hydrochloric acid. This served to stop the reaction and to precipitate the protein. (Control experiments had shown that treatment with trichloroacetic acid precipitated all the radiosulfur-containing material from the original vesicant*-treated insulin preparations.) The major portion of the protein precipitate was removed by centrifugation and the remainder by passing the supernatant liquid through a gravity micro filter. Analyses for radiosulfur[9] were carried out on the filtrate.

The rate of liberation of radiosulfur-containing material from Preparation 8[4] by treatment with alkali was determined under the following conditions: 1.2 *N* sodium hydroxide at 0° (Table I); 0.1 *N* sodium hydroxide at 27° (Table I); and 0.1 *M* borate buffer (*p*H 9.5) at 30° (Fig. 1). Similar studies were made on Preparation 9[4] in 0.1 *M* phosphate buffer (*p*H 12) at 0° and 30°, and in 0.1 *M* borate buffer (*p*H 11) at 0° and 30° (Fig. 1). The final *p*H of the reaction mixture was slightly lower than that of the buffer in some cases. The greatest decrease noted was that of 0.4 *p*H unit in the case of the *p*H 11 buffer.

Identification of Vesicant* Residues Liberated from Vesicant*-treated Insulin.—A solution of benzyl-H*-treated insulin (Preparation 4[4]; 18 mg.) in 1.8 cc. of 0.1 *N* sodium hydroxide was allowed to stand for seventy-two hours and was then extracted with ether. The ether layer contained 57% of the total radioactivity of the original benzyl-H*-treated insulin. To the ether extract were added 370 mg. of non-radioactive benzyl β-hydroxyethyl sulfide and 0.2 cc. of α-naphthyl isocyanate. The solution was evaporated to dryness and the residue was heated on a water-bath for five minutes. The resulting urethan derivative (β-(benzylmercapto)-ethyl 1-naphthalenecarbamate*) was recrystallized from hexane to constant radioactivity and melting point (86°).[10]

Anal. Calcd. for $C_{20}H_{19}NO_2S$: S, 9.50. Found: S, 9.96.

(9) The radioactivity estimations were carried out essentially by the method described by Henriques, Kistiakowsky, Margnetti and Schneider [*Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946)].

(10) All melting points are corrected capillary melting points.

Radioactivity determinations on the purified derivative indicated that at least 90% of the ether-extractable radioactive material split from benzyl-H*-treated insulin by alkali was benzyl β-hydroxyethyl sulfide*.

Preparation 4[4] of benzyl-H*-treated insulin was treated with alkali under milder conditions (borate buffer; *p*H 9) for twenty-four hours. After extraction with ether, 17% of the initial radioactivity was found in the ether layer, and 95% of the radioactivity in the ether layer was shown to be due to the presence of benzyl β-hydroxyethyl sulfide*.

An aqueous solution of butyl-H*-treated insulin (Preparation 6[4]; 10 mg.) was heated at *p*H 6.5 in a sealed tube at 150° for five hours. The resulting solution was extracted with ether. The ether extract contained 30% of the radioactivity of the original protein solution. Nonradioactive *n*-butyl β-hydroxyethyl sulfide (92 mg.) and α-naphthyl isocyanate (0.1 cc.) were added to the ether solution. The mixture was evaporated to a sirup, heated on a steam-bath for a few minutes and extracted with hot hexane. When the hexane solution was cooled, the β-(*n*-butylmercapto)-ethyl 1-naphthalenecarbamate* crystallized. It was recrystallized to constant radioactivity. The product had a melting point of 74.5–75.5°; there was no depression in melting point upon admixture with a sample of the urethan prepared from authentic *n*-butyl β-hydroxyethyl sulfide.

Anal. Calcd. for $C_{17}H_{21}NO_2S$: S, 10.57. Found: S, 11.05.

The results of the radioactivity determinations indicated that 85% of the ether-extractable radioactive material split from butyl-H*-treated insulin by heat was *n*-butyl β-hydroxyethyl sulfide*.

Heating of benzyl-H*-treated insulin (Preparation 4[4]) under the same conditions resulted in the liberation of 53% of the radiosulfur-containing material in an ether-extractable form. In this case, 70% of the radioactivity in the ether extract could be accounted for as benzyl β-hydroxyethyl sulfide*.

Separation of Protein and Nucleic Acid Moieties from Vesicant*-treated Tobacco Mosaic Virus.—The procedure of Cohen and Stanley[11] was used to cleave the virus into nucleic acid and protein. An aliquot of a solution of benzyl-H*-treated TMV (Preparation 11[4]), which contained 1.25 mg. of virus per cc., was adjusted to *p*H 5.5 and made 0.1 *M* with respect to sodium chloride by the addition of salt. The solution was boiled for two minutes and cooled overnight. The precipitate of protein was collected, washed and analyzed for radiosulfur. It contained 84% of the radioactivity of the original benzyl-H*-treated TMV preparation. Control experiments indicated that protein separated in this manner contained less than 0.25% nucleic acid.

A cleavage experiment was also carried out using butyl-H*-treated TMV (Preparation 12[4]). The protein moiety was separated as a precipitate by the heat treatment described above. The supernatant liquid was made acid to congo red paper and the nucleic acid was precipitated by the addition of an equal volume of ethanol. The protein precipitate contained approximately 75% of the radioactivity originally present in the butyl-H*-treated TMV preparation, while the nucleic acid contained approximately 5% of the radioactivity of the original TMV preparation. The nucleic acid was dissolved as the ammonium salt, the solution was acidified, and the nucleic acid was reprecipitated with ethanol. The specific radioactivity of the nucleic acid was unchanged by this process.

The reprecipitated nucleic acid was treated with 5% sodium hydroxide for two hours at 0°, the solution was acidified and the nucleic acid was again precipitated with ethanol. The alkali-treated nucleic acid had a specific radioactivity equivalent to two-thirds that of the original nucleic acid, thus indicating that 33% of the vesicant* residues was attached to the nucleic acid moiety through alkali-labile linkages. The protein moiety was treated with 5% sodium hydroxide for two hours at 0° and then precipitated with trichloroacetic acid. Analyses for radiosulfur on the precipitate and the supernatant liquid indicated that 86% of the vesicant* residues attached to the protein moiety had been liberated by the action of alkali.

Acknowledgment.—The authors wish to thank Dr. Julian R. Rachele who supervised the radioactivity measurements and Mr. Roscoe C. Funk, Jr., who carried out the microanalytical procedures. They would also like to take this opportunity to express their appreciation to Dr. Mary Elizabeth Wright for invaluable aid in the preparation of this manuscript.

Summary

A study was made of the cleavage by alkali of the linkages between protein and vesicant residues in preparations obtained by the treatment of insulin, pepsin and tobacco mosaic virus with benzyl β-chloroethyl sulfide (benzyl-H) or *n*-butyl β-chloroethyl sulfide (butyl-H) containing radiosulfur. The extent of liberation of vesicant residues varied with the different proteins; in all cases, a certain fraction of the vesicant residues was not cleaved by the alkali under the conditions studied.

A more detailed investigation of the action of alkali on vesicant-treated insulin showed that the rate of liberation of vesicant residues was dependent upon the temperature and *p*H of treatment. Heating of vesicant-treated insulin at 150° in neutral solution also resulted in the liberation of vesicant residues.

By application of the "washing-out" technique to the radiosulfur-containing material cleaved from butyl-H- or benzyl-H-treated insulin, the cleavage product was demonstrated to consist mainly of the corresponding alkyl β-hydroxyethyl sulfide.

Studies on vesicant-treated tobacco mosaic virus indicated that vesicant residues were attached to both the nucleic acid and protein moieties of the virus.

NEW YORK, N. Y. RECEIVED FEBRUARY 9, 1948

(11) Cohen and Stanley, *J. Biol. Chem.*, **144**, 589 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Studies on Acid Hydrolysates of Vesicant-treated Insulin[1]

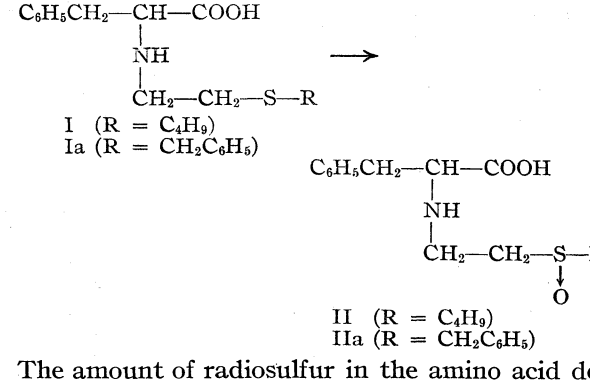
BY CARL M. STEVENS,[2] JOHN L. WOOD,[3] JULIAN R. RACHELE AND VINCENT DU VIGNEAUD

The treatment of insulin with benzyl β-chloroethyl sulfide (benzyl-H*) and *n*-butyl β-chloroethyl sulfide (butyl-H*) containing radiosulfur[4] has already been described.[5] Studies on these vesicant*-treated insulin preparations, containing an amount of vesicant* residues comparable to that found in tissues at the site of a burn, have shown that approximately 30% of the vesicant* residues was bound to the protein through linkages that were relatively stable to alkali.[6]

The experiments discussed in the present communication were designed to determine whether the vesicant* had reacted with the free amino groups in the insulin molecule. If such a reaction had occurred, the resultant linkages would be expected to be not only relatively stable to alkali but also stable to acid. The presence of such linkages in the protein might then be detected by the isolation of N-substituted vesicant* derivatives of amino acids from the acid hydrolysates of vesicant*-treated insulin.

A preparation of butyl-H*-treated insulin which contained approximately 5 vesicant* residues[7] per molecule of insulin was hydrolyzed with acid under various conditions. The "washing-out" technique was used to test for the presence of vesicant* derivatives of amino acids in the hydrolysates. The non-radioactive vesicant derivative of a given amino acid[8] was added to the hydrolysate to serve as a "carrier." The reference compound was then isolated from the mixture and examined for radiosulfur. The absence of radiosulfur in the isolated material indicated that the compound in question was not present in detectable amounts in the original hydrolysate. The presence of radiosulfur in the isolated material was not in itself regarded as sufficient evidence for the existence of the radioactive form of the reference compound in the hydrolysate. However, if the specific radioactivity of the isolated derivative reached a value which remained constant through successive recrystallizations and through chemical conversion of the compound to a suitable derivative, it was concluded that the hydrolysate contained the vesicant* derivative of the amino acid in question.

Since Jensen and Evans[9] had obtained evidence that the amino group of some of the phenylalanine moieties in insulin was chemically reactive,[10] we examined a sulfuric acid hydrolysate of butyl-H*-treated insulin for the presence of N-(β-butylmercapto)-ethyl-phenylalanine* (I). The non-radioactive form of I was dissolved in the hydrolysate and the N-(β-butylmercapto)-ethylphenylalanine was isolated from the mixture and recrystallized. It was found to contain radiosulfur; the content of radiosulfur did not change through several additional recrystallizations or through conversion to the sulfoxide (II).



The amount of radiosulfur in the amino acid derivative was equivalent to 5% of the total radiosulfur of the original butyl-H*-treated insulin. When the same preparation of butyl-H*-treated insulin was hydrolyzed with a mixture of hydrochloric and formic acids, the radiosulfur content of the isolated and purified compound I was equivalent to 3% of the total radiosulfur of the original protein preparation. This observed discrepancy in values from the two types of hydrolyses casts doubt upon the quantitative aspects of the results. Accordingly they are interpreted only in a qualitative manner to indicate the presence of N-(β-butylmercapto)-ethyl-phenylalanine* (I) in the acid hydrolysate of butyl-H*-treated insulin.

It is conceivable that the phenylalanine derivative I was formed during the hydrolysis procedure and was not actually present in the original vesicant*-treated insulin. If this were the case, one would expect to be able to detect in these insulin hydrolysates vesicant* derivatives of other amino acids known to be present in insulin. Accordingly,

(1) The work described in this paper was carried out under Contract OEMsr-144 between the Office of Scientific Research and Development and Cornell University Medical College, and is described in Progress Reports to the National Defense Research Committee, August, 1943, to January, 1944.

(2) Present address: Department of Chemistry, State College of Washington, Pullman, Wash.

(3) Present address: School of Biological Sciences, The University of Tennessee, Memphis, Tenn.

(4) An asterisk (*) indicates the presence of radiosulfur (S^{35} of 87-day half-life) in a compound.

(5) Wood, Rachele, Stevens, Carpenter and du Vigneaud, THIS JOURNAL, **70**, 2547 (1948).

(6) Carpenter, Wood, Stevens and du Vigneaud, *ibid.*, **70**, 2551 (1948).

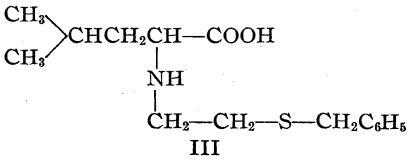
(7) This value represents a statistical average of the number of vesicant residues per molecule in the particular preparation, and is not intended to indicate that every molecule contains this number of residues.

(8) du Vigneaud, Stevens, McDuffie, Wood and McKennis, *ibid.*, **70**, 1620 (1948).

(9) Jensen and Evans, *J. Biol. Chem.*, **108**, 1 (1935).

(10) Sanger [*Biochem. J.*, **39**, 507 (1945)] has since reported data indicating that there are free amino groups of both phenylalanine and glycine in the insulin molecule.

a hydrolysate of benzyl-H*-treated insulin was tested for the presence of N-(β-benzylmercapto)-ethyl-leucine* (III) by the "washing-out" technique. Despite the fact that insulin contains approximately 30% leucine, none of the leucine derivative III could be detected in the hydrolysate.



III

The possibility of the formation of new vesicant* molecules and their reaction with released amino acids or protein fragments during the hydrolysis of the insulin preparation was also investigated. When mixtures of benzyl-H* and phenylalanine or N-benzoyl-phenylalanine were treated with acid under conditions used for protein hydrolysis, no detectable amount of N-(β-benzylmercapto)-ethyl-phenylalanine* (Ia) was formed. Moreover, after a mixture of insulin and butyl-H* had been hydrolyzed together, the radioactive phenylalanine derivative I could not be detected in the hydrolysate.

It was also conceivable that there might be some transfer of the radiosulfur onto the "carrier" compound from vesicant* decomposition products in the hydrolysate of vesicant*-treated insulin. A mixture of non-radioactive N-(β-benzylmercapto)-ethyl-DL-phenylalanine (Ia) and benzyl-H* was treated with acid under the conditions of protein hydrolysis. The phenylalanine derivative Ia was isolated from the mixture and was found to contain radiosulfur. However, the radiosulfur was lost upon conversion to the sulfoxide (IIa).

Because of the interruption of this work by more pressing wartime studies, the investigations were not carried further. However, the data obtained strongly indicate that when a vesicant* derivative of an amino acid is found in a hydrolysate of vesicant*-treated insulin, the derivative was originally present in the protein preparation before hydrolysis and was not formed by subsequent reactions during the hydrolysis procedure. On this basis it may be concluded that when insulin was treated with a minute amount of vesicant at *p*H 7.4, a fraction of the vesicant became attached to the amino group of phenylalanine.

Experimental

Detection of N-(β-Butylmercapto)-ethyl-phenylalanine* (I) in Hydrolysates of Butyl-H*-treated Insulin.—One hundred milligrams of crystalline insulin was dissolved in 5 cc. of *p*H 7.4 borate buffer and the solution was stirred gently for twenty-four hours with approximately 4 mg. of butyl-H*.[5] The solution was extracted three times with ether, and the protein was precipitated by the addition of 2 volumes of 0.3 *N* trichloroacetic acid, ground with several portions of dry ether and dried *in vacuo*. A determination of radiosulfur[11] on this material showed it to contain 5.3 vesicant* residues per molecule of insulin (on the basis of a molecular weight of 40,000 for insulin).

In one experiment, 9.5 mg. of the butyl-H*-treated insulin was hydrolyzed by heating it in a sealed tube with 1 cc. of concentrated sulfuric acid and 4 cc. of water at 95–105° for four days. The hydrolysate was diluted to 5.3 cc. To 2 cc. of the hydrolysate was added 54 mg. of N-(β-butylmercapto)-ethyl-DL-phenylalanine[8] (I) and enough acetic acid to give a clear solution. Addition of 50 cc. of water caused the derivative to separate from the solution. The material was recrystallized and then analysed for radiosulfur. On successive recrystallizations of the material the radiosulfur content remained constant and was equivalent to 5% of the total radiosulfur originally attached to the insulin. Repetition of the experiment using 3 cc. of the hydrolysate and 96 mg. of the phenylalanine derivative I gave a similar result. A sample of the isolated radiosulfur-containing derivative I was then converted to the sulfoxide II by the procedure described below. The radiosulfur content of the sulfoxide was equivalent to that of the starting derivative I.

A second sample of the same butyl-H-treated insulin preparation (5 mg.) was heated with 1 cc. of a 1:1 mixture of hydrochloric and formic acids at 100° for six days. The solution was evaporated to dryness to remove the acids. The residue was dissolved in 5 cc. of water and 100 mg. of the phenylalanine derivative I was added. The solution was made 30% in acetic acid and was heated to boiling. After centrifugation to remove a small amount of insoluble material, the supernatant liquid was diluted with water. The derivative was recovered and recrystallized from dilute acetic acid. The radiosulfur content of the derivative was equivalent to 3% of the original radiosulfur in the protein preparation. The value did not change after four recrystallizations.

Test for N-(β-Benzylmercapto)-ethyl-leucine* (III) in a Hydrolysate of Benzyl-H*-treated Insulin.—One hundred milligrams of crystalline insulin was treated with 4 mg. of benzyl-H*[5] and then precipitated with trichloroacetic acid under conditions similar to those described above for the preparation of butyl-H*-treated insulin. Analysis for radiosulfur showed that 4.1 vesicant* molecules had combined with 1 molecule of insulin.

A portion of this preparation (20.4 mg.) was allowed to stand in 2 cc. of 0.1 *N* sodium hydroxide for thirty-six hours. The vesicant* residues that had been cleaved by the alkali were extracted into ether. Analyses for radiosulfur on the aqueous layer indicated that 1.4 vesicant* residues were attached to 1 molecule of insulin through linkages stable to this alkali treatment. Ten cubic centimeters of a 1:1 mixture of hydrochloric and formic acids was added to the aqueous layer and the resulting solution was heated at 100–110° for fifty hours. Aliquots of this hydrolysate were used for the experiments below.

To 1 cc. of the hydrolysate were added 79.5 mg. of N-(β-benzylmercapto)-ethyl-DL-leucine[8] (III), 1 cc. of glacial acetic acid, 1 cc. of hydrochloric acid and 3 cc. of water. The resulting solution was heated on the steam-bath for one and one-half hours, and then concentrated to dryness. The residue was recrystallized twice from 33% aqueous acetic acid. The resulting product did not contain a detectable amount of radiosulfur. From the sensitivity of the measurement, it was calculated that the hydrolysate contained less than 0.5% of its radiosulfur in the form of the leucine derivative III.

On the other hand, when 82 mg. of the N-(β-benzylmercapto)-ethyl-DL-phenylalanine[8] (Ia) was added in place of the leucine derivative III and the mixture was treated in exactly the same manner as that described above for the leucine derivative III, the purified phenylalanine derivative Ia contained an amount of radiosulfur equivalent to approximately 5% of that originally present in the hydrolysate.

Preparation of Sulfoxides.—N-(β-Butylmercapto)-ethyl-DL-phenylalanine (I) (100 mg.) was dissolved in 5 cc. of glacial acetic acid. Then 0.4 cc. of a 3% solution of hydrogen peroxide in acetic acid was added and the flask was warmed on the water-bath for one hour. The

(11) The analyses for radiosulfur were carried out essentially by the method of Henriques, Kistiakowsky, Margnetti and Schneider [*Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946)].

solution was then concentrated to dryness. The resulting solid crystallized from 10 cc. of hot water in the form of needles, m. p. 208–210°.[12]

Anal. Calcd. for $C_{15}H_{23}NO_3S$: C, 60.6; H, 7.80. Found: C, 61.3; H, 7.97.

The sulfoxide of N-(β-benzylmercapto)-ethyl-DL-phenylalanine was prepared in exactly the same way except that the recrystallization in this case was from a large volume of aqueous acetone. The product melted at 219–220°.

Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.2; H, 6.39. Found: C, 64.9; H, 6.45.

Control Experiments. A.—In a series of experiments, DL-phenylalanine (68 mg.) was dissolved in 15 cc. of either 5 *N* hydrochloric acid, 30% (by weight) sulfuric acid, or a 1:1 mixture of 5 *N* hydrochloric acid and glacial acetic acid. Benzyl-H* (0.2–0.5 mg.) was added and the mixtures were heated at 100–110° for twelve to fifty-four hours. To each reaction mixture was added non-radioactive N-(β-benzylmercapto)-ethyl-DL-phenylalanine (Ia). The derivative Ia was isolated from the mixture, recrystallized, and analysed for radiosulfur. In no case did the isolated compound contain as much as 0.1% of the radiosulfur added as benzyl-H*.

B.—A mixture of N-benzoyl-DL-phenylalanine and benzyl-H* was heated in a 1:1 mixture of 5 *N* hydrochloric acid and glacial acetic acid. The phenylalanine derivative Ia was added, isolated from the mixture, and then analysed for radiosulfur. It contained less than 0.1% of the radiosulfur added as benzyl-H*.

C.—A mixture of 50 mg. of crystalline insulin and 1 mg. of butyl-H* was heated at 100° in 10 cc. of 5 *N* hydrochloric acid for forty-four hours. The mixture was diluted to 25 cc., and to an aliquot (2.5 cc.) were added 100 mg. of the phenylalanine derivative I and 2 cc. of 50% aqueous acetic acid. The derivative I was isolated from the mixture, purified, and analysed for radiosulfur. It contained no measurable amount of radiosulfur.

D.—The phenylalanine derivative Ia (0.53 g.) and benzyl-H* (0.38 g.) were heated under reflux for nineteen hours in 5 cc. of 5 *N* hydrochloric acid and 10 cc. of glacial acetic acid. When the reaction mixture was diluted with water to a volume of 100 cc. and cooled, the product separated. It was recrystallized from 45 cc. of 30% aqueous acetic acid to give 0.36 g. of product which contained 7.1% of the radiosulfur added to the reaction mixture as benzyl-H*.

A portion of this product (105 mg.) was converted to the sulfoxide by the procedure described above. After the sulfoxide had been recrystallized twice from hot water and once from 50% acetone, it had a melting point of 218–220°, and did not contain a detectable amount of radiosulfur.

(12) All melting points are corrected micro melting points.

Acknowledgment.—The authors wish to thank Mr. Roscoe C. Funk, Jr., for performing the microanalyses and for aid in the radioactivity measurements. They also wish to thank Dr. G. H. A. Clowes for supplying the crystalline insulin. They would also like to express their appreciation to Dr. Mary Elizabeth Wright for invaluable aid in the preparation of this manuscript.

Summary

Insulin which had been treated with a minute amount of *n*-butyl β-chloroethyl sulfide (butyl-H) containing radiosulfur was subjected to acid hydrolysis. By application of the "washing-out" technique, evidence was obtained for the presence of radiosulfur-containing N-(β-butylmercapto)-ethyl-phenylalanine in the hydrolysate. Various control experiments provided no evidence for the attachment of vesicant residues to the amino group of phenylalanine during the hydrolysis procedure. Therefore it was concluded that in the vesicant-treated insulin, a fraction of the vesicant had been attached to the free amino group of some of the phenylalanine moieties in the intact protein molecule.

NEW YORK, N. Y. RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Studies of the Effect of Mustard-type Vesicants on the Phenol Color Reaction of Proteins[1]

BY CARL M. STEVENS,[2] HERBERT MCKENNIS, JR.,[3] AND VINCENT DU VIGNEAUD

In the course of the wartime studies on the reaction of H (bis-(β-chloroethyl) sulfide) and H-type vesicants ($RSCH_2CH_2Cl$) with proteins, the action of Folin's phenol reagent[4] on vesicant-treated proteins was investigated. Herriott, Anson and Northrop[5] found that proteins which had been treated with vesicant at *p*H 6 gave less color with the phenol reagent at *p*H 8 than the corresponding untreated proteins. These investigators also noted that in most instances the chromogenic power of the vesicant-treated proteins toward the phenol reagent returned to normal after treatment with alkali for various lengths of time.

One possible interpretation of this phenomenon was that a chemical reaction had occurred between the vesicant and the tyrosine or tryptophan groups in the intact proteins, the subsequent action of the alkali being to cleave the linkages thus formed and to free the phenolic or indolyl groups for reaction with the phenol reagent.

(1) The work described in this paper was carried out under Contract OEMsr-144 between the Office of Scientific Research and Development and Cornell University Medical College and is described in Progress Reports to the National Defense Research Committee, December, 1942, to September, 1943.

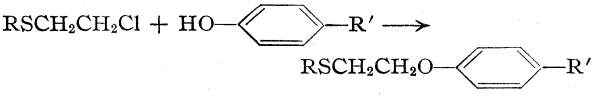
(2) Present address: Department of Chemistry, State College of Washington, Pullman, Wash.

(3) Present address: Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md.

(4) Olcott and Fraenkel-Conrat [*Chem. Rev.*, **41**, 151 (1947)] have presented a synoptic critique of the Folin phenol method, including references to the literature regarding its use in studies on proteins.

(5) Northrop, *et al.*, Informal Progress Reports to NDRC Section B4C (1942); for the published results of this work, see Herriott, Anson and Northrop, *J. Gen. Physiol.*, **30**, 185 (1946).

During the course of our wartime researches on the reaction of H-type vesicants with proteins,[6] we had prepared numerous derivatives of amino acids by their reaction with the one-handed vesicants, *n*-butyl β-chloroethyl sulfide (butyl-H) and benzyl β-chloroethyl sulfide (benzyl-H).[6b] In these studies we had found no evidence for a reaction of the vesicants with the indolyl group of tryptophan or with the phenolic group of tyrosine when the *p*H of the reaction mixture was in the range 6–8. However, in strongly basic solution the vesicants did react appreciably with the phenolic group of tyrosine to yield phenolic ethers of the type



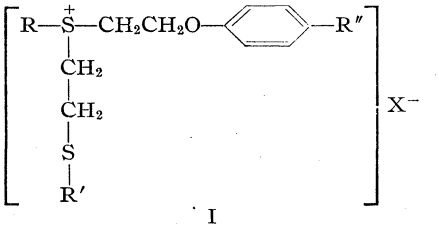
Phenolic ethers are in general very stable.[7] The stability of the O,N-disubstituted benzyl-H derivative of tyrosine to alkali was tested. After this tyrosine derivative was boiled for ten minutes in 0.5 *N* sodium hydroxide, the reaction mixture produced no color upon treatment with the phenol reagent. This result indicated that the linkage between the vesicant and the phenolic group of tyrosine was stable to alkali. In view of this stability, it was difficult to attribute the recovery of chromogenic power which followed alkali treatment of vesicant-treated proteins to cleavage of phenol-vesicant linkages.

In exploring other possible explanations for the behavior of the vesicant-treated proteins toward the phenol reagent, it occurred to us that the methods used by Miller[8] in studying the loss of chromogenic power toward the phenol reagent of tobacco mosaic virus upon treatment with various acylating agents might be applied to the study of the vesicant-treated proteins. Miller found that following treatment of the virus derivatives with sodium dodecyl sulfate in acid solution there was partial recovery of the chromogenic power toward the phenol reagent at *p*H 8 without any significant cleavage of acyl groups from the protein. He concluded that the amount of color produced by tobacco mosaic virus or its derivatives on treatment with the phenol reagent at *p*H 8 depended to a large extent on the degree of denaturation of the virus protein.

In the present publication, experiments are described which applied this concept to the vesicant-treated proteins. Pepsin and tobacco mosaic virus which had been treated with butyl-H gave a much smaller amount of color with the phenol reagent at *p*H 8 than did the untreated proteins. However, if the vesicant-treated or untreated proteins were first submitted to the action of Duponol C (sodium dodecyl sulfate) in acid solution and then subjected to the phenol reagent at *p*H 8, the same amount of color was produced from both the vesicant-treated and untreated proteins. Furthermore, it was possible to show that no significant amount of vesicant residues was liberated from vesicant-treated proteins by the action of Duponol C. These results demonstrate that the increase in the amount of phenol color from vesicant-treated proteins after the action of Duponol C is in all probability not due to the cleavage of vesicant residues from the tyrosine or tryptophan groups of the proteins. Thus it appears that the decreased chromogenic power of vesicant-treated proteins toward the phenol reagent at *p*H 8 is not due to the reaction of the vesicant with tyrosine or tryptophan groups in the protein molecule.[9]

This conclusion is in harmony with the results of the studies of Herriott, Anson and Northrop[5] on the nature of the alkali-labile linkages between vesicants and proteins. They were able to show that the number of free carboxyl groups lost from the protein upon treatment with H equalled, in several cases, the number of alkali-labile H residues bound to the vesicant-treated protein. Thus, not enough alkali-labile H residues were attached to the vesicant-treated protein to have combined both with the free carboxyl groups and the tyrosine phenolic groups of the protein.

Rydon,[10] in considering the decreased determinable phenolic groups of a vesicant-treated protein and the reversibility of this effect by alkali, suggested the possibility of the formation of sulfonium compounds[11] of the type I and their subsequent cleavage with release of tyrosine phenolic groups.



I

We have prepared such a compound (I, R = CH_3, R′ = C_4H_9, R″ = H) by the reaction of butyl-H with methyl β-phenoxyethyl sulfide and isolated it as the dilituarate. This compound gave almost no color with the phenol reagent at *p*H 8 either before or after treatment with Duponol C.

(6) (a) du Vigneaud and Stevens, THIS JOURNAL, **69**, 1808 (1947); (b) du Vigneaud, Stevens, McDuffie, Wood and McKennis, *ibid.*, **70**, 1620 (1948); (c) Wood, Rachele, Stevens, Carpenter and du Vigneaud, *ibid.*, **70**, 2547 (1948); (d) Carpenter, Wood, Stevens and du Vigneaud, *ibid.*, **70**, 2551 (1948); (e) Stevens, Wood, Rachele and du Vigneaud, *ibid.*, **70**, 2554 (1948).

(7) Lüttringhaus and Sääf, *Angew. Chem.*, **51**, 915 (1938).

(8) Miller, *J. Biol. Chem.*, **146**, 339, 345 (1942).

(9) In a report from this Laboratory (Informal Progress Report to NDRC Section B4C, December 21, 1942) to the coöperating groups it was suggested that ". . . a decrease in phenol color value of a protein resulting from treatment with [H] or related vesicants may not involve any reaction directly with the tyrosine or tryptophan groups, but may be due rather to an effect of substitution on the stability of the molecule to denaturation."

(10) Rydon, unpublished British Report, February 19, 1943.

(11) For studies involving other sulfonium compounds of the S-mustards, see: Stahmann, Fruton and Bergmann, *J. Org. Chem.*, **11**, 704 (1946); Stein and Moore, *ibid.*, **11**, 681 (1946).

TABLE I

PHENOL COLOR VALUES[a]

Sample	Method A (Duponol + acid)	Method B (no treatment)	Method C (Duponol)	Method D (acid)	Method E (alkali-20°)	Method F (alkali-50°)
Tobacco mosaic virus	132	70	78	70	125[p]	135[p]
Butyl-H-treated tobacco mosaic virus	132	30[p]	52[p]	30[p]	38[p]	113[p]
Pepsin	191	190	195		200	204
Butyl-H-treated pepsin	188	106	179		199	102[p]
Dimethyl β-phenoxyethyl sulfonium iodide[b]	24	20[p]			335	
Methyl β-phenoxyethyl β-butylmercaptoethyl sulfonium diliturate[b]	21	20[p]			293	

[a] The figures given are the actual colorimeter readings. Under these conditions, a sample containing 0.02 mg. of tyrosine gave a reading of 75. [b] One cubic centimeter of an 0.001 *M* aqueous solution was used. [p] Samples thus marked indicate that a precipitate formed. In order that colorimetric determinations could be made, the precipitates were removed as completely as possible by centrifugation. It seems possible that precipitation may in some cases involve loss of reactive groups.

Experimental

Stability of the Benzyl-H Derivative of Tyrosine.—O,N-Di-(β-benzylmercaptoethyl)-L-tyrosine[6b] gave a negative test with Folin's phenol reagent[12] in alkaline solution. After the derivative had been allowed to stand in 0.5 *N* sodium hydroxide for one week at room temperature, or had been heated in the alkali for ten minutes at 100°, it still gave no color with the phenol reagent.

Reaction of Tobacco Mosaic Virus with Butyl-H.—A dialyzed solution of tobacco mosaic virus[13] (7.5 cc.) containing 300 mg. of virus was added to 7.5 cc. of 0.5 *M* sodium bicarbonate. To this solution was added 0.4 cc. of butyl-H and the mixture was stirred gently for seven hours. The resulting solution was shaken with ether and the aqueous layer was dialyzed against running water. This solution was diluted with 3 volumes of water; 0.2-cc. aliquots were removed and diluted to 1 cc. for use in the phenol color determinations.

Reaction of Pepsin with Butyl-H.—To 10 cc. of an aqueous solution of pepsin (1.2 mg. N/cc.)[14] was added 0.2 cc. of butyl-H. The mixture was stirred for one and one-half hours, the *p*H being kept at approximately 7 by the dropwise addition of 1 cc. of 0.5 *M* sodium bicarbonate. The aqueous layer was decanted and stirred gently with an equal volume of ether. The aqueous layer was then dialyzed, diluted to 20 cc., and 0.2-cc. aliquots were removed and diluted to 1 cc. for use in the phenol color determinations.

Determination of "Phenol Color Values."—The modified procedures utilized for the phenol color determinations were developed from the methods of Miller,[8] who used sodium dodecyl sulfate as a denaturing agent.

Method A.—One cubic centimeter of the unknown (containing a suitable amount of the protein or other material) was placed in a test-tube containing 0.2 cc. of a 10% solution of Duponol C.[15] One-tenth cubic centimeter of 0.2 *N* hydrochloric acid was added and the mixture was allowed to stand for fifteen minutes. Then 0.1 cc. of 0.2 *N* sodium hydroxide was added, followed by 0.6 cc. of water, 1 cc. of diluted phenol reagent and 2 cc. of phosphate buffer. The buffer was prepared by adding 10 cc. of 10% sodium hydroxide to 90 cc. of 0.5 *M* disodium hydrogen phosphate. The phenol reagent[12] was diluted so that 1 cc. mixed with 2 cc. of phosphate buffer and 1 cc. of water had a *p*H of 7.7 at the end of thirty minutes.

Method B.—The same as Method A except that 0.2 cc. of water was added in place of the Duponol C solution, and 0.2 cc. of 0.1 *M* sodium chloride was added in place of the acid and alkali.

Method C.—The same as Method A except that 0.2 cc. of 0.1 *M* sodium chloride replaced the acid and alkali.

Method D.—The same as Method A except that 0.2 cc. of distilled water was used in place of the Duponol C solution.

Method E.—One cubic centimeter of the unknown was added to 0.1 cc. of 0.2 *N* sodium hydroxide, and the mixture was allowed to stand for fifteen minutes at 20°. Then 0.1 cc. of 0.2 *N* hydrochloric acid, 0.8 cc. of water, 1 cc. of diluted phenol reagent, and 2 cc. of phosphate buffer were added in this order.

Method F.—Identical with Method E except that the treatment with alkali was at 50° rather than 20°.

In all cases the color was allowed to develop for thirty minutes at room temperature and then was estimated in a Klett–Summerson photoelectric colorimeter using the No. 54 (green) filter. The data are recorded in Table I.

Stability of Protein-Vesicant Linkages to Sodium Dodecyl Sulfate.—If vesicant residues were split from butyl-H-treated proteins by the action of Duponol C, the expected hydrolysis product[5d] would be *n*-butyl β-hydroxyethyl sulfide ($C_4H_9SCH_2CH_2OH$) (IV). Preliminary experiments showed that this compound could be extracted almost quantitatively from water by an equal volume of ether; after removal of the ether the amount of IV could be determined by Northrop's procedure[16] for the determination of mustard gas and related compounds. Since, in the case of the vesicant-treated proteins, no other ether-soluble compounds were likely to be present in the system, this method was considered to be quite specific for vesicant residues.

Samples (2 cc.) of the solutions of the vesicant-treated and untreated pepsin were added to 0.4 cc. of 10% Duponol C and 0.2 cc. of 0.2 *N* hydrochloric acid, and the resulting solutions were allowed to stand for twenty minutes. At the end of this period the liberated butyl-H residues were determined. The solutions were shaken for one minute with 2 volumes of peroxide-free ether; 1-cc. aliquots of the ether solutions were added to 2 cc. of water, and the ether was evaporated *in vacuo* at room temperature. One cubic centimeter of 2 *M* sulfuric acid and 2 cc. of water were added, and the solution was titrated by the procedure described by Northrop.[16] The untreated pepsin gave a titration value which was equivalent to approximately 0.01 mg. of butyl-H residues per 7 mg. of protein; this value was used as a blank. The vesicant-treated pepsin gave a corrected titration value equivalent to less than 0.02 mg. of vesicant residues per 7 mg. of vesicant-treated pepsin. If the increase in the phenol color value of the vesicant-treated pepsin after treatment with Duponol C were due to cleavage of the linkages between tyrosine and vesicant residues, it would require the liberation of approximately 0.2 mg. of butyl-H residues per 7 mg. of protein, a value ten times that actually found.

(12) Folin and Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

(13) This sample of virus was kindly supplied by Dr. W. M. Stanley.

(14) The pepsin was kindly supplied by Dr. R. M. Herriott.

(15) This Duponol C (du Pont) was stated to be 92% sodium dodecyl sulfate and 8% sodium sulfate. The suspension obtained upon dissolving the Duponol C in water was allowed to settle, and the clear liquid was decanted for use.

(16) Northrop, Informal Progress Report to NDRC Section B4C, July 23, 1942; for published method, see Ref. 5.

Identical experiments with solutions of vesicant-treated and untreated tobacco mosaic virus gave similar results. After the action of Duponol C on the vesicant-treated virus, a value of 0.01 mg. of vesicant residues per 7 mg. of virus was obtained.

These results demonstrate that the restoration of phenol color value in vesicant-treated pepsin and tobacco mosaic virus by the action of Duponol C is not accompanied by any appreciable degree of cleavage of vesicant residues from the proteins.

Dimethyl β-Phenoxyethyl Sulfonium Iodide.—This salt was prepared by treatment of methyl β-phenoxyethyl sulfide with methyl iodide under the conditions described by Crane and Rydon.[10,17]

Methyl β-Phenoxyethyl β-Butylmercaptoethyl Sulfonium Dilituratе.—Methyl β-phenoxyethyl sulfide (1.68 g.) and butyl-H (3.0 g.) were dissolved in 20 cc. of 95% ethanol. After four days, the mixture was diluted with 3 volumes of water and centrifuged. The upper layer was removed and treated with 3 volumes of a saturated aqueous solution of dilituric acid (5-nitrobarbituric acid). The light yellow prisms which separated were collected and washed with cold methanol and cold acetone. The product (1.5 g.) was purified by one recrystallization from acetone and two recrystallizations from methanol. The recrystallizations were carried out at a maximum temperature of 25° on account of the instability of the compound. The purified sulfonium salt melted on the hot stage with decomposition and evolution of gas at 120–130°.

Anal. Calcd. for $C_{15}H_{25}OS_2 \cdot C_4H_2O_5N_3$: N, 9.18; S, 14.01. Found: N, 9.18; S, 13.85.

Phenol Color Reactions of the Sulfonium Compounds.—The phenol color reactions of the sulfonium compounds are summarized in Table I. A very small amount of color was produced by the action of the phenol reagent at *p*H 8 on the sulfonium compounds; the amount of color produced remained unchanged after preliminary treatment with Duponol C. However, considerable color was produced with the phenol reagent after the compounds had been treated with alkali.

Acknowledgment.—The authors would like to take this opportunity to express their appreciation to Dr. Mary Elizabeth Wright for invaluable aid in the preparation of this manuscript.

Summary

A study has been made of the decreased chromogenic power toward Folin's phenol reagent at *p*H 8 displayed by pepsin and tobacco mosaic virus which had been treated with *n*-butyl β-chloroethyl sulfide (butyl-H). After treatment with sodium dodecyl sulfate (Duponol C), the vesicant-treated and untreated proteins give the same amount of color with the phenol reagent. Moreover, no significant amount of vesicant residues is liberated by the action of Duponol C on the vesicant-treated proteins.

It is concluded that the increase in the amount of phenol color from these vesicant-treated proteins after the action of Duponol C is not due to the cleavage of vesicant residues from the tyrosine or tryptophan groups of the proteins. It is further concluded that the decreased chromogenic power of vesicant-treated proteins toward the phenol reagent at *p*H 8 is not due to reaction of the vesicant with the tyrosine or tryptophan groups in the proteins.

(17) Crane and Rydon, *J. Chem. Soc.*, 766 (1947).

NEW YORK, N. Y. RECEIVED FEBRUARY 9, 1948

[CONTRIBUTION NO. 78 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

The Reaction of α-Methylstyrenes with Thioglycolic Acid

BY CHEVES WALLING, DEXTER SEYMOUR AND KATHERINE P. WOLFSTIRN

Studies of the relative reactivities of meta- and para-substituted styrenes[1] and α-methylstyrenes[2] with free radicals derived from copolymerizing monomers have been useful in determining the nature of the "alternating effect" in copolymerization. An entirely similar approach may be made to the study of the nature of the attack of solvent radical on monomer in the chain transfer reaction.[3] This paper presents an investigation of the relative reactivities of six meta and para substituted α-methylstyrenes toward the radical $\cdot SCH_2COOH$ derived from thioglycolic acid.

Since the transfer constant for an α-methylstyrene with thioglycolic acid is very large,[4] when two α-methylstyrenes are heated with thioglycolic acid in the presence of a free-radical catalyst, virtually the only reaction by which styrenes will be consumed will be by reaction with the $\cdot SCH_2COOH$ radical (to give, eventually, β-phenylpropylmercaptoacetic acid), and the kinetic equations will be identical with those for the system of two α-methylstyrenes and maleic anhydride.[2] *I.e.*, $d[M_1]/d[M_2] = k_1[M_1]/k_2[M_2]$ where M_1 and M_2 represent the two styrenes and k_1 and k_2 the rate constants for their reaction with the mercaptide radical.[5] Calculations of relative reactivities including the determination of experimental errors were, accordingly, carried out as described previously.[2]

Experimental

Materials.—Thioglycolic acid was obtained by fractionating commercial material. Its physical constants were b. p. 79–80 (1 mm.), m. p. −17.5 to −15.5°. The α-

(1) Walling, Briggs, Wolfstirn and Mayo, THIS JOURNAL, **70**, 1537 (1948).

(2) Walling, Seymour and Wolfstirn, *ibid.*, **70**, 1544 (1948).

(3) Mayo, *ibid.*, **65**, 2324 (1943).

(4) The styrene radical reacts with ethyl thioglycolate 58 times as readily as with styrene. *Cf.* Gregg, Alderman and Mayo, *ibid.*, in press. Since α-methylstyrene shows relatively little tendency to polymerize with itself, its transfer constant with thioglycolic acid is presumably even larger.

(5) It is of interest that the equation describing chain transfer, in general, is a special case of the copolymerization equation in which the "monomer reactivity ratio" for the solvent is zero and the "transfer constant" is the reciprocal of the "monomer reactivity ratio" for the monomer considered.

methylstyrenes were portions of the same samples used in the maleic anhydride work.[2,6]

Technique.—Experiments were carried out using 0.1 mole of mixed styrenes, 0.05–0.1 mole of thioglycolic acid, and 0.14–0.18 millimole of benzoyl peroxide. Techniques of polymerization, isolation of unreacted monomers, and analysis were identical with those used with the maleic anhydride systems.[2] Results are listed in Table I.

TABLE I

REACTION OF MIXED SUBSTITUTED α-METHYLSTYRENES (M_1 AND M_2) WITH THIOGLYCOLIC ACID (S) AT 60°. (ALL QUANTITIES IN MILLIMOLES)

$[M_1]_0$	$[M_2]_0$	$[S]_0$	Time, hr.	$[M_1]$	$[M_2]$
α-Methylstyrene (M_1)–α,p-dimethylstyrene (M_2)					
49.2	49.8	49.8	31.8	39.7	33.9
32.3	65.7	98.4	31.8	17.74	13.01
64.9	32.6	98.5	31.8	37.7	8.05
α,p-Dimethylstyrene (M_1)–p-fluoro-α-methylstyrene (M_2)					
49.0	46.0	49.0	14.0	36.0	42.6
32.0	59.0	98.0	10.2	15.31	50.0
66.0	27.0	98.0	10.2	37.3	24.1
28.0	46.0	97.0	15.5	1.33	30.3
α,p-Dimethylstyrene (M_1)–p-bromo-α-methylstyrene					
49.0	49.0	49.7	6.75	30.4	36.6
33.0	63.0	99.3	6.75	9.80	47.4
66.0	32.0	98.5	6.75	40.3	23.9
α,p-Dimethylstyrene (M_1)–m-bromo-α-methylstyrene (M_2)					
33.0	66.0	98.0	6.75	11.50	49.3
65.0	38.0	98.0	8.5	33.50	24.0
25.8	42.6	49.0	15.5	8.63	24.8
α,p-Dimethylstyrene (M_1)–p-methoxy-α-methylstyrene (M_2)					
56.0	42.0	49.0	3.25	47.2	5.12
34.0	44.5	101	0.50	32.4	14.30
68.0	21.5	101	0.25	65.2	2.87

Discussion

Relative reactivities of the six α-methylstyrenes toward the mercaptide radical from thioglycolic acid are listed in Table II, together with relative reactivities toward the maleic anhydride type radical, included for comparison. In each case, reactivities have been referred to α-methylstyrene as unity even though the actual comparison was with α,p-dimethylstyrene. Experimental errors have been taken as the standard deviation of separate experiments and are somewhat greater than those reported for the maleic anhydride study.[2] While they could doubtless be reduced by further refinement of technique, accuracy is ample for the discussion which follows.

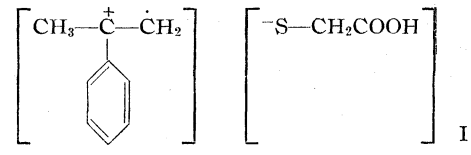
TABLE II

RELATIVE REACTIVITIES OF α-METHYLSTYRENE TOWARD THIOGLYCOLIC ACID AND MALEIC ANHYDRIDE-TYPE RADICALS

Substituent	Reactivities toward Thioglycolic acid radical	Maleic anhydride radical[2]
p-OCH_3	215 ± 100	18.5
p-CH_3	2.28 ± 0.54	1.72
None	1.00	1.00
p-F	0.51 ± 0.13	0.72
p-Br	0.90 ± 0.56	0.73
m-Br	0.96 ± 0.56	0.96

(6) Seymour and Wolfstirn, *ibid.*, **70**, 1177 (1948).

Copolymerization studies[1,2] have shown that the reactivity of styrene toward carbonyl conjugated radicals is increased by substituents in the order p-CH_3 < p-OCH_3 < $N(CH_3)_2$, and that the effect of each substituent increases with the tendency of the monomer from which the attacking radical was derived to alternate in copolymerization with styrene. Table II indicates a similar effect of substitution on reactivity toward the $\cdot SCH_2COOH$ radical, but even greater than that encountered toward maleic anhydride, the most powerfully "alternating" radical studied.[7] In the copolymerization experiments, the effect was suggested as arising from the presence of special (chiefly non-bonded) resonance forms in the transition state in which an electron had been donated from the styrene to the carbonyl-conjugated molecule. Similar structures such as (I) can be postulated here and stabilization anticipated both from the many structures available to the styrene carbonium-ion radical and the electronegativity of sulfur (the mercaptide ion is an even weaker base than the enolate ion postulated as stabilizing the transition state in the copolymerization reaction[1,2]).



I

Heretofore, discussions of radical addition reactions have been directed entirely toward a consideration of the resonance stability of the radicals produced.[8]

However, in view of our knowledge of copolymerization phenomena,[9] important contributions of polar resonance forms to the transition state in the attack of other free radicals on double bonds should probably be anticipated whenever the radical may gain stability by electron donation or acceptance. Thus, for example, in the attack of a bromine atom on a double bond, contributions involving the bromide ion should be important, and relative reactivities of olefins in the free radical chain additions of both bromine and hydrogen bromide should parallel those observed toward the radicals from mercaptans and carbonyl conju-

(7) In this paper no competitive experiments using p-dimethylamino-α-methylstyrene were attempted as it was presumed that the ratio of reactivities would be too great to measure.

(8) See, for example, Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944; Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

(9) For recent summaries, see Mayo, Lewis and Walling, THIS JOURNAL, **70**, 1529 (1948); *Trans. Faraday Soc.*, in press.

gated monomers, rather than an order based solely on radical stabilization.[9]

Summary

1. Relative reactivities of six α-methylstyrenes toward the $\cdot SCH_2COOH$ radical derived from thioglycolic acid have been determined.

2. Reactivities lie in the order p-OCH_3 > p-CH_3 > p-H $\gtrsim$ p-halogen and closely parallel those toward the maleic anhydride type radical observed in copolymerization. Results are interpreted in terms of contributions of non-bonded resonance forms to the transition state.

3. The possibility that contributions of polar (probably non-bonded) forms to the transition state may be important in a variety of free radical reactions is discussed.

PASSAIC, NEW JERSEY RECEIVED FEBRUARY 18, 1948

[CONTRIBUTION NO. 79 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

The Use of S^{35} in the Measurement of Transfer Constants

BY CHEVES WALLING

The use of radioactive tracer elements as a method of end-group analysis should provide an elegant means of following chain transfer with solvents in polymerizing systems. This paper describes the measurement of the transfer constant of n-butyl mercaptan containing S^{35} with styrene, methyl methacrylate, methyl acrylate and vinyl acetate. While the work was undertaken primarily to gain experience in the use of radioisotopes in polymer chemistry, the results, taken with recent measurements of the absolute rate of the chain-growth step in polymerization of vinyl acetate,[1] styrene,[2] and methyl methacrylate,[2] give further evidence of the importance of ionic forms in the transition state of free radical reactions.

Method.—The fundamental measurement employed in this work has been the comparison of the radioactivity of samples of polymer carried to different degrees of conversion in the presence of the same amount of S^{35}-containing mercaptan. Since the maximum penetration of the soft β-radiation from S^{35} in ordinary polymers is under 0.2 mm., for thicker films of identical area (as obtained by the technique described below) measured activity is proportional to the concentration of —SR groups in the polymer and independent of film thickness.[3] Mathematically, this may be expressed in the form

$$\frac{[S]_0 - [S]_1}{[M]_0 - [M]_1} \Big/ \frac{[S]_0 - [S]_2}{[M]_0 - [M]_2} = R \qquad (1)$$

where R is the ratio of measured activities of polymer from two experiments and [M] and [S] are concentrations of monomer and solvent (mercaptan), respectively, present initially (subscript zero) and at the end of the two experiments (subscripts one and two). Recalling that the usual integrated form of the transfer equation is given by

$$\log [S]/[S]_0 = C \log [M]/[M]_0 \qquad (2)$$

where C is the "transfer constant,"[4,5] (1) may be rewritten as

$$R \frac{1 - [M]_1/[M]_0}{1 - [M]_2/[M]_0} = \frac{1 - ([M]_1/[M_0])^C}{1 - ([M]_2/[M]_0)^C} \qquad (3)$$

Using data giving R and yields from two experiments, C may, in principle, be obtained by graphical solution of (3). However, in cases where the transfer constant of the system is greater than unity,[6] the calculation can be greatly simplified by choosing as one of the samples for the determination of R a polymer which has been carried to complete conversion. Here, equation (3) reduces to

$$C = \log (1 - R + R[M]/[M]_0)/\log [M]/[M_0] \qquad (4)$$

Since the only quantities needed for the determination of transfer constants by the tracer technique are yields and relative activities, measurements of absolute amounts of transfer agent or molecular weights are unnecessary. The chief requirement is the use of enough mercaptan for measurement of its activity yet little enough so that material is produced which can be handled as polymer (rather than the simple addition product). Some judgment is required, also, in the selection of the extent of reaction to which monomer–solvent mixtures are carried before polymer isolation, particularly when a high transfer constant is anticipated. In Fig. 1 is plotted the variation of R with per cent. reaction for various values of C, and it will be seen that the rapid consumption of active solvents with large transfer constants makes high conversion experiments useless for evaluating C. This phenomenon, of course, applies to *any* method of measuring transfer constants and a useful generalization is that experi-

(1) (a) Swain and Bartlett, *ibid.*, **68**, 2381 (1946); (b) Burnett and Melville, *Proc. Roy. Soc.* (*London*), **A189**, 456 (1947); (c) Bamford and Dewar, *ibid.*, **192A**, 309 (1948).

(2) Matheson, Bevilacqua, Aver and Hart, unpublished work from this laboratory.

(3) See, for example, Henriques, Kistiakowsky, Margnetti and Schneider, *Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946).

(4) Mayo, THIS JOURNAL, **65**, 2324 (1943).

(5) Walling, Seymour and Wolfstirn, *ibid.*, **70**, 2559 (1948).

(6) Even in cases where the transfer constant is less than unity (so that complete inclusion of the mercaptan in the polymer is not assured, even when polymerization is carried to completion) equation (4) may be employed by using a reference sample of a different monomer carried to complete reaction. Also, it is frequently advantageous (when the transfer constant differs widely from unity) to employ a reference sample prepared in the presence of a different (but known relative) mercaptan concentration.

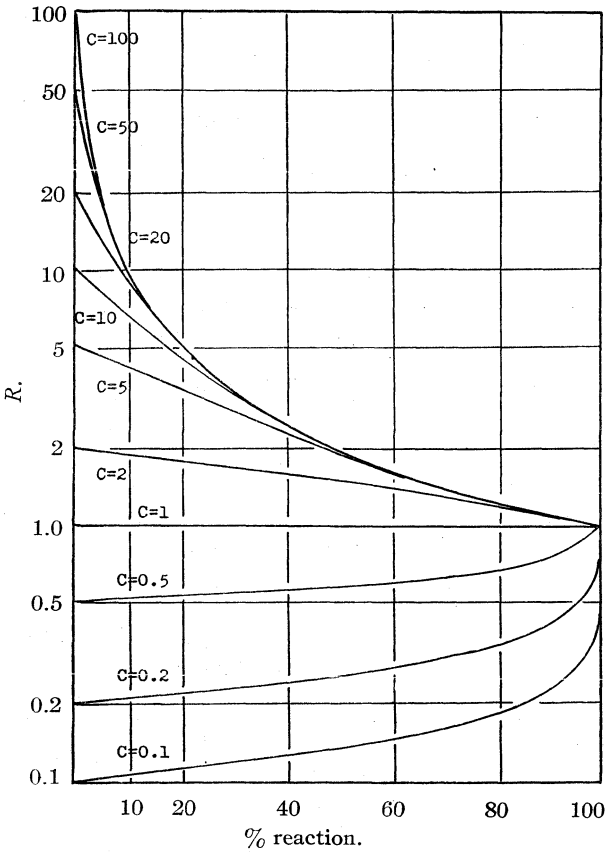


Fig. 1.—Variation of R, the relative activity of polymer samples, with % reaction for differing values of C, the transfer constant.

ments should not be carried to extents of reaction greater than the reciprocal of the anticipated transfer constant of the system. As a technique, the tracer method enjoys its greatest advantage in systems having a high transfer constant and in which the radioactive solvent is readily prepared, and should even compare favorably with titration of unreacted solvent[7,8] when the latter is possible. On the other hand in systems having low transfer constants (under $\sim$ 0.1) measurement by molecular weight determination is certainly to be preferred.[4,9]

Results and Discussion.—Experimental results and calculated transfer constants are listed in Table I. Experimental errors given are, in general, standard deviations of the separate experiments. For methacrylate, however, agreement seems fortuitously good and the error is taken as 5% of the measured value. Transfer constants for styrene and methyl methacrylate are in good agreement with the values reported for *n*-amyl mercaptan with these monomers (20 and 0.8, respectively) by W. V. Smith[7] and for other straight-chain mercaptans by Gregg, Alderman and Mayo.[8] Measurements at two temperatures with the methyl acrylate system indicate that the reaction of chain growth has a lower activation energy than chain transfer (by 600 calories), but, since it has a smaller PZ factor, proceeds more slowly. Although this is the reverse of the situation observed with styrene and mercaptans,[8] differences are too small to have much real significance.

TABLE I

TRANSFER CONSTANTS OF *n*-BUTYL MERCAPTAN SYSTEMS AT 60°

Yield, %	R	C	
	Styrene[a]		
8.25	9.58	18.1	22 ± 3
1.25	21.5	24.9	
10.62	8.70	23.0	
8.68	9.93	21.8	
	Methyl methacrylate[a]		
7.48	0.653	0.667	0.67 ± 0.03
16.8	.702	.675	
23.8	.706	.679	
39.5	.713	.658	
	Methyl acrylate[b]		
27.3	1.45	1.58	1.69 ± 0.17
43.0	1.51	1.86	
21.2	1.59	1.71	
6.6	1.49	1.52	1.53 ± 0.04[c]
16.2	1.51	1.58	
12.2	1.45	1.49	
	Vinyl acetate[d]		
3.80	23.5	58	48 ± 14
4.12	19.6	39	

[a] 1 ml. mercaptan solution to 10 ml. monomer. [b] 1 ml. mercaptan solution to 10 ml. monomer, 10 ml. ethyl acetate. [c] At 30°. [d] 1 ml. mercaptan solution to 40 ml. monomer.

In an earlier paper[5] it was shown that a factor analogous to the "alternating effect" in copolymerization may be important in determining reactivity of olefins in simple free radical addition reactions. The data of this paper, taken with recent measurements of the absolute rates of the chain-growth reaction in vinyl polymerizations,[1,2] gives strong indication that similar forms are important in the conjugate reaction of chain transfer in which the radical from the olefin attacks the solvent, breaking a single bond. In Table II are listed rate constants for chain growth, transfer constants, and rate constants for reaction with *n*-butyl mercaptan for polymerizing styrene, methyl methacrylate, and vinyl acetate. Although in the general series of reactivities obtained from copolymerization studies methacrylate lies between styrene and vinyl acetate,[10] toward *n*-butyl mercaptan it has the lowest reactivity. In copolymerization[11] and addition of

(7) Smith, *ibid.*, **68**, 2059 (1946).
(8) Gregg, Alderman and Mayo, *ibid.*, in press.
(9) Gregg and Mayo, *ibid.*, **70**, 2373 (1948).
(10) Mayo, Lewis and Walling, *ibid.*, **70**, 1529 (1948).
(11) Walling, Briggs, Wolfstirn and Mayo, *ibid.*, **70**, 1537 (1948).

TABLE II

RATE CONSTANT FOR CHAIN GROWTH (k_p) AND REACTION WITH *n*-BUTYL MERCAPTAN (k_t) FOR THREE MONOMERS

Monomer	k_p[a]	C	k_t
Styrene	207	22	4,550
Methyl methacrylate	367	0.67	246
Vinyl acetate	3700	48	178,000

[a] From Matheson, *et al.*,[2] in reasonable agreement with Bamford and Dewar[1c] (styrene) and Swain and Bartlett[1a] (vinyl acetate).

simple radicals to olefins[5] such anomalies have been explained on the basis of additional ionic forms in the transition state arising from electron transfer from radical to olefin or *vice versa*. In the present case, the analogous phenomenon would be contributions from non-bonded resonance structures such as

$$\underset{\text{I}}{R^+H\cdot{}^-S{-}R},\quad \underset{\text{II}}{R^+H{-}S^-\cdot R},\quad \underset{\text{III}}{R^+H{-}S\cdot{}^-R},\ \text{etc.}$$

if an electron were transferred from the attacking radical, and

$$\underset{\text{IV}}{R^-H\cdot S^+{-}R},\quad \underset{\text{V}}{R^-H^+\cdot S{-}R},\ \text{etc.}$$

if transfer were in the opposite direction. The heightened reactivity of styrene and vinyl acetate radicals (which are electron donors, rather than acceptors[10,11]) compared with methacrylate indicate that forms involving donation *to* the mercaptan are preferred, as might be expected from the relative electronegativities of sulfur and carbon. In short, in the case of a chain transfer reaction, as we have seen previously in copolymerization, certain structures increase the rates of both of two conjugate free radical reactions and give each more of an "ionic" character. Further confirmation is thus obtained for the suggestion made in previous papers from this laboratory that polar contributions to the transition state may be of importance in determining the effects of structure on reactivity in a great number of free radical reactions.

Experimental

Active *n*-Butyl Mercaptan.—This compound was prepared from active ZnS* by the sequence of reactions

$$ZnS^* \xrightarrow{HCl} H_2S^* \xrightarrow{H_2N{-}CN} NH_2CS^*NH_2 \xrightarrow{C_4H_9Br} C_4H_9{-}S^*{-}C(=NH_2^+)(NH_2)\ Br^- \xrightarrow[HCl]{NaOH} C_4H_9S^*H$$

Thiourea.—S^{35}, received originally as a trace constituent of potassium chloride supplied by the Clinton Laboratories of the Monsanto Chemical Company and subsequently diluted with inactive sulfur, was obtained from Dr. W. V. Smith of these Laboratories as a slurry of zinc sulfide in water containing some ammonia and zinc sulfate. Fifteen cc. of this suspension (containing approximately 2 mg. of sulfide sulfur and 30 microcuries of activity per cc.), 10 millimoles of inactive zinc sulfide, and 75 cc. of water were placed in a 500-cc. round-bottomed flask equipped with gas inlet tube, dropping funnel and reflux condenser. The gas inlet tube was attached to a hydrogen cylinder through a system consisting of a wash bottle containing sulfuric acid to act as a bubble counter and a side tube dipping into mercury serving as a safety valve. The exit tube of the condenser was connected to a Y-shaped reactor with a bottom limb of 10-cc. capacity containing a solution of 0.42 g. (10 millimoles) cyanamide (prepared from thiourea and mercuric oxide in ether, and purified by sublimation) in 5 cc. of 95% ethanol. The exit tube of the reactor led, in turn, to two wash-bottles in series each containing 10% zinc sulfate in 1:1 concd. ammonium hydroxide–water diluted five-fold.

After the entire system had been flushed with hydrogen, the reactor was cooled in liquid nitrogen and 60 cc. of 6 *N* hydrochloric acid added to the zinc sulfide slurry through the dropping funnel. Gradual heating of the slurry to boiling resulted in the smooth evolution of hydrogen sulfide and remaining traces were swept into the reactor by gently refluxing the mixture while slowly passing hydrogen through the system. Complete absorption was achieved, since no precipitate appeared in the wash-bottles. The reactor was next sealed off, warmed to −80°, shaken to insure solution of the hydrogen sulfide, and heated for twenty-four hours on the steam-bath. After cooling in liquid nitrogen, the reactor was opened and connected to a hydrogen source and two wash-bottles containing ammoniacal zinc sulfate. The reactor was then allowed to warm to room temperature, its contents refluxed for fifteen minutes, and finally swept slowly with hydrogen for an additional hour. Practically complete reaction was indicated since only a trace of precipitate appeared in the wash-bottles (pilot experiments in which the reactor was heated for three days at 60° gave a 67% yield of crystalline material), and, on cooling, beautiful needles of thiourea separated from the alcohol. For storage the thiourea was washed with additional alcohol into a 50-cc. volumetric flask.

Butyl Mercaptan.—In a 200-cc. flask equipped with dropping funnel and condenser which could be swiveled for either reflux or distillation was placed 10 cc. of the radioactive thiourea solution (*i. e.*, ~2 millimoles of thiourea), 0.76 g. (10 millimoles) of inactive thiourea and 3 cc. of butyl bromide, and the mixture refluxed for two and one-half hours under a hydrogen atmosphere. After cooling, the volatile material was distilled into a liquid nitrogen cooled trap under vacuum. With the condenser still in reflux position, hydrogen was readmitted and 10 cc. of *N* sodium hydroxide solution run in through the dropping funnel. The solution was then boiled for forty-five minutes to destroy the isothiourea. Next, the apparatus was arranged for distillation into a receiver consisting of a separatory funnel containing 10 cc. of chlorobenzene (chosen as an inert solvent with density greater than water), and 25 cc. of 0.5 *N* hydrochloric acid introduced through the dropping funnel.

Approximately half of the contents of the flask was now distilled, the receiver disconnected and shaken gently and the chlorobenzene layer run off into a small glass-stoppered bottle. The water layer was then extracted with the balance of 25 cc. of chlorobenzene and the chlorobenzene extracts all combined. Since experiments using inactive thiourea gave almost quantitative yields by this procedure, the chlorobenzene contained ~0.4 millimole mercaptan and 2 microcuries activity/cc. In the transfer experiments described in the next section the chlorobenzene solution was used directly without isolation or titration of the mercaptan since exact concentrations were not necessary. The absence of any contaminants which might interfere with the determination of transfer constants was shown by the good agreement of the constants for styrene and methyl methacrylate with those for *n*-amyl mercaptan and other normal mercaptans reported previously.

Transfer Experiments

Mixtures of freshly distilled monomer and mercaptan solution in mole ratios of 10 to 50:1, depending upon the expected transfer constant of the monomer, were placed in reaction tubes, degassed on a high vacuum line, sealed in absence of air, and heated for varying lengths of time in a 60° (or 30°) thermostat. In general, no catalyst

was added. With styrene the thermal polymerization proceeded at a convenient rate, while methyl acrylate and methacrylate apparently contained enough adventitious catalyst to effect reaction. Vinyl acetate samples were polymerized by irradiating with a mercury vapor lamp. Samples and heating times were chosen to yield 100–300 mg. of polymer. Methyl methacrylate and acrylate polymers were worked up by precipitating three times from ethyl acetate with petroleum ether in a 50-ml. centrifuge tube. The polymers were then redissolved in approximately 5 cc. of ethyl acetate and transferred in portions to tared aluminum dishes 26 mm. in diameter and 3 mm. deep and the solvent evaporated under an infrared lamp. The centrifuge tubes were washed with additional benzene and the dishes dried under the lamp overnight (approx. 8 in. from a 250-watt bulb was found to yield a smooth bubble-free film). Blank experiments showed that this treatment was adequate to remove all solvent, and yields were determined by weighing the dishes. Relative polymer activities were then measured by placing the dishes covered by a mask with a hole approximately 20 mm. in diameter under the thin mica window of a Radiation Counter Laboratories Mark I Model 2 Geiger–Mueller counter attached to an Instrument Development Laboratories Scaling Circuit. For the styrene and vinyl acetate experiments, the polymer isolation procedure was modified in that the partially polymerized samples were transferred to a large side-arm test-tube and unreacted monomer distilled off *in vacuo* at room temperature. The polymer was redissolved (in chlorobenzene or toluene, respectively) and the solvent again distilled off. This procedure was repeated twice more and the residual polymer transferred to an aluminum dish for counting.

Actually, for the determination of the relative activity, R, theoretical activities of completely polymerized samples were calculated from a completely polymerized polystyrene sample, correcting for differences in mercaptan concentration in the reaction mixtures and polymer densities. Thus the measured activity of the styrene sample was multiplied by 1.06/1.19 for comparison with methacrylate since, because polymethacrylate has a greater density, the measured β-radiation is coming from a thinner layer of the polymer surface. Counts of relative activities were always extended to several thousand impulses to avoid significant random variations and comparisons of any set of polymers with the standard were always carried out consecutively since background count and sensitivity of the instruments varied from day to day.

Acknowledgment.—The writer wishes to thank Dr. Herbert N. Campbell for aid in operating the electronic apparatus.

Summary

1. A convenient method for the synthesis of radioactive mercaptans from zinc sulfide containing S^{35} has been worked out.

2. The transfer constants of n-butyl mercaptan with styrene, methyl methacrylate, methyl acrylate and vinyl acetate have been measured using radioactive mercaptan, and the advantages of tracer methods in polymer chemistry are discussed.

3. The results are shown to indicate that ionic forms in the transition state, similar to those involved in radical addition reactions, may be important in determining reactivity in radical displacement reactions as well.

PASSAIC, NEW JERSEY RECEIVED FEBRUARY 18, 1948

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, A DIVISION OF SOCONY-VACUUM OIL CO., INC., RESEARCH AND DEVELOPMENT DEPARTMENT]

The Chlorination of Thiophene. II. Substitution Products; Physical Properties of the Chlorothiophenes; the Mechanism of the Reaction

BY HARRY L. COONRADT, HOWARD D. HARTOUGH AND GEORGE C. JOHNSON

The preceding paper[1] in this series reported the isolation and identification of chlorine addition products formed by the chlorination of thiophene. This paper describes the chlorine substitution products, reports their physical properties, and presents a mechanism for the reaction.

The substitution products formed by the chlorination of thiophene have been reported to be 2-chloro-,[2,3] 2,5-dichloro-,[2,3] 2,3,5-trichloro-,[2] and 2,3,4,5-tetrachlorothiophene.[2] In contrast with these results we have isolated and identified eight chlorine substitution products. The ninth and remaining possible substitution product, 3-chlorothiophene, was identified by infrared absorption spectrograms as present in small amounts.

The pure substitution products were separated by fractionation after the chlorine addition products had been removed. This prior removal or destruction of addition products generally was necessary because they decomposed into chlorothiophenes and hydrogen chloride during the course of the distillation and interfered with the fractionation. The method previously used[2,3,4] to destroy the addition products consisted of prolonged heating of the chlorination products with alcoholic potassium hydroxide. The preceding paper[1] described how addition products could be isolated from the reaction mixture. This had a pronounced effect on the ratio of the different substitution products.

The chlorine addition products were destroyed when chlorinated thiophene, like brominated thiophene,[5] was heated with solid sodium hydroxide or with potassium hydroxide. Calcium oxide was not effective. Other satisfactory procedures were prolonged pyrolysis or steam distillation of the reaction mixture from aqueous alkali or from a suspension of zinc or iron powder in water. Different

(1) Coonradt and Hartough, THIS JOURNAL, **70**, 1158 (1948).

(2) Steinkopf and Köhler, *Ann.*, **532**, 250 (1937).

(3) Weitz, *Ber.*, **17**, 792 (1884).

(4) Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopff, Dresden, 1941, p. 35.

(5) Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942).

yields and ratios of substitution products resulted when different methods of converting the addition products were used.

The monochlorosubstitution product produced by the chlorination of thiophene (I) at 50° was 99.7% 2-chlorothiophene (II) and 0.3% 3-chlorothiophene (III). The latter was indicated to be present in the higher boiling monochlorothiophene fractions by infrared absorption at wave lengths characteristic of *beta*-substituted thiophenes. Chlorination of II gave a dichlorothiophene fraction of 99% 2,5-dichlorothiophene (IV) and 1% 2,3-dichlorothiophene (V). The far faster rate of substitution of α-hydrogen as contrasted with β-hydrogen was indicated by these two reactions. Substitution reactions occur less readily after both α-hydrogens have been replaced.

While the only dichlorothiophene previously reported from chlorinated thiophene was 2,5-dichlorothiophene (IV), fractionation of the reaction mixture revealed the other three possible dichlorothiophenes: 2,3-dichlorothiophene (V), 2,4-dichlorothiophene (VI), and 3,4-dichlorothiophene (VII). Direct and random substitution of thiophene cannot be the source of all of these isomers in view of the strong directive influence of the sulfur atom shown above. Further, if direct substitution were the only source of VII the yield would be limited by the intermediate III; but a much higher proportion of VII than of III was obtained.

The origin of these isomers was clarified by the study of the dehydrohalogenation of the chlorine addition products.[1] Pyrolysis of the α-isomer of 2,3,4,5-tetrachlorothiolane (XI) gave a dichlorothiophene fraction composed of about 50% V, 50% VI with a trace of IV and no VII. The same compound with ethanolic potassium hydroxide formed a dichlorothiophene fraction composed of approximately 54% VII, 44% VI, 2% IV and no V. Since XI consisted of at least two geometrical isomers, the composition of XI would also influence the ratio of isomeric dichlorothiophenes. *The principal source of V, VI and VII is, therefore, the dehydrohalogenation of tetrachlorothiolane.*

The structure of 2,5-dichlorothiophene (IV) has been established.[4] The general method of preparation of 2,3-dichlorothiophene reported[2] in the literature was used to prepare the compound for comparison with V. The structure of VII was established when further chlorination yielded a trichlorothiophene fraction consisting of 2,3,4-trichlorothiophene (VIII), rather than 2,3,5-trichlorothiophene (IX) which would be the expected isomer from the other dichlorothiophenes. The properties of VII also were in satisfactory agreement with those previously reported for 3,4-dichlorothiophene prepared by a different procedure.[2] VI, by elimination, must be 2,4-dichlorothiophene.

The proof of structure of the two isomeric trichlorothiophenes, VIII and IX, was necessary since their properties differed from those previously reported. Steinkopf and Köhler stated[2] that two substances which they believed to be 2,3,4-trichlorothiophene and 2,3,5-trichlorothiophene possessed amazingly similar physical properties, formed numerous derivatives with similar melting points, and gave no depression of the melting point when corresponding derivatives of the two compounds were mixed. Our results indicate that the two materials they studied were probably samples of the same isomer, VIII, of slightly different degree of purity. The structure of the two isomers obtained in the present study was indicated when chlorination of IV yielded a trichlorothiophene fraction composed solely of IX, thus indicating IX was 2,3,5-trichlorothiophene and VIII, by elimination, was 2,3,4-trichlorothiophene. Further evidence was that VIII reacted and IX did not react with mercuric chloride. This reaction is characteristic of thiophene compounds with an α-hydrogen atom.[4,6]

Since the principal dichlorothiophene formed in the reaction of thiophene with chlorine was 2,5-dichlorothiophene, it might be expected that the principal trichlorothiophene formed would be 2,3,5-trichlorothiophene. However, when the chlorination was conducted near room temperature and the product treated with solid alkali, the trichlorothiophene fraction was 98% 2,3,4-trichlorothiophene and 2% IX. The principal source of VIII cannot be a substitution reaction because the direct formation of its intermediate, VII, under these conditions is indicated to be small. In view of the dehydrohalogenation of 2,2,3,4,5-pentachlorothiolane (XII) to 65% VIII and 35% IX with ethanolic potassium hydroxide and the effect of the method of dehydrohalogenation upon the ratio of isomers,[1] *the mechanism accounting for the formation of most of VIII is the conversion of the reaction intermediate II to XII and subsequent alkaline dehydrohalogenation of the latter.*

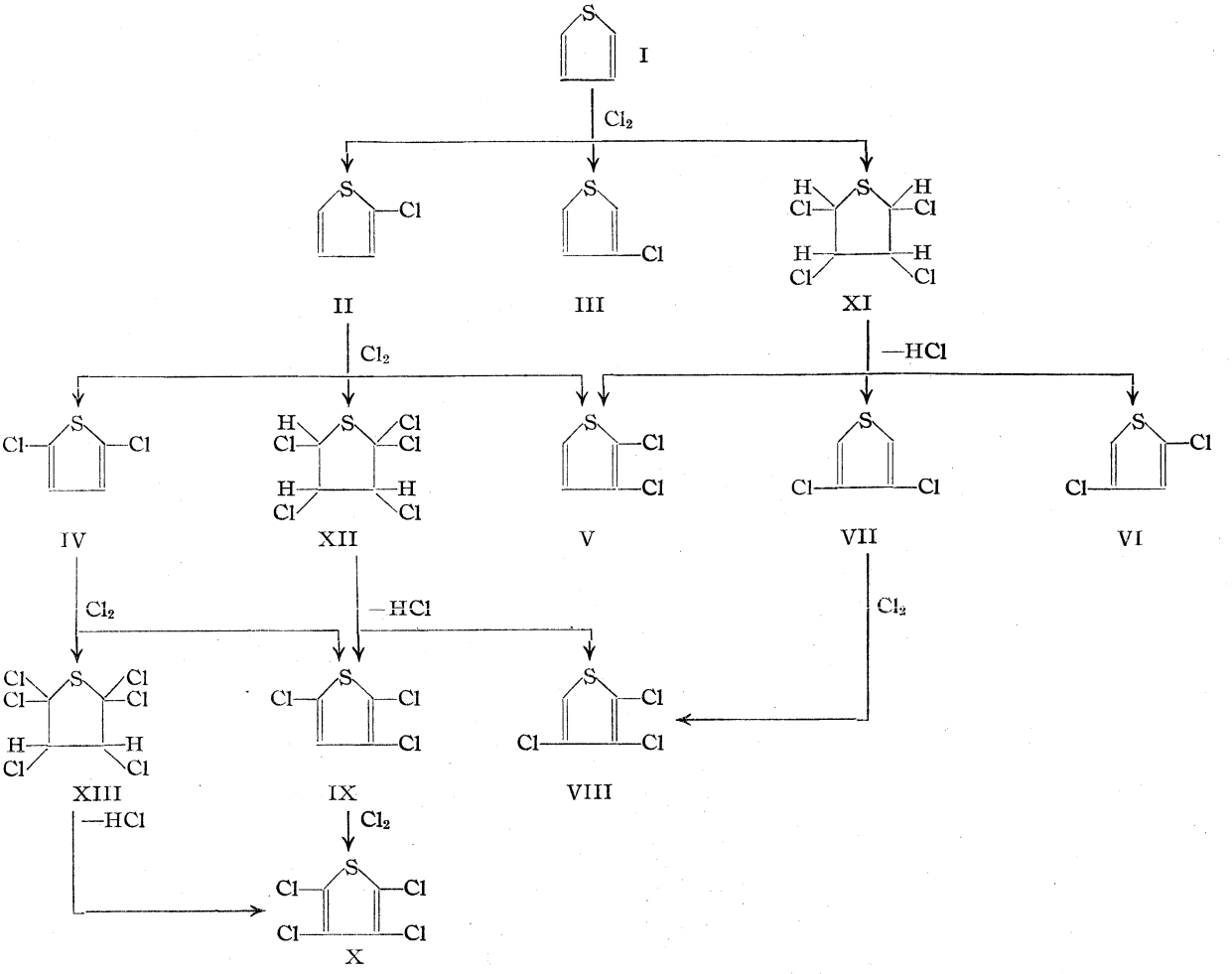
When chlorination at or near reflux temperatures and subsequent or concomitant pyrolysis was employed, however, the principal isomer obtained was IX, not VIII. This is in accord with the observation that pyrolysis of XII gave 92% IX and only 8% VIII. It was also found that the reaction intermediate IV could be converted to IX, preferably at elevated temperatures. *The source of IX in the chlorination of thiophene is thus both the dehydrohalogenation of XII and the direct substitution of IV.* Both of these reactions are favored by elevated temperatures.

The statement has been made[2,4] that trichlorothiophene was the most difficult of the substitution products to prepare since it was readily chlorinated further to 2,3,4,5-tetrachlorothiophene (X). However, it was found that IX was substituted by chlorine only with difficulty. For example, after a ten mole excess of chlorine was passed through

(6) Volhard, *Ann.*, **267**, 172 (1892).

TABLE I

ESTABLISHED CHLORINATION REACTIONS OF THIOPHENE



IX at 180°, 42% of IX was recovered unchanged. Furthermore, the other trichlorothiophene, VIII, arises mainly in the alkaline dehydrohalogenation reaction and forms only in minor amounts in the chlorination reaction itself.

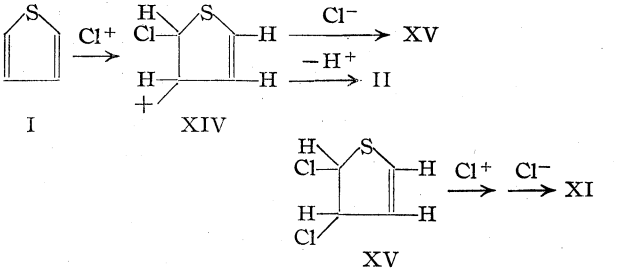
The yield and ratio of tetrachlorothiophene (X) and 2,2,3,4,5,5-hexachlorothiolane (XIII) is dependent upon the extent of chlorination and dehydrohalogenation. Extensive chlorination with concomitant pyrolysis gave a product containing 80% X and 14% IX. Extensive chlorination at lower temperatures, however, yielded primarily XIII. In the latter case substitution of IV was negligible and addition of chlorine to form XIII occurred. Dehydrohalogenation of XIII by pyrolysis or alkali yielded X.

A compound isolated in small yields from the still residues of products obtained by the action of excess chlorine on thiophene at elevated temperatures was identified as hexachlorodithienyl.[7]

(7) Eberhard, *Ber.*, **28**, 2385, 3302 (1895), reported the action of sulfuryl chloride on 2,2′-dithienyl gave 3,4,5,3′,4′,5′-hexachloro-2,2′-dithienyl, orange crystals, m. p. 189.5–190° (cor.).

Table I outlines the established parts of the course of the reaction of chlorine with thiophene in the absence of a catalyst.

Mechanisms have been postulated for the chlorination, alkaline dehydrohalogenation and pyrolysis. I adds first a positive chlorine ion to form a positive chlorothiolene ion (XIV) which either loses a positive hydrogen ion to give II or adds a negative chlorine ion to give a dichlorothiolene (XV) which then adds chlorine to form XI.



Similar ionic reactions account for the conversion of II to both IV and XII, and the conversion of

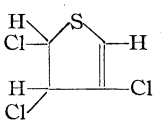
TABLE II

THE PHYSICAL PROPERTIES OF EIGHT CHLOROTHIOPHENES

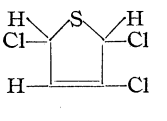
Cpd.	Chloro-thio-phenes	B. p., °C.	F. p., °C.	n^{20}_D	n^{20}_e	n^{20}_g	n^{20}_D	d^{20}_4	d^{30}_4	Vis-cos-ity, c. p. 30°	Surf. tens., dynes/cm., 30°	R^{20}_D	R^{30}_D	Mol. vol., ml. at 20°	Mol. vol., ml. at 30°
II	2-[a]	128.32	−71.91	1.5487	1.5530	1.5726	1.5430	1.2863	1.2737	0.803	34	29.32	29.34	92.19	93.10
IV	2,5-[a]	162.08	−40.46[b]	1.5626	1.5672	1.5880	1.5572	1.4422	1.4288	0.997	35.5	34.44	34.49	106.11	107.14
VI	2,4-[c]	167.58	−37.2	1.5660	....	....	....	1.4553	....	1.091	..	34.30	...	105.15	....
V	2,3-[a]	172.70	−37.3	1.5651	....	....	....	1.4605	....	...	..	34.14	...	104.78	....
VII	3,4-[a]	182.01	−0.54	1.5762	....	....	....	1.4867	....	1.465	..	34.07	...	102.93	....
IX	2,3,5-[d]	198.66	−16.06	1.5791	1.5837	1.6046	1.5741	1.5856	1.5724	1.464	38	39.30	39.35	118.24	119.23
VIII	2,3,4-[a]	209.60	−2.76	1.5861	....	....	....	1.6125	....	2.181	..	39.02	...	116.27	....
X	2,3,4,5-[a,e]	233.39	+29.09[f]	....	....	....	1.5915	....	1.7036	3.318	40	...	44.05	....	130.27

[a] Infrared analysis did not disclose the presence of any impurities in the specimen. [b] A second form freezes at −50.92°. [c] The properties are for a material containing 96 mole % 2,4-dichlorothiophene, 3% 2,5-dichlorothiophene and 1% 3,4-dichlorothiophene. [d] Infrared analysis showed a trace of 3,4-dichlorothiophene as impurity. *Anal.* Calcd. for C_4HCl_3S: Cl, 56.8; S, 17.0. Found: Cl, 57.0; S, 17.3. [e] *Anal.* Calcd. for C_4Cl_4S: Cl, 63.9; S, 14.5. Found: Cl, 64.2; S, 14.8. [f] Refs. 2 and 3 list m. p. 36°; ref. 14 lists 38°. These products were obtained by chlorination of 2,5-dibromothiophene. Repetition of this method using a large excess of chlorine gave a product, m. p. 51–52.5°, containing Br, 39.7%, Cl, 30.6%. The X froze sharply with a time–temperature cooling curve typical of highly purified materials.

IV to both IX and XIII. Ethanolic potassium hydroxide acts on the α-isomer of XI to effect the initial preferential elimination of the more negative α-chlorine ion and a β-hydrogen ion. This leads to the intermediate 3,4,5-trichloro-2-thiolene (XVI). XVI then loses α-chlorine and β-



XVI



XVII

hydrogen to give VII, or now since the chlorine on carbon atom four is allylic and more easily expelled, XVI also dehydrohalogenates in a different manner to give the other principal product VI. The mechanism of the pyrolytic dehydrohalogenation of the α-isomer of XI must differ from that of the ethanolic potassium hydroxide dehydrohalogenation in view of the greatly different products. The formation of the two isomers is consistent with the formation of 2,3,5-trichloro-3-thiolene (XVII) as an intermediate which dehydrohalogenates to V and VI.

Physical Properties.—The physical property data which have been obtained are collected in Table II. The methods used for the measurements of the physical properties have been described previously.[8] Some of the densities were determined with a 2-ml. pycnometer of the type described by Lipkin and co-workers[9] rather than by the suspended sinker method used before. The boiling points determined by measurements made relative to the freezing point of water and to the freezing point of tin were extensively checked by direct intercomparisons.

The chlorothiophenes dissolved at 25° in equal volume mixtures with *n*-heptane, diisobutene, cyclohexane, decalin, tetralin, benzene, thiophene, acetic acid, nitromethane, carbon tetrachloride, carbon disulfide, acetone, ethyl acetate, dioxane and *n*-propanol. The chlorothiophenes were not miscible with water, ethylene glycol or propylene glycol at 25°. The critical solubility temperatures of the chlorothiophenes lay close to 25° and varied from compound to compound in glycerol-α-mono-chlorohydrin, diethylene glycol, triethylene glycol, methanol and ethanol.

The chlorothiophenes changed from colorless to light yellow when stored for several months in partially filled bottles in diffuse light at room temperature. On boiling in air for a few hours a similar color change was noted. In both cases the change in refractive index did not exceed 0.0001.

Calculations from Table II show that substitution of a chlorine atom for a hydrogen atom at an α-position increases the molecular volume more than substitution at a β-position. This observation, together with arithmetic estimations, indicated that the molecular volume of 3-chlorothiophene at 20° is 91.73 ml. and d^{20}_4 1.292. Interpolations of the present data indicate that the previously reported values[2] are substantially correct for the b.p., 136–137°, and for the refractive index, n^{20}_D 1.5543 (calcd. from 22°).

It is believed that the values determined in this study supersede previously published determinations.[2,3,10–14] Most of the earlier preparations were made with very small quantities of materials with attendant difficulty.

Experimental

Chlorinations.—The conditions and results of nine chlorinations are given in Table III. Identification of products was made by the boiling points and by infrared absorption spectra.

Specimens for Physical Property Measurements.—The 2-chlorothiophene and 2,5-dichlorothiophene were first redistilled in a 10-theoretical plate column and then in a 90–95 theoretical plate column at a reflux ratio above 120:1. The 2,3-dichlorothiophene was made by chlorin-

(8) Johnson, THIS JOURNAL, **69**, 150 (1947).

(9) Lipkin, Davison, Harvey and Kurtz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 56 (1944).

(10) Rosenberg, *Ber.*, **19**, 650 (1886).

(11) Steinkopf and Otto, *Ann.*, **424**, 61 (1921).

(12) Auwers and Kohlhaas, *J. prakt. Chem.*, [2] **108**, 321 (1924).

(13) Bonino and Manzoni-Ansidei, *Z. physik. Chem.*, **B25**, 327 (1934).

(14) Perkin and Haddock, *J. Chem. Soc.*, 541 (1938).

TABLE III

CHLORINATION OF THIOPHENE AND CHLOROTHIOPHENES

Reactant	Chlorination: Moles Cl_2: moles reactant	Chlorination: Temp., °C.	Chlorination: Time, hr.	Dehydrohalogenation: Method	Dehydrohalogenation: Temp., °C.	Dehydrohalogenation: Time, hr.	Composition of product, g.
I	25:25	50	3	KOH, NaOH	80–100	36	II, 1088[a]; IV, 519; V, 63; VI, 64; VII, 113; trichlorothiophene,[b] 123
I	3.2:3.2	25–35	4	10% Na_2CO_3[c]	100	..	I, 52; II, 181; IV, 64; residue, 19
I	3.2:3.2	25–35	4	Zn[d]	100	..	I, 62; II, 182; IV, 66; residue, 10
II[e]	6.8:6.8	50	1.5	KOH, NaOH	125	22	II, 201; IV, 507; V, 5; VIII, 116; IX, 65
I	140:35	45–190[g]	14.5	Pyrolysis	190	2.5	IV, 1227; other dichlorothiophenes, 316; VIII, 496; IX, 2283; X, 1503; residue, 88
I	75:10	40–205[g]	5.5	10% Na_2CO_3[h]	120	3	IX, 275; b. p. 95–118° (26 mm.), 11; X, 1548; b. p. 125–135° (26 mm.), 79; residue,[f] 32
IV[e]	1:1	150	2	KOH, NaOH	125	24	IV, 55; VIII, 0; IX, 8; X, 43
VII	0.1:0.15	90–100	3	KOH, NaOH	125	24	VII, 64%; VIII, 27%; X, 9%
IX	5.3:0.53	180	2	Pyrolysis	180	2	IX, 42; X, 47; residue, 8

[a] Contained 99.7% II, 0.3% III concentrated in higher boiling monochlorothiophene fractions in 90–95 theoretical plate distillation. [b] VIII, 98%; IX, 2%. [c] 28 g. of solid α-XI first separated by cooling in Dry Ice–acetone bath and was filtered off. [d] 0.4 g. lead sulfide was formed in a lead acetate trap. [e] Purified by fractionation in a 90–95 theoretical plate column. [f] Residue washed with petroleum ether, recrystallized several times from chloroform, to give yellow-white hexachlorodithienyl, m. p. 188.5–90°. *Anal.* Calcd. for $C_8Cl_6S_2$: Cl, 57.0; S, 17.2; mol. wt., 372.9. Found: Cl, 56.9; S, 17.3; mol. wt. 350 (ebullioscopic method). [g] Mixture kept below reflux temperature until about one-third of chlorine added, then kept at reflux temperature. [h] Pyrolysis occurs at chlorination temperature; 300 ml. of sodium carbonate was used.

ating 2-thiophenecarboxylic acid to 4,5-dichloro-2-thiophenecarboxylic acid and then decarboxylating the latter by the method of Steinkopf and Köhler.[2] The crude product, containing ether, acetic acid and 2,3-dichlorothiophene was distilled in a 28-theoretical plate column. The 2,3-dichlorothiophene fraction was shaken with sodium hydroxide solution to remove possible traces of acetic acid. The 2,4-dichlorothiophene and 3,4-dichlorothiophene were prepared from *alpha*-2,3,4,5-tetrachlorothiolane by dehydrohalogenation with ethanolic potassium hydroxide. After a preliminary fractionation in a 28-theoretical plate column at a 30–35:1 reflux ratio, each was redistilled in the same column. The 2,3,4-trichlorothiophene was redistilled in a 28-theoretical plate column. The 2,3,5-trichlorothiophene and 2,3,4,5-tetrachlorothiophene were each redistilled in a 25-theoretical plate column.

Acknowledgment.—The authors are grateful to Dr. D. E. Badertscher and Dr. C. C. Price for their advice and interest in this problem, to Mr. J. G. Ehlers for infared absorption spectra analyses, and to Miss Emily Burns for assistance in the laboratory work.

Summary

The substitution products formed by the reaction of chlorine with thiophene were investigated. Eight of the nine possible isomers were isolated. The remaining isomer, 3-chlorothiophene, was identified by infrared absorption spectrograms as present in small amounts.

Pronounced orientation during substitution in the thiophene nucleus was indicated by a monochlorothiophene fraction consisting of 99.7% 2-chlorothiophene and 0.3% 3-chlorothiophene. Similarly, chlorination of 2-chlorothiophene yielded a dichlorothiophene fraction composed of 99% 2,5-dichlorothiophene, 1% 2,3-dichlorothiophene and no 2,4-dichlorothiophene.

2,3-, 2,4- and 3,4-dichlorothiophenes were formed largely by the dehydrohalogenation of 2,3,4,5-tetrachlorothiolane and not by substitution. 2,5-Dichlorothiophene was formed by substitution.

2,3,4-Trichlorothiophene was prepared by low temperature chlorination and was formed largely after the chlorination by the action of alkali on 2,2,3,4,5-pentachlorothiolane. 2,3,5-Trichlorothiophene was prepared by high temperature chlorination and was formed both by the substitution of 2,5-dichlorothiophene and by the pyrolysis of pentachlorothiolane.

Tetrachlorothiophene was formed both by substitution of 2,3,5-trichlorothiophene and by pyrolytic or alkaline dehydrohalogenation of 2,2,3,4,-5,5-hexachlorothiolane.

Physical properties were determined on eight chlorothiophenes.

RECEIVED[15] APRIL 20, 1948

(15) Original manuscript received July 28, 1947.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF SARAH LAWRENCE COLLEGE]

The Reversible Dissociation of *t*-Butyl Esters. Structural Effects and Reactions Mechanism

BY ROLF ALTSCHUL

The conversions of three carboxylic acids to the corresponding *t*-butyl esters by means of *i*-butene have been described in a previous paper.[1] Quantitative measurements defined this esterification as a reversible reaction, with its drive to the equilibrium state supported by catalytic amounts of sulfuric acid under anhydrous conditions in dioxane.

$$RCOOC(CH_3)_3 \underset{k_1}{\overset{k_2}{\rightleftharpoons}} RCOOH + CH_2{=}C(CH_3)_2 \quad (1)$$

The dissociation equilibrium constants K_d represent the relationship between the three components.

$$K_d = (\text{acid})(\text{isobutene})/(\text{ester}) \quad (2)$$

$$K_d = k_1/k_2 \quad (3)$$

The quantitative measurements in this present publication have been carried out on a larger series of esters to supplement the original exploratory data. This study has the dual objective commonly served by kinetics: its results permit a more accurate interpretation of the reaction mechanism, and they afford additional insight into the general problem of structure and reactivity in a manner to reveal a rigid law for some cases while facilitating at least semiquantitative predictions for all. In the outline below the experimental results will be tabulated first; their significance to the relationship between structure and reactivity will be discussed next, along with some conclusions about the elementary reaction steps.

Results

In Table I the K_d constants for seven esters are summarized. They were determined, as previously, by acidimetric and bromometric titrations of samples at equilibrium.[1] The pK_a values in the table refer to the known parent acid ionization constants.[2] These quantities as well as the k_2 data in the third column are included here for the subsequent discussion. The specific esterification rates (k_2) were computed by means of equation 3 from the experimental results for K_d and for k_1, the latter being summarized in Table II below. The K_d values above were substantiated later by readings on the equilibrated kinetic runs.

TABLE I

CONSTANTS FOR THE ESTERIFICATION OF CARBOXYLIC ACIDS WITH *i*-BUTENE IN DIOXANE CONTAINING 0.835 M./L. OF H_2SO_4, AT 25°

Ester	K_d m./l.	k_2 l./(hr. × m.)	pK_a
t-Butyl benzoate, I	0.68[a]	0.49[b]	4.203
t-Butyl *p*-nitrobenzoate, II	.28[a]	.24	3.425
t-Butyl acetate, III	.70[a]	.99	4.757
t-Butyl anisate, IV	.72	.82	4.47
t-Butyl *p*-chlorobenzoate, V	.35	.57	3.979
t-Butyl *m*-nitrobenzoate, VI	.44	.19	3.494
t-Butyl 3,5 dinitrobenzoate, VII	.11	.22	2.80

[a] These constants have been reported previously, *cf.* ref. 1. [b] This constant has been checked experimentally as reported below.

TABLE II

DISSOCIATION RATES OF *t*-BUTYL ESTERS IN DIOXANE CONTAINING 0.835 M./L. OF SULFURIC ACID AT 25°

Ester	Run	Method	k_1[a] (hr.)$^{-1}$	pk_1
I	..	Acidim., Manometr.	0.33[b]	0.48
II	8	Manometr.	.067	1.18
III	6H[c]	Acidim.	.69	0.16
IV	5	Manometr.	.59	0.23
V	10	Manometr.	.20	0.70
VI	6	Manometr.	.082	1.09
VII	11	Acidim.	.024	1.62

[a] These recorded k_1 constants are *corrected* values, the catalyst concentration varying within 1.5% of the indicated average value (0.835 m./l.). The corrections were easily applicable since k_1 has been previously determined as a function of sulfuric acid molarity (*cf.* ref. 1). The consequent shifts from the experimental values are small and insignificant even in the most extreme case. [b] This constant has been reported before, see ref. 3. [c] This run was carried out by Miss Joanne Herbert.

Manometric studies, based on the vapor pressure of *i*-butene, greatly facilitated the determinations of the k_1 rate constants in Table II. This method utilized a thermostated Van Slyke instrument; it has been described in detail before.[3] It could not be applied to the volatile ester III.

The preceding papers have described the mathematical analysis of the data to yield the rate constants.[1,3] All graphs were linear over the entire reaction course, thus precluding autocatalysis. The initial ester concentrations were selected according to considerations of maximum accuracy compatible with solubility requirements. The *primary* readings of typical runs are included in the experimental part.

An additional check on our formulations was afforded through the *experimental* constant k_2 for Compound I, for which the values of K_d and k_1 are most accurately known.[1,3] The calculated quantity (Table I) and the manometric measurement matched perfectly, better than the experimental accuracy would promise. Since this is our first experimentation with an esterification rate, the

(1) Altschul, THIS JOURNAL, **68**, 2605 (1946).

(2) Dippy, *Chem. Rev.*, **25**, 151 (1939).

(3) Altschul and Herbert, THIS JOURNAL, **70**, 351 (1948).

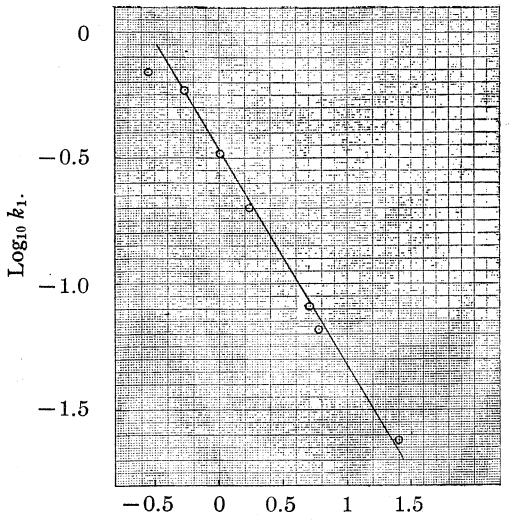


Fig. 1.—Evaluation of Hammett reaction constant for the dissociation rates of *t*-butyl esters in dioxane, containing 0.835 m./l. of sulfuric acid, at 25°: from left to right, compounds III, IV, I, V, VI, II, VII.

relevant data are fully reported in this publication (Table V). Over at least 80% of its course the addition reaction observes the linear relationship postulated by the mathematical function for a reversible bimolecular process.[4] The resulting rate constant is $k_2 = 0.49$ liter (moles × hours)$^{-1}$.

Interpretation.—The previously exposed nearly constant (k_1K_a) product[5] appears to prevail for all aromatic esters, over a forty-seven-fold

$$pk_1 + pK_a = 4.61 \pm 0.07 \qquad (4)$$

range of K_a constants within the indicated limits. This is perhaps relevant to the reaction mechanism,[1,6] for which the initiating step was written as a reversible conversion of the ester to its conjugate acid, necessary for the subsequent slow and rate-controlling dissociation.[7] The inverse function represented by Equation (4) above can be interpreted as progressively further displacements of the precursor equilibria to the left for the stronger carboxylic acids.

A more quantitative formulation is possible for the functional relationship between *Structure and Reactivity*. An apparent simple correlation, widely recognized between series of equilibrium or rate constants pertaining to reactions of para- or meta-substituted benzoic acid derivatives, has found its expression in the "Reaction Constants ρ" and "Substituent Constants σ."[8] Such rigid parallelism of reactivity is credited to identical entropy differences between reactants and products, thus reducing changes of chemical activity to elementary physical concepts, welcome and amenable in their simplicity.[9]

In line with the Hammett definition

$$\sigma = \log K_a - \log K_a^0 \qquad (5)$$

our substituent constants were computed either from the known K_a values (Table I), or were taken directly from the literature,[5] to be plotted against the logarithm of the k_1 constants. Our case exemplifies the fundamental relationship particularly well, as is evident from Fig. 1. The resulting reaction constant, derived graphically from the slope, $\rho = -0.841$. It is clearly relevant only to the aromatic esters, while the aliphatic compound III does not fall within the limitations of the rigid law.[10] The *negative* value of the reaction constant indicates least reactivity for the derivative of the strongest acid, in distinct contrast to other reaction of esters.[8]

Although all three series of constants (k_1, k_2, and K_d) rise with falling K_a values, this dependence is sensitive only for the k_1 data (Table I). For the others a ninety-fold depression of acidity effects only a 6.4-fold increase of K_d and a 4.5-fold increase of k_2 (compare III and VII). These differences are so small that a precise interpretation according to the Hammett formulation is incompatible with the relatively large experimental error.[1]

From a synthetic point of view, the K_d and k_2 constants are of course most essential, defining, as they do, the speed and extent of esterification with *i*-butene. Qualitatively speaking, the trend promises slightly *faster* yet *less complete* conversions for the *weaker* carboxylic acids.

Activation Energies.—In combination with preceding measurements at 35° the data provide for an estimate of the energies of activation for the dissociation of three esters in the presence of 0.835 m./l. of sulfuric acid.[1] Ester I, $\Delta E = 17$ kcal./mole[3]; Ester II, $\Delta E = 16$ kcal./mole; Ester III, $\Delta E = 20$ kcal./mole.

Experimental

Materials.—The previous batches of dioxane, 100% sulfuric acid and benzoic acid were used.[3] The esters were generally synthesized either by direct esterification of the carboxylic acids with *i*-butene,[1] or by the pyridine–acid chloride method.[6,11] Much of the relevant information is listed in Table III.

The solid esters were purified by crystallization, while distillations through all-glass distilling assemblies was applied to the liquids. Samples of esters prepared through the acid chloride were tested with alcoholic silver nitrate; the results were uniformly negative, with the exception of compound V which gave a very slow positive reaction,

(4) Conant and Bartlett, *ibid.*, **54**, 2881 (1932).
(5) Reference 1, footnote 16.
(6) Cohen and Schneider, THIS JOURNAL, **63**, 3382 (1941).
(7) Reference 1, Equation 3.
(8) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapter VII.
(9) (a) Ref. 5, Chapters III, IV, VII; (b) Remick, "Electronic Interpretation of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943, Chapter VII; (c) Wheland, "The Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, Chapters VII, VIII.
(10) For Compound III, the substituent constant obviously has no physical meaning. It was obtained through Equation (5) only in order to be presented in the graph along with the related benzoate esters.
(11) Norris and Rigby, THIS JOURNAL, **54**, 2088 (1932).

TABLE III

PREPARATION AND PHYSICAL CONSTANTS OF *t*-BUTYL ESTERS

Ester	Method	Physical constants	Reference
I	Pyr. + RCOCl	B. p. (2–3 mm.) 75–79°;	6, 11
	Acid + C_4H_8	$n^{23}D$ 1.4893; d_{24} 0.993	1
II[a]	Acid + C_4H_8	M. p. 115–116°	1, 12
III[a]	Acid + C_4H_8	B. p. (755 mm.) 95.5–96.5°	1
	Ac_2O + C_4H_9OH	$n^{27}D$ 1.3827; $d_{2\ell}$ 0.855	11
IV	Pyr. + RCOCl	B. p. (2.5–3 mm.) 162–162.5°; $n^{25}D$ 1.5370; d_{25} 1.0424	...
V[b]	Pyr. + RCOCl	B. p. (3 mm.) 158.5°; $n^{25}D$ 1.5041; d_{25} 1.1011	...
VI	Pyr. + RCOCl	M. p. 31°; d_{25} 1.1513; $n^{25}D$ 1.511[c]	...
VII[d]	Pyr. + RCOCl	M. p. 141–142°	13
	Acid + C_4H_8	M. p. 141–142°	

[a] This preparation was carried out by Miss Lucille J. Holljes. [b] This preparation was carried out by Mrs. Cynthia H. Yoder. [c] Density and refractive index were determined for the supercooled liquid. [d] This preparation was carried out by Mr. Jon J. Sugrue.

presumably due to solvolysis of the nuclear-substituted halogen.

For more complete details as to synthetic procedures the previous publications should be consulted.[1]

Combustion analyses of the previously unrecorded esters IV, V and VI, were carried out by Dr. Carl Tiedcke: Calcd. for IV: C, 69.22; H, 7.75. Found: C, 69.71; H, 8.01. Calcd. for V: C, 62.11; H, 6.16. Found: C, 61.90; H, 6.10. Calcd. for VI: C, 59.21; H, 5.87. Found: C, 59.63; H, 5.96.

Quantitative Measurements. K_d Constants.—The previous technique was applied in all details. Samples of known initial molarities were stored in sealed ampoules in a thermostatic bath at 25 ± 0.1° until equilibrium was attained within a few days. They were then analyzed for the concentration of acid and of *i*-butene by means of acidimetric and by means of bromometric titrations, respectively.[1,3] The results are summarized in Table I in the text.

k_1 Constants.—Both the manometric and the volumetric methods have been outlined in detail before[1,3] and were followed throughout with only one minor change for the acidimetry involving compound VII, as follows: Aliquot samples were added to a slight excess of *warm* standard aqueous alkali. This prevented temporary precipitation of the organic acid, which, without this modification, tended to separate along with the ester and was slow to redissolve. After immediate rapid cooling, back-titration with standard hydrochloric acid followed as usual. Blank tests revealed absence of saponification under these conditions. The experimental results of two representative runs are tabulated below in the customary manner.

The terminology in the column heads of Table IV has been chosen in accord with the preceding publications[1,3]: p_i signifies the partial pressure of

(12) Hueckel, Nerdel and Reimer, *J. prakt. Chem.*, **149**, 311 (1937).

(13) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1941, p. 430.

TABLE IV

DISSOCIATION OF *t*-BUTYL ESTERS IN DIOXANE SOLUTIONS, CONTAINING SULFURIC ACID, AT 25 ± 0.1° (MANOMETRIC MEASUREMENTS)

Hours	p_i, cm.	Q	Hours	p_i, cm.	Q
Run 5; $(IV)_0$ = 0.481 m./l. $(H_2SO_4)_0$ = 0.818 m./l.			Run 10; $(V)_0$ = 0.277 m./l. $(H_2SO_4)_0$ = 0.847 m./l.		
0.28	0.45	2.53	0.58	0.08	3.72
.40	1.46	2.78	0.77	0.49	4.03
.57	3.15	3.32	1.58	1.89	5.49
.72	4.75	3.96	2.07	2.55	6.48
.94	6.52	4.98	2.42	2.95	7.29
1.06	7.54	5.76	3.00	3.67	9.21
1.30	8.84	7.13	3.45	4.06	10.62
1.55	10.19	9.30	3.87	4.39	12.26
1.75	11.11	11.58	4.53	4.94	16.23
1.92	11.69	13.62	5.10	5.27	20.02
2.47	13.22	24.42	5.78	5.67	27.30
2.90	14.02	40.90	7.12	6.27	62
3.67	14.92	148	7.60	6.37	78
4.12	15.07	....	8.03	6.49	112
4.59	15.27	....	9.35	6.77	....
4.90	15.27	....	9.62	6.77	....

i-butene, while Q stands for the variable term in the integrated rate equation.

k_2 Constant.—For the manometric determination of the esterification rate, 5 cc. of 1.695 molar sulfuric acid and 1 cc. of dioxane was introduced into the van Slyke chamber and degassed, followed by admission of 4 cc. of a dioxane solution containing 1.572 m./l. of benzoic acid and roughly 1.72 m./l. of *i*-butene. Readings were taken as usual, and, at equilibrium, samples were titrated in the customary manner indicating an equilibrium concentration of 0.372 m./l. of benzoic acid (calcd., 0.37 m./l.). Table V contains the experimental data which were substituted into the relevant equation after transformation from pressure into concentration.[3]

TABLE V

ESTERIFICATION OF *i*-BUTENE WITH BENZOIC ACID IN DIOXANE, CONTAINING 0.847 M./L. OF SULFURIC ACID AT 25 ± 0.1°

Hours	p_i, cm.	(*i*-butene), m./l.	Q
0.09	32.77	0.643	7.69
.20	31.14	.611	8.74
.42	29.75	.583	10.2
.70	28.42	.557	11.5
.85	27.40	.536	13.4
1.13	26.42	.518	15.7
1.40	25.54	.500	19.4
1.77	24.47	.480	25.5
2.63	22.85	.459	38
3.00	22.20	.435	99
—	21.5		

The Q term stands for

$$Q = \frac{X + (X_e + c + K_d)}{X - X_e} \qquad (6)$$

to be substituted into the rate equation.[4]

Summary

The equilibrium and dissociation rate constants are reported for the acid-catalyzed reversible dissociation of seven *t*-butyl esters into the respective carboxylic acids and *i*-butene, in dioxane solution at 25°. The reverse esterification rate constant, determined experimentally in one case, matches the value calculated from the preceding data.

The relationship between these results and the known parent acid ionization constants, viewed in terms of the general problem of structure and reactivity, indicates faster yet less complete esterification for the weaker carboxylic acids. The dissociation rate constants yield to quantitative treatment, and the Hammett reaction constant is calculated graphically for the aromatic esters.

Additional clues for more intimate analysis of the reaction mechanism are interpreted.

Physical constants for three new *t*-butyl esters are presented.

BRONXVILLE 8, N. Y. RECEIVED FEBRUARY 24, 1948

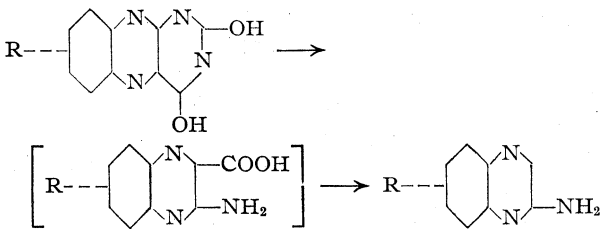
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK AND CO., INC.]

Substituted Sulfaquinoxalines. II. Some Derivatives and Isomers of 2-Sulfanilamidoquinoxaline[1]

BY F. J. WOLF, R. H. BEUTEL AND J. R. STEVENS[2]

In view of the promising chemotherapeutic action of sulfaquinoxaline[3,4] as well as its unique pharmacological properties,[5] the preparation of isomers and derivatives was undertaken.

The preparation of 6,7-dimethyl-2-aminoquinoxaline, 6(or 7)-chloro-2-aminoquinoxaline and a mixture of 2(and 3)-amino-5,6-benzoquinoxaline was carried out by degradative cleavage of the corresponding alloxazine under essentially the same conditions as those described in the literature for the cleavage of alloxazine[3] and substituted alloxazines.[6]



Only one of the two possible isomers was obtained when 7(or 8)-chloroalloxazine was cleaved; whereas, cleavage of benzalloxazine yielded 2- and 3-amino-5,6-benzoquinoxaline.

As the above method is not applicable to the preparation of 2-amino-3-alkylquinoxaline compounds, 2-amino-3-methylquinoxaline was prepared from 2-hydroxy-3-methylquinoxaline[7] by chlorination and amination of the resulting chloro compound.

Attempts to convert 2-hydroxy-3-methylquinoxaline into the amine by modifications of the Bucherer reaction were unsuccessful. However, when more rigorous conditions were applied to 2-hydroxyquinoxaline[8] the desired 2-aminoquinoxaline was obtained[9] in low yield.

In addition, the isomeric 5-aminoquinoxaline and 6-aminoquinoxaline[10] were prepared. The former was obtained from the reaction of 2,3-diaminoacetanilide with sodium glyoxal bisulfite followed by hydrolysis of the resulting 5-acetaminoquinoxaline to the desired product.

The amines were converted into the desired sulfonamides by the usual procedures and in addition the *p*-aminobenzoate of 2-aminoquinoxaline was prepared.

Acknowledgment.—The authors are indebted to Dr. R. T. Major and Dr. M. Tishler for their kind encouragement and advice.

Experimental

Alloxazines.—The preparation of 7(or 8)-chloroalloxazine is typical of the method.

7(or 8)-Chloroalloxazine.—A mixture of 60 g. of 4-chloro-2-nitroaniline and 200 g. of iron powder in 300 ml. of ethanol was stirred and refluxed and 12 ml. of 6 *N* hydrochloric acid was added dropwise during the first three hours. After eighteen hours the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in 135 ml. of 2.5 *N* hydrochloric acid and 400 ml. of water, heated to 85° and added to a solution of 50 g. of alloxan monohydrate in 400 ml. of water at 85°. The mixture was stirred for one hour at 85–90° (a yellow precipitate appeared almost instantly) and filtered. The precipitate, after washing with water and ethanol and drying, weighed 75.4 g. (88% yield based on the nitro compound). The product was sufficiently pure for degradation purposes and did not melt when heated at 360°.

2-Amino-6,7-dimethylquinoxaline.—7,8-Dimethylalloxazine[11] (lumichrome) is not attacked by prolonged boiling with 30% sodium hydroxide. It was cleaved to 2-amino-3-carboxy-6,7-dimethylquinoxaline by heating at 170–175° with concentrated aqueous ammonia.

(1) For the previous paper in this series see Stevens, Pfister and Wolf, THIS JOURNAL, **68**, 1035 (1946).

(2) Present address, J. T. Baker Co., Phillipsburg, N. J.

(3) Weijlard, Tishler and Erickson, THIS JOURNAL, **66**, 1957 (1944).

(4) Smith and Robinson, *Proc. Exptl. Biol. Med.*, **57**, 292 (1944).

(5) Seeler, Mushett, Graessle and Silber, *J. Pharm.*, **82**, 357 (1944).

(6) Weijlard and Tishler, THIS JOURNAL, **67**, 1231 (1945).

(7) Hinsberg, *Ann.*, **292**, 249 (1896).

(8) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945).

(9) This work was carried out by Mr. Weijlard in this Laboratory.

(10) Hinsberg, *Ann.*, **237**, 345 (1887).

(11) Kuhn and Rudy, *Ber.*, **67**, 1826 (1934).

TABLE I

SULFANILAMIDOQUINOXALINES

Compound	Yield, %	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-[N⁴-Acetylsulfanilamido]-6,7-dimethylquinoxaline	65	239–240	58.36	4.90		57.98	4.90	
2-[N⁴-Acetylsulfanilamido]-6-(or 7)-chloroquinoxaline	65	266–268	50.99	3.48		51.04	3.51	
2-(and 3-)[N⁴-Acetylsulfanilamido]-5,6-benzoquinoxaline	95	155–205	61.21	4.11		61.35	4.33	
2-[N⁴-Acetylsulfanilamido]-3-methylquinoxaline	65	244–245	57.30	4.53		57.39	4.97	
5-[N⁴-Acetylsulfanilamido]-quinoxaline	94	234	56.13	4.12		56.13	4.22	
6-[N⁴-Acetylsulfanilamido]-quinoxaline	...	279	56.13	4.12	16.36	56.08	4.31	16.1
2-Sulfanilamido-6,7-dimethylquinoxaline	85	246–247	58.52	4.91	17.05	58.44	5.15	16.81
2-Sulfanilamido-6-(or 7)-chloroquinoxaline	45	241–242	50.27	3.32	16.75	50.20	3.63	16.62
2-(and 3-)-Sulfanilamido-5,6-benzoquinoxaline	78	205–208			15.98			16.11
2-Sulfanilamido-3-methylquinoxaline	54	211–212	57.31	4.47	17.82	57.62	4.63	17.98
5-Sulfanilamidoquinoxaline	92	169–170	55.98	4.03	18.66	56.36	4.15	18.2
6-Sulfanilamidoquinoxaline	93.5[a]	230–231	55.98	4.03	18.66	56.10	3.99	18.8

[a] Based on 6-aminoquinoxaline.

A suspension of 28 g. of lumichrome in 150 ml. of 28% ammonia water was heated in bomb tubes at 170–175° for thirteen hours. The mixture was diluted with 10 volumes of water, heated to 90° and filtered. The amorphous orange precipitate was extracted with 300 ml. of hot 2 *N* ammonium hydroxide; the combined filtrates were acidified with acetic acid and the flocculent orange precipitate was filtered and dried. The product, 14.4 g. (60% yield), decomposed with evolution of gas at 215–220°.[12]

A mixture of 5.0 g. of crude 2-amino-3-carboxy-6,7-dimethylquinoxaline and 50 ml. of nitrobenzene was slowly heated to boiling. The elimination of carbon dioxide was rapid at first and was almost complete by the time the mixture had reached boiling temperature. The solution was refluxed for ten minutes, and the dark solution was allowed to stand for eighteen hours. The reaction mixture was filtered and the precipitate washed well with benzene. The combined filtrates were extracted three times with 25-ml. portions of 2.5 *N* hydrochloric acid. The aqueous extracts were combined, washed twice with benzene and made alkaline with sodium hydroxide. The crude product was filtered, taken up in 100 ml. of warm 2.5 *N* hydrochloric acid, treated with Darco G-60 and precipitated by the addition of 2.5 *N* sodium hydroxide. The yellow amorphous product, 2.97 g. (93% yield) melted at 270–273°. It was suitable for conversion into the sulfonamide compound. An analytical sample prepared by recrystallization from ethyl acetate melts at 275–278°.

Anal. Calcd. for $C_{10}H_{11}N_3$[13]: C, 69.35; H, 6.40. Found: C, 69.12; H, 6.67.

2(and 3)-Amino-5,6-benzoquinoxaline.—"Benzalloxazine,"[14] 60 g., was heated with 450 ml. of 28% aqueous ammonia at 175° for twelve hours. The reaction mixture was diluted with 2 l. of water, heated to 90°, treated with Norit and filtered. The filtrate was cooled and acidified with acetic acid, and the orange gelatinous precipitate was filtered and dried. The crude product, 15.5 g. (28.6% yield), melting with evolution of gas at 212–215°, was used in the next step.

The crude amino acid, 15.5 g., was decarboxylated as described for the 6,7-dimethyl derivative. The crude product, 8.0 g. (63.5% yield), was dissolved in 250 ml. of hot benzene. On cooling 5.4 g. of bright yellow material, m. p. 190–195°, was obtained. The mother liquor on concentration yielded solids 2.0 g., m. p. 140–180°. By fractional crystallization of the first crop, it was possible to obtain a low yield of analytically pure material, melting at 215–217°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.89; H, 4.65; N, 21.52. Found: C, 73.79; H, 5.07; N, 21.64.

When the residue, obtained by evaporating the mother liquor from recrystallization of the second crop from benzene, was again recrystallized, evaporation of the mother liquor yielded a bright yellow analytically pure material, m. p. 150–152°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.89; H, 4.65. Found: C, 73.91; H, 4.52.

The intermediate fractions contained most of the product and melted over wide ranges. Since preparation of either isomer in a pure state involved a large loss of material, the mixture was converted to the sulfonamides.

2-Amino-6(or 7)-chloroquinoxaline.—A mixture of 7.0 g. of 7(or 8)-chloroalloxazine and 30 ml. of 28% ammonia water was heated in a bomb at 165° for ten hours. The mixture was diluted with 10 volumes of water, heated to 90° and filtered. The filtrate was acidified with hydrochloric acid, and the gelatinous precipitate was filtered and dried. The crude product, 5.1 g. (81.5% yield), was difficult to purify and was used without purification in the next step. The compound melted with evolution of gas at 188–190°.

The amine was obtained when 4 g. of the crude amino acid was refluxed with 40 ml. of nitrobenzene for fifteen minutes. The product was extracted with dilute hydrochloric acid and precipitated with sodium hydroxide. The crude amine, 1.2 g. (37% yield) melted at 192–196° (skeleton unmelted at 225°). When 0.5 g. of the product was heated with 20 ml. of ethanol, 0.15 g. of insoluble material that did not melt at 400° was obtained. The ethanol filtrate when concentrated to 5 ml. and cooled yielded material, m. p. 193–195° (0.2 g.). An analytical sample, m. p. 197–200°, was obtained by sublimation at 150° in high vacuum.

Anal. Calcd. for $C_8H_6N_3Cl$: C, 53.50; H, 3.37; N, 23.39. Found: C, 53.36; H, 3.70; N, 23.19.

The amine was obtained more readily by cleaving 7(or 8)-chloroalloxazine with approximately 75% sulfuric acid. 7(or 8)-Chloroalloxazine was added to the solution obtained by mixing 50 ml. of water and 200 ml. of concentrated sulfuric acid. The mixture was heated to 200° as rapidly as foaming would allow and held at this temperature for twenty minutes and then poured on ice, and the solution was made strongly alkaline with sodium hydroxide. The precipitate, 7.0 g. (23% yield), was purified by dissolving in hot 1.3 *N* hydrochloric acid, treating with Darco G-60, and precipitating with sodium hydroxide. The product, 5.0 g. (16% over-all yield) melting at 198–199°, was used without further purification for the preparation of the sulfonamide derivative.

2-Chloro-3-methylquinoxaline.—200 ml. of phosphorus oxychloride was added to a refluxing mixture of 57.5 g. of 2-hydroxy 3-methylquinoxaline[7] and 300 ml. of benzene. After refluxing for two hours, most of the material had dissolved to give a dark purplish solution. The re-

(12) All melting points are uncorrected.

(13) Microanalyses were kindly performed by R. N. Boos, W. K. Humphry, E. H. Thornton and E. Meiss.

(14) Kuhn and Cook, *Ber.*, **70**, 761 (1937).

action mixture was added to a stirred mixture of 2 kg. of ice and water. The benzene layer was separated, and the water layer was extracted with six 250-ml. portions of benzene. The benzene extracts were combined, heated with 10 g. of Norit, and concentrated to dryness *in vacuo*. Recrystallization of the residue from ethanol gave the product (37.5 g.) in 52% yield, m. p. 84–86°.

Anal. Calcd. for $C_9H_7N_2Cl$: C, 60.50; H, 3.95. Found: C, 60.97; H, 4.61.

2-Amino-3-methylquinoxaline.—A mixture of 40 g. of 2-chloro-3-methylquinoxaline, 30 ml. of liquid ammonia and 250 ml. of absolute ethanol was heated for eight hours at 120°. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was extracted with 200 ml. of warm 1.2 *N* hydrochloric acid. The insoluble non-reacted chloro compound weighed 8.0 g. The acid solution was filtered, heated with Norit for five minutes, filtered again and the crude amine precipitated with sodium hydroxide. The crude product was purified by recrystallization from 200 ml. of benzene, and the mother liquor was used for two extractions of the insoluble material, total yield 20.4 g. (70% of theoretical based on the chloro compound used), m. p. 163–165°.

Anal. Calcd. for $C_9H_9N_3$: C, 67.89; H, 5.70. Found: C, 68.20; H, 5.95.

5-Acetylaminoquinoxaline.—A solution of 6.0 g. of 2,3-dinitroacetanilide[15] in 150 ml. of methanol was shaken with hydrogen in the presence of Raney nickel catalyst until the reduction was complete. The reaction mixture was quickly filtered from the catalyst into a solution of 8.0 g. of sodium glyoxal bisulfite in 150 ml. of water. After removing the methanol and heating at 100° for one hour, the reaction mixture was cooled and made alkaline with 25 ml. of 2.5 *N* hydroxide. After cooling to 5° the product, 2.76 g. (55% yield), m. p. 131°, was obtained by filtration. Without further purification the product was converted into the amine.

5-Aminoquinoxaline.—A mixture of 2.5 g. of 5-acetylaminoquinoxaline and 25 ml. of 2 *N* sulfuric acid was heated one hour on the steam-bath, cooled and neutralized with sodium bicarbonate. After cooling to 5° the product was filtered and washed with ice-water, yielding 1.9 g. (87.5% yield) of bright yellow crystals, m. p. 92°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.17; H, 4.86; N, 28.94. Found: C, 66.24; H, 4.78; N, 28.4.

2-*p*-Aminobenzamidoquinoxaline.—A mixture of 11.0 g. of *p*-nitrobenzoyl chloride and 8.5 g. of 2-aminoquinoxaline in 15 ml. of pyridine was heated on the steam-bath for one hour and poured into 170 ml. of water. The crude product, 13.6 g., was recrystallized from ethyl acetate. The purified material, m. p. 211°, weighed 7.8 g.

A suspension of 10 g. of the *p*-nitrobenzoate in 300 ml. of methanol was shaken with hydrogen in the presence of 2 g. of Raney nickel catalyst. The hydrogenation was stopped when 3.1 moles of hydrogen had been absorbed. After adding an equal volume of acetone the solution was filtered from the catalyst and concentrated to dryness *in vacuo*. The residue was dissolved in 50 ml. of 2.5 *N* hydrochloric acid, filtered from a small amount of insoluble material and precipitated by adding 1 *N* sodium hydroxide. The crude product, 7.9 g., was recrystallized from a mixture of equal parts of ethanol and ethyl acetate. The pure material, 5.5 g. (62% yield), melts at 229–230°

Anal. Calcd. for $C_{15}H_{13}ON_4$: C, 67.90; H, 4.58; N, 21.19. Found: C, 68.07; H, 4.73; N, 21.6.

Sulfonamides.—The amines were treated with *p*-acetylaminobenzenesulfonyl chloride in pyridine solution. The acetyl compounds were obtained in yields of 70–95%. The preparation of 2(and 3)-sulfanilamido-5,6-benzoquinoxaline is typical.

2(and 3)-[N⁴-Acetylsulfanilamido]-5,6-benzoquinoxaline).—At room temperature 5.6 g. of *p*-acetylaminobenzenesulfonyl chloride was added to a solution of 4.5 g. of 2(and 3)-amino-5,6-benzoquinoxaline in 25 ml. of pyridine. The mixture was stirred for one and one-half hours and then poured into 500 ml. of water. Heating and stirring the mixture made the gum that first separated solidify. The precipitate was filtered and dissolved in 200 ml. of 2 *N* sodium hydroxide and filtered from the insoluble material (0.2 g.). After being stirred for ten minutes with 1 g. of Norit, the solution was filtered and made acidic. The dried yellow product weighed 8.6 g. (95% yield). The acetyl derivatives were hydrolyzed with ethanolic hydrogen chloride.

2(and 3)-Sulfanilamido-5,6-benzoquinoxaline.—A mixture of 8.6 g. of the acetyl compound, 50 ml. of absolute ethanol and 25 ml. of concentrated hydrochloric acid was stirred and refluxed one and one-half hours. The solution darkened, and a reddish precipitate appeared. The mixture was poured into 300 ml. of water and 30% sodium hydroxide added until the solution was alkaline. After 2 g. of Norit was added the solution was heated to boiling, filtered, and the product precipitated by acidification with acetic acid. The light yellow powder weighed 6.0 g. (78% yield).

Summary

Isomers and nuclear substituted derivatives of 2-sulfanilamidoquinoxaline were prepared. The degradation of 7,8-dimethylalloxazine, 7(or 8)-chloroalloxazine and "benzalloxazine" to the corresponding 2-aminoquinoxaline has been carried out. The preparation of 2-amino-3-methylquinoxaline by another method has been described.

RAHWAY, N. J. RECEIVED FEBRUARY 28, 1948

(15) Kaufmann and Hussy, *Ber.*, **41**, 1740 (1908).

[JOINT CONTRIBUTION FROM MELLON INSTITUTE AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF PITTSBURGH]

Some Physical Properties of 2-Picoline

BY HENRY FREISER[1] AND WILLIAM L. GLOWACKI[2]

Most of the work reported here was done as a part of an extensive program sponsored by the Koppers Company for the determination of physical constants of coal tar bases. A number of factors pointed to the need for this program. Interest in 2-picoline and other tar bases has mounted in recent years. Much of the physical constant data necessary for their full exploitation are either lacking or old. With large amounts of materials available it seemed desirable to purify 2-picoline carefully and redetermine its physical properties.

Purification of 2-Picoline.—Over two liters of commercial 2-picoline (Koppers Company 2° alpha picoline) was subjected to a careful fractional distillation at atmospheric pressure by means of a 40-in rectifying column of one-inch inner diameter, packed with 3/32 in. Fenske stainless steel helices. The temperature of the distilling picoline was measured with a single-junction copper–constantan thermocouple and a portable potentiometer. The product was collected at a rate of 30 ml./hr. Thirty-seven fractions of 50 ml. each, boiling within 0.1°, were collected. The distillate was protected from atmospheric moisture and carbon dioxide by a stream of dry nitrogen and was later stored in a dry box. The cuts were examined preparatory to further purification by the determination of the freezing points of selected fractions.[3] The freezing points of cuts 7–36 (*ca.* 1500 ml.) were substantially constant at −66.63° and of a purity estimated from the melting point slope of 99.76 mole %.

Distillation cuts 6–39 were further purified by crystallization and centrifugation. The recrystallized 2-picoline was dehydrated by distillation in the one-inch laboratory column, most of the material distilling over a 0.05° range. The purity of this material, which was used in the determination of the physical properties, was estimated from its melting point curve slope to be 99.85 mole %. It is of interest to note that the dehydration distillation data of the recrystallized picoline indicated that the total moisture picked up during the entire series of manipulations involved in the recrystallization was somewhat less than 0.5 weight % (the mother liquor fraction may have more than this amount). The literature reports about the extreme hygroscopicity of 2-picoline and perhaps those about the other tar bases may be somewhat in error.

Experimental

Determination of Properties

Freezing Point.—The apparatus and procedure was essentially a modification of that in use at the National Bureau of Standards.[4] The single-junction copper–constantan thermocouple was calibrated at the sublimation point of carbon dioxide. The potentiometer used was sensitive to 0.1 microvolt (0.003°) and reproducible from day to day to 1 microvolt (0.03°). Two modifications of crystalline 2-picoline were observed, needle-like prisms and white opaque platelets, the former being more stable at the freezing point. Due to excessive supercooling, melting curves instead of freezing curves were used to determine the freezing point for zero impurity. The freezing point of pure 2-picoline (saturated with nitrogen) was found to be −66.55 ± 0.08° at 730–740 mm. pressure, and the purity of the sample was estimated, from the slope of its melting curve, to be 99.85 mole %, assuming its cryoscopic constant to have the same value as that of 3-picoline.[5] This assumption is approximately confirmed by an experiment in which approximately 0.71 mole % water was found to depress the freezing point of 2-picoline by 0.31°. Previously reported values of the freezing point are −69.9°[6] and −64°.[7]

Density and Expansion Coefficient.—Two 20-ml. flask-type pycnometers having graduated 1-mm. capillary necks were used. The capillaries were calibrated by measuring lengths of weighed mercury threads by means of a traveling microscope. The volumes of the pycnometers were determined at 20, 40, 60 and 80° in a water-bath maintained to ±0.005°. The bath temperatures were measured by thermometers which had been compared with those certified by the Bureau of Standards and used at the points tested, with a probable accuracy of ±0.03°. When no further change occurred in the level of the liquid in the pycnometer, the level was read with the aid of a telescope, and suitable calculations made to relate the volume to a certain mark. Fillings with 2-picoline were made in the dry box using a filling tube constructed of stainless steel and nickel tubing. The picoline was protected from the atmosphere by a device which kept dry nitrogen flowing over it at all times, including that of level adjusting. The densities were determined in duplicate at 20, 40, 60, and 80° on the same sample of picoline, and pycnometers being refilled for the series at 30, 50, and 70°. Weighings were made using as tares identical pycnometers which received the same external treatment as the ones in which the measurements were made. The weights employed were certified by the Bureau of Standards. All weights were corrected to values *in vacuo*. The respective density values obtained at 10° intervals from 20 to 80° are 0.94432_0, 0.93491_3, 0.92556_5, 0.91607_2, 0.90665_8, 0.89706_6 and 0.88722_2 g./ml. with an average deviation of duplicate measurements of 0.000027 g./ml. The following equation, obtained by the application of least squares to the data, d_t (g./ml.) = $0.962809 - 9.0569 \times 10^{-4}t - 1.369 \times 10^{-6}t^2 + 2.45 \times 10^{-8}t^3 - 1.7 \times 10^{-10}t^4$, reproduces the experimental results with an average departure of 0.000017 g./ml. The density of 2-picoline at 25° calculated from the above equation is 0.93963 g./ml. The values previously reported in the literature are 0.9395,[8] 0.9400,[9] 0.9401,[10] 0.9494,[11] and 0.94099.[12]

(1) Chemistry Department, University of Pittsburgh.

(2) Present address: Eastern Gas and Fuel Associates, Boston, Mass.

(3) A. J. Streiff, E. T. Murphy, V. A. Sedlak, C. B. Willingham and F. D. Rossini, *J. Research N. B. S.*, **37**, 331 (1946).

(4) A. R. Glasgow, Jr., A. J. Streiff and F. D. Rossini, *ibid.*, **35**, 355 (1945).

(5) W. L. Glowacki, unpublished work.

(6) J. Timmermans, *Bull. soc. chim. Belg.*, **30**, 62 (1921).

(7) F. M. Jaeger, *Z. anorg. allgem. Chem.*, **101**, 1 (1917).

(8) M. A. G. Rau and B. N. Narayanaswamy, *Z. physik. Chem.*, **26B**, 23 (1934).

(9) T. Eguchi, *Bull. Chem. Soc. Japan*, **2**, 176 (1927).

(10) A. L. Wilkie and B. D. Shaw, *J. Soc. Chem. Ind.*, **46**, 469 (1927).

(11) J. G. Heap, W. J. Jones and J. B. Speakman, THIS JOURNAL, **43**, 1936 (1921).

(12) A. E. Dunstan, F. B. Thole and J. S. Hunt, *J. Chem. Soc.*, **91**, 1728 (1907).

The expansion coefficients of 2-picoline at various temperatures were calculated simply by dividing the instantaneous rate of change of density with temperature by the density at that temperature employing the density equation and its temperature derivative. The values thus obtained varied from 0.000992 at 20° to 0.001127 at 80° and are consistently from 2–7% lower than those calculated from the only other reported data.[13] This earlier work was done before any distinction between the isomeric picolines was recognized and probably was carried out on impure material.

Viscosity.—A Cannon–Fenske viscometer (size 50), having an efflux time for water at 20° of 265.22 seconds, was used for the determination of viscosities from 0–80° in 10° intervals. Efflux times were measured in triplicate with an electrical timer having an average reproducibility of 0.05 second. The viscometer, placed in a bath held constant to 0.01° was calibrated at each temperature with distilled water. Efflux times obtained from two separate fillings checked to within better than 0.1 second. The identical procedure was employed with 2-picoline with additional precautions taken to prevent contamination with atmospheric moisture. The viscometer was charged in the dry box and while in the bath was protected by means of devices which kept dry nitrogen in contact with the picoline. Results from two fillings checked to ±0.04 second.

Since the viscosity determinations were made at temperatures other than that at which the viscometer was charged, a correction for the change in the average driving head due to thermal changes in volume was applied to the observed efflux time. For water, this correction was always less than 0.3 second, while with the picoline, whose expansion coefficient is greater than that of water, the maximum correction amounted to 0.8 second.

Another correction applied to the efflux time was that needed to compensate for the change in driving head with surface tension of the liquid under test. This correction enters because of the difference of capillary action in the upper and lower reservoirs which are of different diameter. For the convenient calculation of this correction, water at 40° was used as a standard. The correction for the other water runs was always less than 0.4 second, but for the picoline, whose surface tension is about half that of water, the correction varied from 0.7 to 1.3 seconds. A graphical interpolation of Jaeger's data[7] for the surface tension of 2-picoline was employed for these calculations.

The corrected efflux times of the water determinations, in conjunction with the viscosity and density data for water in the "International Critical Tables," were used for the calculations of the viscometer constant. In an analogous manner, the observed efflux times for 2-picoline were corrected and employed along with the density data herein obtained to calculate the viscosities presented in Table I.

TABLE I

VISCOSITY OF 2-PICOLINE

Temp., °C.	Viscosity, cp.	Temp., °C.	Viscosity, cp.
0	1.0970	50	0.5621
10	0.9351	60	.5054
20	0.8102	70	.4585
30	0.7096	80	.4165
40	0.6296		

The results presented here have a probable accuracy of somewhat better than 1%. The value of the viscosity at 25° interpolated from a graphical representation of the data of Table I is 0.757 cp., as compared to the value of 0.7918 cp. reported in 1907.[12] The difference of 4.7% is probably due in large part to the use of insufficiently pure picoline by these early workers.

The relation between the viscosity and the temperature may also be expressed by the following equation obtained graphically from the data

$$\log_{10}\eta \text{ (centipoise)} = 504.4/T - 1.811$$

where T is the absolute temperature and which reproduced the data to an average of 5 p. p. m. with an extreme of 14 p. p. m. The activation energy of viscous flow, $E_{vis.}$, may be found from the above equation to be 2308 cal./mole.

Boiling Point.—A simple Swietoslawski ebulliometer, suitably modified to protect its contents from atmospheric moisture, was dried and charged with 2-picoline in the dry box. The condensation temperature was measured with a single-junction copper–constantan thermocouple that was calibrated with an accuracy of 0.02° at the melting point of a Bureau of Standards sample of benzoic acid. Barometric pressure readings were made simultaneously with boiling temperature measurements. The observed boiling temperatures were corrected to 760 mm. by means of the dT/dp value of 0.046° C./mm. calculated from the vapor pressure data of Riley and Bailey.[14]

The boiling point so obtained, 129.44°, remained constant even after several portions of the liquid were distilled away. The probable accuracy of the value is somewhat better than 0.1°. Previously reported values are 129.21,[15] 129.27–129.32,[9] 128.9,[14] and 129.1°.[8]

Refractive Index.—The refractive indices of 2-picoline at 20 and 30° in a Bausch & Lomb Precision Refractometer at three wave lengths, 5893 Å. (Na_D line), 5461 Å., and 4358 Å. (Hg green and blue lines). Circulating water from a constant temperature bath maintained the prisms to ±0.02° during the measurement. The refractometer was calibrated by means of highly pure benzene and chlorobenzene. These results, along with the molar refractions, are presented in Table II.

TABLE II

REFRACTIVE INDEX AND MOLAR REFRACTION OF 2-PICOLINE

Wave length, Å.	Temp., °C.	n	R_M
5893	20	1.50105	29.056
	30	1.49592	29.093
5461	20	1.50493	29.246
	30	1.49982	29.286
4358	20	1.52170	30.062
	30	1.51667	30.118

Other values of the $n^{20}D$ are 1.50122[14] (corrected from the value reported at 18° by means of the temperature dependence of n_D found in this work) and 1.501.[16]

(13) T. E. Thorpe, *J. Chem. Soc.*, **37**, 222 (1880).

(14) F. T. Riley and K. C. Bailey, *Proc. Roy. Irish Acad.*, **38B**, 450 (1929).

(15) E. J. Constam and J. White, *Am. Chem. J.*, **29**, 2 (1903).

(16) "International Critical Tables," Vol. I.

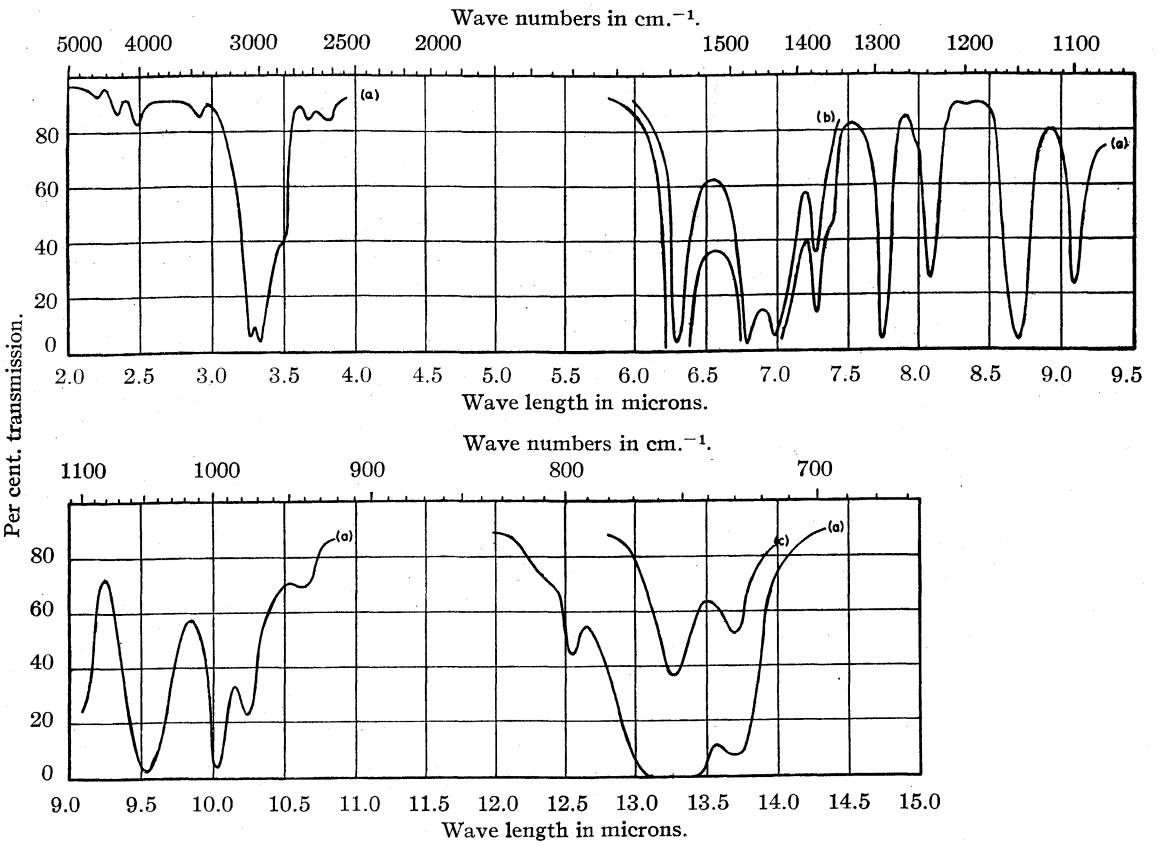


Fig. 1.—Infrared spectra of 2-picoline: α-picoline (2-methylpyridine), 99.8%, liquid at 27°; cell length, (a) 0.08 mm., (b) 0.04 mm., (c) 0.02 mm.

The n_∞^{30} and corresponding MR_∞ were calculated for use in the dipole moment work by means of a simple Sellmeier expression, $n - 1 = a\lambda^2/\lambda^2 - b$, using the refractive indices of two of the three reported above. In order to estimate the validity of this expression, the value of n_∞^{30} was calculated by using two pairs of $n\lambda$. In this manner n_∞^{30} was found to have an average value of 1.4729 ± 0.00016 with a corresponding MR_∞ = 27.94 ml.

Dipole Moment.—The dipole moment of 2-picoline in benzene solution at 30.00 ± 0.03° was measured by means of a heterodyne beat method. The apparatus used for the dielectric constant measurements will be described in a future publication. The densities of the solutions were measured in pycnometers of 100 ml. capacity similar to the ones described in the section on density.

The dielectric constants ϵ and d of the solutions containing mole fraction f_2 of the polar solute and the polarization of polar solute P_2 are given in Table III.

TABLE III

DIELECTRIC CONSTANTS, DENSITIES AND POLARIZATION

f_2	ϵ	d	P_2
0.042803	2.4860	0.871443	103.5
.053407	2.5421	.872239	102.8
.074254	2.6588	.873802	102.5

A value of 104.7 ± 0.4 ml. was obtained for P_∞ by extrapolating the P_2–f_2 curve to infinite dilu-

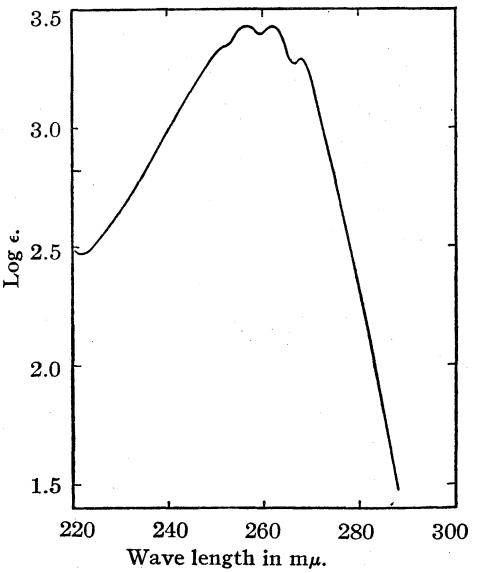


Fig. 2.—Ultraviolet spectra of 2-picoline: purity, 99.8 mole %; solvent, cyclohexane.

tion. The electronic polarization P_E was obtained from the molar refraction at infinite wave length, 27.9 ml. Assuming P_A to be 10% of P_E, the dipole moment of 2-picoline is calculated to be 1.92 D with a probable accuracy of $\pm 0.01°$. This value is not in good agreement with that of 1.72 D (the only previously reported work) obtained by Rau and Narayanaswany[7] because these workers employing the temperature solution method obtained a falsely high value, 23.2 ml. for P_A.[17] The value obtained by Rau and Narayanaswany for the total polarization at infinite dilution $P^{30}{}_{2\infty}$ is 111.36 ml., in fair agreement with the value obtained here.

Absorption Spectra.—In Figs. 1 and 2 are presented the infrared and ultraviolet absorption curves, respectively, for 2-picoline. The main infrared absorption maxima are presented in Table IV. The main ultraviolet absorption maxima are located at 252, 256.5, 262, and 268 millimicrons. The data were kindly determined by the Koppers Spectrographical Research Laboratory under the direction of Dr. J. J. McGovern.

TABLE IV

MAIN INFRARED ABSORPTION MAXIMA OF 2-PICOLINE

λ in μ	I^a	λ in μ	I^a
1.70	w	7.74	m
2.20	w	8.09	m
2.34	w	8.70	m
2.47	w	9.09	m
2.93	w	9.53	m-i
3.33	m	10.03	m-i
3.66	w	10.24	m
3.82	w	10.65	w
6.29	m-i	11.29	w
6.80	m-i	12.55	w
6.99	m	13.28	i
7.28	w	13.69	m

[a] Approximate intensity: w = weak, m = moderate, i = intense.

Summary

1. 2-Picoline has been purified by fractional distillation and recrystallization to an estimated 99.85 mole % purity.

2. The following properties have been determined for the purified material: freezing point, boiling point, density at 10° intervals from 20 to 80°, the expansion coefficients in the same temperature range, the viscosity at 10° intervals from 0 to 80°, refractive indices at 20 and 30° at 5893, 5461 and 4358 Å., the dipole moment, and the infrared and ultraviolet absorption spectra.

PITTSBURGH, PENNSYLVANIA RECEIVED MARCH 2, 1948

(17) "The temperature solution method gives only the dipole moment qualitatively and seriously misleads investigators regarding the magnitude of the atomic polarization," H. O. Jenkins, *Trans. Faraday Soc.*, **30**, 741 (1934).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMICAL ENGINEERING AND OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Density of Aqueous Hydrogen Peroxide Solutions[1]

BY CHARLES E. HUCKABA AND FREDERICK G. KEYES

Introduction

A relatively small amount of exact density data exists for aqueous solutions of hydrogen peroxide, due to the decomposition caused by the catalytic activity of glass surfaces which introduces error in the density determination because of combined gas formation and loss of peroxide. A solution of this major problem was found in the preconstruction treatment of the interior surface of the glass from which the vessels were blown, combined with the employment of certain precautions during their use.

The literature reveals that the determinations of Maass and Hatcher[2] reported at both 0 and 18° are the most accurate data available. Independent verification of the data, however, has not appeared, and independent values in the region of high peroxide concentration are particularly desirable in view of the surface activity of the glass unless very special precautions are taken.

In this investigation a technique has been developed for preparing vessels whose interior surfaces are insensitive toward the decomposition of peroxide, determining with precision the densities of aqueous solutions of hydrogen peroxide at 0°. The mean coefficient of change of density with temperature to 20° has also been measured.

Treatment to Render Glassware Inactive to Hydrogen Peroxide.—The following procedure was found to produce inactive container Pyrex glass surfaces.

All glassware was constructed of Pyrex tubing, selected for freedom from visible surface imperfections. Prior to the glassblowing the tubing was cleaned with hot fuming sulfuric acid (150–175°), rinsed with conductivity water, and allowed to drain until dry in a dust-free case. This treatment is important in that it removes foreign matter which might otherwise decompose or "ash" and become embedded in the surface of the glass during the glassblowing operation. The air required in the glassblowing was passed through a filter of fresh medicinal cotton to prevent contamination through air-borne dust or decomposition of organic vapors from the breath.

After the vessels had been constructed, they were filled with hot fuming sulfuric acid and allowed to stand overnight. Following thorough rinsing with conductivity water, the vessels were tested with 90–95% peroxide. If no bubbles of oxygen appeared, the vessels were ready for use.

In the few instances where decomposition was detected,

(1) The authors express their acknowledgment to the Naval Bureau of Ordnance for the support and release of this work.

(2) O. Maass and W. H. Hatcher, THIS JOURNAL, **42**, 2548 (1920).

the peroxide was removed and the vessels re-rinsed with conductivity water. Then the vessels were treated with 10% hydrofluoric acid for three or four minutes. If, after this treatment had been repeated several times, the vessel still decomposed the peroxide, it was concluded that some foreign matter was deeply embedded in the surface of the vessel and the vessel was discarded.

Although precautions were taken to keep the vessels in a dust-free place, occasionally a vessel would become contaminated between times of use. This contamination, however, was always successfully removed by repeating the cleaning procedure with fuming sulfuric acid, hydrofluoric acid, and conductivity water. It was also found that the tendency of the vessels to become contaminated was reduced by keeping them filled with concentrated peroxide when not in use.

It has been found that cleaning a vessel with chromate–sulfuric acid cleaning solution usually increased rather than decreased the catalytic action of the vessel toward the decomposition of the peroxide.

Density Determinations at 0°

Experimental Procedure for Measuring Densities.—The densitometers consisted of Erlenmeyer-type glass bulbs of about 20 cc. capacity, to which was attached a short section of 2 mm. capillary tubing, and to which in turn was attached a ground glass cap. At a point at mid-distance along the capillary, a small scratch or level mark was made on the capillary tubing.

Calibration of the volume at 0° of the densitometers was carried out with conductivity water at 0°. The densitometer was filled with water to a level somewhat above the mark and placed in an ice-bath for approximately forty-five minutes. Tests showed that this time was more than sufficient to reduce the temperature of the water in the densitometer to 0°. The liquid level was finally adjusted to the mark by removing the excess liquid with a fine capillary. Any small drops of liquid clinging to the walls of the capillary above the mark were removed by using a fine capillary tube connected to a water aspirator.

The densitometer was transferred from the ice-bath to a water-bath at room temperature to warm the densitometer and contents quickly to room temperature in preparation for weighing. The densitometer was removed from the water-bath, dried and weighed. The precision of the calibrations was in round numbers a part in 10,000.

In making density determinations, the densitometers were filled with peroxide which had been twice distilled to ensure purity. The same manipulations were employed as were followed in the calibrations. Thus having determined the weight of a known volume of the peroxide solution at 0°, the density at 0° could be calculated easily. The precision of the density measurements was close to a part in 10,000.

Analytical Procedure

After density weighing, samples of peroxide for analysis were withdrawn by means of a capillary pipet constructed and treated according to previous indications relative to the densitometers. In a previous investigation,[3] it has been shown that the analysis of aqueous solutions of hydrogen peroxide can be carried out with great accuracy by titration with potassium permanganate provided a definite procedure is followed. To achieve the maximum possible accuracy, both the standardization of the permanganate and the titration of the peroxide were carried out according to the recommendations given in the reference cited.

To analyze concentrated peroxide solutions by titration with permanganate, a dilution step is necessary. All quantities of material involved in the dilutions were determined by weighing rather than by the less accurate volumetric method. Weight burets were also used for the titrations. The precision of the analyses was not inferior to a part in 5000.

(3) C. E. Huckaba and F. G. Keyes, THIS JOURNAL, **70**, 1640 (1948).

An attempt was made to determine directly the amount of impurities in the best obtainable grade of sodium oxalate[4] used to obtain the titer of the potassium permanganate by comparing the oxalate with purified anhydrous oxalic acid. Although the oxalic acid was sublimed in high vacuum eight times, for some undetermined reason the results showed a lack of uniformity to a part in 800.

The same oxalate as used in the comparison of the permanganate titration with the decomposition method was also used in the density determinations. The results of the earlier comparisons[2] by direct peroxide decomposition indicated that the oxalate purity is not inferior to a part in 3500. It is believed that the concentration determinations are reliable to a part in 5000.

Experimental Results

The experimental results of the density determinations at 0° are given in Table I.

TABLE I

DENSITIES OF AQUEOUS SOLUTIONS OF HYDROGEN PEROXIDE AT 0°

Weight fraction of water	Density at 0°, g. per cubic cm.	Weight fraction of water	Density at 0°, g. per cubic cm.
0.90343	1.0379	0.10621	1.4100
.80021	1.0803	.04013	1.4483
.59991	1.1660	.03772	1.4493
.40829	1.2539	.03718	1.4499
.28646	1.3139	.00521	1.4681
.19977	1.3590	.00395	1.4685

An attempt to express the data algebraically showed that no simple function would represent the densities as a function of weight fraction or mole fraction with sufficient precision. An equation of the following form was found to be the best approximation representation.

$$\log v_m = \log v_{H_2O_2} + \log (v_{H_2O}/v_{H_2O_2})x \qquad (1)$$

where

v_m represents specific volume of H_2O_2 solution cc./g.
$v_{H_2O_2}$ represents the specific volume of 100% H_2O_2 cc./g.
v_{H_2O} represents the specific volume of H_2O cc./g.
x represents the weight fraction of water

or

$$\log [(v_m)(10)] = 0.83241 + 0.16767x \qquad (1a)$$

The deviation of the data from this curve exhibits a maximum with a value of about a part in 400. Since representing the data algebraically to a part in 5000 appeared impractical, a table of densities for each 0.01 interval of weight fraction was prepared with the aid of a deviation chart. The density values are given in Table II, and the specific volumes in Table II R.

Linear interpolation between the values given in Table II is accurate to at least a part in 5000 as illustrated in Table III.

The interpolated densities were obtained by linear interpolation using the tabulated values of Table II. The calculated densities were obtained from Equation (1a) corrected by the use of the deviation plot.

The comparison of the results of this investigation with those reported by Maass and Hatcher[1] is shown in Table IV.

(4) A portion of this oxalate is being preserved and is available for further investigation.

TABLE II

DENSITIES IN VACUUM, G. PER CC., OF AQUEOUS SOLUTIONS OF HYDROGEN PEROXIDE AT 0°, AS A FUNCTION OF THE WEIGHT

	Fraction of water									
	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.0	1.4709	1.4651	1.4593	1.4535	1.4478	1.4421	1.4364	1.4307	1.4250	1.4193
.1	1.4136	1.4080	1.4024	1.3968	1.3913	1.3858	1.3804	1.3750	1.3696	1.3642
.2	1.3589	1.3536	1.3483	1.3430	1.3378	1.3326	1.3275	1.3223	1.3172	1.3121
.3	1.3071	1.3022	1.2971	1.2921	1.2871	1.2822	1.2773	1.2724	1.2676	1.2627
.4	1.2579	1.2531	1.2483	1.2436	1.2389	1.2342	1.2295	1.2248	1.2202	1.2156
.5	1.2110	1.2064	1.2018	1.1973	1.1928	1.1883	1.1838	1.1793	1.1749	1.1705
.6	1.1661	1.1617	1.1573	1.1529	1.1485	1.1441	1.1398	1.1355	1.1312	1.1269
.7	1.1226	1.1183	1.1140	1.1098	1.1056	1.1014	1.0972	1.0930	1.0888	1.0846
.8	1.0804	1.0763	1.0722	1.0680	1.0639	1.0598	1.0557	1.0516	1.0475	1.0434
.9	1.0393	1.0353	1.0313	1.0273	1.0233	1.0193	1.0154	1.0115	1.0076	1.0037
1.0	0.9998									

TABLE IIR

SPECIFIC VOLUMES G. PER CC. OF AQUEOUS SOLUTIONS OF HYDROGEN PEROXIDE AT 0°, AS A FUNCTION OF THE WEIGHT FRACTION OF WATER

	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.0	0.67986	0.68255	0.68526	0.68799	0.69070	0.69343	0.69618	0.69896	0.70175	0.70457
.1	.70741	.71023	.71306	.71592	.71875	.72160	.72443	.72727	.73014	.73303
.2	.73589	.73877	.74167	.74460	.74750	.75041	.75330	.75626	.75919	.76214
.3	.76505	.76793	.77095	.77393	.77694	.77991	.78290	.78592	.78889	.79195
.4	.79498	.79802	.80109	.80412	.80717	.81024	.81334	.81646	.81954	.82264
.5	.82576	.82891	.83209	.83521	.83836	.84154	.84474	.84796	.85114	.85434
.6	.85756	.86081	.86408	.86738	.87070	.87405	.87735	.88067	.88402	.88739
.7	.89079	.89421	.89767	.90106	.90449	.90794	.91141	.91491	.91844	.92200
.8	.92558	.92911	.93266	.93633	.93994	.94357	.94724	.95093	.95465	.95841
.9	.96219	.96590	.96965	.97343	.97723	.98107	.98483	.98863	.99246	.99631
1.0	1.00020									

TABLE III

ACCURACY OF LINEAR INTERPOLATION IN TABLE II

Wt. fraction of water	Interpolated density	Calculated density
0.105	1.4108	1.4106
.505	1.2087	1.2087
.905	1.0373	1.0374

TABLE IV

COMPARISON OF DENSITIES OBTAINED BY MAASS AND HATCHER WITH THOSE IN THIS INVESTIGATION

Density at 0°	Weight fraction water	
Maass and Hatcher	Maass and Hatcher	Huckaba and Keyes
1.0419	0.8943	0.8938
1.0894	.7767	.7783
1.1655	.5986	.6014
1.2404	.4330	.4368
1.2610	.3880	.3935
1.3235	.2656	.2677
1.3839	.1514	.1535
1.4144	.0958	.0984
1.4596	.0111	.0202
1.4649	.0000	.0105

The densities reported by Maass and Hatcher are lower than the ones reported here. These investigators reported great difficulty in eliminating decomposition of the peroxide during the density measurements. However during the measurements here reported no visible decomposition occurred. It will be perceived that if decomposition occurs during a density measurement, the value obtained will be lower than the true value.

The Change of Density with Temperature.—The effect of temperature on the densities of peroxide solutions was found by using a dilatometer constructed to permit the observation of expansions of volume of solutions from 0 to 20°. The dilatometer differed from the densitometer only in that the capillary section was much longer (9.5 cm.) and accurately divided into millimeters and calibrated. The diameter of the capillary section was obtained by determining the amount of mercury at a known temperature that filled the space between successive portions of the millimeter division marks. The first mark above the bulb of the dilatometer was taken to be the zero mark, and the total volume of the dilatometer from this mark was determined with conductivity water in the same manner as with the simpler densitometers. The following procedure was used in making a dilatometer measurement.

The density of the peroxide solution was determined at 0° by adjusting the liquid level to the zero mark following the same procedure used earlier. From the density at 0°, the concentration was established from Table II. The dilatometer was then placed in a 20° bath, and after equilibrium had been attained, the new liquid level was read. To ensure that the reading was made at equilibrium the level was observed twice by ap-

proaching the 20°[5] from both a lower and a higher temperature. From the level reading and the diameter of the capillary tube, the volume of liquid at 20° above the zero mark was calculated. The volume of liquid below the zero mark was corrected from 0 to 20° using the coefficient of cubical expansion of Pyrex glass. Thus, the total volume at 20° of a known weight of peroxide and also the density at 20° are determined.

Since an adequate correlation of the volumetric coefficients with weight fractions of hydrogen peroxide is possible, the coefficients of change are presented on a specific volume rather than density basis. The average coefficients of expansion between 0 and 20° to be listed were obtained by using the data to determine the constant α of Equation (2).

$$v_{t_2} = v_{0°C}\,(1 + \alpha\Delta t) \qquad (2)$$

where

v represents specific volume cc./g.
Δt represents change in temperature ($t_2 - 0°$)
α represents average coefficient of expansion between 0° and t_2

The experimental results are given in Table V. The relationship between α and weight fraction is adequately represented by the expression

$$\alpha = \frac{\log\,[(1.10344 - x)(10)] + 0.16908}{1523} \qquad (3)$$

where

x = weight fraction water
α = average coefficient of change in specific volume between 0 and 20°

A comparison of the specific volumes at 20° computed from the coefficients using Equation (3) with the direct experimental specific volumes is shown in Table VI. The differences are negligible in each case, demonstrating the adequacy of Equation (3).

For convenience, the coefficients have been calculated using Equation (3) for each 0.01 interval of weight fraction, and appear in Table VII. Linear interpolation in this table is satisfactory.

To determine the specific volume at some temperature, t_2, intermediate 0 and 20° of a hydrogen peroxide solution, subject to the assumption of temperature independence of α, the specific volume at 0° is obtained from Table II; α is then either obtained from Table VII or calculated by Equation (3); and finally the specific volume at t_2 obtained by the use of Equation (2).

TABLE V

AVERAGE COEFFICIENTS OF CHANGE IN SPECIFIC VOLUME OF HYDROGEN PEROXIDE SOLUTIONS BETWEEN 0 AND 20°

Weight fraction water	α
0.03123	0.0007759
.21471	.0007344
.40917	.0006656
.60841	.0005846
.78475	.0004326
1.00000	.0001206

TABLE VI

COMPARISON OF COMPUTED AND EXPERIMENTAL SPECIFIC VOLUMES

Weight fraction water	v exptl. at 20°	v calcd. at 20°
0.78475	0.92818	0.92826
.60841	.87037	.87006
.40917	.80836	.80836
.21471	.75103	.75101
.03123	.69888	.69918

TABLE VII

AVERAGE COEFFICIENTS OF SPECIFIC VOLUME CHANGE[a] FROM 0–20° OF AQUEOUS SOLUTIONS OF HYDROGEN PEROXIDE AS A FUNCTION OF THE WEIGHT FRACTION OF WATER

The entries of the table are to be multiplied by 10^{-4}.

	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.0	7.957	7.931	7.905	7.878	7.852	7.825	7.797	7.770	7.742	7.714
.1	7.685	7.657	7.629	7.599	7.570	7.540	7.510	7.480	7.449	7.418
.2	7.387	7.355	7.323	7.290	7.258	7.224	7.191	7.157	7.122	7.087
.3	7.052	7.016	6.980	6.944	6.906	6.869	6.831	6.792	6.753	6.713
.4	6.673	6.632	6.591	6.549	6.506	6.463	6.419	6.374	6.329	6.283
.5	6.236	6.188	6.140	6.090	6.040	5.989	5.937	5.884	5.830	5.775
.6	5.719	5.662	5.604	5.544	5.483	5.421	5.357	5.292	5.226	5.158
.7	5.088	5.016	4.943	4.867	4.790	4.710	4.629	4.544	4.457	4.368
.8	4.275	4.180	4.081	3.979	3.872	3.762	3.647	3.528	3.403	3.272
.9	3.135	2.992	2.840	2.680	2.511	2.331	2.139	1.933	1.711	1.470
1.0	1.206									

[a] This coefficient, designated herein as α, is defined by Equation (2).

Summary

The densities of aqueous solutions of hydrogen peroxide at 0° have been determined with a precision of a part in 5000. The coefficients of change with temperature in these densities have been determined from 0 to 20° with a precision such that densities calculated using the coefficients also have a precision of a part in 5000.

CAMBRIDGE, MASS. RECEIVED MARCH 20, 1948

(5) The mercury thermometer used in the 20° temperature bath could be estimated to 0.01°, and was checked against a platinum resistance thermometer.

[CONTRIBUTION FROM THE UNIVERSITY OF CHICAGO TOXICITY LABORATORY]

The Vapor Pressure of Eleven Organic Compounds[1]

BY C. ERNST REDEMANN,[2] SAUL W. CHAIKIN AND RALPH B. FEARING[3]

In order to complete other work in progress in this Laboratory, it was necessary to have accurate data over the temperature range 0 to 60° for the volatility of the compounds reported in this study. The volatility is readily computed from the vapor pressure but a search of the literature revealed that trichloronitromethane (chloropicrin)[4] was the only compound in the group for which data were available. For the remaining compounds data were so scarce as to make it difficult even to estimate their volatility. The volatility was therefore measured for these compounds by the method described in earlier reports.[5] The vapor pressure has been computed from the experimentally measured volatility and is here reported since it is more generally useful than the volatility.

were repeated until a constant reproducible volatility was obtained. If in any series of measurements there was a trend from high values to lower ones this series was continued until the results varied only in a random manner.

All the compounds here reported were prepared in laboratories other than the authors'. The source of each compound is given in a footnote to Table I. The compounds were submitted to our laboratory as pure compounds; however, whenever the sample was large enough to allow further purification it was carefully fractionally distilled in all-glass equipment containing a short Vigreux column before making any measurements upon it. In a few cases the sample submitted was too small to allow any further purification before use. The boiling point (or range), refractive index, and density reported in Table I were those observed for the sample just prior to use. The identity of each compound was assumed to be that stated by the submitter.

Nitrogen was used as the inert carrier gas as in previous

TABLE I

CONSTANTS OF THE COMPOUNDS STUDIED

Compound	Formula	Boiling point °C.	Mm.	Refractive index n_D	°C.	Density G./ml.	°C.	Constants A	A'	B
Trichloronitromethane[a]	Cl_3CNO_2	109.5–110	755	1.4611[i]	20	1.6558[i]	20	8.27526	11.69636	2054.3
Dimethyl acetylenedicarboxylate[b]	$(CCOOCH_3)_2$							9.20815	12.56598	2941.4
Methyl cyanoformate[c]	$CH_3OCO(CN)$	97	751			1.072[j]	20	8.4433	11.5782	2053.6
Vinyl mucochlorate[d]	$CH_2{=}CH{-}O{-}CH(CCl{=}C{-}Cl)(O{-}C{=}O)$	115	15	1.5028	25			9.8293	13.3245	3340.3
Phenylcarbylamine chloride[e]	$C_6H_5N{=}CCl_2$	104–105	28	1.5673	25	1.2830[k]	25	8.907	12.353	2820
3-Bromopentanone-2[f]	$CH_3COCH(Br)C_2H_5$	56	21	1.4579	20	1.3406	25	8.4256	11.84841	2359.4
		63–64	32							
1-Chloro-2-triazoethane[f]	$N_3CH_2CH_2Cl$	38–38.5	22	1.4658	20	1.2216[l]	20	8.7112	11.9397	2287.3
2-Nitrobutene-1[g]	$CH_2{=}C(NO_2)C_2H_5$	61	50	1.4373	20	1.0188	20	8.6073	11.8172	2298.7
1-Nitropropene[g]	$NO_2CH{=}CHCH_3$	59–60	34	1.4539[m]	20	1.0650[m]	20	8.4592	11.6041	2306.3
2-Nitropropene[g]	$CH_2{=}CH(NO_2)CH_3$	54	74			1.0660[n]	20	7.9272	11.0721	1993.1
1-Hydroxy-2-pentyne-4-one[h]	$HOCH_2C{\equiv}CCOCH_3$	88.5–89.5	5	1.4571	20	1.0765	20	10.1725	13.3691	3362.6

[a] Eastman Kodak Co. White Label. [b] From Dr. M. S. Kharasch, University of Chicago. The sample was too small to permit further purification before use. [c] From Dr. C. D. Hurd, Northwestern University. [d] From Dr. C. A. Thomas, Monsanto Chemical Co. [e] From Dr. Henry Gilman, Iowa State College. [f] From Dr. G. H. Coleman, University of Iowa. [g] From Dr. Marvin Gold, Visking Corp. [i] Brühl, *Z. physik. Chem.*, **16,** 214 (1895), gave $n^{22.8}D$ 1.46075 and d^{20}_4 1.6539. [j] Karvonen, *C. A.*, **18,** 1981–1982, gives d^{20} 1.0719. [k] Dyson and Harrington, *J. Chem. Soc.*, 193 (1940), report a density of 1.285 at 15°. [l] Foster and Newman, *ibid.*, **97,** 2576 (1910), give the density as 1.2885 at 24°. [m] Schmidt and Rutz, *Ber.*, **61,** 2146 (1928), give $n^{20}D$ 1.4527 and d^{20}_4 1.0661. [n] Blomquist, Tapp and Johnson, THIS JOURNAL, **67,** 1519 (1945), give a density, which corrected to d^{20}_4 is 1.0509, appreciably less than we found. Their boiling range of 48–49° (59.5 mm.) agrees moderately well with the temperature calculated from our equation at which the pressure is 59.5 mm.

Experimental

A description of the apparatus used and details of the measurements were reported in an earlier paper.[5b] For each compound at each temperature studied determinations studies.[5] No evidence of polymerization or oxidation during any of the studies was observed.

Results

In Table I are recorded, in addition to the physical constants of the compounds, the three constants A, A' and B for the two equations

$$\log p = A - B/T \quad (1)$$

$$\log WT = A' - B/T \quad (2)$$

computed by the method of least squares from the experimental points. These constants apply when the pressure is expressed in millimeters of mercury, the temperature, T, is the absolute tem-

(1) This work was carried out under contract with the National Defense Research Committee of the Office of Scientific Research and Development.

(2) Present address: 770 S. Arroyo Parkway, Pasadena 2, Calif.

(3) Present address: 622 N. East Ave., Oak Park, Ill.

(4) (a) Baxter, Bezzenberger and Wilson, THIS JOURNAL, **42,** 1388 (1920); (b) Herbst, *Kolloid Beihefte,* **23,** 330 (1927); (c) Blaszkowska-Zakrzewska, *Roczniki Chem.*, **8,** 210 (1928); **8,** 219 (1928); (d) Stull, *Ind. Eng. Chem.*, **39,** 517 (1947).

(5) (a) Bent and Francel, THIS JOURNAL, **70,** 634 (1948); (b) Redemann, Chaikin and Fearing, *ibid.*, **70,** 631 (1948).

perature and the volatility, W, is expressed in milligrams of agent per liter of nitrogen (or air). From these equations it is possible to calculate the vapor pressure, volatility, mean molar heat of vaporization, etc.

In Table II are recorded data pertaining to the precision of measurements for each compound described in this report. While these data would

TABLE II

PRECISION OF EXPERIMENTAL DATA

Compound	Percentage deviation from smoothed curve of Experimental points Maximum	Experimental points Mean	Points calculated from least squares equation Maximum	Points calculated from least squares equation Mean
Trichloronitromethane	0.99	0.46	0.36	0.24
Dimethyl acetylenedicarboxylate	1.7	.57	.52	.23
Methyl cyanoformate	0.89	.53	.47	.33
Vinyl mucochlorate	1.8	.98	.68	.27
Phenylcarbylamine chloride	2.43	1.24	.63	.38
3-Bromopentanone-2	1.34	0.54	.24	.18
1-Chloro-2-triazoethane	1.05	.66	.22	.21
2-Nitrobutene-1	1.84	.99	.12	.07
1-Nitropropene	1.60	.80	.18	.09
2-Nitropropene	1.07	.67	.49	.33
1-Hydroxy-2-pentyne-4-one	0.35	.18	.17	.11

indicate a precision of about 1% for most of the measurements, the vapor pressure, as computed by the equations given, may have an error somewhat larger than this amount since the vapor pressures calculated from the volatility in an inert gas stream are too large according to Gerry and Gillespie.[6] The values from which the constants given in Table I were determined were not corrected for this factor since the volatility in an inert gas was the quantity desired at the time the experimental work was done and consequently no additional measurements were made by which these corrections could be made.

Discussion

Since considerable data[4] were available for trichloronitromethane, redetermination of its vapor pressure was primarily for comparison of results. In Table III the results of several workers are compared at four temperatures. Blaszkowska-Zakrzewska[4c] also give two different values for the vapor pressure at 100° from direct measurements by two different methods, 532.0 and 524.3 mm. From the above Table and these data, the Hertz equation would appear best for the entire temperature range. Both Baxter's equation and ours are satisfactory at lower temperatures where the measurements were made, but give values which are too large at elevated temperatures by 9–11%. In the range 0 to 40° the first three equations give values agreeing within 2%.

TABLE III

COMPARISON OF VAPOR PRESSURES COMPUTED FOR CHLOROPICRIN FROM VARIOUS EQUATIONS

Equation	Pressure in millimeters at ° C. 0	20	40	100
Our	5.70	18.57	52.02	590
Hertz[4c]	5.68	18.56	51.31	530
Baxter[4a]	5.64	18.30	51.32	579
Blaszkowska-Zakrzewska[4c]	6.88	20.75	54.40	527

The generalizations for chloropicrin probably are also approximately true for all the compounds reported here, namely: within the temperature range 0 to 60° the results are good to 1 to 2%, but outside this range the error may become much larger.

Acknowledgment.—We wish to acknowledge the assistance of Miss Drusilla Van Hoesen for her helpful work in making some of the measurements.

Summary

1. The volatility of eleven organic compounds has been measured by a dynamic method.

2. The corresponding vapor pressures have been computed from the volatilities, and the constants for logarithmic equations for both the volatility and vapor pressure have been calculated.

3. The vapor pressure found for trichloronitromethane has been compared with measurements made by previous workers.

CHICAGO, ILLINOIS RECEIVED MARCH 15, 1948

(6) Gerry and Gillespie, *Phys. Rev.*, **40**, 269 (1932).

[CONTRIBUTION FROM THE LABORATORIES OF UNIVERSAL OIL PRODUCTS COMPANY]

Isomerization of Certain Olefins by Silica Gel at Room Temperature

BY W. S. GALLAWAY AND M. J. MURRAY

Silica gel adsorption techniques for the analysis and separation of hydrocarbon types have, in recent years, found wide application.[1] There has, however, been little published on the effect of the gel upon olefins although difficulty with this type of hydrocarbon has been mentioned by Mair.[2]

The present authors have made use of silica gel techniques together with infrared spectroscopy in a study of the composition of the various fractions of thermally cracked gasolines. The comparisons of the infrared spectra of these hydrocarbon mixtures before and after contact with the silica gel showed, in general, that the intensities of the absorption bands characteristic of olefin types were as expected. There were, however, two very striking exceptions. The strength of the 890 cm.$^{-1}$ band (normally associated with the structure RR'C=CH_2) in the spectrum of the starting material was always much greater than that found by summation over the cuts from the silica adsorption column. At the same time, the bands near 825 cm.$^{-1}$ (usually found in the spectra of tri-alkylethylenes) became stronger in the cuts than was anticipated. Such a change in double bond position might be caused either by polymerization or by isomerization.

The effect of silica gel upon two olefins of the type RR'C=CH_2 and one of the type RCH=CR'R'' was then investigated. All these olefins were found to isomerize rapidly at room temperature. 2-Ethyl-1-hexene isomerizes almost completely (90%) when passed through a silica gel column at 25° whereas 20% of 2,4,4-trimethyl-1-pentene is converted to the -2 isomer. The latter case was shown to have closely approached thermodynamic equilibrium by an experiment wherein 2,4,4-trimethyl-2-pentene was passed through the silica tower. A conversion of 80% was realized yielding an effluent found, by infrared, to be almost identical with that obtained on charging the 2,4,4-trimethyl-1-pentene. It appears probable that the composition of the effluent when 2-ethyl-1-hexene was charged also approximates the equilibrium mixture. 1-Hexene was not detectably isomerized under similar conditions.

The isomerization of the tertiary olefins which were studied occurs so readily at room temperature by contact with silica that the reaction was easily followed by an infrared examination of samples decanted from a vial containing the hydrocarbon and the gel. The results of this semi-quantitative study are given in Fig. 1a and 1b wherein the intensity of a characteristic band of each of the 2,4,4-trimethylpentene isomers is shown as a function of contact time.

As is to be expected, the rate of isomerization is dependent upon the ratio of gel to olefin. In the experiment just cited, in which there was a low gel to olefin ratio, only 29% of the 2,4,4-trimethyl-2-pentene was found to isomerize in two hours. However, in a silica gel adsorption column where the ratio was many times larger, the equilibrium composition was approached in a comparable time.

An infrared analysis of the effluent from the silica gel runs with the two diisobutylenes showed that, for these olefins, polymerization exerts a very minor effect compared to isomerization. As may be seen from Fig. 2, only 2,4,4-trimethylpentenes are present in measurable amounts in the main portion of the effluent. The last portion of the effluent was found to contain minor amounts of other materials, either polymers or oxidation products, which can account for no more than 3 or 4% of the total. A similar conclusion was reached in the case of 2-ethyl-1-hexene wherein by infrared study and by distillation of the effluent from the gel column, only minor amounts of higher boiling material were shown to be present.

The effect of temperature upon the degree of isomerization is very striking. When a C_7 fraction of a thermally cracked gasoline was passed through a silica gel adsorption column at room temperature, only 20 to 25% of the material having an 890 cm.$^{-1}$ infrared absorption band was recovered in the effluent. However, when the column was cooled to −20°, there was, within experimental error, no loss of this type of olefin.

In another test of the temperature effect, 2-ethyl-1-hexene was added to an excess of gel in each of two tubes which were held at −24° and +24°, respectively, for one hour. Infrared analyses of the recovered hydrocarbons showed that only 5% of this olefin isomerized at the lower temperature while 65% was converted at the higher temperature. The product recovered from the low temperature test had an odor similar to the charge, whereas the product obtained from the room temperature experiment had an odor suggesting contamination with oxygenated compounds. The infrared spectrum, however, showed only weak OH bands at 3300 cm.$^{-1}$ and no C=O absorption at 1725 cm.$^{-1}$.

The authors feel that the above-reported results though somewhat qualitative in nature, emphasize the necessity of carrying out the adsorption at low temperatures when certain types of olefinic hydrocarbons are present.

Experimental

The silica gel used in these experiments was from the

(1) A number of references on the use of silica gel may be found in a recent article by Mair, Gaboriault and Rossini, *Ind. Eng. Chem.*, **39**, 1072 (1947).

(2) B. J. Mair, *J. Research, Natl. Bur. Standards*, **34**, 435 (1945).

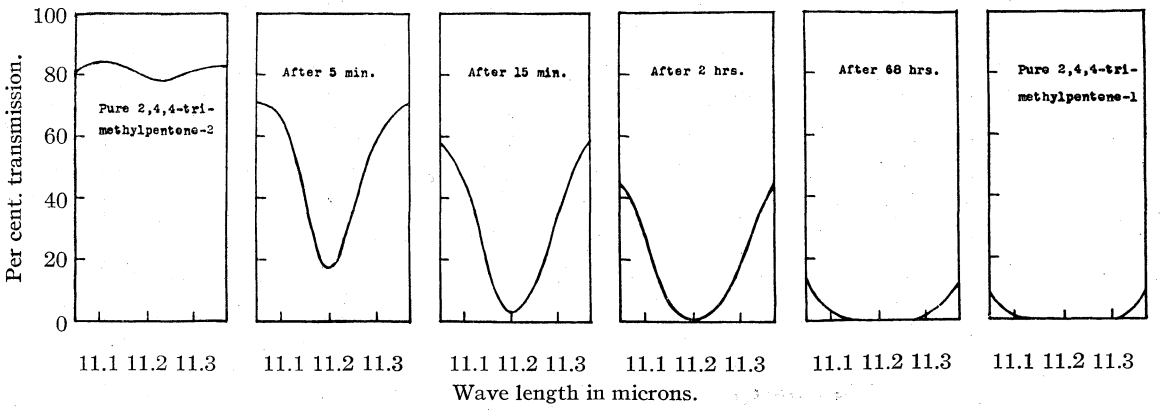


Fig. 1a.—The isomerization of 2,4,4-trimethyl-2-pentene to 2,4,4-trimethyl-1-pentene upon contact with silica gel at room temperature as evidenced by the increase in intensity of the 11.2 μ absorption band of 2,4,4-trimethyl-1-pentene.

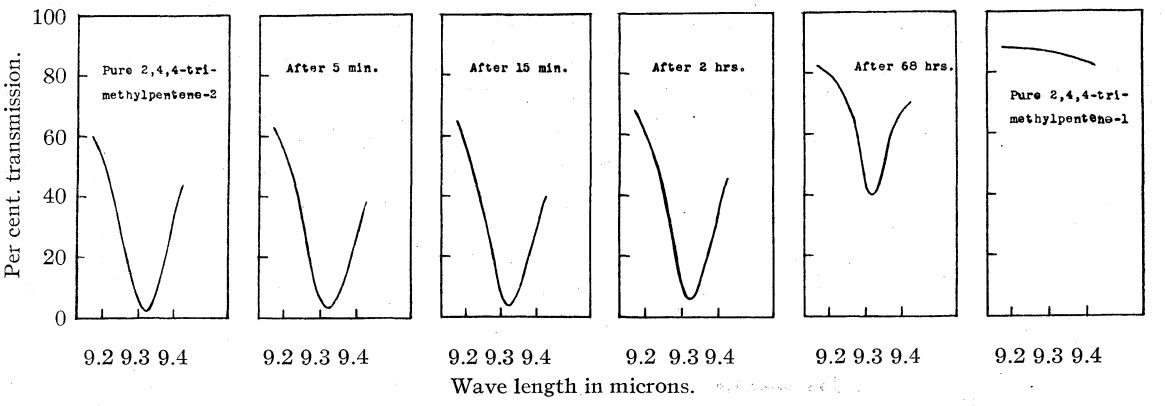


Fig. 1b.—The isomerization of 2,4,4-trimethyl-2-pentene to 2,4,4-trimethyl-1-pentene upon contact with silica gel at room temperature as evidenced by the decrease in intensity of the 9.3 μ absorption band of 2,4,4-trimethyl-2-pentene.

Davison Chemical Corporation. It had a mesh size of 28–200.

The two isomeric 2,4,4-trimethylpentenes were obtained by painstaking fractionation of the product from sulfuric acid polymerization of isobutylene. The infrared absorption spectra of the fractions selected for use followed closely those published by API Project 44. The spectra also showed that the samples of each isomer contained less than 0.5% of the other isomer.

The 2-ethyl-1-hexene was obtained by fractionation of the crude product supplied by the Connecticut Hard Rubber Co. using a Podbielniak Hyper-Cal column. Only the heart cut was used. From the intensity of the characteristic olefin band at 890 cm.$^{-1}$, the spectra of the distillation fractions, and the absence of bands characteristic of other types of olefins, the purity of the sample used is estimated to be of the order of 95%.

The 1-hexene used contained a small amount of other hexenes, both straight chain and of the tri-alkylethylene type. The conclusion drawn as to the non-isomerizing tendency of 1-hexene was based on spectroscopic data which showed no measurable increase in the total amounts of these other olefins.

The technique followed in the silica gel adsorption tests was essentially that described by Mair.[2] The desorbing agent was methanol which was removed from the final fraction of the effluent by water washing. For the low temperature runs, brine at $-20°$ was circulated through the jacket surrounding the adsorption tower.

The semiquantitative experiment involving the rate of isomerization of 2,4,4-trimethyl-2-pentene was performed by shaking intermittently 10 ml. of the olefin with 5 ml. of the gel. At specified times, samples of the hydrocarbon were pipetted out for infrared examination.

In order to study the effect of temperature upon the rate of isomerization of 2-ethyl-1-hexene, two tubes, each containing 15 ml. of silica gel, were cooled to $-80°$. To each was added 5 ml. of the olefin cooled to nearly the same temperature to minimize the effect of the heat of adsorption. One tube was then placed in iced hydrochloric acid at $-24°$ while the other was immersed in water at $+24°$. After one hour, ethanol cooled to about $-80°$ was added to each sample. Following the addition of water, the upper layer was removed, dried and examined by infrared.

The infrared spectra were obtained on a large Gaertner spectrometer equipped with automatic recording. The samples were examined in a rock-salt cell which provided a 0.10-mm. liquid film and allowed no contact with sealing compounds or waxes. The compositions of the mixtures of the 2,4,4-trimethylpentenes were calculated by standard methods[3] since all the components present were identified and reliable spectra of the pure hydrocarbons were at hand. However, in the case of the 2-ethyl-1-hexene samples, wherein the spectra of the other isomers were not available, it was not possible to allow for the interference of the other components. The results reported were calculated by direct comparison of the absorption intensities for the original material and the products, and therefore represent maximum amounts of 2-ethyl-1-hexene present.

(3) G. M. Webb and W. S. Gallaway, *Petroleum Processing*, **2**, 365 (1947).

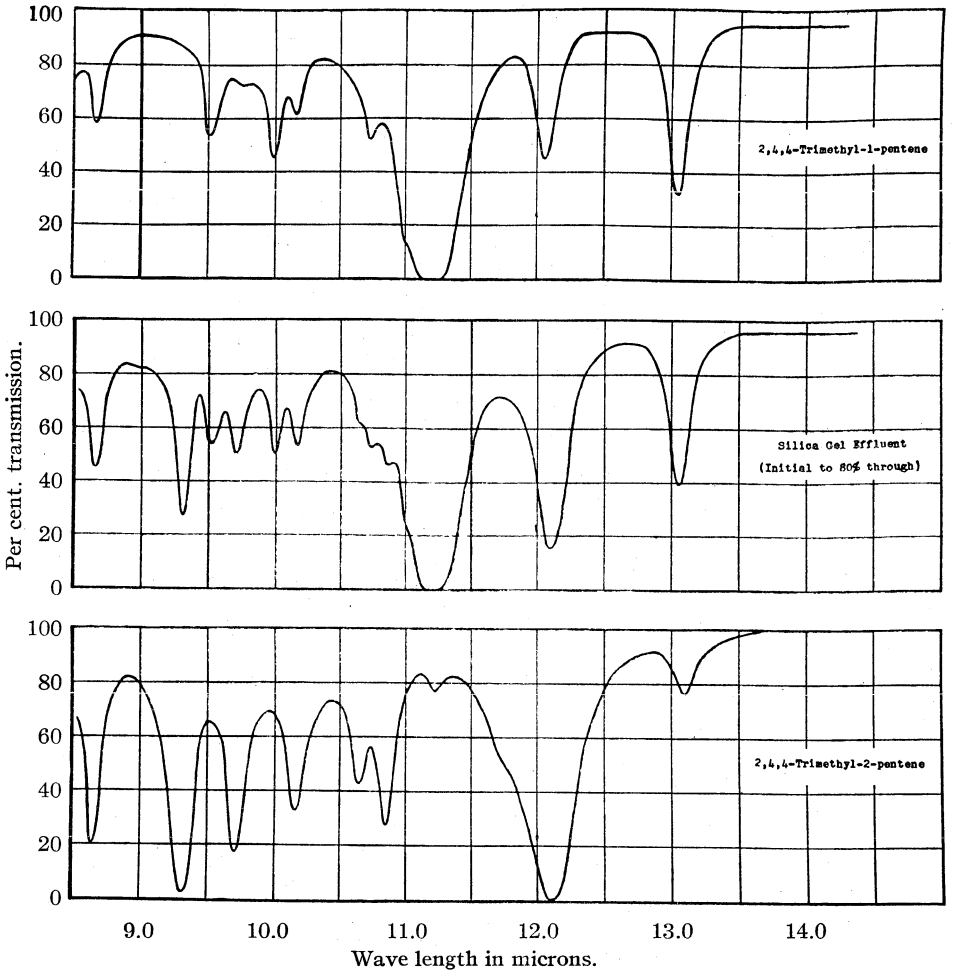


Fig. 2.—Comparison of the spectra of the 2,4,4-trimethylpentenes with the spectrum of the major portion of the effluent from a silica gel adsorption column to which the 2-isomer was charged.

Acknowledgment.—The authors wish to thank Mr. M. J. Stross for his coöperation in running the silica gel adsorption tests and Drs. Louis Schmerling and C. B. Linn for supplying the pure 2,4,4-trimethylpentenes.

Summary

1. At room temperature, each of the 2,4,4-trimethylpentenes is isomerized approximately to the equilibrium mixture of these olefins during passage through a silica gel adsorption column. Under the same conditions, 2-ethyl-1-hexene is almost completely isomerized, probably also to the equilibrium concentration.

2. Olefins of the $RR'C{=}CH_2$ type which are present in thermally cracked gasoline are also isomerized. The isomerization of hexene-1 is not appreciable.

3. Reduction of the temperature of the adsorption column to about −20° nearly halts the isomerization of the olefins studied.

RIVERSIDE, ILLINOIS RECEIVED FEBRUARY 26, 1948

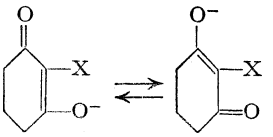
[CONTRIBUTION NO. 122 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Dihydropyrogallol, A New Ene-diol and its Oxidation Product. 1,2,3-Cyclohexanetrione Dihydrate—A Ketonic Isomer of Pyrogallol

BY B. PECHERER, L. M. JAMPOLSKY AND H. M. WUEST[1]

The ene-diols, compounds containing the group —COH=COH—, may be divided into two classes. The first class comprises about a dozen highly hindered stilbene diols which were studied by Fuson and his students[2] while the second class embraces those ene-diols containing a carbonyl group adjacent to the double bond. In the second group there are similarly a few well-defined members, which include ascorbic acid and its analogs,[3] reductone,[4] reductinic acid,[5] dihydroxymaleic acid, its salts and esters,[6] and hydroxytetronic acid.[7] To the second group may be added a miscellany of compounds such as 2,3-dihydroxy-1,4-benzoquinone, the corresponding naphthalene analog,[8] rhodizonic acid[9,10] and croconic acid.[9,10] A few other compounds containing the carbonyl group conjugated with the ene-diol group are mentioned in the literature, but if the further proviso is added that an ene-diol must react stoichiometrically with one molecule of iodine, then the rigid classification of these latter compounds is better deferred until this property has been demonstrated.

This paper describes a new ene-diol, dihydropyrogallol (I), prepared by the catalytic hydrogenation of pyrogallol in the presence of one mole of alkali. Previous workers[11,12,13,14,15] who studied the hydrogenation of pyrogallol obtained complex mixtures ranging from hexahydropyrogallols to cyclohexane, but the product after uptake of one mole of hydrogen has not been described previously. This method of reducing 1,3-dihydroxybenzenes, first used by Klingenfuss[16] for the preparation of dihydroresorcinol, works successfully for pyrogallol, but not for 4-substituted pyrogallols.[17] The success of this method is probably due to the formation of the resonating system



where X = H for resorcinol and X = OH for dihydropyrogallol.

Dihydropyrogallol is a typical ene-diol; it behaves as a monobasic acid and consumes two equivalents of iodine. With ferric chloride it gives a deep blue color which gradually fades. It has been further characterized by the preparation of a monoacetate and the bis- and tris-(phenylhydrazones) of 1,2,3-cyclohexanetrione.

Since dihydropyrogallol was originally prepared as a stabilizer for edible fats it was desirable to determine the nature of its oxidation products. Observations, recorded below, indicated that pyrogallol was not the primary oxidation product. On oxidation with iodine, using the method of Reichstein and Oppenauer[18] for reductinic acid, a white crystalline product melting at 106°, having the composition $C_6H_{10}O_5$, was obtained. This product was a neutral substance that did not decolorize iodine solution, slowly reduced silver nitrate, immediately reduced ammoniacal silver nitrate and gave a bis-(phenylhydrazone) identical with that obtained from dihydropyrogallol. Treatment with hydrogen sulfide gave dihydropyrogallol in high yield. These properties indicated the structure of a dihydrated 1,2,3-cyclohexanetrione (IIa or IIb).

(1) Present address: William R. Warner & Co., New York, N. Y.

(2) Fuson, *et al.*, THIS JOURNAL, **61**, 975, 2010 (1939); **62**, 600, 2091, 2962 (1940); **63**, 1500, 1679, 2645, 2648 (1941); **64**, 2152, 2891 (1942).

(3) *Cf.* the excellent review by Haworth and Hirst in "Ergebnisse der Vitamin und Hormonforschung," Vol. II, Akademische Verlag., Leipzig, 1939, p. 160–191.

(4) v. Euler and Martius, *Ann.*, **505**, 73 (1933); *Svensk Kem. Tidskr.*, **45**, 73 (1933).

(5) Reichstein and Oppenauer, *Helv. Chim. Acta*, **16**, 988 (1933).

(6) Fenton, *et al.*, *J. Chem. Soc.*, **69**, 561 (1896); **73**, 71 (1898); **87**, 804 (1905); **101**, 1571 (1912); Fox, *J. Org. Chem.*, **12**, 535 (1947).

(7) Micheel and Jung, *Ber.*, **66**, 1291 (1933); Micheel and Haarhoff, *Ann.*, **545**, 28 (1941).

(8) This substance has been found to react quantitatively with one mole of iodine and therefore may be classed as a true ene-diol.

(9) Nietzki and Benckiser, *Ber.*, **19**, 293 (1886); Carpéni, *J. chim. phys.*, **35**, 193 (1938).

(10) Sprinson and Chargaff, *J. Biol. Chem.*, **164**, 433 (1946).

(11) Senderens and Aboulenc, *Compt. rend.*, **174**, 616 (1922); Senderens and Mailhe, *ibid.*, **146**, 1193 (1908).

(12) Somlo, *Z. Elektrochem.*, **35**, 769 (1929).

(13) Lindemann and de Lange, *Ann.*, **483**, 31 (1930).

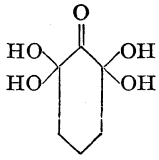
(14) Packendorff, *Ber.*, **68**, 1251 (1935).

(15) Thiele and Jaeger, *Ber.*, **34**, 2842 (1901).

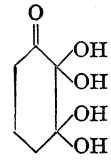
(16) U. S. Patent 1,965,499, *C. A.*, **28**, 5476 (1934); Barell Festschrift, Fredrick Reinhardt, Basel, 1936, p. 217.

(17) Unpublished work in this laboratory. Klingenfuss[16] states that 4-substituted resorcinols can be hydrogenated to dihydro derivatives.

(18) Reichstein and Oppenauer, *Helv. Chim. Acta*, **17**, 290 (1934).



IIa



IIb

Attempts to dehydrate or isomerize II yielded impure pyrogallol. Treatment with acetic anhydride gave pyrogallol triacetate in further support of structure II. Borsche[19] attempted to prepare a ketonic isomer of pyrogallol[20] from 1,3-dioximinocyclohexanone without success.

The absence of color in II is explained by the hydration which destroys the conjugation of the carbonyl groups. Although other 1,2,3-triones, such as tetramethyl-1,2,3-cyclopentanetrione[21] and 2,3,4-pentanetrione[22,23] form colorless hydrates which can be converted to colored anhydrous forms, it is unlikely that II can be dehydrated without isomerization to pyrogallol in view of the stabilization afforded by formation of the resonating benzene ring.

Reichstein and Oppenauer[18] oxidized reductinic acid, the next lower homolog of dihydropyrogallol to 1,2,3-cyclopentanetrione but failed to isolate a crystalline product. These workers noted the appearance of crystals during the isolation but on continued distillation, the crystals were converted to a sirup which yielded only the tris-(phenylhydrazone) of 1,2,3 - cyclopentanetrione. Whether their failure to isolate the crystalline trione is due to a lower stability is difficult to judge; however, in the present case, strict adherence to the procedure described below is necessary to obtain any crystalline product.

Attempts to use hydrogen peroxide for the oxidation of dihydropyrogallol showed that a trace of ferric ion was necessary for reaction to occur. From this reaction, an unexpected product, m. p. 169–170°, having the composition $C_6H_7O_3$ was isolated. This product was not reduced by hydrogen sulfide and gave no color with ferric chloride, but on the steam-bath yielded the same tris-(phenylhydrazone) obtained from I and II. Molecular weight determinations in acetone solution gave values corresponding to a monomer, but since the simple formula $C_6H_7O_3$ is unlikely, further work is necessary to elucidate the structure of this substance.[24]

Experimental[25]

Dihydropyrogallol (I).—This was prepared by the method of Klingenfuss[16,26] taking precautions to protect the alkaline pyrogallol solution from atmospheric oxygen with nitrogen.

One kg. of pyrogallol (E. K. Practical) (7.95 moles on a 100% basis) was dissolved in 2 liters of water containing 320 g. of sodium hydroxide (8 moles) and reduced at 60° under 1000 lb. hydrogen pressure using 50 g. of Raney nickel. The reduction was complete in about five hours. When cool, the catalyst was filtered off, and the filtrate acidified at −5° with 675 ml. of concentrated hydrochloric acid whereupon a light tan solid precipitated. After thirty minutes at −5°, the mixture was filtered and yielded 816 g. (80%) of material melting at 89–93°. Another 87 g. of product of the same m. p. was isolated after taking to dryness under nitrogen and extracting with benzene.

For purification, the dried material was recrystallized from dry benzene (550 ml. for 100 g.) using iron-free charcoal[27] to decolorize the solution. Dihydropyrogallol crystallizes from benzene in clusters of needles which are transformed to plates of m. p. 109–112° on drying. A sample after repeated recrystallization melted at 114°.

Anal. Calcd. for $C_6H_8O_3$: C, 56.22; H, 6.28. Found: C, 56.20; H, 6.16.

The substance behaves as a monobasic acid on titration with standard alkali. Fifty mg. of dihydropyrogallol consumed 0.782 milliequivalent of iodine; theory 0.780.

At room temperature, 100 ml. of benzene, ethanol, glycerol and ether dissolve 1.2, 20, 3 and 0.33 g., respectively.

The substance is stable in dry air for a few days after which decomposition sets in at an accelerated rate. In an inert atmosphere dihydropyrogallol has been stored for two years without deterioration.

Ferric chloride gives a blue color which fades in a short time. This "vanishing blue" color test can be repeated until all of the dihydropyrogallol has been consumed, but further additions give only the color of dilute ferric chloride solution. This observation indicated that an abnormal oxidation product was present.

Monoacetate of Dihydropyrogallol.—This derivative was prepared from 5 ml. of acetic anhydride and 4.0 g. of dihydropyrogallol in 10 ml. of pyridine. After two recrystallizations from ethyl acetate 3.05 g. of long prismatic crystals were obtained, m. p. 154–155.5°. The position of the acetyl group is uncertain; a red-purple color is obtained with ferric chloride.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.78; H, 6.15. Calcd. for one CH_3CO: 25.3. Found: 26.1, 26.4.

1,3-bis-(Phenylhydrazone) of 1,2,3-Cyclohexanetrione.—This was prepared by treating dihydropyrogallol in dilute acetic acid solution with an excess of phenylhydrazine at 100°. Recrystallization from methanol gave bronze-red crystals, m. p. 131–132.5°. The position of the phenylhydrazone groups is inferred from the work of Henle and Schupp[28] who found that the reaction of mesoxalic aldehyde with phenylhydrazine gave a 1,3-bis-(phenylhydrazone).

Anal. Calcd. for $C_{18}H_{18}ON_4$: C, 70.56; H, 5.92. Found: C, 70.09; H, 5.63.

tris-(Phenylhydrazone) of 1,2,3-Cyclohexanetrione.—After heating the above bis-(phenylhydrazone) with phenylhydrazine at 130° for two hours, the cooled mixture deposited a dark oil on dilution with water. The aqueous layer was decanted and the oil dissolved in a minimum of hot ethanol. On cooling, yellow crystals were obtained which were filtered and washed with a little ether. After three recrystallizations from ethanol the m. p. was con-

(19) Wallach Festschrift, 301 (1909); *C. A.*, **5**, 883 (1911).

(20) Phenylhydrazine does not react with pyrogallol under the conditions described in the Experimental Section.

(21) Shoppee, *J. Chem. Soc.*, 269 (1936).

(22) Sachs and Barschall, *Ber.*, **34**, 2047 (1901).

(23) Calvin and Wood, THIS JOURNAL, **62**, 3152 (1940).

(24) This will form the subject of a later communication.

(25) All melting points are uncorrected.

(26) One of the Referees has pointed out that a detailed procedure for the preparation of dihydroresorcinol has been published by Thompson, "Organic Syntheses," **27**, 21 (1947). This volume was received on January 20, 1947; this paper submitted on January 9.

(27) Charcoal containing iron imparts a blue color to the product.

(28) Henle and Schupp, *Ber.*, **38**, 1372 (1905), gave the first rigorous proof for structure of the reaction product of phenylhydrazine with a 1,2,3-tricarbonyl compound. A few years earlier Sachs and Röhmer, *ibid.*, **35**, 3308 (1902), assigned a 1,3 structure for the bis-(phenylhydrazone) of 2,3,4-triketopentanetrione, but their evidence is not convincing.

stant at 186°. Borsche,[22] who prepared this substance in another way, reported 182–183°.

Preparation and Properties of 1,2,3-Cyclohexanetrione Dihydrate (II).—To a stirred solution of 32 g. of dihydropyrogallol (0.25 mole) in 250 ml. of water at 3–5°, 63.1 g. of finely powdered iodine was added in portions of 1 or 2 g. over a period of one and one-half hours.[29] After 45.2 g. of iodine had been added the solution was brown but a test for free iodine was negative; the brown color disappeared however on dilution. Freshly precipitated and washed silver chloride (0.75 mole) was then added to convert the hydriodic acid to hydrochloric acid. As the conversion took place the dark brown color faded. Next the bulk of the hydrochloric acid was neutralized with silver carbonate (0.385 mole); removal of more acid will result in reduction of the silver carbonate to metallic silver. After the evolution of carbon dioxide became very slow (twenty to thirty minutes), the silver salts were filtered off and washed with several portions of cold water. The clear yellow filtrate was then evaporated *in vacuo* below 35° until the volume was 20–30 ml. whereupon the contents set to a mass of white crystals. At this point evaporation should be stopped or the crystals will disappear and be converted to a red sirup from which no crystalline material can be isolated.

The crystals were filtered and copious amounts of ether used to rinse out the flask and wash the precipitate. The product was then stored for a day or two *in vacuo* over calcium chloride and sodium hydroxide to remove traces of adherent acid. If traces of acid remain, indicated by the formation of a pink color, the product should be ground under ether which dissolves only the colored material.

The yield of dry material, m. p. 104–105°, averages about 20 g. Repeated recrystallization from dry ethyl acetate, which results in considerable loss, raises the m. p. to 106°.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.28; H, 6.32.

The substance has the formula of a dihydrated pyrogallol, $C_6H_6O_3 \cdot 2H_2O$, and has the following properties: It is very soluble in water and alcohol, but insoluble in ether and benzene. Silver nitrate solution gives no turbidity but is slowly reduced. Ammoniacal silver nitrate is reduced immediately. A five per cent. aqueous solution has a *p*H of 5 and gives no color with ferric chloride.

From 100 mg. of II and phenylhydrazine, 95 mg. of a red crystalline compound was obtained, m. p. 134–135°; mixed m. p. with a sample of the 1,3-bis-(phenylhydrazone) of 1,2,3-cyclohexanetrione, 131–133°.

A stream of hydrogen sulfide was passed into a solution of 0.5 g. of the substance in 10 ml. of water. Free sulfur was precipitated, and from the filtrate 0.44 g. of dihydropyrogallol, m. p. 108–110°, was recovered.

Attempts to dehydrate the substance by azeotropic distillation were unsuccessful but indicated that dehydration was accomplished by isomerization to pyrogallol.

A few mg. of II in pyridine gave a purple gray flash when heated to about 80° and after evaporation of the solvent a little impure pyrogallol, m. p. 125–130°, could be sublimed from the residue. Control experiments with pyrogallol gave about 50% recovery of impure pyrogallol of m. p. 132–135°.

Preparation of Pyrogallol Triacetate from II.—One and eighteen-hundredths g. of II was suspended in 5 ml. of acetic anhydride at 0°, and a drop of sulfuric acid added. The solution assumed a momentary pink color and warmed to about 35°. After standing overnight, the mixture was diluted with water whereupon a mass of fine white needles separated. The crystals were filtered off, washed with water and recrystallized from ethanol. The crystalline product, m. p. 160.5–162°, weighed 0.5 g.

One gram of pyrogallol treated similarly gave 1.49 g. of the triacetate, m. p. 162–163°.[30] The mixed melting point was 160.5–162°.

The Preparation of $(C_6H_7O_3)_n$.—Sixty-four grams of dihydropyrogallol (0.5 mole) was dissolved in 1 liter of water containing 2 drops of ferric chloride solution (10%). To the stirred solution 54 ml. of "30% hydrogen peroxide" (0.3164 g. of hydrogen peroxide per ml.) was added dropwise, whereupon the color of the dihydropyrogallol-ferric ion-complex reappeared. Considerable heat was evolved, but the rate of addition was so adjusted that the internal temperature was 45°. The pale yellow solution (*p*H 2) was concentrated *in vacuo* at 30° to about 75 ml. whereupon the residue set to a crystalline mass, which was filtered off and dried *in vacuo*. Twenty-six g. of slightly yellow product, m. p. 85–88°, was obtained. Recrystallization from ethyl acetate-ether gave 10 g. of white crystals, m. p. 169–170°, dec.

Anal. Calcd. for $C_6H_7O_3$: C, 56.68; H, 5.51. Found: C, 56.55, 56.62; H, 5.57, 5.61. Molecular weight, calcd.: 127. Found: 120 (by isothermal distillation against azobenzene in acetone).

Treatment of this product with phenylhydrazine and a few drops of acetic acid gave a red precipitate *immediately*. The mixture was warmed overnight on the steam-bath and worked up in the usual manner. On recrystallizing from ethanol orange crystals, m. p. 187°, were obtained that gave no depression with the tris-(phenylhydrazone) of 1,2,3-cyclohexanetrione.

The new product does not react with iodine nor hydrogen sulfide, but has not been investigated further.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and molecular weight determination reported in this paper.

Summary

The preparation of a new ene-diol, dihydropyrogallol, is described.

Oxidation of dihydropyrogallol with iodine yields 1,2,3-cyclohexanetrione dihydrate, a ketonic isomer of pyrogallol; while oxidation with hydrogen peroxide in the presence of a trace of ferric ion yields a product $(C_6H_7O_3)$ of unknown constitution.

NUTLEY, N. J. RECEIVED JANUARY 12, 1948

(29) Addition of a few ml. of carbon tetrachloride, or any other indifferent organic solvent, accelerates the reaction. This is probably due to the better solubility of iodine in the organic solvent.

(30) The literature records melting points of 162–163, 165, and 172–173° for pyrogallol triacetate.

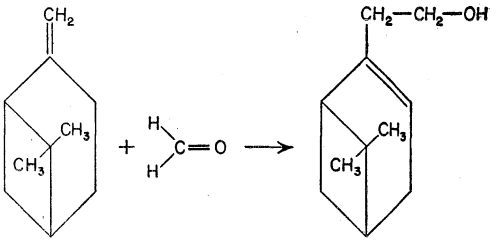
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Preparation and Reactions of Methylenecyclohexane

BY RICHARD T. ARNOLD AND JOHN F. DOWDALL[1]

It has been shown repeatedly during the past few years that many monoölefins will react with maleic anhydride,[2,3] sulfur trioxide,[4] formaldehyde[5] and azodicarboxylic ester[2] to form 1-1 adducts in which the original olefinic double bond has migrated to an adjacent position.

β-Pinene, for example, undergoes a thermal reaction with formaldehyde at 180° to form "nopol" (I) in excellent yields.[5]



(I)

Assignment of the double bond position in (I) rests upon the fact that nopinone is not obtained on ozonolysis.

Our investigation was initiated in the hope that independent syntheses could be found for these 1–1 adducts if a symmetrical olefin of the "isobutylene type" were used as one of the starting materials. Consequently, we have examined the products formed when methylenecyclohexane is allowed to react (separately) with paraformaldehyde, maleic anhydride and sulfur trioxide. It appears that in each of these cases, the reaction is accompanied by a shift of the exocyclic double bond into the six-membered ring. A summary of the observed transformation is shown on the chart.

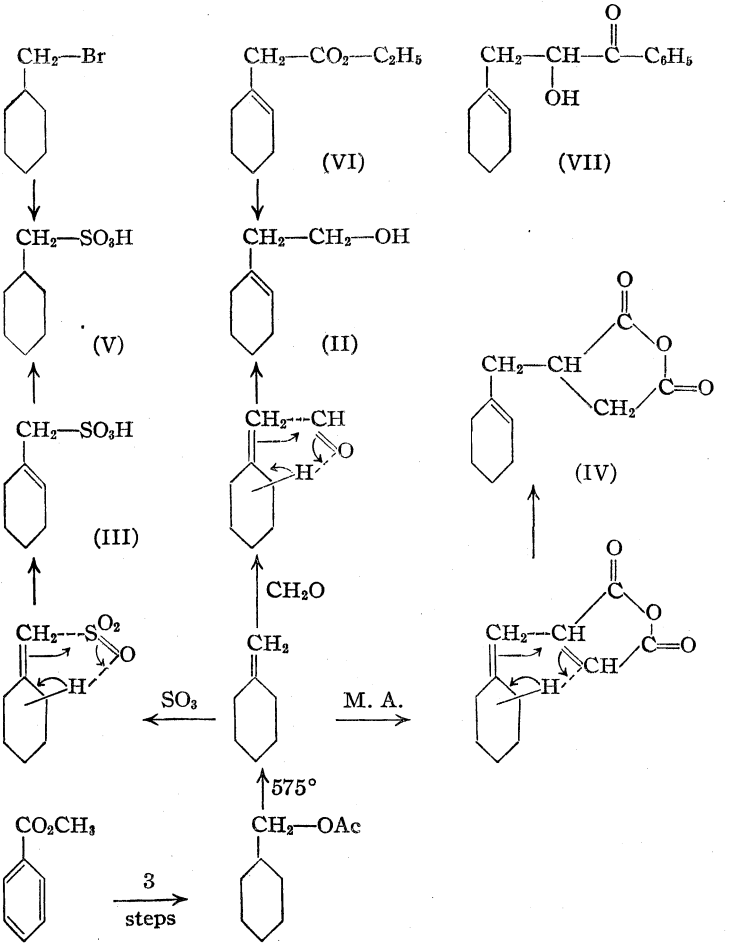
2-(Δ[1]-Cyclohexenyl)-ethanol (II) obtained from the reaction between methylenecyclohexane and formaldehyde was synthesized independently from ethyl Δ[1]-cyclohexenylacetate by reduction with sodium and alcohol.[6] Samples prepared by each of these two routes formed identical 3,5-dinitrobenzoates (m. p. 80–81°).

Location of the sulfonic acid residue in III was established by catalytic reduction to cyclohexylmethane sulfonic acid (V). This in turn was prepared independently from hexahydrobenzyl bromide.

Careful oxidation of compounds III and IV gave no identifiable cyclohexanone, thus indicating that the carbon–carbon double bond in these molecules does not occupy the exocyclic position.

During the course of this study, it was shown that highly reactive aldehydes other than formaldehyde will form 1–1 adducts with certain monoolefins. The product resulting from methylenecyclohexane and phenylglyoxal is tentatively regarded as having the structure VII.

We regard the formation of these adducts as occurring *via* a transient cyclic complex which is formed by a simultaneous attack of the reagent at an α-methylenic group and a carbon atom of the double bond which is furthest removed from this methylene group. A shift of the double bond



(1) Du Pont Post-doctorate Fellow, 1946–1947.

(2) Alder, Posher and Schmitz, *Ber.*, **76**, 27 (1943).

(3) Ross, Gebhart and Gerecht, THIS JOURNAL, **68**, 1373 (1946).

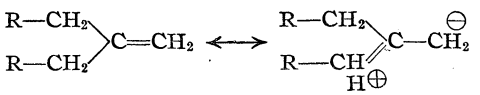
(4) Bordwell, Suter and Webber, *ibid.*, **67**, 827 (1945).

(5) Bain, *ibid.*, **68**, 638 (1946). See also Ritter, U. S. Pat. 2,335,027 (1943).

(6) Cook and Dansi, *J. Chem. Soc.*, 500 (1935).

is a necessary consequence of this mechanism.[7]

The unusual reactivity shown by isobutylene type olefins is probably due, in large part, to hyperconjugation (*i. e.*, no bond resonance).



A study of the reactivity of methylenecyclopentane with formaldehyde, maleic anhydride, sulfur trioxide and azodicarboxylic ester is now in progress in this laboratory.

Experimental

Hexahydrobenzyl Acetate.—Three hundred grams of freshly distilled methyl benzoate was reduced to ethyl hexahydrobenzoate employing Raney nickel (10 g.) with hydrogen (2500 lb./sq. in.) at 125°. Reduction was complete in thirty minutes. After removing the catalyst, by filtration, the filtrate was reduced with hydrogen (4000 lb./sq. in.) and copper–chromite catalyst (15 g.) at a temperature of 250°. Direct acetylation of the product (after removing the catalyst) gave hexahydrobenzyl acetate; yield 275 g. (80%); b. p. 195–196° (745 mm.).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.20; H, 10.36. Found: C, 69.65; H, 10.10.

Methylenecyclohexane.—Hexahydrobenzyl acetate was passed continuously at the rate of 25 ml./hr. through a one-inch stainless steel pipe having a four-inch hot zone held at 570–575°. Dry nitrogen was passed slowly through the apparatus during the entire reaction. Removal of the acetic acid formed was effected by thorough extraction of the total liquid product with aqueous sodium carbonate (10%). Careful distillation of the neutral fraction gave pure methylenecyclohexane (72–88%) and unreacted hexahydrobenzyl acetate (8–22%). The olefin distilled sharply at 101–102° (738 mm.) and was identical with a sample prepared using the Tschugaeff[8] method following the directions of Faworski and Bergmann.[9]

2-(Δ-^{1}Cyclohexenyl)-ethanol.—To methylenecyclohexane (100 g.) contained in four Carius tubes was added paraformaldehyde (22.4 g., 95%). These tubes were cooled, flushed with nitrogen, sealed and heated at 200–205° for four hours. Direct fractional distillation of the combined products gave unused methylenecyclohexane (50 g.) and the 1-1 unsaturated alcohol; yield 50 g. (77%); b. p. 66–68° (1.8 mm.).

This alcohol gave a 3,5-dinitrobenzoate (m. p. 80–81°) identical with that formed from an authentic sample of 2-(Δ^1-cyclohexenyl)-ethanol.[6]

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.20; H, 11.10.

Reaction of Methylenecyclohexane with Phenylglyoxal.—A mixture containing phenylglyoxal (67 g.) and methylenecyclohexane (38.4 g.) was sealed under nitrogen and heated at 200° for twelve hours. Direct distillation gave a pale yellow oil; yield 80 g. (70%); b. p. 130–133° (0.4 mm.).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.89; H, 7.92.

Δ^1-Cyclohexenylmethylsuccinic Acid.—A solution composed of methylenecyclohexane (40 g.) maleic anhydride (19.6 g.), and dry benzene was heated (under nitrogen) at 220–225° for eight hours. Distillation gave a viscous oil; b. p. 176–178° (12 mm.). This material failed to crystallize and was dissolved in warm potassium carbonate solution (10%). Careful acidification gave an oil which crystallized and, when pure, melted at 121°. It depressed the melting point of maleic acid 20°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.59; N. E. 106.1. Found: C, 62.37; H, 7.75; N. E. 105.8.

Oxidation of this sample at 30° with aqueous permanganate was rapid but no cyclohexanone could be detected.

Δ^1-Cyclohexenylmethane Sulfonic Acid.—Sulfur trioxide (22 g.) was distilled slowly into a mixture of dioxane (37 ml.) and ethylene chloride (20 ml.) maintained at −5°. To this was added over a period of one hour methylenecyclohexane (26.4 g.) dissolved in ethylene chloride (20 ml.). The solution, after standing overnight in an ice chest, was poured into ice water (800 ml.). When the aqueous phase was treated with barium carbonate (55 g.), reduced in volume (by evaporation on a steam-bath) to 200 ml. and chilled, there was obtained barium Δ′-cyclohexenylmethanesulfonate (20 g.). An additional 35 g. was produced on further evaporation. Treatment with one equivalent of sodium sulfate gave the sodium salt which in turn was converted into an S-benzylthiouronium salt[10]; m. p. 173–173.5°.

Anal. Calcd. for $C_{15}H_{22}O_3S_2N_2$: C, 52.60; H, 6.48. Found: C, 52.75; H, 6.61.

Cyclohexylmethanesulfonic Acid.—(a) Hexahydrobenzyl bromide (20 g.) was heated for thirty hours under reflux with sodium sulfite (10% excess) dissolved in water (100 ml.). When the solution cooled, a large quantity of sodium cyclohexylmethanesulfonate precipitated. Two recrystallizations from water gave a material which was free from bromide ion. An S-benzylthiouronium salt melted at 182–183°.

(b) Catalytic hydrogenation of an aqueous solution of sodium Δ^1-cyclohexenylmethanesulfonate was effected slowly with hydrogen (45 lb./sq. in.) and palladium–charcoal (10%) catalyst. Conversion to an S-benzylthiouronium salt in the usual manner[10] gave a product (m. p. 182–183°) which did not depress the melting point of the authentic sample described above.

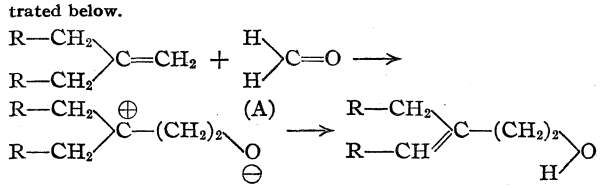
Summary

1. It has been shown that methylenecyclohexane reacts with formaldehyde, phenylglyoxal, maleic anhydride and sulfur trioxide to form 1–1 adducts.

2. A mechanism which necessitates a shift of the double bond to an adjacent position is suggested.

MINNEAPOLIS 14, MINN. RECEIVED JANUARY 10, 1948

(7) It does not appear possible at present to exclude an alternate mechanism involving a short-lived ionic intermediate (A) as illustrated below.



The rate of decomposition of (A) may be so rapid that its detection experimentally will be difficult or even impossible.

(8) Tschugaeff, *Ber.*, **32**, 3335 (1899).

(9) Faworski and Bergmann, *Ber.*, **40**, 4865 (1907).

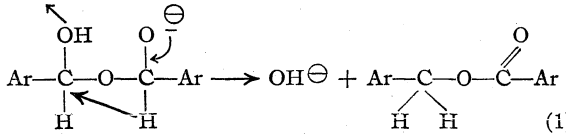
(10) Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of the Cannizzaro Reaction. II. Hydroxy and Amino Aldehyde Derivatives

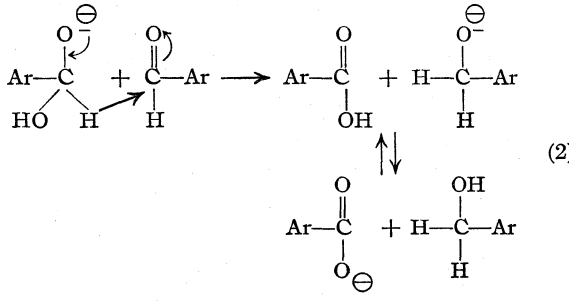
BY ELLIOT R. ALEXANDER

In an earlier communication[1] it was shown that the Cannizzaro reaction of benzaldehyde in a homogeneous system does not involve a chain reaction of the kind which is usually greatly influenced by the presence of peroxides or peroxide inhibitors. There are, then, two ionic mechanisms based upon the transfer of a hydrogen atom with its pair of electrons (*i. e.*, a hydride ion), which are in accord with much of the data. In one of the mechanisms which has been proposed by Geissman,[2,1] the essential feature of the reaction involves the *displacement* of a hydroxyl group from a saturated carbon atom (equation 1).



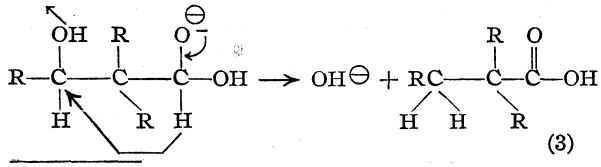
(1)

In the other mechanism, which is a slight modification of one originally proposed by Hammett[3,1] the *addition* of a hydride ion to a carbonyl group is postulated (equation 2).



(2)

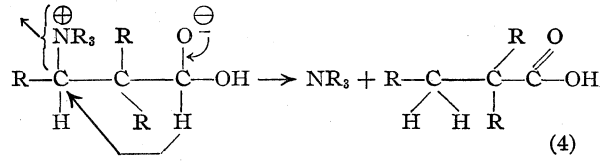
With respect to the first mechanism it appears that the direct chemical displacement of a hydroxyl group from a saturated carbon atom is unknown in alkaline solution.[4] If, however, such a displacement does occur over the carbon–oxygen–carbon system shown in equation 1, a similar displacement might be expected over the carbon–carbon–carbon system of a β-hydroxy aldehyde (equation 3).



(3)

Thus a saturated, non-hydroxylated acid should be a by-product in the transformation provided that the intramolecular reaction proceeded at a rate comparable to the normal Cannizzaro reaction or reverse aldolization. The normal reaction, of course, would be expected to give a molecule of a β-hydroxy acid and a molecule of a β-glycol.

A particularly favorable situation for such an intramolecular displacement is a quaternary aminoaldehyde. In this case the approach of the hydride ion to the carbon atom is favored by the positively charged nitrogen atom and subsequent bond-breaking would involve the separation of a neutral molecule.[5]



(4)

Accordingly it was the object of this work to isolate unsubstituted saturated acids from the Cannizzaro reaction of hydroxy and amino aldehyde derivatives.

Experimental[6]

Preparation of Starting Materials—With the exception of the methiodide of α-dimethylaminoisobutyraldehyde which is described below, all of the starting materials were known and were prepared by the procedures given in the footnotes of Table I. The physical properties of these compounds agreed with those which were recorded in the literature.

α-Bromoisobutyraldehyde and α-Bromoisobutyraldehyde Diethylacetal.—In a one-liter, three-necked round-bottomed flask fitted with a stirrer, a dropping funnel, and a reflux condenser were placed isobutyraldehyde diethylacetal (146 g., 1.0 mole), calcium carbonate (150 g., 1.5 moles) and 300 ml. of carbon tetrachloride. The flask was immersed in an ice–salt mixture, stirring was commenced, and bromine (51 ml., 1.0 mole) was added dropwise over the course of an hour. The reaction mixture was then filtered, the filter cake was washed with two 50-ml. portions of carbon tetrachloride and the filtrate was fractionally distilled through an eight inch column packed with glass helices. The distillation gave 23 g. (15%) of α-bromoisobutyraldehyde, b. p. 110–113°, and 108 g. (48%) of α-bromoisobutyraldehyde diethylacetal, b. p. 99–100° (40 mm.).

Additional quantities of α-bromoisobutyraldehyde were prepared by the hydrolysis of the acetal. The optimum conditions were found to be the following: α-bromoisobutyraldehyde diethylacetal (50.0 g., 0.22 mole), dioxane (100 ml.), water (50 ml.) and concentrated hydrochloric acid (10 ml.) were refluxed for about one minute at which time the cloudy solution abruptly became clear. The reaction mixture was then cooled rapidly in an ice-bath, poured into 300 ml. of cold water and extracted with

(1) Alexander, THIS JOURNAL, **69**, 289 (1947).

(2) Geissman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 96.

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 350.

(4) The Strecker and Bücherer reactions may involve such a displacement, however.

(5) The author is indebted to Dr. T. A. Geissman for this suggestion.

(6) All melting points and boiling points are uncorrected.

ether. The ether solution was dried over anhydrous magnesium sulfate and distilled. The fraction boiling at 108–113° amounted to 15.6 g. (47%).

α-Dimethylaminoisobutyraldehyde and α-Dimethylaminoisobutyraldehyde Methiodide.—α-Bromoisobutyraldehyde (40.0 g., 0.265 mole) was added dropwise to a cooled solution of aqueous 35% dimethylamine (300 g., 2.33 moles) at such a rate that the temperature did not rise above 10°. The resulting homogeneous solution was then allowed to come to room temperature and to stand overnight. After extracting the solution thoroughly with ether and drying over anhydrous magnesium sulfate, the ether extracts were distilled through a small six inch column packed with glass helices. The yield of α-dimethylaminoisobutyraldehyde was 9.9 g. (32%), b. p. 126–129°.

Since this material appeared to absorb carbon dioxide from the air, it was quickly rinsed into a 300-ml. round-bottomed flask with 100 ml. of dry benzene and refluxed on a hot water-bath with excess methyl iodide for two hours. The white amorphous solid which formed was filtered with suction, washed with benzene and dried in a vacuum desiccator. The yield of α-dimethylaminoisobutyraldehyde methiodide was 20.3 g. (92%); m. p. 119–121° (dec.).

No suitable solvent was found for the large scale recrystallization of this quaternary salt. It was almost insoluble in hot acetone, absolute alcohol, and methanol. In methanol–water or ethanol–water mixtures the recovery was very poor and the material appeared to decompose with the evolution of methyl iodide. It was sparingly soluble in nitroethane and nitromethane from which it crystallized in the form of clear compact crystals, m. p. 119–121° (dec.).

Anal. Calcd. for $C_7H_{16}ONI$: C, 32.75; H, 6.28. Found: C, 32.88; H, 6.37.

The Cannizzaro Reaction.—The reaction itself was carried out with the amounts of material indicated in Table I. The aldehyde was added portion-wise to 5 molar equivalents of potassium hydroxide solution,[7] (50% in a mixture of equal parts of water and methanol) at such a rate that the temperature did not rise above 20°. The reaction mixture (which was sometimes non-homogeneous) was then stirred overnight at room temperature and finally refluxed one hour to complete the reaction.

The reactions were worked up in the usual way.[8] With the more water soluble products a continuous ether extractor was used to separate them from the aqueous solution of inorganic salts. The properties of the products which were obtained agreed well with those recorded in the literature with the exception of *o*-ethoxymethyl benzoic acid. Repeated recrystallization of this material gave a melting point of 83–84° rather than the reported 85–86°.[9]

The runs with the quaternary salts were acidified with concentrated hydrogen iodide, extracted thoroughly with ether and evaporated to dryness *in vacuo* on a steam-bath. Evaporation of the ether extracts left no higher boiling material showing that no unsubstituted acid was formed. The residue was then broken up with a spatula and taken to dryness twice with a mixture of 50 ml. of benzene and 50 ml. of absolute alcohol. This residue was then extracted three times with 50 ml. portions of absolute alcohol and these extracts fractionally crystallized. A similar procedure was used for the isolation of the hydrochloride of dimethylaminopivalic acid.

In the run with the methiodide of dimethylaminopivaldehyde only the methiodide of β-dimethylamino-α,α-dimethyl propyl alcohol was isolated. When the methiodide of α-dimethylaminoisobutyraldehyde was employed both the quaternary aminoalcohol and the hydrate of the quaternary aminoacid were isolated.

The methiodide of α-dimethylaminoisobutyl alcohol crystallized from absolute alcohol in which it was sparingly soluble in the form of clear compact crystals melting at 233–235° (dec.).

Anal. Calcd. for $C_7H_{18}ONI$: C, 32.50; H, 7.05. Found: C, 32.52; H, 7.15.

The hydrate of α-dimethylaminoisobutyric acid methiodide crystallized from hot absolute alcohol in which it was fairly soluble in the form of sponge-like microcrystalline clusters melting at 188–189° (dec.).

Anal. Calcd. for $C_7H_{18}O_3NI$: C, 28.90; H, 6.24. Found: C, 29.11; H, 6.50.

TABLE I

CANNIZZARO REACTION WITH HYDROXY AND AMINO ALDEHYDE DERIVATIVES

Aldehyde	Moles used	% Yield of the corresponding Acid[a]	Alcohol[a]
Aldol	1.00	..[b]	..[b]
Propionaldol[c]	0.30	..[b]	..[t]
Isobutyraldol[d]	.27	93[e] (isobutyric acid only)	75
Hydroxypivaldehyde[g]	.60	77[h]	84[h]
Dimethylaminopivaldehyde[i]	.70	59[j]	87[k]
Dimethylaminopivaldehyde methiodide[i]	.10	..[l]	37[k]
α-Hydroxy-α-ethyl-phenylacetaldehyde[m]	.15	60[n]	61[o]
o-Ethoxymethyl-benzaldehyde[p]	.13	18[q]	56[r]
o-Ethoxymethyl-benzaldehyde[s]	.24	27[q]	53[r]
α-Dimethylaminoisobutyraldehyde methiodide[t]	.05	32[t]	21[t]

[a] The physical properties of the compounds listed in this table agreed with the values given in the references unless it is indicated otherwise. [b] An aldehyde resin only was obtained. [c] Grignard and Abelmann, *Bull. soc.c him.*, [4] **7**, 639 (1910). [d] Saunders, *et al.*, THIS JOURNAL, **65**, 1715 (1943). [e] Calculated on the basis that from one mole of aldol 0.5 moles of acid would be expected. [f] Krestinski and Perssianzewa, *Ber.*, **63**, 182 (1930). [g] Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1787 (1942). [h] Wesseley, *Monatsh.*, **22**, 66 (1901). This author also carried out the Cannizzaro reaction on hydroxypivaldehyde. He reported yields of 90 and 100% for the hydroxy acid and glycol, respectively. [i] Mannich, Lesser and Stilton, *Ber.*, **65**, 378 (1932). [j] Isolated as the hydrochloride. [k] Fourneau, Benoit and Firmenich, *Bull. soc. chim.*, [4] **47**, 880 (1930). [l] Any quaternary aminoacid which may have been present could not be separated from the potassium iodide formed by neutralizing the reaction mixture with hydrogen iodide. [m] Freon, *Ann. chim.*, **11**, 501 (1939). [n] Grignard, *Compt. rend.*, **135**, 629 (1902). [o] Stoerner, *Ber.*, **39**, 2300 (1906). [p] Arditti, *Compt. rend.*, **223**, 635 (1946). [q] Noyes and Coss, THIS JOURNAL, **42**, 1283 (1920). Repeated recrystallization of this material gave a melting point of 83–84° rather than the reported 85–86°. [r] Braun and Zobel, *Ber.*, **56**, 2148 (1923). [s] This run was carried out with 1.2 moles of sodium ethoxide instead of potassium hydroxide. [t] See the experimental part.

Discussion

In Table I are summarized the results which were obtained by carrying out the Cannizzaro reaction on several α, β and γ-hydroxy and amino

(7) In one run with *o*-ethoxymethyl benzaldehyde, sodium ethoxide in absolute ethanol was employed (see Table I).

(8) See ref. 2, p. 111–113.

(9) Footnote *q*, Table I.

aldehyde derivatives. Aldol and propionaldol formed aldehyde resins and isobutyraldol apparently underwent a simultaneous dealdolization and Cannizzaro reaction since the glycol was isolated but only isobutyric acid could be found in the acid fraction. In the other examples the normal Cannizzaro reaction occurred.

Obviously it cannot be concluded from this work that a displacement reaction such as the one shown in equation 1 does not occur, but it is quite clear that even in what appears to be the most favorable case (the quaternary amino aldehydes) the displacement shown in equations 3 and 4 does not proceed at a rate comparable to the Cannizzaro reaction.

Summary

A study of the products obtained by carrying out a Cannizzaro reaction on a number of hydroxy and amino aldehyde derivatives revealed that aldol and propionaldol formed aldehyde resins. Isobutyraldol gave the corresponding glycol and isobutyric acid, but in the other cases which were investigated the Cannizzaro reaction proceeded normally. These reactions are of interest since the occurrence of an intramolecular hydride ion displacement similar to one postulated for the Cannizzaro reaction would be expected to result in the formation of unsubstituted acids of the same carbon skeleton.

URBANA, ILLINOIS RECEIVED MARCH 29, 1948

NOTES

Catalytic Oxidation of Alcohols at Low Temperatures

BY ROBERT H. BAKER AND DAVID STANONIS

By making use of the ease of oxidation of anthrahydroquinone by air, it has been possible to modify the usual Oppenauer reaction[1] and to demonstrate a catalytic oxidation of the alcohols. Thus, instead of anthraquinone being used as the oxidant in the reversible reaction,[2] RCH(OH)R + quinone $\rightleftarrows$ RCOR + hydroquinone, it is used only in catalytic amounts, and the progress of the reaction is followed manometrically. The conventional catalyst, aluminum *t*-butoxide, must be used in sufficient quantity to react with the water produced in the reaction, but this amount is no larger than that which is generally used.[1] The catalytic oxidation fails with aluminum *t*-butoxide made from certain batches of metal, but this is remedied by the addition of anhydrous cupric sulfate, or better cupric oleate, to the reaction mixtures.

Cholesterol was found to take up more than two atoms of oxygen while 4-cholesten-3-one with the same catalyst took up none. This is in agreement with the observations of Bergstrom and Wintersteiner[3] on the emulsion oxidation of steroid derivatives, in which those containing the 5,6 double bond are oxidized more extensively than those with 4,5 unsaturation.

Experimental

Apparatus.—The reactions were carried out in flasks shaken by a motor-driven eccentric and connected to a 100-ml. buret by means of a spiral of copper tubing bearing standard taper brass connections. Rubber connections were found to be unsatisfactory because of the rapid uptake of oxygen.

Oxidations.—The conditions of typical runs are shown in Table I. The amount of solvent used was 5 ml. per millimole of alcohol. Unpurified aluminum *t*-butoxide was used and the cupric salt was added only when necessary. The oxygen pressure was maintained at one atmosphere by means of a leveling bulb containing mercury.

TABLE I

Run	Compound	Millimoles	Al-(O-*t*-Bu)$_3$, millimoles	Cupric oleate, mg.	Quinone, millimoles	Solvent	*T*, °C.	O_2, atoms/mole compound	Time, hr.
1	Benzohydrol	50	30	..	5	*m*-Xylene	60	..	56
2	Same	3	4	50	0.3	Toluene	35	0.3	71
3	Fluorenol	3	4	50	0.3	Benzene	30	0.5	65
4	Same	3	4	..	0.3	Benzene	25	0.78	114
5	Cholesterol	15	20	..	15	Benzene	30	2.0	407
6	Cholestenone	3	4	..	15	Benzene	30	0.04	144

In numerous experiments fluorenol was found to take up oxygen more rapidly than benzohydrol, but duplicate rates on either compound could not be obtained. The yield of benzophenone from Run 1 was 56% (determined polarographically[2]). Fluorenone was isolated by steam

(1) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937); *Org. Syn.*, **21**, 18 (1941).

(2) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

(3) Bergstrom and Wintersteiner, *J. Biol. Chem.*, **145**, 327 (1942).

distillation of the reaction mixtures. From Run 4 its yield was 78%, corresponding to the oxygen uptake. In other experiments yields as high as 85% were encountered. Attempts to obtain crystalline products from the cholesterol oxidation products which had taken up from 0.7–2.0 atoms of oxygen were unsuccessful. The total oxygen uptake of cholesterol was not measured, the rate in Run 5 having diminished only slightly when the reaction was stopped.

NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED FEBRUARY 2, 1948

The Synthesis of β-Oxoesters from Acyl Pyruvates

BY ALICE M. DESSERT AND I. F. HALVERSTADT[1]

β-Oxoesters were prepared by several methods for intermediates in the synthesis of thiouracils.[2] Another method used in this investigation was the decarbonylation of methyl acyl pyruvates. The procedure involved pyrolyzing the pyruvates by heating with powdered soft glass. In the case of the compounds which readily decomposed, a flash distillation procedure was used instead of batch heating.

The mechanism of this decarbonylation is not known but it is presumably similar to that by which ethyl pyruvate is pyrolyzed to ethyl acetate. In this latter case Calvin and Lemmon[3] found, by using C^{14}, that the carbon monoxide was evolved from the carbethoxy group.

Experimental

Pyruvates: The methyl acyl pyruvates were all prepared from methyl ketones by the method of Royals.[4] His method was slightly modified in that the alcohol was removed before working up the sodium salt. The methyl pyruvates prepared were: pivalo, b. p. 111–112° (11 mm.) (76% yield)[5]; butyl, b. p. 107–108° (5–6 mm.) (55%); propiono, b. p. 86–87° (2–3 mm.) (35%); and myristyl, a new compound, m. p. 52–53° (cor.).

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19. Found: C, 68.91.

β-Oxoesters: Methyl β-oxo-γ-dimethylvalerate[6] was prepared by heating a mixture of 18.62 g. (0.1 mole) of methyl pivalopyruvate and 2 g. of ground soft glass at 175°. In five hours approximately 95% of the theoretical volume of carbon monoxide was collected, so heating was discontinued and the residual liquid distilled. An 80% yield of the β-oxoester, b. p. 91–96°, chiefly 91–93°, at 20 mm. was obtained. A run using 950 g. (5.1 moles) of methyl pivalopyruvate yielded 80.1% of β-oxoester.

Methyl β-oxopalmitate was prepared by heating a mixture of 3.2 g. (0.01 mole) of methyl myristylpyruvate and 0.3 g. of ground soft glass at 185°. After twenty minutes heating was discontinued when more than the theoretical amount of gas had been collected. Most of the residue dissolved in alcohol. The alcoholic solution was evaporated and the residue distilled at 155–165° at 1 mm. The distillate solidified in the condenser. After recrystallization from dilute alcohol, the solid melted at 34–35°. The copper salt was made and recrystallized from petroleum ether, m. p. 78–81°.

Anal. Calcd. for $C_{34}H_{64}CuO_6$: Cu, 10.1. Found: Cu, 10.3.

In a typical run for the preparation of **methyl β-oxocaproate,**[7] 17.2 g. (0.1 mole) of methyl butyropyruvate was flash distilled over 2 g. of ground soft glass. The flask containing the glass was heated in a metal-bath kept at 365°. The pyruvate was forced over the hot glass in 0.5-cc. portions and distilled as rapidly as possible at 240° to prevent side reactions. On fractional distillation of the mixture, 4.46 g. (31% yield) of the β-oxoester, b. p. 85–95° at 14 mm. and 9.09 g. of methyl butyropyruvate, b. p. 110–112° at 7 mm., were collected. The yield corrected for recovered pyruvate was 65%.

Methyl β-oxovalerate[6] was prepared by flash distillation as was the methyl β-oxocaproate. On fractional distillation, in the most successful run, 4.44 g. (31% yield) of β-oxoester, b. p. 60–65° at 14 mm. and 6.52 g. of pyruvate were obtained. The yield corrected for recovered pyruvate was 50%. The crude copper salt, m. p. 155–157°, checked the melting point of the crude salt given in the literature.[6]

(1) Present address: Cutter Laboratories, Berkeley, Calif.

(2) (a) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945); (b) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).

(3) Calvin and Lemmon, *ibid.*, **69**, 1232 (1947).

(4) Royals, *ibid.*, **67**, 1508 (1945).

(5) A 67.5% yield was obtained from a run using 9 moles of pinacolone.

(6) Baumgarten, Levine and Hauser, *ibid.*, **66**, 864 (1944).

(7) Levine and Hauser, *ibid.*, **66**, 1768 (1944).

CHEMOTHERAPY DIVISION
STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY
STAMFORD, CONNECTICUT RECEIVED APRIL 29, 1948

The Removal of Aluminum Chloride from Friedel–Crafts Mixtures Containing Water-Labile Phosphorus Halides

BY WILLIAM T. DYE, JR.[1]

The most useful of three methods developed by Michaelis for the synthesis of aromatic phosphine halides is the Friedel–Crafts reaction of aromatic hydrocarbons and phosphorus trichloride.[2,3] This method has one serious drawback, its incomplete and malodorous method of product isolation by extraction. Two new methods of separating the product have been developed. One is an adaptation of Robinson's method[4] to the recovery of phosphine halides. The other depends upon the precipitation of the complex $Al_2Cl_6 \cdot 2POCl_3$.[3] Although both of these methods have been successfully used in the preparation of several aromatic phosphine halides, only the application to phenyldichlorophosphine is presented in detail.

Experimental

Reagents.—The aluminum chloride, benzene (dried over phosphorus pentoxide) and phosphorus trichloride were J. T. Baker C. P. quality.

Preliminary Procedure.—In all experiments, various molar proportions of aluminum chloride, benzene and phosphorus trichloride were refluxed in three-neck flasks fitted with a rubber-sealed glass stirrer, thermometer, reflux condenser, hydrogen chloride trap, and mantle heater. Reaction times, usually one to four hours, were only long enough for practical cessation of hydrogen chloride evolution. The catalyst was then removed by either of the following methods.

(1) Present address: Central Research Laboratories, Monsanto Chemical Co.

(2) Michaelis, *Ber.*, **12**, 1009 (1879).

(3) Michaelis, *Ann.*, **293**, 198–200 (1896).

(4) Robinson, U. S. Patent 2,211,704; *C. A.*, **35**, 468 (1941).

With Water.—The reaction mixture was cooled to room temperature and diluted with benzene or low-boiling petroleum ether. An optimum quantity of 3 moles of water per mole of catalyst was stirred in as rapidly as foam control would allow. (Water was added either pure or as concentrated hydrochloric acid.) About 50 cc. more of solvent was then added. During the following brief period in which hydrogen chloride evolution ceased, the supernatant liquid was decanted. The solvent was then removed and the product vacuum-distilled.

Table I shows the effect of stirring different quantities of water, as concentrated hydrochloric acid, into 0.1:0.4:0.4-mole reaction mixtures of aluminum chloride, benzene and phosphorus trichloride.

TABLE I

YIELD OF PHENYLDICHLOROPHOSPHINE AFTER REMOVAL OF CATALYST WITH WATER

Moles water added	Yield $C_6H_5PCl_2$, g.
0.25	10.7
.275	15.3
.30	20.6
.325	20.9
.35	20.2
.40	16.8

The yield of phenyldichlorophosphine rose rapidly as the critical point of 3 moles water per mole aluminum chloride was approached, and as much as a 10% excess of water did no harm. When sufficient water was added, the hydrated catalyst separated as soft slightly coherent granules, free of product and easily filtered or decanted.

With Phosphorus Oxychloride.—One mole of phosphorus oxychloride per mole of aluminum chloride was added to the hot reaction mixture (with a temperature rise of about 5°), excess phosphorus trichloride and benzene were recovered by vacuum-stripping, the residue was cooled to 40° or below, the catalyst complex was completely precipitated by dilution with about three volumes of light petroleum, and the liquid layer was decanted and distilled. (Caution: In a few instances, involving large excess of phosphorus trichloride and benzene, the mixture separated into two layers when the oxychloride had been partly added, with consequent vigorous boiling of the more volatile layer. This can be prevented by stripping the excess of reactants before addition of phosphorus oxychloride.)

The utility of the latter procedure in Friedel–Crafts reactions in general seems limited only by the provision that the phosphorus oxychloride–aluminum chloride complex must be the most stable one possible in any given reaction mixture. The method has the advantage over the foregoing hydration process that there is no evolution of hydrogen chloride and consequently no tendency for the precipitate to float. Both of these methods appear suitable for isolating other Friedel–Crafts products decomposed by the conventional catalyst quenching process.

CHEMISTRY DIVISION
NAVAL RESEARCH LABORATORY
WASHINGTON, D. C.

RECEIVED[5] MAY 6, 1948

(5) Original manuscript received May 26, 1947.

A Synthesis of α,β-Unsaturated Amides

BY ALEXANDER GALAT

In a previous communication[1] we have reported a synthesis of α,β-unsaturated esters which involved the condensation of an aldehyde with a monoester of malonic acid. It appeared that a similar direct synthesis of α,β-unsaturated amides could be accomplished by condensing an aldehyde with the mono-amide of malonic acid

$$R{-}CHO + CH_2\begin{matrix}CONH_2\\COOH\end{matrix} \xrightarrow[-CO_2]{-H_2O} R{-}CH{=}CH{-}CONH_2$$

It was found that malon-monoamide did, in effect, readily condense with several representative aldehydes (benzaldehyde, *p*-dimethylaminobenzaldehyde, naphthaldehyde and furfural) to give satisfactory yields of the expected unsaturated amides.

The monoamide of malonic acid was prepared by treating diethyl malonate with one mole of potassium hydroxide in methanol, followed by ammonolysis of the monoester thus formed. The amide is a white, crystalline solid which melts at 110–115° with evolution of carbon dioxide and quantitative formation of acetamide. Its solution in water is strongly acid and can be accurately titrated. Heated with salts of primary amines, malon-monoamide reacts as an acetylating agent

$$R{-}NH_2{\cdot}HCl + CH_2\begin{matrix}CONH_2\\COOH\end{matrix} \xrightarrow[-NH_4Cl]{-CO_2} R{-}NHCOCH_3$$

Experimental

Malon-monoamide.—To a solution of 160 g. (1 mole) of diethyl malonate in 450 ml. of methanol was added slowly with stirring 280 ml. (1 mole) of 20% methanolic potassium hydroxide. After the addition was completed the mixture was stirred until the reaction became neutral. The crystalline precipitate was filtered off and the filtrate evaporated to dryness *in vacuo*. The combined solids weighed 132 g. (85%). The product is the potassium salt of mono-methyl malonate (ester interchange takes place when working in methanol).

The potassium salt was dissolved in 500 ml. of concentrated ammonium hydroxide and the solution kept at room temperature for one week. It was then evaporated to dryness *in vacuo*, treated with 76 ml. of concentrated hydrochloric acid and stirred until homogeneous. To the mixture was added 275 ml. of isopropanol, the precipitated potassium chloride filtered off, washed with isopropanol and the filtrate evaporated to dryness *in vacuo*. To the resulting sirup was added 150 ml. of hot isopropanol and an additional amount of potassium chloride removed by filtration. Malonmonoamide crystallized upon cooling and was filtered off, washed with isopropanol and dried at room temperature; yield, 52 g. (61%), m. p. 110–115° (dec.).

Anal. Calcd.: N, 13.59; neut. equiv., 103. Found: N, 13.4.; neut. equiv., 103.5.

Cinnamamide.—One gram of benzaldehyde (*ca.* 0.01 mole), 2 g. (*ca.* 0.02 mole) of malon-monoamide, 2 drops of piperidine and 5 ml. of pyridine were heated on a water-bath until the evolution of gas ceased. To the mixture was added 25 ml. of boiling water, the solution cooled and the precipitated amide recovered by filtration; yield, 0.8 g. (57%), m. p. 146–147° (cor.), lit. 142°.

61 So. BROADWAY
YONKERS, N. Y.

RECEIVED APRIL 30, 1948

(1) Galat, THIS JOURNAL, 68, 376 (1946).

Preparation of Aliphatic Fluorides

BY FRIEDRICH W. HOFFMANN

The exchange of halogen in aliphatic —CHX— and $-CH_2X$ groups (X = Cl, Br) by means of an-

hydrous potassium fluoride has been described recently.[1,2,3] Since this reaction takes place only at higher temperatures, the use of pressure equipment is required and much trouble is due to coating of potassium fluoride with potassium chloride or potassium bromide, respectively. Only in the special case of the preparation of fluoroacetamide from chloroacetamide the use of xylene as reaction medium allows the reaction to be carried out at atmospheric pressure.[3]

By using suitable organic solvents for anhydrous potassium fluoride, it is possible to exchange the halogens in —CHX— and —CH_2X groups (X = Cl, Br, I) in a one-step reaction at atmospheric pressure in ordinary glass equipment. In order to obtain reasonably fast reaction rates, the method requires a temperature of about 140° and over, so that low-boiling solvents for potassium fluoride, such as methanol and ethanol cannot be used. Satisfactory solvents are aliphatic di- and polyhydroxy compounds such as ethylene glycol, glycerol, diethylene glycol, polyethylene glycol, etc., either singly or mixed.

In this procedure the yields are fair and frequently considerably higher than those obtained by the pressure method. *n*-Hexyl fluoride can thus be obtained from *n*-hexyl chloride in 54% yield, whereas the halogen exchange under pressure without solvent for the potassium fluoride gives only a 20% yield.[2] 2-Fluoroethanol, which could not be obtained by heating of ethylene chlorohydrin with potassium fluoride under pressure by Gryszkiewicz-Trochimowski[4], was, however, prepared by McCombie and Saunders[1] by the same method at 135–140° (no yield indicated). The subject method permits the preparation of this compound in 42.5% yield by using potassium fluoride in a glycol solvent at atmospheric pressure. Another advantage of the use of a solvent for the halogen exchange is the fact that the presence of small amounts of moisture in one of the reactants can lead to serious hazards by enormous pressure increase in the conventional method,[2] whereas in the described method only the yield of fluorinated product is correspondingly decreased.

Although the subject method is in some respects inferior to conventional methods using fluorides of mercury, etc., the ready availability of the inexpensive potassium fluoride makes it another convenient means for the preparation of aliphatic fluorides, especially since some fluorides such as 2-fluoroethanol, β-difluoroethyl ether, etc., which cannot be obtained by fluorination with silver or mercuric fluoride, are accessible from the corresponding chlorine compounds by fluorination with potassium fluoride.

A large number of new aliphatic fluorine compounds was synthesized by this method by the writer in collaboration with R. Geier in the laboratories of W. Bockemüller in Würzburg, Germany.

The syntheses of 2-fluoroethanol and *n*-hexyl fluoride from the corresponding chlorine compounds by halogen exchange with anhydrous potassium fluoride in glycol solution are described in detail in the following.

Preparation of FCH_2CH_2OH.—A mixture of dry, powdered potassium fluoride (350 g., 6 moles), ethylene glycol (320 g.), and diethylene glycol (130 g.) was heated to 170° in a 3-neck, 1-liter, round-bottom flask fitted with a stirrer, dropping funnel, and a 30-cm., 3-step Vigreux column with attached condenser and receiver. Ethylene chlorohydrin (322 g., 4 moles) was added dropwise in the course of three hours to the reaction mixture maintained at 170–180° with constant stirring at such a rate that the distillate at the still head showed a temperature of 95–105°. After addition of ethylene chlorohydrin was complete, a slow stream of air was sucked through the apparatus for one hour in order to distil off the fluoroethanol completely. In the receiver, 152.5 g. of crude reaction product was obtained as a colorless liquid. After standing with 10 g. of sodium fluoride for two days to remove traces of hydrogen fluoride, distillation of the reaction product yielded 109 g. (42.5%) of fluoroethanol (b. p. 101°,[1] 100–102°[2]) between 97° and 104°.

Preparation of $CH_3(CH_2)_4CH_2F$.—A mixture of dry, powdered potassium fluoride (116 g., 2 moles), ethylene glycol (200 g.), and diethylene glycol (50 g.) was heated to 180° in a 3-neck, 1-liter, round-bottom flask fitted with a stirrer, dropping funnel and a 30-cm., 3-step Vigreux column with attached condenser and receiver. *n*-Hexyl chloride (120.6 g., 1 mole) was added dropwise in the course of eight hours to the reaction mixture maintained at 175–185° with constant stirring. Since the reaction product boils at 93.2°, it distils out of the reaction mixture at about the same rate at which the reagent is added. After addition of hexyl chloride was complete, the reaction mixture was allowed to cool to 110°. A slow stream of air was sucked through the apparatus in order to distil off the remaining reaction product from the mixture. In the receiver, 79.6 g. of distillate was collected. This consisted of *n*-hexyl fluoride with some hexene and some unreacted hexyl chloride. Fractionation yielded 56.3 g. (54.1%) of *n*-hexyl fluoride, boiling at 91–93.5°.

CHEMICAL CORPS TECHNICAL COMMAND
ARMY CHEMICAL CENTER, MARYLAND
RECEIVED FEBRUARY 24, 1948

(1) McCombie and Saunders, *Nature*, **158**, 382 (1946).
(2) Gryszkiewicz-Trochimowski, Sporzyński and Wnuk, *Rec. trav. chim.*, **66**, 413–418 (1947).
(3) Bradley, U. S. Patent 2,403,576 (July 9, 1946).
(4) Gryszkiewicz-Trochimowski, *Rec. trav. chim.*, **66**, 427 (1947).

The Terpenes of Oil Sweet Goldenrod

BY BRYANT R. HOLLAND

In a study of the production of essential oils, oil of Sweet Goldenrod (*Solidago odora*)[1] has been investigated. Miller and Moseley[2] examined this oil fairly extensively, but did not identify the terpenes. They identified methyl chavicol as the main constituent, and showed borneol to be present. To extend the findings of Miller and Moseley, the oil has been partially fractionated and the terpenes determined.

Experimental

A 600-ml. sample of fresh oil was fractionated using a Stedman column (24 inch packing, 1 inch diameter) at a pressure of 5 mm. with a reflux ratio of 0.5 (50% of the condensate returned to the column). The starch–glycerol

(1) The complete investigation is to be reported in a Texas Engineering Experiment Station Bulletin.
(2) Miller and Moseley, THIS JOURNAL, **37**, 1285 (1915).

stopcock lubricant described by Herrington and Starr[3] was a satisfactory lubricant for the stopcocks and ground joints used in the distillation apparatus. The following fractions were obtained:

Fraction	Volume, ml.	Temp., °C.	$n^{29}D$	$\alpha^{29}D$
1	20	30	1.4677	+84.17°
2	60	31	1.4683	+96.67°
3	10	32	1.4690	+92.00°
Residue	510	..	1.5173	− 0.50°

Fractions 1, 2 and 3 account for 15% of the oil. The physical properties of fraction 2 are similar to those of *d*-limonene. The presence of *d*-limonene was confirmed by preparing the β-nitrol anilide, m. p. 153°, and the tetrabromide, m. p. 103.5°, $[\alpha]^{30}D$ +72.0° (0.1785 g. of *d*-limonene tetrabromide in 5 ml. of carbon tetrachloride solution).

A 1500-ml. portion of the fresh oil was subsequently fractionated, as above, at a pressure of 22 mm., with a reflux ratio of 0.9 (90% of the condensate returned to the column). The first fraction, 3.1 ml., boiling at 55°, had a refractive index of 1.4628^{25}, and a rotation of −37.67°. Calculated for *l*-α-pinene this would be a specific rotation of −43.70°, which is near the reported −48.63°.[4] The presence of *l*-α-pinene was confirmed by the preparation of α-pinene nitrolpiperidine, m. p. 118.5°. The quantity found by distillation represents 0.2% of the oil.

The specific rotation of *d*-limonene as calculated from the rotation of fraction 2 would be +114°, as compared to a specific rotation for pure *d*-limonene of +126°.[5] This plus the refractive index of fraction 2 indicates the probable presence of dipentene. No direct evidence for the presence of dipentene or other terpenes was obtained. The negative rotation of the terpeneless residue indicates that the borneol is probably *l*-borneol. Methylchavicol, an isomer of anethol, is responsible for the anise-like odor and flavor. The odor and flavor of the oil are decidedly improved by the removal of the terpenes.

(3) Herrington and Starr, *Ind. Eng. Chem., Anal. Ed.*, **14**, 62 (1942).

(4) Gildemeister and Hoffmann, "The Volatile Oils," second edition, John Wiley and Sons, Inc., New York, N. Y., 1913, Vol. I, p. 293.

(5) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 575.

TEXAS ENGINEERING EXPERIMENT STATION
AGRICULTURAL AND MECHANICAL COLLEGE OF TEXAS
COLLEGE STATION, TEXAS RECEIVED FEBRUARY 20, 1948

Preparation of Tetraacetyl-α-D-glucopyranosyl Bromide

BY C. G. JEREMIAS, G. B. LUCAS AND C. A. MACKENZIE

There are many references in the literature pertaining to the preparation of tetraacetyl-α-D-glucopyranosyl bromide. Most authors recommend the use of an acetic acid solution of hydrogen bromide with pentaacetyl-β-D-glucose. They differ in their experimental details, particularly with respect to the use of vacuum distillations, solvents and purifications methods. The description given below eliminates vacuum distillations, simplifies the purification process and gives a pure product in good yield with a minimum of effort.

Experimental

A mixture of 20 g. of pentaacetyl-β-D-glucose and 20 ml. of hydrobromic acid–acetic acid solution (Eastman Kodak Co. 30–32% hydrobromic acid–acetic acid) is stirred at room temperature for two hours in a flask protected from moisture. The clear, yellow solution is poured, in a thin stream, into 400 ml. of vigorously stirred ice water. A finely divided, crystalline material is obtained. If the addition is made too rapidly the product solidifies in the form of large lumps. The crude acetobromoglucose is filtered with suction and then transferred to a small separatory funnel. Fifty ml. of carbon tetrachloride is added to put the solid into solution. The water layer formed is drawn off with a suction pipet and the product remaining is washed once with 20 ml. of ice water and then with a few ml. of cold, saturated sodium bicarbonate solution until all free acid has been removed. The solution is finally washed with two 20-ml. portions of ice water. The carbon tetrachloride layer is filtered through glass wool into an erlenmeyer flask and dried over calcium chloride. The dry solution is poured slowly, with stirring, into 200 ml. of petroleum ether (35–75° boiling range was used; a good quality reagent is necessary or a yellowing of the product may occur at this point). When crystallization at room temperature is complete, an ice-salt-bath is placed around the container and an additional crop of crystals form. The crystals are filtered with suction and air-dried or dried in a vacuum desiccator. The product at this point has a m. p. 88–89°; yield, about 18 g. (80–85%).

RICHARDSON CHEMISTRY LABORATORIES
DEPARTMENT OF CHEMISTRY
THE TULANE UNIVERSITY OF LOUISIANA
NEW ORLEANS, LOUISIANA RECEIVED APRIL 9, 1948

Heats of Mixing of Some Fluorinated Ethers with Chloroform

BY J. R. LACHER, J. J. MCKINLEY AND J. D. PARK

It is well known that chloroform and monofluorodichloromethane will form hydrogen bonds with solvents containing donor atoms such as nitrogen and oxygen.[1] Diethyl ether[2] and polyethylene glycol ethers[3] show a considerable heat evolution when mixed with chloroform or monofluorodichloromethane. The substitution of chlorine in an aliphatic ether[4] or the replacing of an alkyl by an aryl group[5] reduces considerably the tendency for bonding. Recently[6] a number of polyfluoro alkyl ethers have been prepared in this Laboratory. If one interprets hydrogen bonds as the result of an interaction between dipoles,[7,8,9] one might expect that these fluorinated ethers would also show only a slight tendency for hydrogen bonding. The moments are not known for these molecules. However, one can calculate,

(1) C. S. Marvel, M. J. Copley and E. Ginsberg, THIS JOURNAL, **62**, 3263 (1940). This paper gives references to earlier work by these and other authors.

(2) D. B. McLeod and F. J. Wilson, *Trans. Faraday Soc.*, **31**, 598 (1935).

(3) G. F. Zellhoefer and M. J. Copley, THIS JOURNAL, **60**, 1343 (1938).

(4) G. F. Zellhoefer, M. J. Copley and C. S. Marvel, *ibid.*, **60**, 1337 (1938).

(5) C. S. Marvel, M. J. Copley and E. Ginsberg, *ibid.*, **62**, 3109 (1940).

(6) J. D. Park, D. K. Vail, K. R. Lea and J. R. Lacher, THIS JOURNAL, **70**, 1550 (1948).

(7) G. Briegleb, *Z. Elektrochem.*, **50**, 35 (1944).

(8) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1944.

(9) G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944.

using bond moments,[10] the dipoles for similar compounds. Dimethyl ether has a moment of 1.32 debye units and the negative end may be regarded as being on the oxygen atom. Hexafluorodimethyl ether, on the other hand, has a calculated dipole moment of 0.40 debye unit and the direction of the moment is reversed. Methyl trifluoromethyl ether has a calculated moment of 1.31 and it makes an angle of 37° with the methyl–oxygen bond. Its negative end lies between the oxygen and the trifluoromethyl group. As a result the negative charge is spread out between the two. A similar situation will obtain for the ethers dealt with here. Experiments were undertaken to measure their hydrogen bonding tendencies and the method chosen involves measuring their heats of mixing with chloroform at 0°.

The mixing calorimeter was modified after those described by McLeod and Wilson,[2] Vold,[11] Von Steinwehr,[12] and Zellhoefer and Copley.[4] The mixing chamber consisted of a 170-cc. Pyrex dewar which could be evacuated by means of a diffusion pump. A tight fitting lid contained holes to receive two pipets and a long Pyrex tube. The latter contained a 12-junction copper–constantan thermocouple, nichrome heater, and also served as a stirrer. The lower end of the tube was fitted with a glass disk and stirring was accomplished by means of a reciprocating motor. The whole assembly was contained in a gallon dewar and maintained at 0° with ice. The output from the thermel was fed into a Leeds–Northrup "Speedomax" recorder. In making a run, the temperature change produced on mixing two liquids was compared with that produced by electrical heating in the usual way.

The preparation of the fluoroalkyl ethers has been previously described.[6] Diethyl ether was dried over sodium and distilled. Acetone was purified by the method of Shipsey and Werner[13] using sodium iodide. Monofluorodichloromethane, furnished us through the courtesy of Mr. A. F. Benning of the du Pont Company, was distilled in a twenty-plate column.

Discussion.—In order to check the reliability of the apparatus and develop the necessary technique, the heats of mixing of chloroform with diethyl ether and with acetone were measured. The former system has been studied by McLeod and Wilson[2] at 0° and the latter by Hirobe[14] at 25°. The data obtained are shown in Figs. 1 and 2. The heat evolved in calories per mole of solution may be represented by a parabolic curve of the type: $-\Delta H = (N - N^2)A$. N represents the mole fraction of the halogenated hydrocarbon and A is an adjustable constant. These curves, also shown in the figures, give heats of mixing of −670 and −470 cal./mole for diethyl ether and acetone, respectively, at $N = 0.5$. This compares with −714 and −460 cal./mole determined by McLeod and Wilson and by Hirobe, respectively.

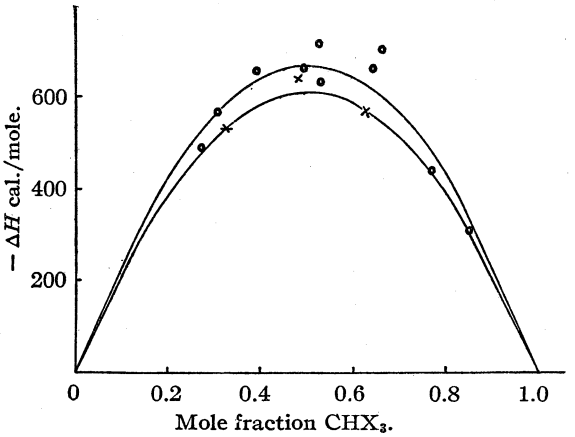


Fig. 1.—Heats of mixing in calories per mole of solution—systems: diethyl ether–chloroform, O, and diethyl ether–$CHFCl_2$, X.

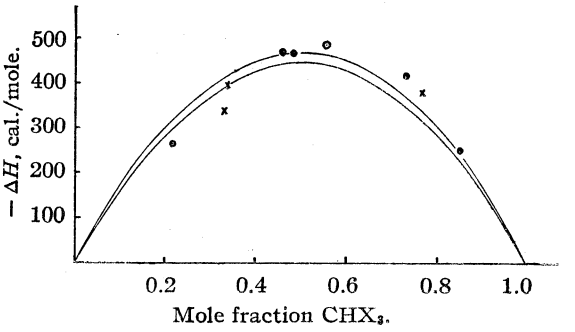


Fig. 2.—Heats of mixing in calories per mole of solution for the systems: O, acetone–chloroform; X, acetone–$CHFCl_2$.

A few runs using monofluorodichloromethane in place of chloroform were made. The results, shown in Figs. 1 and 2, suggest that less heat is liberated when the monofluorinated compound is used. The effect, however, is of the same order of magnitude as the experimental error. Zellhoefer and Copley[3] using polyethylene glycol ethers found a similar situation. The solubility[1] of chloroform in the dimethyl ether of tetraethylene glycol is, however, measurably greater than that of the monofluorinated derivative. This may be interpreted to mean that some C—H ← F bonds were present in $CHFCl_2$. It may also be explained by the fact that, whereas in chloroform the dipole moment is along the carbon–hydrogen bond, in $CHFCl_2$ it is askew. Consequently, a larger decrease in entropy will result when the latter forms a hydrogen bond with the ether. This will account for the larger difference shown between chloroform and $CHFCl_2$ in solubility measurements (which involve a free energy change) than is given in a measurement of ΔH.

(10) C. P. Price, *Chem. Revs.*, **29**, 37 (1941).
(11) R. D. Vold, THIS JOURNAL, **59**, 1515 (1937).
(12) H. Von Steinwehr, *Z. physik. Chem.*, **38**, 139 (1901).
(13) K. Shipsey and E. A. Werner, *J. Chem. Soc.*, **103**, 1255 (1913).
(14) H. J. Hirobe, *Fac. Sci. Imp. Univ., Tokyo*, **1**, 155 (1925).

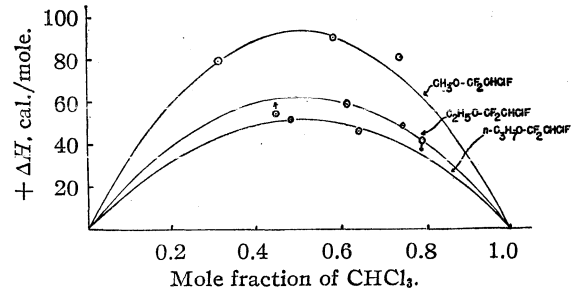


Fig. 3.—Heats of mixing in calories per mole of solution for the systems: chloroform with polyfluoro alkyl ethers.

The results obtained on mixing chloroform with the methyl, ethyl and *n*-propyl derivatives of 1,1,-2-trifluoro-2-chloroethyl alkyl ethers are shown in Fig. 3 and Table I gives the heats of mixing per mole of solution at a mole fraction of 0.5.

TABLE I

HEATS OF MIXING OF 1,1,2-TRIFLUORO-2-CHLOROETHYL ALKYL ETHERS WITH CHLOROFORM AT 0°

Ether	ΔH, cal./mole
Methyl	93 ± 3
Ethyl	62 ± 4
n-Propyl	52 ± 3

The isopropyl derivative gave heat effects of the same magnitude as the normal compound. Sufficient material was not on hand for quantitative study. In contrast to the behavior shown by diethyl ether and acetone, the heats of mixing were small and positive. The slight cooling effect produced indicates the lack of formation of hydrogen bonds, at least in large numbers.

UNIVERSITY OF COLORADO
BOULDER, COLORADO RECEIVED FEBRUARY 9, 1948

The Structure of Dioxadiene Dibromide

BY GERALD R. LAPPIN[1] AND R. K. SUMMERBELL

Some time ago dioxadiene was found to react with only one molar equivalent of bromine to give a crystalline compound, dioxadiene dibromide, of unknown structure.[2] This was presumed to be 5,6-dibromo-*p*-dioxene. However, the possibilities that it had an oxonium bromide structure or that the dioxadiene ring had been ruptured were not excluded.

We have now found that I does not react with aqueous potassium iodide solution, a characteristic reaction of oxonium bromides.[3] Furthermore, I reacts with the magnesium–magnesium iodide dehalogenating reagent[2] and with phenylmagnesium bromide to regenerate dioxadiene in high yield. Thus the structure of I must be 5,6-dibromo-*p*-dioxene.

Attempted Reaction of I with Aqueous Potassium Iodide Solution.—To a solution of 1.0 g. of potassium iodide in 20 ml. of water was added 0.5 g. of I. No iodine was liberated on heating at 60° for twenty-four hours.

Reaction of I with Magnesium–Magnesium Iodide Reagent.—In a two-necked flask fitted with a mercury-sealed stirrer and a side-arm connected to a condenser arranged for downward distillation were placed 10 g. of magnesium turnings and 75 ml. of anhydrous butyl ether. To this was added slowly 4 g. of iodine. The solution was heated until distillation started and to it was added dropwise a solution of 10 g. (0.04 mole) of I in 50 ml. of butyl ether. A total of 100 ml. of distillate was collected during this addition. Redistillation through a 10-cm. Vigreux column gave 3.4 g. (97%) of dioxadiene, b. p. 74–75°, $n^{20}D$ 1.4351.

The Reaction of I with Phenylmagnesium Bromide.—To a solution of phenylmagnesium bromide prepared from 2.64 g. (0.11 atom) of magnesium and 17.3 g. (0.11 mole) of bromobenzene in 100 ml. of dry ether was slowly added a solution of 12.3 g. (0.05 mole) of I in 75 ml. of dry ether. After the moderately vigorous reaction subsided the mixture was allowed to stand for twelve hours and was then hydrolyzed by pouring into ice and ammonium chloride solution. The ether solution was separated and dried over magnesium sulfate. Distillation gave 5.9 g., b. p. 75–80°, and a sirupy residue. The distillate was dissolved in 50 ml. of carbon tetrachloride and to it was added dropwise a solution of bromine in carbon tetrachloride at 0° until a faint permanent color remained. Removal of the solvent *in vacuo* gave 9.6 g. of crystalline residue identified as I by mixture melting point. Assuming an average yield of 90% on the addition of bromine to dioxadiene this represents an 87% conversion to dioxadiene.

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED APRIL 12, 1948

The Solubility of Aluminum Bromide in Cyclohexane[1]

BY PHILIP A. LEIGHTON AND JOHN B. WILKES

During the course of a study of the isomerization of cyclohexane with aluminum bromide catalyst, the solubility of aluminum bromide in cyclohexane has been determined.

Materials.—Aluminum bromide was prepared and distilled into glass ampoules in the manner described by Leighton and Heldman.[2]

The cyclohexane was the gift of the Shell Oil Company. The stated analysis as received was 99.7 vol. % cyclohexane (by correlation of freezing point and mass spectrograph analysis), 0.0003 wt. % sulfur, less than 0.0005 vol. % benzene and less than 0.001 vol. % phenols. The freezing point was 6.0°. This material was further purified by "freezing out" cyclohexane crystals, followed by percolation of the remelted crystals through silica gel. The "freezing out" was performed as follows: About 300 ml. of cyclohexane contained in a 500-ml. Erlenmeyer flask was placed in a cooling bath of ice and water, and, with frequent hand stirring and scraping, a thick slurry of cyclohexane crystals was produced. The crystals were filtered off, melted, and the process repeated. The resultant cyclohexane was percolated through a column of silica gel to remove water and any trace of olefins. The product was stored over sodium in brown glass bottles. Physical properties of the purified cyclohexane were: m. p. 6.5°, $n^{25}D$ 1.4235.

(1) Present address, Chemistry Department, Antioch College, Yellow Springs, Ohio.

(2) Summerbell and Umhoeffer, THIS JOURNAL, **61**, 3020 (1939).

(3) McIntosh, *ibid.*, **32**, 1330 (1910).

(1) This work was supported by a grant from the Research Corporation.

(2) Leighton and Heldman, THIS JOURNAL, **65**, 2276 (1943).

Determination of Solubility.—The purified cyclohexane was placed in a flask attached to the vacuum system by a ground glass joint, thoroughly degassed, and distilled into the ampoules containing aluminum bromide. Each ampoule was sealed off from the vacuum line when it was estimated that it would be nearly full of solution upon reaching the solution temperature. Solution temperatures were determined as described by Heldman and Thurmond.[3] All the solutions were clear and colorless. Samples were analyzed as follows: The aluminum bromide was precipitated in finely divided form[2] and the ampoule placed tip down in a long narrow flask equipped with standard taper joint and glass stopper. The flask and contents were weighed, and the flask shaken to break open the ampoule. The flask was then connected to a trap by all-glass connections using unlubricated standard taper joints. The trap was in turn connected to a vacuum pump. The vacuum pump was turned on and the flask cooled by immersion in a slurry of dry ice, chloroform, and carbon tetrachloride. After the system was evacuated, the dry ice slurry was removed and pumping continued until some time after the flask had reached room temperature. The cyclohexane was condensed in the trap. The aluminum bromide remained behind as a finely divided, white powder. The flask and contents were weighed and the cyclohexane calculated by difference. The aluminum bromide was removed by washing successively with nitrobenzene, water, and acetone. The flask and glass parts were weighed and the aluminum bromide calculated by difference.

TABLE I

SOLUTION TEMPERATURES OF ALUMINUM BROMIDE–CYCLOHEXANE MIXTURES

	Al_2Br_6			Al_2Br_6	
t, °C.	Mole fract.	Wt. % liq. phase	t, °C.	Mole fract.	Wt. % liq. phase
6.2	0.0503	25.1	38.7	0.178	57.9
8.8	.0568	27.6	39.8	.183	59.4
17.2	.0788	35.2	44.5	.220	64.2
26.4	.115	45.1	57.0	.333	76.0
28.5	.124	47.4	60.3	.380	79.5
36.0	.162	55.0	61.7	.393	80.4
37.6	.169	56.4	97.5	1.000	100.0

Results

The solution temperatures and compositions of the solutions examined are given in Table I. The moles of aluminum bromide are calculated on the basis of the formula Al_2Br_6. No correction was made for the cyclohexane in the vapor phase because of the comparatively low vapor pressure of cyclohexane and the small vapor volume present in the ampoules. The results show that aluminum bromide is appreciably more soluble in cyclohexane than in *n*-butane[2] or *n*-hexane[4] when calculated on a mole fraction basis. On a weight basis aluminum bromide is more soluble in cyclohexane than in *n*-hexane throughout the temperature range for which data are available and is more soluble in cyclohexane than in *n*-butane throughout much of the lower temperature range.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD, CALIFORNIA

RECEIVED MARCH 2, 1948

(3) Heldman and Thurmond, *ibid.*, **66**, 427 (1944).

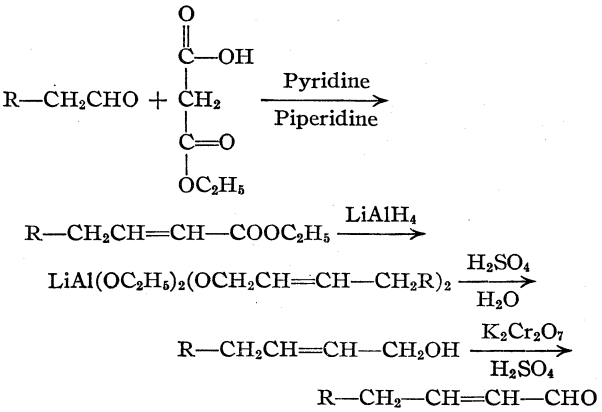
(4) Boedeker and Oblad, *ibid.*, **69**, 2036 (1947).

The Preparation of 2-Heptenal and 2-Nonenal

BY C. J. MARTIN, A. I. SCHEPARTZ AND B. F. DAUBERT[1]

Recent work in this Laboratory on the isolation and identification of flavor components in "reverted" soybean oil has necessitated the preparation of a number of α,β-unsaturated aldehydes of a high degree of purity. The recent availability of lithium aluminum hydride as a reducing agent[2] led to the development of a suitable method for the preparation of such aldehydes free of their saturated isomers.

The general scheme of reaction may be outlined as follows



Experimental

Preparation of 2-Heptenal.—Ethyl hydrogen malonate (256 g.) was condensed with *n*-valeraldehyde (83.3 g.) in pyridine (469 g.) with piperidine (1.2 ml.) as a catalyst, according to the method of Galat.[3] After removal of the pyridine and piperidine, the ethyl 2-heptenoate was distilled *in vacuo* under nitrogen: yield, 118 g. (78.2%), b. p. 58–58.8° (3 mm.), $n^{25}D$ 1.4355.

To a solution of lithium aluminum hydride (10.9 g., 14% excess) in absolute ether (450 ml.) there was added ethyl 2-heptenoate (78 g.) according to the method of Nystrom and Brown.[2] Although the crude yield of 2-heptenol was 45 g. (79%), distillation, under nitrogen, through a Vigreux column, resulted in a loss of approximately 50% because of partial polymerization of the alcohol. The 2-heptenol had a boiling point of 75–75.5° at 15 mm.

The 2-heptenol (21.7 g.) was oxidized by the low-temperature oxidation procedure of Delaby and Guillot-Allègre,[4] yielding 2-heptenal, 15.9 g. (74.6%).

The product was stabilized with hydroquinone and distilled in a glass helix-packed column; b. p. 80–85° at 14 mm., $n^{20}D$ 1.4314. The aldehyde was identified by preparation of the following derivatives: semicarbazone, m. p. 168–168.4° (Delaby, *et al.*,[4] 169°); *p*-nitrophenylhydrazone, m. p. 115.5–116° (Delaby, *et al.*,[4] 110–112°); 2,4-dinitrophenylhydrazone, m. p. 131.5–132°.

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.41; H, 5.52; N, 19.17. Found: C, 53.17; H, 5.23; N, 19.03.

Preparation of 2-Nonenal.—Ethyl hydrogen malonate (143.6 g.) was condensed with heptaldehyde (63 g.) in the manner described above: yield of ethyl 2-nonenoate, 79.4 g. (78.2%); b. p. 104° at 8 mm.

The ethyl 2-nonenoate (79.4 g.) was reduced with

(1) The financial assistance of the National Association of Margarine Manufacturers is gratefully acknowledged.

(2) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(3) Galat, *ibid.*, **68**, 376 (1946).

(4) Delaby and Guillot-Allègre, *Bull. soc. chim.*, **53**, 301 (1933).

lithium aluminum hydride (7.4 g., 14% excess) to yield 60 g. (97.7%) of 2-nonenol. The product, after low-temperature oxidation, was fractionally distilled by the same procedure as for 2-heptanal. The fraction (12.2 g.) boiling at 119.5–126.5° at 21 mm. and $n^{20}D$ 1.4426 was stabilized with hydroquinone and identified by preparation of the following derivatives: semicarbazone, m. p. 164–165° (Delaby, *et al.*,[4] 160–161°; von Braun and Rudolph,[5] 163°); *p*-nitrophenylhydrazone, m. p. 109.6–110.3° (Delaby, *et al.*,[4] 113°; von Braun and Rudolph,[5] 109°); 2,4-dinitrophenylhydrazone, m. p. 124.4–125°.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.30; N, 17.49. Found: C, 56.08; H, 6.03; N, 17.62.

(5) von Braun and Rudolph, *Ber.*, **67**, 269 (1934).

CONTRIBUTION No. 671
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PENNSYLVANIA RECEIVED APRIL 2, 1948

The Vapor Phase Fluorination of Acetyl Fluoride[1]

BY WILLIAM T. MILLER, JR., AND MAURICE PROBER[2]

In the direct fluorination of aliphatic acids and their derivatives, Bockemüller[3] observed β- and γ- but no α-substitution. It was of interest to determine if hydrogen substitution occurred in the direct fluorination of acetyl fluoride, where only α-replacement was possible.

Equivalent quantities of fluorine and acetyl fluoride, both diluted with nitrogen, were passed into a steam-jacketed copper reactor, which was packed with copper gauze.[4] The products were condensed, caused to react with ethyl alcohol, and the resulting esters fractionally distilled. The fluorinated esters comprised approximately 50% by weight of the total esters plus some unreacted alcohol. The isolation of appreciable unreacted ethyl acetate was consistent with Bockemüller's observation on the low reactivity of the α-hydrogen. All of the possible substitution products were formed. Ethyl fluoroacetate and ethyl difluoroacetate were isolated in approximately 6:1 ratio. Only trace amounts of ethyl trifluoroacetate were isolated.

Experimental

Acetyl fluoride was prepared according to the procedures of Calloway[5] and Nesmejanov and Kahn.[6] Fractional distillation from antimony trifluoride and treatment with sodium fluoride yielded a product free of acetyl chloride and hydrogen fluoride, b. p. 18.0–18.2° at 734 mm.

The reaction was carried out in a steam-jacketed copper tube, 75 × 3.5 cm., packed with a roll of 40-mesh copper wire gauze. Fluorine diluted with dry, oxygen-free nitrogen, and acetyl fluoride carried by a stream of nitrogen, were passed into the reactor in an equal molar ratio. The molar ratio of nitrogen to fluorine varied from 2:1 to 3:1. The reactants were condensed in ice, Dry Ice, and liquid air traps, arranged in series. The hydrogen fluoride was removed by sodium fluoride which preceded the Dry Ice trap. The condensates were combined and the theoretical amount of absolute ethyl alcohol added at Dry Ice temperature. The reaction product was allowed to warm up to room temperature, kept at room temperature for a day, and refluxed for three hours. It was diluted with ether, and washed with cold, saturated solutions of potassium fluoride, potassium carbonate and calcium chloride. The reaction mixture was fractionally distilled at an atmospheric pressure of 740 mm.

In a typical run, 500 g. (0.804 mole) of acetyl fluoride was passed into the reactor, and 48.0 g. of organic products were condensed in the traps, with a 16.5 g. weight increase of the sodium fluoride. After distilling off the ether, the following fractions were obtained: 0.2 g., b. p. 37–68°; 15.4 g., b. p. 68–78° (ethyl acetate and ethyl alcohol–ethyl acetate azeotrope); 1.0 g., b. p. 78–96°; 0.5 g., b. p. 96–103°; 3.4 g., b. p. 103–114°; 6.4 g., b. p. 114–115°; 2.2 g. residue. Fluorinated compounds were present in all but the 68–78° b. p. fraction.

In order to obtain sufficient product to permit isolation of pure reaction products, six runs were made, and the appropriate fractions combined and distilled. A fraction boiling fairly sharply at 115–116° reacted with excess liquid ammonia at room temperature to form an amide, m. p. 107.5–108.0°. The earlier reported boiling points of ethyl fluoroacetate, 121.6°[7] and 126°[8] are higher than the value observed in the present work, but the m. p. of the amide is in excellent agreement with the literature value of 108°.[9] Recently a boiling point of 117–118° has been reported[10] which is in better agreement with our value. A second fraction, ethyl difluoroacetate, boiled at 98.2–99.2°, reported[11] 99.2°, and gave an amide m. p. 51.0–51.9°,[9] reported[9] 51.8°. A small amount of a low-boiling fraction gave a plateau at 53°, and yielded a fluorine containing amide, m. p. 72.7–74.0°. An azeotrope of ethyl alcohol and ethyl trifluoroacetate was reported to boil at 56°[12] and the melting point of trifluoroacetamide was reported to be 74.8°.[13] A trace amount of high boiling ester was obtained in one run, and it was hydrolyzed with 10% hydrochloric acid to yield an impure fluorine containing acid (or mixture) of m. p. 187–205°. All of the fluoroacetic acids are liquids, and the isolation of a solid acid indicated that coupling reactions had occurred during fluorination.

(1) Taken from the thesis presented by Maurice Prober to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Master of Science, January, 1943. Work on this problem was interrupted in 1941 because of the war research program.

(2) Present address: General Electric Co., Schenectady, N. Y.

(3) Bockemüller, *Ann.*, **506**, 20 (1933).

(4) Compare: Miller, Calfee and Bigelow, THIS JOURNAL, **59**, 198 (1937); Calfee and Bigelow, *ibid.*, **59**, 2072 (1937), and following papers by Bigelow, *et al.*

(5) Calloway, THIS JOURNAL, **59**, 1476 (1937).

(6) Nesmejanov and Kahn, *Ber.*, **67**, 370 (1934).

(7) Swarts, *J. chim. phys.*, **28**, 634 (1931).

(8) Ray and Ray, *J. Ind. Chem. Soc.*, **13**, 427 (1936).

(9) Swarts, *Bull. classe sci., Acad. roy. Belg.*, 28 (1909).

(10) Gryszkiewicz-Trochimowski, Sporzyfiski and Wnuk, *Rec. trav. chim.*, **66**, 413–418 (1947).

(11) Swarts, *Bull. classe sci., Acad. roy. Belg.*, **41**, 628 (1903).

(12) Bigelow and Fukuhara, THIS JOURNAL, **63**, 788 (1941).

(13) Swarts, *Bull. classe sci., Acad. roy. Belg.*, **8**, 343 (1922).

RECEIVED MARCH 4, 1948

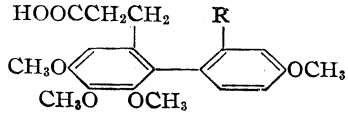
1-(β-Carboxyethyl)-3,4,7-trimethoxydibenzofuran

BY PAUL E. FANTA

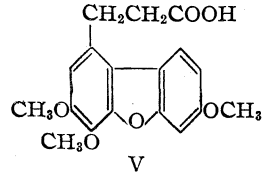
The attempted preparation of acid IV by a crossed Ullmann reaction[1] of methyl β-(2-iodo-3,-4,5-trimethoxyphenyl)-propionate and methyl 2-iodo-5-methoxybenzoate was described in an earlier paper.[2] This note concerns an alternative synthetic approach which was also unsuccessful.

(1) For a survey of the Ullmann reaction see Fanta, *Chem. Rev.*, **38**, 139 (1946).

(2) Frank, Fanta and Tarbell, THIS JOURNAL, **70**, (1948).



I, R = NO_2 II, R = NH_2
III, R = CN IV, R = COOH



V

A crossed Ullmann reaction of methyl β-(2-iodo-3,4,5-trimethoxyphenyl)-propionate and excess 4-bromo-3-nitroanisole yielded β-[2-(4,5-6,4′-tetramethoxy-2′-nitro)-biphenyl]-propionic acid (I), which was readily reduced to the corresponding amino compound (II). When II was diazotized and treated with cuprous cyanide under conditions calculated to yield the nitrile III, only 1-(β-carboxyethyl)-3,4,7-trimethoxydibenzofuran (V) was obtained. The formation of dibenzofuran from 2-amino-2′-methoxybiphenyl[3] and of 3,4,7-trimethoxydibenzofuran from 2,3,4,4′-tetramethoxy-2′-aminophenyl[4] under similar conditions has been reported.

The structure assigned to V is supported by a comparison of its absorption spectrum with that of 3,4,7-trimethoxydibenzofuran and compounds I and II as shown in Fig. 1. The spectrum of each dibenzofuran derivative exhibits a maximum near 300 mμ which has the same extinction coefficient as the corresponding maximum at 260 mμ. In the case of the biphenyl derivatives I and II, the extinction coefficients of the higher and lower wave length maxima differ greatly.

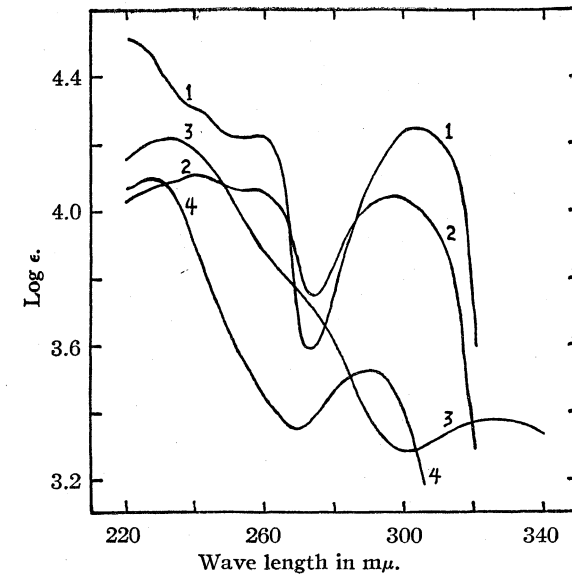


Fig. 1.—Molar extinction curves in ethanol: (1) 3,4,7-trimethoxydibenzofuran[4]; (2) dibenzofuran derivative, V; (3) nitrobiphenyl derivative, I; (4) aminobiphenyl derivative, II.

Experimental[5]

β-[2-(4,5,6,4′-Tetramethoxy-2′-nitro)-biphenyl]-propionic Acid (I).—A mixture of 7.60 g. (0.02 mole) of methyl β-(2-iodo-3,4,5-trimethoxyphenyl)-propionate and 27.8 g. (0.12 mole) of 4-bromo-3-nitroanisole was heated at 220–255° while 20 g. of electrolytic copper dust was added in small portions with stirring. The product was extracted with six 25-cc. portions of benzene. Evaporation of the benzene gave a red-brown tar which was refluxed for an hour with 25 cc. of Claisen alkali. Fifty cc. of water was added and the mixture was centrifuged to remove 4,4′-dimethoxy-2,2′-dinitrobiphenyl. Acidification of the aqueous solution with hydrochloric acid gave a dark oil which was purified by refluxing with Darco and Celite in aqueous methanol. Cooling and scratching gave a fine, yellow solid which was recrystallized from benzene with the addition of ligroin, when it formed granular, yellow crystals, yield 2.20 g. (28%), m. p. 100–102°.

Anal. Calcd. for $C_{19}H_{21}O_8N$: C, 58.30; H, 5.41. Found: C, 58.31; H, 5.54.

β-[2-(2′-Amino-4,5,6,4′-tetramethoxy)-biphenyl]-propionic Acid (II).—A portion of the nitro compound in ethanol was shaken for one-half hour with Raney nickel and hydrogen at 1000 lb. and 155°. Evaporation of the solvent and crystallization of the residue from benzene–ligroin gave a light tan crystalline powder, yield 42%, m. p. 125.5–126°.

Anal. Calcd. for $C_{19}H_{23}O_6N$: C, 63.15; H, 6.41. Found: C, 64.95; H, 6.61.

1-(β-Carboxyethyl)-3,4,7-trimethoxydibenzofuran (V).—A 360-mg. (0.001 mole) portion of the amino acid II was dissolved in a mixture of 10 cc. of water and 10 drops of sulfuric acid and diazotized at −5° by the addition of 74 mg. of solid sodium nitrite. Upon standing for an hour at room temperature gas was evolved and a flocculent orange precipitate separated. The yield of crude product melting at 132–145° was 76%. Crystallization from dilute methanol gave 191 mg. (58%) of tan needles, m. p. 146–148°. An analytical sample, m. p. 148°, was obtained by successive recrystallization from dilute methanol (Darco) and benzene.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.16; H, 5.29.

The same product was obtained in lower yield when the diazonium solution was poured into a solution of cuprous cyanide in aqueous sodium cyanide.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASSACHUSETTS

RECEIVED APRIL 2, 1948

(3) Mascarelli and Pirona, *Gazz. chim. ital.*, **68**, 117 (1938); *C. A.*, **32**, 6235 (1938).

(4) Tarbell, Frank and Fanta, THIS JOURNAL, **68**, 502 (1946).

(5) All melting points are corrected and were taken on the heated stage. The microanalyses are by C. W. Beazley, S. M. Nagy and Mrs. O. C. Sauvage. Absorption curves were determined with a Beckmann Spectrophotometer.

The Fluorination of Periodic Acid

BY GILSON H. ROHRBACK AND GEORGE H. CADY

As part of the research now under way to produce compounds in which the hydrogen atoms of acids have been replaced by fluorine, the study of the reaction of fluorine with periodic acid was undertaken. Fluorination of both solid $HIO_4 \cdot 2H_2O$ and KIO_4 as well as an aqueous or sulfuric acid solution of the acid were carried out, but the desired compound fluorine periodate was not obtained. The reaction of fluorine with $HIO_4 \cdot 2H_2O$

was studied in some detail, however, and the complete reaction was found to take place in three stages. As the change commenced, water of hydration was removed from the acid without a change in the valence of iodine according to the equations

$$HIO_4 \cdot 2H_2O + 2F_2 \longrightarrow O_2 + 4HF + HIO_4 \quad (1)$$
$$HIO_4 \cdot 2H_2O + 4F_2 \longrightarrow 2OF_2 + 4HF + HIO_4 \quad (2)$$

In three experiments performed, the percentage of OF_2 in the gaseous product of O_2 and OF_2 varied from about 3 to 27%, the higher percentage being favored by a shorter reaction time. In the second stage, the continued action of fluorine caused the formation of iodine pentoxide, probably as the result of the dehydration of HIO_4, and in the final step iodine pentafluoride was formed by a reaction which became rapid only at temperatures above 250°.

$$HIO_4 \cdot 2H_2O \xrightarrow[\text{1st stage, Room temp.}]{F_2} HIO_4 \xrightarrow[\text{2nd stage, Room temp.}]{F_2}$$
$$I_2O_5 \xrightarrow[\text{3rd stage, Heat}]{F_2} IF_5$$

To investigate the first phase of the reaction a copper chamber with a volume of about one-half liter was employed. This was fitted with a brass ground-joint union which had been blanked off and polished to make a tight seal. Acid samples were placed in the reaction chamber which was then evacuated. A known volume of undiluted F_2 gas, freed of HF, was admitted and the course of the subsequent reaction was followed by observing an attached manometer. At the desired time the gas mixture within the reaction vessel was sampled by admitting a portion to an evacuated sample bottle.

Preliminary experiments showed that $HIO_4 \cdot 2H_2O$ could be caused to lose weight upon fluorination without a loss in total oxidizing capacity. However, it was found difficult during the steady fluorination of small samples to prevent some loss in oxidizing capacity before a weight loss had occurred which would correspond to the removal of all the water of hydration. Therefore to study the reaction of fluorine with the water of hydration alone, the described copper chamber was employed and relatively large samples of acid were used. Thus three samples of 3.083, 3.467 and 3.510 g. of the acid were successively fluorinated at room temperature in the apparatus for periods of one and one-third, five and twenty-four hours, respectively. After fluorination under these conditions the total oxidizing capacities were found by iodometric titrations to have been substantially unchanged, indicating that within experimental error there was no reduction in the valence of the iodine.

Gaseous reaction products of the above runs were determined by analysis of samples collected in glass bulbs. It was shown qualitatively that the gases produced were oxygen, oxygen difluoride, and hydrogen fluoride. They may be considered to have been formed from the water of hydration of the acid by the reactions (1) and (2). Since the hydrogen fluoride was removed from the gas by absorption on sodium fluoride held in a boat near the periodic acid, the observed drop in pressure during the reaction was equal to one-half of the decrease in the partial pressure of the fluorine. The amount of OF_2 was determined by analysis by allowing a sample of the gas to react with a solution of potassium iodide containing an excess of standard hydrochloric acid solution. One-half the equivalent weight of hydrogen ion consumed, as determined by back-titration with sodium hydroxide solution, was taken as equal to the moles of OF_2 in the sample. The following equation for the reaction of OF_2 indicates that this relationship should be correct.

$$OF_2 + 4I^- + 2H^+ = 2I_2 + 2F^- + H_2O \quad (3)$$

Using the two equations for the reaction of fluorine with water of hydration of the acid, the number of moles of oxygen formed was calculated to equal one-half the moles of fluorine consumed minus the number of moles of OF_2 produced. Likewise the number of moles of HF produced should be equal to 2 times (number of moles of F_2 consumed − number of moles of OF_2 formed). The values so calculated for the moles of HF produced should be equal to those obtained by determining the increase in weight of the sodium fluoride held in the reaction vessel.

Data for the three runs, which are given in Table I, show that the total effect of reactions (1) and (2) is to produce more oxygen than oxygen fluoride and that the latter substance appears to be consumed slowly with the consequent production of oxygen. There is good agreement between the calculated and observed hydrogen fluoride values.

TABLE I

REACTION OF FLUORINE WITH EXCESS PERIODIC ACID

Sample	I	II	III
Weight of acid, g.	3.08	3.47	3.51
Time of reaction, hr.	1⅓	5	24
Temp., °C.	24.3	23.0	25.2
Vol. of reaction vessel, liters	0.411	0.411	0.411
Initial pressure, cm.	42.0	41.0	40.0
Final pressure, cm.	38.3	28.6	21.8
Millimoles gas entering	9.32	9.10	8.88
Millimoles F_2 consumed	1.64	5.50	8.08
Millimoles OF_2 by analysis	0.22	0.72	0.13
Millimoles O_2 produced	0.60	2.0	3.9
Millimoles HF calculated	2.8	9.6	16
Millimoles HF observed, absorbed by NaF	2.7	9.6	16
% OF_2 by volume, in O_2–OF_2, total	27	26	3.2

Although no attempt was made to show the presence of the acid HIO_4 in the product, its existence may be reasonably inferred in the light of

Lamb's[1] work, which showed that the dihydrate was decomposed by dehydration directly to HIO_4 without intermediate compounds. He also found that stronger dehydrating conditions in no instance gave the seven valent anhydride, but rather resulted in decomposition to I_2O_5.

The second stage in the fluorination was studied by allowing samples of the acid to react in a continuous stream of fluorine at room temperature. The remaining white solid was shown to be iodine pentoxide. It was a non-hygroscopic substance which failed to oxidize manganous ion to permanganate in solution containing sulfuric acid, and its water solution gave a white precipitate with silver ion. During the fluorination of a 2.310-g. sample of $HIO_4 \cdot 2H_2O$, the loss in weight was 0.613 g. This may be compared with the theoretical loss of 0.619 g. according to the equation

$$2HIO_4 \cdot 2H_2O \longrightarrow I_2O_5 + 5H_2O + O_2$$

Likewise this sample should yield a product with a total oxidation equivalent of 0.0608; the equivalency found iodometrically was 0.0607. Such a change to give iodine pentoxide is in accord with the findings of Lamb.[1]

The final stage of the fluorination was accomplished by an increase in temperature to about 250°. On so doing, the iodine pentoxide disappeared while a white solid condensed in a product receiving trap cooled by Dry Ice. This solid was determined to melt at −8° to a colorless liquid which fumed in air. When a weighed sample of this liquid was treated with an acidified solution of potassium iodide and the liberated iodine titrated with standard sodium thiosulfate, an equivalent weight of 36.8 was found. This is in good agreement with the theoretical value of 36.9 for IF_5 (m. p. −8°, b. p. +97°).

The boiling point of the iodine pentafluoride was not determined as the reaction with the glass container was found to be too rapid above 30°. Such a behavior was also reported for IF_5 by Ruff and Braida.[2]

Acknowledgment.—This work was performed under contract with the Office of Naval Research, U. S. Navy Department.

(1) Arthur B. Lamb, *Am. Chem. J.*, **27**, 134 (1902).

(2) Otto Ruff and A. Braida, *Z. anorg. allgem. Chem.*, **220**, 43–48 (1934).

DEPARTMENT OF CHEMISTRY AND
CHEMICAL ENGINEERING
UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON RECEIVED DECEMBER 17, 1947

The Esterification of Acylated α-Amino Acids

BY HEINRICH RINDERKNECHT AND CARL NIEMANN

Esters of the acylated α-amino acids or peptides are ordinarily prepared by the acylation of the α-amino acid or peptide ester or by the traditional acid catalyzed esterification of the acylated α-amino acid or peptide.[1] In seeking a more attractive procedure than either of the above it has been found that as with other carboxylic acids[2,3] certain of the acylated α-amino acids may be readily esterified by simply heating an alcoholic solution of the acid at approximately 180° in the absence of added catalyst. While this procedure appears to be useful for the esterification of many acylated α-amino acids it is to be anticipated that a number of acids will form products other than esters. For example with benzoyl-L-arginine the principal reaction product proved to be racemic 5-benzamido-piperidone-2.

Aside from convenience of the above method for the preparation of esters of acylated α-amino acids and carboxylic acids in general[3] it is one of the few procedures that can be used for the esterification of ketals of polyhydroxy acids such as 1;2,3;4-diisopropylidene-D-galacturonic acid.[4]

Experimental

Methyl Hippurate.—A solution of 18.0 g. of hippuric acid in 200 ml. of methanol under an initial pressure, at 25°, of 1000 lb./sq. in. of hydrogen was heated at 180–185° for ten hours. The reaction mixture was evaporated to dryness, the residue extracted with ether, the ethereal extract evaporated to dryness and the residue recrystallized from benzene to give 15.9 g. (82.5%) of methyl hippurate, m. p. 81–82°, uncor.

Benzoyl-DL-alanine Methyl Ester.—Benzoyl-DL-alanine (19.3 g.) in 200 ml. of methanol was heated at 180° for twelve hours. The reaction mixture was fractionally distilled and the distillate, b. p. 129–131° (0.15 mm.) was recrystallized from benzene to give 16.9 g. (91%) of benzoyl-DL-alanine methyl ester, m. p. 80–82°, uncor.

Carbobenzoxy-DL-alanine Methyl Ester.—A solution of 22.3 g. of carbobenzoxy-DL-alanine in 200 ml. of methanol heated at 180° for twelve hours was fractionally distilled and the fraction, b. p. 129–131° (0.2 mm.), recrystallized from ligroin to give 13.3 g. (59%) of carbobenzoxy-DL-alanine methyl ester, m. p. 49–50°, uncor.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.8; H, 6.3; N, 5.9. Found: C, 61.0; H, 6.5; N, 5.6.

Attempted Esterification of α-Benzoyl-L-arginine.—α-Benzoyl-L-arginine (27.6 g.) in 200 ml. of methanol was heated at 170° for fifteen hours, the reaction mixture filtered (ppt. 7.0 g.), the filtrate evaporated to dryness and the residue recrystallized from hot water to give 8.5 g. (39%) of 5-benzamido-piperidone-2, m. p. 183–184°, insoluble in aqueous acid and alkali, soluble in hot water and ethanol.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.1; H, 6.4; N, 12.8. Found: C, 66.4; H, 6.7; N, 12.5. The benzamidopiperidone was hydrolyzed with 20% hydrochloric acid and the dipicrate of DL-ornithine, m. p. 198–199°, isolated from the hydrolysate. A solution of α-benzoyl-L-nitroarginine in methanol heated at 170° for seventeen hours gave 68% of 5-benzamido-piperidone-2, m. p. 183–184°.

Methyl Benzoate—Fractional distillation of a solution of 12.2 g. of benzoic acid in 200 ml. of methanol previously heated at 185° for fifteen hours gave 12.2 g. (90%) of methyl benzoate, b. p. 83° (12 mm.).

Methyl Lactate.—A solution of 12.0 g. of freshly distilled lactic acid, b. p. 78° (0.1 mm.), in 250 ml. of methanol heated at 170° for fourteen hours upon fractional distillation gave 9.6 g. (69%) of methyl lactate, b. p. 143–145°.

(1) E. Fischer, "Untersuchungen über Aminosäuren, Polypeptide und Protein," Julius Springer, Berlin (1906, 1923).

(2) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd ed., Longmans, London, 1948, p. 100.

(3) Private communication from Prof. Homer Adkins, University of Wisconsin, Madison.

(4) C. Niemann, unpublished data.

Attempted Esterification of Gallic Acid.—Gallic acid monohydrate (9.4 g.) in 250 ml. of methanol was heated at 200° for fourteen hours, the solution evaporated to dryness and the residue recrystallized from benzene to give 6.2 g. (98%) of pyrogallol, m. p. 129–130°, uncor.

CONTRIBUTION NO. 1192
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIF. RECEIVED APRIL 6, 1948

An Approximate Method for the Determination of Active Halogens

BY JOHN R. SAMPEY, ANNE B. KING AND BARBARA C. BLITCH

The observation of Wanscheidt[1] that sodium bromide precipitates when 9-bromofluorene is dissolved in an acetone solution of sodium iodide has been made the basis for an approximate determination, within one or two per cent., of this active halogen in a mixture of bromofluorenes. Data are given to show that the method is applicable to two other compounds containing active halogen, namely, phenacyl bromide and benzyl bromide.

Analyses of 9-Bromofluorene, Phenacyl Bromide and Benzyl Bromide.—Samples (1.0000 g.) of the halogen compounds are dissolved in 20.00 ml. of a saturated solution of sodium iodide in acetone, and are filtered after standing several hours at 25°. Sodium bromide starts separating immediately upon solution of the halogen compounds, but in the case of 9-bromofluorene, if the sample stands too long, large amounts of difluorenyl precipitate; if this does occur, the difluorenyl and sodium bromide may be weighed together, and then the latter may be washed out with water; another weighing gives the amount of sodium bromide present before washing. The sodium iodide adhering to the sodium bromide after the filtration is readily washed out with 60 ml. of acetone; tests are made on the last washings for iodide ion (nitrous acid test). A correction is made for the solubility of the sodium bromide in the acetone. The sodium bromide is filtered and dried at 110°.

TABLE I

ANALYSES OF 9-BROMOFLUORENE, PHENACYL BROMIDE AND BENZYL BROMIDE

Compound	Sample, g.	NaBr ppt., g.	NaBr dissolved, g.	Sum, g.	%
9-Bromofluorene	1.000	0.407	0.003	0.410	97
9-Bromofluorene	1.000	.406	.003	.409	97
Phenacyl bromide	1.000	.501	.003	.504	97
Phenacyl bromide	1.000	.508	.003	.511	99
Benzyl bromide	0.907	.540	.003	.543	99
Benzyl bromide	1.285	.774	.003	.777	100

Solubility of Sodium Bromide in Acetone.—A correction must be applied for the solubility of sodium bromide in the acetone used. Column 4 of Table I gives the solubility of sodium bromide in the particular sample of acetone used in these analyses; other samples of reagent grade acetone dissolved as much as 0.119 g. of the salt; agitation of this moist sample of acetone with anhydrous calcium chloride reduced the amount of sodium bromide to less than 10 mg. on a second solubility determination. The solubility of sodium bromide in any sample of reagent grade acetone is determined by suspending 1.000-g. samples of the salt in 20.00-ml. portions of the acetone saturated with sodium iodide; to ensure solution, the flasks are placed on a shaking machine for several hours; the solutions are run through Gooch filters, and the adhering sodium iodide is washed out with 60 ml. of the same acetone used in making the solution.

The solubility of sodium bromide in acetone changes little with change in temperature. When the temperature is raised from 25 to 41°, the solubility decreased only two or three milligrams over that recorded in Column 4 of Table I. Sodium iodide shows a more marked decrease in solubility at elevated temperatures, for when a saturated solution of this salt in acetone is refluxed, large amounts of sodium iodide separate, and then on cooling redissolve.

The effect of changes in relative humidity on the solubility of sodium bromide in acetone has been noted. The acetone solutions were cooled to 0° and the samples were filtered slowly in an atmosphere in which the relative humidity was 95; under these conditions the solubility of sodium bromide increased five to six milligrams over that found by rapid filtration on a day in which the relative humidity was 40. The same quantities of salt and acetone were used as in previous runs. These effects of wide changes in humidity do not alter the usefulness of this approximate method for the determination of active halogens in the three classes of compounds analyzed in Table I.

This research was supported by a grant from the Office of Naval Research. The authors acknowledge the interest of Dr. E. Emmet Reid.

DEPARTMENT OF CHEMISTRY
FURMAN UNIVERSITY
GREENVILLE, S. C. RECEIVED JULY 3, 1947

(1) A. Wanscheidt, *Ber.*, **59**, 2092–2100 (1926).

The Exaggerated Effect of Iodine as Carrier in the Bromination of Fluorene

BY JOHN R. SAMPEY AND ANNE B. KING

Discovery of the Exaggerated Effect of Iodine.—In an attempt to relate the rate of bromination to the intensity of the irradiation in the photobromination of fluorene the observation was made that a considerable amount of bromine disappeared regardless of the illumination. This led to experiments in the dark in which 10 cc. of a 1 molar solution of bromine in carbon disulfide was added to 0.01 mole of fluorene in 20 cc. of the same solvent. The reaction was stopped by adding potassium iodide solution after which the liberated iodine was titrated. The results were surprising. In 5 runs the bromination was 8 to 10% in one-half minute, in 3 runs, 8 to 11% in three minutes and in 2 runs, only 11 to 13% in ten minutes. Tests showed that none of the bromine had entered the side chain. The first supposition was that the fluorene contained an easily brominated impurity. To test this, samples of fluorene from three different sources were recrystallized repeatedly, vacuum distilled and sublimed. All three showed 8 to 11% bromination in one-half and three minute periods. This surprising result was finally traced to the effect of the iodine that was liberated on the addition of the potassium iodide solution. For a part of the time during the shaking, fluorene, bromine and iodine were present in the carbon disulfide solution. This led to a study of the effect of iodine on the bromination of fluorene.

Iodine as a Carrier in the Bromination of Fluorene in the Dark.—A saturated solution of iodine in carbon tetrachloride was found to contain 0.29 g. in 10 cc. Dilutions of this, 1 to 10, and 1 to 100 were made. Fluorene, 0.01 mole, was added to 10 cc. of the carbon tetrachloride solution and then 10 cc. of a 1 molar solution of bromine in the same solvent was added quickly. The reaction was stopped by the addition of potassium iodide solution as usual. The results are in Table I.

TABLE I

BROMINATION OF FLUORENE IN THE DARK WITH IODINE AS CARRIER

Time, min.	0.29 g.	0.029 g.	0.0029 g.
0.5	79%	..	8
0.5	80	..	..
3.0	89	20	..
3.0	89	19	..

For comparison the same concentration of toluene and bromine in the same solvent were tried with 0.29 g. of iodine. There was no bromination in three minutes.

The bromine used was freed from traces of iodine by prolonged shaking with concentrated sulfuric acid, washing with water, drying over phosphorus pentoxide and fractionally distilling.

The authors acknowledge the interest of Dr. E. Emmet Reid in this research.

DEPARTMENT OF CHEMISTRY
FURMAN UNIVERSITY
GREENVILLE, S. C. RECEIVED OCTOBER 15, 1947

The Optical Rotatory Power of *epi*-Ergostanol

BY KARL J. SAX, LOUIS DORFMAN[1] AND SEYMOUR BERNSTEIN

In their development of a theory on the relationship between optical rotatory power and constitution of the steroids, Bernstein, Kauzmann and Wallis[2] noted a number of compounds for which large discrepancies existed between observed and calculated values of the optical rotation. For *epi*-ergostanol it was stated that the observed value for this compound was in error by at least 10°.[3] Also it has been pointed out[4] that the C_3-diastereomers, ergostanol and *epi*-ergostanol, do not conform to the rule that the C_3 α-form of any steroid will have a higher positive rotatory power than the corresponding β-form.

Accordingly it was of interest to redetermine the optical rotations of ergostanol and *epi*-ergostanol for evaluating the above discrepancies. The rotation of ergostanol was found to be +15.3° which is in excellent agreement with the recorded values of +15.3°[5] and +15.9°.[6] However, for *epi*-ergostanol we have found the rotation to be +16.9° which is higher than the recorded values of +13.5°[7] and +14.6°.[8]

These results show that the diastereomers, ergostanol and *epi*-ergostanol, do not constitute an exception to the above stated rule. Also it may be assumed that the value (+2300) for the constant, E_t^2, derived from *epi*-cholestanol, and used in the calculation of the rotation of *epi*-ergostanol, is incorrect. Use of *epi*-stigmastanol, $[\alpha]_D$ + 25,[9] as the standard substance, gave a E_t value of 0. Recalculation of the rotation of *epi*-ergostanol with this revised value gave +19.1°, which is in good agreement with the observed rotation of +16.9°.

(1) Present address, William R. Warner and Company, Inc., New York.

(2) Bernstein, Kauzmann and Wallis, *J. Org. Chem.*, **6**, 319 (1941).

(3) All rotations are for sodium D light and chloroform solution.

(4) Bernstein, Hicks, Clark and Wallis, *J. Org. Chem.*, **11**, 646 (1946).

(5) Windaus and Brunken, *Ann.*, **460**, 225 (1928).

(6) Reindel, Walter and Rauch, *Ann.*, **452**, 34 (1927).

(7) Reindel and Detzel, *Ann.*, **475**, 78 (1929).

(8) Windaus, *et al.*, *Ann.*, **477**, 268 (1930).

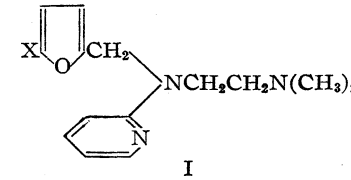
(9) Dalmer, *et al.*, *Ber.*, **68**, 1814 (1935).

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK RECEIVED APRIL 9, 1948

Antihistamine Agents. II. Furan Derivatives

BY J. R. VAUGHAN, JR., AND G. W. ANDERSON

In a continuation of our investigation on the effect of substituting various heterocyclic systems into compounds of known antihistamine activity,[1] we have prepared and tested N,N-dimethyl-N′-(2-pyridyl)-N′-furfurylethylenediamine (I, X = H) and N,N-dimethyl-N′-(2-pyridyl)-N′-(5-bromofurfuryl)-ethylenediamine (I, X = Br). The first of these (I, X = H) has been reported by Viaud to be an active antihistaminic.[2] The compounds may be considered as oxygen analogs of the thiophene substituted ethylenediamines previously reported in which the furan nucleus replaces the thiophene group.



I

They were synthesized by an initial reaction of furfuryl alcohol, or 5-bromofurfuryl alcohol, with thionyl chloride in toluene solution at −30 to −40°. The intermediate furfuryl chlorides obtained are extremely unstable[3] and were not isolated but were treated directly with the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine, also in toluene solution, at low tempera-

(1) Clapp, Clark, Vaughan, English and Anderson, THIS JOURNAL, **69**, 1549 (1947).

(2) Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947); *Drug Trade News*, **22** [9], 63 (1947). We have been unable to obtain the original article but have been advised that the name "methylfurfuryl" used by the *Drug Trade News* is intended to mean "furylmethyl" or furfuryl.

(3) Gilman and Vernon, THIS JOURNAL, **46**, 2576 (1924).

ture. Two molar equivalents excess of the sodium salt were used to neutralize the acidic by-products present from the chlorination reaction. After hydrolysis of the reaction mixture, the desired products were obtained by distillation of the toluene layer *in vacuo* as light yellow, unstable oils which decompose rapidly at room temperature and slowly even at −80°. In the presence of mineral acids, the compounds are destroyed within a few seconds to yield blue–violet solutions or tars. They are stable, however, to alkali and to organic acids and were isolated crystalline as their colorless, non-hygroscopic dihydrogen citrate salts.

When tested in guinea pigs by the histamine aerosol technique or by intravenous injection of histamine,[4] the furfuryl derivative (I, X = H) was found to be equally as effective as N,N-dimethyl - N′ - (2 - pyridyl) - N′ - benzylethylenediamine (Pyribenzamine)[5] in protecting against death while the bromofurfuryl derivative (I, X = Br) was only slightly less effective. The results on the furfuryl derivative are in agreement with those reported by Viaud.[2] When tested for acute, twenty-four-hour toxicity by intraperitoneal injection in white mice, the furfuryl derivative had the same toxicity as Pyribenzamine, whereas the bromofurfuryl derivative was approximately 50% less toxic.

We are indebted to Dr. J. T. Litchfield, Jr., and to the Misses Maxine R. Adams and Marion S. Jaeger of these Laboratories for the pharmacological data reported here.

Experimental[6]

N,N-Dimethyl-N′-(2-pyridyl)-N′-furfurylethylenediamine.—To a suspension of 36 g. (1.5 moles) of sodium hydride in 1500 cc. of dry toluene was added 248 g. (1.5 moles) of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine[5,7] and the mixture heated at reflux for one and one-half hours, or until the evolution of hydrogen ceased, and then cooled to 15° in an ice-bath. In a separate flask, 49 g. (0.5 mole) of redistilled furfuryl alcohol was placed in 300 cc. of dry toluene and the solution cooled with stirring to −30° in a Dry Ice–acetone-bath. A solution of 59.5 g. (0.5 mole) of thionyl chloride in 50 cc. of toluene was then added dropwise at this temperature over a twenty to thirty minute period while passing a steady stream of nitrogen through the apparatus. A large amount of tar and resin was formed toward the end of the addition. The clear, dark green toluene solution was decanted from the resin and added over a five- to ten-minute period to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine also in toluene. The resulting exothermic reaction was maintained at 15° for forty-five minutes. The reaction mixture was then allowed to warm to room temperature and hydrolyzed cautiously with 750 cc. of water. The toluene layer was separated, concentrated, and the residue distilled *in vacuo* to yield 30.2 g. (25%) of impure product as a light yellow oil, b. p. 100–140° (0.4 mm.). Also obtained was 137.5 g. (83% of theoretical recovery) of the excess starting ethylenediamine, b. p. 70–85° (0.5 mm.). The crude material was refractionated to yield 18.6 g. (15%) of pure product, b. p. 136–137° (0.7 mm.); $n^{30}D$ 1.5486. This is obtained in 95% yield as a stable, non-hygroscopic dihydrogen citrate by precipitation of the salt from alcohol solution with ether and recrystallization from methyl ethyl ketone, m. p. 95–97°.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot C_6H_8O_7$: C, 54.91; H, 6.22; N, 9.61. Found: C, 54.96, 55.22; H, 5.98, 6.06; N, 9.34, 9.49.

N,N-Dimethyl-N′-(2-pyridyl)-N′-(5-bromofurfuryl)-ethylenediamine.—The sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine was prepared as in the previous example from 13 g. (0.54 mole) of sodium hydride and 89 g. (0.54 mole) of the diamine in 200 cc. of toluene. In a separate flask 32 g. (0.18 mole) of 5-bromofurfuryl alcohol[8] dissolved in 150 cc. of toluene was treated with 21.5 g. (0.18 mole) of thionyl chloride in 50 cc. of toluene at −30°, as described above, and the reaction mixture was added to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine. After reaction and hydrolysis were complete, the product was isolated as before and distilled *in vacuo* to yield 26.5 g. (44% of the theoretical recovery) of the excess ethylenediamine used, and 16 g. (28%) of impure product, b. p. 140–175° (1 mm.). This material was refractionated to yield 10 g. (17%) of pure product as a greenish yellow oil, b. p. 156–158° (0.5 mm.); $n^{30}D$ 1.5603. Treatment of this with one equivalent of alcoholic citric acid and precipitation with ether gave the stable dihydrogen citrate salt in 97% yield. After recrystallization from methyl ethyl ketone, the colorless crystals melt at 105–107°.

Anal. Calcd. for $C_{14}H_{18}BrN_3O \cdot C_6H_8O_7$: C, 46.52; H, 5.08; Br, 15.48; N, 8.14. Found:[9] C, 46.88, 46.91; H, 5.12, 5.28; Br, 15.41, 15.31; N, 8.14, 8.24.

(4) Litchfield, Adams, Goddard, Jaeger and Alonso, *Bull. Johns Hopkins Hosp.*, **81**, 55 (1947).

(5) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(6) All melting points are corrected. The microanalyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted for these data.

(7) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(8) Prepared from 5-bromofurfural [Gilman and Wright, THIS JOURNAL, **52**, 1170 (1930)] by the crossed Cannizzaro reaction method of Davidson and Bogert, *ibid.*, **57**, 905 (1935); *cf.* Chute, Orchard and Wright, *J. Org. Chem.*, **6**, 157 (1941).

(9) Carbon values were obtained using silver pumice mixed with copper oxide as a substitute for the copper oxide–lead chromate layer in the Pregl microcombustion tube. Unsatisfactory high values were consistently obtained when the conventional tube filling was used.

CHEMOTHERAPY DIVISION
STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY
STAMFORD, CONNECTICUT RECEIVED MARCH 24, 1948

Concerning the Acylation of Kojic Acid at Elevated Temperatures

BY L. L. WOODS

The acylation of kojic acid at elevated temperatures with acetic anhydride in a modified Nencki[1] reaction is anomalous. The reaction described produces a ketone, I, having an empirical formula $C_{10}H_{13}O_7$. Under hydrolytic conditions the latter compound loses an acetyl group (compound II). Data are lacking for assignment of structures to these two compounds, although some pertinent observations should be noted. The compounds do not have the phenolic character of the parent compound and do contain one aceto group as evidenced by their reactivity toward carbonyl reagents.

(1) Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, New York, N. Y., p. 304.

Experimental

Acylation of Kojic Acid (I).—Twenty grams (0.142 mole) of kojic acid was mixed with 125 g. (1.22 moles) of acetic anhydride and 10 g. of zinc chloride. The mixture was heated over a water-bath under reflux and protected from moisture with a calcium chloride tube until the first vigorous reaction had subsided. The water-bath was then removed and replaced with an oil-bath. The heating was continued by gradually increasing the temperature to 145°, and then maintaining the temperature between 135–145° for one and one-half hours. Upon completion of the heating of the mixture, the excess acetic anhydride and acetic acid were removed under reduced pressure.

The residue was then treated with 200 ml. of boiling water and set aside to cool. After cooling, the crystals were filtered off. The filtrate was extracted with three successive 100-ml. portions of benzene. The combined benzene fractions were added to the crystals, which immediately dissolved. The mixture was washed once with cold water, dried with anhydrous magnesium sulfate, and decolorized with Norite.

The benzene was allowed to evaporate and 24.8 g. of a pale yellow compound were obtained. The substance was recrystallized by dissolving it in the smallest quantity of boiling water necessary to obtain complete solution (500–600 ml.). The white compound thus obtained was air dried. The analytical sample was dried in the vacuum desiccator over sulfuric acid for three weeks, m. p. 106°. The compound was quite soluble in ether, alcohol, benzene and ethyl acetate as well as hot water.

Anal. Calcd. for $C_{10}H_{13}O_7$: C, 48.98; H, 5.30; mol. wt., 245. Found: C, 49.06, 49.28, 49.10; H, 5.39, 5.72, 5.62; mol. wt. 248. (Each of the three carbon–hydrogen analyses was on a sample from a different run.[2])

Impure samples of the compound always gave a faint red color with dilute ferric chloride solutions; however, the pure samples failed to give the test. The compound did not react with dilute sodium bicarbonate solution. When 1.6137 g. of the ketone was heated ten hours in the electric drying oven at a temperature of 100–102° it lost 0.0376 g. (2.31%) of its weight, one molecule of water would require a loss of 7.34%. This loss of weight, perhaps, cannot be entirely attributed to the loss of moisture because the material developed a faint odor at this temperature.

The 2,4-dinitrophenylhydrazine derivative of compound (I) had a melting point of 114°.

Anal. Calcd. for $C_{10}H_{13}O_8$ $(C_6H_4N_4O_4)_4$: N, 23.21. Found: N, 23.18, 23.40.

Hydrolysis of Compound (I) to Form Compound (II).—A small portion (1 g.) of purified compound (I) dissolved in 50 ml. of hot water was refluxed for fifteen hours. The solution was cooled, decolorized with a little Norite, and filtered. After the water was evaporated and the solid dissolved in absolute ethanol, the solvent was removed under reduced pressure; and the compound was completely dried in the vacuum desiccator. The compound was a colorless glassy material which had a m. p. of 55–57°. Its semicarbazide had a m. p. of 247°. The compound was very soluble in water and in alcohol, but insoluble in acetone and ether. The material was not acidic and did not give any color with dilute ferric chloride solution.

Anal. Calcd. for $C_8H_{11}O_6$: C, 47.29; H, 5.41. Found: C, 47.50; H, 5.84.

(2) Analyses by Dr. Carl Tiedcke.

SAINT AUGUSTINE'S COLLEGE
RALEIGH, N. C.

RECEIVED FEBRUARY 24, 1948

NEW COMPOUNDS

Esters of Mucic Acid

The new compounds[1] listed in Table I were prepared by refluxing and stirring mechanically a mixture of 50 g. of mucic acid and 500 g. of the corresponding alcohol in the presence of 2 g. of *p*-toluenesulfonic acid. The esters all crystallized directly from the cooled reaction mixtures, after removal of unreacted mucic acid by filtration, and were recrystallized from 95% ethanol.

TABLE I

ESTERS OF MUCIC ACID

Di-esters	M. p., °C.	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sapon. equiv. Calcd.	Sapon. equiv. Found
n-Propyl	149–150	48	$C_{12}H_{22}O_8$	48.98	48.9	7.54	7.64	147.1	146.8
n-Butyl	142.5–143.5	93	$C_{14}H_{26}O_8$	52.16	52.2	8.13	8.17	161.2	160
n-Amyl	147–147.5	74	$C_{16}H_{30}O_8$	54.84	54.9	8.63	8.68	175.2	174.2
n-Hexyl	143–144	55	$C_{18}H_{34}O_8$	57.12	57.0	9.06	8.94	189.2	189.1
Allyl	156.5–158	78	$C_{12}H_{18}O_8$	49.65	49.6	6.25	6.35	145.1	145.6

The *n*-propyl and *n*-butyl mucates were prepared by refluxing the reaction mixtures for thirty and ten hours, respectively. The *n*-amyl and *n*-hexyl esters were prepared in essentially the same manner except that 200 g. of xylene was added to the mixture, which was refluxed under a Bidwell–Sterling water trap for twenty and forty hours, respectively. In the preparation of allyl mucate, 250 g. of benzene was added, and refluxing and stirring continued for thirty hours, after which benzene, allyl alcohol and water were slowly distilled through a fractionating column until the final reaction solution was approximately 150 ml.

(1) Dimethyl and diethyl mucates were prepared by Fischer and Speir (*Ber.*, **28**, 3252 (1895)), the former by reaction of mucic acid and methanol–hydrochloric acid in a sealed tube at 100° and the diethyl ester by refluxing mucic acid with ethanol and hydrochloric acid.

WESTERN REGIONAL RESEARCH LABORATORY
BUREAU OF AGRICULTURAL AND
INDUSTRIAL CHEMISTRY
U. S. DEPARTMENT OF AGRICULTURE
ALBANY, CALIFORNIA J. F. CARSON

RECEIVED FEBRUARY 16, 1948

N-(Acetylsalicyloyl)-piperidine

Fifty grams of acetylsalicylic acid and 250 ml. of thionyl chloride were refluxed for two hours. Excess thionyl chloride was removed on a steam-bath and with vacuum. The residue was taken up in dry benzene and a solution of 55 ml. (100% excess) of piperidine in dry benzene was added cautiously and with cooling. After filtering off the piperidine hydrochloride, the combined liquors and

washings were boiled down to a thick oil. This product was recrystallized from ligroin, the separation of unreacted, ligroin-insoluble acetylsalicylic acid being conveniently carried out in the same operation. Further recrystallization from dioxane–water and pyridine–water gave 24.5 g. (36%) of N-(acetylsalicyloyl)-piperidine in the form of white needles, m. p. 145–146°. *Anal.* Calcd. for $C_{14}H_{17}NO_3$: N, 5.66. Found: N, 5.51.

NUTRITION RESEARCH LABORATORIES
CHICAGO 30, ILLINOIS ARTHUR J. TOMISEK

RECEIVED MAY 10, 1948

COMMUNICATIONS TO THE EDITOR

DESTHIOBENZYLPENICILLIN

Sir:

"From the standpoint of organic chemistry, the most convincing evidence"—for the lactam formula of benzylpenicillin—"was secured by a study carried out in the Merck laboratories of the action of Raney nickel catalyst upon sodium benzylpenicillinate." A monocarboxylic acid $C_{16}H_{20}O_4N_2$ benzyldesthiopenicillin and phenylacetyl-L-alanyl-D-valine were obtained.[1] Through the kindness of Dr. Ellis V. Brown and Mr. John L. Smith of Chas. Pfizer and Co., Inc., we were given an ample supply of sodium benzylpenicillinate and have studied its desulfurization with the active W-6 Raney nickel catalyst.[2]

It proved possible to remove the sulfur from sodium benzylpenicillin in alcohol at about 15° under 5000 p. s. i. of hydrogen, within one or two hours. However, under these conditions the phenyl group is hydrogenated to cyclohexyl, to some extent. The preferred procedure has been to carry out the desulfurization in 96% alcohol under about 45 p. s. i. of hydrogen for a period of four hours at 10–20°. The reaction appears to be complete after an hour or two.

Eleven desulfurizations, each on 500 mg. of sodium benzylpenicillinate with 16 g. of W-6 Raney nickel, have been carried out under the preferred conditions. A crude product was obtained by extracting with chloroform the reaction mixtures, made acid to *p*H 2, after the removal of the catalyst and alcohol. Chloroform soluble neutral products were then removed by converting the desthiobenzylpenicillin to its salt and extracting the alkaline solution with chloroform. The desired acid was then obtained by extraction of the acidified solution with chloroform. The average weight of crude desthiobenzylpenicillin obtained was 220 mg. This product is free of basic or neutral compounds and of those containing sulfur. After crystallization from an alcohol–water mixture, the average yield of product, m. p. above 100°, was 150 mg. from seven desulfurizations. In four cases where the product so obtained was recrystallized, there was obtained 120–130 mg. of desthiobenzylpenicillin, m. p. 106–109°, 108–110°, 108.5–110.5° and 110–113°. The product shows a neutral equivalent and analyses corresponding to the molecular formula given above.

These results, obtained under so mild conditions of reaction, support the conclusion of Kaczka, Mozingo and Folkers of the Merck laboratories that an intramolecular rearrangement is not involved in the formation of desthiobenzylpenicillin.

LABORATORY OF ORGANIC CHEMISTRY HOMER ADKINS
UNIVERSITY OF WISCONSIN FRED J. BRUTSCHY[3]
MADISON, WISCONSIN MARGARET MCWHIRTER

RECEIVED FEBRUARY 16, 1948

(1) *Science*, **105**, 657 (1947).

(2) Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

(3) Du Pont Post-doctorate Fellow 1946–1947.

THE ENZYMATIC SYNTHESIS OF N-CARBOBENZOXY-D AND L-*o*-FLUOROPHENYLALANYLPHENYLHYDRAZIDES

Sir:

Previous studies on the resolution of acylated DL-amino acids by the asymmetric enzymatic synthesis of the anilide or phenylhydrazide of the acylated L-amino acid[1] have given no indication that appreciable quantities of the anilide or phenylhydrazide of the acylated D-amino acid may also be formed. We wish to report a case where substantial quantities of the D-phenylhydrazide have been synthesized despite the fact that the amount of amine present was insufficient to permit quantitative conversion of both the D- and L-acids.

25.0 g. (0.079 mole) of N-carbobenzoxy-DL-*o*-fluorophenylalanine was incubated with 20 g. of activated papain, 36.0 g. of L-cysteine hydrochloride, and 4.3 g. (0.040 mole) of redistilled phenylhydrazine at 40° for five days. The precipitated N-carbobenzoxy-*o*-fluorophenylalanylphenylhydrazide was recovered and recrystallized from toluene to give 11.0 g. of N-carbobenzoxy-*o*-fluorophenylalanylphenylhydrazide (I); m. p. 152–160°; 5.0 g. of additional papain, 12.0 g. of cysteine hydrochloride and 1.00 g. of phenylhydrazine was added to the filtrate from (I), the solution was incubated for five days at 40°, and the precipitate recrystallized from toluene to give 3.0 g. of N-carbobenzoxy-DL-*o*-fluorophenylalanyl-

(1) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

phenylhydrazide (II); m. p. 153.5–155.7° (cor.); $[\alpha]^{25}D$ 0.0° (3% in acetone). (I) was fractionally recrystallized from toluene to give 4.0 g. of N-carbobenzoxy-L-*o*-fluorophenylalanylphenyl-hydrazide (III); m. p. 171.0–172.0° (cor.); $[\alpha]^{25}D$ −31.0° (3% in acetone). *Anal.* Calcd. for $C_{23}H_{22}O_3N_3F$: C, 67.8; H, 5.4; N, 10.3. Found: C, 67.9; H, 5.7; N, 10.3; and 4.0 g. of (II); m. p. 155.5–156.5° (cor.); $[\alpha]^{25}D$ 0.0° (3% in acetone). *Anal.* Calcd. for $C_{23}H_{22}O_3N_3F$: C, 67.8; H, 5.4; N, 10.3. Found: C, 67.9; H, 5.6; N, 10.3. The filtrate from (II) was concentrated under reduced pressure, acidified, and the oily solid recrystallized from toluene to give 5.6 g. of an approximately equimolar mixture of N-carbobenzoxy-D-*o*-fluorophenylalanine and N-carbobenzoxy-DL-*o*-fluorophenylalanine. Fractional recrystallization from toluene gave 1.0 g. of N-carbobenzoxy-D-*o*-fluorophenylalanine (IV); m. p. 103–105° (cor.); $[\alpha]^{25}D$ +15.7° (5% in acetone). *Anal.* Calcd. for $C_{17}H_{16}O_4NF$: C, 64.3; H, 5.1; N, 4.4. Found: C, 64.4; H, 5.1; N, 4.2; and 1.9 g. of N-carbobenzoxy-DL-*o*-fluorophenylalanine (V); m. p. 108.5–110.0° (cor.); $[\alpha]^{25}D$ 0.2° (5% in acetone). *Anal.* Calcd. for $C_{17}H_{16}O_4NF$: C, 64.3; H, 5.1; N, 4.4. Found: C, 64.5; H, 5.3; N, 4.5.

A simultaneous enzymatic resolution of N-carbobenzoxy-DL-alanine using an aliquot of the same enzyme preparation gave N-carbobenzoxy-L-alanylphenylhydrazide in 75% yield after one recrystallization; m. p. 154.5–155.5° (cor.); $[\alpha]^{25}D$ −27.2° (5% in acetone).

Other experiments not reported here indicate that the behavior noted with *o*-fluorophenylalanine is not unique and it is clear that further study on the effect of the nature of the side chain, of the base, and of the acyl group on the course of the enzymatic synthesis is required. Such investigations are now in progress.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA EDWARD L. BENNETT
CARL NIEMANN

RECEIVED JULY 6, 1948

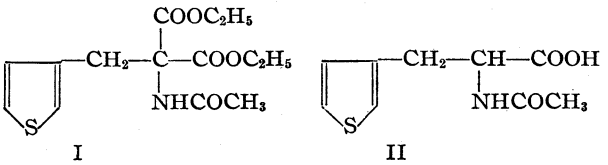
THE SYNTHESIS OF β-3-THIENYLALANINE

Sir:

Due to the current interest in metabolite–antimetabolite relations, and in particular to the discovery by du Vigneaud and associates[1,2] that β-2-thienylalanine functioned as a phenylalanine anti-metabolite with yeast, we are prompted to describe an isomer of this compound, β-3-thienylalanine, which we have prepared for testing as a phenylalanine antagonist.

The synthesis involves the reaction of 3-thienyl bromide with sodioacetamidomalonic ester to form 3-thenylacetamidomalonic ester (I). The 3-thenyl bromide was prepared by the peroxide-catalyzed reaction of N-bromosuccinimide with 3-methylthiophene, as previously described.[3] I melted at 90–91° after recrystallization from water.

Anal. Calcd. for $C_{14}H_{19}O_5NS$: S, 10.20. Found: S, 9.92. Alkaline hydrolysis of I, followed



I II

by acidification and heating, yielded N-acetyl-β-3-thienylalanine (II), m. p. 148–149°. *Anal.* Calcd. for $C_9H_{11}O_3NS$: S, 15.03; N, 6.57. Found: S, 15.14; N, 6.82.

β-3-Thienylalanine was prepared by complete hydrolysis of I in barium hydroxide, acidification with sulfuric acid, decarboxylation, and neutralization with barium carbonate. The water solution thus obtained was concentrated to dryness, and the residue recrystallized from water. β-3-Thienylalanine precipitated as fine white crystals, which browned at 260° and melted with decomposition from 265–267°. *Anal.* Calcd. for $C_7H_9O_2NS$: S, 18.71; N, 8.19. Found: S, 18.43; N, 8.10.

Complete details on the synthesis and biological testing of this compound will be published at a later date.

(3) Campaigne and LeSuer, THIS JOURNAL, **70**, 1555 (1948).

E. CAMPAIGNE
R. CLIFFORD BOURGEOIS
CHEMISTRY LABORATORY ROGER GARST
INDIANA UNIVERSITY WALTER C. MCCARTHY
BLOOMINGTON, INDIANA ROBERT L. PATRICK
HARRY G. DAY

RECEIVED MARCH 13, 1948

THE PREPARATION AND POLYMERIZATION OF MONOMERIC CYCLIC DISULFIDES

Sir:

Carothers extensively described the reversible polymerization relationships existing between monomeric cyclic anhydrides,[1] esters,[2] and formals.[3] Patnode and Wilcock[4] recently described the reversible conversion of methyl polysiloxanes to cyclic compounds. We have found that a similar reversible polymerization is possible between high-molecular weight disulfide polymers and the corresponding monomeric disulfide ring.

Steam distillation of aqueous dispersions of disulfide polymers yields very small amounts of

(1) du Vigneaud, McKennis, Simonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

(2) Dittmer, Ellis, McKennis and du Vigneaud, *ibid.*, **164**, 761 1946).

(1) J. W. Hill and W. H. Carothers, THIS JOURNAL, **55**, 5023 (1933).

(2) W. H. Carothers, G. L. Dorough and F. J. Van Natta, *ibid.*, **54**, 761 (1932).

(3) J. W. Hill and W. H. Carothers, *ibid.*, **57**, 925 (1935).

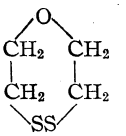
(4) W. Patnode and D. F. Wilcock, *ibid.*, **68**, 358 (1946).

low-molecular weight organic compounds in the distillate. The rate of production of monomer is extremely slow but has not diminished with time, indicating that actually depolymerization is occurring. Addition of small amounts of sodium hydroxide to the polymeric dispersion significantly increases the rate of depolymerization.

The polymer resulting from the condensation of bis-(2-chloroethyl) ether and sodium disulfide[5] yields a pale yellow oil of characteristic odor. Attempts to distil it have resulted in decomposition. The compound is stable indefinitely if completely dry but water converts it slowly back to the original polymer. Aqueous sodium sulfide or polysulfide converts the oil rapidly to the polymeric form.

$(—CH_2CH_2OCH_2CH_2SS—)$

I

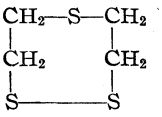


II

The physical properties of the oil were determined and compared with those calculated for structure II.

	Found	Calculated
Index of refraction $n^{20}D$	1.5823	...
Molecular refraction	36.7	36.3
Specific gravity	1.2737	...
Molecular weight	137	136
Sulfur, %	46.3	47.1

Cyclic compounds containing one or more heterocyclic sulfur atoms are well represented in the literature but heterocyclics with a disulfide group are not well known. Fromm and Joerg[6] reported on the ring



which they obtained by the reaction of $ClC_2H_4SSC_2H_4Cl$ with Na_2S or $ClC_2H_4SC_2H_4Cl$ with Na_2S_2. They reported a melting point of 74 to 75° for the product obtained by either method.

The production of polymer would appear more probable from this method of preparation than would the formation of a cyclic monomer. By substantially the same procedure, we have prepared polymeric products.

Cyclic compounds similar to that resulting from the ether disulfide have been obtained from disulfide polymers of different structures, but the products have yet to be characterized. A complete account of this work, together with theoretical considerations, will appear at a later date.

COMMUNICATION FROM THE THIOKOL CORPORATION TRENTON, N. J.
F. O. DAVIS
E. M. FETTES

RECEIVED APRIL 20, 1948

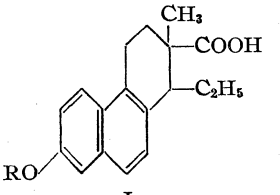
(5) J. C. Patrick, *Trans. Faraday Soc.*, **32**, 347 (1946).

(6) Fromm and Joerg, *Ber.*, **58**, 304 (1925).

BIS-DEHYDRODOISYNOLIC ACID

Sir:

The substance I (R = H) has recently attracted considerable attention because it is one of the most potent estrogens known. In a series of brilliant studies Miescher, Heer and Billeter obtained I (R = H) both as a degradation product



I

of natural equilenin and by total synthesis.[1] More recently Anner and Miescher[2] announced an improved synthesis involving about ten steps from 1-aminonaphthalene-6-sulfonic acid (Cleve's acid) to the methyl ether I (R = CH_3). We wish to disclose herewith a facile total synthesis of this substance utilizing the Stobbe condensation of diethyl succinate with 2-propionyl-6-methoxynaphthalene (readily available by Friedel–Crafts acylation of β-naphthyl methyl ether[3]). Catalytic hydrogenation of the resulting condensation product over platinum oxide gave β-carboxy-γ-(6-methoxy-2-naphthyl)-caproic acid (m. p. 157–158°, dec. *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.30; H, 6.30) which on cyclization *via* the anhydride with aluminum chloride in nitrobenzene produced 1-ethyl-4-keto - 7 - methoxy - 1,2,3,4 - tetrahydrophenanthrene-2-carboxylic acid, m. p. 215.5–216.5° (*Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.31; H, 6.03). Hydrogenation of the keto acid over palladium-on-charcoal catalyst in the presence of a trace of perchloric acid gave 1 - ethyl - 7 - methoxy - 1,2,3,4 - tetrahydrophenanthrene-2-carboxylic acid, m. p. 203.5–206°. (*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.36; H, 7.07), which on treatment in ether solution with diazomethane followed by sodium triphenylmethyl and methyl iodide afforded upon hydrolysis normal bis-dehydrodoisynolic acid methyl ether I (R = CH_3), m. p. 230–231° alone or when mixed with an authentic specimen of the same melting point which was kindly supplied by Dr. C. R. Scholz of Ciba Pharmaceutical Products. The methyl ester of I (R = CH_3) melted at 74.5–76.5° and gave no melting point depression on admixture with the ester (m. p. 75–76.5°) prepared from authentic I (R = CH_3).

Bioassays kindly performed by Drs. R. K. Meyer and E. G. Shipley of the University of Wisconsin Zoology Department showed our acid

(1) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); Heer, Billeter and Miescher, *ibid.*, **28**, 991, 1342 (1945).

(2) Anner and Miescher, *Helv. Chim. Acta*, **29**, 586 (1946).

(3) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

to be of the same order of activity as the authentic material.

LABORATORY OF ORGANIC CHEMISTRY
UNIVERSITY OF WISCONSIN WILLIAM S. JOHNSON
MADISON, WISCONSIN ROBERT P. GRABER

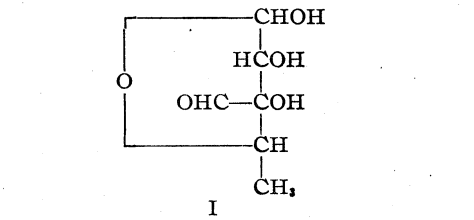
RECEIVED JUNE 14, 1948

STREPTOMYCES ANTIBIOTICS. XIX. DIHYDROSTREPTOSONIC ACID LACTONE AND CONFIGURATION OF STREPTOSE AND STREPTOBIOSAMINE

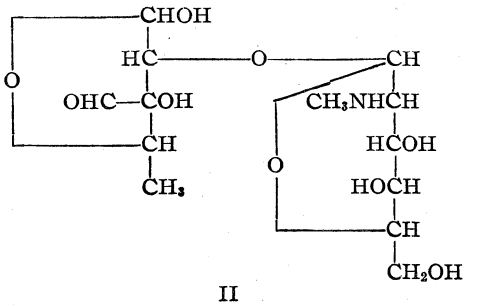
Sir:

2-Methyl pentaacetyldihydrostreptobiosaminide[1] was allowed to react stepwise with ethyl mercaptan–hydrogen chloride, acetic anhydride, and mercuric chloride for the preparation of amorphous pentaacetyldihydrostreptobiosamine.[2] Acetylation of this compound gave hexaacetyldihydrostreptobiosamine.[2] Oxidation by bromine and hydrolysis by hydrochloric acid of pentaacetyldihydrostreptobiosamine gave the known N-methyl-L-glucosamine and the new dihydrostreptosonic acid lactone, m. p. 143–144°, $[\alpha]_D$ −32° (*c*, 0.40 in water). Reaction of the lactone with hydrazine gave dihydrostreptosonic acid hydrazide, m. p. 137–139°, $[\alpha]_D$ +23° (*c*, 0.9 in water).

Application of Hudson's rules of rotation to streptosonic acid diamide[3] and dihydrostreptosonic acid hydrazide shows that the hydroxyl group at C_2 of streptose lies on the right. Since it has already been shown[4] that the hydroxyl groups at C_2 and C_3 of streptose are *cis*, and that the configuration about C_4 is *levo*,[5] the configuration of L-streptose is represented by structure I. On the basis of these data, and the calculations of the glycosidic linkage between streptose and N-methyl-L-glucosamine to be α-L,[6] the configuration of streptobiosamine is represented by structure II. The levorotations of streptosonic acid lactone[3] and dihydrostreptosonic acid lactone support the applicability of Hudson's rules to these streptose derivatives, since it is established conclusively that the configuration about C_4 of these lactones is L. That the lactone of dihydrostreptosonic acid lactone involves the secondary hydroxyl group at C_4 is shown by the liberation of formaldehyde when the lactone reacts with two equivalents of periodic acid.



I



II

(1) Brink, Kuehl, Flynn and Folkers, THIS JOURNAL, **68**, 2557 (1946).

(2) Stavely, Wintersteiner, Fried, White and Moore, *ibid.*, **69**, 2742 (1947).

(3) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).

(4) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2405 (1945).

(5) Fried, Walz, and Wintersteiner, *ibid.*, **68**, 2746 (1946).

(6) Lemieux, DeWalt and Wolfrom, *ibid.*, **69**, 1838 (1947).

FREDERICK A. KUEHL, JR.
RESEARCH DEPARTMENT MARY NEALE BISHOP
MERCK AND CO., INC. EDWIN H. FLYNN
RAHWAY, N. J. KARL FOLKERS

RECEIVED MAY 27, 1948

CHARACTERISTICS OF THE DROPPING MERCU ELECTRODE IN FUSED SALTS

Sir:

In a preliminary investigation of the applicability of polarographic techniques to fused salt media we have obtained typical polarographic reduction waves for the cations of a number of salts dissolved in a fused salt solvent. The results indicate that the Ilkovic equation[1,2] is applicable to the melt employed, a ternary eutectic consisting of 66.65 mole % ammonium nitrate, 25.76% lithium nitrate, and 7.59% ammonium chloride (m. p. 86.2°).[3]

Mercury was used for the dropping electrode and the stationary unpolarized anode pool in a cell maintained at 125 ± 0.5° in an oil-bath. Drops were collected in a Pyrex spoon, washed, dried, and weighed for tests of the Ilkovic equation.

Characteristic reduction waves were obtained with nickel(II), copper(II), and bismuth(III), the latter two exhibiting maxima. A trace of potassium iodide eliminated the maximum in the case of copper. Varying degrees of success have been had with other solute salts, prime difficulties being limited solubility in or reaction with the solvent electrolyte.

TABLE I

TEST OF THE ILKOVIC EQUATION

No.	C, mmol./l.	i_d, μ amp.	m mg./sec.	$t_{max.}$, sec.	$\frac{i_d}{Cm^{2/3}t^{1/6}_{max}}$
1	1.95	3.74	1.41	4.0	1.21
2	4.98	10.0	1.45	4.5	1.22
3	6.77	12.8	1.37	3.9	1.22
4	9.97	17.2	1.45	3.4	1.10
5	12.8	21.6	1.40	3.5	1.09
6	12.8	16.6	0.658	7.6	1.22

(1) D. Ilkovic, *Coll. Czechoslov. Chem. Commun.*, **6**, 498 (1934).

(2) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 38.

(3) E. P. Perman and R. H. Wilson, *J. Chem. Soc.*, **125**, 1709 (1924).

The results obtained by varying the concentration of nickelous nitrate in the ternary solvent are presented in Table I.

Test no. 6 was made on same solution as no. 5 but with a different capillary. With a value of 13.29 g./cc. for the density of mercury at 125°, the Ilkovic equation becomes

$$i_d = 614nD^{1/2}Cm^{2/3}t_{max}^{1/6}$$

with the symbols having the usual meaning given by Kolthoff and Lingane.[2] The agreement of the experimental data with the Ilkovic equation can be seen from the essential constancy of the ratio $i_d/Cm^{2/3}t_{max}^{1/6}$ in the last column of the table. The average deviation in the ratio is ±4.3%. Substitution of the average ratio, 1.18, into the Ilkovic equation gives a diffusion coefficient equal to 9.2×10^{-7} cm.²/sec. for the nickel bearing ion.

Work is in progress to eliminate the solubility and solvent instability difficulties by employing more stable solvent electrolytes, *e. g.*, alkali halides, at higher temperatures. This will also allow investigation of a number of metals for the dropping electrode.

INSTITUTE FOR THE STUDY OF METALS
UNIVERSITY OF CHICAGO N. H. NACHTRIEB
CHICAGO, ILL. M. STEINBERG

RECEIVED MAY 7, 1948

EXCHANGE REACTIONS BETWEEN IODINE ATOMS AND ORGANIC IODIDES

Sir:

Several workers have reported exchange reactions between organic iodine compounds and inorganic iodides, but there are very few known examples of exchanges with neutral iodine atoms or molecules. Methyl iodide[1] and several diiodophenols[2] have been shown to exchange with elementary iodine in polar solvents, but the mechanisms of these reactions were not elucidated. Noyes, Dickinson and Schomaker[3] demonstrated that neutral atoms were involved in the exchange of 1,2-diiodoethylene with elementary iodine in saturated hydrocarbon solvents.

We have now observed atomic exchange reactions with some other representative organic iodides. The experiments were conducted with iodine-131 supplied by the Oak Ridge National Laboratory and obtained on allocation from the United States Atomic Energy Commission. Hexane solutions 0.002 molar (0.004 normal) in radioactive iodine and 0.04 molar in organically combined iodine were illuminated with a tungsten lamp at about 30°. The iodine in each solution was then extracted by shaking it with an acidic aqueous solution of sodium sulfite, and the activities in one or both of the separated solutions were measured with a jacketed counter. Comparative approximate rate constants based on *trans*-diiodoethylene as unity were as follows:

Allyl iodide	much greater than	200
Trans-diiodoethylene		1.0
Iodobenzene		0.002
Ethyl iodide	less than	0.001

The rate constant for allyl iodide could not be obtained with any precision, for exchange was 60% complete in twenty seconds under the normal illumination of the laboratory desk. This amount of exchange corresponds to a rate approximately 200 times as fast as the rate of exchange of *trans*-diiodoethylene under the much more intense illumination employed in the other experiments. When the laboratory was darkened to an extent such that the necessary operations could barely be carried out, exchange of allyl iodide was 25% complete in twenty seconds. Therefore, at least a large fraction of the exchange appears to involve free atoms, but the possibility of an accompanying dark reaction is not excluded. Studies of the separation procedure demonstrated that allyl iodide underwent no more than 1% of exchange with iodide ion under the conditions employed in the reduction of the iodine.

A solution of ethyl iodide which was illuminated for one week underwent a significant amount of exchange, but the data did not permit the calculation of a reliable rate constant.

That exchange in the last three compounds in the table requires free atoms is indicated by the fact that duplicate solutions stored in the dark for as much as one week underwent no more than 1% of exchange.

We are undertaking a more thorough investigation of the kinetics of these reactions.

CONTRIBUTION FROM THE CHEMICAL LABORATORIES
OF COLUMBIA UNIVERSITY
NEW YORK 27, N. Y. RICHARD M. NOYES

RECEIVED JUNE 7, 1948

AN INTERRELATIONSHIP OF THYMIDINE AND VITAMIN B_{12}

Sir:

In a series of studies on factors functionally related to folic acid and *p*-aminobenzoic acid, thymidine was isolated from liver as a factor preventing the toxicity of a competitive antagonist of folic acid.[1] The recently reported isolation of vitamin B_{12} as a growth factor for *Lactobacillus lactis* Dorner[2,3] necessitated a study of the function of the vitamin to determine whether or not it is identical with a factor found in this Laboratory to be concerned with the biosynthesis of thymidine. As vitamin B_{12} has been isolated using an assay with *Lactobacillus lactis* Dorner, this organism was utilized in the present investigation.

A medium suitable for assay techniques has not

(1) H. A. C. McKay, *Nature*, **139**, 283 (1937).

(2) W. H. Miller, G. W. Anderson, R. K. Madison and D. J. Salley, *Science*, **100**, 340 (1944).

(3) R. M. Noyes, R. G. Dickinson and V. Schomaker, THIS JOURNAL, **67**, 1319 (1945).

(1) Shive, *et al.*, THIS JOURNAL, in press.

(2) Rickes, *et al.*, *Science*, **107**, 396 (1948).

(3) Shorb, *ibid.*, **107**, 397 (1948).

been adequately described for this organism; however, a previously described medium[4] in which the phosphate buffer was replaced by sodium acetate and which was supplemented with an oleic acid source, "Tween 80," 10 mg. per 10 cc., enzymatic digest of casein,[5] 10 mg. per 10 cc., and Wilson's liver fraction LR, 100γ per 10 cc., supports good growth of the organism in the presence of liver extracts containing anti-pernicious anemia principles and can be used successfully as an assay medium. The enzymatic digest of casein replaces clarified tomato juice.[3] Tests were incubated for twenty-four hours at 37–38°.

With the above medium or one containing clarified tomato juice (0.5 cc. per 10 cc.) in place of the enzymatic digest of casein, thymidine adequately replaced the liver extracts containing anti-pernicious anemia principles. Half-maximum stimulation of growth was obtained at a concentration of 1–3 γ of thymidine per 10 cc. Thymine was inactive at concentrations as high as 100 γ per 10 cc.

When the medium containing tomato juice was utilized, as little as 1 cc. of sterile, aerated distilled water added aseptically to 10 cc. of medium replaced the liver extract, and this effect was enhanced by aseptic addition of ascorbic acid. However, when the enzymatic digest of casein was used in place of tomato juice, the aerated water was inactive, but ascorbic acid (1 mg. in 1 cc. of sterile, aerated water per 10 cc. of medium) added aseptically still adequately replaced the liver extracts containing anti-pernicious anemia principles for the nutrition of this organism. The function of ascorbic acid in replacing the liver extract will be reported separately.

Since thymidine adequately replaces vitamin B_{12} in the nutrition of *Lactobacillus lactis* Dorner, it appears probable that vitamin B_{12} functions in the biosynthesis of thymidine.

(4) Guirard, *et al.*, *Arch. Biochem.*, **9**, 361 (1946).
(5) Roberts and Snell, *J. Biol. Chem.*, **163**, 499 (1946).

THE BIOCHEMICAL INSTITUTE AND
THE DEPARTMENT OF CHEMISTRY WILLIAM SHIVE
THE UNIVERSITY OF TEXAS AND JOANNE MACOW RAVEL
THE CLAYTON FOUNDATION FOR ROBERT E. EAKIN
RESEARCH, AUSTIN, TEXAS

RECEIVED JUNE 1, 1948

A NEW COLOR TEST FOR TRYPTOPHAN

Sir:

It has been observed that at room temperature perchloric acid converts trytophan to a fluorescent yellowish green compound. Fluorescence is particularly strong in ultraviolet light. Tryptophan may readily be identified in untreated proteins by this test. This reaction is not given by other amino acids and biologic substances with which it is usually associated. Indol acetic acid, however, gives a slight pink color and slight fluorescence under the conditions of the test.

The Test.—One-half of 1 cc. of water containing 0.5 mg. of tryptophan, or about 10 mg. of albumen (egg powder) or any other tryptophan-containing protein, is placed in a test-tube. The protein does not have to be in solution. Three cc. of perchloric acid (C. P. 70–72%) is added and the contents of the tube are well mixed. A quite stable, intense greenish-yellow color develops within a few minutes attaining maximum intensity in about ten minutes. Upon the addition of 0.1 cc. of a 1% ferric chloride solution, the greenish-yellow color becomes reddish-orange. If the ferric chloride solution is added to the tryptophan-containing solution before the perchloric acid, the reddish-orange color is formed instantaneously. For the detection of minute amounts of tryptophan, ultraviolet light and perchloric acid without ferric chloride should be employed.

The following tryptophan-containing materials gave the reaction: casein, albumen (egg powder), human blood serum, pepsin and crystalline soybean trypsin inhibitor.

The following amino acids did not give the reaction: glycine, alanine, leucine, isoleucine, valine, phenylalanine, tyrosine, cysteine, cystine, methionine, threonine, proline, hydroxyproline, histidine, arginine, lysine, serine, aspartic acid, glutamic acid, and *p*-aminobenzoic acid.

S. S. Cohen (*J. Biol. Chem.*, **156**, 691 (1944)) made the interesting observation that when carbohydrates and tryptophan were heated for ten minutes at 100° in 30% perchloric acid colored condensation products form. In Cohen's reaction boiling is an essential factor. The green fluorescent compound described in the present communication, however, forms readily at room temperature, carbohydrates do not interact and this reaction does not take place in 30% perchloric acid.

VENEREAL DISEASE RESEARCH LABORATORY
U. S. PUBLIC HEALTH SERVICE
U. S. MARINE HOSPITAL HENRY TAUBER
STATEN ISLAND 4, N. Y.

RECEIVED JUNE 7, 1948

NEW BOOKS

The Systematic Identification of Organic Compounds. By RALPH L. SHRINER, Professor of Chemistry, The State University of Iowa, and REYNOLD C. FUSON, Professor of Chemistry, The University of Illinois. Third Edition, John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1948. viii + 370 pp. 15 × 22 cm. Price $4.00.

The first edition of this laboratory manual appeared in 1935 as 195 pages; for reviews of this edition, see THIS JOURNAL, **58**, 536 (1936), and *J. Chem. Education* **12**, 596–597 (1935). Five years later a second edition had grown to 312 pages; for reviews of it, see THIS JOURNAL, **62**, 2569 (1940), and *J. Chem. Education*, **17**, 501 (1940). The present third edition requires 370 pages.

Although the approach to its subject is broadly retained, the material has been substantially amplified and the new incorporated with the old in a different sequence. By inclusion of new methods the chapter on the preparation of derivatives has been increased from 51 to 65 pages; that comprising tables of derivatives occupies the same space, but many new constants have been inserted in what were formerly gaps in the tables. The two chapters on separation of mixtures and interpretation of experimental data appear to be unchanged, but the eleven pages of problems have by new additions been expanded to twenty.

The utility of the index has been increased and ease of location of a given tabular entry facilitated by the inclusion of the melting or boiling point of the compound in the index itself.

In recent years increasing attention is being given to the special values of adequate training in the field to which this treatment comprises a valuable introduction; the new edition is, therefore, timely and welcome.

ERNEST H. HUNTRESS

Répertoire des Composés organiques polymorphes. (Encyclopedia of Polymorphic Organic Compounds.) By LOUIS DEFFET, Assistant à l'Université de Bruxelles. Editions Desoer, 21 Rue Sainte-Véronique, Liége, 1942. 155 pp.

This book is a compilation of thermal and crystallographic data on organic compounds which exhibit polymorphism. After a very brief explanatory introduction, it lists, in its first section, 1188 organic compounds found to be polymorphic at atmospheric pressure, in its second section, 32 substances polymorphic under high pressure, in a third section, a bibliography of 994 references, and, in a fourth section, an alphabetical list of the substances, referring by number to those in the first two sections, which are arranged according to the system used by Richter. After the formula and name of each compound in the first two sections, abbreviations indicate the number of modifications, the occurrence of enantiotropy or monotropy, and the crystal forms, when known, and occasionally other information. Also listed are the melting and transition temperatures, and the heats of fusion and of transition, when available. The lists appear to have been prepared with the care that one would expect from a pupil of Professor Timmermans. On looking up a few familiar polymorphic substances, the reviewer has found no omissions of data published prior to December, 1941. The book should be very useful to investigators of polymorphism, and generally valuable as a reference work for data on the subject.

CHARLES P. SMYTH

BOOKS RECEIVED

May 10, 1948—June 10, 1948

HARRY BARRON. "Modern Rubber Chemistry." D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N.Y., 1948. 502 pp. $7.50.

J. E. BELCHER and J. C. COLBERT. "Properties and Numerical Relationships of the Common Elements and Compounds." Fourth Edition. Appleton-Century-Crofts, Inc., 35 West 32d Street, New York 1, N.Y., 1948. 374 pp. $3.00.

ERNST DAVID BERGMANN. "The Chemistry of Acetylene and Related Compounds." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N.Y., 1948. 108 pp. $3.00.

ERNST DAVID BERGMANN. "Isomerism and Isomerization of Organic Compounds." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N.Y., 1948. 138 pp. $3.50.

JOHN BURCHARD. "M.I.T. in World War II. Q.E.D." John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N.Y., 1948. 354 pp. $3.50.

TENNEY L. DAVIS, Editor-in-Chief. "Chymia. Annual Studies in the History of Chemistry." Vol. I. University of Pennsylvania Press, 1948. Lancaster Press, Inc., Pa. 189 pp. $3.50.

RENÉ DUBRISAY. "Propriétés des Corps et Constitution chimique." Presses Univérsitaires de France, 108 Boulevard Saint-Germain, Paris, France, 1948. 151 pp. 200 fr.

T. P. HILDITCH. "The Chemical Constitution of Natural Fats." Second Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N.Y., 1947. 554 pp. $9.00.

C. A. JACOBSON. "Encyclopedia of Chemical Reactions." Vol. II. Reinhold Publishing Corporation, 330 West 42d Street, New York 18, N.Y., 1948. 917 pp. $12.00.

RICHARD KUHN. "Biochemistry. Part I." Published by Office of Military Government for Germany, Field Information Agencies Technical, Economics Division, Research Control Branch, Berlin, Germany. 218 pp.

J. S. LONG and H. V. ANDERSON. "Chemical Calculations." Fifth Edition. International Chemical Series. McGraw-Hill Book Company, 330 West 42nd Street, New York 18, N.Y., 1948. 401 pp. $3.75.

W. C. PIERCE and E. L. HAENISCH. "Quantitative ANALYSIS." Third Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N.Y., 1948. 520 pp. $3.75.

W. W. PIGMAN and M. L. WOLFROM. "Advances in Carbohydrate Chemistry." Vol. III. Academic Press, Inc., 125 E. 23rd Street, New York 10, N.Y., 1948. 424 pp. $8.50.

W. THEILHEIMER. "Synthetic Methods of Organic Chemistry." Vol. I. Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N.Y., 1948. 254 pp. $5.00.

E. J. W. VERWEY and J. TH. G. OVERBEEK. "Theory of the Stability of Lyophobic Colloids. The Interaction of Sol Particles having an Electric Double Layer." Elsevier Publishing Company, 215 Fourth Avenue, New York, N.Y., 1948. 205 pp. $4.50.

"A Symposium on the Use of Isotopes in Biology and Medicine." Contributors: Drs. CLARKE, UREY, SEABORG, AEBERSOLD, NIER, CORYELL, KAMEN, MELVILLE, SPRINSON, WOOD, BLOCH, GREENBERG, CHAIKOFF, HAMILTON, HALL, HERTZ, BALE, NICKSON and DANIELS. The University of Wisconsin Press, Madison, Wis., 1948. 445 pp. $5.00.

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 70 SEPTEMBER 1, 1948 NUMBER 8

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Preparation of *cis*- and *trans*-Decahydroisoquinolines and of Bz-Tetrahydroisoquinoline

BY BERNHARD WITKOP[1]

Of the possible hydrogenated derivatives of isoquinoline, the *cis*- and *trans*-decahydro compounds, py-tetrahydroisoquinoline, and very recently bz-tetrahydroisoquinoline, have been prepared mainly by ring-synthetic methods.[2,3] The latter has lately gained importance as an intermediate in the synthesis of morphane.[4]

In this communication a simple method for the preparation of 5,6,7,8-tetrahydroisoquinoline (bz-tetrahydroisoquinoline), and of the pure *cis*- and *trans*-decahydroisoquinolines directly from quinoline is reported.

Skita obtained by catalytic hydrogenation of isoquinoline in glacial acetic acid with colloidal platinum a substance which was very probably largely *cis*-decahydroisoquinoline; the physical properties of his substance, however, suggest the presence of a certain amount of the *trans*-isomer.[5] We have found that the hydrogenation of isoquinoline in glacial acetic acid with a trace of sulfuric acid gives a mixture of decahydroisoquinoline which contains 70–80% of the *cis*-isomer and 20% of the *trans*-compound.[6] The *cis*-compound was readily isolated from the crude mixture of isomers as the pure picrate (m. p. 150°). On the other hand, if the mixture of isomers was subjected to dehydrogenation over palladium at 210°, a mixture of bases was formed, from which 10% of *trans*-decahydroisoquinoline, 10–25% of 5,6,7,8-tetrahydroisoquinoline and isoquinoline were isolated by fractional extraction with 0.1 *N* hydrochloric acid.[7] These relationships are summarized in the chart. The 5,6,7,8-tetrahydroisoquinoline alternately was prepared by boiling *cis*-decahydroisoquinoline in tetralin with selenium for forty eight hours.

These experiments demonstrate the striking fact that *cis*-decahydroisoquinoline is much more readily dehydrogenated than the corresponding *trans*-isomer, a behavior which parallels that of the decahydroquinolines, and, to a lesser extent, that of the decalins (Ehrenstein[7]). Model considerations suggest that the determining factor may lie in the relatively easier approach of the *cis*-compound to the catalyst in a configuration favorable to the removal of hydrogen atoms in pairs.[8]

Experimental[9]

***cis*-Decahydroisoquinoline.**—The catalytic perhydrogenation of isoquinoline[7] was effected at room temperature and normal pressure as follows: isoquinoline (reagent, 1 g.) was dissolved in glacial acetic acid (10 cc.) and five drops of concentrated sulfuric acid was added.[10] In the presence of 1 g. of platinum oxide the tetrahydro stage was reached after about forty minutes, and the decahydro state after about four to eight hours. Omission of the concentrated sulfuric acid or use of less catalyst blocked the hydrogenation at the tetrahydro stage. The catalyst was removed by filtration, the diluted solution was made strongly alkaline and extracted with ether. After evaporation of the ether the base was neutralized with hydrochloric acid and evaporated to dryness. The crystallized hydrochloride (1.24 g., over 90%) showed an unsharp melting point, 165°. It was converted into the picrate. The dry picrate (2.5 g.) was treated five

(1) Fellow of the Mathew T. Mellon Foundation.

(2) Helfer, *Helv. Chim. Acta*, **9**, 814 (1926).

(3) Schlittler and Merian, *ibid.*, **30**, 1339 (1947).

(4) *Cf.* Grewe, *Naturwiss.*, **33**, 333 (1946).

(5) Skita, *Ber.*, **57**, 1977 (1924).

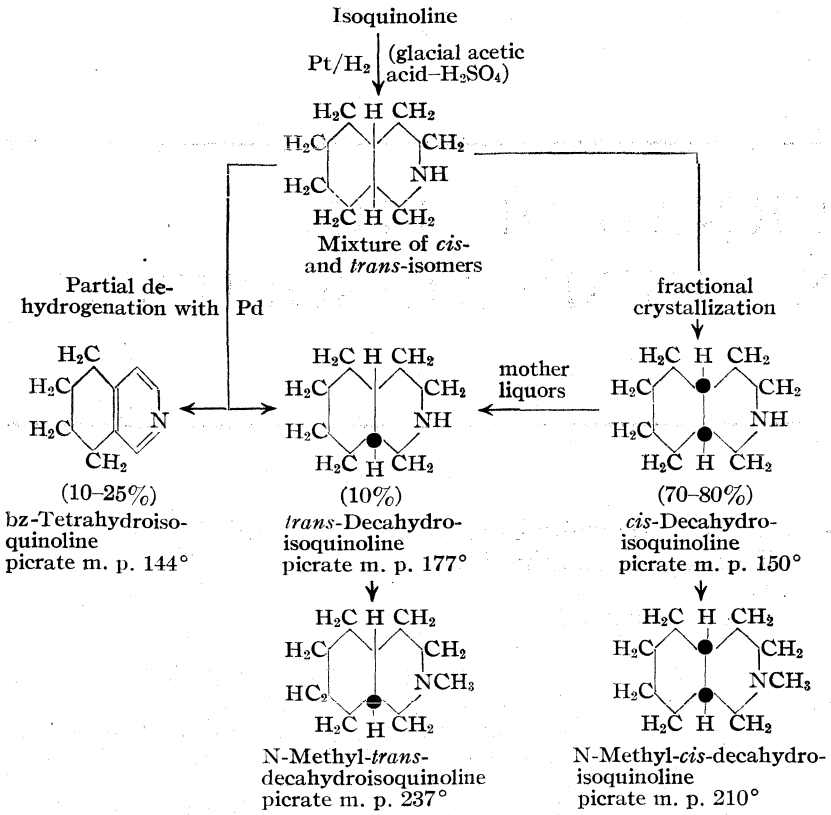
(6) In analogy with the catalytic hydrogenation of quinoline: both decahydroquinolines are formed in ratios dependent on the acidity of the solvent, Hückel and Stepf, *Ann.*, **453**, 163 (1934).

(7) All these reactions were observed in the quinoline series by Ehrenstein who developed the method of partial dehydrogenation and the procedure for the separation of the dehydrogenation products [*Ber.*, **67**, 1715 (1934)].

(8) *Cf.* Linstead, THIS JOURNAL, **64**, 1985 (1942), on the stereochemistry of catalytic hydrogenation.

(9) All melting points corrected.

(10) Kindler and Kwok, *Ann.*, **554**, 9 (1942).



times with 1–2 cc. of cold methanol, which chiefly removed *trans*-decahydroisoquinoline. The residue was dissolved in hot methanol and filtered after an hour from the crystals which separated. The final solution yielded uniform crystals which were recrystallized twice from methanol; melting point 150° (1.91 g., 73%). The picrate was converted into the hydrochloride by adding hydrochloric acid to the methanolic solution and extracting the picric acid with ether. The dry hydrochloride was treated with 1 cc. of absolute alcohol and the residue was crystallized from alcohol–ether. The beautifully crystallized hydrochloride melted sharply at 183° (0.41 g.).

N-Methyl-*cis*-decahydroisoquinoline Picrate.—The above hydrochloride (100 mg.) was boiled under reflux with 2 cc. of 95% formic acid and 2 cc. of 40% aqueous formaldehyde for two hours. The solution was evaporated to dryness and converted into the picrate. The picrate of the N-methyl base is much less soluble in methanol than that of the original base. It crystallizes from methanol in tufts of small needles, m. p. 210°, yield over 90%.

Anal. Calcd. for $C_{10}H_{19}N \cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.52; H, 5.45.

***trans*-Decahydroisoquinoline. A. By Fractional Crystallization.**—The combined cold methanol extracts of the *cis*-picrate contained mainly *trans*-compound. It could be obtained by careful slow fractional crystallization. The *trans*-picrate formed large prisms possessing a full yellow color and was separated mechanically from smaller light yellow aggregates of crystals that consisted chiefly of *cis*-picrate. The recrystallized *trans*-picrate melted at 175–178°.

B. By Dehydrogenation of the Accompanying *cis*-Compound.—The mixture of the *cis*- and *trans*-bases (1 g.), as obtained directly by hydrogenation, was heated under reflux with 0.2 g. of palladium black. The reaction was carried out in an apparatus similar to the one designed by H. Heymann.[11] After about four hours 650 cc. of hydrogen was evolved. The major part of the reaction mixture was distilled at 210° (760 mm.). The distillate was taken up in 20 cc. of ether and extracted with consecutive portions of 2 cc. of 0.1 *N* hydrochloric acid. Every fraction was converted separately into the picrate. The fractions 1–4 (Table I) were recrystallized from absolute methanol. The accompanying small amount of isoquinoline picrate could be easily separated owing to its much smaller solubility. The pure *trans*-decahydroisoquinoline picrate melted at 177°. On admixture with the *cis*-picrate (m. p. 150°) the melting point was depressed to 143°.

Anal. Calcd. for $C_9H_{17}N \cdot C_6H_3O_7N_3$: C, 48.91; H, 5.44. Found: C, 49.07; H, 5.38.

Hydrochloride.—The picrate was dissolved in methanol, treated with hydrochloric acid and ether; the aqueous solution after evaporation left the hydrochloride which crystallized from alcohol in needles, m. p. 224°. The salt is not very hygroscopic.

Anal. Calcd. for $C_9H_{17}N \cdot HCl$: C, 61.5; H, 9.8. Found: C, 61.1; H, 10.2.

Dehydrogenation.—Treatment of 30 mg. of the above chloride with 30 mg. palladium at 210° for one-half hour failed to have any dehydrogenating effect (the *cis*-chloride was easily converted into isoquinoline under these conditions). When 30 mg. of *trans*-base was heated with 90 mg. of palladium for three hours under reflux, one obtained a reaction product which was no longer miscible with water, picrate 223°, identical with isoquinoline picrate.

TABLE I

The melting points (cor.) were carried out on a micro hot stage; the figures in parentheses are sintering points.

Picrate fraction no.	Weight, mg.	Appearance	M. p., °C.	Compound
1	260	lemon-yellow, crystalline	170 (160)	*Trans*-decahydro isoquinoline (isoquinoline)
2			167 (160)	
3			169	
4			168	
5	67	amorphous	130	intermediate fraction
6	270	glistening needles, pale-yellow	158 (rest 168)	Bz-tetrahydroisoquinoline (isoquinoline)
7			155 (rest 175)	
8			155 (rest 180)	
9			155 (rest 180)	
10	65	mixture	190 (158)	intermediate fraction
11	70	small crystals	200 (185)	isoquinoline
12	67	dull,	215 (190)	
13	68	bright yellow	220	
14	65		221	
15 etc.	65		223	

N-Methyl-*trans*-decahydroisoquinoline Picrate.—The compound was prepared in exactly the same way as described for the corresponding *cis*-compound. The picrate crystallized from methanol in thin needles which underwent crystalline transformation at 215° and melted at 237°.

(11) L. F. Fieser, "Experiments in Organic Chem.," 1941, p. 462.

Anal. Calcd. for $C_{10}H_{19}N \cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.57; H, 5.75.

Bz-Tetrahydroisoquinoline. A. By Partial Dehydrogenation with Palladium Black.—The picrate fractions 6–9 (Table I) were combined (270 mg.) and freed from the much less soluble isoquinoline picrate by sufficient recrystallizations from acetone. The pure product finally crystallized in golden-yellow needles of uniform appearance, m. p. 144°.

Anal. Calcd. for $C_9H_{11}N \cdot C_6H_3O_7N_3$: C, 49.73; H, 3.87. Found: C, 50.25; H, 3.87.

In another experiment, starting with the same amount (1 g.) of decahydro bases, dehydrogenation was stopped after the evolution of 310 cc. of hydrogen (calcd. for 5 moles of hydrogen, 781 cc.). In this case the medium fractions yielded 690 mg. of picrate, corresponding to about 25% yield of Bz-tetrahydroisoquinoline.

Picrolonate.—The free base, prepared from the above picrate, had a smell reminiscent of substituted pyridines (*e. g.*, collidine). Aqueous picrolonic acid precipitated from the solution of the hydrochloride the picrolonate which, recrystallized from methanol, melted at 214°.

Anal. Calcd. for $C_{19}H_{19}O_5N_5$: C, 57.43; H, 4.78. Found: C, 57.94; H, 5.03.

B. By Partial Dehydrogenation with Selenium in Tetralin.—*cis*-Decahydroisoquinoline (0.8 g.) was boiled under reflux in 15 cc. of freshly distilled tetralin with 0.5 g. of black selenium dust for forty-eight hours. The reaction mixture was filtered from the selenium, diluted with ether and extracted with 2-cc. portions of 0.1 *N* hydrochloric acid. The fractions were converted into the picrates, which had the properties: 1–3, *cis*-decahydroisoquinoline picrate (0.19 g.), m. p. 150°; 4, mixture, not crystallized, sticky; 5, Bz-tetrahydroisoquinoline picrate, m. p. (after removal of little accompanying isoquinoline picrate) 144°; 6, isoquinoline picrate, m. p. 223°. After evaporation of the ether and tetralin a small amount of naphthalene was obtained.

Summary

Catalytic hydrogenation of isoquinoline in glacial acetic acid with sulfuric acid leads to a mixture containing 70–80% *cis*- and at least 10% *trans*-isomer. The *cis*-isomer is more readily dehydrogenated with Pd than the *trans* isomer. By controlled dehydrogenation of the *cis*-isomer bz-tetrahydroisoquinoline was obtained.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 15, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Basically Substituted Quinoxalines

BY HENRY GILMAN AND H. SMITH BROADBENT

Of the many thousands of compounds synthesized and tested for antimalarial activity, those which have shown by far the greater promise, in general, are the derivatives of nitrogen-containing heterocycles bearing basic side chains, in particular the derivatives of quinoline. At the inception of this investigation very few basically substituted quinoxalines had been described in the chemical literature and even fewer had been tested for *antimalarial* activity.[1] Since quinoxaline differs from quinoline only in having a tertiary nitrogen substituted for the carbon in the 4-position of the ring, derivatives of quinoxaline appeared to have some interest as antimalarials.

In order to explore this possibility, a series of substituted aminoquinoxalines and their 2,5-dimethyl-1-pyrryl derivatives was prepared and subjected to pharmacological testing. In addition the rather high tuberculocidal activity of some related types of compounds prompted the synthesis of 2,3-bis-(*p*-aminophenyl)-quinoxaline, 2,3-bis-(*p*-hydroxyphenyl)-quinoxaline and 2,3-bis-(*p*-hydroxyphenyl)-6-aminoquinoxaline.

(1) While this investigation was in progress and since its completion three years ago, several papers have appeared dealing with the synthesis of quinoxaline derivatives for pharmacological purposes, *viz.*, (a) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945); (b) Hall and Turner, *ibid.*, 699 (1945); (c) King and Beer, *ibid.*, 792 (1945); (d) Gawron and Spoerri, THIS JOURNAL, **67**, 514 (1945); (e) Mizzoni and Spoerri, *ibid.*, **67**, 1652 (1945); (f) Cavagnol and Wiselogle, *ibid.*, **69**, 795 (1947); (g) Stevens, Pfister and Wolf, *ibid.*, **68**, 1035 (1946); (h) Weijlard, Tishler and Erickson, *ibid.*, **66**, 1957 (1944); (i) Linsker and Evans, *ibid.*, **68**, 874 (1946); and (j) Wiedling, *Acta Path. Microbiol. Scand.*, **22**, 379 (1945), as well as a few notes.

The quinoxaline nuclei of the compounds synthesized in the course of this work were prepared by condensing appropriately substituted α-diketones with either *o*-phenylenediamine or 1,2,4-triaminobenzene dihydrochloride in acetic acid or aqueous ethanol solutions, respectively. In all cases the yields were satisfactory, although in the latter case, the removal of resinous by-products was troublesome.

The 1,2,4-triaminobenzene required was prepared and used in the form of its dihydrochloride. The original method of Hinsberg[2] for its preparation did not prove to be satisfactory. The complex formed between the amine and chlorostannous(ic) acids was often difficult to decompose completely and a tin-containing product was secured only difficultly purified by recrystallization. In addition, the frequent exposure to the air entailed in this process was deleterious to the very easily oxidized polyamine. In order to circumvent these difficulties, it was found that the catalytic reduction of 2,4-dinitroaniline in ethanol over Raney nickel was more rapid, convenient, and less expensive than the former method, and it yielded the product desired in greater yields of at least equal purity.

In the preparation of substituted benzoins, the experimental conditions necessary in order to get good yields of crystalline products are often quite rigid.[3] Rather than isolate the intermediate benzoins, anisoin and *o,o'*-dichlorobenzoin, in the prep-

(2) Hinsberg, *Ber.*, **19**, 1253 (1886).

(3) Dewar and Read, *J. Soc. Chem. Ind.*, **55T**, 347T (1936).

aration of the corresponding benzils, it was found that the crude nitrogenous mixtures containing less than 50% of the benzoin obtained from the potassium cyanide–aldehyde reaction could be oxidized directly with copper sulfate in pyridine.[4] This method converted the contained benzoin to the pure crystalline benzil in nearly quantitative yields.

The reported preparation of 4,4′-dihydroxybenzil by the demethylation of anisil[5] requires hydrobromic acid of 1.78 density, which is not conveniently available. Neither aqueous hydrobromic acid (d. 1.48, 48%) nor 33% hydrogen bromide in acetic acid was found to be efficacious alone; however, the use of equal parts of the two acid solutions was found to cleave smoothly the methyl groups from anisil resulting in a good yield of pure 4,4′-dihydroxybenzil.

The preparation of 2,3-bis-(*p*-aminophenyl)-quinoxaline was conveniently effected by Raney nickel reduction of the corresponding nitro compound (*cf.* ref. 1d and 1f) without reduction of the heterocyclic nucleus.[6]

The 2,5-dimethyl-1-pyrrylquinoxalines were synthesized from the corresponding amines by condensation with 2,5-hexanedione. In the case of 2-aminoquinoxaline we were not able to isolate any pure product other than starting material.

Solutions of 2,3-bis-(*p*-hydroxyphenyl)-6-aminoquinoxaline in strong acids are a bright, cherry-red color and in bases a brilliant yellow. On adding small amounts of the indicator dissolved in a dilute sodium hydroxide solution to a series of Clark and Lubs buffers, the transition point was found to lie between *p*H 3.4 and 3.6 indicating an approximate pK_{In} of 3.5 assuming the color intensities of the acidic and basic forms to be equal.

The 6-aminoquinoxalines and their pyrryl derivatives all have an intense yellowish-green fluorescence observable even in extremely dilute solutions, being red by transmitted light. An interesting observation on the effect of molecular structure on solubility is afforded by the 2,3-diphenyl-, 2,3 bis-(*p*-methoxyphenyl)-, and 2,3-bis-(*o*-chlorophenyl)-6-aminoquinoxalines and their pyrryl derivatives. The amino compounds are very soluble in ethanol and only moderately soluble in benzene whereas the corresponding pyrryl compounds are almost completely insoluble in hot ethanol and exceedingly soluble in hot benzene.

The results of the pharmacological tests on these compounds will be published elsewhere, and the authors are grateful to Parke, Davis and Company for arranging for the tests.

Experimental

1,2,4-Triaminobenzene Dihydrochloride.—(A) Tin and Hydrochloric Acid Method.—Following the general procedure of Hinsberg,[2] 0.5 mole of 2,4-dinitroaniline yielded 40 g. (41%) of 1,2,4-triaminobenzene dihydrochloride. A second 0.25-mole run gave a 35-g. (71.5%) yield.

(B) Catalytic Reduction Method.—In 300 ml. of absolute ethanol 61 g. (0.33 mole) of 2,4-dinitroaniline and 4–5 g. of "wet" Raney nickel catalyst were suspended and shaken under 1–3 atm. of hydrogen until the required amount for complete reduction of the nitro groups had been absorbed (*ca.* twelve hours). The violet solution was filtered free of catalyst and treated with an excess of concentrated hydrochloric acid with cooling in an ice-bath. A fine, purple, crystalline solid separated, which was filtered off, washed with ethanol and ethyl acetate, and finally dried *in vacuo*. The yields of dry, purplish solid in six successive runs were 81, 86, 93, 86, 98 and 85%, respectively, of a purity superior to that obtained by the Hinsberg procedure.

Anisil.—Anisoin was prepared from purified anisaldehyde according to the directions of Dewar and Read[3] in yields of 40% and 43% (m. p. 113°). A run made according to the procedure of Boesler[7] gave only a 22% yield.

Eleven grams (0.0405 mole) of anisoin, 45 g. (0.18 mole) of copper sulfate, 20 ml. of water, and 60 g. of pyridine were heated on a steam-bath with stirring for four hours. On filtering and washing with water, 10.5 g. (96%), of fine, pale yellow crystals melting sharply at 131–132° was obtained without crystallization (reported,[7] 133° by another technique). Two successive runs gave yields of 96% and 100%.

2,2′-Dichlorobenzil.—2,2′-Dichlorobenzoin was prepared from 100 g. (0.712 mole) of *o*-chlorobenzaldehyde following the procedure of Hodgson and Rosenberg[8]; however, the product was an oil which would not crystallize (reported,[8] m. p. 56–57° in 40% yield).

The crude mixture consisting of approximately 40% aryloin from the above reaction was stirred and heated at 100° for four hours with 180 g. copper sulfate, 80 ml. water, and 240 ml. pyridine. This crude product obtained on diluting with water was crystallized from benzene as beautiful, yellow needles melting at 128–129° (reported,[8] 128° by another method). The over-all yield was 38.5 g. (39%), nearly 100% based upon the contained aryloin.

4,4′-Dihydroxybenzil.—Ten grams (0.037 mole) of anisil, 50 ml. of aqueous hydrobromic acid (d. 1.48), and 50 ml. of 33% hydrogen bromide in glacial acetic acid were refluxed with vigorous stirring for six hours while a slow current of dry carbon dioxide was passed over the mixture. The solution was poured into water precipitating a fine gray powder, which was dissolved in a small volume of 15% sodium hydroxide, filtered, and then precipitated with hydrochloric acid. A light, gray powder melting at 245–247° was obtained. The melting point was unchanged on crystallizing from a large volume of boiling water. The yield was 8 g. (89%) (reported,[5] m. p. 235°).

6-Amino-2,3-bis-(*p*-methoxyphenyl)-quinoxaline: Procedure A.—A suspension of 10 g. (0.037 mole) of anisil and 7.5 g. (0.038 mole) of 1,2,4-triaminobenzene dihydrochloride in 100 ml. of ethanol and water (1:1) was refluxed with stirring for four hours on the steam-bath. Sodium hydroxide solution was added in slight excess, and the mixture was cooled. The hard cake of crude product was pulverized, taken up in hot ethanol, charcoaled and cooled. The dark purplish crystals separating out were then recrystallized to constant melting point from benzene giving a yield of 8.1 g. (61%) of light brown crystals melting at 194–196°.

2,3-bis-(*p*-Aminophenyl)-quinoxaline: Procedure B.—4,4′-Dinitrobenzil was prepared by the nitration of 4,5-diphenylglyoxalone according to the method of Chattaway and Coulson.[9] The yield of 2,3-bis-(*p*-nitrophenyl)-

(4) Clarke and Dreger, "Organic Syntheses," Coll. Vol. I, 1941, p. 87.

(5) Schönberg and Kraemer, *Ber.*, **55**, 1188 (1922).

(6) Since the work was completed, a similar reduction has been reported (see ref. 1b).

(7) Boesler, *Ber.*, **14**, 327 (1881).

(8) Hodgson and Rosenberg, *J. Chem. Soc.*, 16 (1930).

(9) Chattaway and Coulson, *J. Chem. Soc.*, 1361 (1928).

TABLE I

QUINOXALINES

Quinoxaline derivative	Procedure[a]	M. p., °C.[b]	Yield, %	Recrystallized from	Formula	N Analyses, % Calcd.	Found
6-Amino-2,3-dimethyl	A	186–187	100	Benzene–ethanol	$C_{10}H_{11}N_3$	24.2	23.9
6-Amino-2,3-diphenyl[c]	A	172–173	57	Benzene	$C_{20}H_{15}N_3$	...	...
6-Amino-2,3-bis-(*p*-methoxyphenyl)	A	194–196	61.5	Benzene	$C_{22}H_{19}O_2N_3$	11.76	11.71
6-Amino-2,3-bis-(*o*-chlorophenyl)	A	178–179	54	Benzene–ligroin	$C_{20}H_{13}N_3Cl_2$	11.47	11.48
6-Amino-2,3-bis-(*p*-hydroxyphenyl)	A	338–340	...	Ethanol–water	$C_{20}H_{15}O_2N_3$	12.77	12.84
2,3-bis-(*p*-Aminophenyl)[e]	B	260–262	18	Acetone–ethanol	$C_{20}H_{16}N_4$	17.94	17.95
2,3-bis-(*p*-Nitrophenyl)[d]	B	203–204	100	Acetic acid	$C_{20}H_{12}O_4N_4$	...	...
2,3-bis-(*p*-Hydroxyphenyl)	C	326–328	94	Ethanol	$C_{20}H_{14}O_2N_2$	8.91	9.02
6-(2,5-Dimethyl-1-pyrryl)-2,3-dimethyl	D	161–163	74	Ethanol	$C_{16}H_{17}N_3$	16.72	16.75
6-(2,5-Dimethyl-1-pyrryl)-2,3-diphenyl	D	151–153	44	Benzene–ethanol	$C_{26}H_{21}N_3$	11.19	11.12
6-(2,5-Dimethyl-1-pyrryl)-2,3-bis-(*p*-methoxyphenyl)	D	189–190	59	Benzene–ethanol	$C_{28}H_{25}O_2N_3$	9.65	9.70
6-(2,5-Dimethyl-1-pyrryl)-2,3-bis-(*o*-chlorophenyl)	D	211–212	29	Benzene–ethanol	$C_{26}H_{19}N_3Cl_2$	9.46	9.67

[a] An example representative of each procedure is described in the experimental part. The others were prepared in analogous fashion. [b] All melting points are uncorrected. The two above 300° were taken with a Berl–Kuhlmann type block, the others by capillary or hot-stage methods. [c] This compound has been prepared by Hinsberg, *Ann.*, **292**, 254 (1896), and Bertels, *Ber.*, **37**, 2277 (1904), m. p. 175°. [d] See ref. 11. [e] See ref. 12.

quinoxaline, obtained from the benzil and *o*-phenylenediamine, on recrystallization from acetic acid was 2.45 g. (100%) of large, tan crystals melting at 203–204° (reported,[7] 201°).

Two and three-tenths grams (0.0062 mole) of the nitrophenylquinoxaline was suspended in 60 ml. of absolute ethanol with 1–2 g. Raney nickel and shaken under 3 atm. pressure of hydrogen until the required amount was absorbed. The insoluble deposit was dissolved in methyl cellosolve, and the solution filtered free of catalyst. On evaporation of most of the solvent and diluting with water, brownish-yellow crystals melting at 255–258° were obtained. The product was recrystallized successively from acetone and water, and then acetone and ethanol until the melting point was raised to 260–262°.[10] The final yield of shining yellow plates of product was 0.350 g. (18%).

2,3-bis-(*p*-Hydroxyphenyl)-quinoxaline: Procedure C.—In 75 ml. of glacial acetic acid, 1.1 g. (0.01 mole) of *o*-phenylenediamine and 2.4 g. (0.01 mole) of 4,4′-dihydroxybenzil were refluxed for three hours. On cooling, glistening, yellow crystals of product separated. They were recrystallized from ethanol to a melting point of 326–328°. The yield was 2.9 g. (94%). The compound is easily soluble in sodium hydroxide, but very difficultly soluble in hydrochloric acid.

2,3-Dimethyl-6-(2,5-dimethyl-1-pyrryl)-quinoxaline: Procedure D.—Three grams (0.017 mole) of 2,3-dimethyl-6-aminoquinoxaline in 12 ml. of absolute ethanol was refluxed for four hours with 2.18 g. (0.0191 mole) of 2,5-hexanedione and 1 ml. of glacial acetic acid. The mixture was poured with rapid stirring into 50 ml. of water, cooled and filtered. The granular product after treatment with Norit was crystallized from ethanol as long, straw-colored needles melting at 161–163°. The yield was 3.2 g. (74%).

Attempted Preparation of 2-(2,5-Dimethyl-1-pyrryl)-quinoxaline.—2-Aminoquinoxaline was prepared from alloxazine in 67% over-all yield.[11] From 3.5 g. (0.0242 mole) of 2-aminoquinoxaline refluxed for two hours in 15 ml. of absolute ethanol with 3 ml. of 2,5-hexanedione, and 1 ml. of glacial acetic acid, a dark brown gum, and 2 g. of crystalline material was isolated on drowning in water. The gum could not be readily purified. The crystalline portion after several recrystallizations from ethanol–water (1:3) followed by sublimation melted at 156–157°. It was shown by mixed melting point to be recovered 2-aminoquinoxaline.

On a second attempt only a dark unmanageable gum was obtained.

Summary

Several quinoxaline derivatives have been synthesized for testing for antimalarial activity and some of them, as noted, for tuberculostatic activity also.

They are strongly fluorescent in benzene solution and one of them, 6-amino-2,3-bis-(*p*-hydroxyphenyl)-quinoxaline has the properties of an acid-base indicator at *p*H 3 to 4.

The results of the pharmacological tests will be published elsewhere.

AMES, IOWA RECEIVED MARCH 17, 1948

(10) Previously prepared by another method by Kuhn, Moller and Wendt, *Ber.*, **76**, 412 (1943), who give its melting point as 267–268°.

(11) Weijlard, Tishler and Erickson, THIS JOURNAL, **66**, 1957 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of 2,3-Disubstituted Cinchoninic Acids from Propoxymethyl Alkyl (or Phenyl) Ketones by Means of the Pfitzinger Reaction[1]

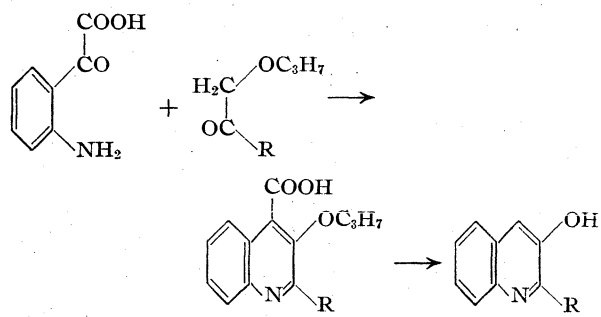
BY HENRY R. HENZE, JOE W. MELTON[2] AND EUGENE O. FORMAN

In 1925 Dilthey and Thelen[3] reported the initial utilization of an alkoxy ketone according to the Pfitzinger method[4] in preparing 3-methoxy-2-phenylcinchoninic acid. More recently, Cross and Henze[5] used this method to convert ethoxyacetone and ethoxymethyl ethyl ketone into the corresponding 2-alkyl-3-ethoxycinchoninic acids. Later, Lesesne and Henze[6] extended this reaction to include the utilization of alkoxy ketones in the synthesis of 2-alkoxyalkyl and 2-alkoxyalkyl-3-alkylcinchoninic acids. Thus, 1-alkoxyethyl methyl ketones appeared to yield cinchoninic acids having the 1-alkoxyethyl grouping attached to the 2-position.

In an attempt to extend the study to a higher homolog of the 1-alkoxyethyl alkyl ketone series, isoamyl 1-methoxyethyl ketone was warmed with isatin under the usual conditions without evidence of reaction. When the attempt was repeated, but using enough alcohol to make the reaction mixture homogeneous, only unsubstituted cinchoninic acid was isolated. Utilization of a 40% aqueous solution of alkali resulted in the formation of a molecular compound of anthranilic acid and 2-(1-methoxyethyl)-3-(2-methylpropyl)-cinchoninic acid.[7]

The availability of certain alkyl (or phenyl) propoxymethyl ketones[8] made it possible to study their behavior with isatinic acid in hot alkaline solution. By this procedure, twelve propoxymethyl ketones were converted into disubstituted cinchoninic acids. The structure of the two heterocyclic compounds derived from the phenyl propoxymethyl ketones was scarcely in doubt. However, their structure was completely established through conversion (by means of decarboxylation and ether group cleavage) into the known 3-hydroxy-2-phenylquinoline.[3]

Confirmation of the structure of this phenylcinchoninic acid did not establish that of the quinoline acids derived from the aliphatic keto ethers, since the latter contain the RCH_2COCH_2OR' grouping which might permit formation of either or both of two isomeric disubstituted cinchoninic acids depending upon which methylene group was involved in the ring closure. It is possible to distinguish between these two isomers by a study of the products of decarboxylation, of cleavage of the ether linkage, or of both. The cinchoninic acids derived from ethyl isopropoxymethyl ketone and *n*-propoxymethyl *n*-propyl ketone, respectively, could be converted into alkali-soluble quinolines, such as the known 2-ethyl-3-hydroxyquinoline.[9] Thus it was established that the hydrogens of the methylene group to which are attached both the ether and carbonyl groupings, are the more reactive in condensation with isatinic acid to form the heterocyclic nucleus



Experimental

The 2,3-disubstituted cinchoninic acids were prepared according to Pfitzinger's procedure by placing 25–50 cc. of 33% potassium hydroxide solution in a small flask and adding equivalent weights of isatin and an alkyl (or phenyl) propoxymethyl ketone. In most cases involving the isopropoxy ketones, enough alcohol was added to render the mixture homogeneous. The mixture was heated for forty-eight hours at about 100°, then was treated (hot) with Norite and filtered. After dilution with water, the filtrate was acidified with 50% acetic acid, usually causing immediate formation of a creamy precipitate. If necessary the acid solution was chilled before separation of the crystalline product. Each acid was purified by recrystallization to constant melting point from diluted alcohol or acetone. Only the purified products could be dried without decomposition in an oven. Data for the melting points and analyses of these acids are listed in Table I.

Proof of Structure of 2-Phenyl-3-propoxycinchoninic Acid.—This product, obtained through interaction of isatin and phenyl *n*-propoxymethyl ketone, was placed together with 15 cc. of concentrated hydrochloric acid in a sealed tube and heated at 175° for twelve hours. After opening the tube, the mixture was neutralized with sodium bicarbonate, and the substituted quinoline removed by filtration and recrystallized from an acetone–water solution. The melting point of the alkali soluble **3-hydroxy-2-phenylquinoline** (228° (cor.)) is somewhat higher than that (218–220°) reported by Dilthey and Thelen[3] for this product.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.31; H, 4.89; N, 6.49.

One-half gram of the hydroxyquinoline derivative was dissolved in 75 cc. of alcohol and treated with 40 cc. of saturated aqueous picric acid solution. A picrate soon

(1) From the M. A. theses of J. W. M. (Aug., 1940) and E. O. F. (June, 1941).

(2) Present address: Department of Chemistry, Northwestern State College, Alva, Oklahoma.

(3) Dilthey and Thelen, *Ber.*, **58**, 1588 (1925).

(4) Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 582 (1888); **56**, 283 (1897).

(5) Cross with Henze, THIS JOURNAL, **61**, 2730 (1939).

(6) Lesesne with Henze, *ibid.*, **64**, 1897 (1942).

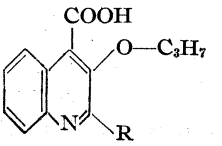
(7) Isbell with Henze, *ibid.*, **66**, 2096 (1944).

(8) Henze, Duff, Matthews, Melton and Forman, *ibid.*, **64**, 1222 (1942).

(9) Cross with Henze, see ref. 5, p. 2731.

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR 2,3-DISUBSTITUTED CINCHONINIC ACIDS



C_3H_7–	R	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n	$-CH_2CH_3$	64	187.0	69.48	69.66	6.61	6.48	5.40	5.40
iso-	$-CH_2CH_3$	20	197.0	69.48	69.33	6.61	6.63	5.40	5.50
n-	$-(CH_2)_2CH_3$	56	157.0	70.31	70.39	7.01	6.81	5.13	5.32
iso-	$-(CH_2)_2CH_3$	42	120.5	70.31	70.07	7.01	7.16	5.13	5.20
n-	$-(CH_2)_3CH_3$	55	123.0	71.05	71.63	7.37	7.28	4.88	5.25
iso-	$-(CH_2)_3CH_3$	41	104.6	71.05	70.74	7.37	7.25	4.88	4.75
iso-	$-CH_2CH(CH_3)_2$	50	163.7	71.05	70.64	7.37	7.52	4.88	4.98
iso-	$-(CH_2)_4CH_3$	32	68.3	71.73	71.55	7.69	7.89	4.65	4.74
n-	$-(CH_2)_2CH(CH_3)_2$	53	129.0	71.73	71.73	7.69	7.61	4.65	4.66
iso-	$-(CH_2)_2CH(CH_3)_2$	43	110.0	71.73	70.13	7.69	7.88	4.65	4.63
n-	$-C_6H_5$	48	216.0	74.25	74.27	5.58	5.45	4.56	4.78
iso-	$-C_6H_5$	59	210.0	74.25	74.07	5.58	5.49	4.56	4.596

separated and was recrystallized from alcohol; it melted[10] with decomposition at 245° (cor.).

Anal. Calcd. for $C_{21}H_{14}N_4O_8$: N, 12.44. Found: N, 12.59.

Proof of Structure of 3-(*n*-Propoxy)-2-(*n*-propyl)-cinchoninic Acid.—One gram of the product from interaction of isatin and *n*-propyl *n*-propoxymethyl ketone was dissolved in 15 cc. of concentrated hydrochloric acid, sealed in a tube and heated at 165° for twelve hours. When cooled, solid material separated from solution and, after drying in the oven at 110°, melted at 223° (cor.). This proved to be the hydrochloride of a substituted quinoline. It was dissolved in water and decomposed by addition of sodium bicarbonate; the liberated quinoline was recrystallized from an acetone–water mixture. The product, **3-hydroxy-2-*n*-propylquinoline,** melts at 256° (cor.), and is readily soluble in alkaline solution.

Anal. Calcd. for $C_{12}H_{13}NO$: N, 7.48. Found: N, 7.91.

A small amount of this disubstituted quinoline was dissolved in 95% alcohol, and mixed with 10 cc. of saturated aqueous solution of picric acid. After chilling the *picrate* separated as long crystals melting with decomposition at 158° (cor.).

Anal. Calcd. for $C_{18}H_{16}N_4O_8$: N, 13.46. Found: N, 13.73.

Proof of Structure of 2-Ethyl-3-isopropoxycinchoninic Acid.—Three methods were used in the conversion of this acid into 2-ethyl-3-hydroxyquinoline.

A. A mixture of 1.5 g. of 2-ethyl-3-isopropoxycinchoninic acid and 15 cc. of concentrated hydrochloric acid was sealed in a tube and heated at 175° for twelve hours. Upon dilution of the resulting solution with water, a white precipitate formed and was purified by solution in dilute sodium hydroxide solution with subsequent reprecipitation with dilute acetic acid solution. After recrystallization from acetone, the solid melted with decomposition at 205.5–208.0° (cor.).[11]

B. A sample of 2-ethyl-3-isopropoxycinchoninic acid was decarboxylated by heating to its melting point of 197°. The dark oil thus formed was distilled at 209–214° (42 mm.): 78% yield of 2-ethyl-3-isopropoxyquinoline. This material was sealed in a tube with concd. hydrochloric acid and heated to 200° for five hours. After diluting the solution with water, creamy white crystals separated and were purified as above; m. p. 205–208°.

Anal. Calcd. for $C_{11}H_{11}NO$: N, 8.07. Found: N, 8.22.

C. A mixture of 2 g. of 2-ethyl-3-isopropoxycinchoninic acid, 15 cc. of hydriodic acid and 1.25 g. of red phosphorus was refluxed for twenty-four hours. The hot mixture was filtered through asbestos and cooled to yield a yellow precipitate. The latter was filtered off, dissolved in sodium hydroxide solution and precipitated by addition of acetic acid. The solid was recrystallized to a constant m. p. of 206–207° (cor.) from alcohol and water.

Anal. Calcd. for $C_{11}H_{11}NO$: N, 8.07. Found: N, 8.27.

The yellow acidic filtrate from above was steam distilled and the residual solution concentrated by evaporation to 25 cc. It was neutralized with dilute sodium hydroxide solution; the yellow precipitate which first formed was redissolved in excess alkaline solution and reprecipitated with dilute acetic acid. The purified material melted at 179–182° with evolution of a gas and re-fused at 206–208° (cor.).[12]

Preparation of Picrates.—Certain of the cinchoninic acids were decarboxylated by being heated at a temperature approximately 40° above their melting points. After decarboxylation seemed complete, the resin was subjected to distillation under diminished pressure; about 90% of the theoretical yield of quinoline could be obtained. The quinoline was dissolved in alcohol and treated with a saturated solution of picric acid, which usually resulted in the immediate separation of the solid picrate. Re-

TABLE II

PICRATES OF CERTAIN 2-SUBSTITUTED-3-*n*-PROPOXYQUINOLINES

Alkyl-	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl	203	54.05	53.81	4.54	4.34	12.64	12.73
n-Propyl	191	55.02	54.83	4.84	4.67	12.22	12.41
n-Butyl	175	55.93	55.79	5.12	5.11	11.86	11.84
Isoamyl	198	56.78	56.66	5.36	5.21	11.52	11.67
Phenyl	206	58.53	58.24	4.09	3.97	11.38	11.65
Phenyl[a]	210	58.53	58.35	4.09	4.24	11.38	11.53

[a] Represents the picrate of 2-phenyl-3-isopropoxyquinoline.

(10) Bargellini and Berlingozzi, *Gazz. chim. ital.*, **53**, 3 (1923), reported m. p. 235–238° (dec.).

(11) Cross with Henze, ref. 5, reported m. p. 206–208° (cor.)(dec.).

(12) Cross with Henze, ref. 5, page 2732, reported m. p. of 2-ethyl-3-hydroxycinchoninic acid as 208–209° (dec.); the m. p. was noted after introducing the sample into the bath heated to about 200°. When warmed from room temperature at the usual rate, this material softens with evolution of gas at 179–181° (cor.) and melts at 206–208° (cor.).

crystallization was effected from alcohol. The melting points of the picrates were sharp with decomposition occurring only after fusion was complete. Data for the picrates are collected in Table II.

Summary

Twelve new 2,3-disubstituted cinchoninic acids have been prepared from alkyl (or phenyl) propoxymethyl ketones. Certain of these derivatives have been decarboxylated and their ether grouping cleaved to produce 2-alkyl (or 2-phenyl)-3-hydroxyquinolines, thus establishing the structures as 2-alkyl (or 2-phenyl)-3-propoxycinchoninic acids.

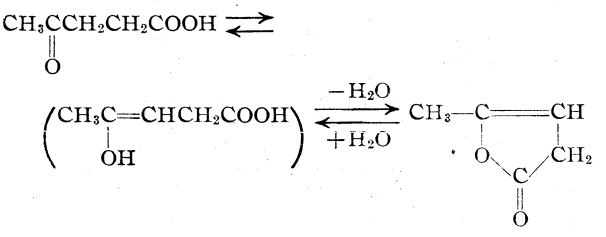
AUSTIN, TEXAS RECEIVED APRIL 20, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE A. E. STALEY MANUFACTURING COMPANY]

Pseudo Esters of Levulinic Acid

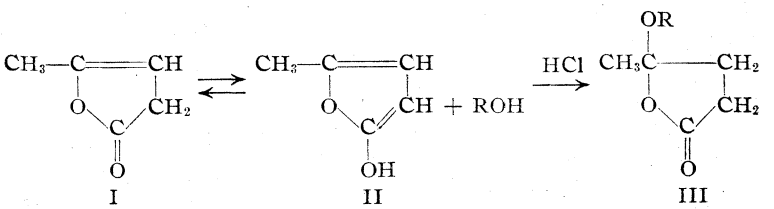
BY DAVID P. LANGLOIS AND HANS WOLFF

The dehydration of levulinic acid to α-angelica lactone is a reversible reaction. In the presence of traces of mineral acids water can be added to α-angelica lactone re-forming levulinic acid.[1] The enolic form of levulinic acid may be an intermediate in the reaction



If instead of water an alcohol is added to α-angelica lactone, the corresponding ester of levulinic acid would be expected as the reaction product. With the intention of preparing levulinic esters by this method, methanol and ethanol were added to α-angelica lactone in the presence of hydrogen chloride. The corresponding methyl and ethyl esters were obtained in quantitative yields.

Attempts to prepare cyclohexyl levulinate by this same method led to an unexpected result; an ester was obtained in 95% yield, but its physical and chemical properties differed from cyclohexyl levulinate prepared from levulinic acid and cyclohexanol by conventional methods. A further examination of the product revealed that it consisted predominately of the pseudo cyclohexyl ester of levulinic acid (III), which could result either from the addition of cyclohexanol to the double bond of α-angelica lactone (I) or from a 1–4 addition of the alcohol to the enol form of angelica lactone (II) followed by rearrangement to structure (III).



R = cyclohexyl

(1) Wolff, *Ann.*, **229**, 249 (1885).

The presence of an enol form of α-angelica lactone is indicated by a Zerewitinoff determination in which approximately one third of a mole of methane is liberated from one mole of α-angelica lactone. Additional evidence for an enol form is given by a comparison of the ultraviolet absorption spectra of furfuryl alcohol and α-angelica lactone (Fig. 1). Furfuryl alcohol was chosen for comparison because it possesses the same molecular weight as angelica lactone and has a structure quite similar to the enol form of α-angelica lactone. The maximum of absorption at 2170 Å., indicative of two double bonds in conjugation, is common to both compounds; the considerably lower absorption of the lactone would indicate that only a partial enolization occurs.

Pseudo esters of aromatic keto acids have been described. Meyer[2] prepared pseudo methyl 2-benzoylbenzoate; Lutz[3] reported the pseudo esters of substituted benzoylacrylic acid and Newman[4] discussed the synthesis of pseudo esters of the benzoylbenzoic acid type. It appears that the pseudo esters of levulinic acid described in this paper are the first examples of pseudo esters in the purely aliphatic series.

In studying the various alcohols it was observed that secondary alcohols form pseudo esters quite readily. This is also true in the case of reactive primary alcohols such as allyl and benzyl alcohols. On the other hand, normal primary alcohols, especially the lower members, give only the normal esters of levulinic acid unless special precautions are taken. The pseudo ester of methanol can be obtained, however, if ether is used as a solvent and the quantity of hydrogen chloride is regulated carefully.

The rate of reaction for each alcohol is controlled by the amount of catalyst used. The reaction is exceedingly violent if a large excess of hydrogen chloride is added at the start, and

(2) Meyer, *Monatsh.*, **25**, 475 (1904).

(3) Lutz and Winne, THIS JOURNAL, **56**, 445 (1934); Lutz, *ibid.*, **56**, 1378 (1934); Lutz, *et al.*, *J. Org. Chem.*, **4**, 95 (1939); **6**, 77 and 91 (1941).

(4) Newman and McClearly, THIS JOURNAL, **63**, 1537 (1941); Newman and Lord, *ibid.*, **66**, 731 (1944).

the resulting product is largely, if not entirely, the normal ester. A pure pseudo ester can be rearranged quantitatively to the normal ester by the catalytic action of hydrogen chloride. Thus, hydrogen chloride appears to catalyze both the addition of an alcohol to the lactone and the rearrangement of the adduct to a normal ester. By carefully adjusting the amount of hydrogen chloride, it is possible to control the addition reaction without effecting an appreciable rearrangement of the pseudo ester to the normal ester.

Pseudo esters of levulinic acid can also be prepared from the alcohols and levulinyl chloride. This method of pseudo ester preparation is similar to the one employed by Meyer.[2] Levulinyl chloride has been shown to exist in the form of γ-chlorovalerolactone,[5] which may be regarded as a pseudo acid chloride.

The boiling points of the pseudo and normal esters (Table I) of any given alcohol are identical or differ only slightly. Therefore, it is not possible to separate a mixture of pseudo and normal ester by fractional distillation. However, a means for isolating some of the pseudo esters in pure form has been developed; it is based on the observation that pseudo esters do not react with carbonyl reagents whereas the normal esters give crystalline semicarbazones or 2,4-dinitrophenylhydrazones, which can be separated from the liquid pseudo esters. This procedure was successful for the preparation of pure pseudo methyl and allyl levulinate. The other pseudo esters listed in Table I contained small amounts of the normal ester which could not be separated by a carbonyl reagent on account of the slight solubility of these reagents in the reaction mixture.

TABLE I

PHYSICAL CONSTANTS OF NORMAL (N) AND PSEUDO (P) ESTERS OF LEVULINIC ACID

	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Molecular refraction Observed	Calcd.
Methyl (N)	89–91	15	1.4225	1.0495	31.52	31.57
Methyl (P)	90–92	15	1.4390	1.1071	30.90	30.93
Isopropyl (N)	103–105	15	1.4220	0.9842	40.80	40.81
Isopropyl (P)[a]	103–105	15	1.4300	1.0151	40.22	40.16
Allyl (N)	106–108	10	1.4413	1.0277	40.03	40.34
Allyl (P)	106–108	10	1.4525	1.0677	39.46	39.70
Methyl isobutyl (P)[a]	107–108	2	1.4384	0.9828	53.56	54.02
Cyclohexyl (N)	108–110	1	1.4595	1.0308	52.43	52.46
Cyclohexyl (P)[a]	112–113	1	1.4668	1.0632	51.66	51.82

[a] Above 90% pseudo.

It will be noted in Table I that the densities and refractive indices of the pseudo esters are higher than those of the corresponding normal esters. The molecular refractions are accordingly lower. The close agreement of the observed values with the ones calculated from the Eisenlohr constants[6] furnishes a good evidence for the proposed structures of the pseudo esters. In the case of the pseudo esters an exaltation of −0.16 was introduced for the lactone ring.

(5) Helberger, *Ann.*, **522**, 269 (1936).

(6) Gilman, "Organic Chemistry," Vol. II, 1938, p. 1737.

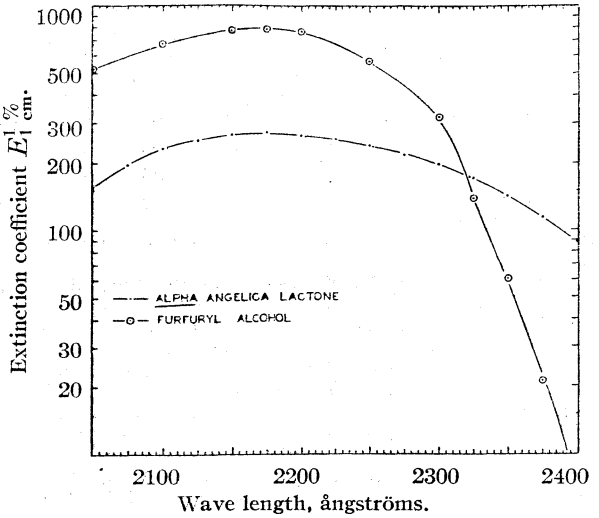


Fig. 1.—Absorption spectra of α-angelica lactone in neohexane and of furfuryl alcohol in water. Beckman Model D. V. used.

Chemically, the pseudo esters are distinguished from the normal esters of levulinic acid by their sensitivity to hydrolysis. The pseudo esters are saponified by treatment with cold 0.1 *N* sodium hydroxide. Advantage is taken of this reaction to determine the percentage of pseudo and normal esters in a reaction mixture. Total esters were determined by saponification at boiling temperature and pseudo esters by titration at room temperature. From the difference the percentage of normal esters can be determined.

Experimental

Preparation of Normal Esters of Levulinic Acid.—The method described in "Organic Syntheses" (Coll. Vol. I, p. 256) was used for the preparation of the esters. The esters were fractionated at reduced pressure, and the fractions boiling within a 2° range were collected. The foreruns and residues were small, and the esters were obtained in high yields.

Zerewitinoff Determination on α-Angelica Lactone: a sample of 0.2149 g. (0.00219 mole) of α-angelica lactone which had been standing at room temperature for several months gave 0.000777 mole of methane, corresponding to 28% of enol. A freshly distilled sample of 0.2079 g. (0.002122 mole) lactone yielded 0.000465 mole of methane; corresponding to 46% of enol.

Preparation of Pseudo Esters of Levulinic Acid.—Pseudo Methyl Levulinate: (a) From α-angelica lactone and methanol.—To a solution of 25 ml. of α-angelica lactone in 50 ml. of diethyl ether was added 25 ml. of methanol containing 0.1 g. of hydrogen chloride. The temperature of the mixture rose until the ether started to reflux. The mixture was kept at reflux in a water-bath for three hours. The ether and excess methanol were then removed under vacuum, and the residue was distilled, yielding 29 g. of a distillate, b. p. 88–92° (15 mm.).

Determination of Pseudo Ester in the Distillate.—A 0.187-g. sample was swirled in 50 ml. of water at 50° for a few minutes, then cooled and titrated with 0.1000 *N* sodium hydroxide; the cold titer found was 6.5 ml. of the 0.1 *N* sodium hydroxide. A saponification equivalent taken on the same sample required 14.4 ml. of alkali, thus

Alcohol used	Mg. HCl	Yield of ester	Pseudo, % ester in mixture	Sapn. equiv. Calcd.	Sapn. equiv. Found	Calcd. for	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isopropyl	6	90	92	158	156	$C_8H_{14}O_3$	60.7	60.7	8.9	8.8
Methylisobutylcarbinol	300	93	96	200	200	$C_{11}H_{20}O_3$	66.0	65.5	1.0	9.7
Cyclohexyl	38	95	90	198	197	$C_{11}H_{18}O_3$	66.7	66.7	9.1	9.3
Benzyl	25	92	93	206	206	$C_{12}H_{14}O_3$	70.0	69.8	6.8	6.7

indicating the presence of 45% of pseudo ester in the mixture.

Separation of the Pseudo Ester from the Normal Ester.—To 28 g. of the ester was added 80 ml. of methanol, 14.4 g. of semicarbazide hydrochloride, and 12.8 g. of potassium acetate. After shaking the mixture for twenty-four hours, 50 ml. of ether was added, and the mixture was filtered. The residue was washed with ether, and the ether added to the filtrate. The ether and methanol were evaporated at reduced pressure, and the pseudo methyl levulinate distilled b. p. 90–92° (15 mm.). Cold titer gave a neutral equivalent of 129 (calcd. 130). *Anal.* Calcd. for $C_6H_{10}O_3$: C, 55.4; H, 7.7. Found: C, 55.0; H, 8.0.

(b) **From Levulinyl Chloride and Methanol.**—To 50 g. of levulinic acid 60 g. of thionyl chloride was added dropwise with stirring; the reaction temperature was not allowed to exceed 50°. The mixture was then maintained at 50° under reduced pressure in order to remove hydrogen chloride, sulfur dioxide and excess thionyl chloride. The levulinyl chloride was then added under vigorous stirring to a mixture of 125 ml. of methanol and 50 g. of sodium carbonate. The addition rate was carefully controlled in order to keep the *p*H of the reaction mixture above 6 and avoid warming of the mixture above 30°. The mixture was stirred for thirty minutes after all levulinyl chloride had been added. Approximately 200 ml. of ether was then added, and the mixture was filtered. After evaporating the ether and excess methanol *in vacuo*, the ester b. p. 90–92° (15 mm.) was obtained in 62% yield; it titrated for 92% of the pseudo ester.

Pseudo Allyl Levulinate: To 25 ml. of α-angelica lactone 25 ml. of allyl alcohol containing 0.4 g. of hydrogen chloride was added. The temperature of the reaction mixture rose gradually to 60°. After allowing to stand for three hours the mixture was distilled yielding 36.5 g. of ester. Cold titer and saponification equivalent indicated the presence of 10% of normal ester in the distillate. Addition of 70 ml. of allyl alcohol, 5 g. of 2,4-dinitrophenylhydrazine and one drop of glacial acetic acid, shaking the mixture for twelve hours followed by filtration removed the normal ester. On distillation 25 g. of pseudo allyl levulinate was obtained b. p. 93° (3 mm.); sapn. equiv. calcd. 156, found 153 (cold titer 98% of sapn. equiv.). *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.4; H, 7.5.

Pseudo Isopropyl, 4-Methyl-2-pentyl, Benzyl, and Cyclohexyl Levulinate: These esters were prepared from 25 ml. of α-angelica lactone and 35 ml. of the corresponding alcohol. The amount of hydrogen chloride used, yields obtained, and analytical data found are given in the table.

Rearrangement of Pseudo Esters to Normal Esters.—The pseudo ester was diluted with the corresponding alcohol containing a small amount of a mineral acid. As little as 0.3% hydrogen chloride was sufficient. The mixture was heated to boiling until the cold titer became constant and equal to the mineral acid present. The pure normal ester was obtained in a quantitative yield.

Summary

1. Alcohols add to α-angelica lactone to form pseudo esters of levulinic acid.

2. The pseudo esters of levulinic acid are quantitatively converted to the normal esters by heating in the presence of a mineral acid.

3. Pseudo esters do not form carbonyl derivatives and may thus be separated from the normal esters.

4. Pseudo esters of levulinic acid are readily hydrolyzed by cold water.

5. Several pseudo esters of levulinic acid have been prepared, and their properties are tabulated.

RECEIVED[7] MAY 13, 1948

(7) Original manuscript received January 15, 1947.

[CONTRIBUTION FROM STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Dipole Moments of Thiouracil and Some Derivatives

BY W. C. SCHNEIDER AND I. F. HALVERSTADT[1]

In certain molecules where oxygen or sulfur atoms are attached to carbon atoms adjacent to heterocyclic ring nitrogens, the amide-iminoalcohol, $-\overset{\overset{O}{\|}}{C}-NH- \rightleftarrows -\overset{\overset{OH}{|}}{C}=N-$, type of tautomerism may exist. The relative contributions of these tautomeric forms will be affected by changes in substituents, solvents, temperature, state, etc.

The thiouracil molecule contains two such groups, both of which are usually shown in the amide form. Classical structural formulas can be assigned to those derivatives in which the labile hydrogens of the amide groups have been replaced by alkyl, aralkyl, etc., substituents, but occasionally these formulas may not adequately represent the properties of the compound. In some of these cases the assumption of tautomeric forms having a separation of charge has proved helpful.

The structure of 2-thiouracil was of interest to us because of its marked antithyroid activity. Certain dipole moment and infrared absorption data on thiouracil and a large number of derivatives are reported in this paper. On this basis a tentative classification of the compounds according to classical structure is made.

(1) Associated with Cutter Laboratories, Berkeley, California.

Experimental

A heterodyne beat apparatus similar to that described by Hudson and Hobbs[1a] was used to make the electrical measurements. A cathode ray oscilloscope was used for a detector. The standard capacitor was a General Radio type 722-D variable condenser. By using the low capacity section of this condenser, it was possible to obtain a precision of about ± 0.002 $\mu\mu$f in the capacity measurements.

The dielectric constant cell was of the design used by Sayce and Briscoe as described in Le Fèvre.[2] The particular cell used had a replaceable capacity of approximately 30 $\mu\mu$f and a fixed capacity of about 4 $\mu\mu$f.

Densities were determined with a U-shaped pycnometer having calibrated capillaries in each arm. The 10-ml. pycnometer used allowed a precision of ± 0.00002 in the density.

All measurements were at 35°. This temperature was chosen to eliminate the need for cooling the bath during the summer months and to take advantage of any increased solubility at this temperature. An oil-bath was used to thermostat the dielectric constant cell and the pycnometer was thermostated in a water-bath. Both baths were regulated to ± 0.005°.

1,4-Dioxane, used as solvent, was purified by partial freezing, discarding the unfrozen liquid. After remelting, the partially purified material was dried by refluxing over sodium, and any remaining impurities were removed by

TABLE I

Compound	M. p. (cor.), °C.
2-Thiouracil	245
4-Thiouracil	294–295
2,4-Dithiouracil	280
3-Ethyl-2-thiouracil	165–165.5
5-Ethyl-2-thiouracil[a]	190–192
6-Ethyl-2-thiouracil	228–229
5-Cyano-2-thiouracil[b]	281–282
6-Trifluoromethyl-2-thiouracil[b]	247–249
2-Methylthio-pyrimidone-4	205.5–203
2-Methylthio-5-ethylpyrimidone-4[a]	187–189
2-Methylthio-4-thiouracil	192–193
2-Ethylthio-3-methylpyrimidone-4	76.5–77.5
2-Ethylthio-3-ethylpyrimidone-4	29–30
2-Ethylthio-4-ethoxypyrimidine	B. p. 123–124.5 at 10 mm.
2-Benzylthiopyrimidone-4	193.5–194.5
2-Benzylthio-3-methylpyrimidone-4	119.5–120.0
1-Ethyl-2-thiouracil	241–241.5
1-Methyl-2-ethylthiopyrimidone-4	133.5–134.0
1-Methyl-2-benzylthiopyrimidone-4	146–146.5
1-Ethyl-2-benzylthiopyrimidone-4	107–108
1,3-Diethyl-2-thiouracil	67–68

[a] Furnished by Dr. G. W. Anderson, Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn. [b] Furnished by Dr. W. H. Miller, same laboratories.

TABLE II

w	ϵ	d	w	ϵ	d
2-Thiouracil			3-Ethyl-2-thiouracil		
0.0	(2.1870)[a]	1.01685	0.0	2.2126	1.01488
.0005409	2.1983	1.01713	0.0006835	2.2210	1.01508
.0007236	2.1990	1.01713	.001004	2.2249	1.01514
.0009306	2.2056	....	.001328	2.2287	1.01520
.001218	2.2081	1.01722	.001572	2.2311	1.01528
.001547	2.2131	1.01740			
4-Thiouracil			5-Ethyl-2-thiouracil		
0.0	(2.2050)	(1.01658)	0.0	2.1834	1.01685
0.9002923	2.2106	1.01667	0.0004191	2.1910	1.01694
.0005090	2.2148	1.01675	.0006755	....	1.01710
.0006591	2.2179	1.01677	.0008580	2.1996	1.01704
.0008120	2.2205	1.10685	.001139	2.2052	....
			.001421	2.2112	....
2,4-Dithiouracil			6-Ethyl-2-thiouracil		
0.0	(2.1922)	(1.01629)	0.0	2.1884	1.01685
0.0003293	2.1961	1.01646	0.0005190	2.1971	1.01694
.0004332	2.2004	1.01648	.0006041	2.1983	....
.0008025	2.2033	1.01655	.0008874	2.2033	1.01698
.0008202	2.2076	1.10660	.001172	2.2079	1.01713
			.001444	2.2141	1.01718
5-Cyano-2-thiouracil			2-Ethylthio-3-ethylpyrimidone-4		
0.0	2.1806	1.01692	0.0	(2.1882)	1.01650
0.0002360	2.1855	1.01703	0.0003961	2.1902	1.01655
.0004669	2.1907	1.01717	.0007236	2.1930	....
.0006617	2.1944	1.01719	.001270	2.1968	1.01666
.0008292	2.1979	1.01724	.001524	2.1987	1.01669
2-Methylthio-4-thiouracil			2-Benzylthio-3-methylpyrimidone-4		
0.0	2.1940	1.01658	0.0	2.2122	(1.01499)
0.0004878	2.1987	1.01677	0.0006900	2.2146	1.01504
.0007971	2.2041	1.01696	.001359	....	1.01518
.001006	2.2073	1.01697	.001907	2.2194	1.01522
.001695	2.2166	1.01716	.002539	2.2239	1.10538
2-Ethylthio-2-methylpyrimidone-4			2-Methylthio-5-ethylpyrimidone-4		
0.0	2.1896	(1.01633)	0.0	2.1876	(1.01670)
0.0006813	2.1952	1.01644	0.0004846	2.1905	1.01679
.0008772	2.1962	1.01646	.001045	2.1948	1.01687
.001095	2.1982	1.01650	.001296	2.1966	1.01694
.001746	2.2057	1.01656	.001829	2.1992	1.01706
2-Ethylthio-4-ethoxypyrimidine			1-Ethyl-2-thiouracil		
0.0	(2.1904)	1.06159	0.0	(2.1790)	(1.01685)
0.0006445	2.1934	1.01666	0.0009439	2.1959	1.01702
.001067	2.1953	1.01669	.001862	2.2112	1.01743
.001382	2.1964	1.01671	.003026	2.2313	1.01758
.001812	2.1992	1.01680	.004178	2.2487	1.01795
2-Benzylthio-pyrimidone-4			1-Methyl-2-ethylthiopyrimidone-4		
0.0	(2.2092)	1.01531	0.0	(2.1950)	(1.01632)
0.0006730	2.2125	1.01552	0.0001992	2.2006	1.01637
.0009503	2.2132	1.01554	.0002760	2.2032	1.01642
.001408	2.2160	1.01566	.0003762	2.2059	1.01644
.002030	2.2186	1.10582	.0005387	2.2106	1.01649
1-Ethyl-2-benzylthiopyrimidone-4			1-Methyl-2-benzylthiopyrimidone-4		
0.0	2.2053	1.01531	0.0	(2.2065)	(1.01531)
0.0007093	2.2225	1.01552	0.0003383	2.2153	1.01542
.001518	2.2414	1.01573	.0006090	2.2229	1.01542
.001859	2.2486	....	.001029	2.322	1.01557
.002316	2.2586	....	.001341	2.399	1.01566
2-Methylthiopyrimidone-4			1,3-Diethyl-2-thiouracil		
0.0	2.1978	(1.01582)	0.0	2.2033	(1.01603)
0.0003144	2.2013	1.01588	0.0005871	2.2101	1.01612
.0006082	2.2032	1.01599	.0007859	2.2129	1.01618
.0007098	2.2048	1.01601	.001098	2.2161	1.01615
.0008789	2.2056	1.01604	.002194	2.2290	1.01640
6-Trifluoromethyl-2-thiouracil					
0.0	2.1987	(1.01582)			
0.0002193	....	1.01591			
.0003519	2.1995	1.01596			
.0005568	2.2004	1.01604			
.0008236	2.2013	1.01610			

[a] Values in parentheses obtained by extrapolation.

(1a) B. E. Hudson and M. E. Hobbs, *Rev. Sci. Inst.*, **13**, 140 (1942).

(2) R. J. W. Le Fèvre, "Dipole Moments," Chemical Publishing Co., New York, 1938, p. 32.

TABLE III

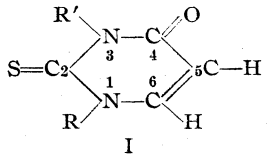
	α	β	$_\infty p_T$	Mol. wt.	$_\infty P_T$	P_D	P_O	$\mu \times 10^{18}$
2-Thiouracil	16.94	0.4240	3.013	128	385.7	30.7	355.0	4.21
4-Thiouracil	19.04	.3202	3.379	128	432.5	33.0	399.5	4.47
2,4-Dithiouracil	18.78	.4145	3.319	144	478.0	40.7	437.3	4.67
1-Ethyl-2-thiouracil	17.28	.2610	3.126	156	487.7	28.6	459.1	4.73
3-Ethyl-2-thiouracil	10.18	.2481	1.910	156	297.9	39.5	257.4	3.58
1,3-Diethyl-2-thiouracil	11.71	.1686	2.193	184	403.5	50.1	353.4	4.20
5-Ethyl-2-thiouracil	19.50	.2200	3.506	156	546.9	39.9	507.0	5.03
5-Cyano-2-thiouracil	20.98	.3929	3.712	153	568.0	36.0	532.0	5.15
6-Ethyl-2-thiouracil	16.64	.2264	3.016	156	470.6	39.9	430.7	4.64
6-Trifluoromethyl-2-thiouracil	3.157	.3764	0.7058	196	138.3	35.4	102.9	2.27
2-Methylthiopyrimidone-4	9.216	.2536	1.755	142	249.2	35.6	213.6	3.26
2-Methylthio-4-thiouracil	13.25	.3887	2.396	158	379.0	43.9	326.1	4.04
2-Methylthio-5-ethylpyrimidone-4	6.667	.1917	1.348	170	229.1	44.9	184.2	3.03
2-Ethylthio-3-methylpyrimidone-4	9.221	.1317	1.794	170	305.0	44.8	260.2	3.60
2-Ethylthio-3-ethylpyrimidone-4	6.908	.1378	1.404	184	259.1	46.8	213.3	3.26
2-Ethylthio-4-ethoxypyrimidine	4.636	.1048	1.030	184	189.5	50.4	139.1	2.64
2-Benzylthiopyrimidone-4	4.680	.2808	0.9852	218	214.8	54.8	160.0	2.83
2-Benzylthio-3-methylpyrimidone-4	4.218	.1858	0.9344	232	216.8	59.4	157.4	2.80
1-Methyl-2-ethylthiopyrimidone-4	29.33	.3156	5.114	170	869.4	44.8	824.6	6.42
1-Methyl-2-benzylthiopyrimidone-4	24.91	.2535	4.371	232	1014	59.4	954.7	6.90
1-Ethyl-2-benzylthiopyrimidone-4	23.29	.2833	4.095	246	1007	64.0	943.4	6.86

fractionation using an efficient distilling column. The best material obtained had the following physical properties: b. p. (uncor.) 100.5–100.7°, n^{35}_4 1.4150, d^{35} 1.01690 and ϵ_{35} 2.1776.

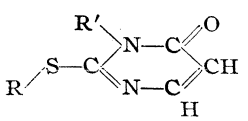
The compounds investigated and their melting points are listed in Table I. The experimental results are listed in Table II where w is weight fraction, ϵ is dielectric constant and d is density. Dipole moments were calculated by a modified Hedestrand method similar to that introduced by Halverstadt and Kumler,[3] differing in that densities were used rather than specific volumes. Atomic polarization was neglected, and the molecular refractions were calculated from the atomic refractions given in the Landolt–Börnstein "Tabellen." The values obtained from these calculations are listed in Table III where α and β refer, respectively, to the slopes of the dielectric constant and density curves as a function of concentration. $_\infty p_T$ is the specific polarization at infinite dilution and $_\infty P_T$ is the total molar polarization at infinite dilution. P_D and P_O represent the distortion and orientation polarizations, respectively, and μ is the dipole moment.

Discussion

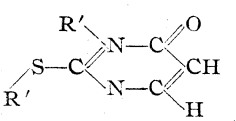
Five possible classical structures may be postulated from a consideration of the various tautomeric positions of the two acidic hydrogen atoms in 2-thiouracil. These structures may be represented as



I

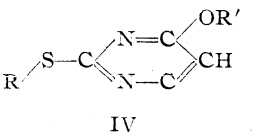


II

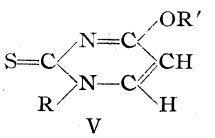


III

(3) I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 2988 (1942).



IV



V

where R and R′ may be hydrogen, methyl, ethyl or benzyl. Examples of all but Type V were found among the derivatives investigated.

Due to the complexity of the molecules, it was not feasible to assign structures by comparing the observed moments with theoretical, calculated moments. Instead the following procedure was used. Those thiouracils in which the two labile hydrogens were replaced by alkyl groups offered convenient starting points, inasmuch as at least their classical formulas were known. Structures were then assigned to the other compounds by a comparison of dipole moments, assuming that similar moments indicate similar structures. To illustrate the method, the dipole moment of 2-thiouracil is identical with that of 1,3-diethyl-2-thiouracil; accordingly, 2-thiouracil has a Type I structure. Following this procedure, the other derivatives were classified according to type and are listed in Table IV together with their moments. The classification of 3-ethyl-2-thiouracil is least certain since from dipole evidence alone it could have either a Type I or a Type II structure.

However, ultraviolet absorption measurements[4] indicate that the above assignment to a Type I structure is correct.

From a consideration of Austin's[5] work on the ultraviolet absorption spectra of uracils one would postulate a Type II structure for 2-thioura-

(4) Presented at the Atlantic City Meeting, A. C. S., April, 1947, by Dr. P. H. Bell, Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn.

(5) J. E. Austin, THIS JOURNAL, **56**, 2143 (1934).

TABLE IV

Compound	$\mu \times 10^{18}$
Type I	
1,3-Diethyl-2-thiouracil	4.20
2-Thiouracil	4.20
4-Thiouracil	4.47
2,4-Dithiouracil	4.67
5-Ethyl-2-thiouracil	5.03
5-Cyano-2-thiouracil	5.15
6-Ethyl-2-thiouracil	4.64
6-Trifluoromethyl-2-thiouracil	2.27
3-Ethyl-2-thiouracil	3.58
1-Ethyl-2-thiouracil	4.73
Type II	
2-Ethylthio-3-ethylpyrimidone-4	3.26
2-Methylthio-pyrimidone-4	3.26
2-Ethylthio-3-methylpyrimidone-4	3.60
2-Methylthio-4-thiouracil	4.03
2-Methylthio-5-ethylpyrimidone-4	3.03
2-Benzylthiopyrimidone-4	2.83
2-Benzylthio-3-methylpyrimidone-4	2.80
Type III	
1-Methyl-2-ethylthiopyrimidone-4	6.42
1-Methyl-2-benzylthiopyrimidone-4	6.90
1-Ethyl-2-benzylthiopyrimidone-4	6.86
Type IV	
2-Ethylthio-4-ethoxypyrimidone	2.64

cil. Unfortunately, it was not possible to determine the dipole moment of uracil because the compound proved to be too insoluble in dioxane. However, there is no *a priori* reason why uracil and 2-thiouracil should have identical structures.

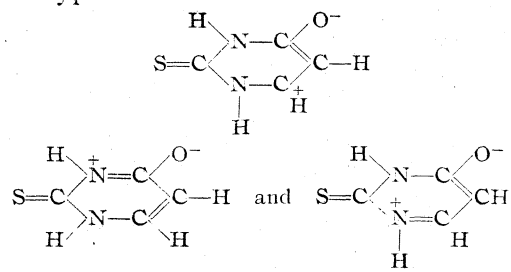
The above structure assignments are not consonant with some recent ultraviolet studies of Elion, Ide and Hitchings.[6] These workers concluded that uracil, thymine, 2-thiouracil, 4-thiouracil and 2,4-dithiouracil have a Type IV structure.

This conclusion was qualified by the statement that more work on substituted thiouracils was necessary to clarify the situation completely. However, it must be noted that although the present work was carried out in dioxane solution whereas the above workers employed aqueous solutions, the discrepancy between structure assignments cannot be simply attributed to a solvent effect, because ultraviolet studies in these laboratories,[4] using both dioxane solutions and aqueous solutions at various *p*H's, have indicated that in aqueous solution at the proper *p*H to assure the molecular form of the compound, the structures in dioxane and water are identical.

While most of the thiouracil derivatives are too complex for a detailed analysis of their electric moments, it is possible to attain fair agreement between observed and calculated moments for several of the Type I derivatives if certain assumptions are made concerning the carbon–oxygen and carbon–nitrogen link moments.

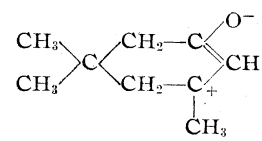
(6) G. Elion, W. Ide and G. Hitchings, THIS JOURNAL, **68**, 2137–2140 (1946).

The Carbon–Oxygen Moment.—The high moment of 2-thiouracil, 4.2*D*, would seem to indicate that the bond moment of the carbon-oxygen linkage is increased over its normal value of 2.5*D*. In all probability resonance structures of the types



with negatively charged oxygen are the direct cause of the observed high moment. Alkyl groups in the five and six positions seem to enhance the contributions from the ionic structures as can be seen from Table V. This behavior is reasonable when one considers that carbon is more negative than hydrogen and thus facilitates the transfer of negative charge to the oxygen. Although it is not possible to calculate the contributions of the various resonance structures to the total moment, one can estimate a value for the carbon–oxygen moment and then check the accuracy of this estimate by comparing the observed moments of a series of derivatives with calculated moments obtained using the assumed moment. In the present case a moment of 4.0*D* was assumed for the carbon–oxygen linkage.

This value is not unreasonable in view of the fact that Kumler and Fohlen[7] have observed a moment of 3.96*D* for isophorone where resonance structures of the type



which are similar to those proposed for 2-thiouracil, are assumed to account for the observed high moment. This high moment would indicate a carbon–oxygen moment of 3.6*D* in isophorone.

TABLE V

Compound	$\mu \times 10^{18}$	$\Delta\mu \times 10^{18}$
2-Thiouracil	4.21	....
6-Ethyl-2-thiouracil	4.64	+0.43
5-Ethyl-2-thiouracil	5.03	+0.82

The Carbon–Nitrogen Moment.—Although the classical structures for heterocyclic ring systems involving nitrogen are written with both single and double bonds between the nitrogen atom and adjacent carbon atoms, the situation is perhaps better represented by assuming some type of hybrid bond between the ring nitrogen and

(7) W. D. Kumler and G. M. Fohlen, *ibid.*, **67**, 437–441 (1945).

all attached atoms. The ring nitrogen will have a definite electronegativity, and the link moment between this nitrogen and attached atoms will depend upon the electronegativity difference. Measurements on simple heterocyclic compounds[8] indicate a moment of 1.9*D* for the carbon–nitrogen linkage. Further evidence supporting this value can be obtained by considering 2-thiouracil and its 1,3-diethyl derivative. These compounds have identical moments; accordingly, the carbon–nitrogen moment would seem to approximate the hydrogen–nitrogen moment which is about 1.3*D*.

If, as indicated above, a value of 4.0*D* is assigned to the carbon–oxygen linkage, a value of 1.9*D* to the carbon–nitrogen linkage and a plane hexagonal ring assumed, one obtains the calculated values listed in Table VI, together with observed values. The various bond moments used in these calculations are listed in Table VII. The agreement obtained is excellent and in view of the number of derivatives considered would seem to be more than simply fortuitous. Although the nature of the assumptions used in the above calculation precludes using the results in Table VI to confirm the structural assignments made earlier (Table IV), the agreement obtained is certainly good enough to indicate that the assumptions themselves are reasonably correct.

TABLE VI

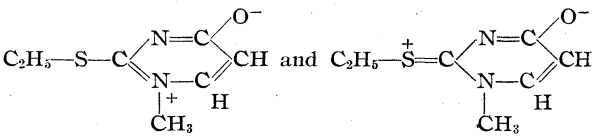
Compound	$\mu_{calcd.} \times 10^{18}$	$\mu_{obs.} \times 10^{18}$
2-Thiouracil	4.1	4.21
1,3-Diethyl-2-thiouracil	4.0	4.20
1-Ethyl-2-thiouracil	4.6	4.73
3-Ethyl-2-thiouracil	3.6	3.58
5-Cyano-2-thiouracil	5.2	5.15
6-Trifluoromethyl-2-thiouracil	2.3	2.27

TABLE VII

$\mu_{C=S}$	2.5*D*	$\mu_{C-C\equiv N}$	4.0
μ_{H-N}	1.3*D*	μ_{C-F}	1.4
μ_{H-C}	0.4*D*		

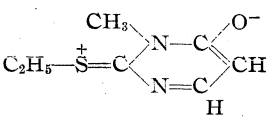
When the positions of the oxygen and sulfur atoms in 2-thiouracil are interchanged to give 4-thiouracil, the moment changes from 4.21*D* to 4.47*D*. This increase is probably a consequence of the larger size of the sulfur atom, since an additional increase in the electric moment results when the other oxygen is replaced by sulfur to give 2,4-dithiouracil with a moment of 4.67*D*, the average increase per sulfur atom being about 0.25*D*. However, these differences are relatively small and may result from solvent effects, atomic polarization, which was neglected in the moment calculations, or errors in the molecular refractions which were calculated from atomic refractions and not measured directly.

Measurements on several Type III compounds yielded rather unexpected results; an exceedingly large moment of 6.4–6.9*D* was obtained. Varying the substituent groups by measuring 1-methyl-2-benzylthiopyrimidone-4, 1-ethyl-2-benzylthiopyrimidone-4 and 1-methyl-2-ethylthiopyrimidone-4 resulted in no significant change in the order of the moment. Accordingly, this increased moment is attributed to the presence of forms having a separation of charge, which in the case of 2-ethylthio-1-methylpyrimidone-4 may be represented by



A structure analogous to the first form probably exists in 4-oxopyridine according to Leis and Curran,[9] who report a moment of 6.0 in dioxane solution.

The latter form provides a convenient correlation with the enhanced lability of the 2-alkyl group, which can be much more readily split from the sulfur atom by dry hydrogen chloride than it can in those isomers in which the N-alkyl group is in the 3-position. For the 3-isomer the analogous form having the positive charged sulfur



would involve a shift of the relatively fixed[10] 5,6 double bond and therefore might be expected to be less likely.

As a matter of general interest the vibration frequency of the carbonyl group in the compounds investigated was determined from infrared absorption spectra.[11] Since a carbonyl frequency was obtained for every compound where it might

TABLE VIII

Compound	ω cm.$^{-1}$
2-Thiouracil (6)[a]	1700
1,3-Diethyl-2-thiouracil (14)	1690
1-Ethyl-2-thiouracil (8)	1670
3-Ethyl-2-thiouracil (4)	1670
5-Ethyl-2-thiouracil (10)	1650
5-Cyano-2-thiouracil (9)	1675
6-Ethyl-2-thiouracil (7)	1671
6-Trifluoromethyl-2-thiouracil (15)	1692
2-Methylthiopyrimidone-4 (3)	1649
2-Benzylthiopyrimidone-4 (2)	1664
2-Ethylthio-3-methylpyrimidone-4 (5)	1700
2-Benzylthio-3-methylpyrimidone-4 (1)	1668
1-Methyl-2-ethylthiopyrimidone-4 (11)	1637
1-Methyl-2-benzylthiopyrimidone-4 (13)	1638
1-Ethyl-2-benzylthiopyrimidone-4 (12)	1640

[a] Numbers refer to points on plots given in Figs. 1 and 2.

(8) William C. Schneider, THIS JOURNAL, **70**, 627–630 (1948).

(9) D. G. Leis and B. C. Curran, *ibid.*, **67**, 79 (1945).

(10) In the catalytic hydrogenation of uracil, the first product is 5,6-dihydrouracil, indicating that the double bond acts like an isolated double bond rather than a benzenoid bond.

(11) Measurements carried out by R. C. Gore, Stamford Research Labs., American Cyanamid Company, Stamford, Conn.

be expected, it is reasonably certain that no compound has a Type V structure. The experimental values of the vibration frequencies are listed in Table VIII. A relatively large number of these are considerably lower than the normal vibration frequency, 1710–1720 cm.$^{-1}$, of an isolated carbonyl group. Since the lowering of the carbonyl frequency can result from conjugation or electrical charging effects, the observed lowering can be considered as a measure of the relative contribution of ionic resonance structures. In the compounds studied these ionic forms tend to increase the dipole moment; accordingly, there should be an increase in dipole moment with decreasing carbonyl frequency.

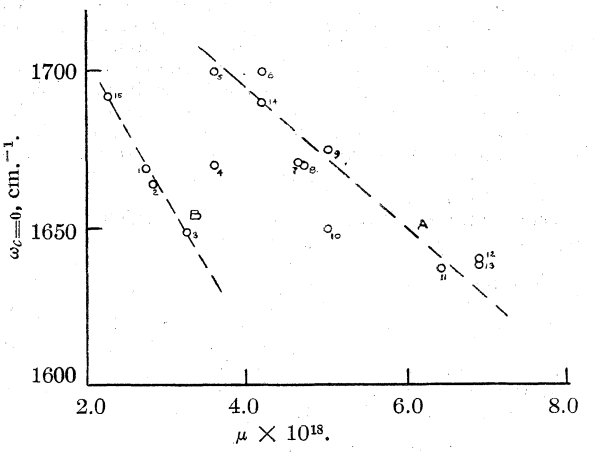


Fig. 1.—Relation between carbonyl vibration frequency and dipole moment for several thiouracil derivatives.

In Fig. 1 the vibration frequencies listed in Table VIII are plotted as a function of the dipole moment. As predicted, there is an increase in dipole moment with decreasing carbonyl frequency, and with the Type III compounds the lowest observed carbonyl frequency 1640 cm.$^{-1}$ is associated with the highest dipole moment, 6.9*D*. In the above plot the points are rather widely scattered and appear to be divided into two distinct groups, A and B. This results from neglecting the effects of different types of structures and substituent groups upon the dipole moment. These effects can be greatly reduced by considering a series of compounds having identical structures and similar substituent groups. 2-Thiouracil (6) and its 1,3-diethyl (14), 1-ethyl (8), 5-ethyl (10) and 6-ethyl (7) derivatives form such a series, which is plotted in Fig. 2. This plot clearly shows the nature of the relation between carbonyl frequency and dipole moment.

Acknowledgment.—The authors wish to express their indebtedness to Dr. P. H. Bell of the Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut, for much helpful discussion and criticism and to the American Cyanamid Company for permission to publish these results.

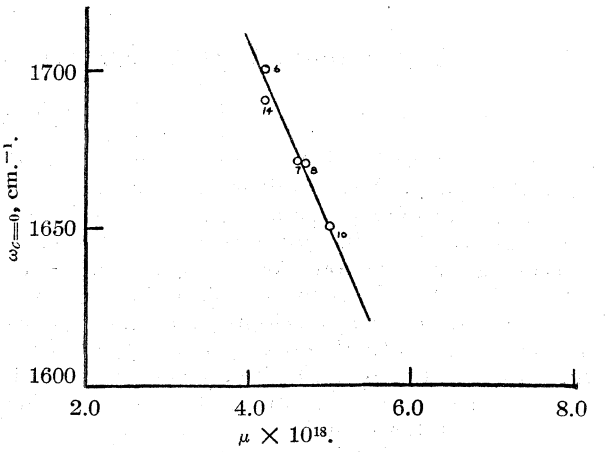


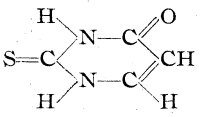
Fig. 2.—Relation between carbonyl vibration frequency and dipole moment for a series of thiouracil derivatives having similar structures.

Summary

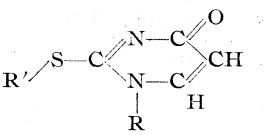
It must be emphasized that the following conclusions apply only to the form of the compound existing in dioxane solution. In aqueous solution the particular form present is a function of the *p*H, therefore, it is not permissible to make conclusive statements about the behavior of the compounds in water.

(1) The dipole moments in dioxane solution at 35° have been determined for 4-thiouracil, 2,4-dithiouracil, 2-methylthio-4-thiouracil and 2-thiouracil and seventeen derivatives.

(2) Thiouracil in dioxane solution is best represented by the formula



(3) Compounds of the type



have the abnormally high dipole moments of 6.4–6.9 *D*.

(4) The carbonyl group in 2-thiouracil seems to be activated in the same manner as in isophorone due to conjugation with a double bond.

(5) Alkyl groups substituted in the five or six position slightly increase this activation.

RECEIVED APRIL 5, 1948.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

The Phenyl–Carbon–Phenyl Angle in 1,1-Diphenylcyclopropane[1]

BY M. GOLDSMITH AND G. W. WHELAND

Several recent theoretical[2-4] and experimental[5-7] papers have dealt with the exterior valence angle in cyclopropane. In the experiments which are reported in this present paper the value of the angle in question is determined from the dipole moments of 1,1-bis-(*p*-chlorophenyl)-cyclopropane, 1,1-diphenylcyclopropane and chlorobenzene; the method here employed is, of course, the same as the one which has been previously used for the measurement of the corresponding angles in diphenylmethane[8,9] and 1,1-diphenylethylene.[10] Evidence regarding the direction of the cyclopropyl–phenyl bond moment, discussed by Rogers,[11] has also been obtained.

Experimental

Materials

Benzene.—Eastman Kodak Co. White Label thiophene-free benzene was stored over, and distilled from, sodium hydride. The center cut (b. p. 80.0–80.1° at 760 mm., $n^{20}D$ 1.501) was redistilled from sodium hydride immediately before use.

***p*-Xylene.**—Eastman White Label *p*-xylene was purified in a manner identical with that described for benzene; b. p. 137.9–138.0° (751 mm.), $n^{20}D$ 1.496.

Tetrachloroethylene.—Eastman White Label tetrachloroethylene was dried over anhydrous calcium sulfate and fractionated; b. p. 120.8–121.0° (756 mm.), $n^{23.7}D$ 1.503.

Benzophenone.—Eastman White Label benzophenone was recrystallized from ethanol and from petroleum ether; m. p. 48.0–48.5°.

1,1-Diphenylcyclopropane.—This compound was prepared from 1,1-diphenylethylene and diazomethane by the method of Wieland and Probst.[12] The crude cyclopropane was freed of unreacted olefin by titration with bromine in carbon tetrachloride at 0° and by subsequent fractionation; b. p. 117.0–117.5° (2 mm.), $n^{20}D$ 1.590.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.73; H, 7.27; mol. wt., 194. Found: C, 92.9; H, 7.3; mol. wt. (f. p. benzene), 193.

1,1-bis-(*p*-Chlorophenyl)-cyclopropane.—This compound was prepared by the reaction of 1,1-bis-(*p*-chlorophenyl)-ethylene with diazomethane. The conditions for this reaction are identical with those for the preparation of 1,1-diphenylcyclopropane. The compound separates from methanol in white needles, m. p. 105.5–106°, and reacts at room temperature neither with bromine in carbon tetrachloride nor with neutral 0.2 *N* potassium permanganate.

Anal. Calcd. for $C_{15}H_{12}Cl_2$: C, 68.45; H, 4.60; Cl, 26.95; mol. wt., 263. Found: C, 68.5; H, 4.5; Cl, 27.0; mol. wt. (f. p. benzene), 260.

1,1-bis-(*p*-Chlorophenyl)-cyclopropane has not been reported previously in the literature. A sample of this compound previously prepared by Mr. Joseph R. Schwartz of this Laboratory proved to be identical with our preparation.

Apparatus

Dielectric Constants.—The circuit diagram of our heterodyne beat apparatus is given in Fig. 1. "Locking in" of the oscillators is rendered negligible at 100 K. C. by the use of very light coupling. Any error due to frequency drift may be eliminated by measurement of the zero beat capacitance of the variable frequency oscillator both with and without the test condenser in the circuit. The test cell, which had a volume of 10 cc. and a capacitance of 80 $\mu\mu$f., was constructed according to Fairbrother's design[13] and was calibrated, at each temperature at which dielectric constants were measured, in the manner described[13] by him.

Temperatures.—The temperatures at which measurements were made were maintained, with a maximum variation of 0.03°, in an oil thermostat.

Densities.—The densities of the solutions were measured with a modified Ostwald Sprengel pycnometer which was calibrated at the temperatures below 80° with distilled water. The volume of the pycnometer at 98.6°, and at 122.0°, was obtained by extrapolation.

Refractive Indices.—Measurements were made with a refractometer of the Abbé type.

Experimental Results

Optical Determinations.—Values of the mole fractions f_2 of the solutes, the dielectric constants ϵ of the solutions, the densities d of the solutions, and the total molar polarizations P_1 and P_2, of the solvents and solutes, respectively, are given in Table I for some typical measurements. Table II contains the values of P_2^∞, the total molar polarizations of the solutes at infinite dilution, obtained by graphical extrapolation; the values of the molecular refractions for the sodium D lines MR_D of the solutes; and the values of the dipole moments μ calculated from the formula

$$\mu = 0.0128 \sqrt{[P_2^\infty - 1.05(MR_D)]T}\ D$$

Temperature Variation Determinations.—Table III contains values of P_2^∞ measured at a series of absolute temperatures T in tetrachloroethylene and in *p*-xylene. Equations of the form

$$P_2^\infty = A + B/T$$

were obtained by the method of least squares. The respective values of A and B are given in Table IV.

Discussion of Results

The dipole moment of benzophenone was measured as a test of our experimental technique. Our optical value 2.97 D agrees well with the value

(1) An abstract of the thesis submitted by Mark Goldsmith in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Coulson and Mofitt, *J. Chem. Phys.*, **15**, 151 (1947).

(3) Duffey, *ibid.*, **14**, 342 (1946).

(4) Kilpatrick and Spitzer, *ibid.*, **14**, 463 (1946).

(5) Spinrad, THIS JOURNAL, **68**, 617 (1946).

(6) O'Gorman and Schomaker, *ibid.*, **68**, 1138 (1946).

(7) Hassel and Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947).

(8) Bergmann, Engel and Wolff, *Z. physik. Chem.*, **B17**, 81 (1932).

(9) Hampson, Farmer and Sutton, *Proc. Roy. Soc. (London)*, **A143**, 147 (1934).

(10) Coates and Sutton, *J. Chem. Soc.*, 567 (1942).

(11) Rogers, THIS JOURNAL, **69**, 2544 (1947).

(12) Wieland and Probst, *Ann.*, **530**, 274 (1937).

(13) Fairbrother, *Proc. Roy. Soc. (London)*, **A142**, 173 (1933).

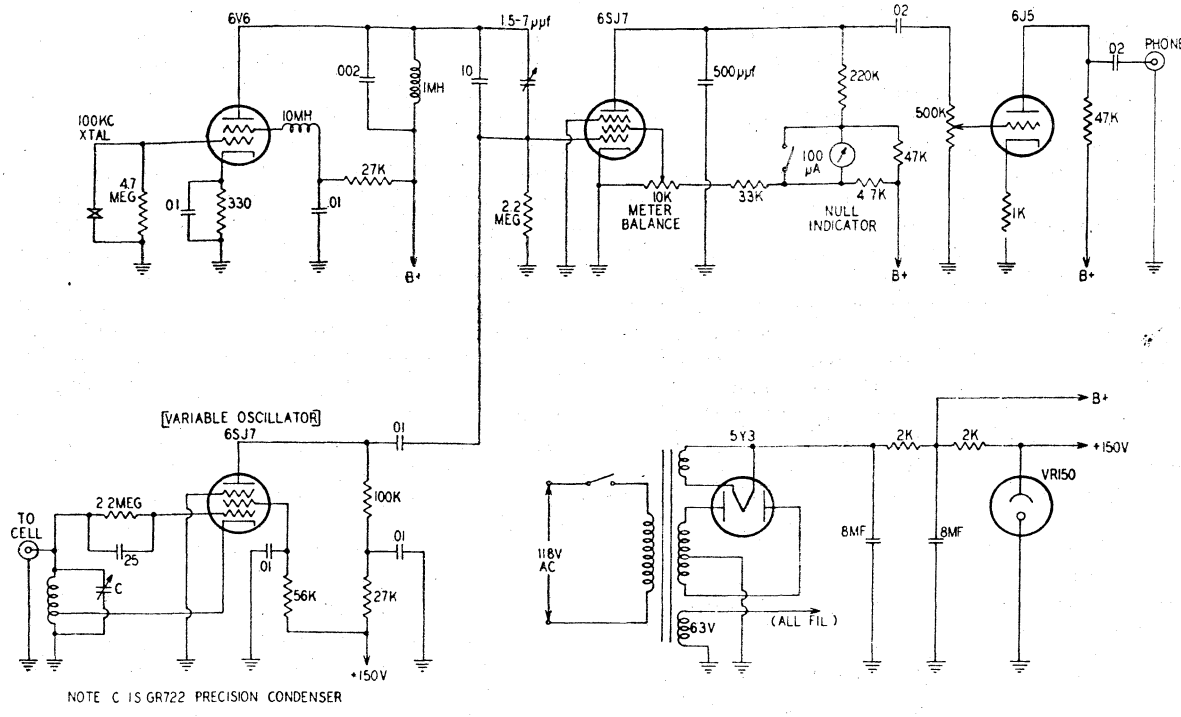


Fig. 1.—Heterodyne beat apparatus.

TABLE I

DIELECTRIC CONSTANTS, DENSITIES AND POLARIZATIONS

f_2	ϵ	d	P_2
	$C_{15}H_{12}Cl_2$ in Benzene (23.7°)		
0	2.275	0.8742	(P_1 = 26.65)
0.03302	2.487	.9010	158
.02224	2.421	.8926	160
.01878	2.396	.8897	158
.01451	2.371	.8863	161
.009852	2.342	.8827	162
	$C_{15}H_{14}$ in *p*-Xylene (23.7°)		
0	2.263	0.8575	(P_1 = 36.68)
0.02929	2.281	.8655	67
.02428	2.280	.8642	70
.01551	2.273	.8618	68
.01239	2.271	.8610	69
.01227	2.270	.8609	67
	Benzophenone in *p*-Xylene (30.6°)		
0	2.250	0.8517	(P_1 = 36.67)
0.02763	2.499	.8612	225
.01412	2.378	.8566	230
.009251	2.334	.8548	233

2.98 *D* which is the average of twelve optical-solution values reported[14] in the literature.

The temperature variation values of the dipole moment of 1,1-bis-(*p*-chlorophenyl)-cyclopropane are in poor agreement with the values (Table II) obtained by the optical method. Presumably, these discrepancies are due, at least in part, to a variation of the solvent effect with temperature.[15]

(14) *Trans. Faraday Soc.*, **30**, Appendix (1934).
(15) Glasstone, *Ann. Reports Chem. Soc.*, **33**, 117 (1936).

TABLE II

OPTICAL DETERMINATIONS OF DIPOLE MOMENTS

Compound	P_2^∞	MR_D[a]	T, °K.	μ	Solvent
$C_{15}H_{12}Cl_2$	163	73	296.8	2.05	Benzene
$C_{15}H_{12}Cl_2$	158	73	296.8	1.99	Tetrachloroethylene
$C_{15}H_{12}Cl_2$	158	73	303.7	2.01	*p*-Xylene
$C_{15}H_{14}$	69	63	296.8	0.2–0.5	*p*-Xylene
Benzophenone	237	57[b]	303.7	2.97	*p*-Xylene

[a] These values of the molecular refraction were measured in the solvents stated, with f_2, the mole fraction of the solute, in the range 0.01–0.02. [b] Auwers and Eisenlohr, *J. prakt. Chem.*, **84**, 37 (1911).

TABLE III

VARIATION OF POLARIZATION WITH TEMPERATURE

$C_{15}H_{12}Cl_2$ in *p*-xylene		$C_{15}H_{12}Cl_2$ in C_2Cl_4		Benzophenone in *p*-xylene	
$1/T \times 10^3$	P_2^∞	$1/T \times 10^3$	P_2^∞	$1/T \times 10^3$	P_2^∞
3.293	158	3.369	158	3.293	237
2.995	149	3.182	154	2.995	220
2.839	147	2.995	149	2.839	209
2.690	146	2.839	145	2.690	204
2.531	145	2.690	145	2.531	197

TABLE IV

TEMPERATURE VARIATION DETERMINATIONS OF DIPOLE MOMENTS

Compound	Solvent	A	$B \times 10^{-4}$	μ	Temp. range, °C.
$C_{15}H_{12}Cl_2$	C_2Cl_4	83.6	2.18	1.89	23.7–98.6
$C_{15}H_{12}Cl_2$	*p*-Xylene	102	1.68	1.66	30.6–122.0
Benzophenone	*p*-Xylene	52.6	5.58	3.02	30.6–122.0

The possibility that the discrepancies are primarily due instead to unexpectedly large atom polarizations seems unlikely for two reasons. First, with compounds, such as *p*-benzoquinone, which do have large atom polarizations, the sum *A* of the electronic and atom polarizations is essentially independent of solvent[16]; with 1,1-bis-(*p*-chlorophenyl)-cyclopropane, on the other hand, *A* is 18.4 cc. per mole greater in *p*-xylene than it is in tetrachloroethylene (Table IV). Second, the atom polarizations of several closely analogous compounds, such as *p*-bromophenyl ether, are evidently small since, with these substances, the sums of the atom plus orientation polarizations have been found to be of the order of only 10 cc. per mole.[17] For these reasons, the optical values will be accepted in preference to the temperature variation ones, and the dipole moment of 1,1-bis-(*p*-chlorophenyl)-cyclopropane will be taken as 2.02 ± 0.03 *D*.

The phenyl–carbon–phenyl angle, θ, may be calculated in the manner previously described[9] by Sutton and his co-workers. If it is assumed that the optical-solution value of the dipole moment of chlorobenzene[14] is 1.57 *D*, and that the cyclopropylidene–phenyl and phenyl–chlorine bond moments are in the same direction, the angle θ is found to be equal to 116 ± 10°. If it is instead assumed that these bond moments are in opposite directions, the angle is found to be 81 ± 10°. A value of θ which is almost 30° less than the normal tetrahedral angle is improbable. It is therefore considered that θ is equal to 116 ± 10°; this conclusion supports the value, 112 ± 4°, assigned by electron diffraction to the Cl–C–Cl angle[8] in 1,1-dichlorocyclopropane. (The limits of error cited above are based merely on the internal consistency of the optical measurements reported in this paper. The true limits of error, as in all analogous measurements of bond angles, must be somewhat greater when allowance is made for the uncertainty in the value of the atom polarization and in the moment of chlorobenzene, and for the possibility of variations in bond angles, in bond moments, and in the solvent effect.)

(16) *Cf.* Finn, Hampson and Sutton, *J. Chem. Soc.*, 1254 (1938); Hammick, Hampson and Jenkins, *ibid.*, 1263 (1938); Coop and Sutton, *ibid.*, 1269 (1938).

(17) Coop and Sutton, *J. Chem. Soc.*, 1869 (1938).

Acknowledgments.—The authors are indebted to Messrs. P. R. Bell, Jr.,[18] and P. Shevick[19] for the design and construction of the heterodyne beat apparatus, and to Mr. W. Saschek and Mr. D. E. Mann of this Laboratory for their aid and suggestions.

Summary

The dipole moments of 1,1-bis-(*p*-chlorophenyl)-cyclopropane and 1,1-diphenylcyclopropane have been measured.

The phenyl–carbon–phenyl angle in 1,1-diphenylcyclopropane has been estimated as 116 ± 10°.

(18) Present address: Clinton Laboratories, Oak Ridge, Tenn.

(19) Nuclear Physics Institute, University of Chicago.

CHICAGO, ILLINOIS RECEIVED MARCH 18, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Quadridentate Amines. I. Some Coördination Compounds of Cobalt(III) and Triethylenetetramine[1]

BY FRED BASOLO

It was first shown by Mann[2] and later by Morgan and Burstall[3] that certain tetramines are capable of behaving as quadridentate donors to form complex inorganic compounds of cobalt(III). Mann[2] used β,β',β''-triaminotriethylamine and obtained *cis*-[Co tren(SCN)$_2$]SCN. Because of the structure of this amine, the corresponding *trans*-salt is sterically too unstable to exist. The amine used by Morgan and Burstall[3] was 2,2′,2″,2‴-tetrapyridyl and yielded *trans*-[Co tetrpyCl$_2$]Cl. They point out that the pyridine rings of the coordinated tetrapyridyl must remain in the same plane, and therefore the chloro groups must be in *trans*-positions. In both of these investigations the analyses of the resulting compounds agreed with those calculated for the respective compounds, but in neither case was any attempt made to establish conclusively the configuration of the complex cation.

More recently, Jonassen, Dexter and Douglas[4] have studied the complexes formed between triethylenetetramine and copper(II) and nickel(II) ions in water solution. They found that triethylenetetramine behaves as a quadridentate amine. The present work was undertaken to determine whether coördination compounds of triethylenetetramine and cobalt(III) can be isolated and also to study the configuration and stability of these compounds.

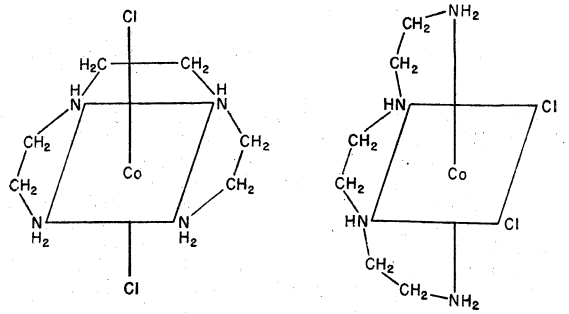
The dichlorotriethylenetetraminecobalt(III) ion can theoretically exist in three stereoisomeric forms

(1) Presented before the Physical and Inorganic Division at the 113th meeting of the American Chemical Society, Chicago, Ill., April 19–23, 1948.

(2) Mann, *J. Chem. Soc.*, 409 (1929).

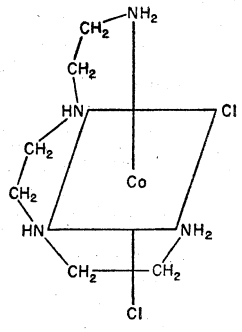
(3) Morgan and Burstall, *ibid.*, 1672 (1938).

(4) Reported by Jonassen, Dexter and Douglas at the 112th meeting of the American Chemical Society.



I

II



III

The salt, [Co trien Cl_2]Cl, was prepared by the air oxidation of a reaction mixture containing cobalt(II) chloride and triethylenetetramine. This cation has been assigned a *cis*-configuration, II or III, because the salt obtained is purple, which is a characteristic color for *cis*-dichlorotetrammine compounds of cobalt(III) and chromium(III). Additional indication that the salt has the *cis*-configuration was obtained by comparing the ultraviolet absorption spectrum (Fig. 1) of this salt with those for the corresponding ethylenediamine salts, *cis*- and *trans*-[Co en_2 Cl_2]Cl. The ions II and III are asymmetric and an attempt was made to resolve the purple salt by the method[5] used for the corresponding complex, *cis*-[Co en_2 Cl_2]Cl, but this was not successful. It would be extremely difficult to distinguish between II and III and, since it does not appear important, this was not done.

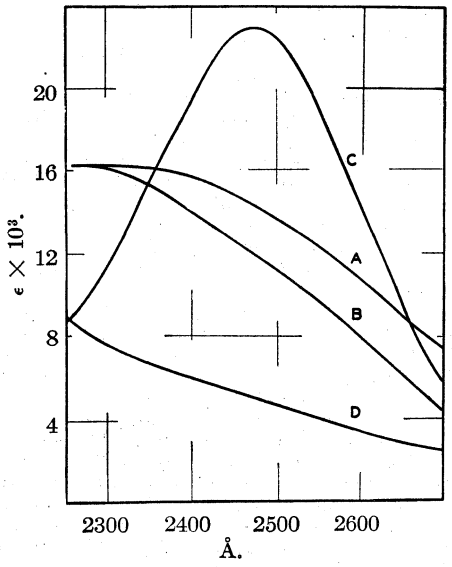


Fig. 1.—Absorption spectra of dichlorotetramminecobalt(III) chlorides: A, [Co trien Cl_2]Cl; B, *cis*-[Co en_2 Cl_2]Cl; C, *trans*-[Co en_2 Cl_2]Cl; D, unidentified mixture.

Although a study of molecular models indicates that I may exist, several attempts to prepare the *trans*-salt were unsuccessful. No rearrangement of the *cis*-salt occurred in concentrated hydrochloric acid, as is generally true of similar salts.[6] The reactions of both *cis* and *trans*-dinitrotetramminecobalt(III) chloride with triethylenetetramine in absolute alcohol gave the *cis*-salt [Co trien $(NO_2)_2$]Cl. This *cis*-configuration of this salt was indicated by its reaction with concentrated hydrochloric acid and by a comparison of its ultraviolet absorption spectrum (Fig. 2) with the spectra of the corresponding ethylenediamine salts, *cis* and *trans*-[Co en_2 $(NO_2)_2$]Cl, and also of the salt, [Co trien $(NO_2)_2$]Cl, obtained from the reaction of II or III with sodium nitrite. A third attempt was made by a slight modification of the method used by Morgan and Burstall[3] and a green product was obtained. This material dissolved in water to give an orange solution and did not have an absorption spectrum (Fig. 1) similar to that of the complex, *trans*-[Co en_2 Cl_2]Cl. The behavior of this unidentified substance suggests it may be a mixture of cobalt(II) chloride (blue)

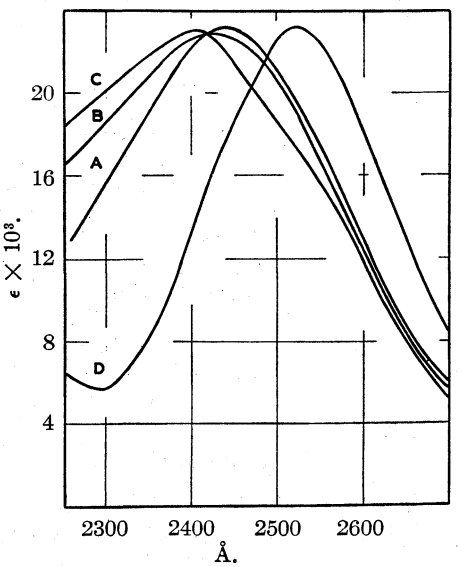


Fig. 2.—Absorption spectra of dinitrotetramminecobalt (III) chlorides: A, [Co trien $(NO_2)_2$]Cl obtained from *cis* or *trans* [Co $(NH_3)_4$ $(NO_2)_2$]Cl; B, [Co trien $(NO_2)_2$]Cl obtained from II or III; C, *cis*-[Co en_2 $(NO_2)_2$]Cl; D, *trans*-[Co en_2 $(NO_2)_2$]Cl.

(5) Bailar, *Inorg. Syntheses*, **2**, 223 (1946).
(6) Jörgensen, *Z. anorg. Chem.*, **14**, 415 (1897).

and tris(triethylenetetramine) dicobalt(III) chloride (orange).

The fact that many inorganic complex compounds have been resolved is a good indication of the firmness with which the donor molecule is held or, in other words, of the stability of the coordination compound. The resolution of certain asymmetric complexes of cobalt(III) containing triethylenetetramine would conclusively show that the tetramine behaves as a strong quadridentate donor. Compounds similar to tris(ethylenediamine)cobalt(III) chloride were prepared and the method used by Werner[7] and also by Jaeger[8] for the resolution of this type of a cation was studied. These hexammine salts are all extremely soluble and could not be resolved by the methods employed. All of these salts, however, are highly crystalline and stable at temperatures as high as 150°.

The ultraviolet absorption spectrum obtained, particularly with the dinitrotetrammine series of compounds, is of interest. Shibata[9] showed that in addition to the two absorption bands always observed in the cobalt ammines, certain of these compounds have an additional absorption band in the shorter ultraviolet region which he designated as the "third band." A much more extensive study has been made by Tsuchida[10] who concludes that any two negative ligands, when in *trans*-positions to each other, cause a third absorption band at approximately 2500 Å., whereas if they occupy *cis*-positions, the third band is absent. Contrary to this, however, the ultraviolet absorption spectra (Fig. 2) obtained for some *cis*-dinitrotetrammine salts show very definite absorption bands at approximately 2425 Å. Although these results are not conclusive, they indicate that some cobalt(III) ammines with two negative ligands in the *cis*-positions also have additional absorption bands but in the shorter ultraviolet region. A more thorough investigation of this phenomenon is now in progress.

Experimental[11]

Reagents.—The cobalt(II) chloride hexahydrate was Merck reagent grade. The triethylenetetramine was obtained from Carbide and Carbon Chemicals Corporation. This amine was refluxed for six hours in presence of metallic sodium and then distilled *in vacuo* over sodium. The fraction collected had a boiling point range of 128–131° at 3 mm.

Spectral Measurements.—Ultraviolet absorption spectra were measured with the Beckman quartz spectrophotometer, using 1 cm. silica cells. Extinction coefficients were calculated from the familiar equation

$$\epsilon = 1/cd \log_{10}(I_0/I)$$

where I_0 is the intensity of the light passing through the solvent, I, the intensity of the light passing through the solution, c, the concentration of solute in moles per liter, and d, the thickness of the cell in centimeters.

Aqueous solutions (1.0×10^{-5} molar) of the complex salts were used and measurements were made at room temperature as rapidly as possible (total operation time less than twenty minutes) to keep the reaction of the complex with water at a minimum.

cis-Dichlorotriethylenetetraminecobalt(III) Chloride, (II) or (III).[12]—The procedure described by Bailar[5] for the preparation of *trans*-dichloro-bis-(ethylenediamine)-cobalt(III) chloride was slightly modified. A solution of 75 g. (0.50 mole) of triethylenetetramine in 525 cc. water was added, with stirring, to a solution of 160 g. (0.67 mole) of cobalt(II) chloride hexahydrate in 500 cc. of water contained in a two-liter flask. A vigorous stream of air, previously washed with a dilute solution of sodium hydroxide, was passed through the solution for approximately eleven hours. After 350 cc. of concentrated hydrochloric acid was added, the solution was concentrated on a steam-bath until finely divided crystals began to separate (650 cc.). Upon standing overnight at room temperature the bluish-purple crystalline product was collected on a filter and washed with a small amount of cold water followed by alcohol and ether. The salt was dried at 110° and 86 g. of material was obtained. Further concentration (400 cc.) of the combined filtrate and washings from this salt gave an additional 40 g. of product. This preparation was carried out six times and found to progress smoothly to give an over-all yield of 80% of crude dichlorotriethylenetetraminecobalt(III) chloride based on triethylenetetramine. The crude salt was recrystallized twice from dilute hydrochloric acid and dried at 110° for two days.

Anal. Calcd. for [Co trien Cl_2]Cl: C, 23.12; H, 5.82; N, 18.03; Co, 18.91; Cl, 34.13. Found: C, 23.42; H, 5.85; N, 18.18; Co, 18.68; Cl, 34.04.

The salt is purple in color, which is characteristic of the *cis*-dichlorotetrammine compounds of cobalt and chromium, indicating a *cis* configuration represented either by II or III. Additional indication for a *cis* structure was obtained from the fact that the ultraviolet spectrum (Fig. 1) of this salt closely resembles that of *cis*-dichloro-bis-(ethylenediamine)-cobalt(III) chloride.

The procedure described by Bailar[5] for the resolution of *cis*-[Co en_2 Cl_2]Cl was followed with *cis*-[Co trien Cl_2]Cl, but did not yield any crystals of the complex *dextro*-α-bromocamphor-π-sulfonate. The salt was obtained, however, by adding 15 cc. of a solution containing 9 g. (0.028 mole) of ammonium *dextro*-α-bromocamphor-π-sulfonate to 25 cc. of a solution containing 5 g. (0.016 mole) of *cis*-[Co trien Cl_2]Cl and immediately cooling the mixture in an ice–salt-bath. The crystals which separated were collected on a filter and washed with a very small amount of ice-water followed by alcohol and ether. A 0.32% solution of the air-dried crystals had a stable optical rotation of 0.18°, $[\alpha]^{25}D$ +55.6. One gram of the salt was ground in an ice-cold mortar with 10 cc. of an ice-cold mixture (1:1:1) of concentrated hydrochloric acid, alcohol, and ether. The purple residue was then collected on a filter and washed with absolute alcohol and ether. A 0.25% solution of this substance was immediately prepared and found to have no optical activity at the D line of sodium.

An attempt was made to effect the rearrangement of *cis*-[Co trien Cl_2]Cl to the *trans* configuration by the method which Jörgensen[6] used for the preparation of *trans*-[Co $(NH_3)_4$ Cl_2]HSO_4. Five grams of the *cis*-dichloro complex, II or III, was dissolved in 25 cc. of concentrated sulfuric acid and the solution was allowed to stand six hours at room temperature. The solution was then surrounded by an ice–salt bath and 25 cc. of concentrated hydrochloric acid was added dropwise with vigorous stirring. After standing for three days the well-defined purple crystals, which separated from the dark purple solution, were collected on a sintered glass filter and washed with dilute sulfuric acid, cold water, alcohol and ether. There were no signs of the *cis* (purple) salt rearranging to

(7) Werner, *Ber.*, **45**, 121 (1912).

(8) Jaeger, *Rec. trav. chim.*, **38**, 185 (1919).

(9) Shibata, *J. Coll. Sci. Imp. Univ. Tokyo*, **37**, 1–18 (1915).

(10) Tsuchida, *Bull. Chem. Soc. Japan*, **11**, 785 (1936).

(11) Carbon, hydrogen and nitrogen analyses by Miss Patricia Craig and Miss Margaret Hines.

(12) Preliminary preparation by Miss Ruth Slaton.

the *trans* (green) configuration. This salt was dried at 110° overnight.

Anal. Calcd. for [Co trien Cl_2]HSO_4: C, 19.00. Found: Cl, 19.21.

The method used by Morgan and Burstall[3] for the preparation of *trans*-dichloro-(2,2′,2″,2‴-tetrapyridyl)-cobalt(III) chloride was modified in another attempt to obtain I. A solution which contained 10 g. (0.042 mole) of cobalt(II) chloride hexahydrate and 6 g. (0.041 mole) of triethylenetetramine in 10 cc. of water was kept on a steam-bath under an atmosphere of nitrogen for four hours. At the end of this time an excess of alcohol and ether was added and the reddish-brown oil which separated was washed three times with absolute alcohol. This oil was finally dried in a vacuum over sulfuric acid; analysis of the brown residue for chlorine checked favorably with that calculated for the cobalt(II) complex, [Co trien $(H_2O)_2$]Cl_2.

Anal. Calcd. for [Co trien $(H_2O)_2$]Cl_2: Cl, 22.72. Found: Cl, 22.97.

Three grams of this residue, ground to a fine powder and suspended in 50 cc. of absolute ethyl alcohol, was treated with an excess of dry chlorine. Almost immediately the brown particles became a bright green. This product was collected on a filter, washed with absolute alcohol and dried at 110° for two days. The green product appeared to be a mixture of the hexammine cobalt(III) chloride and unchanged cobalt(II) chloride. This was indicated by the fact that it dissolved to give an orange colored solution and the analysis for chlorine was consistently high. The ultraviolet spectrum of the green material (Fig. 1) showed no signs of any *trans*-salt.

Diammine-(triethylenetetramine)-cobalt(III) Chloride.—A solution of 3.2 g. (0.022 mole) of triethylenetetramine in 25 cc. of absolute ethanol was added to 5 g. (0.017 mole) of finely ground *trans*-dichlorotetramminecobalt-(III) hydrogen sulfate. The flask was equipped with a reflux condenser fitted with a calcium oxide drying tube, and the mixture was allowed to reflux on the steam-bath for five days. Ammonia was liberated and even after refluxing for five days traces of ammonia could still be detected. The grayish-orange reaction mixture was collected on a filter and washed with absolute alcohol and ether. A portion of this material was added to cold water and a small amount of slightly soluble violet-red residue was removed on a filter leaving an orange filtrate. An excess of alcohol and ether was added to the filtrate, causing an orange precipitate to separate. This precipitate was collected on a filter and washed with alcohol and ether and then dried at 110°.

Anal. Calcd. for [Co trien $(NH_3)_2$]Cl_3: Cl, 30.78. Found: Cl, 30.93.

cis-Dinitrotriethylenetetraminecobalt(III) Chloride.—A solution of 2.9 g. (0.020 mole) of triethylenetetramine in 25 cc. of absolute ethanol was added to 5 g. (0.020 mole) of finely ground *trans*-dinitrotetramminecobalt-(III) chloride. The flask was equipped with a reflux condenser fitted with a calcium oxide drying tube, and the mixture was allowed to reflux on the steam-bath for two days. A small amount of ammonia was still being liberated at the end of this time and the reaction mixture had not changed noticeably in appearance. The orange residue, which gave a qualitative test for ammonia, was purified by recrystallization from water. The crystals were washed successively with a small amount of cold water, alcohol and ether, and dried in a vacuum over sulfuric acid.

Anal. Calcd. for [Co trien $(NO_2)_2$]$Cl \cdot H_2O$: C, 20.60; H, 5.76; N, 24.03; Cl, 10.14; Co, 16.85. Found: C, 20.64; H, 5.79; N, 24.18; Cl, 9.98; Co, 16.93.

The *cis* configuration of this dinitro salt was suggested by the fact that boiling it with concentrated hydrochloric acid liberated nitrogen dioxide and formed a red solution which quickly turned purple. This is a qualitative test commonly used to distinguish between *cis*- and *trans*-dinitrotetramminecobalt(III) salts, the *trans*-salt forming a red precipitate of the corresponding chloronitro complex. No such precipitate separated from the purple hydrochloric acid solution even after prolonged standing at room temperature. It was likewise found that the ultraviolet spectrum (Fig. 2) of this salt is similar to that obtained for *cis*-dinitro-bis-(ethylenediamine)cobalt(III) chloride.

The same results were obtained when the experiment was repeated starting with the corresponding *cis*-salt, [Co $(NH_3)_4$ $(NO_2)_2$]Cl.

Anal. Found: C, 20.72; H, 5.80; N, 24.21; Cl, 10.05; Co, 16.89.

cis-Dinitrotriethylenetetraminecobalt(III) chloride prepared from II or III was found to have properties similar to the salt obtained from the *cis*- or *trans*-dinitrotetrammine complex. Six grams (0.019 mole) of II or III was mixed with 20 g. (0.218 mole) of sodium nitrite and 40 cc. of water. This mixture was heated to boiling and then cooled in an ice–salt-bath. The orange crystals which separated were collected on a filter and washed with a small amount of cold water followed by alcohol and ether. The ultraviolet absorption spectrum (Fig. 2) of this salt and its reaction with concentrated hydrochloric acid indicate the presence of the ion, *cis*-[Co trien $(NO_2)_2$]$^+$.

Carbonatotriethylenetetraminecobalt(III) dextro-Camphor-π-sulfonate.—Forty grams (0.129 mole) of II or III and 61 g. (0.219 mole) of freshly precipitated moist silver carbonate were ground in a mortar for two hours. The mixture was extracted with 200 cc. of distilled water and analysis of the filtrate revealed that it was free of chloride ion and contained 30 g. (0.051 mole) of the carbonate complex. It was mixed with a solution of 0.051 mole of barium *dextro*-camphor-π-sulfonate and the barium carbonate was removed on a filter. A portion of the filtrate was slowly concentrated in a drying oven at 40°. Crystals of the complex *dextro*-camphor-π-sulfonate were not obtained because the salt is extremely water soluble.

Oxalatotriethylenetetraminecobalt(III) dextro-Camphor-π-sulfonate.—The second portion of the carbonatotriethylenetetraminecobalt(III) *dextro*-camphor-π-sulfonate solution was allowed to react with 4.6 g. (0.051 mole) of oxalic acid. Carbon dioxide was liberated and the resulting solution was concentrated to 150 cc. This concentrate was cooled in an ice-bath and the pink crystals which separated were collected, washed with a small amount of cold water followed by alcohol and ether and the ether was removed at room temperature by a stream of air. A 1% solution of air-dried salt was immediately prepared and found to have an optical rotation of +0.12°, $[\alpha]^{25}D$ +12. The optical rotation of this solution had not changed after one week at 50°.

Two grams of this salt was also immediately ground, in an ice-cold mortar, with 30 cc. of an ice-cold mixture of concentrated hydrochloric acid, alcohol, and ether (1:1:1). After approximately ten minutes of constant grinding, the residue was collected on a filter and washed with cold alcohol and ether. A solution of a portion of this residue exhibited no optical activity at the D line of sodium. A major portion of the salt was dried in a vacuum over sulfuric acid.

Anal. Calcd. for [Co trien C_2O_4]Cl: Cl, 10.79. Found: Cl, 10.86.

Careful recrystallization of the oxalatotriethylenetetraminecobalt(III) *dextro*-camphor-π-sulfonate gave no indication of any separation of the optically active antipodes of the complex cation.

Ethylenediamine(triethylenetetramine)cobalt(III) Chloride.—Thirty grams (0.096 mole) of finely ground II or III, 12.8 g. (0.147 mole) of 69% ethylenediamine, and 500 cc. of absolute ethyl alcohol were placed in a three-necked round-bottomed flask containing some glass beads and equipped with an agitator and reflux condenser. The mixture was allowed to reflux with vigorous agitation for eight hours. The orange residue which formed was freed from any excess amine by washing with alcohol and ether. The theoretical yield of crude product was obtained and some of it was purified for analysis by recrystallization from water and drying at 110°.

Anal. Calcd. for [Co en trien]Cl_3: C, 25.84; H, 7.05; N, 22.64; Cl, 28.61; Co, 15.85. Found: C, 25.63; H, 6.98; N, 22.42; Cl, 28.57; Co, 15.93.

The salt can be purified more easily by conversion to the much less soluble iodide. Five grams (0.013 mole) of the salt in 20 cc. of water and 5 g. (0.033 mole) of sodium iodide in 10 cc. gave a crystalline iodide which was washed with cold water, recrystallized from 20 cc. of distilled water and dried in a vacuum over sulfuric acid.

Anal. Calcd. for [Co en trien]I_3: I, 58.92. Found: I, 58.67.

Attempts to resolve the ion, [Co en trien]$^{+++}$, from the bromide *dextro*-tartrate[7] and *dextro*-α-bromocamphor-π-sulfonate were not successful. The difficulty encountered was largely due to the extreme solubility of these salts.

Tetrakis-(ethylenediamine)-triethylenetetraminedicobalt(III) Chloride.—Thirty grams (0.105 mole) of finely ground *cis* or *trans*-dichloro-bis-(ethylenediamine)-cobalt(III) chloride, 11.5 g. (0.079 mole) of triethylenetetramine, and 500 cc. of absolute alcohol were allowed to react as described for the preparation of [Co en trien]Cl_3. An orange residue was formed, in practically theoretical amount. It was recrystallized from water and dried at 110°.

Anal. Calcd. for [Co_2 en_4 trien]Cl_6: C, 23.43; H, 7.02; N, 23.46; Cl, 29.65; Co, 16.43. Found: C, 23.23; H, 6.89; N, 23.58; Cl, 29.43; Co, 16.35.

Preparation and purification of the much less soluble iodide was accomplished by the method outlined for the corresponding [Co en trien]I_3.

Anal. Calcd. for [Co_2 en_4 trien]I_6: I, 60.14. Found: I, 59.93.

The resolution of this ion, [Co_2 en_4 trien]$^{+6}$, was not accomplished using the bromide *dextro*-tartrate[7] and the *dextro*-α-bromocamphor-π-sulfonate.

tris-(Triethylenetetramine)-dicobalt(III) Chloride.—Twenty grams (0.064 mole) of finely ground II or III, 9.6 g. (0.065 mole) of triethylenetetramine, and 300 cc. of absolute ethyl alcohol were allowed to react as described for the preparation of [Co en trien]Cl_3. A portion of the orange product was recrystallized from water and dried at 110°.

Anal. Calcd. for [Co_2 $trien_3$]Cl_6: C, 28.09; H, 7.07; N, 21.87; Cl, 27.64; Co, 15.32. Found: C, 27.87; H, 6.97; N, 21.93; Cl, 27.39; Co, 15.47.

The complex iodide was obtained by the addition of a small excess of sodium iodide solution to a solution of the complex chloride. This slightly soluble iodide was purified by recrystallization from water and dried in a vacuum over sulfuric acid.

Anal. Calcd. for [Co_2 $trien_3$]I_6: I, 58.92. Found: I, 58.67.

Again all efforts to resolve this ion, [Co_2 $trien_3$]$^{+6}$, from the bromide *dextro*-tartrate[7] and *dextro*-α-bromocamphor-π-sulfonate were without avail.

Summary

Salts of the following cations containing triethylenetetramine and cobalt(III) have been prepared and some of their properties are described: [Co trien Cl_2]$^+$, [Co trien $(NO_2)_2$]$^+$, [Co trien CO_3]$^+$, [Co trien C_2O_4]$^+$, [Co trien $(NH_3)_2$]$^{+3}$, [Co en trien]$^{+3}$, [Co_2 en_4 trien]$^{+6}$, and [Co_2 $trien_3$]$^{+6}$.

A *cis*-configuration seems to be indicated for the ions, [Co trien Cl_2]$^+$ and [Co trien $(NO_2)_2$]$^+$.

An absorption band was obtained at approximately 2425 Å. for several *cis*-dinitrotetramminecobalt(III) compounds and this same band was less clearly shown by the corresponding *cis*-dichloro compounds.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 20, 1948

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Determination of Position of Tracer Atom in a Molecule: Mass Spectra of Some Deuterated Hydrocarbons[1]

BY JOHN TURKEVICH,[2] LEWIS FRIEDMAN,[2] ERNEST SOLOMON AND FRANCES M. WRIGHTSON[3]

The problem of determining the position of a tracer atom in a complex molecule arose during the study of the mechanism of catalytic reduction of acetone to propane with deuterium. Since the mass spectrum of a molecule consists of fragment ions obtained by rupture of valence bonds it was thought that the relative abundance of appropriate ions would indicate the position of an isotopic atom. Thus C_3H_7D-1 should give among others, ions of mass 16 and 15.

$$H_3C—CH_2—CH_2D \longrightarrow \underset{16}{C_2H_5 + CH_2D^+} + E$$

$$\underset{15}{C_2H_4D + CH_3^+} + E$$

While C_3H_7D-2 should give no ions of mass 16.

$$CH_3—CH_2D—CH_3 \longrightarrow \underset{15}{C_2H_4D + CH_3^+} + E$$

The purpose of this study was to establish the validity of this approach and to study in general the changes in the mass spectrographic pattern of hydrocarbons produced by replacing some of the hydrogens with deuterium. With this in mind monodeuteromethane, tetradeuteromethane, monodeuteroethane, monodeuteropropane-1 and monodeuteropropane-2 were prepared and studied on two standard mass spectrographs, that of Nier and the one of the Consolidated Engineering Corporation.

A mass spectrometric study of dideuteroethylene has been made by Delfosse and Hipple.[4] More recently Evans, Bauer and Beach[5] have investigated the mass spectrum of monodeuteromethane and Mohler and Dibeler,[6] mono- and dideuteroacetylenes. These studies show that the

(1) Presented at the meeting of the American Chemical Society in Atlantic City, April 15, 1947.

(2) Princeton University.

(3) M. W. Kellogg Co.

(4) J. Delfosse and J. A. Hipple, *Phys. Rev.*, **54**, 1060 (1938).

(5) M. Evans, N. Bauer and J. Y. Beach, *J. Chem. Phys.*, **14**, 701 (1946).

(6) F. L. Mohler and V. Dibeler, *Phys. Rev.*, **72**, 158A (1947).

carbon–deuterium bond does not break as readily as the carbon–hydrogen bond.

Experimental

The mass spectrometer was a Nier type[7] instrument. The gas analyzed was introduced into the spectrometer tube through a capillary leak. The gas pressure in the sample system was kept at 10 mm. The bombarding electrons responsible for the ionization and dissociation processes were accelerated from an incandescent tungsten filament through a slit into the ion gun by a potential of 67.5 volts.

The mass spectra were also determined in a Consolidated Engineering Corporation instrument.[8] In this case the electron accelerating voltage was 55 volts and the gas analyzed was permitted to leak into the spectrometer tube from a sample reservoir at a pressure of approximately 20 microns.

Materials

The monodeuteromethane was prepared by decomposing methylmagnesium iodide with 100% heavy water. The Grignard reagent was prepared by adding 14.5 g. of C. P. methyl iodide to 20 cc. of dry Eastman Kodak butyl ether and 2.8 g. of magnesium turnings in a 250-ml. round-bottom flask. The magnesium was carefully drilled from a block of pure metal without the aid of any cutting oils or fluids. The flask was fitted with a vertical water cooled reflux condenser which in turn was fitted at the top with a calcium chloride tube. The reaction was initiated by gentle heating and then controlled by cooling in a water-bath. The flask containing the Grignard reagent was attached to a vacuum line by means of a standard taper ground glass joint, cooled in Dry Ice and evacuated. The reagent was thoroughly out gassed by melting, freezing and then evacuating several times. A small quantity of heavy water vapor (approximately 10–15 cc., N. T. P. estimated from the volume of the products formed) was distilled into the flask containing the Grignard reagent. The purity of the methane was determined by abundance ratio of masses 16 and 17. The first sample gave for this ratio a value of 0.83. The reaction mixture was cooled in Dry Ice and this sample of gas pumped off. A second batch of heavy water vapor was distilled into the Grignard reagent and the ratio of 16 to 17 in the deuteromethane formed was found to be 0.73. In the third and fourth batches the values were found to be 0.710 and 0.709. The constant values observed indicate that the reagent had been cleaned up of any light water contamination and the limit of purity had been reached. A larger sample of gas was then generated for final analysis.

Monodeuteroethane was prepared in a similar manner by the decomposition of ethylmagnesium bromide with heavy water. Ethylmagnesium bromide was prepared by adding 11 g. of ethyl bromide to 10 cc. of dry butyl ether and 2.8 g. of magnesium turnings in a 250-ml. round-bottom flask. Mild heating was used to initiate the reaction. The Grignard reagent was decomposed by using successive batches of heavy water. The ratios of the abundances of the ions of masses 30 and 31 were 0.80 for the first batch and 0.79 for the second, third and final batches prepared.

Propane-D-1 and Propane-D-2 were prepared from the corresponding normal and isopropylmagnesium bromides and heavy water. Both alkyl halides were purified by fractional distillation. In the preparation of propane-D-1 the ratios of the abundances of the ions of mass 44 and 45 were 1.05, 1.00, 0.895, and finally 0.863 for the following four successive batches. In the preparation of propane-D-2 the ratios for these ions were 0.83, 0.725, 0.74 and 0.74.

A sample of **tetradeuteromethane** containing approximately 7% monoprotium trideuteromethane was given to us by Mr. M. W. Wright. This material was prepared by the decomposition of aluminum carbide with heavy water. Excess hydrogen formed was removed by freezing the deuteromethane in solid nitrogen and pumping off the more volatile components.

It should be pointed out that in the preparation of deuterium compounds by the Grignard reagent extreme care must be observed to avoid introduction of light hydrogen into the molecule. The following precautions were observed. In the first place the heavy water was added in small successive portions to the Grignard reagent and samples were analyzed for the highest masses in the mass spectrograph. Two criteria of purity could then be applied. Successive samples should show a constant low value for the mass one smaller than the maximum, as the hydrogen impurity is removed from the sample (thus the relative abundance of mass 30 from C_2H_5D should reach a steady minimal value). Another criterion is that the sensitivity coefficient (absolute intensity) of the ion of parent mass be the same as that of the corresponding light hydrogen compound.

The second method of determining the purity of the preparation is to determine the hydrogen–deuterium ratio in the product. In this method the hydrocarbon was oxidized by copper oxide at 500°. The water formed was condensed in a Dry Ice trap and the carbon dioxide pumped off. The water was decomposed over zinc at 330°. The hydrogen so formed was analyzed in a Nier type mass spectrometer for the deuterium–hydrogen ratio. The instrument was calibrated by measuring the ratio of masses three and two of hydrogen from standard heavy water samples whose deuterium content was known from density determinations. The following two examples illustrate the results obtained using some early impure compounds. A preparation of monodeuteroethane has a sensitivity coefficient for the parent mass of 15 while the value of the corresponding light hydrogen ethane was 20.0. Assuming that the sensitivity coefficient is independent of deuterium content, this result would indicate that the preparation of monodeutero compound was 75% pure. Combustion and deuterium analysis indicated 12.0% deuterium and the monodeuteroethane (theoretical value is 16.7%). Thus deuterium analysis indicates again a 73% purity. Another example is furnished by the experiments on monodeuteropropane-2. The sensitivity coefficient for the mass of parent ion was 12.0 while that of the light hydrogen compound was 24.56. This would indicate 49% purity. The deuterium analysis showed 6.45% deuterium (theoretical value for a monodeuteropropane is 12.5%), or a purity of 50%. Thus the purity determinations based on an assumption of equal sensitivity coefficients of the ion of parent mass irrespective of deuterium substitution lead to the same result as an ultimate analysis based on hydrogen deuterium analysis.

Results

The experimental results obtained are expressed in terms of the sensitivity coefficients of the ion of parent mass and relative ion intensities. The sensitivity coefficient of the ion of parent mass is the relative value of the ion current of the parent mass at an inlet pressure of one micron under identical operating conditions. The relative ion intensities are expressed in the following way. The intensity of ion of parent mass is given the value of 100 and the intensities of the other ions are presented relative to the intensity of the ion of parent mass. Using the sensitivity coefficient as given and the relative ion intensity one can obtain intensities of all other ions at the standard operating conditions of the instrument.

The data presented in Tables I, II and III permit a comparison of the results obtained by the two standard instruments: that of Nier and that

(7) A. O. Nier, *Rev. Sci. Inst.*, **11**, 212 (1940).

(8) Washburn, Wiley and Rock, *Ind. Eng. Chem., Anal. Ed.*, **15**, 541 (1943).

TABLE I

RELATIVE ION INTENSITIES

Mass	CH_4 a	CH_4 b	CH_4 c	CH_3D a	CH_3D b	CH_3D c	CD_3H a	CD_4 a
20								100.0
19							100.0	
18							?	82.8
17				100.0	100.0	100.0	51.2	...
16	100.0	100.0	100.0	78.2	76.0	71.3	?	14.5
15	83.5	83.1	81.2	22.3	22.5	18.7	6.1	...
14	17.0	17.1	12.5	8.8	9.4	6.8	?	7.9
13	8.3	8.2	5.7	5.0	5.2	3.7	1.5	...
12	2.6	2.4	1.8	2.5	2.4	1.8	2.5	2.5
Total ions	211.4	...	...	216.8	...	...	...	207.7
Sensitivity coefficient of ion parent mass	61.8	...	...	65.0	...	...	63.3	63.3

[a] Consolidated Engineering Corporation Mass Spectrometer (M. W. Kellogg Company, Jersey City, N. J.). [b] Evans Bauer and Beach. [c] Nier type mass spectrometer. The values are corrected for C^{13} isotope.

TABLE II

RELATIVE ION INTENSITIES

Mass	C_2H_6 c	C_2H_6 a	C_2H_5D c	C_2H_5D a
31	...	...	100.0	100.0
30	100.0	100.0	73.1	74.3
29	76.5	78.0	330.4	320.1
28	393.4	394.0	196.3	(177.3)[a]
27	127.5	130.3	96.1	105.5
26	87.2	92.8	49.9	60.4
25	16.2	15.1	10.8	11.6
Total C_2 ions	800.8	810.2	856.6	....
16	...	0.2	6.2	8.5
15	12.5	17.9	9.7	18.2
14	8.4	12.2	5.4	(14.3)[a]
13	3.1	4.2	2.3	3.9
12	1.9	1.9	1.2	5.0
Total C_1 ions	25.9	36.4	24.8	....
Total ions	826.7	846.6	881.4	....

[a] Unreliable.

TABLE III

RELATIVE ION INTENSITIES

Mass	Propane c	Propane a	Propane D-1 c	Propane D-1 a	Propane D-2 c	Propane D-2 a
45	...	....	100.0	100.0	100.0	100.0
44	100.0	100.0	87.6	93.9	74.1	62.5
43	82.2	82.4	34.5	30.3	51.9	48.5
	21.0	20.1	47.6	53.9	40.2	51.6
41	43.4	46.3	35.7	41.6	56.6	36.0
40	8.7	7.4	36.7	39.9	23.2	31.9
39	55.7	62.9	44.0	57.4	13.1	49.4
38	...	17.3	....	18.2	....	14.6
37	...	10.5	....	11.3	....	8.9
Total C_3 ions	321.0	346.9	386.1	446.5	359.1	403.4
31[d]						
30	...	....	151.5	179.7	323.1	329.5
29	312.2	350.0	223.2	291.4	218.4	218.4
28	188.6	208.1	143.9	193.5	132.4	(60.0)[a]
27	113.5	142.3	77.1	122.3	85.2	89.9
26	24.4	30.1	17.5	28.4	20.2	18.7
Total C_2 ions	7638.7	730.5	613.5	815.3	779.3	.....
16	...	0.3	7.4	11.4	3.3	2.7
15	13.5	22.5	10.3	18.7	12.3	22.9
14	4.1	7.0	3.9	6.8	4.1	(1.0)[d]
13	1.5	2.1	1.2	2.3	1.5	2.3
12	0.7	1.0	0.7	0.1	0.7	1.9
Total C_2	19.8	32.9	23.5	39.3	21.9	.....
Total ions[e]	979.5	1110.3	1023.1	1301.1	1160.3	.....

[d] Unreliable. [e] Total ions includes all peaks recorded.

of the Consolidated Engineering Corporation. One should first note in Table I the concordance of our results for monodeuteromethane obtained on the Consolidated instrument of the M. W. Kellogg Company at Jersey City with the results obtained by Evans, Bauer and Beach on a similar instrument on the West Coast. The values obtained on the Nier instrument at Princeton University are slightly lower.[9] An examination of the results of Tables II and III shows more marked differences in the individual values of the relative ion intensities for the various ethanes and propanes as obtained on the two different instruments. One must note, however, that the two instruments agree on both the order of abundance of the various ions and their magnitude. For that reason the results will be discussed for the most part in terms of the values obtained on the Nier instrument. The values obtained on the Consolidated instrument are placed in parentheses in the text of the paper.

(9) This may be due to differences in the ambient temperatures of the ionization chambers in the two instruments.

Methane.—The sensitivity coefficients of the ion of parent mass for all three compounds CH_4, CH_3D and CD_4 is approximately the same.

The CH_3D pattern had been previously reported by Evans, Bauer and Beach and our results using the Consolidated instrument agree with those they reported. The results we obtained with the Nier instrument are slightly lower. The CH_3D pattern is different from that of CH_4 and CD_4. Evans, Bauer and Beach have made a detailed analysis of this difference in terms of statistics and the relative dissociation probabilities of the C–H and C–D bonds in CH_3D and of the CH bond in CH_4 compared to the C–H bond in CH_3D. We shall limit ourselves to a more elementary analysis. The number of processes of ionization increases from five to six when one goes from CH_4 to CH_3D while the sum total of the ion currents

remains the same (211.4, 216.8, 207.7). This brings of necessity a redistribution of the cracking pattern. This kind of redistribution is not statistical as has been pointed out by Evans, Bauer and Beach in the case of CH_3D and by Delfosse and Hipple for $C_2H_2D_2$.

The mass 16 in the spectrum of CH_3D results from the removal of a hydrogen atom and an electron from the molecule. Statistically this should correspond to $^3/_4$ the value obtained for the removal of a hydrogen from CH_4 or 60.9 (62.6). The observed values are 71.3 (78.2) indicating that the hydrogen removal is 1.17 (1.25) more probable if the carbon atom contains a deuterium atom. The mass 15 may arise from two processes. It may arise from a removal of two hydrogens from CH_3D and should have $^3/_6$ the value of the CH_2^+ produced from CH_4 or 6.2 (8.5). The second process is the removal of a deuterium from CH_3D. The statistical value should be one-quarter of the removal of a hydrogen from CH_4 or 20.3 (20.9). The total for the two processes is 26.5 (29.4) and is larger than the experimentally observed value 18.7 (22.3). If one assumes that the probability of breaking a deuterium–carbon bond is one-half that of breaking a hydrogen–carbon bond while the breaking of a hydrogen–carbon bond is 1.17 more probable if the carbon atom contains a deuterium atom we get a predicted value of 18.4 (21.1) in better agreement with experimental values 18.7 (22.3). The mass 14 arises again from two processes. The first produces a CD^+ which should be one-third of the CH^+ from CH_4 or 1.9 (2.8). If we multiply this by 1.17 we get 2.2 (3.5). The second is due to CH_2^+ which should be $^3/_6$ of the CH_2^+ peak of CH_4 or 6.2 (8.5). If we multiply this by (0.5) (1.17) we get 3.8 (5.0). The predicted value is thus 6.0 (8.5) where the experimental value is 6.8 (8.8).

A part of the CD_3H pattern can be obtained from the 7% CD_3H impurity in CD_4 sample by considering the relative intensities of the ions of odd mass in the spectrum of CD_4 (after correcting for the 1.1% C^{13} isotope). One then obtains 100 for the CD_3H^+ and 51.2 for the CD_2H^+. The other masses cannot be obtained from the data available. For CD_2H^+, on purely statistical grounds, one would expect three-quarters of 83.5, or 62.6. An interpretation of the CD_3H spectrum must await synthesis of pure CD_3H.

The CD_4 as prepared contained 7.2% CD_3H as revealed by ions of odd mass. The spectrum of CD_4 should consist solely of ions of even mass when a correction is made for the contribution due to 1.1% C^{13} isotope. The presence of an impurity of 7.2% CD_3H affects the spectrum but slightly since the currents for even masses from this molecule would be small in view of the small amount of the impurity present. The only correction applied was to the mass 18 where it was calculated on statistical grounds to be $7.2 \times 0.835 \times {}^1/_4 = 1.5$. The value in Table I is so corrected. The process of removing a hydrogen from CH_4 to give CH_3^+ has the value 83.5 while the similar process of removal of D from CD_4 has the value 82.8.

The removal of two hydrogens from CH_4 gives the value of 17.0 while the corresponding process in CD_4 has the value 14.5. The removal of three hydrogens from CH_4 gives a value of 8.34 while that of three deuteriums from CD_4 is 7.85. One thus sees that the probability of breaking a carbon–deuterium bond in tetradeuterium methane is the same as the probability of breaking a carbon–hydrogen bond in tetrahydrogen methane. The probability of breaking a carbon hydrogen bond is greater if there is a carbon–deuterium bond present and also the probability of breaking a carbon–deuterium bond is less if there is a carbon–hydrogen bond present.

Ethanes.—The mass spectra of ethane and monodeuteroethane are presented in Table II. The sensitivity coefficients of the parent masses were found to be approximately the same. The total number of ions formed from ethane (827–847) is slightly less than the total from monodeuteroethane (881). The relative ion intensities are different first because new masses 31 (C_2H_5D) and 16 (CH_2D) appear and secondly because alternative processes involving the removal of either D or 2H atoms give ions of the same mass. Ninety-five per cent. of the ions are in the C_2 group indicating that it is easier to break C–H bonds than the –C–C bonds. The total number of ions in the C_2 group in deuteroethane 857 is greater than in ethane 801 (824). In the C_2 group mass 30 arises from the loss of a hydrogen and an electron from deuteroethane. Its value should be $^5/_6 \times (1.17)$ of that observed for the 29 peak in ethane or 74.6 (81.2). The experimental value is 73.1 (74.3). The mass 29 arises by two processes: (a) the removal of a deuterium and an electron which should be equal to $^1/_6 \times (0.5)$ the value of removing a hydrogen from ethane 76.5 (78.0) or 6.5 (6.5); (b) removal of two hydrogens and an electron from deuteroethane which should be $^{10}/_{15} \times (1.17)$ of a similar process in ethane 393 (394) or 307 (328). The predicted value is 314 (335) while the observed value is 330 (320). The mass 28 arises again two processes (a) the removal of three hydrogens and an electron which should be $^{10}/_{20} \times (1.17)$ of analogous process for ethane 127.5 (130.3) or 74.6 (81.4) and (b) the removal of a deuterium, hydrogen and electron which should be $^5/_{15}$ of the removal of two hydrogens from ethane 393.4 (394) or 131 (131). The predicted value is 206 (213) while the observed value is 196. The agreement with experiment is better if one drops the weighing factors (1.17) and (0.5) for the simultaneous removal of an H and a D.

Mass 27 arises from (a) removal of 4 hydrogen atoms and an electron from C_2H_5D and should be equal to $^5/_{15}$ of (1.17) 87.2 (92.8) or 34.0 (38.6), (b) removal of 3 hydrogen and one deuterium atom

and an electron. The value for this process should be $^{10}/_{20}$ of 127.5 (130.3) or 63.8 (65.2). The total is 98 (104). The observed value is 96 (105.5). The mass 26 arises from (a) removal of five hydrogens and an electron from C_2H_5D and should be equal to $^1/_5 \times (1.17) \times 16.2$ (15.1) = 3.8 (3.8) and (b) removal of three hydrogen and one deuterium and electron. The value for this process should be $^{10}/_{20} \times 87.2$ (92.8) or 43.6 (46.4). The total predicted value is 47.4 (50.2) as contrasted with the experimental value of 49.9 (60.4). The mass 25 arises from sole process of removal of four hydrogens and a deuterium atom and an electron. This should be equal to $^5/_6$ of 16.2 (15.1) = 13.5 (12.6) whereas the experimental value is 10.8 (11.6).

The C_1 group constitutes about 3% of the total ions produced from ethane. The values for the ethane are 25.9 (36.4) and for the deuteroethane 24.8. The mass 16 in monodeuteroethane arises from a split of the molecule in two and should be one-half of the mass 15 from ethane or 6.2 (9.0). The experimentally observed values are 6.2 (8.5). The close concordance between the predicted and experimentally observed results indicates that the presence of the deuterium isotope does not appreciably affect the probability of breaking the C—C bond. The mass 15 in monodeuteroethane arises from CH_3^+ and CHD^+. The amount of the CH_3^+ can be calculated as one-half the 15 peak in C_2H_6 or 6.2 (8.5). The amount of the CHD^+ is $^1/_2 \times ^2/_3 \times (1.17)$ of the CH_2^+ from C_2H_6 or 3.3 (5.1). The total is therefore 9.5 (13.6) while the observed value is 9.7 (18.2).

The value of 14 peak in C_2H_5D is due to contributions of CH_2 and CD^+. The CH_2^+ that comes from CH_3 is $^1/_2$ of 8.4 or 4.2 and the amount that comes from CH_2D is $^1/_2 \times ^1/_3$ (0.5) $\times$ 8.4 or 0.7. The CD^+ that comes from CDH_2 should be $^1/_2$ (3.1) $\times$ $^4/_6$ = 0.7. The total is 4.2 + 0.7 + 0.7 = 5.6. The value obtained on the Nier instrument is 5.4.

Propanes.—The mass spectra of propane, propane D-1 and propane D-2 are presented in Table III. The presence of only one deuterium in the deuterated propanes is established by the absence of masses higher than 45. The sensitivity coefficients of the three propanes examined were the same. The total number of ions was 979.5 (1110), 1023 (1301) and 1160, respectively, and cannot be considered equal within the experimental error. The C_3 group contains about one-third of the ions. An analysis of the ions formed is difficult. The high value of the 44 peak in the D-1 and the low value in the D-2 compound seems to indicate that the primary carbon-hydrogen bond is more strongly held than the secondary and it is the secondary hydrogen that comes off first. A detailed discussion of the C_3 ions in the deuterium compounds must be postponed until further deuterium compounds are synthesized and studied. The C_2 group contains about two-thirds of the ions. The mass 30 results from the loss of a methyl radical and an electron from the deuteropropane. In the case of the D-1 compound its value should be equal to one-half of the mass 29 for propane or 156 (175). The observed value 151.5 (180) is in good agreement. In the case of the D-2 compound the value of the 30 mass should be equal to the value of the 29 mass in propane or 312 (350). The experimental values are 323 (330). The explanation for the value of the 29 mass in propane D-1 is satisfactory. It can arise in two ways

$$CH_3CH_2—CHD_2 \longrightarrow CH_4 + C_2DH_3 + E$$

and its value should be one-half times $^4/_5$ the value of the 28 peak in propane 75.5 (83). The other process is

$$CH_3{\cdot}CH_2{\cdot}CDH_2 \longrightarrow CDH_2 + CH_3{\cdot}CH_2^+ + E$$

which should be one-half the value of the 29 peak in propane or 156 (175). The total is 232 (258) to be compared with the experimental 223 (291). The value of the 29 mass in propane D-2 can arise only from a removal of a CH_4 from the molecule and should be equal to the 28 peak in propane, or 189 (208). The value found experimentally is 218 (218).

The C_1 group contains about 2% of the total ions. The mass 16 should occur only in the case of propane D-1 where it should be equal to one-half the value for the 15 mass in propane or 6.7 (11.2). The observed values are 7.4 (11.4) in good agreement with prediction. There should be no 16 mass in propane D-2. The small value obtained for this mass may be due to re-arrangement in the preparation of the deuterated propane. The mass 15 for propane D-2 should be the same as that from propane, *i.e.*, 13.5 (22.5). The experimental value is 12.3 (22.9) in good agreement with calculation. The value for propane D-1 arises by two processes

$$CH_3{\cdot}CH_2CH_2D \longrightarrow CH_3^+ + CH_2{\cdot}CHD$$

or one-half the value for propane 6.7 (11.2) and

$$CH_3{\cdot}CH_2CH_2D \longrightarrow CHD^+ + CH_3{\cdot}CH_3$$

or two-thirds of the value for mass 14 (2.7, 4.7) from propane to give a predicted value of 9.4 (15.9). The experimental value is 10.3 (18.7). Thus we see that the C_1 group provides unequivocal evidence for the disposition of the deuterium atoms in the molecule.

In conclusion it may be stated that one can determine the position of the tracer atom in a propane molecule by examination of the intensities of masses 30 and 16. Furthermore, one can reconstruct the fine details of the mass spectrum of monodeuteromethane, monodeuteroethane using the assumption of equal probability of rupture of hydrogen carbon bonds, a 7/6 factor for a carbon–hydrogen bond on a carbon atom that has deuterium and a one-half factor for a carbon–deuterium bond. One further drops these factors if both D and H are removed simultaneously.

Conclusion

1. Monodeuteromethane, tetradeuteromethane, monodeuteroethane, monodeuteropropane-1 and monodeuteropropane-2 have been synthesized and their mass spectra determined on a Nier type and a Consolidated mass spectrometer.

2. A method of calculating the mass spectrum of monodeuteromethane and monodeuteroethane from the corresponding light hydrogen compounds, has been indicated.

3. A method has been given to indicate the position of a deuterium atom in monodeuteropropanes.

RECEIVED JANUARY 27, 1948

[CONTRIBUTION FROM CHEMICAL LABORATORY, UNIVERSITY OF MISSOURI]

The Quantum Efficiency of the Mercury Sensitized Photochemical Decomposition of Hydrogen

BY LLOYD B. THOMAS AND WM. D. GWINN[1a]

Introduction

The reaction between mercury atoms excited by absorption of light of λ 2537 Å. and hydrogen molecules to produce hydrogen atoms was reported by Cario and Franck[1] in 1922. The analogous reaction between hydrogen molecules and mercury atoms excited by streaming electrons of controlled energy through the gas mixture has been carried out.[2] These and more recent studies in this laboratory have indicated that the 6^3P_1 state of mercury to which the photochemical reaction is ascribed may play only a slight part, if any, in the electron initiated reaction. The immediate occasion for undertaking the present study is to obtain the necessary reaction rate data to compare the kinetics of the electron and photon activated reactions in the hope that the mechanism of the former will be clarified.

Attention has been devoted by a number of investigators—Stuart, Zemansky, Bates[3] and Evans[4]—to the quenching of fluorescent resonance radiation from Hg^3P_1 atoms by collision of the Hg^3P_1 atoms with added foreign gas molecules. An over-all effective cross section for quenching is obtained through the method but it is not possible to distinguish between processes which may contribute to the quenching. By the method of the present paper it appears possible to determine the effective cross section for a specific process, *i.e.*, the interaction of Hg^3P_1 atoms with hydrogen molecules to cause their removal from the gas phase, presumably through dissociation.

Experimental

The reaction system and light source are shown in Fig. 1. The reaction cell is a cylinder of fused silica which has an internal length of 3.53 cm. and an internal diameter of 2.25 cm. The walls of the cell are lined with a thin cylinder of oxidized copper. The ends of the cylinder are flat polished fused silica windows 2 mm. thick and are fused on. The cell is attached to the rest of the system, which is of Pyrex, by a graded seal. The Pirani gage consists of a 0.0025 cm. platinum filament mounted as shown and immersed in a kerosene filled thermostat which is maintained at 30°. Precaution was taken to prevent a film of kerosene, which was found to absorb λ-2537, from creeping over the entrance window. The system in the thermostat was connected through a U-tube and mercury cut-off to a conventional high vacuum system with mercury condensation pump, McLeod gage, mercury cut-offs, and with no stopcocks in the high vacuum line. Hydrogen was admitted from a gas flame through a palladium tube. The pressure was brought to the desired values, as shown by the McLeod gage, through manipulation of the flame and cut-offs.

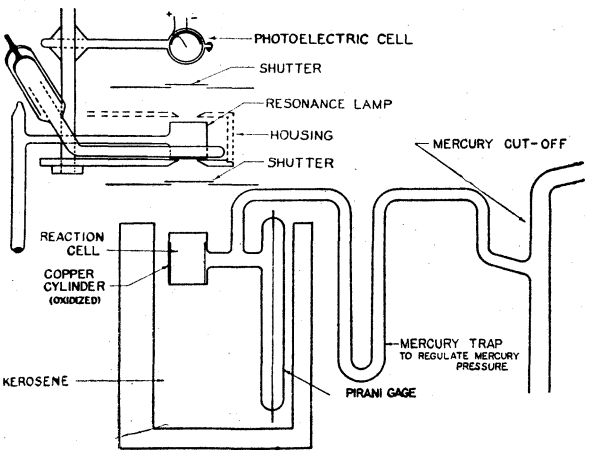


Fig. 1.—Experimental apparatus.

The light source is a monochromatic resonance lamp[5] which operates several degrees above room temperature and gives a very narrow line breadth—about 20% greater than the Doppler breadth at 30°. A fused silica photoelectric cell with a cadmiun coated cathode was mounted above the resonance lamp as shown and served as a check on the lamp intensity. The intensity of λ 2537 in this upper position was strictly proportional to that at the reaction cell window when the mercury vapor pressure in the resonance lamp cylinder was kept constant. The procedure in taking data is as follows: The thermostat is replaced by an oven. Oxygen is admitted to the system to about 10 mm. pressure. When the oven temperature becomes sufficiently high the oxygen pressure starts to diminish due to consumption by the copper of

(1a) Present address of W. D. G. is Department of Chemistry, University of California, Berkeley, Calif.

(1) Cario and Franck, *Z. Physik*, **11**, 155 (1922).

(2) Glockler and Thomas, THIS JOURNAL, **57**, 2352 (1935).

(3) A. C. G. Mitchell and M. W. Zemansky, "Resonance Radiation and Excited Atoms," Cambridge University Press, 1934.

(4) Evans, *J. Chem. Phys.*, **2**, 445 (1934).

(5) Thomas, *Rev. Sci. Inst.*, **12**, 309 (1941).

the cylinder. After the oxygen pressure has diminished about 1 mm. the oxygen is pumped out and the system is baked and flamed while open to the pumps. The thermostat is then replaced, the temperature of a mercury droplet introduced to the U-tube is set at the desired value, hydrogen is introduced to the desired pressure, and the cut-off to the reaction system is closed. After bringing the Pirani gage to balance and bringing the lamp to a steady intensity, the foot-operated shutter below the resonance lamp is opened for a measured time interval. This interval is regulated from four to sixty seconds, depending on the pressures of hydrogen and mercury vapor in the system, to give a Pirani galvanometer excursion of from 10 to 30 scale divisions (readable to 0.1 division), which corresponds to the disappearance of less than 10^{-10} gram of hydrogen. After about five such average exposures the baking-out procedure is repeated. This is necessary because it was found that the observed rates of decomposition began to decrease measurably with total decomposition in excess of this amount. This effect seems to be attributable to the inability of the silica surface to maintain its full capacity for removal of the products of the reaction. All of the data reported in this paper were taken in the initial period after baking out and forming a fresh oxide surface when the reaction rates at a given set of concentration and radiation conditions were quite constant and at a maximum.

The lamp intensity was determined by use of two multiple junction bismuth–silver vacuum thermopiles, one bismuth–(bismuth, 5% tin) vacuum thermopile, two quartz–cadmium photocells, the chloroacetic acid actinometer, and two N.B.S. calibrated lamps along lines described earlier.[6] Ten sets of determinations of the resonance lamp intensity gave 25.6×10^{12} quanta entering the reaction vessel per second for unit (upper position) photocell galvanometer deflection. The absorption (including reflection) of light from the resonance lamp and N.B.S. standard lamps in thermopile and reaction cell windows was measured and the proper corrections were made. As a check on the reliability of the lamp standardization the quantum yield of the chloroacetic acid hydrolysis was run. A quantum yield of 0.29 at 26° was found, which is to be compared with the value 0.33 obtained by Smith, Leighton and Leighton.[7] (The value of 0.342 previously given by Thomas[6] should be revised to 0.29 when correction is allowed for absorption of the radiation of the N.B.S. lamps in the two mm. fused silica ground and polished windows of the thermopiles.)

The absorption for the resonance lamp by the mercury vapor in the reaction cell was calculated from measurements made in a cell similar to the reaction cell but of better optical quality and described with equations used in reference 5. The value of ω (ref. 5, p. 311) was found to be approximately 1.2 and the integral expression with this value of ω and the "l" for the reaction cell of Fig. 1 was used to calculate the absorption in the reaction cell at the various pressures of mercury vapor. This absorption, multiplied by the number of quanta entering the cell per second per unit photocell galvanometer deflection, is plotted in Fig. 2, Curve A.

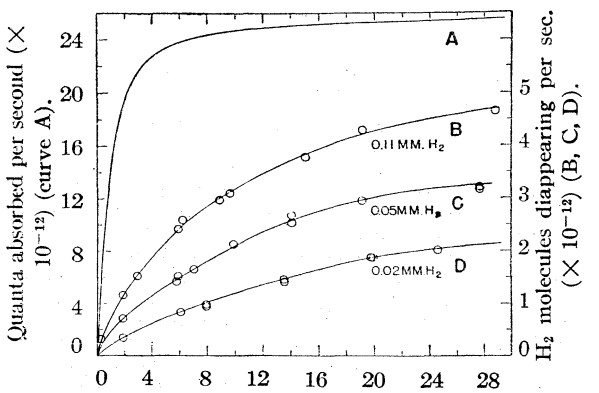


Fig. 2.—Experimental data.

(6) L. B. Thomas, THIS JOURNAL, **62**, 1879 (1940).

(7) Smith, Leighton and Leighton, *ibid.*, **61**, 2299 (1939).

The Experimental Data

The measurements were made at three hydrogen pressures, 0.02, 0.05 and 0.11 mm. over a range of mercury vapor pressures from 0.3×10^{-4} to 30×10^{-4} mm. These data, expressed in hydrogen molecules disappearing per second per unit photocell galvanometer deflection (photocell mounted above resonance lamp), are shown plotted against the pressure of mercury vapor in Fig. 2, Curves B, C, D. Most of the points shown in these curves represent an aggregate of several points so closely placed that they could not be plotted distinctly on a graph of this scale. The data considered in determining the curves are given below in Table I under the column headings I and II, representing, respectively, the mercury vapor pressure in mm. $\times 10^4$ and the rate of removal of hydrogen in molecules per second per unit photocell galvanometer current $\times 10^{-12}$. The number of separate measurements taken to obtain the average value given is indicated by the numbers in parentheses in case of more than one. Column III lists the quanta of λ 2537 ($\times 10^{-12}$) absorbed in the cell per second per unit photocell current over the range of mercury vapor pressures. These are plotted in Curve A, Fig. 2.

TABLE I

REACTION RATE MEASUREMENTS AND LIGHT ABSORPTION IN THE CELL

I, Pressure of Mercury Vapor ($\times 10^4$). II, Hydrogen molecules removed per second per unit photocell current ($\times 10^{-12}$). III, Quanta of λ-2537 absorbed within cell per second per unit photocell current ($\times 10^{-12}$).

0.11 mm. H_2		0.05 mm. H_2		0.02 mm. H_2			
I	II	I	II	I	II	I	III
0.3	0.277	1.85	0.70 (3)	1.85	0.303 (3)	0.0	0.0
1.85	1.22 (5)	1.85	0.694 (3)	1.85	0.3 (3)	1.0	14.3
2.95	1.53 (2)	5.8	1.42 (2)	6.0	0.83 (3)	2.0	19.5
5.8	2.37 (3)	5.9	1.54 (3)	6.1	0.848	4.0	22.8
5.9	2.415 (2)	7.05	1.65 (3)	7.95	0.945 (3)	8.0	24.5
6.2	2.62	9.9	2.14	13.5	1.44 (2)	16.0	25.1
8.7	2.86	14.05	2.60 (3)	19.8	1.91 (2)	24.0	25.4
8.9	2.97	19.15	3.02 (2)	19.95	1.87 (2)		
9.0	3.12	27.7	3.15 (2)	24.6	2.01		
9.6	3.10	27.7	3.20				
15.1	3.78 (3)						
19.15	4.3						
28.8	4.65 (3)						

Discussion

To express the data in more significant form, curves were put through the experimental points (Curves B, C, and D of Fig. 2) and the ordinates of these curves were divided respectively by the ordinates of Curve A, Fig. 2 at corresponding abscissas. The resulting values are plotted in Fig. 3 for each of the hydrogen pressures investigated. The ordinates of these curves are the quantum efficiencies at the various mercury vapor

pressures. It is seen that the quantum efficiency rises markedly over the mercury pressure range—more than eight-fold at 0.02 mm. hydrogen and 4 fold at 0.11 mm. hydrogen pressure. At the pressure conditions of these experiments the chance that the Hg^3P_1 atoms will radiate is much greater than the chance that they will be quenched. The increasing quantum yield with increasing mercury pressure is due no doubt to the increasing reabsorption of fluorescent λ 2537 within the reaction cell. One of the problems of this paper is to give a quantitative statement of the contribution of this reabsorption process to the reaction kinetics.

The curves of Fig. 3 permit quite definite extrapolation to the axis of zero mercury vapor pressure. The limiting values of the quantum efficiencies at zero mercury vapor pressure are 0.0095 at 0.02 mm. of hydrogen; 0.023 at 0.05 mm. of hydrogen; and 0.045 at 0.11 mm. of hydrogen. These extrapolated values should give the probabilities that single mercury atoms excited to the $^3P_1$ state will react with hydrogen molecules at the specified pressures to cause disappearance of the hydrogen from the gas phase and they should be free from complications resulting from reabsorption of the fluorescent quanta. They may be used to calculate the effective cross section for the process through use of the collision frequency expression: $Z = 5.64 \times 10^5 n_{H_2} \cdot n_{Hg^*} \cdot \sigma^2$ (for hydrogen and mercury at 30°) in which σ^2 is often termed the "effective cross section" for the given process.[3] To apply the present case consider the absorption of one quantum per cc. per second. Then the number of effective collisions per cc. per second, Z, becomes the quantum efficiency, ϕ, and the n_{Hg^*} becomes the product of τ, the average life of the Hg^3P_1 state (1.07×10^{-7} sec.), and $(1 - \phi)$. Substitution of the appropriate values in (1) gives for the intercept with 0.02 mm. of hydrogen:

$$0.0095 = \frac{5.64 \times 10^5 \times 6.42 \times 10^{14} \times 1.07 \times 10^{-7}}{(1 - 0.0095)\sigma^2}$$

From this, $\sigma^2 = 2.45 \times 10^{-16}$ cm.^{2} at 0.02 mm. of hydrogen. Similarly σ^2 is found to be 2.43×10^{-16} and 2.21×10^{-16} at 0.05 mm. and 0.11 mm. of hydrogen, respectively. It appears likely that other quenching processes are competing with that resulting in disappearance of hydrogen. The over-all cross section for quenching of Hg^3P_1 atoms by hydrogen is variously given from 27 to 6.01×10^{-16} cm.^{2} by several investigators.[3,4] The last value of Zemansky,[3] confirmed by Evans[4] using the same apparatus and theory, should be most reliable. The ϕ value used in the $\tau(1 - \phi)$ term to calculate n_{Hg^*} should refer to total quenching rather than to dissociation of hydrogen. In calculating the σ^2 values below, the ϕ in $(1 - \phi)$ is multiplied by the ratio of the σ^2 for quenching (σ_Q^2) to the σ^2 for dissociation of hydrogen (σ_D^2). This gives σ_D^2 values 2.50, 2.50 and 2.37×10^{-16} cm.^{2} for $\sigma_Q^2 = 6.01 \times 10^{-16}$ cm.^{2}, or 2.53, 2.57 and 2.51×10^{-16} cm.^{2} for $\sigma_Q^2 = 8.6 \times 10^{-16}$ cm.^{2} given earlier by Zemansky.[3] The value 2.5×10^{-16} cm.^{2} is selected for σ^2 for the process resulting in disappearance of hydrogen from the intercept measurements.

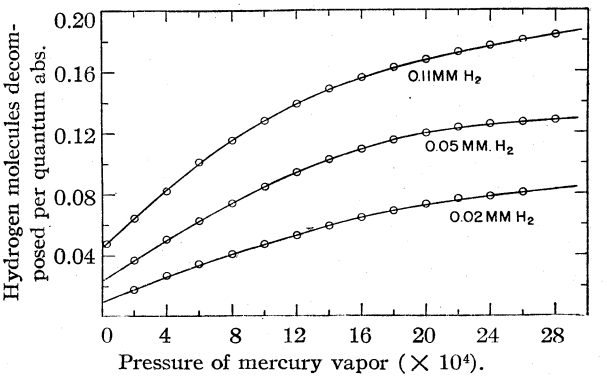


Fig. 3.—Quantum efficiency.

A series of reactions which constitutes the mechanism will be postulated and on the basis of this mechanism the rate constants and the contribution of the reabsorption of fluorescent radiation to the reaction rates will be determined. The reactions postulated are: 1, absorption of λ 2537 quanta by the mercury atoms in the gas mixture; 2, fluorescence of λ 2537 quanta followed by partial reabsorption to an extent depending on the mercury atom concentration; 3, reaction of Hg^3P_1 atoms resulting in dissociation of hydrogen; 4, collision of Hg^3P_1 atoms and hydrogen resulting in quenching of the Hg^3P_1 atoms but not resulting in dissociation of hydrogen. These processes may be written as

(1) $Hg^1S_0 + h\nu\ (\lambda\ 2537) \longrightarrow Hg^3P_1$
(2) $Hg^3P_1 \longrightarrow Hg^1S_0 + h\nu\ (\lambda\ 2537)$
(3) $Hg^3P_1 + H_2 \longrightarrow Hg^1S_0 + 2H + K.\ E.$
(4) $Hg^3P_1 + H_2 \longrightarrow Hg^1S_0 + H_2 + K.\ E.$

The removal of Hg^3P_1 atoms by Process (2) is greatly modified by reabsorption by the Hg^1S_0 atoms. It is desired that Process (2) represent the net fluorescence, *i.e.*, only those quanta that leave the reacting mixture should be counted as fluorescence. The remainder of the quanta are supplied for repetition of Process (1). It is seen from superficial examination of Fig. 3 that the number of quanta supplied for Process (1) by Process (2) may be of the order of eight times as great as that supplied directly from the lamp. The velocity constant for Process (2) is simply the Einstein "A" coefficient or the reciprocal of the mean life, τ, of the 6^3P_1 state, and this will be modified to represent the net fluorescence by multiplying by a factor which will be designated F (Hg^1S_0). This function of the concentration of Hg^1S_0, *i.e.*, F (Hg^1S_0), will have the characteristic that it approaches unity as the concentration of Hg^1S_0 atoms approaches zero, and it tends toward zero as (Hg^1S_0) becomes large. F(Hg^1S_0) may be defined as the mean probability that a quantum

of fluorescent radiation will escape reabsorption within the reaction system. It is of course a function of the size and shape of the reaction vessel as well as the mercury vapor pressure.

Reaction (3) represents the main feature of the Cario and Franck reaction, *i.e.*, a collision of the second kind with utilization of the energy of excitation of mercury atoms to supply the energy of dissociation of hydrogen.

It appears necessary to postulate reaction (4) to take into consideration the above-mentioned variance of σ_Q^2 and σ_D^2, and to develop a proper over-all kinetic expression to fit the data. Reaction (4) represents a process unspecified as to detail whereby mercury atoms lose their excitational energy at a rate proportional to the hydrogen pressure but the process does not result in a pressure decrease as would be expected if dissociation occurred. This proposed process would contribute to the over-all kinetics in somewhat the same manner as would failure of the apparatus to achieve complete clean-up of the H atoms by a factor proportional to the hydrogen pressure but this, as is discussed later, is not thought to be the case. Reaction (4) would, superficially at least, be considered improbable because of the larger (than reaction (3)) amount of kinetic energy developed. However, if the hydrogen molecule comes out of the collision in a high vibrational state, this kinetic energy term would not necessarily be much larger than the 0.3 e.v. of reaction (3).

One can write many other reactions which conceivably could occur under the conditions of this experiment. There is no doubt some production of Hg^3P_0 metastable atoms from collision of Hg^3P_1 atoms with Hg^1S_0 atoms or hydrogen molecules. The possibility was considered that the equivalent of reaction (4) might occur through conversion of Hg^3P_1 atoms to Hg^3P_0 atoms by collision with hydrogen if the Hg^3P_0 atoms were unable to react efficiently with hydrogen to give a pressure decrease. The results of Meyer[8] (which we have confirmed with monochromatic λ 2537) indicate that the Hg^3P_0 atoms can react with hydrogen. The effective cross section for the reaction may be quite low and still give the observed augmented reaction rate with nitrogen added because, with the great excess of nitrogen used, the diffusion time of the Hg^3P_0 atoms (formed by collision of Hg^3P_1 atoms with nitrogen) to the wall would allow a great many collisions with hydrogen. At the pressure conditions of the present work the Hg^3P_0 atoms would mostly reach the wall (if the Hg^3P_0–H_2 cross section were low). However, against this mechanism for reaction (4) is the fact that the first vibrational quantum of hydrogen is approximately 0.5 e.v. which leads one to expect low probability of conversion of Hg^3P_1 to Hg^3P_0 atoms which involves only 0.218 e.v.(see ref. (4), p. 450, or ref. (3), p. 225).

(8) Meyer, *Z. Physik* **37**, 639 (1926).

On the basis of Reactions (1) to (4) one obtains an expression for the rate $R = -\mathrm{d}(H_2)/\mathrm{d}t$ in terms of the constants, concentrations, and I_a, which is the number of quanta absorbed per (cc. $\times$ sec.). Noting that the quantum yield, $\phi = R/I_a$, one obtains the expression:

$$\frac{1}{\phi} = \frac{k_2 F(Hg^1S_0)}{k_3(H_2)} + \frac{k_3 + k_4}{k_3}$$

If the postulated mechanism fits the reaction, the data of Fig. 3 plotted as $1/\phi$ *vs.* $1/(H_2)$ should give straight lines with slopes $k_2F(Hg^1S_0)/k_3$ and a common intercept of $(k_3 + k_4)/k_3$. Figure 4 shows the data at the three hydrogen pressures plotted for seven values of pressure of mercury vapor. It is seen that the plots do give quite closely a family of straight lines with a common intercept. The intercepts lie between 4.0 and 5.5 with an average about 4.5 for $1/\phi$. Since Curve A, Fig. 4, is for $(Hg^1S_0) = 0$, the value of $F(Hg^1S_0)$ is unity and the slope of this curve, 1.96, is the ratio k_2/k_3. The value of k_2 is the Einstein "A" coefficient for the transition $6^3P_1 \rightarrow 6^1S_0$ and has the value $1/\tau = 1/1.07 \times 10^{-7}$, hence $k_3 = 1/1.07 \times 10^{-7} \times 1.96 = 4.77 \times 10^6$. This is the velocity constant for the reaction (3) in the postulated mechanism and this work constitutes, so far as we are aware, the only attempt at its measurement for this classic reaction. The above constant gives the rate at 30° in molecules of hydrogen per cc. decomposed per second per millimeter of hydrogen pressure per unit concentration of Hg^3P_1 atoms in atoms/cc. If the hydrogen concentration is expressed in molecules per cc. instead of millimeters of pressure, k_3 becomes $4.77 \times 10^6/3.20 \times 10^{16} = 1.49 \times 10^{-10}$. It is of interest to calculate the collision cross section from this constant and to compare with the result obtained previously. In the collision frequency expression Z may be set equal to k_3 when $n_{H_2} = 1$ and $n_{Hg^*} = 1$. The value of σ^2 is found to be 2.64×10^{-16} cm.^{2} as against 2.50×10^{-16} found from consideration of the intercepts of Fig. 3 and published values of σ_Q^2.

It has been pointed out that the intercepts of the lines on Fig. 4 on the $1/\phi$ axis average about 4.5 which is, according to the postulated mechanism, $(k_3 + k_4)/k_3$. The value of k_4/k_3 is 3.5 and $k_4 = 3.5 \times 1.49 \times 10^{-10} = 5.22 \times 10^{-10}$. One would expect so far as the extrapolation to infinite hydrogen pressure, *i.e.*, $1/(H_2) = 0$, is valid that the intercept value, 4.5, would agree with the σ_Q^2/σ_D^2 ratio. It is larger than the ratios obtained using either of the σ_Q^2 values previously mentioned (8.6 and 6.01×10^{-16} cm.^{2}) and σ_D^2 (2.64×10^{-16}) which give 3.3 and 2.3, respectively. Larger values of σ_Q^2 have been reported but are considered less reliable.[3] This discrepancy, if real, is perhaps explainable on the assumption of a collision-induced emission of λ 2537 (by hydrogen on Hg^3P_1 atoms) with the line sufficiently broadened to allow these quanta to escape reabsorption. These quanta would be quenched from the stand-

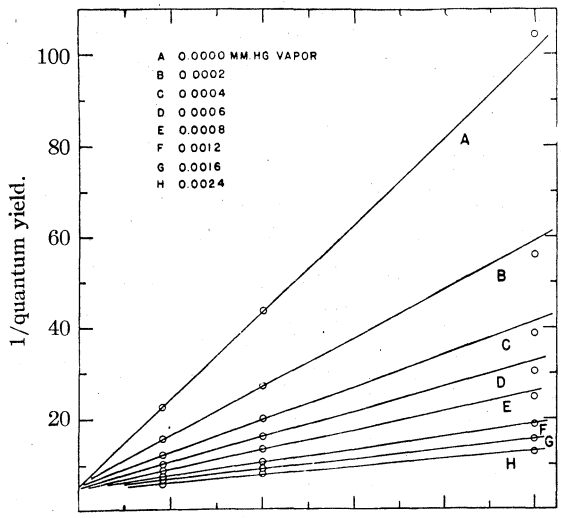


Fig. 4.

point of the present experiment but would show up as fluorescence in the quenching studies.

The ratios of the slopes of the lower lines of Fig. 4 to that of the upper line (A), for which $F(Hg^1S_0)$ is unity, are the values for $F(Hg^1S_0)$ for the various pressures of mercury vapor. These values are plotted in Fig. 5, Curve A. The ordinates of this curve are the probabilities, for the mercury vapor pressures in the particular vessel used, that a quantum of λ 2537 emitted as fluorescent radiation will escape reabsorption within the bounds of the vessel. The quantity $[1 - F(Hg^1S_0)]$ is then the probability that the fluorescent quantum will be reabsorbed, and, since the time spent by a quantum of energy as radiation is negligible compared to τ, the same quantity may be interpreted as the fraction of the quanta of energy, present in the system with the light source on, which are still present at the time, τ, after the light source is cut off. Also $[1 - F(Hg^1S_0)]^n$ is the fraction of quanta still in the system after $n\tau$. This leads to an exponential decay function for the intensity of radiation emitted after excitation is cut off and we may write approximately $I_t/I_0 = [1 - F(Hg^1S_0)]^n = e^{-\beta t}$ in which $t = n\tau$. The values of β calculated from $F(Hg^1S_0)$ are shown in Fig. 5, Curve C. It is possible to estimate β theoretically through a series of methods due to Milne, Zemansky, Samson, Kenty, summarized in reference (3), p. 228 *et seq.* It is necessary to consider a distance, l, through which the radiation must diffuse which we have estimated as 1.125 cm., the radius of the reaction vessel. The values of β so calculated are shown in Curve B, Fig. 5. The experimental values from $F(Hg^1S_0)$ deviate an average of 10% from the calculated values over the range of mercury vapor pressures shown. The agreement is of about the same order as that obtained by comparison of direct measurements of β with the calculated values.[3] Such close agreement must be regarded as fortuitous but the fact that it was possible to arrive, through treatment of the data of this paper, at the $F(Hg^1S_0)$ values which are consistent with existing theory and experiment applied to the "imprisonment" of resonance radiation in the strictly physical (not chemically reacting) system, mercury vapor, seems to support the essential validity of the data and its treatment.

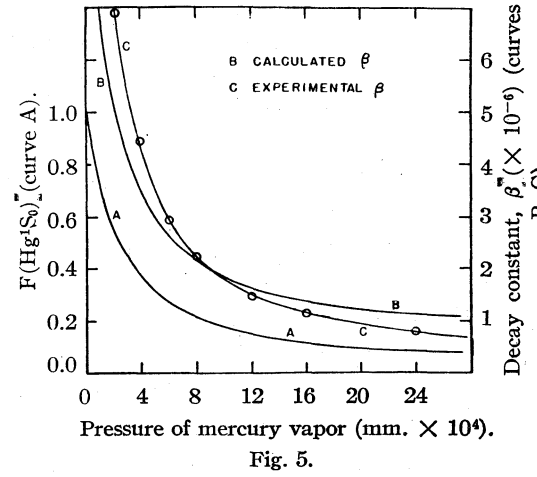


Fig. 5.

We have carried through an application of Milne's theory of the diffusion of "imprisoned" resonance radiation to calculate the number of Hg^3P_1 atoms present in the system and thence the rate of disappearance of hydrogen, *i. e.*, Curve B, C, D, Fig. 2. The expression for the rate involves two effective cross sections, one for reaction (3) of this paper and the other for over-all quenching of Hg^3P_1 atoms by H_2. It is found that rate curves of the general characteristics of B, C, D, Fig. 2 are obtained and that quantitative agreement with experiment is much better if the σ_D^2 and σ_Q^2 values 2.5×10^{-16} from this work and 8.6×10^{-16} cm.^{2} from ref. (3) both are used than if either value is used as the sole cross section involved.

The question arose in conversation with J. Franck as to the possibility that these experiments might be used to distinguish between the two proposed mechanisms involving direct dissociation of hydrogen molecules as against formation of mercury hydride in the process. If one assumes that the hydrogen in the mercury hydride is not cleaned up and is eventually returned as hydrogen to the gas and if one assumes that no other quenching processes than one of the two proposed are involved, a study of the quenching externally and hydrogen removal internally should be able to distinguish between the two mechanisms. One quantum per hydrogen molecule disappearing would be quenched in the first case and two quanta in the second case. Quenching measurements have been made giving an estimated quenching, averaged over the surface of a sphere concentric with and about the cylinder, of

3.5 times the quantum yield observed internally. This is again a measure of σ_Q^2/σ_D^2 and constitutes further confirmation that one or more other quenching processes than that resulting in hydrogen removal is in preponderance. It seems doubtful then that the two mechanisms can be distinguished by this means.

An important assumption upon which the validity of much of the interpretation of the data of this paper rests is that the cleanup of the supposed atomic hydrogen produced is complete. This would be a very difficult assumption to demonstrate conclusively by experiment but we have little doubt of its validity because of the evidence presented below. As mentioned in the **Experimental** section of this paper, all of the data presented were taken at the limiting condition of maximum rate following reoxidation of the copper and thorough outgassing of the vessel. The reproducibility and consistency of the data is in itself strong evidence of the essential completeness of the cleanup. It would be difficult to imagine a kind of adsorption process at the silicon dioxide and cupric oxide surfaces which consistently returned a constant fraction of the reaction products as hydrogen to the gas phase. The following experiment substantiates the assumption of complete clean-up. The reaction was carried out in a fused silica cell without any cupric oxide in it. The rate of reaction as observed on the Pirani gage under constant conditions (except for the inside walls) falls gradually to zero when the walls can no longer remove the products and complete recombination of hydrogen atoms then occurs. The rate becomes practically zero when amounts of hydrogen of the order of 100-fold those used in taking the data of this paper were consumed. When the reaction cell with its cupric oxide lining cylinder is used in a similar attempt to exhaust the capacity for removal of the reaction products it is found that the rate falls off less rapidly than in the former case and becomes flat at a fraction of the initial rate which agrees to within a few per cent. with the fraction of the internal area of the vessel which consists of cupric oxide. (These experiments were carried out with the mercury vapor pressure low in order to spread the reaction more uniformly through the vessel.) (One might be tempted to attribute the sustained behavior with cupric oxide to the steady conversion of hydrogen to water, hence due to the smaller heat conductivity of water, the Pirani gage would show a pressure decrease. However, the accommodation coefficients and C_V values of hydrogen and water are such that in the "free molecule" heat conduction range here applicable, water is 40% more effective than hydrogen in heat conduction from bright platinum.[9]) The interpretation then that we place on the above experiments is that both silicon dioxide and cupric oxide have the same initial efficiencies of removal of the reaction products and this is very unlikely unless both efficiencies are unity. That cupric oxide has sustained, constant efficiency is found in the extensive work done in this laboratory with the electron initiated mercury sensitized decomposition of hydrogen in which the reaction region is more completely surrounded with oxidized copper surface and the initial rates are maintained longer than with the silica, copper oxide cell. The electron work shows constancy of clean-up efficiency with varying reaction rate and with varying mercury pressure, complete quantitative reproducibility of data, and is entirely consistent with the assumption of complete clean-up efficiency.

Lastly, mentioned in connection with completeness of cleanup and general validity of the quantum yield measurements, an independent check was made of four points on Fig. 3. A new vacuum and gas handling system, new Pirani gage and electrical measuring system with new calibrations, new reaction cell with reaction volume more completely surrounded with cupric oxide, and a new photocell were used and the uranyl sulfate–oxalic acid actinometer, following the specifications and general procedures of Leighton and Forbes, was used to determine the lamp intensity. The quantum yields at each hydrogen pressure with mercury at 0° and with hydrogen at 0.11 mm. and mercury at 24° were determined. The four new values of ϕ averaged 1.5% (of ϕ) higher than the four original values with a maximum discrepancy of 5.5%, *i. e.*, a ϕ of 0.036 became 0.038 in the new determination.

Summary

The quantum efficiency of the Cario and Franck mercury sensitized decomposition of hydrogen with λ 2537 has been investigated as a function of mercury and hydrogen pressures. On the basis of the postulated mechanism the velocity constant and the effective cross section are determined for the interaction of Hg^3P_1 atoms and hydrogen resulting in disappearance of hydrogen from the gas phase, presumably through dissociation and removal of the resulting hydrogen atoms on cupric oxide or silicon dioxide walls. The contribution of the reabsorption of fluorescent radiation to the efficiency is singled out and from this the time decay constant of λ 2537 from pure mercury vapor in the reaction vessel after excitation is cut off is calculated and compared with physical theory and measurement. The evidence from several aspects indicates consistently that other quenching processes than that resulting in removal of hydrogen are effective and that the rate of quenching of Hg^3P_1 atom is several times as great as the rate of removal of hydrogen from the gas.

(9) Thomas and Olmer, THIS JOURNAL, **65**, 1036 (1943).

COLUMBIA, MISSOURI RECEIVED MARCH 6, 1948

[CONTRIBUTION FROM U. S. NAVAL RESEARCH LABORATORY]

The Solubility of Quartz in Sodium Carbonate Solutions at High Temperature

BY I. I. FRIEDMAN[1]

This work was undertaken as a preliminary investigation of the system at 300, 350, 400 and 450°, and is restricted to solutions in equilibrium with quartz.

To define completely this system at the liquidus it would be necessary to fix three independent variables. The usual variables which are experimentally controllable are the temperature and two others, such as total pressure, the partial pressure of one of the components of the vapor, and the liquid or vapor composition. The apparatus available did not permit sampling the liquid or vapor phases, nor was it possible to get accurate pressure measurements. However, while the following data do not define the system completely, they provide a valuable preliminary basis for such investigations.

Experimental

The runs were made by placing weighed blocks of quartz in 18-ml. pressure bombs together with weighed amounts of sodium carbonate, pipetting in 10 ml. of distilled water, sealing the bombs and allowing them to remain at a predetermined temperature. The bombs were continuously rocked to provide agitation. Further details of the equipment are given in a previous paper.[2] After equilibrating for from forty to one hundred and fifty hours, the bombs were removed from the furnaces and quenched by directing a stream of cold water onto them.

The sodium carbonate was reagent grade, and was dried at 120° for several hours. Quartz slabs (2.5 × 1.5 × 0.5 cm.), cut from piezo-electric grade natural quartz were used throughout.

Results and Discussion

It was noted in many runs at 400° and in all runs at 450° that considerable pressure was released upon opening the bombs after quenching. Evidently at these temperatures silica displaces carbon dioxide from the sodium carbonate, resulting in a high partial pressure of carbon dioxide in the vapor. This parallels the results of Morey and Fleischer[3] in the system K_2O–SiO_2–H_2O–CO_2, who found that the distribution ratio of carbon dioxide between the liquid and vapor increased in the direction of the vapor at 500° and K_2O–SiO_2 ratios above 1:1.

As a check on the solubility curves many runs were equilibrated at 450° and slowly cooled to various temperatures from 425 to 300°. They were then allowed to equilibrate at the lower temperature and quenched. In all cases all of the excess quartz recrystallized on the remains of the original quartz block. This indicated that: (1) The curves represent true equilibrium values; (2) Quartz can be grown from sodium carbonate solutions by slowly cooling a saturated solution of quartz in sodium carbonate in contact with a quartz seed plate.

Figure 1 shows the solubility of silica in sodium carbonate solution as a function of sodium carbonate concentration at various temperatures. The spread of experimental points, particularly at 450° can be explained by the high temperature dependence of the solubility at the higher temperatures. The bombs that were used varied slightly (5% max.) in the size of the chamber. This variation in the degree of filling would also contribute to the error.

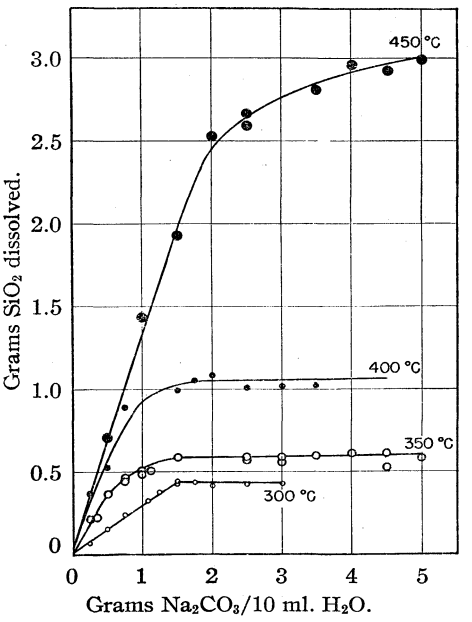


Fig. 1.

The leveling off of the solubility curves with increasing sodium carbonate concentration might be due to the formation of a solid phase containing sodium oxide. Sodium carbonate crystals were found in most runs, but it is not clear if the crystals formed during the quench or represent a stable solid phase at the temperature of the runs.

Upon opening the quenched runs a hard water-soluble glass was found in most of the bombs in addition to the liquid and crystalline phases. The glass was not found in runs made at 300° that contained less than 1.5 g. of sodium carbonate, nor was it observed in runs made at 450° that contained over 3.5 g. of sodium carbonate. These glasses are similar in character to the glasses observed in the Na_2O–SiO_2–H_2O system,[2] and can be assumed to have been liquid at the temperature of the runs. It seems quite probable that the liquid immiscibility reported in the Na_2O–SiO_2–H_2O sys-

(1) Present address: Department of Geology, University of Chicago, Chicago 37, Illinois.

(2) Tuttle and Friedman, THIS JOURNAL, **70**, 919 (1948).

(3) Morey and Fleischer, *Bul. Geo. Soc. Am.*, **51**, 1035 (1940).

tem extends into the Na_2O–SiO_2–H_2O–CO_2 system. However the correctness of this assumption will have to be checked by a more elaborate investigation of this system.

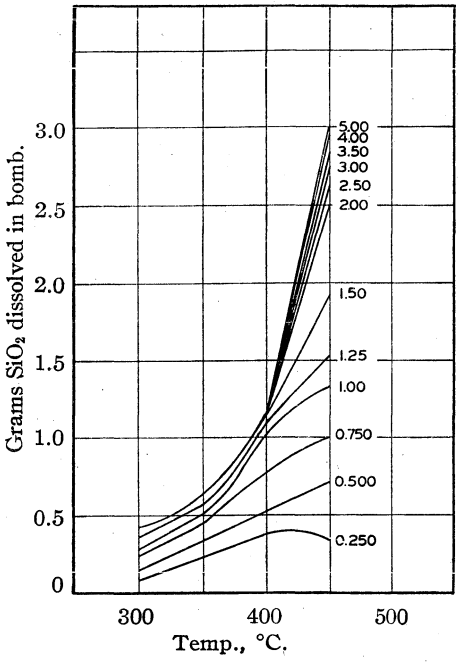


Fig. 2.

As can be seen from Fig. 2, this system would be a desirable one from which to grow quartz. The steep slope of the Solubility *vs.* Temperature curve would be favorable for growing quartz by the temperature lowering as previously stated, while the low solubility of quartz in sodium carbonate solutions as compared to its solubility in sodium hydroxide solutions, as shown in Table I, suggests that carbon dioxide might be used to displace quartz from sodium hydroxide solutions at constant temperature.

TABLE I

Temp., °C.	% Na_2O	Solubility, of quartz, g./l. NaOH solutions	Na_2CO_3 solutions
300	1	20	5
	5	135	28
	15	514	43
350	1	25	13
	5	152	50
	15	515	60
400	1	35	22
	5	155	90
	15	560	105
450	1	35	24
	5	163	124
	15	560	285

The author again wishes to emphasize the preliminary nature of the present paper. Much careful experimentation remains to be done before our understanding of equilibrium in multicomponent systems containing volatile and non-volatile components can be extended very far.

The assistance rendered by Mr. Charles Jackson was of great aid in carrying out the experimental work.

WASHINGTON, D. C. RECEIVED FEBRUARY 24, 1948

[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Heats of Combustion of Some Organic Nitrogen Compounds

BY D. J. SALLEY AND J. B. GRAY[1]

The need for accurate values of heats of combustion for thermodynamic calculations has often been emphasized, and the lack of such data seems especially noticeable for organic compounds containing nitrogen. We therefore record here heats of combustion, determined with relatively high accuracy, of eight such compounds: cyanamide, dicyandiamide, melamine, 3-cyanopyridine, phthalonitrile, dimethylol urea, diisopropyl cyanamide, and diisopropyl carbodiimide.

Experimental

Apparatus and Procedure.—The bomb calorimeter used was modeled after that of Dickinson,[2] being a replica of that of Huffman and Ellis,[3] and of Richardson and Parks[4]; the calorimeter was in fact made in the shops of the California Institute of Technology.

The samples were burned in a Parr bomb (380 ml. capacity), containing initially 1 ml. of water and commercial tank oxygen at 30 atm. pressure at about 24°. The air was usually flushed out by two fillings with oxygen to 15 atm. pressure when solid samples were burned, but no flushing was made with liquids. The weight of water for the calorimeter, usually 2770 g., was measured to 0.05 g. on a high capacity balance.

Pellets of solid samples were weighed in a platinum crucible to 0.05 mg. on an analytical balance, after they had been kept in a desiccator over phosphorus pentoxide for several days. As far as is known, the compounds are not hygroscopic (except cyanamide, discussed below), and no changes in the heats of combustion with drying times of three to ten days were noticed. For liquids, thin-walled soft glass ampoules were completely filled by means of a fine hypodermic syringe, through a single stem, which was then sealed off. The liquids were not freed of any dissolved air.

Either of two methods of firing the sample have been employed, the platinum wire-string fuse of Richardson and Parks,[4] or the usual iron wire. In the former, the electrical energy (*EIT*) introduced was obtained by accurate measurements of voltage, current, and time. These

(1) Present address: Guymon, Oklahoma.
(2) Dickinson, *Bull. Bureau of Standards*, **11**, 243 (1915).
(3) H. M. Huffman and E. L. Ellis, THIS JOURNAL, **57**, 41 (1935).
(4) J. W. Richardson and G. S. Parks, *ibid.*, **61**, 3543 (1939).

TABLE I

CALIBRATION OF CALORIMETER

Obs. rise, °C.	Cor. rise, °C.	Benzoic acid, wt. in vacuum, g.	Heat from benzoic acid, cal.	Heat from *EIT* + string, cal.	Heat from HNO_3, cal.	Energy equiv. cal./deg.	Dev. from mean cal./deg.
1.96923	1.97697	1.00010	6318.2	21.5	1.3	3207.4	+0.3
1.97121	1.97886	1.00102	6324.0	22.6	1.3	3207.9	+ .8
1.97270	1.98074	1.00179	6328.9	23.2	1.3	3207.6	+ .5
2.14473	2.15266	1.08907	6880.3	20.2	1.4	3206.2	− .9
1.97062	1.97856	1.00040	6320.1	23.9	1.3	3207.1	.0
1.86123	1.86878	0.94462	5967.7	24.3	1.3	3207.1	.0
2.13143	2.13995	1.08183	6834.6	25.8	1.3	3206.4	− .7

Mean = 3207.1 cal./g.

Calibration error = ±0.016%

were facilitated by an auxiliary circuit so arranged that on closing the switch to fire the charge the current reached a steady value within a small fraction of the firing time. Nearly identical current and time conditions were maintained from run to run, and the *EIT* introduced was checked frequently by direct measurement of the rise in temperature of the calorimeter in blank runs. The string, conditioned and weighed at 73° F. and 50% R. H., had a heat of combustion of 3950 calories per gram. The energy correction when an iron wire fuse was employed was determined by independent measurement of the temperature rise produced by the burning fuse alone in blank runs.

The temperature rise in the calorimeter was measured by a platinum resistance thermometer calibrated by the Bureau of Standards, a Mueller resistance bridge, and a high sensitivity galvanometer. A change of 0.00003 ohm (0.0003°) in the resistance of the thermometer caused a shift of 1 mm. in the reflection from the galvanometer mirror on the scale. The galvanometer was used as a null instrument, the time at which a predetermined resistance was reached being recorded on a drum-type chronograph which was precise to 0.1 sec.

Two methods of determining the corrected temperature rise have been employed, that described by Dickinson,[5] and that by Eckman and Rossini.[6] When using the former method, the jacket was at 25°, and in the latter at 26.1°. In either case the initial temperature of the run was so arranged that the average temperature of the combustion was 25 ± 0.1°. Jacket temperatures were maintained constant to at least 0.001°.

The nitric acid produced in the combustion was determined by titration with standardized alkali using brom cresol green as the indicator. The thermal correction was calculated on the basis of $\Delta H_R = -15{,}070$ cal./mole,[7] which yields 13,950 cal. evolved for one mole of aqueous acid formed in the bomb process. For all the nitrogen compounds the nitric acid correction was relatively high, 0.3 to 0.7% of the total heat involved, and a change of 1000 cal. in the value of 13,950 cal. for nitric acid formation can effect changes of 0.02 to 0.05% in the final figures for the heats of combustion.

Units.—The unit of energy used is the defined calorie = 4.1833 int. joules. The unit of mass is the gram true mass derived from the weight in air against brass weights. The appropriate buoyancy correction depends on the density of the substance and this was obtained from the literature or measured independently. 1947 atomic weights[8] were used in calculating molecular weights.

Calibration.—The calorimeter was calibrated by burning benzoic acid (Bureau of Standards standard sample 39f; heat of combustion 26.4284 int. kj./g.) under conditions meeting as closely as possible the standard calorimetric conditions specified by the Bureau of Standards. Deviations from the specifications were so small as to require an entirely negligible change (0.003%) in the NBS value for the benzoic acid. Table I presents some early determinations which were carried out using the platinum wire-string fuse for firing, and the Dickinson procedure for correcting the temperature rise. The figures recorded are the experimental values of the energy equivalent of the bomb and contents. These runs give an indication of the precision of the experimentation; the calibration error shown is calculated according to Rossini.[9] Numerous calibrations made from time to time have shown an even better degree of precision. No marked advantage in precision has been found between the various procedures tested.

Materials.—All of the compounds were purified by various members of these Laboratories or of the Calco Chemical Division of the American Cyanamid Company, and analyses were made by our Analytical Department. Nitrogen analysis was obtained in several instances, but since it is not a very good criterion of purity with these compounds, whenever possible, analytical procedures or other means of characterization specific for the compound in question were employed.

Cyanamide.—Free cyanamide was recrystallized from ether, then vacuum distilled at whatever pressure was obtainable with a mercury pump when the melt was held at 80° and the distillate was trapped at 0°. Ampoules of the material, filled as described in the following, showed only a trace of dicyandiamide, the only likely impurity.

The handling of cyanamide deserves special mention. This material is a solid melting at about 41°, but its hygroscopic and corrosive nature precludes pelleting. However, its low melting point allowed it to be handled as a liquid. The door of an electric oven was fitted with two sleeves ending in rubber gloves. Trays of Drierite and Ascarite were placed in the oven to absorb water vapor and carbon dioxide. The temperature was kept at 50–60°. A hypodermic syringe and glass ampoules were placed in the oven several hours before use. The cyanamide, in an evacuated flask, was melted rapidly under a steam jet, then opened inside the oven. A glass tube having a fitted ground joint was substituted for the needle, and the molten material quickly drawn into the syringe; the needle was then replaced for filling the ampoules. Since the rather high viscosity of the melt made the expulsion of the liquid through the fine needle difficult, it was convenient to clamp the syringe firmly in a small stand which also carried a small adjustable platform on which the ampoule rested. After filling all the ampoules they were removed from the oven one by one and sealed off. Since supercooling often took place, each bulb was chilled with a piece of ice to induce crystallization. In the molten state cyanamide converts slowly to dicyandiamide so that all the operations were carried out as rapidly as possible. To insure consistent firing of these samples

(5) H. C. Dickinson, *Bull. Bureau of Standards*, **11**, 189 (1914).

(6) J. R. Eckman and F. D. Rossini, *Bur. Standards J. Research*, **3**, 597 (1929); Rossini, *ibid.*, **6**, 1 (1931).

(7) Tables of Selected Values of Chemical Thermodynamic Properties, Series I, Table 8–1 and 18–6, National Bureau of Standards, March 31, 1947.

(8) G. P. Baxter, M. Guichard and R. Whytlaw-Gray, *J. Chem. Soc.*, 983 (1947).

(9) F. D. Rossini, *Chem. Rev.*, **18**, 235 (1935).

when using the iron wire method, small weighed disks of filter paper (0.011–0.012 g.; heat of combustion, 3992 cal./g.) were stuck to the ampoule by a tiny smear of water glass. This technique of handling hygroscopic solids has been used satisfactorily with other such materials of sufficiently low melting point.

Dicyandiamide.—Commercial material was twice recrystallized from water. Nitrogen analysis showed 66.54%, indicating a purity of 99.82%.

Melamine. This sample was purified by recrystallization from dilute sodium hydroxide. Specific analysis for melamine showed it to be 99.7% pure, free of ammeline and ammelide, with less than 0.01% ash.

3-Cyanopyridine.—This compound, prepared from 3-bromopyridine by reaction with cuprous cyanide, was twice redistilled. The product of the second distillation boiled constantly at 98° at 23 mm. and melted at 49–50°. The nitrogen analysis was: found 26.66%, theoretical 26.90%.

Phthalonitrile.—A commercial material was purified by recrystallization from alcohol; m. p. 138.5–140°. Nitrogen analysis was 21.65% *versus* 21.87% theoretical.

Dimethylol Urea.—This compound was recrystallized from 75% alcohol. It showed a m. p. of 137–139° with decomposition. Nitrogen analysis was 23.18% found, 23.33% theoretical.

Diisopropyl Cyanamide and Diisopropyl Carbodiimide.—Both of these compounds were purified by several fractional distillations. The former boiled at 75° at 5 mm., the sample being a middle cut. The latter boiled at 25 mm., a middle cut being taken; infrared examination showed that it conformed to other samples of high purity.

Data

As a typical example, Table II presents the experimental data for the heat of combustion runs on melamine. The Rossini method of correcting for the temperature rise was followed in this case, K and U being the heat leak corrections. The calorimeter calibration had also been done using this method. ΔR_i is the ignition correction (*EIT* and string), and ΔR_n is the correction for the nitric acid formed. These quantities as well as the temperature rise R, are in ohms, while the energy equivalent obtained in calibration runs is stated in cal. per ohm. The quantity, $-\Delta U_{B/m}$, in this and the following table, represents the heat evolved per gram in the isothermal bomb process at 25°. Correction to the isothermal reaction using known or estimated specific heats was negligible, being in all cases less than 0.01%.

TABLE II

DATA ON HEAT OF COMBUSTION OF MELAMINE

Wt. in vacuum, g.	ΔR obs., ohm	K, ohm $\times 10^3$	U ohm $\times 10^4$	ΔR_i ohm $\times 10^4$	ΔR_n, ohm $\times 10^3$	ΔR corr., ohm	$-\Delta U_{B/m}$ cal., g.
1.71222	0.20620	2.545	4.97	7.00	1.194	0.20126	3735.2
1.70679	.20540	2.472	3.71	7.29	1.215	.20061	3735.0
1.71574	.20700	2.538	9.13	6.94	1.173	.20168	3735.4
1.70903	.20560	2.456	2.30	7.87	1.150	.20098	3736.9
1.71390	.20620	2.459	3.48	6.64	1.180	.20155	3736.9
1.71530	.20630	2.425	2.02	6.87	1.252	.20173	3737.2
						Mean	3736.1

Reaction error ±0.021%; precision error ±0.028%. Energy equivalent of calorimeter 31777.1 cal./ohm.

In Table III there are collected the data on the eight compounds burned. The headings are self-explanatory, except perhaps that of the seventh column. This is the "precision error" calculated using an assigned error of 0.010% for the heat of combustion of benzoic acid, a "calibration error" of 0.016%, and the "reaction error" that obtained in each case. The Washburn correction[10] involved in calculating ΔU_R was derived on the basis that the ternary mixture of nitrogen, oxygen, and carbon dioxide behaved like the binary mixture, oxygen and carbon dioxide; we are indebted to Mr. A. B. Bestul for these calculations. The heats of formation of the compounds from the elements, ΔH_f, were calculated using 94,051.8 and 68,317.4 cal./mole for the heats of formation of gaseous carbon dioxide and of liquid water,[11] respectively.

Discussion

The precision of the calorimetric procedure, as indicated by the calibration runs, appears to be entirely satisfactory. This is further borne out by the fact that equally good results have been obtained with other non-nitrogen compounds (not published). However, the results with the nitrogen materials have never reached the same precision. This may have been due to irregularities in the course of the combustion process. Some support for this view is provided by the fact that ignition difficulties were often encountered, and that incompleteness of combustion (as evidenced by carbon deposition) was rather frequent. It seems evident that to obtain highest precision the combustion process for nitrogen compounds would require detailed study, and that direct determination of carbon dioxide and the nitrogen oxides

TABLE III

HEATS OF COMBUSTION AND FORMATION AT 25°

Substance	Formula	Mol. wt.	Density	No. of runs	$-\Delta U_{B/m}$, cal./g.	Prec. err., %	$-\Delta U_R$, kcal./mole	$-\Delta H_R$, kcal./mole	ΔH_f, kcal./mole
Cyanamide(s)	CH_2N_2	42.042	1.282	6	4206.4	0.069	176.72	177.20	14.65
Dicyandiamide(s)	$C_2H_4N_4$	84.084	1.40	4	3943.1	.036	331.29	331.88	7.14
Melamine(s)	$C_3H_6N_6$	126.126	1.573	6	3736.1	.028	471.22	471.76	− 15.35
3-Cyanopyridine(s)	$C_6H_4N_2$	104.108	1.159	4	7181.4	.027	747.14	747.73	46.78
Phthalonitrile(s)	$C_8H_4N_2$	128.128	1.125	4	7457.3	.025	954.81	955.40	66.35
Dimethylol urea(s)	$C_3H_8N_2O_3$	120.110	1.49	4	3202.0	.043	384.34	384.64	−170.78
Diisopropyl cyanamide(l)	$C_7H_{14}N_2$	126.198	0.949	7	8899.9	.066	1122.81	1124.88	− 11.70
Diisopropyl carbodiimide(l)	$C_7H_{14}N_2$	126.198	0.909	5	8958.0	.051	1130.14	1132.21	− 4.37

(10) E. W. Washburn, *Bur. Standards J. Research*, **10**, 525 (1933).

(11) D. D. Wagman, J. E. Kilpatrick, W. J. Taylor, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **34**, 143 (1945).

would be necessary. In the present work, no direct test for completeness of combustion by measurement of carbon dioxide or carbon monoxide formation was made on any of the compounds.

The accuracy of the values reported here is almost certainly poorer than the precision of the determinations, since the purity of the samples—in spite of the effort to obtain high-grade materials—probably is the limiting factor. The compounds were all taken as 100% pure even though in some instances the analysis throws some doubt on this, and in the case of the liquids no attempt was made to correct for any dissolved gases. This appears to be the best policy to follow, first, because the significance of the analysis may be questioned and, second, because the kind and amount of impurity is indeterminate. The cyanamide, dicyandiamide and melamine figures are considered to be the most reliable in this respect.

The heats of combustion of cyanamide, dicyandiamide and melamine were measured by Lemoult,[12] his figures being 171.6, 328.7 and 469 kcal./mole, respectively. These values are nominally 5.6, 3.2 and 2.8 kcal./mole lower than those obtained here. Since the corresponding heats of formation have rather low absolute values, these differences naturally result in large percentage differences between the old and new heats of formation. The present values are considered to be the more trustworthy. No values have been located in the literature for the other substances.

(12) P. Lemoult, *Ann. chim. phys.*, [7] **16**, 338 (1898). See also F. R. Bichowsky and F. D. Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936, p. 50.

Acknowledgment.—Acknowledgment is made to Mr. P. Adams, Dr. P. R. Averell, Dr. I. Heckenbleikner, Dr. R. F. Stamm, and members of the Analytical Department of these Laboratories for the preparation, purification, and analysis of the compounds used, and to the Directors of these Laboratories for permission to publish these results.

Summary

A bomb calorimeter, calibrated with benzoic acid, has been used for determining the heats of combustion of eight organic nitrogen compounds at 25° and constant volume. From these data, the corresponding heats of combustion and of formation at constant pressure have been calculated. The substances burned were cyanamide, dicyandiamide, melamine, 3-cyanopyridine, phthalonitrile, dimethylol urea, diisopropyl cyanamide, and diisopropyl carbodiimide.

STAMFORD, CONN. RECEIVED MARCH 30, 1948

[CONTRIBUTION FROM THE STAMFORD LABORATORIES OF THE AMERICAN CYANAMID CO.]

Some Amides and Esters of Fluoroacetic Acid

BY J. C. BACON, C. W. BRADLEY,[1] E. I. HOEGBERG, PAUL TARRANT[2] AND J. T. CASSADAY

The toxicity of certain derivatives of fluoroacetic acid to insects and rodents was established in these Laboratories several years ago and has led to the synthesis of additional compounds of this type.

The problem of preparing economically a simple derivative of α-fluoroacetic acid to be used as a starting material for the rest of these syntheses was solved by the discovery of a method for converting chloroacetamide into fluoroacetamide by reaction with potassium fluoride. This method is discussed below. The literature[3-5] has subsequently indicated that during the course of our investigations methods were simultaneously in the process of development in England, Poland, and elsewhere in the United States for the large-scale production of methyl, ethyl and sodium fluoroacetates, the latter being known as rodenticide "1080." Analytical methods have been reported[4] for the determination of extremely small traces of fluorine in these and similar types of materials and reports[6,7] have also been published covering the effect of "active" fluorine compounds on warm-blooded animals.

Numerous unsuccessful attempts were made to replace the chloro group of chloroacetic acid and ethyl chloroacetate using hydrogen fluoride alone or in combination with antimony trifluoride.

Fluoroacetamide was finally prepared by the reaction of chloroacetamide with potassium fluoride. A mixture of the fluoro- and chloroamides was obtained both by dry distillation under reduced pressure and by distillation at atmospheric pressure using xylene as a carrier. The yields of fluoroacetamide based upon the chloroacetamide consumed were greater than 50%. The mixture of amides was converted into a

(1) Deceased.

(2) Present address: University of Florida, Gainesville, Florida.

(3) H. McCombie and B. C. Saunders, *Nature*, **158**, No. 4011, 382 (1946).

(4) W. B. Reed for R. L. Jenkins and E. E. Hardy, Office of Technical Service Report, PB 24903; C. W. Mason and C. B. De La-Mater, PB 5484; J. H. Yoe, Jason M. Salsbury and James W. Cole, PB 5955, PB 4220, PB 6020, PB 6021; John H. Yoe and Lyle G. Overholser, PB 4216; Benjamin Witten, Bernard Gehauf and Melvin M. Falkof, PB 17207; Joseph M. Sanchis, PB 9511; Irving S. Goldman, Mary Catherine Flannery, Louis J. Arent, John B. Hoag, Arthur M. Buswell, PB 9510; Charles C. Price and William G. Jackson, PB 5904; Nathan L. Drake, PB 5863, R. H. Kimball and Lewis E. Tufts, PB 52707.

(5) E. Gryszkiewics-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413–418 (1947).

(6) Maynard B. Chenoweth and Alfred Z. Gilman, PB 9577; Sidney P. Colowick, Louis Berger and Milton W. Slein, PB 5873.

(7) Marais and Onderstepoort, *J. Vet. Sci. Animal Ind.*, **18**, 203 (1943); **20**, 67 (1944).

mixture of ethyl chloro- and fluoroacetates by the use of ethanol and hydrogen chloride or sulfuric acid, and the combined esters were separated by fractional distillation. The pure ethyl fluoroacetate was then converted by customary methods into other esters or amides.

A similar conversion of ethyl bromoacetate into the corresponding fluoro ester was effected by refluxing with potassium fluoride or, in lower yield, with thallous fluoride. The use of bismuth trifluoride produced none of the desired ester.

Since potassium fluoride had proved useful in the production of fluoroacetamide from chloroacetamide as outlined above, other fluorides were tested. Sodium fluoride, when tried in the fusion method for the production of the amide and in the attempted conversion of ethyl bromoacetate to the fluoroacetate, gave none of the desired products. When ammonium fluoride was used in the fusion method, a small amount of fluoroacetamide was isolated.

Another relatively economical material, ammonium glycolamide sulfate, has been converted into fluoroacetamide by fusion with potassium fluoride.[8]

Experimental

The Preparation of Fluoroacetamide from Chloroacetamide

A. Dry Fusion Method.—Chloroacetamide, 187 g. (2.0 moles), and anhydrous potassium fluoride, 200 g. (3.5 moles), were ground together in a ball mill for two hours. The reagents were placed in a one-liter three-necked flask and heated with a Glas-Col mantle. The reaction was carried out at a pressure of about 25 mm. produced by a water pump. When the temperature of the mixture reached 130°, distillation began and continued until 121 g. of solid condensed in the receiver. This material, based on a fluorine analysis, appeared to be 82.2% fluoroacetamide, a yield of 64.5%.

B. Inert Carrier Method.—A method for preparing fluoroacetamide in xylene has been described by one of the authors.[9] Although the yield (55%) was somewhat lower than that obtained in the dry fusion method, a purer product was obtained. The use of tetrachloroethylene (b. p. 121°) instead of xylene resulted in a slightly lower yield of product.

The Preparation of Ethyl Fluoroacetate Using Potassium Fluoride.—Ethyl bromoacetate, 110 g. (0.66 mole), and 75 g. (1.32 moles) of anhydrous potassium fluoride were placed in a 500-ml., round-bottomed flask equipped with a 12″ Vigreux column and a variable take-off fractionating head. The column was maintained under total reflux until the vapor temperature reached 120°, whereupon the ethyl fluoroacetate was stripped off. Heating was continued for sixteen hours, during which time 59 g. of distillate was collected. Refractionation gave 32 g. (45% yield) of ethyl fluoroacetate, b. p. 117.5°.

The Preparation of Ethyl Fluoroacetate Using Thallous Fluoride.—Ethyl bromoacetate, 60 g. (0.36 mole), thallous fluoride, 72 g. (0.32 mole), and ethanol, 50 ml., were placed in a round-bottomed flask with a reflux condenser and heated on a steam-bath for twenty-eight and one-half hours. At the end of this period the mixture was filtered and the liquid distilled under reduced pressure. A refractionation gave 5 g. (13% yield) of ethyl fluoroacetate, b. p. 115.5–118°.

The Esterification of Crude Fluoroacetamide.—The esterification of fluoroacetamide was carried out by allowing it to react with ethanol in the presence of enough acid to neutralize the ammonia formed. A typical example of an experiment using gaseous hydrogen chloride as the neutralizing agent follows:

The esterification of the crude amides prepared from a mixture of chloroacetamide and potassium fluoride in a 1:2 ratio was carried out in a two-liter, three-necked flask equipped with reflux condenser, stirrer and inlet for hydrogen chloride. The hydrogen chloride was passed slowly into a mixture of 462 g. of crude amide and 328 g. (410 ml.) of absolute ethanol. During the first two hours 90 g. of hydrogen chloride was absorbed; 200 g. was added during the next hour. The mixture was then allowed to stand for about thirty-six hours.

The slurry of ammonium chloride and esters was centrifuged and the solid washed with 75 ml. of ethanol. The filtrate and wash solutions were treated with about 400 ml. of saturated calcium chloride solution. The organic layer was separated and washed with 400 ml. of a saturated sodium bicarbonate solution and again with a calcium chloride solution. The product was dried with anhydrous sodium sulfate and distilled at atmospheric pressure through a 24″ column packed with glass helices, giving 272 g. of ethyl fluoroacetate boiling at 115.5–120° and 133 g. of ethyl chloroacetate. Since analysis had shown the crude amide to contain 64.7% fluoroacetamide and 32.9% chloroacetamide, the conversions of the two amides to the corresponding esters were 66 and 67%, respectively.

It was later found that sulfuric acid could be substituted for hydrogen chloride without decreasing the yield of ethyl fluoroacetate. Although the recovery of ethyl chloroacetate was not complete, the ease with which the reaction could be carried out offset this disadvantage.

Preparation of Purified Fluoroacetamide.—Fluoroacetamide was prepared from ethyl fluoroacetate and aqueous ammonia by a method analogous to one commonly used for the preparation of chloroacetamide.[10] However, presumably because of the more stable fluorine atom in the molecule, the yields were usually 90% or better. Several small batches were synthesized to give a total of 457 g. melting at 107–108°.

Ammonium Glycolamide Sulfate.—Anhydrous glycolonitrile was added gradually with vigorous stirring to an equimolecular quantity of 100% sulfuric acid below 60°; then the reaction mixture was added to a slight excess of aqueous ammonia with cooling.[11] Because the reaction product of glycolonitrile and sulfuric acid often solidified immediately to a hard cake, a modification of this procedure was also used, whereby anhydrous glycolonitrile (114 g., 2 moles) was added gradually at 55–65° to 95.5% sulfuric acid (392 g., 3.8 moles) with mechanical stirring. The viscous, liquid reaction mixture was then added with ice-bath cooling to a slurry of powdered calcium carbonate (200 g., 2 moles) in 28% aqueous ammonia (750 ml., 11 moles), and the reaction mixture was allowed to stand for about twelve hours, followed by warming to 80° for one-half hour to insure complete reaction. The calcium sulfate was removed by filtration and the filtrate was concentrated under water pump vacuum to a small volume, cooled and filtered to give 402 g. of ammonium glycolamide sulfate contaminated with a little ammonium sulfate. Recrystallization of the crude product from hot water gave a purified product as colorless crystals melting at 183–185° (cor.).

Anal. Calcd. for $C_2H_8N_2O_5S$: N, 16.4; SO_4, 55.8. Found: N, 16.3; SO_4, 56.3.

Conversion of Ammonium Glycolamide Sulfate to Fluoroacetamide.—Ammonium glycolamide sulfate (180 g., 1.05 moles) and potassium fluoride (116 g., 2 moles) were mixed in a ball mill for three hours, during which time some ammonia was liberated. The resulting powdered mixture was placed in a one-liter, two-necked distilling flask equipped with a thermometer and air conden-

(8) J. C. Bacon, U. S. Patent 2,416,607 (1946).

(9) C. W. Bradley, U. S. Patent 2,403,576 (1946).

(10) Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 153.

(11) Attempts to add concentrated sulfuric acid to anhydrous glycolonitrile, rather than the reverse procedure, caused violent exothermic decomposition and carbonization.

TABLE I

ESTERS OF FLUOROACETIC ACID, FCH_2COOR

R	% Yield	B. p., °C.	$n^{25}D$	Sap. equiv. Calcd.	Sap. equiv. Found	% Analyses Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found
2-Ethylhexyl[12]	79.5[a]	65–68 (2 mm.)	1.4173			63.1	62.5	10.1	10.1 9.9	10.0	9.9
1-Dodecyl	59	106–128[b] (1 mm.)	1.4317	246	244	68.2	68.9	11.0	11.2 11.4	7.7	7.7

[a] On the basis of ethyl fluoroacetate converted. [b] Distilled without fractionation.

TABLE II

AMIDES OF FLUOROACETIC ACID, FCH_2CONHR

R	Yield, %	M. p.,[c] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine[e] Calcd.	Fluorine[e] Found
Cyclohexyl[a]	61	99–100	60.3	60.3 60.3	8.9	9.0 9.2		
1-Dodecyl[a]	74	63–66	68.5	68.8	11.5	11.5	7.7	8.0
1-Octadecyl[a]	39	73–75	72.8	72.5 72.4	12.2	12.1 12.2	5.8	5.9
4-Tolyl[b]	77[d]							

[a] Prepared by Procedure A. [b] Prepared by Procedure B; synthesized by a different method by C. C. Price and W. G. Jackson, PB 5904 (1946); THIS JOURNAL, **69**, 1065 (1947). [c] Corrected. [d] Crude yield; m. p. of purified sample checks with that of Price and Jackson. [e] Difficulties were sometimes encountered in obtaining fluorine analyses which checked closely.

ser. The flask was heated under reduced pressure with the temperature maintained below 200°. Twenty-nine grams of solid sublimed from the mixture at a vapor temperature of about 140°. The crude solid was recrystallized from ethanol to give 20 g. (25% of the theoretical) of fluoroacetamide, m. p. 104°.

Esters of Fluoroacetic Acid.—Esters of greater chain length than ethyl were prepared by heating ethyl fluoroacetate (usually in about 5% excess) with an equivalent amount of the higher alcohol to 100–170° in the presence of a trace of *p*-toluenesulfonic acid as catalyst, and distilling the liberated ethanol as it was formed, thus driving the reaction to completion. Two or three hours were normally required. The reaction product was washed with saturated sodium bicarbonate solution, dried over calcium sulfate, and distilled. Examples of esters prepared by this method are listed in Table I.

Amides of Fluoroacetic Acid.—Either of two procedures was used: **Procedure A.** Ethyl fluoroacetate was heated with an equivalent amount of the proper amine to 100–160° until approximately the theoretical amount of ethanol had been distilled off and measured. The reaction product was purified by distillation if a liquid, or by recrystallization from heptane if a solid. **Procedure B.** Fluoroacetamide and the proper amine were heated in equivalent amounts in glacial acetic acid on a steam-bath for about three hours, then thrown into excess cold water and separated. The crude product was recrystallized from aqueous ethanol for purification.

Several of the amides prepared are listed in Table II.

Acknowledgment.—We are indebted to the Analytical Laboratories for the analyses shown above, to the Chemotherapy Division for preliminary toxicological data, and to the Agricultural Chemicals Laboratories for numerous insecticidal evaluations as well as to Drs. R. C. Swain and J. T. Thurston who offered considerable helpful advice during the course of this problem.

Summary

1. Some new methods for the preparation of fluoroacetamide are described. Two convenient methods for the preparation of N-substituted fluoroacetamides are also given.

2. Three new amides and one new ester of fluoroacetic acid are listed.[13]

STAMFORD, CONN. RECEIVED MARCH 20, 1948

(12) J. L. Horsfall, U. S. Patent, 2,409,859 (1946).

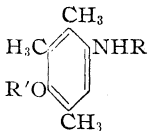
(13) The toxicity of these types of compounds to warm-blooded animals both orally and by skin absorption is high, and due caution should be exercised in handling them.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

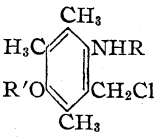
Polyalkylbenzenes. XXXIV.[1] The Reaction between Polymethyl-*p*-methoxyanilines and Formaldehyde

BY LEE IRVIN SMITH AND W. M. SCHUBERT[2]

If the reaction between formaldehyde, hydrochloric acid, and a polymethyl-*p*-aminophenol or some derivative of it (I, II, III) could be controlled in such a way that simple chloromethylation resulted, the products, such as IV, would be of great value as starting materials for synthesis of 6-hydroxytetrahydroquinolines, the nitrogen analogs of the tocopherols. The reaction between simple



I, R′ = CH_3; R = H
II, R′ = CH_3; R = —CHO
III, R′ = CH_3; R = Ac

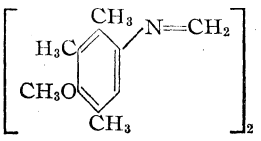


IV

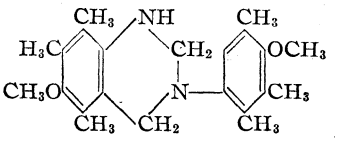
aromatic amines and formaldehyde, under a variety of conditions has been rather extensively studied[3]; in general, when the *p*-position of the aromatic amine is occupied by a substituent, the primary products have included *o*-aminobenzylanilines, *o,o′*-diaminodiphenylmethanes, and substances produced from these by further action of formaldehyde: hydroxytetrahydroquinazolines, dihydroquinazolines, tetrahydroquinazolines, the N-methyl derivatives of the original amines, and "Troeger's base," the last type obtained only from *p*-toluidine, *p*-anisidine, and *p*-phenetidine.

When either 2,3,5-trimethyl-4-methoxyaniline (I) or its formyl derivative (II) was subjected to the action of formaldehyde and hydrochloric acid at room temperature for some sixty hours, it was converted in a yield of 86%, into a basic compound, A. Two other basic compounds, B and C, resulted when dilute hydrochloric acid was used and the time of the reaction was reduced. No compounds corresponding to IV were even obtained.

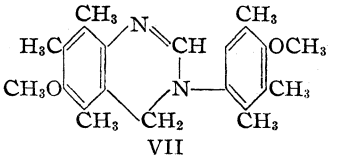
Base A was isolated from the reaction mixture as the hydrochloride, which could not itself be recrystallized, for it was insoluble in non-polar solvents, and solvolyzed in polar solvents. The free base A, however, was easily purified and the analytical values and molecular weight of it and of its hydrochloride showed that two molecules of amine, and two or three molecules of formaldehyde, were involved in the formation of A. On the basis of the analytical values, and in analogy with previous work described in the literature, four structures for A had to be considered: the azomethine dimer V; the tetrahydroquinazoline VI; the dihydroquinazoline VII; and the "Troeger's base" VIII.



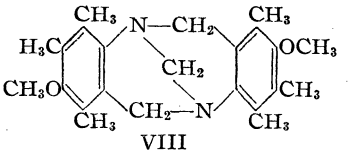
V



VI

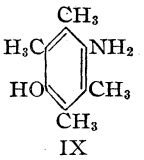


VII

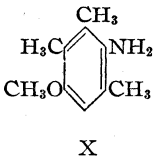


VIII

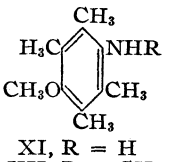
VIIIa, OH in place of OCH_3



IX



X



XI, R = H
XII, R = CH_3

Base A failed to react with acetic anhydride and sulfuric acid at 100°, and was unaffected by the action of sodium and alcohol, of stannous chloride and hydrochloric acid, or of hydrogen in the presence of Raney nickel catalyst. Moreover, base A was unchanged by boiling alcoholic sodium hydroxide, and when boiled in hydrochloric acid and acetic acid, the only effect was a partial cleavage of the methoxyl groups to hydroxyl groups (VIIIa). These properties showed that no amino hydrogen atom was present in A, and that the grouping —N=C was also absent; the structure VIII for A was strongly indicated. Final proof that structure VIII was the correct one was obtained when A was reductively cleaved by action of hydriodic acid and phosphorus at 170°; there resulted, in 71% yield, 2,3,5,6-tetramethyl-4-aminophenol, IX. On one occasion, the temperature during the reductive cleavage of A reached 280°, and in this case, the product was the hydrocarbon durene, a tetramethylbenzene. Thus, base A is a "Troeger's base"—and is the only example of such

(1) XXXIII, THIS JOURNAL, **65**, 1594 (1943).

(2) Abstracted from a thesis by W. M. Schubert, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, August, 1947.

(3) (a) Maffei, *Gazz. chim. ital.*, **58**, 261 (1928); **59**, 3 (1929); (b) Wagner, THIS JOURNAL, **54**, 660, 3698 (1932); **57**, 1296 (1935); (c) Wagner and Eisner, *ibid.*, **56**, 1938 (1934); **59**, 879 (1937); (d) Simons, *ibid.*, **59**, 518 (1937); (e) Spielman, *ibid.*, **57**, 583 (1935); (f) Miller and Wagner, *ibid.*, **63**, 832 (1941).

a base completely substituted in the benzene rings.[4]

When I, formaldehyde and dilute hydrochloric acid were allowed to react at 65–70° for fifteen minutes, the yield of A was reduced to 25% and there appeared a greater yield of a lower-melting (137–138°) base, B; when the reaction was carried out at 50° for eight minutes, the yield of B was nearly doubled and no A at all resulted. The filtrate, after removal of B, deposited crystals of the hydrochloride of a third base, C, melting at 136–137°, almost the same temperature as B. Base B was converted into base C by the action of sodium and alcohol. Base B failed to react with acetic anhydride, whereas base C was converted to a monoacetyl derivative, soluble in dilute hydrochloric acid. These facts showed that the group —N=C was present in B and the group —NHCH— as well as a tertiary N atom, were present in C. Finally, base B, when reductively cleaved by action of hydriodic acid and phosphorus at 170°, gave a mixture of 2,3,6-trimethyl-4-aminophenol and 2,3,5,6-tetramethyl-4-aminophenol (IX) in a yield of 71%. These facts establish the structure of B as the dihydroquinazoline VII, and the structure of C as the tetrahydroquinazoline VI.

The question as to how the three bases VI, VII, and VIII are related chemically is difficult to decide. The fact that the yield of VIII increased with time at the expense of VI and VII may mean that the latter bases are intermediates in the formation of VIII; the fact that VI was precipitated (as the hydrochloride) from the acidic filtrate after removal of VII may mean that VI is formed later than, and perhaps by reduction of VII. The tetrahydroquinazoline VI was converted into VIII by action of formaldehyde and hydrochloric acid, or by action of formic acid, alone or in the presence of hydrochloric acid. Hence, VI is probably an intermediate in the formation of VIII, but a reduction must have occurred when VI was converted into VIII by action of formic acid. Some sort of oxidation process must have occurred during the formation of the dihydroquinazoline VII; it may have resulted from a condensation of formic acid with an *o*-aminobenzylamine, formed earlier in the reaction and the evidence, though indirect, indicates that VII is a precursor of VI. Thus, action of formalin and 4% hydrochloric acid upon I for eight minutes at 50° produced VII in 52% yield, and no VI or VIII was isolated; when the temperature was maintained at 65–70°, and the reaction time was prolonged to fifteen minutes, VII, VI, and VIII were produced in yields of 31, 7, and 25%, respectively. However, VII was not converted into VIII by action of formaldehyde, formic acid, and hydrochloric acid, so VII is certainly not a direct precursor of VIII.

Many attempts, and under a great variety of conditions, were made to condense 2,3,6-trimethyl-4-aminophenol, its N-formyl, N-acetyl derivatives and their *o*-methyl ethers (I, II, III) with dienes (isoprene, 2,3-dimethylbutadiene), allylic halides (allyl bromide, isoprene hydrobromide, α-methallyl bromide), and an allylic alcohol (methylvinylcarbinol), but without any success. In the great majority of experiments, the starting material was recovered unchanged or else the reaction consisted merely in cleavage of the N-acyl group. Likewise, no success attended any of the many attempts to introduce an aldehyde group into the vacant position of these compounds: zinc cyanide and hydrochloric acid, or N-methyl formanilide and phosphorus oxychloride, were without significant action. No useful product resulted when the free aminophenol or its *o*-methyl ether were condensed with β-methoxybutanone-2, and finally, the acetanilide III could not be chloromethylated.

In connection with the work on the structures of the bases derived from I, a comparative study was made of the action of formaldehyde and hydrochloric acid upon 2,3,6-trimethyl-4-methoxyaniline, X (a position isomer of I), and upon 2,3,5,6-tetramethyl-4-methoxyaniline, XI. Neither of these methoxyanilines was affected by the action of warm formaldehyde and hydrochloric acid and X was recovered unchanged after it was heated in a mixture of paraformaldehyde, acetic acid, hydrochloric acid and phosphoric acid. The completely substituted aniline XI, however, under the latter conditions, gave a good yield of the methylaniline XII. This is the first case in which a methylaniline has been obtained as the major product of the action of formaldehyde upon an aromatic amine.

Experimental Part[5,6]

2,3,5-Trimethyl-4-aminophenol, m. p., 149–152°, was prepared from 2,3,5-trimethylphenol by the method of Smith, Hoehn and Whitney.[7]

Trimethylquinone was prepared from the above aminophenol by the procedure of Carlin[8] and was converted into the 1-*p*-nitrophenylhydrazone by the procedure of Smith and Irwin.[9]

2,3,5-Trimethylquinone-1-semicarbazone.—A solution of trimethylquinone (10 g.) and semicarbazide hydrochloride (7.5 g.) in alcohol (40 cc.) and water (60 cc.) was allowed to stand at room temperature for a few hours. The yellow semicarbazone (12.7 g., 78%) was removed and crystallized from alcohol; it then melted at 252–253° (dec).

Anal. Calcd. for $C_{10}H_{13}O_2N_3$: C, 57.97; H, 6.32. Found: C, 58.09; H, 6.50.

(4) The failure of the Troeger's base A to react with acetic anhydride is noteworthy for all other such bases so far prepared react rather readily. The benzene rings of base A, however, are completely substituted, and molecular models of this base indicate that there should be a considerable hindrance to attack at the nitrogen atoms. Such hindrance is not present in the tetrahydroquinazoline (Base C) which readily undergoes acetylation.

(5) All melting points are corrected.

(6) Microanalyses by Roger Amidon, Jay S. Buckley, W. H. T. Hunter and Sherman Sundet.

(7) Smith, Hoehn and Whitney, THIS JOURNAL, **62**, 1863 (1940).

(8) R. B. Carlin, Ph.D. Thesis, University of Minnesota, 1940, p. 80.

(9) Smith and Irwin, THIS JOURNAL, **63**, 1036 (1941).

1-(2,3,5-Trimethyl-4-hydroxyphenyl)-semicarbazide.—Sodium hydrosulfite (5 g.) in water (25 cc.) was added to a suspension of the above semicarbazone (1.22 g.) in boiling alcohol (35 cc.). The mixture became homogeneous and colorless at once; the white solid (1.12 g.) was removed from the cooled solution. It melted at 194° (dec).

Anal. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.22. Found: C, 57.65; H, 7.38.

The white semicarbazide, or a solution of it in alcohol, slowly became yellow when exposed to air; the oxidation was quite rapid when the semicarbazide (0.3 g.) was dissolved in aqueous sodium hydroxide (20 cc., 5%) and exposed to air for one hour. The product (0.28 g., 93%) was the semicarbazone, m. p., and mixed m. p. 250–251° (dec).

2,3,5-Trimethylquinone-1-oxime.—Hydroxylamine hydrochloride (56 g.) in water (75 cc.) was added to a solution of crude trimethylquinone (115 g.) in methanol (325 cc.). The mixture was warmed (40–45°) to bring about complete solution and was then allowed to stand at room temperature for two days. The solid was removed and washed with water until free from acid. It weighed 114 g. (91%), melted at 177–179°, and was sufficiently pure for use in subsequent operations. The analytical sample, crystallized from aqueous ethanol (50%), melted at 181–182°.[10]

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.43; H, 6.71. Found: C, 65.62; H, 6.63.

N-(2,3,5-Trimethyl-4-hydroxyphenyl)-hydroxylamine.—The above oxime (25 g.) was stirred with sodium hydroxide (7.0 g.) in water (300 cc.) while sodium hydrosulfite (40 g.) was added. The temperature rose to 35°, and a solid separated. The mixture was cooled to 10°, the solid was removed, and washed with water containing a little sodium hydrosulfite. The crude solid melted at 100–103° (dec.), and was very unstable, becoming oxidized to the oxime when attempts were made to recrystallize it. In alkaline solution, the substance was oxidized in air rapidly and quantitatively to the oxime, but addition of excess sodium hydrosulfite to the alkaline solution converted the hydroxylamine quantitatively into 2,3,6-trimethyl-4-aminophenol, m. p. 134–136° (dec.).

2,3,5-Trimethylquinone-1-oxime-O-methyl Ether.—A solution of the oxime (23 g.) in water (175 cc.) and sodium hydroxide (9 g.) was stirred at room temperature as methyl sulfate (29 g.) was added dropwise (one hour). Stirring was continued for one hour, and then the solid was removed, washed with water, and crystallized from aqueous ethanol (350 cc., 60%). The product (21.7 g., 87%) melted at 82–83°; the analytical sample, crystallized again, melted at 83–84°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.30. Found: C, 66.78; H, 7.57.

The oxime ether (2 g.) in methanol (15 cc.) was catalytically hydrogenated (Raney nickel 1 g.) at 60° in fifteen minutes under an initial hydrogen pressure of 1900 lb. to 2,3,6-trimethyl-4-aminophenol, isolated as the N-acetyl derivative (93% over-all yield), m. p., 211–212°. The oxime ether did not react with sodio malonic ester; instead, it underwent self-condensation in the presence of alkali to give, in poor yield, an amphoteric substance which melted at 213–214°. This substance gave a positive Folin-Denis test for phenols, but a negative vat test. It was analyzed, but was not investigated further.

Anal. Found: C, 70.79, 70.40; H, 6.59, 6.81; N, 9.27.

2,3,6-Trimethyl-4-aminophenol.—The aminophenol could be obtained by reductive cleavage of any of the 1-carbonyl derivatives of trimethylquinone. From the *p*-nitrophenylhydrazone (1.69 g.) in boiling alcohol (35 cc.) by action of sodium hydrosulfite (6 g.) in water (35 cc.): yield 0.43 g. (48%), m. p. 132–134° (dec.).[9] From the semicarbazone (1.22 g.) by action of stannous chloride (3 g.) and hydrochloric acid (3 cc.) in hot water (20 cc.) and alcohol (30 cc.): yield 0.23 g. (33%) of material of poor quality, m. p., 119–123° (dec.). From the semicarbazone (1.5 g.) in alcohol (10 cc.) by catalytic reduction (Raney nickel catalyst, 1 g.) at 95° under an initial hydrogen pressure of 1000 lb.: yield 0.89 g. (65%), m. p. 132–134° (dec). From the oxime (111 g.) dissolved in aqueous sodium hydroxide (110 g. in 1600 cc.) by action of sodium hydrosulfite (280 g.) at 20–30° (one hour): yield nearly quantitative; m. p. 135–137° (dec.). It is important, in this reduction, that enough alkali be present to keep the intermediate hydroxylamine in solution, otherwise the reduction stops at the first stage.

From the oxime (18 g.) in methanol (125 cc.) by catalytic reduction (Raney nickel 2 g.) at 40–50° under an initial hydrogen pressure of 1200 lb.: yield quantitative; m. p. 133–136° (dec). The most convenient preparative method is that involving reduction of the oxime by action of sodium hydrosulfite and alkali.

2,3,6-Trimethyl-4-acetylaminophenol.—Crude trimethylquinone oxime (111 g.) was reduced by action of sodium hydrosulfite, as described above, and the wet cake of crude aminophenol was dissolved in hydrochloric acid (70 cc.) and water (1600 cc.) by warming. The solution was warmed with Norit, filtered, acetic anhydride (81.5 cc.) was added to the filtrate at 50°, followed by addition of a solution of sodium acetate (113 g.) in water (500 cc.). The solid was removed, washed thoroughly with water, and dried. It then weighed 95 g. (74% based on the oxime) and melted at 212–213°. The analytical sample, crystallized from aqueous ethanol (30%), melted at 213–214°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82. Found: C, 68.69; H, 7.87.

2,3,6-Trimethyl-4-formylaminophenol, m. p. 189–190° (9 g., 69%) was prepared by action of formic acid (40 cc., 87%) upon the aminophenol (11 g.) essentially according to the method of King[11] who reported the m. p. as 190–191°.

2,3,6-Trimethyl-4-(N,N-diformylamino)-phenol.—Phosphorus oxychloride (2 cc.) was added to a solution of the aminophenol (0.9 g.) in anhydrous formic acid (5 cc.). The solution was allowed to stand overnight, and was then poured into ice-water (50 cc.). The solid (0.6 g.) was removed and crystallized from aqueous methanol, when it melted at 153–154°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32. Found: C, 63.60; H, 6.51.

The substance was insoluble in dilute hydrochloric acid, but soluble in aqueous sodium hydroxide. The Folin–Denis test was positive. When warmed with hydrochloric acid (5%) it was hydrolyzed to the monoformyl derivative, m. p. 189–190°, and when refluxed for two hours with dilute acid, it was converted into the aminophenol, m. p. 133–135°.

2,3,6-Trimethyl-4-(N-acetyl-N-formylamino)-phenol.—Phosphorus oxychloride (5 cc.) was added to a solution of the acetylaminophenol (1 g.) in anhydrous formic acid (7 cc.), the mixture was allowed to stand overnight, and was poured into water. The solid (1 g.) was removed and crystallized from aqueous ethanol (40%), when it melted at 170–171°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.82. Found: C, 64.97; H, 6.84.

The substance was insoluble in dilute acid, but soluble in dilute alkali, and the Folin–Denis test was positive. When warmed with dilute acid, it was hydrolyzed, first to the acetylaminophenol (m. p. 210–211°), and finally to the aminophenol (m. p. 132–134°).

2,3,5-Trimethyl-4-acetoxyformanilide.—This compound was obtained as the result of an attempt to bring about a condensation between the formylaminophenol and iso-

(10) Karrer and Leiser, *Helv. Chim. Acta*, **27**, 678 (1944), report the m. p. as 182°.

(11) J. A. King, Ph.D. Thesis, University of Minnesota, 1942. p. 134.

prene hydrobromide. The formylaminophenol (1 g.), isoprene hydrobromide (2.5 g.), and stannic chloride were allowed to stand in acetic acid (10 cc.) at room temperature for a week, and then the mixture was poured into water. The solid was removed and washed with ether. There remained 0.9 g. of material (m. p. 154–160°) which, after two crystallizations from aqueous ethanol, melted at 171–172°. The material was insoluble in both dilute hydrochloric acid and dilute sodium hydroxide; the Folin–Denis test was negative.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.02; H, 6.84; N, 6.15.

2,3,5-Trimethyl-4-methoxyacetanilide III.—The crude acetylaminophenol (90 g.) was dissolved in aqueous sodium hydroxide (32 g. in 1000 cc.), and to the well-stirred solution, methyl sulfate (65 cc.) was slowly (one and one-half hours) added dropwise. Stirring was continued for one and one-half hours longer, and the precipitate was removed, washed thoroughly with water, and dried. It weighed 90 g. (93%), melted at 169–170°, and was sufficiently pure for use in subsequent operations. The analytical sample, recrystallized from aqueous ethanol (30%) with the use of a little Norit, was white and melted at 170–171°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.51; H, 8.27. Found: C, 69.56; H, 8.34.

2,3,5-Trimethyl-4-methoxyaniline I.—Crude III (89.5 g.) was refluxed overnight with water (1000 cc.) and hydrochloric acid (200 cc.). A little Norit was added, and the solution was filtered. The colorless filtrate, cooled and neutralized with sodium hydroxide, deposited a solid which was removed, washed and dried. It weighed 63 g. (88%) and melted at 106–107°. The analytical sample, recrystallized from aqueous ethanol (40%), melted at 108–109°.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.70; H, 9.15. Found: C, 72.82; H, 9.47.

2,3,5-Trimethyl-4-methoxyformanilide II.—Methyl sulfate (4.5 cc.) was added dropwise and with stirring to a solution of the crude formylaminophenol (5.5 g.) in aqueous sodium hydroxide (50 cc., 4%). The solid (4.8 g.) was removed, washed with water, and dried. It melted at 142–144°; after crystallization from ethyl acetate, it weighed 4 g. (69%) and melted at 146–147°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82. Found: C, 68.47; H, 8.04.

2,3,5-Trimethyl-4-acetylaminophenol, m. p. 184–186°, was prepared in 81% yield from the aminophenol by the method of Smith, Hoehn and Whitney.[7]

2,3,6-Trimethyl-4-methoxyacetanilide (22 g., 90%), m. p. 176–178°, was prepared from the above acetylaminophenol in alkaline solution by action of methyl sulfate, as described for the isomeric methoxyacetanilide. The analytical sample, crystallized from aqueous ethanol (50%), melted at 181–182°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.51; H, 8.27. Found: C, 69.60; H, 8.39.

2,3,6-Trimethyl-4-methoxyaniline X.—The above crude methoxyacetanilide (21 g.) was hydrolyzed by refluxing it for thirty-six hours with water (300 cc.) and hydrochloric acid (100 cc.). The solution was diluted with water (300 cc.), decolorized with Norit, and neutralized with sodium hydroxide. The solid was removed, washed, and dried, when it weighed 14 g. and melted at 73–74°. The material was sublimed under 2–3 mm., when it formed white needles (13 g., 75%) melting at 74–75°.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.70; H, 9.15. Found: C, 72.62; H, 9.14.

2,3,5,6-Tetramethyl-4-aminophenol IX.—A solution of sulfanilic acid (21.5 g.) and sodium carbonate (6.5 g.) in water (100 cc.) was cooled (12°) and mixed with a solution of sodium nitrite (7.4 g.) in water (20 cc.). The whole was poured, with stirring, into a mixture of cracked ice (80 g.) and hydrochloric acid (21 cc.) and allowed to stand for thirty minutes. The sludge of diazonium salt was added to a stirred mixture of durenol (15 g.) and sodium hydroxide, (20 g.) in water (100 cc.) and then allowed to stand overnight. Sodium hydrosulfite (40 g.) was added and the mixture was stirred and heated to 60–70° for about thirty minutes, when the red color disappeared. The mixture was cooled (20°) and the solid was removed and washed several times with water containing a little hydrosulfite. The crude product was light in color, weighed 15.5 g. (94%), and melted at 175–179°.[12]

2,3,5,6-Tetramethyl-4-acetylaminophenol (18 g., 91%, m. p. 260–262° dec.) was prepared from the crude aminophenol (15.5 g.) by acetylation in hydrochloric acid (9.1 cc. in 250 cc. of water) by action of acetic anhydride (11.7 cc.) and sodium acetate (15 g.) as described above. The analytical sample, recrystallized from aqueous ethanol, melted at 262–263°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.52; H, 8.27. Found: C, 69.68; H, 8.37.

2,3,5,6-Tetramethyl-4-methoxyacetanilide.—The above acetylaminophenol (18 g.) was dissolved in aqueous sodium hydroxide (6 g. in 200 cc. of water) and methylated by action of methyl sulfate (12 cc.) as described before. The crude product melted at 211–213°, and weighed 21 g. (95%). The analytical sample, recrystallized from aqueous methanol (80%), melted at 215–216°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65. Found: C, 70.57; H, 8.73.

2,3,5,6-Tetramethyl-4-methoxyaniline XI.—The above crude methoxyacetanilide (14 g.) was refluxed with hydrochloric acid (100 cc.) and water (300 cc.) for forty hours. The solution was diluted with water (300 cc.), decolorized with Norit, and made alkaline by addition of aqueous sodium hydroxide. The solid was removed, washed, and dried; it weighed 10 g. and melted at 60–65°. This material, sublimed under 2–3 mm., gave a white sublimate (6.7 g., 65%) which melted at 68–69°.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.69; H, 9.56. Found: C, 73.70; H, 9.69.

1,3,4,7,9,10-Hexamethyl-2,8-dimethoxy-5,11(6,12)-methanodibenzo-[b,f][1,5]-diazocine (R. I. No. 2651). VIII.—A mixture of I (5 g.), formalin (7 cc.) and hydrochloric acid (40 cc.) was shaken mechanically for twelve hours and then allowed to stand for forty-eight hours. The mixture was diluted to 500 cc. with water, and the solid (5.5 g.) was removed, washed with water, and dried. The nearly white hydrochloride was warmed with ethanol (50 cc.), aqueous ammonia (5 cc.) was added, and the mixture was diluted to 250 cc. with water. The crystalline solid (5.1 g., m. p. 184–190°) was removed, washed with water, and recrystallized from ethanol (250 cc.). There resulted 4.7 g. (86%) of white needles melting at 191–192°.

Anal. Calcd. for $C_{23}H_{30}O_2N_2$: C, 75.38; H, 8.25; N, 7.64; mol. wt., 336. Found: C, 75.40, 75.29; H, 8.43, 8.41; N, 7.72; mol. wt. (cryoscopically in benzene), 340.

Hydrochloride.—Somewhat impure VIII (0.4 g., m. p. 187–188°) was added to hydrochloric acid (2 cc.). Immediate solution occurred, then deposition of a solid in a very short time. The mixture was allowed to stand overnight, and the solid was removed and washed thoroughly with dry ether. The solid was shaken with ether (30 cc.) for thirty minutes, and was then shaken with petroleum ether (100 cc., b. p. 60–68°) overnight. The residual white, amorphous solid (0.3 g.) melted at 224–226°.

Anal. Calcd. for $C_{23}H_{30}O_2N_2 \cdot HCl$: C, 68.29; H, 7.73; N, 6.95; Cl, 8.80. Found: C, 67.62; H, 7.83; N, 7.16; Cl (Volhard), 8.65.

Compound VIII (0.3 g.) was recovered unchanged after it was heated with acetic anhydride (3 cc.) and sul-

(12) W. B. Irwin, Ph.D. Thesis, University of Minnesota, 1940, p. 65, prepared this compound by a somewhat different method and reported it to melt at 178–181°.

furic acid (1 drop) for one hour or when it was refluxed for two days with alcoholic sodium hydroxide. Compound VIII was also recovered (75–90%) when attempts were made to reduce it by action (a) of sodium and ethanol; (b) of sodium and butanol; (c) of stannous chloride and hydrochloric acid in acetic acid; (d) of hydrogen in the presence of Raney nickel catalyst at 85° and hydrogen pressure of 2300 lb. Action of zinc dust and hydrochloric acid, or of zinc chloride and hydrochloric acid, brought about no reduction but did convert VIII into a high-melting (301–302°) stable solid which was difficult to purify. This substance was apparently a double compound of VIII and zinc chloride, for it reacted with ammonia in aqueous methanol, regenerating VIII. No simple formula for this "stable hydrochloride" could be deduced from the analytical values.

Anal. Found: C, 59.14; H, 7.14; N, 6.49; Cl, 14.39.

Compound VIII was reductively cleaved when it (1 g.) was heated to 170° for twenty-one hours in a Carius tube with hydriodic acid (15 cc., 48%) and red phosphorus (0.1 g.). The cooled mixture was diluted to 100 cc. with water, hydrochloric acid (10 cc.) was added, and the mixture was filtered. The filtrate was made alkaline by addition of aqueous potassium carbonate, and the solid was removed, washed with water, and dried. It weighed 0.64 g. (71%) and melted at 174–177°. When mixed with authentic 2,3,5,6-tetramethyl-4-aminophenol (m. p. 179–181°), the substance melted at 176–178°. A portion (0.5 g.) of this aminophenol was dissolved in hydrochloric acid (50 cc., 3%), ferric sulfate (5 g.) was added, and the mixture was distilled with steam. The distillate contained duroquinone (0.43 g., 86%), m. p. and mixed m. p. 111–112°.

1,3,4,7,9,10-Hexamethyl-2,8-dihydroxy-5,11(6,12)-methanodibenzo[b,f][1,5]-diazocine (R. I. No. 2651). VIIIa.—A solution of VIII (1 g.) in acetic acid (10 cc.) and hydrochloric acid (10 cc.) was refluxed for forty-four hours. The cooled solution was diluted with water (20 cc.) and made alkaline with aqueous ammonia. The solid (0.65 g.) was removed and crystallized twice from carbon tetrachloride and once from methanol. It then melted at 279–280° (dec.) and weighed 0.25 g. The Folin–Denis test was positive.

Anal. Calcd. for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.80. Found: C, 74.43; H, 8.01.

The filtrates from the recrystallizations of VIIIa, on evaporation, yielded 0.1 g. of unchanged VIII.

3-(4-Methoxy-2,3,5-trimethylphenyl)-5,7,8-trimethyl-6-methoxy-3,4-dihydroquinazoline VII.—A solution of I (5 g.) in hydrochloric acid (40 cc., 4%) was prepared by warming the mixture on the steam-bath. The solution was cooled to 50° and formalin (4 cc.) was added. An oil separated almost immediately; the mixture was maintained at 50° for eight minutes, then it was quickly cooled (0°) and rubbed with a spatula. The solid was removed, washed with water (30 cc.) and dissolved in methanol (30 cc.). The solution was made alkaline with aqueous ammonia (5 cc.) and diluted with water (500 cc.). The product appeared as an oil which solidified when set aside in a refrigerator. The solid (3.4 g., m. p. 129–136°) was removed (filtrate, see preparation of VI below) and crystallized from *dry* petroleum ether (b. p. 60–68°). It then weighed 2.8 g. and melted at 136–138°. The analytical sample, crystallized once more from petroleum ether, melted at 138–139°.

Anal. Calcd. for $C_{22}H_{28}O_2N_2$: C, 74.97; H, 8.04. Found: C, 74.78; H, 8.06.

When the above preparation was duplicated, except that the temperature was held at 65–70°, and the reaction was allowed to proceed for fifteen minutes, there resulted VIII (1.39 g., 25%) and VII (crude, 2 g., recrystallized, 1.6 g., 31%). The dihydroquinazoline VII (0.3 g., 75%) was recovered unchanged (a) when it (0.4 g.) was heated for an hour in acetic anhydride (1 cc.); (b) when it was heated with 96% formic acid for an hour; and (c) when it was allowed to stand for a day at room temperature with formalin and hydrochloric acid.

3-(4-Methoxy-2,3,5-trimethylphenyl)-5,7,8-trimethyl-6-methoxytetrahydroquinazoline VI.—The first filtrate obtained in the first preparation of VII above, when allowed to stand overnight, deposited a crystalline hydrochloride (0.42 g., m. p. 163–164°). The salt could not be recrystallized, so it was analyzed directly.

Anal. Calcd. for $C_{22}H_{30}O_2N_2 \cdot HCl$: C, 67.59; H, 8.01. Found: C, 67.79; H, 8.31.

This salt (0.3 g.) was dissolved in a little methanol, and the solution was made alkaline with aqueous ammonia and diluted with water (25 cc.). The product appeared as an oil which soon solidified; the solid was removed and crystallized from petroleum ether (b. p. 40–70°). It weighed 0.15 g. and melted at 136–137°; when mixed with VII (m. p. 137–138°), the substance melted at 129–137°.

Anal. Calcd. for $C_{22}H_{30}O_2N_2$: C, 74.54; H, 8.54. Found: C, 74.70; H, 8.56.

1-Acetyl Derivative of VI.—The tetrahydroquinazoline (0.4 g.) in acetic anhydride (1 cc.) was heated on the steam-bath for one hour. The cooled solution was diluted with water (20 cc.), made alkaline with aqueous ammonia and allowed to stand for an hour. The solid (0.36 g.) was removed and crystallized twice from petroleum ether (10 cc., b. p. 40–70°). It then weighed 0.2 g., and melted at 136–137°. When mixed with VI (m. p. 136–137°) the substance melted at 110–120°.

Anal. Calcd. for $C_{23}H_{32}O_3N_2$: C, 72.64. H, 8.13. Found: C, 72.90; H, 8.33.

Conversion of VI to VIII. A.—The tetrahydroquinazoline (80 mg.) in formic acid (96%) was heated on the steam-bath for forty-five minutes. From the cooled and diluted solution there was obtained 50 mg. (54%) of VIII, m. p. and mixed m. p. 190–191°. **B.** The tetrahydroquinazoline (0.3 g.), in formic acid (0.3 cc., 87%) and hydrochloric acid (3 cc.) was maintained at room temperature for two days. From the cooled and diluted solution there was obtained 0.28 g. of VIII, m. p. and mixed m. p. 189–190°. **C.** A solution of the tetrahydroquinazoline (0.4 g.) and formalin (0.4 cc.) in hydrochloric acid (4 cc.) was maintained at room temperature for two days. The solution was diluted with water (30 cc.) and the solid was removed and dissolved in methanol (10 cc.). The methanol solution was made alkaline with ammonia (1 cc.) and diluted to 50 cc. with water. The solid was removed and crystallized from methanol; it weighed 0.32 g. (78%) and melted at 191–192° alone or when mixed with another specimen of VIII.

Reduction of VII to VI.—Sodium (2 g.) was added portionwise (thirty minutes) to a refluxing solution of VII (0.75 g.) in dry ethanol (30 cc.). The solution was cooled, neutralized with acetic acid, and diluted with water (150 cc.). The product (0.6 g.) separated as an oil which solidified on standing in a refrigerator overnight. The solid was removed and crystallized from dry petroleum ether (b. p. 60–68°), when it weighed 0.51 g. (75%) and melted at 136–137°, alone, or when mixed with VI from the above experiment.

Reduction Cleavage of VII.—The dihydroquinazoline (1 g.) was heated at 170° for twenty-two hours in a Carius tube with hydriodic acid (15 cc., 48%) and red phosphorus (0.1 g.). The mixture was cooled, and the solid hydriodide (0.72 g.) was removed and washed with water. The combined filtrate and washings were neutralized with aqueous potassium carbonate and extracted twice with ether (35 cc. each time). The ether extract was immediately mixed with hydrochloric acid (3%) and placed in a flask arranged for steam distillation. The solid hydriodide was dissolved in methanol (25 cc.); the solution was neutralized with aqueous ammonia, diluted with water (150 cc.), and the solid was removed, washed with a little water, and added to the ether extract in the steam-distillation flask. The ether was carefully distilled from the mixture with a gentle current of steam,

and then ferric sulfate (10 g.) was added and the mixture was steam distilled. The distillate was extracted with several portions of ether (total 70 cc.) and the combined yellow extracts were dried over sodium sulfate. Removal of the solvent left a yellow solid (0.58 g.). This solid was dissolved in methanol (4 cc.) and water (0.5 cc.). Hydroxylamine hydrochloride (0.25 g.) was added, and the mixture was allowed to stand at room temperature for one day. The mixture was diluted with water (30 cc.) and extracted with several portions of ether (total, 70 cc.). The combined ether extracts were then extracted three times with 15-cc. portions of aqueous sodium hydroxide (5%). The alkaline extracts, when neutralized with dilute hydrochloric acid, deposited 2,3,5-trimethylquinone-1-oxime (0.14 g., 16%) which, after one crystallization from aqueous alcohol (50%) melted at 180–182° alone or when mixed with an authentic specimen. The yellow ether solution remaining after the alkaline extraction was washed with water and evaporated. The residue (0.19 g., 21%) melted at 109–111° alone or when mixed with authentic duroquinone.

2,3,5,6-Tetramethyl-4-methoxy-N-methylaniline XII.—The tetramethylmethoxyaniline XI (0.8 g.) and paraformaldehyde (0.25 g.) were heated on the steam-bath for sixteen hours in a mixture of acetic acid (1 cc.), hydrochloric acid (1 cc.) and phosphoric acid (0.6 cc., 85%). The mixture was diluted with water (50 cc.), warmed to bring about complete solution, and decolorized with a little Norit. The cooled filtrate was made alkaline with aqueous sodium hydroxide (10%) and the precipitate (0.6 g., m. p. 77–82°) was removed and dissolved in ether (50 cc.). The solution was filtered and the solvent was allowed to evaporate. The residue was crystallized twice from aqueous ethanol (35%), when it melted at 83–85°. This was sublimed under 3 mm. pressure at a temperature of 70–80°. The first portion of the sublimate melted at 78–84°; the last portion at 84–87°. The high-melting fraction, when resublimed as before, gave 0.12 g. of material melting at 87–88°.

Anal. Calcd for $C_{12}H_{19}ON$: C, 74.56; H, 9.91. Found: C, 74.51; H, 9.86.

The tetramethylmethoxyaniline XI (1.4 g., m. p. and mixed m. p., 63–65°) was recovered unchanged when it (2 g.) was shaken with formalin (2 cc.) and hydrochloric acid (15 cc.) at room temperature for five days. The material was recovered when the reaction mixture was diluted with water (150 cc.) and made alkaline with aqueous sodium hydroxide (10%). The same result was obtained when the experiment was repeated, but for seven hours at a temperature of 75°.

2,3,6-Trimethyl-4-methoxyaniline X (0.32 g.) and paraformaldehyde (0.1 g.) were heated on the steam-bath for fifteen hours in a mixture of acetic acid (0.5 cc.), hydrochloric acid (0.5 cc.) and phosphoric acid (0.25 cc., 85%). The mixture, processed as described above for the tetramethyl analog, yielded a sublimate (0.13 g.) which was unchanged X, m. p. and mixed m. p. 71–73°.

Summary

1. It has been shown that action of formaldehyde and hydrochloric acid upon 2,3,5-trimethyl-4-methoxyaniline produces three basic substances: a new highly substituted "Troeger's Base" VIII, a dihydroquinazoline VII, and a tetrahydroquinazoline VI. The relative amounts of these three bases depend upon the experimental conditions, particularly upon the temperature and the time.

2. The dihydroquinazoline VII has been reduced to the tetrahydro compound VI; the latter has been converted to the "Troeger's Base" VIII by action of hydrochloric acid and formaldehyde or formic acid, whereas the former was not affected by these reagents. The dihydroquinazoline VII therefore cannot be a direct precursor of the "Troeger's Base," whereas the tetrahydroquinazoline VI probably is an intermediate in its formation from the methoxyaniline.

3. Tetramethyl-*p*-methoxyaniline and 2,3,6-trimethyl-4-methoxyaniline gave no compounds analogous to those obtained from the 2,3,5-trimethyl compound. The trimethylaniline underwent no change, whereas the tetramethyl compound was converted into 2,3,5,6-tetramethyl-4-methoxy-N-methylaniline.

4. A convenient five-step synthesis of 2,3,6-trimethyl-4-aminophenol from 2,3,5-trimethylphenol has been developed, and several new derivatives of the aminophenol have been prepared and characterized.

5. Using as starting materials 2,3,6-trimethyl-4-aminophenol and several of its derivatives, a number of synthetic approaches to 6-hydroxy-2,2-disubstituted-1,2,3,4-tetrahydroquinolines, the N-analogs of the tocopherols, have been investigated. None of the reactions was successful.

MINNEAPOLIS 14, MINNESOTA

RECEIVED FEBRUARY 28, 1948

[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, MAYO FOUNDATION]

Hemihydrohalides of 3(α)-Hydroxy Steroids[1]

BY VERNON R. MATTOX, BERNARD F. MCKENZIE AND EDWARD C. KENDALL

The formation of a crystalline compound by treatment of 3(α)-hydroxy-12-keto-$\Delta^{9,11}$-cholenic acid in ether with hydrogen bromide has been observed.[2] The experimental details for preparation of this product have recently been published,[3] and the procedure was suggested as a method for separation of the cholenic acid. However, no structure was suggested for the product and no analysis was given.

In the presence of hydrogen bromide or hydrogen chloride, crystalline products have been prepared in this laboratory with the already mentioned cholenic acid and also with methyl 3(α)-hydroxy-12-ketocholanate. With both of these steroids it was found that the crystalline compounds separated in combination with 0.5 molecule of hydrogen halide.

Subsequently it was observed that, when methyl 3(α)-hydroxy-12(α)-methoxy-$\Delta^{9,11}$-cholenate was treated with hydrogen halides, the 12(α)-halogen derivative which was produced separated in crystalline form and contained in each instance 0.5 molecule of halogen acid.

The diverse nature of the material treated with hydrogen halide and the fact that only 0.5 molecule of halogen acid was combined with the crystalline product indicated that neither the double bond at C_9-C_{11} nor the substituent at C_{12} was essential. It occurred to us that it was desirable to determine what structure of the steroid was necessary for the formation of the hemihydrohalide derivatives. Such an investigation has revealed the fact that all derivatives of cholane, $\Delta^{9,11}$-cholene and Δ^{11}-cholene which have been studied (Table I) in which there was an (α)-hydroxyl group at C_3, form crystalline products and separate with 0.5 molecule of halogen acid. If the 3(α)-hydroxyl group is esterified, as with the acetyl group, addition products are not formed,[4] as shown in the last three lines of the table. No attempt has been made to prepare hemihydrohalides from 3(β)-hydroxy steroids or from steroids which have hydroxyl groups in other positions.

The general method of preparation consisted of the introduction of a stream of dry hydrogen halide into a solution containing from 1 to 3 millimoles of the compound in an appropriate solvent in an ice-bath. It was hoped that a single solvent or a mixture of solvents would be satisfactory for the isolation of all of the hemihydrohalides; however, it was found that this was not possible. For several of the methyl esters methanol was a satisfactory solvent; acetone was used for some of the acids and chloroform–petroleum ether was suitable in other cases.

The hemihydrohalides were dried under reduced pressure over sodium hydroxide or in air at room temperature for one to two days. Methyl 3(α)-hydroxy-12(α)-bromo-$\Delta^{9,11}$-cholenate hemihydrobromide retained 0.5 molecule of hydrogen bromide after it had been dried at 0.1 mm. pressure at room temperature for six hours. Most of the hemihydrohalides melt over a range of several degrees and the melting point is frequently dependent on the rate of heating. Their physical constants are given in Table I.

The halogen content of the compounds was determined by distribution between water and an immiscible solvent and titration of the halogen in the aqueous phase by the method of Volhard. In 6 experiments the amount of acid in the aqueous phase was determined. In each instance the concentration agreed with that of the halogen ion.

That no deep-seated change of the steroid molecule had occurred was shown by isolation of the starting material from the organic phase after removal of hydrogen halide. Two of the reaction products, methyl 3(α)-hydroxy-12(α)-bromo-$\Delta^{9,11}$-cholenate hemihydrobromide and methyl 3(α)-hydroxy-12(α)-chloro-$\Delta^{9,11}$-cholenate hemihydrochloride, were prepared by treatment of methyl 3(α)-hydroxy-12(α)-methoxy-$\Delta^{9,11}$-cholenate with the appropriate hydrogen halide. These two were reconverted into methyl 3(α)-hydroxy-12(α)-methoxy-$\Delta^{9,11}$-cholenate by treatment with methanol.[5,6]

It is thought that these hemihydrohalides of the 3(α)-hydroxy steroids are oxonium compounds. Favorskii[7] has prepared oxonium compounds from the aliphatic alcohols and reports that they are extremely hygroscopic. However, the oxonium compounds of the steroids reported in this paper are not hygroscopic. In addition, Favorskii also prepared from 2,2-dimethylpentanol-3 both a

(1) This paper was presented at the Fifteenth Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, June 24, 1947.

(2) Reported by Dr. E. S. Wallis at a conference of the Committee on Synthesis of Adrenal Hormones held under auspices of the National Research Council, Washington, D. C., 1942.

(3) Hicks, Berg and Wallis, *J. Biol. Chem.*, **162**, 633 (1946).

(4) Since only the 3(α)-hydroxyl group appears to be necessary for formation of hemihydrohalides, separation of 3(α)-hydroxy-12-keto-$\Delta^{9,11}$-cholenic acid from 3(α)-hydroxy-12-ketocholanic acid cannot be made satisfactorily. For a discussion see McKenzie, Mattox, Engel and Kendall, *J. Biol. Chem.*, **173**, 271 (1948).

(5) Mattox, Turner, Engel, McKenzie, McGuckin and Kendall, *J. Biol. Chem.*, **164**, 569 (1946).

(6) When a solution of methyl 3(α)-hydroxy-12(α)-bromo-$\Delta^{9,11}$-cholenate hemihydrobromide in chloroform is repeatedly concentrated under reduced pressure and diluted with petroleum ether, methyl 3(α)-hydroxy-12(α)-bromo-$\Delta^{9,11}$-cholenate is obtained; however, because of its somewhat variable melting point, it is not satisfactory for identification. For this reason the 12-halogen compounds were converted into the 12(α)-methoxy compound, which has characteristic physical properties.

(7) Favorskii, *Chem. Abstr.*, **8**, 493 (1914).

TABLE I

PHYSICAL CONSTANTS OF THE HEMIHYDROHALIDES

Starting material	Halogen acid	Solvent	M. p.,[a] °C.	% yield	Addition product % of 0.5 HX As prepared	After 45 days[b]
Methyl 3(α)-hydroxy-12(α)-bromo-Δ^{9,11}-cholenate[c]	HBr	$CHCl_3$-P. E.[d]	137–138	100	97[e,f]	
Methyl 3(α)-hydroxy-12(α)-chloro-Δ^{9,11}-cholenate[c]	HCl	$CHCl_3$-P. E.	131–137	94	90[f,g]	
3(α)-Hydroxy-12-ketocholanic acid	HBr	Ether	128–133	54	103	
	HCl	$CHCl_3$	115–117	86	83	62
Methyl 3(α)-hydroxy-12-ketocholanate	HBr	CH_3OH	127–130	55	98	
	HCl	CH_3OH	108–109[h]	78	99	55
3(α)-Hydroxy-12-keto-Δ^{9,11}-cholenic acid	HBr	$CHCl_3$-P. E	134–137	97	98	
	HCl	Acetone	119–122	40	95	
Methyl 3(α)-hydroxy-12-keto-Δ^{9,11}-cholenate	HBr	CH_3OH	117–123	65	96	
	HCl[i]	CH_3OH	85–90[j]	86	95	36
3(α)-Hydroxy-Δ^{11}-cholenic acid	HBr	Acetone	118–122	39	98	90
	HCl	$CHCl_3$		96	74	
Methyl 3(α)-hydroxy-Δ^{11}-cholenate	HBr	CH_3OH	93–98	81	94	80
Methyl 3(α)-hydroxycholanate	HBr	CH_3OH	115–122	45	92	
	HCl	CH_3OH	105–106	75	30	10
3(α)-Hydroxy-11-keto-24,24-diphenyl-Δ^{23}-cholene[k]	HBr	Acetone	143–150	93	99	93[l]
Methyl 3(α)-acetoxy-12(α)-chloro-Δ^{9,11}-cholenate	HCl	$CHCl_3$-P. E.			0	
3(α)-Acetoxy-12-ketocholanic acid	HCl	$CHCl_3$-P. E.			0	
3(α)-Acetoxy-12-keto-Δ^{9,11}-cholenic acid	HCl	$CHCl_3$-P. E.			0	

[a] All melting points were determined on the Fisher–Johns apparatus. [b] Samples were exposed to atmosphere. [c] This compound was prepared from methyl 3(α)-hydroxy-12(α)-methoxy-Δ^{9,11}-cholenate. The conversion of the 12(α)-methoxy compound to the 12(α)-halogen derivative has been shown to be nearly quantitative.[5] [d] P. E. is petroleum ether. [e] Analysis by combustion. [f] This figure is based on the halogen found in excess of that calculated for 1 atom of halogen at C_{12}. [g] For halogen determination the sample was heated in 1 *N* methanolic sodium hydroxide for ten minutes and the chloride ion was titrated by the Volhard method. [h] M. p. 112–115° when heated rapidly. [i] Crystals separated when the solution was about 2 *N* with HCl; as the solution became more concentrated with HCl the crystals dissolved. [j] M. p. 90–93° when heated rapidly. [k] Prepared from methyl 3,9-epoxy-11-ketocholanate[9] by treatment with phenylmagnesium bromide and dehydration of the resulting carbinol with acetic acid. The 3,9-epoxy linkage was opened with hydrogen bromide and the halogen was removed from C_{12} with zinc in acetic acid. [l] After 45 days in desiccator over solid sodium hydroxide.

hemihydrohalide, $(C_7H_{15}OH)_2 \cdot HBr$, and a hydrohalide, $C_7H_{15}OH \cdot HBr$. Only the hemihydrohalides of the 3(α)-hydroxy steroids could be isolated.

Favorskii represented the structure of the hemihydrohalide of the aliphatic alcohols by

However, Whitmore[8] suggested

$[Br]^-[OR]^-$ as being more probable.

The halogen content of some of the oxonium compounds was found to be less than the theoretical amount for a hemihydrohalide. This was observed more frequently with the hydrochlorides than with the hydrobromides and may be related to the intrinsic strengths of the two acids.

The steroid hemihydrohalides are unstable compounds and slowly lose halogen acid under atmospheric conditions. A comparison of the last two columns in the table shows the amount of halogen acid lost in forty-five days.

Summary

Crystalline oxonium compounds which contain a half molecule of hydrogen halide are formed by treatment of 3(α)-hydroxysteroids with hydrogen halides. Acetylation of the hydroxyl group prevents formation of the oxonium compound. The preparation of sixteen of these hemihydrohalides is described in this paper.

ROCHESTER, MINN. RECEIVED FEBRUARY 24, 1948

(8) Whitmore, "Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1937, p. 139.

(9) Turner, Mattox, Engel, McKenzie and Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE PITTSBURGH PLATE GLASS CO., COLUMBIA CHEMICAL DIVISION]

A Study of the Reaction of Phenol with Thionyl Chloride

BY WILLIAM E. BISSINGER AND FREDERICK E. KUNG

Studies on the reactions of phenol with thionyl chloride are greatly complicated by the existence of readily-occurring nuclear substitution reactions.[1,2,3,4,5,6] These probably account for the fact that the preparation of diphenyl sulfite by the direct reaction of phenol with thionyl chloride in the absence of hydrogen chloride acceptors had not been reported prior to this time, and that the successful preparation of phenyl chlorosulfinate has been accomplished[7] only recently.

In a previous paper[8] on the reaction of thionyl chloride with alcohols, we described a novel method of operation which appeared to greatly reduce the complicating side reactions resulting from the action of hydrogen chloride on the newly-formed sulfite ester. In that method the reactions were carried out in the presence of a large amount of a refluxing solvent in which the reactants and products were soluble. but in which the hydrogen chloride was insoluble. We have now applied this technique to the phenol–thionyl chloride reaction to determine if the complex reactions previously reported[1-6] could be eliminated. Preliminary experiments showed that diphenyl sulfite and phenyl chlorosulfinate underwent a fairly rapid decomposition in the presence of hydrogen chloride, thereby emphasizing the need for removing this material from the zone of reaction as rapidly as possible. Utilizing the refluxing solvent technique to expel the hydrogen chloride, we then investigated the reaction of phenol with thionyl chloride at temperatures of 10° to 180°, and at molar ratios of 2:1 to 1:4, while observing the effect of temperature and the ratio of reactants on the yields and types of products obtained.

Experimental

Preparation of Materials.—The thionyl chloride used was a purified grade manufactured by this Division. The phenol was Merck reagent grade.

For the preliminary studies the diphenyl sulfite was prepared by the method of Gerrard.[9] On distillation through a 1.5 × 20-cm. Vigreux column, the sulfite was collected at 141–144° (2 mm.), m. p. 13–16°.

The phenyl chlorosulfinate was prepared as follows: Molten phenol (1.0 mole) was added to refluxing thionyl chloride (4.0 moles) in one hour with stirring after which the mixture was refluxed one hour longer. Fractionated through a 1.7 × 20-cm. Fenske column, the phenyl chlorosulfinate, 125 g. (71% yield) distilled at 92–98° (10 mm.). The stability tests in the following section were made with a redistilled product boiling at 95° (10 mm.), m. p. −16° to −13°.

Anal. Calcd. for $C_6H_5SO_2Cl$: S, 18.1; Cl, 20.1. Found: S, 18.8; Cl, 20.6.

Stability of Diphenyl Sulfite and Phenyl Chlorosulfinate to Hydrogen Chloride.—Hydrogen chloride (0.25 mole) was passed into freshly distilled diphenyl sulfite (93 g.; 0.4 mole) over a six-hour period at 70°. A gain in weight of 7.5 g. resulted. Distillation yielded (a) 16.7 g. (0.178 mole) of phenol, b. p. 83–84° (20 mm.), m. p. 40°, which was further identified by its benzoate, m. p. 69°; (b) 51 g. (0.218 mole) of diphenyl sulfite, b. p. 143–157° (3 mm.); (c) 14.5 g. of a viscous residue containing 18.5% sulfur and 1.7% chlorine. The yield of phenol, based on the diphenyl sulfite not recovered, was 98%, assuming that one mole of phenol was formed per mole of sulfite decomposed.

Hydrogen chloride (0.30 mole) was likewise passed into freshly distilled phenyl chlorosulfinate (106 g., 0.60 mole) over a six-hour period at 70° while collecting all volatile products in a Dry Ice trap. A gain in weight of 1 g. occurred. Distillation at 10 mm. yielded (a) a Dry Ice trap fraction of 5.2 g., (b) 79 g. (0.448 mole) of phenyl chlorosulfinate b. p. 92–93.5°, (c) 10 g. (0.04 mole) of diphenyl sulfite, b. p. 152–158°.

Anal. Calcd. for $(C_6H_5)_2SO_3$: S, 13.65. Found: S, 13.9; Cl, 0.9.

Redistillation of (a) at atmospheric pressure gave 4.7 g. (0.04 mole) of thionyl chloride, b. p. 75–76°.

Anal. Calcd. for $SOCl_2$: S, 26.9; Cl, 59.6. Found: S, 26.8; Cl, 58.6.

The yield of thionyl chloride and diphenyl sulfite was 53% each, based on the phenyl chlorosulfinate not recovered.

When phenyl chlorosulfinate (160 g.) was heated for six hours at 70° in the absence of hydrogen chloride and then redistilled, 97% (155 g.) was recovered. Treatment of diphenyl sulfite in a similar manner resulted in a recovery of 96% of the original material.

Reaction of Phenol with Thionyl Chloride in Refluxing Solvents.—The apparatus and the techniques used were the same as had been described previously,[8] except that the phenol was generally maintained slightly above its melting point while being added to the refluxing solvent. The solvents used, and their boiling points, were: ethyl chloride (12°), methylene chloride (42°), carbon tetrachloride (76°), thionyl chloride (78°), chlorobenzene (130°), and *o*-dichlorobenzene (180°). The addition of the phenol and thionyl chloride was made in *one* to *two* hours (with one exception), after which the refluxing was continued for *one* to *three* hours more. In the experiment with ethyl chloride as solvent a forty-eight hour reflux period was used. The yields of diphenyl sulfite and phenyl chlorosulfinate were determined by distillation and redistillation of the product at the reduced pressures already mentioned, through a 1.5 × 15-cm. Vigreux column. The yields were based on the weights of starting materials and on the reactant present in deficiency. A black tarry residue remained from every distillation. The results are summarized in Table I.

In the experiments at 12° and 42°, *p*-chlorophenol was isolated during the distillation of the products. This material had b. p. 107–110° (20 mm.); m. p. 20–25°, $n^{20}D$ 1.5655.

Anal. Calcd. for C_6H_5OCl: Cl, 27.6. Found: Cl, 27.4; S, 0.2. As further identification, the *p*-chlorophenol was converted to *p*-chlorophenyl benzoate, m. p. 87°.

(1) Tassinari, *Gazz. chim. ital.*, **20**, 326 (1890).
(2) Voswinckel, *Pharm. Zeit.*, **40**, 241 (1895).
(3) Carré and Libermann, *Compt. rend.*, **196**, 275 (1933).
(4) Carré and Libermann, *Bull. soc. chim.*, (4) **53**, 1051 (1933).
(5) Courtot and Tung, *ibid.*, **200**, 1541 (1935).
(6) Lüttringhaus, *Ber.*, **72**, 887 (1939).
(7) Gerrard, *J. Chem. Soc.*, 99 (1939).
(8) Bissinger and Kung, THIS JOURNAL, **69**, 2158 (1947).
(9) Gerrard, *J. Chem. Soc.*, 224 (1940).

TABLE I

REACTION OF PHENOL WITH THIONYL CHLORIDE IN REFLUXING SOLVENTS

Reaction temp., °C.	Reactants, moles		Yields, %		Wt. of tarry residue, g.
	Phenol	$SOCl_2$	$(C_6H_5)_2SO_3$	C_6H_5OSOCl	
12	2	1	0	0	90[a,b]
42	2	1	0	0	87[c]
42	1	2	28	43	25
76	2	1	73	0	18[d]
76	2	1	17	0	88[e]
76	1	1	33	19	36
76	1	2	0	35	55
78	1	4	0	71	28
78	1	4	0	83	18[f]
78	2	8	3	81	14[f]
130	2	1	61	0	34[g]
130	2	1	87	0	9[f,h]
130	1	1	56	35	8
130	1	2	44	43	5
180	2	1	0	0	107[i]
180	1	2	32	47	4

[a] Unreacted phenol (48%) was isolated along with 0.104 mole of *p*-chlorophenol. [b] This residue contained 5.4% chlorine and 16.6% sulfur. [c] Fifty-one per cent. of the phenol was recovered and 0.04 mole of *p*-chlorophenol appeared on distillation. [d] One hundred ml. of carbon tetrachloride was placed in the flask while the other 400 ml. was used to prepare equivolume solutions of the phenol and $SOCl_2$, which were then added dropwise. The addition time was extended to seven hours. [e] Phenol (36%) was recovered. [f] The phenol was dissolved in chlorobenzene (100 ml. per mole of phenol) to facilitate addition. [g] Phenol (15%) was recovered. [h] In this experiment the rate of reflux was much higher than in the preceding experiment. [i] On attempted distillation only acidic gases were evolved.

Discussion of Results

In general, the reaction of thionyl chloride with phenol, even in the presence of a refluxing solvent, was observed to be far more sensitive to slight variations in the operating conditions than had been noted in the reaction of thionyl chloride with aliphatic alcohols. For example, very vigorous stirring and strong refluxing of the solvent was found conducive to definitely improved yields in the phenol reaction; in the aliphatic series these factors were not particularly important. There are indications, also, that the time of addition of the phenol and the thionyl chloride to the refluxing solvent may bear very significantly on the results. In the studies reported here, the effect of this variable was investigated in only one experiment, as will be discussed later in the paper. It should be clearly recognized, therefore, that our results were obtained under specific reaction conditions, and any marked deviation from these conditions may lead to considerable differences in yields.

The preparation of diphenyl sulfite by the direct reaction of phenol and thionyl chloride in the absence of hydrogen chloride acceptors has been accomplished for the first time through the use of the refluxing solvent technique. The data of Table I illustrate that at a 2:1 molar ratio of phenol to thionyl chloride the maximum yield (87%) of diphenyl sulfite was obtained at a reaction temperature of 130° with chlorobenzene as the refluxing solvent. It is not fully understood why this maximum yield appeared at such a high temperature. In contrast to the other experiments, it will be noted that in most cases at 130° essentially no tarry residues were obtained. Assuming that these resinous bodies were formed through a reaction of thionyl chloride with the benzenoid ring, it might be concluded that at 130° the esterification reaction becomes very much faster than the coupling reaction, thereby resulting in the predominant formation of diphenyl sulfite.

The fact that no diphenyl sulfite could be isolated from the experiments at 12° and 42° with a 2:1 molar ratio of phenol to thionyl chloride is in accord with the results of earlier workers.[1-6] It is apparent that under these conditions the refluxing solvent method did not eliminate the formation of undesirable by-products, represented by the tarry residues obtained on distillation. The high yield (73%) of diphenyl sulfite obtained at 76° with carbon tetrachloride as solvent was only obtained when a seven-hour addition time for the reactants was used. When the addition time was the usual one-to-two hour period, the yield of diphenyl sulfite was only 17%. These results afford strong evidence that even relatively minor variations in the reaction conditions may materially affect the yield figures.

The refluxing solvent technique, using a 300% excess of thionyl chloride at 78° as the sole refluxing solvent, furnished a very simple means of preparing phenyl chlorosulfinate. The discrepancy between the yields of 71% and 83%, as reported in Table I, can probably be attributed to the less vigorous stirring and the decreased rate of reflux used in the former case.

In all preparations of phenyl chlorosulfinate with thionyl chloride as the sole refluxing solvent, it was found that not more than 3% of diphenyl sulfite was obtained, providing vigorous stirring[10] was employed. The low yield of diphenyl sulfite indicates that in the absence of hydrogen chloride acceptors, the reaction of phenol with phenyl chlorosulfinate at 78° may be a much slower reaction than the corresponding reaction of alkanols with alkyl chlorosulfinates at this temperature. For example, when *n*-propyl alcohol was added to a 500% excess of refluxing thionyl chloride in a four-hour reaction period with vigorous stirring, a 30% yield[8] of *n*-propyl sulfite was obtained, along with the expected chlorosulfinate.

Although phenyl chlorosulfinate can be distilled at 90–100° without decomposition, it was found to be unstable on prolonged standing at room tem-

(10) This is only true under conditions of strong agitation. In one experiment, phenol (2 moles) was added to refluxing thionyl chloride (8 moles), without stirring, over a two-hour period, followed by one additional hour of reflux. No phenyl chlorosulfinate was obtained, but a 41% yield of diphenyl sulfite was produced, along with a residue of 60 g.

perature. A purified sample, stored for about eleven months on the desk top in a glass-stoppered bottle, decomposed violently, rupturing the bottle and evolving heat.[11]

Acknowledgment.—We express our thanks to Dr. A. Pechukas, who suggested the refluxing solvent technique, and to Dr. F. Strain for helpful discussions.

Summary

1. The thermal stability of phenyl chlorosulfinate, although poor, was about equal to that of *n*-propyl chlorosulfinate and much greater than that of isopropyl chlorosulfinate.

2. Diphenyl sulfite reacted with hydrogen chloride producing phenol and a tarry residue; the other expected cleavage product, chlorobenzene, was not found. Phenyl chlorosulfinate, unlike the unreactive alkyl chlorosulfinates, underwent a disproportionation reaction in the presence of hydrogen chloride to form thionyl chloride and diphenyl sulfite.

3. The refluxing solvent technique afforded an excellent means of preparing phenyl chlorosulfinate and diphenyl sulfite in yields of 83% and 87%, respectively. This was the first successful preparation of the latter by the direct reaction of phenol with thionyl chloride without hydrogen chloride acceptors.

4. The variables of temperature and ratio of reactants have been studied in the reaction of phenol with thionyl chloride in a refluxing solvent. *Under the conditions used,* the lower reaction temperatures seemed to favor undesirable side-reactions; at a 2:1 molar ratio of phenol to thionyl chloride the best yield of diphenyl sulfite occurred at 130°, whereas with excess thionyl chloride the best yield of phenyl chlorosulfinate was obtained in refluxing thionyl chloride at 78°.

5. The reaction of phenol with thionyl chloride in a refluxing solvent is apparently very sensitive to relatively minor changes in the reaction conditions, such as stirring for example, and with such modifications quite different results from those reported here may be obtained. Such sensitivity was not apparent in the aliphatic series.

BARBERTON, OHIO RECEIVED MARCH 15, 1948

(11) Carré and Libermann, *Compt. rend.*, **195**, 799 (1932), reported that the decomposition of phenyl chlorosulfinate was instantaneous at room temperature. The presence of impurities in their material may have been responsible for this reduced stability.

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation of Spermine Tetrahydrochloride[1] (1,12-Diamino-4,9-diazadodecane Tetrahydrochloride)

BY HARRY P. SCHULTZ[2]

The reported synthesis of spermine[3,4] appeared impractical for the preparation of the quantity of material required in the antimalarial program. Therefore, a synthesis of spermine tetrahydrochloride was developed, which consisted of the hydrogenation of succinonitrile to putrescine (I); the dicyanoethylation of putrescine to N,N′-bis-(2-cyanoethyl)-putrescine (II); followed by hydrogenation of II to spermine (III). The tetramine was then converted to the tetrahydrochloride.

$$H_2N(CH_2)_4NH_2 \qquad \text{I}$$

$$NC(CH_2)_2NH(CH_2)_4NH(CH_2)_2CN \qquad \text{II}$$

$$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2 \qquad \text{III}$$

The hydrogenation of succinonitrile was carried out at 140° in liquid ammonia over Raney nickel. Even under these conditions, which are usually quite unfavorable to formation of secondary amines, the yield of pyrrolidine was more than twice as large as that of the desired primary amine. The dicyanoethylation reaction proceeded well in water, alcohol, or ether. The yield of II was almost quantitative, judged by the amount of the dihydrochloride that was isolated in some experiments. The preferred procedure was to carry out the cyanoethylation in ether solution and, without isolating II, add liquid ammonia and hydrogenate over Raney nickel at 140° to III. The tetramine (III) was then distilled and isolated and purified as the tetrahydrochloride. The over-all yield of the tetrahydrochloride, starting with putrescine, was 51% of the theoretical.

Experimental

Putrescine.—A steel reaction vessel having a void of 1300 ml. was charged with 200 g. (2.5 moles) of succinonitrile,[5] 9 g. of W-2 Raney nickel,[6] and 350 ml. of liquid ammonia. The contents of the bomb was reduced for two and one-half hours at 140° under a hydrogen pressure of 1700 p. s. i. The catalyst-free reaction mixture was distilled to give 79.7 g. (45% yield) of crude pyrrolidine that boiled at 87–88° (740 mm.), and 43 g. (20% yield) of putrescine, b. p. 60–65° (16 mm.); m. p. 27–28°. Ladenburg[7] reported a m. p. of 23–24° for putrescine, while Ciamician and Zanetti[8] gave m. p. 27–28°.

N,N′-bis-(2-Cyanoethyl)-putrescine.—Acrylonitrile from the Rohm and Haas Company (35.0 g., 0.66 mole)

(1) The work described in this paper was done under Contract OEMcmr-567, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Wisconsin.

(2) Present address: University of Miami, Coral Gables, Florida.

(3) Rosenheim, *Biochem. J.*, **18**, 1253 (1924).

(4) Dudley, Rosenheim and Starling, *ibid.*, **20**, 1082 (1926).

(5) Succinonitrile from du Pont Electrochemical Division was used without further purification.

(6) Mozingo, "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

(7) Ladenburg, *Ber.*, **19**, 781 (1886).

(8) Ciamician and Zanetti, *ibid.*, **22**, 1970 (1889).

was added dropwise for eight hours to a stirred solution of 29.0 g. (0.33 mole) of putrescine in 10 ml. of ether. After all acrylonitrile was added, the solution was stirred at room temperature for fifteen hours, on a steam-bath for one hour, and again at room temperature for one hour. During the time of heating, all the ether distilled out, and the weight of the final reaction product was 64 g. All attempts to distil the dinitrile, even at a pressure of 0.01 mm., resulted in decomposition. When the reaction mixture was allowed to stand for a longer period (forty to fifty hours), the yield of spermine tetrahydrochloride was decreased from 50 to 30%.

A small exploratory run, made as above, when treated with ethanolic hydrogen chloride, gave a 100% yield of N,N′-bis-(2-cyanoethyl)-putrescine dihydrochloride, m. p. 222–228° (dec.). This salt was recrystallized from ethanol–water (3:1) to give an 84% yield of N,N′-bis-(2-cyanoethyl)-putrescine dihydrochloride, m. p. 232–233° (dec.).

Anal. Calcd. for $C_{10}H_{20}N_4Cl_2$: Cl, 26.6. Found: Cl, 26.6.

Spermine Tetrahydrochloride.—A 270-ml. steel reaction vessel was charged with 18 g. (0.092 mole) of crude N,N′-bis-(2-cyanoethyl)-putrescine, 5 ml. of ether, 60 ml. of liquid ammonia, and 3 g. of W-2 Raney nickel catalyst. The contents of the bomb was reduced for thirty minutes at 140° under a hydrogen pressure of 4900 p. s. i. The catalyst-free reaction mixture was distilled to give 10 g. of viscous distillate that boiled at 100–170° (0.1–0.2 mm.), and 3 g. of a yellow residue.

The crude spermine was dissolved in 130 ml. of absolute ethanol, and to it was added 65 ml. of 20% ethanolic hydrogen chloride. The precipitated amine salt was filtered and air-dried to give 23.5 g. of white, impure spermine tetrahydrochloride that melted at 290–310° (dec.), with darkening at 270°. The crude spermine tetrahydrochloride was dissolved in 130 ml. of 12% hydrochloric acid and added to 1300 ml. of hot, absolute ethanol. After cooling the alcohol solution, the crystals were filtered, washed, and air-dried to give 17 g. of crystals, m. p. 300–310° (dec.). This material was placed in 119 ml. of 12% hydrochloric acid, and added to 357 ml. of hot, absolute ethanol. After six hours at room temperature, the spermine tetrahydrochloride was filtered off, rinsed, and dried to give 16.1 g. (51% yield) of light pink crystals, m. p. 310–311° (dec.), darkening at 300°. The value previously reported[9] was m. p. 310–311° (dec.).

Anal. Calcd. for $C_{10}H_{30}N_4Cl_4$: C, 34.5; H, 8.7; Cl, 40.8. Found: C, 34.2; H, 8.6; Cl, 40.8.

The picrate of spermine melted at 246–247° (dec.), darkened at 240°. The value previously reported[9] was m. p. 248–250° (dec.), with darkening at 242°.

Spermine chloroplatinate was also prepared, and found to melt at 242° (dec.), dark at 235°. The value previously reported[9] was m. p. 242–245° (dec.).

Acknowledgments.—I am grateful to Dr. Carnahan, formerly of this Laboratory, for suggesting this method as a possible synthesis of spermine; and to Drs. Adkins and Wilds, of this Laboratory, for advice which made this synthesis successful.

Summary

Spermine tetrahydrochloride has been prepared from succinonitrile through the formation of putrescine, N,N′-bis-(2-cyanoethyl)-putrescine, spermine, and spermine tetrahydrochloride. The yield of putrescine from succinonitrile was low (20%), but the over-all yield for the three subsequent reactions was 51% of the theoretical.

(9) Dudley, Rosenheim and Rosenheim, *Biochem. J.*, **18**, 1263 (1924).

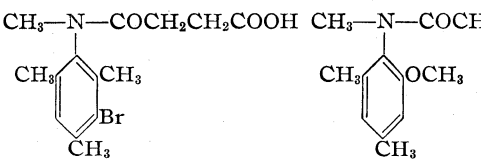
CORAL GABLES, FLORIDA RECEIVED APRIL 28, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. IV. Preparation and Resolution of N-Succinyl-1-methylamino-2,4-dimethyl-6-substituted Benzenes

BY ROGER ADAMS AND N. K. SUNDHOLM[1]

A comparison of the relative interference effects of substituent groups, as deduced from the racemization rates of a series of analogous, optically active biphenyls,[2] showed these groups to fall in the following order: Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F. Two members of a series of aromatic amines in which restricted rotation exists have been previously described.[3] They are shown in I and II. Compound I, in optically active form, has a half-life of nine hours in boiling *n*-butanol (b.p. 117°) and compound II a half-life of two and seven-tenths hours in boiling methyl acetate (b.p. 57°). Although these values are not directly comparable due to the use of different solvents[4] and to the bromine atom in the former, qualitatively they can be accepted as indicative of the relative interference of the methyl and methoxyl groups in this type of molecule. These relative values coincide with those expected from the study of the biphenyls.



I II

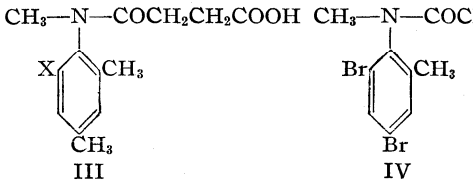
Several new analogs of I and II, as shown in III and IV, have now been synthesized, resolved and their optically active forms racemized. The half-life periods were as follows: IIIa, three and

(1) An abstract of a thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Chemistry. Allied Chemical and Dye Corporation fellow second semester 1941–'942, two semesters 1943–1944; New York Community Trust fellow 1942–1943.

(2) Stoughton and Adams, THIS JOURNAL, **54**, 4426 (1932); Adams and Hale, *ibid.*, **61**, 2825 (1939).

(3) (a) Adams and Dankert, *ibid.*, **62**, 2191 (1940); (b) Adams and Stewart, *ibid.*, **63**, 2859 (1941); (c) Adams and Albert, *ibid.*, **64**, 1475 (1942).

(4) Li and Adams, *ibid.*, **57**, 1565 (1935).



III IV

IIIa X = Br
IIIb X = I
IIIc X = NO_2

one-tenth hours; IIIb, twenty and one-half hours; IIIc, six-tenths hour; IV, one and one-tenth hours. All were taken in boiling *n*-butanol except IIIc which racemized so readily that boiling methyl acetate was employed. In these compounds, the bromine atom is only a third as effective as the methyl group (compare IIIa and I) in contributing to the restricted rotation of the molecule, and the nitro group is only one-fifth as effective as the small methoxyl (compare IIIc and II). It is thus obvious that factors other than the size of the groups are involved.

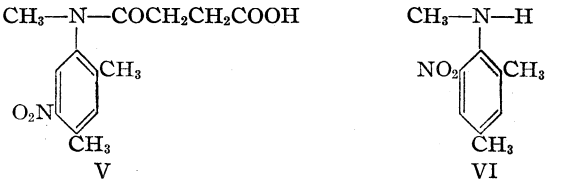
The basicity of aromatic amines is influenced profoundly by the presence of *o*-, *m*- or *p*-substituted electronegative groups as shown by the basic constants of *o*-toluidine, 2.9×10^{-10}; *o*-bromoaniline, 2.1×10^{-12}; *o*-iodoaniline, 0.36×10^{-12}; *o*-nitroaniline, 3.5×10^{-14}.[5a] The difference in basicity of these molecules is usually assigned to the effect of the bromine and iodine atoms or nitro group in inducing a positive nitrogen atom in the amino group. In the case of the nitro compound, a valence formula may be written which indicates the double-bond character of the carbon and amino-nitrogen linkage. For the halogens, an analogous structure cannot be written on a conventional basis but the mere fact that the basicity of the amines is reduced by the substitution of such atoms establishes the fact that the nitrogen is more positive, which condition is compatible with a linkage having double-bond character. For such a double bond to be produced the plane formed by the nitrogen and its two substituents must be coplanar with the ring. The racemization process, in which conversion of a *d*-form to an *l*-form and *vice versa* must take place through a coplanar configuration, should be facilitated by the presence in the optically active amines of groups favoring coplanarity. Thus the anomalous ease of racemization of hindered aromatic amines substituted with halogen or nitro groups in the *ortho* position is probably associated with their decreased basicity. The N-succinyl-1-methylamino-2-methyl-4,6-dibromobenzene (IV) was prepared in order to determine the effect of two electronegative bromine atoms in the *o*- and *p*-positions as compared with that of a single bromine in the *o*-position. The half-life of the former is only about a third of the latter, thus confirming the idea that the stability of these optically active aromatic amines is intimately connected with the base strength of the amino nitrogen atom and is greatly reduced by electronegative substituents. Apparently the larger size of the iodine atom overbalances the increase in ease of racemization induced by decrease in the basicity of the amine (compare I, IIIa, IIIb).

This relationship of basicity of the aromatic amines to the stability of their optically active hindered derivatives serves to explain the shorter half-life (four and one-tenth hours) of N-succinyl-1-methylamino-4-chloro-2-methylnaphthalene in comparison with that of N-succinyl-1-methylamino-2-methylnaphthalene (five and seven-tenths hours).[3c] It may also account for the non-resolvability of N-benzenesulfonyl-1-carboxymethylamino-2,4-dimethyl-6-nitrobenzene reported by Yuan.[5b]

The increase in double-bond character of the carbon and amino-nitrogen bond would result in a decrease in the bond length. The groups on the nitrogen would then be closer to the ring and interfere more readily with the adjacent substituents on the ring. It is assumed that this effect is so small in comparison to that already discussed that it may be disregarded.

The best synthesis of the bromo and iodo derivatives (IIIa and IIIb) was effected by brominating or iodinating 1-amino-2,4-dimethylbenzene, then monomethylating the amino group with dimethyl sulfate. Iodination of 1-methylamino-2,4-dimethylbenzene failed, using conditions successful for the iodination of the primary amine. Succinic anhydride in dry benzene with a drop of 85% phosphoric acid as catalyst was a satisfactory procedure for succinylation of the 1-methylamino compounds although the reaction was slow in the case of the molecules substituted with electronegative groups. 1-Methylamino-2-methyl-4,6-dibromobenzene was prepared by brominating the 1-methylamino-2-methylbenzene.

The production of the nitro compound (IIIc) was attempted first by the action of cold yellow nitric acid upon N-succinyl-1-methylamino-2,4-dimethylbenzene. A mono nitro derivative was readily formed but further study indicated the nitro group to be probably in the 5- (V) rather than in the 6-position. This orientation was observed by Gnehm and Blumer,[6] who nitrated N-acetyl-1-methylamino-2-methylbenzene in sulfuric acid with a nitric acid–sulfuric acid mixture and obtained the 5-nitro compound. The same compound was produced upon using cold yellow



V VI

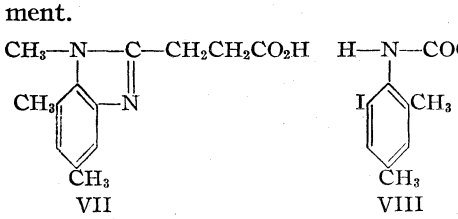
(5a) Williams and Soper, *J. Chem. Soc.*, 2469 (1930); Bennett, Brooks and Glasstone, *ibid.*, 1821 (1935); Myrbäck, *Z. physiol. Chem.*, **158**, 261 (1926).

(5b) Yuan, *J. Chinese Chem. Soc.*, **4**, 131 (1936).

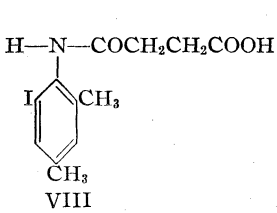
(6) Gnehm and Blumer, *Ann.*, **304**, 99 (1899).

nitric acid. Hydrolysis of the succinyl group of V resulted in the formation of a compound not identical with VI, which had been previously prepared by nitration of the N-nitroso-1-methylamino-2,4-dimethylbenzene followed by denitrosation. Compound IIIc was subsequently synthesized by succinylating VI.

The *d*-modification of the nitro compound (IIIc) was hydrogenated at room temperature in ether solution with platinum oxide as catalyst. The crude product was *dextro*-rotatory. After this product had been heated in boiling *n*-butanol for about an hour, a compound resulted which was optically inactive. This compound was not the amine (III, X = NH_2) since a molecule of water had been lost as shown by analysis. It must be the corresponding benzimidazole (VII). That this is so has been demonstrated by Betrabet and Chakravarti,[7] who obtained benzimidazole-2-β-propionic acid upon refluxing an absolute ethanol solution of N-succinyl-*o*-phenylenediamine. The product from the hydrogenation was undoubtedly the crude optically active amine which condensed to the benzimidazole during the subsequent treatment.



VII



VIII

Compound VIII, which differs from compound IIIb by having the N-methyl group missing, was not resolvable through its crystalline brucine salt. If the compound truly proves to be unresolvable, this would show the important contribution the N-methyl group makes to the restricted rotation in these compounds.

The optically active forms of the nitro compound (IIIc) and the dibromo compound (IV) were partially racemized during the process of crystallizing the crude acids obtained from the decomposition of their cinchonidine salts. For this reason the specific rotations of the crude optically active acids are reported since they should approximate the maximum specific rotations.

No particular complications were encountered in the resolution of the various compounds except in the case of the iodo derivative (IIIb). The salt tended to dissociate so that it was impossible to obtain a product of maximum rotation. The technique employed in the racemization determinations was that described in a previous communication.[3c]

Experimental

1-Methylamino-2,4-dimethyl-6-bromobenzene.—A mixture of 40 g. of 1-amino-2,4-dimethyl-6-bromobenzene,[8] 25 g. of dimethyl sulfate and 100 ml. of water was stirred with gentle warming on a steam-bath until homogeneous. The temperature was not permitted to go over 70°. The cooled solution was acidified with 30 ml. of concentrated hydrochloric acid, cooled to below 10°, and a solution of 14 g. of sodium nitrite in 50 ml. of water added dropwise with stirring, keeping the temperature between 5–10°. Stirring was continued for fifteen minutes after the addition of the sodium nitrite. The cold solution was extracted with ether, the ether layer washed with 5% aqueous sodium hydroxide, and then with water. The ether was evaporated by directing a stream of air over the surface of the solution.

The nitrosamine was reduced by careful addition in portions to a solution of 136 g. of stannous chloride dihydrate in 132 ml. of concentrated hydrochloric acid. The stannous chloride solution was heated to 40° before the first addition of the nitrosamine. In order to keep the temperature under 60° after several portions of the nitrosamine were added, cooling was necessary. After each addition the flask was shaken by hand. A precipitate of the tin complex slowly settled out. After standing overnight, the mixture was cooled in ice, and made strongly alkaline by addition of a solution of 176 g. of sodium hydroxide in 250 ml. of water. The mixture was steam-distilled until the distillate came over clear. The distillate was saturated with sodium chloride, extracted with ether, the extract dried over solid potassium hydroxide and the ether distilled. The secondary amine was distilled *in vacuo*, b. p. 92–94° (4.5 mm.); yield, 21 g. (49%); $n^{20}D$ 1.5682; d^{20}_4 1.3379.

Anal. Calcd. for $C_9H_{12}BrN$: C, 50.50; H, 5.60; M_D, 52.6. Found: C, 50.54; H, 5.78; M_D, 52.4.

N-Succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene.—To a solution of 13 g. of succinic anhydride in 100 ml. of dry benzene was added 15 g. of 1-methylamino-2,4-dimethyl-6-bromobenzene and a drop of 85% phosphoric acid. The solution was refluxed for four hours, cooled, diluted with 100 ml. of ether, and extracted with 5% aqueous potassium hydroxide. The alkaline extract was washed with ether and acidified with 1:2 hydrochloric acid. The product separated as an oil which solidified on stirring in ice. It was recrystallized from a mixture of three volumes of carbon tetrachloride and one volume of petroleum ether (b. p. 60–110°); white crystals, m. p. 115.5–116.5° (cor.); yield, 9 g. (41%).

Anal. Calcd. for $C_{13}H_{16}BrNO_3$: C, 49.68; H, 5.09. Found: C, 49.79; H, 5.16.

Resolution of N-Succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene.—A solution of 5 g. of N-succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene and 4.68 g. of cinchonidine in 180 ml. of 9:1 ethyl acetate–methanol by volume was filtered and evaporated to 145 ml. by directing a stream of air over its surface. After four days in the refrigerator, 3.1 g. of salt had crystallized. These crystals were collected and the filtrate evaporated to 137 ml. Refrigerated, it yielded a second crop of 1.4 g. At 125 ml., 1.3 g. of salt crystallized; at 110 ml., 0.1 g.; at 90 ml., 1.3 g. The first three fractions were combined and recrystallized in the same manner to constant rotation; this produced white feathery crystals m. p. 164–165° (cor.); yield, 1.8 g.

Anal. (*l*B*d*A) Calcd. for $C_{13}H_{16}BrNO_3 \cdot C_{19}H_{22}N_2O$: C, 63.36; H, 6.27. Found: C, 63.44; H, 6.60. *Rotation.* (*l*B*d*A) 0.03 g. made up to 10 ml. with absolute ethanol at 28° gave α_D −0.13°; *l*, 1; $[\alpha]^{28}D$ −43°.

***d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene.**—To 75 ml. of 1:1 hydrochloric acid at 0° was added 1.65 g. of the less-soluble salt. The mixture was stirred for fifteen minutes and then put in a refrigerator overnight. The next day the gummy material had solidified and it was broken up. The mixture was filtered and the solid material again stirred with cold 1:1 hydrochloric acid and put in a refrigerator overnight. This treatment was repeated until the filtrate gave a negative test with Folin's reagent.[9] The residue was dried in a vacuum desiccator; yield, 0.49 g. The acid was crystallized

(7) Betrabet and Chakravarti, *J. Indian Chem. Soc.*, **7**, 191 (1930).

(8) Noelting, Braun and Thesmar, *Ber.*, **34**, 2242 (1901).

(9) Folin and Denis, *J. Biol. Chem.*, **12**, 239 (1912).

from a mixture of benzene and petroleum ether (b. p. 60–110°). The rotation was unchanged by the crystallization.

The *d*-acid was obtained from the less-soluble salt; white crystals, m. p. 118.5–120.5° (cor.).

Anal. (*d*-acid) Calcd. for $C_{13}H_{16}BrNO_3$: C, 49.68; H, 5.09. Found: C, 49.95; H, 5.18. *Rotation.* (*d*-acid) 0.05 g. made up to 10 ml. with absolute ethanol at 28° gave α_D +0.125°; *l*, 1; $[\alpha]^{28}D$ +25°.

Racemization of *d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene.—The racemization was carried out in a polarimeter tube constructed from Pyrex tubing (25 mm. outside diameter, 100 mm. internal length) and fitted at the center to a reflux condenser by means of a ground-glass joint.[30] A solution of 0.15 g. of the *d*-acid made up to 25 ml. with *n*-butanol was added to the polarimeter tube. The rotation was observed, several small carborundum boiling chips added, and the polarimeter tube with its contents weighed. The polarimeter tube was then placed on a hot-plate and the solution concentrated to 15 ml. by boiling without reflux. The reflux condenser was attached and the solution refluxed until the total boiling period was one-half hour. The solution was cooled rapidly by plunging the tube into cold water, made up to the previously determined weight with *n*-butanol, and the rotation observed. By repetition of this process, the following α_D values were obtained: at the start, +0.148°; after one-half hour, +0.133°; after one and one-half hours, +0.105°; after two and one-quarter hours, +0.091°; after three and one-half hours, +0.068°; after five hours, +0.050°; after seven hours, +0.030°. Calculated for a reversible unimolecular reaction, the half-life was three and one-tenth hours. A check racemization gave a half-life of three and two-tenths hours.

1-Amino-2,4-dimethyl-6-iodobenzene.—This procedure was modeled after that for the iodination of *p*-toluidine used by Wheeler and Liddle.[10] To 28.2 g. of 1-amino-2,4-dimethylbenzene 59.5 g. of ground iodine was added with stirring. The addition of the iodine took about forty-five minutes. The reaction mixture was kept below 45° by cooling with cold water. After the completion of the addition of the iodine, the stirring was continued until the heat of the reaction had subsided. After the addition of 60 ml. of ether, 60 ml. of water and 28 g. of calcium carbonate, the mixture was refluxed on a steam-bath until the evolution of carbon dioxide ceased. This took several hours. The ether was distilled on the steam-bath and the residue steam-distilled. The first portion of the distillate was a red oil but after a short time material began to solidify in the lower part of the condenser. The water in the condenser had to be allowed to run out occasionally to permit the solid material to melt and run into the receiver. The solid product was collected on a filter, dried and crystallized twice from ethanol; white crystals that darkened on contact with the air, m. p. 66–67° (cor.); yield, 24 g. (42%). Kerschbaum[11] reported a m. p. of 65°.

1-Methylamino-2,4-dimethyl-6-iodobenzene.—The procedure described for the methylation of 1-amino-2,4-dimethyl-6-bromobenzene was used with several changes. The dimethyl sulfate was added dropwise to a stirred mixture of the 1-amino-2,4-dimethyl-6-iodobenzene and water at 70°. About a 20% excess of dimethyl sulfate was used. It was found that the nitrosamine was not reduced appreciably at 50° in the stannous chloride–hydrochloric acid mixture. The optimum temperature for the reduction was 70°. Above 80° an appreciable amount of the iodine was reduced off. From 83 g. of the primary amine, 24 g. (27.4%) of the secondary amine was obtained; b. p. 108–110° (4 mm.); d^{20}_4 1.5588; $n^{20}D$ 1.6050.

Anal. Calcd. for $C_9H_{12}IN$: C, 41.38; H, 4.60; M_D, 57.7. Found: C, 41.43; H, 4.82; M_D, 57.5.

(10) Wheeler and Liddle, *Am. Chem. J.*, **42**, 441 (1909).

(11) Kerschbaum, *Ber.*, **28**, 2798 (1895).

N-Succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene.—To a solution of 6.6 g. of succinic anhydride in 40 ml. of dry benzene was added 16 g. of 1-methylamino-2,4-dimethyl-6-iodobenzene and a drop of 85% phosphoric acid. The solution was refluxed for four hours, cooled, ether added, and the mixture extracted with 5% aqueous potassium hydroxide. The alkaline extract was acidified with 1:2 hydrochloric acid. After cooling and stirring for an hour, the product remained oily, so it was dissolved in ether and the ether solution dried with anhydrous magnesium sulfate. After removal of the magnesium sulfate by filtration and evaporation of the ether, first on a steam-bath, then *in vacuo*, the product slowly crystallized. The product was recrystallized from a mixture of three volumes of carbon tetrachloride and one volume of petroleum ether (b. p. 60–110°); white crystals, m. p. 103–104° (cor.); yield, 6.6 g. (30%).

Anal. Calcd. for $C_{13}H_{16}INO_3$: C, 43.21; H, 4.43. Found: C, 43.35; H, 4.57.

Resolution of N-Succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene.—A solution of 5.6 g. of N-succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene and 4.56 g. of cinchonidine in 55 ml. of 9:1 ethyl acetate–methanol by volume was filtered and evaporated to 45 ml. by directing a stream of air to the top of the flask. After four days in the refrigerator, 4 g. of salt had crystallized. Upon concentrating the mother liquor to 40 ml. and refrigerating, 1.5 g. of salt crystallized; at 30 ml., 1.6 g.; at 19 ml., 1.0 g.; at 4 ml., 0.5 g. It had been found while working with this salt previously that during recrystallization of the salt it dissociated, so the first crop was not recrystallized further; white crystals, m. p. 140–145° (cor.).

Anal. (*l*BdA) Calcd. for $C_{13}H_{16}INO_3 \cdot C_{19}H_{22}N_2O$: C, 58.62; H, 5.85. Found: C, 58.53; H, 5.97. *Rotation.* (*l*BdA) 0.05 g. made up to 10 ml. with ethanol at 26° gave α_D −0.23°; *l*, 1; $[\alpha]^{26}D$ −46°.

The fourth and fifth fractions were combined and crystallized once; white crystals; yield, 1.1 g.

Rotation. (*l*BlA) 0.05 g. made up to 10 ml. with ethanol at 31° gave α_D −0.315°; *l*, 1; $[\alpha]^{31}D$ −63°.

***d*- and *l*-N-Succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene.**—The salts were decomposed in the same manner as the salt of the 6-bromo compound. From 4 g. of the less-soluble salt, 1.2 g. of the *d*-acid was obtained after one crystallization from a mixture of three volumes of carbon tetrachloride and one volume of petroleum ether (b. p. 60–110°); white crystals, m. p. 105–106° (cor.).

Anal. (*d*-acid) Calcd. for $C_{13}H_{16}INO_3$: C, 43.21; H, 4.43. Found: C, 43.22; H, 4.41. *Rotation.* (*d*-acid) 0.435 g. made up to 25 ml. with *n*-butanol at 33° gave α_D +0.21°; *l*, 1; $[\alpha]^{33}D$ +12°.

This *d*-acid did not have the maximum specific rotation since it was found that recrystallizing the less-soluble salt of another resolution several times, in spite of the dissociation of the salt, and then decomposing gave an acid with a specific rotation of +43° and a m. p. of 108° (cor.).

The decomposition of the more-soluble fraction did not give the pure *l*-acid; white crystals, m. p. 105–106° (cor.).

Rotation. (*l*-acid) 0.05 g. made up to 10 ml. with ethanol at 31° gave α_D −0.09°; *l*, 1; $[\alpha]^{31}D$ −18°.

Racemization of *d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene.—The procedure described for the racemization of *d*-N-succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene was used. A solution of 0.435 g. of the *d*-acid made up to 25 ml. with *n*-butanol was racemized. The following α_D values were obtained: at the start, +0.210°; after four hours, +0.182°; after nine hours, +0.154°; after fifteen hours, +0.127°; after twenty-one and one-half hours, +0.100°; after thirty and one-half hours, +0.075°; after forty-one and one-half hours, +0.052°. Calculated for a reversible unimolecular reaction, the half-life was twenty and one-half hours. A check racemization gave a half-life of nineteen and four-tenths hours.

1-Methylamino-2-methylbenzene.—By the same general procedure described below for the preparation of 1-methylamino-2,4-dimethylbenzene, 214 g. of *o*-toluidine was methylated to give 89 g. (37%) of product having a b. p. of 95° (15 mm.). Monnet, Reverdin and Nölting[12] report a b. p. of 207–208°.

1-Methylamino-2-methyl-4,6-dibromobenzene.—This compound was prepared by the method of Fries.[13] One minor change was made in his procedure in that anhydrous sodium acetate was added to bring the reaction to completion as well as heating. From 89 g. of 1-methylamino-2-methylbenzene was prepared 170 g. (82.5%) of product having a b. p. of 122–123° (1 mm.). Fries reports a b. p. of 187° (50 mm.).

N-Succinyl-1-methylamino-2-methyl-4,6-dibromobenzene.—To a solution of 27 g. of succinic anhydride in 210 ml. of dry benzene was added 69 g. of 1-methylamino-2-methyl-4,6-dibromobenzene and a drop of 85% phosphoric acid. This mixture was refluxed for twenty-two hours. The reaction mixture was worked up in the manner described in the preparation of N-succinyl-1-methylamino-2,4-dimethyl-6-iodobenzene. The product was recrystallized from a carbon tetrachloride–petroleum ether (b. p. 60–110°) mixture; white crystals, m. p. 116–117° (cor.); yield, 19 g. (20.2%).

Anal. Calcd. for $C_{12}H_{13}Br_2NO_3$: C, 38.00; H, 3.43. Found: C, 38.11; H, 3.66.

Resolution of N-Succinyl-1-methylamino-2-methyl-4,6-dibromobenzene.—A solution of 18 g. of N-succinyl-1-methylamino-2-methyl-4,6-dibromobenzene and 13.97 g. of cinchonidine in 200 ml. of 9:1 ethyl acetate–methanol by volume was filtered. This solution was concentrated by means of a gentle air stream to 170 ml. The crop of salt which had crystallized was collected. The dried product weighed 13.3 g. Concentration of the mother liquor to 130 ml. produced a second crop of 3.9 g. At 115 ml., 2.0 g. of salt crystallized; at 80 ml., 3.8 g.; and at 40 ml., 3.7 g. The first crop was recrystallized in the same manner to constant rotation. White feathery crystals were obtained; m. p. 161–163° (cor.); yield, 2.9 g.

Anal. (*l*B*d*A) Calcd. for $C_{12}H_{13}Br_2NO_3 \cdot C_{19}H_{22}N_2O$: C, 55.27; H, 5.20. Found: C, 55.63; H, 5.32. *Rotation.* (*l*B*d*A) 0.05 g. made up to 10 ml. with ethanol at 32° gave α_D −0.245°; *l*, 1; $[\alpha]^{32}D$ −49°.

Recrystallization of the fifth crop failed to change its rotation.

Rotation. (*l*B*l*A) 0.05 g. made up to 10 ml. with ethanol at 30° gave α_D −0.285°; *l*, 1; $[\alpha]^{30}D$ −57°.

***d*- and *l*-N-Succinyl-1-methylamino-2-methyl-4,6-dibromobenzene.**—The salts were decomposed in the same manner as the salt of the 6-bromo compound. From the less-soluble salt the *d*-acid was obtained. The rotation was observed before the acid was crystallized from a carbon tetrachloride–petroleum ether (b. p. 60–110°) mixture.

Rotation. (*d*-acid) 0.10 g. made up to 10 ml. with *n*-butanol at 32° gave α_D +0.07°; *l*, 1; $[\alpha]^{32}D$ +7°.

Crystallization of this acid produced white crystals; m. p. 118° (cor.).

Anal. (*d*-acid) Calcd. for $C_{12}H_{13}Br_2NO_3$: C, 38.00; H, 3.43. Found: C, 38.14; H, 3.52. *Rotation.* (*d*-acid) 0.51 g. made up to 15 ml. with *n*-butanol at 32° gave α_D +0.13°; *l*, 1; $[\alpha]^{32}D$ +3.8°.

Decomposition of the more-soluble salt gave the *l*-acid, which was not entirely pure.

Rotation. (*l*-acid) 0.45 g. made up to 10 ml. with ethanol at 30° gave α_D −0.245°; *l*, 1; $[\alpha]^{30}D$ −5.4°.

Racemization of *d*-N-Succinyl-1-methylamino-2-methyl-4,6-dibromobenzene.—A solution of 0.7 g. of the *d*-acid made up to 15 ml. with *n*-butanol was racemized. The solution was kept at this concentration throughout the racemization. This was done by weighing the polarimeter tube before the first period of refluxing and then making the tube up to this weight after each period of refluxing by adding *n*-butanol. Otherwise the procedure was the same as described for the racemization of *d*-N-succinyl-1-methylamino-2,4-dimethyl-6-bromobenzene. The following α_D values were obtained: at the start, +0.313°; after one-quarter hour, +0.268°; after one-half hour, +0.231°; after one hour, +0.166°; after one and one-half hours, +0.124°; after two and one-half hours, +0.066°. Calculated for a reversible unimolecular reaction, the half-life was one and one-tenth hours. This value was checked by repeating the racemization.

N-Succinyl-1-amino-2,4-dimethyl-6-iodobenzene.—To a solution of 9 g. of succinic anhydride and 21 g. of 1-amino-2,4-dimethyl-6-iodobenzene in 150 ml. of dry benzene was added one drop of 85% phosphoric acid. This mixture was refluxed for one hour, a white solid separating after fifteen minutes of refluxing. The mixture was cooled and allowed to stand at room temperature for several hours to complete the crystallization of the product. The solid was separated from the mother liquor by filtration and dried. It was recrystallized from a mixture of five volumes of ethanol and three volumes of water; white powder, m. p. 207–208° (cor.); yield, 8 g. (27%).

Anal. Calcd. for $C_{12}H_{14}INO_3$: C, 41.52; H, 4.04. Found: C, 41.87; H, 4.19.

Attempted Resolution of N-Succinyl-1-amino-2,4-dimethyl-6-iodobenzene.—A solution of 5 g. of N-succinyl-1-amino-2,4-dimethyl-6-iodobenzene and 5.68 g. of brucine in 230 ml. of ethyl acetate was filtered and concentrated to 210 ml. by directing a stream of air to the top of the flask. At this volume, 3.0 g. of salt had crystallized. At 190 ml., 2.8 g. crystallized and at 185 ml., 0.8 g. All of these crops showed the same rotation. The first two crops were combined and recrystallized in the same manner with no change of rotation; white crystals, m. p. 103–110° (cor.).

Anal. Calcd. for $C_{12}H_{14}INO_3 \cdot C_{23}H_{26}N_2O_4$: C, 56.67; H, 5.39. Found: C, 56.18; H, 5.62. *Rotation.* 0.05 g. made up to 10 ml. with ethanol at 25° gave α_D −0.140°; *l*, 1; $[\alpha]^{25}D$ −28°.

Decomposition of this salt in the previously described manner produced an optically inactive acid.

1-Methylamino-2,4-dimethylbenzene.—The procedure of Fichter and Müller[14] was improved.

A well-stirred mixture of 108.6 g. of 1-amino-2,4-dimethylbenzene and 450 ml. of water was heated to 50°. To this was added dropwise 100 g. of dimethyl sulfate over a period of about forty-five minutes. Cooling was applied to keep the temperature from rising above 50°. After the solution had become homogeneous, it was stirred for a half hour. When cool, it was acidified with 135 ml. of concentrated hydrochloric acid. It was cooled to below 10° and a solution of 62.3 g. of sodium nitrite in 175 ml. of water added dropwise. The cold solution was extracted with ether and the ether evaporated with a stream of air. The nitrosamine was reduced by adding it in portions to a solution of 610 g. of stannous chloride dihydrate in 630 ml. of concentrated hydrochloric acid. The temperature was kept below 60° during the reduction. A heavy precipitate of the tin complex settled to the bottom. After standing overnight, the mixture was made strongly alkaline with 40% aqueous sodium hydroxide and steam-distilled. The distillate was saturated with sodium chloride and extracted with ether. The ether extract was dried with solid potassium hydroxide, the ether removed by distillation and the amine distilled *in vacuo*, b. p. 89–91° (7 mm.); yield, 43 g. (35.5%). Pinnow and Oesterreich[15] report a b. p. of 220.5–221.5° (760 mm.).

N-Succinyl-1-methylamino-2,4-dimethylbenzene.—To a solution of 14.9 g. of succinic anhydride in 200 ml. of dry benzene was added 20 g. of 1-methylamino-2,4-dimethylbenzene and a drop of 85% phosphoric acid. The solution was refluxed for six hours, cooled, diluted

(12) Monnet, Reverdin and Nölting, *Ber.*, **11**, 2278 (1878).

(13) Fries, *Ann.*, **346**, 180 (1906).

(14) Fichter and Müller, *Helv. Chim. Acta*, **8**, 290 (1925).

(15) Pinnow and Oesterreich, *Ber.*, **31**, 2926 (1898).

with ether and extracted with 5% aqueous sodium hydroxide. The alkaline extract was acidified with 1:2 hydrochloric acid. The product separated as an oil which solidified on stirring and cooling. It was recrystallized from benzene; white crystals, m. p. 133–134° (cor.); yield, 22 g. (63%).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23. Found: C, 66.79; H, 7.42.

Nitration of N-Succinyl-1-methylamino-2,4-dimethylbenzene; N-Succinyl-1-methylamino-2,4-dimethyl-5-nitrobenzene.—To 25 ml. of well-stirred fuming nitric acid (sp. gr. 1.49) in a small flask cooled in an ice-bath was added in small portions 6 g. of N-succinyl-1-methylamino-2,4-dimethylbenzene. The mixture was allowed to stand for fifteen minutes and then poured onto ice. The mixture was made alkaline with concentrated aqueous ammonia, cooled with ice, and made acid to litmus with hydrochloric acid. The product settled out as an oil which solidified on standing a day in the refrigerator. The product was treated with Norit in methanol and recrystallized from benzene; light yellow crystals, m. p. 144.5–145.5° (cor.) with sintering at 139°; yield, 2.9 g. (40%).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.71. Found: C, 55.98; H, 5.48.

Hydrolysis of the Product of the Nitration of N-Succinyl-1-methylamino-2,4-dimethylbenzene; 1-Methylamino-2,4-dimethyl-5-nitrobenzene.—To 20 ml. of 1:1 hydrochloric acid was added 2 g. of the nitro compound. This mixture was refluxed for two hours, cooled, and made alkaline with 10% aqueous sodium hydroxide. The precipitate was removed by filtration, washed with water, and recrystallized from ethanol; orange-red needles, m. p. 140–141° (cor.).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.00; H, 6.66. Found: C, 60.18; H, 6.55.

N¹-Succinyl-1-methylamino-2,4-dimethyl-5-aminobenzene.—To a solution of 13 g. of N-succinyl-1-methylamino-2,4-dimethyl-5-nitrobenzene in 150 ml. of absolute ethanol was added 0.2 g. of platinum oxide. At room temperature and an initial pressure of 45 lb. the calculated amount of hydrogen was absorbed. The catalyst was removed by filtration and the ethanol evaporated. The product was recrystallized from absolute ethanol; almost transparent crystals, m. p. 169–172° (cor.); yield, 9.3 g. (80%).

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.40; H, 7.20. Found: C, 62.61; H, 7.35.

Methyl Ester of N¹-Succinyl-1-methylamino-2,4-dimethyl-5-aminobenzene.—A solution of 2 g. of N¹-succinyl-1-methylamino-2,4-dimethyl-5-aminobenzene in 40 ml. of methanol containing 5% of dry hydrogen chloride by weight was allowed to stand for two days at room temperature. The methanol was evaporated at room temperature *in vacuo*. The resulting oil was poured onto a watch glass and allowed to stand one week. This did not cause complete crystallization, so it was shaken with dilute aqueous ammonia, the material solidifying nicely. The solid was removed by filtration, washed with dilute aqueous ammonia and with water, and recrystallized from a mixture of one volume of ethanol and two volumes of water; white crystals, m. p. 109–110° (cor.); yield, 1.5 g. (72%).

Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.63; H, 7.60. Found: C, 64.37; H, 8.07.

N-Acetyl-1-methylamino-2,4-dimethylbenzene.—This was prepared by the acetylation of 1-methylamino-2,4-dimethylbenzene with acetic anhydride in acetic acid. The product had a m. p. of 63–63.5° (cor.). Pinnow and Oesterreich[15] report a m. p. of 65°.

N-Acetyl-1-methylamino-2,4-dimethyl-5-nitrobenzene.—Nitration of 25 g. of N-acetyl-1-methylamino-2,4-dimethylbenzene by the previously described procedure (acidification was unnecessary after treatment of the reaction mixture with concentrated aqueous ammonia) gave 6.3 g. (20%) of product; light yellow crystals from a mixture of three volumes of petroleum ether (b. p. 60–110°) and one volume of benzene, m. p. 109–110° (cor.).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.30. Found: C, 59.40; H, 6.31.

N¹-Acetyl-1-methylamino-2,4-dimethyl-5-aminobenzene.—To a solution of 16 g. of N-acetyl-1-methylamino-2,4-dimethyl-5-nitrobenzene in 150 ml. of absolute ethanol 0.1 g. of platinum oxide was added. At room temperature and an initial pressure of 47 lb. the calculated amount of hydrogen was absorbed. The catalyst was removed by filtration and the ethanol evaporated. The residue was recrystallized from benzene; white crystals, m. p. 134–134.5° (cor.); yield, 11 g. (80%).

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.75; H, 8.33. Found: C, 68.81; H, 8.50.

N-Acetyl-1-methylamino-2-methyl-5-nitrobenzene.—N-Acetyl-1-methylamino-2-methylbenzene[12] was nitrated in the previously described manner (acidification was unnecessary after treatment of the reaction mixture with ammonia). The product was recrystallized from dilute ethanol; light yellow crystals, m. p. 119° (cor.). Gnehm and Blumer[6] report a m. p. of 119° for the product they received on nitrating the same compound in sulfuric acid with a nitric acid–sulfuric acid mixture.

N-Nitroso-1-methylamino-2,4-dimethyl-6-nitrobenzene.—The method of Pinnow and Oesterreich[15] for the preparation of the same compound was used.

Methylation and nitrosation of 217 g. of 1-amino-2,4-dimethylbenzene following the procedure given for the preparation of 1-methylamino-2,4-dimethylbenzene gave 106 g. of wet, crude N-nitroso-1-methylamino-2,4-dimethylbenzene. Nitration in acetic acid gave 65 g. of N-nitroso-1-methylamino-2,4-dimethyl-6-nitrobenzene (17.4% based on the 1-amino-2,4-dimethylbenzene used); light yellow crystals (not pure), m. p. 58–61° (cor.). Pinnow and Oesterreich report a m. p. of 63°.

1-Methylamino-2,4-dimethyl-6-nitrobenzene.—The same procedure that Pinnow and Oesterreich used for the removal of the nitroso group was followed. From 60 g. of the nitrosamine, 25.4 g. (49%) of the secondary amine was obtained. The product was purified by steam distillation and recrystallization from methanol; dark red plates, m. p. 56–57° (cor.). Pinnow and Oesterreich report a m. p. of 58°.

N-Succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene.—To a solution of 28 g. of succinic anhydride and 24 g. of 1-methylamino-2,4-dimethyl-6-nitrobenzene in 100 ml. of dry benzene was added one drop of 85% phosphoric acid. This mixture was refluxed for seventy-two hours, cooled, diluted with ether and extracted with 5% aqueous sodium hydroxide. The alkaline extracts were acidified with dilute hydrochloric acid. The oil which was formed slowly solidified on standing. It was recrystallized from benzene. One treatment with Norit in benzene removed a tan color from the crystals; light yellow crystals, m. p. 129–131° (cor.); yield, 9 g. (24%).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.71. Found: C, 55.89; H, 5.92.

Resolution of N-Succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene.—A solution of 5.5 g. of N-succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene and 5.775 g. of cinchonidine in 100 ml. of 9:1 ethyl acetate–methanol by volume was filtered. The filtrate was evaporated to 65 ml. by directing a stream of air to the top of the flask. It was seeded with crystals obtained by allowing 1 ml. of the solution to evaporate slowly in a small test-tube. After five days in the refrigerator, 1.9 g. of salt had crystallized. Upon concentrating the mother liquor to 35 ml. and refrigerating, 4.7 g. of salt crystallized; at 20 ml., 1.8 g.; and at 5 ml., 0.25 g. The first two fractions were combined and recrystallized in the same manner to constant rotation. White feathery crystals were obtained; m. p. 141–143° (cor.); yield, 1.5 g.

Anal. (*l*Bd*A*) Calcd. for $C_{13}H_{16}N_2O_5 \cdot C_{19}H_{22}N_2O$: C, 66.90; H, 6.67. Found: C, 66.32; H, 6.60. *Rotation.* (*l*Bd*A*) 0.05 g. made up to 10 ml. with ethanol and 26° gave α_D −0.20°; *l*, 1; $[\alpha]^{26}D$ −40°.

***d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene.**—The less-soluble salt was decomposed with 0.5% hydrochloric acid in the same manner as the salt of the 6-bromo compound. Before crystallization from benzene the specific rotation was determined.

Rotation. (*d*-acid) 0.05 g. made up to 10 ml. with ethanol at 25° gave α_D +0.125°; *l*, 1; $[\alpha]^{25}D$ +25°.

Crystallization from benzene produced light yellow crystals; m. p. 130–131° (cor.).

Anal. (*d*-acid) Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.71; N, 10.00. Found: C, 56.22; H, 5.87; N, 10.07. *Rotation.* (*d*-acid) 0.05 g. made up to 10 ml. with ethanol at 25° gave α_D +0.05°; *l*, 1; $[\alpha]^{25}D$ +10°.

Racemization of *d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene.—The *d*-acid was completely racemized in a half hour in boiling *n*-butanol.

A solution of 0.25 g. of the *d*-acid made up to 15 ml. with methyl acetate was racemized using the technique described for the racemization of *d*-N-succinyl-1-methylamino-2-methyl-4,6-dibromobenzene. The following α_D values were obtained: at the start, +0.215°; after fifteen minutes, +0.164°; after thirty minutes, +0.121°; after forty-five minutes, +0.091°; after sixty minutes, +0.067°; after ninety minutes, +0.037°. Calculated for a reversible unimolecular reaction, the half-life was thirty-six minutes. A check racemization gave a half-life of thirty-eight minutes.

Catalytic Hydrogenation of *d*-N-Succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene; 1,5,7-Trimethylbenzimidazole-2-β-propionic Acid.—A solution of 0.25 g. of *d*-N-succinyl-1-methylamino-2,4-dimethyl-6-nitrobenzene in 125 ml. of ether was hydrogenated at room temperature and 40 lb. pressure with 0.1 g. of platinum oxide as catalyst. At the end of the reduction, the catalyst was removed by filtration and the ether evaporated by directing a stream of air onto the solution. The residue was dried in a vacuum desiccator.

No quantitative specific rotation was determined for this crude product. However, a qualitative reading showed the material to be *dextro*-rotatory.

When a solution of the crude product in *n*-butanol was refluxed for about an hour, and cooled, white crystals separated. Recrystallized from ethanol, the material melted at 265–267° (cor.). It was soluble in 5% aqueous sodium bicarbonate and was optically inactive.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.06. Found: C, 67.22; H, 6.82; N, 12.06.

Summary

1. Several new N-succinyl-1-methylamino-2,4-dimethyl-6-substituted benzenes and N-succinyl-1-methylamino-2-methyl-4,6-dibromobenzene have been prepared, resolved and the half-lives of the optically active forms determined.

2. The half-lives of the series are as follows: bromine, three and one-tenth hours; iodine, twenty and one-half hours; nitro, six-tenths hour; and the dibromo compound, one and one-tenth hours. Boiling *n*-butanol was used as solvent except in the case of the nitro compound where boiling methyl acetate was employed. The corresponding methyl and methoxyl analogs have been prepared previously and their half-lives are nine hours in boiling *n*-butanol and two and seven-tenths hours in boiling methyl acetate, respectively.

3. From these values, after comparison with the interference effects produced by the same groups in the biphenyl series, it was concluded that factors other than size of the groups were influencing the rates of racemization.

4. The basicity of aryl amines is reduced by the substitution of electronegative groups in the *o*-, *m*- or *p*-positions. A decrease in the expected stability of the optically active amines is observed with similar substituents. From these facts it appears that the increased double-bond character of the carbon–nitrogen bond in these amines of decreased basicity facilitates racemization. The tendency to form a double bond will aid in forcing the substituents on the amino nitrogen into a coplanar configuration with the ring.

URBANA, ILLINOIS RECEIVED MARCH 11, 1948

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

The Reaction of Formaldehyde with Proteins. V. Cross-linking between Amino and Primary Amide or Guanidyl Groups

BY HEINZ FRAENKEL-CONRAT AND HAROLD S. OLCOTT

According to the opinion of most experts in the field, the tanning or hardening action of formaldehyde is probably not due to its primary addition to the amino or any other type of protein group, but rather to a secondary condensation reaction which transforms the methylol (—CH_2OH) groups into cross-linking methylene (—CH_2—) bridges. The first experimental evidence for the occurrence of condensation was supplied by Nitschmann and his co-workers, who showed that there was a loss of water during the reaction of casein with gaseous formaldehyde.[2,3] Proof for cross-linking was obtained in studies from this Laboratory, in which it was demonstrated that the average molecular weights of salmine[4] and other proteins[5] could be increased by formaldehyde treatment.

The question arose: Which protein group or groups are available for such condensation reactions with formaldehyde? Nitschmann, *et al.*,[2] showed that the amino groups were directly concerned.[6] Thus casein, in which the amino groups were largely protected with acetyl groups, bound formaldehyde only by addition, while condensation occurred when unmodified casein was used. However, experiments with salmine,[4] which con-

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Nitschmann and Hadorn, *Helv. Chim. Acta*, **27**, 299 (1944).

(3) Nitschmann and Lauener, *ibid.*, **29**, 174 (1946).

(4) Fraenkel-Conrat and Olcott, THIS JOURNAL, **68**, 34 (1946).

(5) Mecham and Fraenkel-Conrat, in preparation.

(6) See also Gustavson, *J. Int. Soc. Leather Trades Chem.*, **24**, 377 (1940); *Kolloid Z.*, **103**, 43 (1943); *J. Biol. Chem.*, **169**, 531 (1947).

tains no primary amino groups,[7] suggested that at 70° guanidyl groups also react with formaldehyde to form cross-linking methylene groups. The isolation of djenkolic acid ($HOOC-CHNH_2-CH_2-S-CH_2-S-CH_2-CHNH_2-COOH$) from reduced keratins that had been treated with formaldehyde at elevated temperature[8] indicated that, under these conditions, cross-linking occurred between sulfhydryl groups. Nitschmann and Hadorn[2] proposed that the formation of methylene bridges between amino and peptide groups accounts for the tanning action of formaldehyde but this was not proved. Reactions involving pairs of amino[6] or of peptide groups[9] have also been hypothesized but appear to be chemically improbable. On the basis of experiments with formaldehyde and casein or casein derivatives, Wormell and Kaye[10] proposed the hypothesis that acid-hardening of this protein "occurs largely by means of cross-linking on to the amide groups using the formaldehyde already attached to amino groups."

It will be shown in the present study that, at room temperature and over a wide *p*H range, formaldehyde can form cross-linking methylene bridges between *amino* groups on the one hand, and *primary amide* or *guanidyl* groups on the other. The

$$R-NH_2 + HCHO + H_2NCO-R \longrightarrow R-NH-CH_2-NHCOR + H_2O \quad (I)$$

$$R-NH_2 + HCHO + NH_2-C(=NH)-NHR \longrightarrow R-NH-CH_2-NH-C(=NH)-NHR + H_2O \quad (II)$$

secondary amide groups of peptide bonds do not participate in Reaction I at room temperature. It will further be shown that, by the same reactions, ammonia or simple primary amines can be bound to protein amide groups; and simple amides or guanidines to the protein amino groups. The data suggest that the tanning action of formaldehyde on proteins at room temperature may be due largely to Reactions I and II.

Condensation products of low molecular weight secondary amines, formaldehyde and primary amides were described by Einhorn[11] but the reaction apparently has not since been studied in detail nor have its implications for the tanning mechanism been previously recognized.

Results

A. Model Experiments.—Model experiments with simple compounds were helpful in ascertaining which types of protein groups might be expected to become cross-linked through methylene bridges. For most of these experiments, 0.4–0.5 molar solutions of two different compounds were treated with about 2 molar formaldehyde at room temperature and at a *p*H where each compound by itself bound little if any formaldehyde in a manner which was not reversed in the presence of dimedon at *p*H 4.6. The binding of appreciable amounts, under such conditions, was regarded as evidence for a condensation reaction involving both nitrogenous components of the system. This conclusion was usually corroborated by other means of analysis and, in some cases, by isolation of the reaction products.

The limitations of such an experimental approach are two-fold: (1) Results obtained with compounds which by themselves bind formaldehyde over a wide *p*H range, *e. g.*, guanidines,[12] cannot be unequivocally interpreted as evidence for cross-linking. (2) Some methylene compounds may be so unstable as to yield their formaldehyde in the presence of dimedon.[13]

With amides and most amines, however, these limitations do not apply. Pairs formed by a primary amide, on the one hand, and a primary or secondary amine or an amino acid on the other, give condensation products with formaldehyde over the range of *p*H 3.2 to 7.6 (Reaction I) (Tables I and II).[14] More alkaline or more acid solutions could not be studied in this manner, since they catalyze the stable fixation of increasing amounts of formaldehyde by the amides alone[12]

(7) Fraenkel-Conrat and Olcott, *Fed. Proc.*, **6**, 253 (1947).

(8) Consden, Gordon, and Martin, *Biochem. J.*, **40**, 580 (1946); Middlebrook and Phillips, *ibid.*, **41**, 218 (1947).

(9) Küntzel, *Angew. Chem.*, **50**, 309 (1937).

(10) Wormell and Kaye, *J. Soc. Chem. Ind.*, **64**, 75 (1945).

(11) Einhorn, *Ann.*, **343**, 207 (1905); **361**, 113 (1908).

(12) Unpublished experiments have shown that, at room temperature, guanidines bind formaldehyde slowly over the range of *p*H 3–7, but much more rapidly above *p*H 10 and below *p*H 2; between *p*H 10 and 11 about one-half mole of formaldehyde per mole guanidine was bound in eight hours. The reactivity at elevated temperature was studied previously.[4]

(13) The apparent non-participation of sulfhydryl groups in methylene compound formation (Table XI) is possibly ascribable to such lability. A reaction involving amino and sulfhydryl groups might be assumed to occur in view of the ease with which cysteine condenses with formaldehyde to form the cyclic thiazolidine carboxylic acid [Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); Ratner and Clarke, THIS JOURNAL, **59**, 200 (1937)].

(14) Methylamine alone, of all amines studied, bound formaldehyde at *p*H 3.0 in a manner stable to dimedon but reversible by acid hydrolysis (Table II). The fact that the cyclic trimer of methylamine and formaldehyde also did not release most of its formaldehyde in the presence of dimedon suggests that this compound may form in the solution at *p*H 3.0. This trimer differs from other amine–aldehyde reaction products, including the butylamine–formaldehyde trimer, in yielding a water-soluble stable condensation product with dimedon at *p*H 4.6. Thus, if first exposed to buffers of *p*H 3–5 for twenty-four hours at room temperature, almost the entire formaldehyde of the trimer (94%) can be precipitated with dimedon, but if dimedon and *p*H 4.6 buffer are added as usual, simultaneously, only about 10% of the expected amount of the insoluble condensation product is obtained; and upon addition of excess free formaldehyde to the solution, only about 60% of the added dimedon is precipitated, indicating some fixation in soluble form. Higher aliphatic amines were found to bind formaldehyde in an acid-irreversible manner when acetic acid or its homologs were used as buffers. ε-Aminocaproic acid showed the same phenomenon by itself (Table II). It appears probable that this may be attributed to the availability of the $-CH_2-COOH$ group for a Mannich type of condensation[15] with the amines and formaldehyde. This reaction is largely suppressed in favor of Reaction I if amides are also present. In contrast to amine acetates, amino acids and amine hydrochlorides do not condense to an appreciable extent with formaldehyde and acetic acid within three days at room temperature and *p*H 3–5 (Table II).

(15) Blicke, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942.

TABLE I

CONDENSATION REACTION OF FORMALDEHYDE WITH AMINO OR IMINO ACIDS AND AMIDES[a]

Reactants	*p*H	Time, days	Formaldehyde bound, equivalents/basic N[b] Total	Irreversibly
Alanine + acetamide	3.5	1 2 5 12	0.61 0.67 0.64 0.72	0.0 (2 days)
Alanine	3.5	1 2 5 12	.0 0.0 0.03 0.09	
Acetamide	3.2	1 2 5 12	.05 0.10 0.20 0.40	
Alanine + acetamide	4.3	2 4	.60 0.71	.16 (4 days)
Alanine	4.3	2 4	.0 0.23	
Acetamide	4.3	2 4	.06 0.11	
Alanine + acetamide	7.6	1 7	.75 1.15	
Alanine (0.4 *M*)	7.6	1 7	.22 0.78	.04 0.40
Acetamide	7.6	1 7	.05 0.44	
Alanine + propionamide	3.5 4.0	1 1	.38 0.48	.0 (*p*H 4.0)
Propionamide	3.5 4.0	1 1	.10 0.08	
Alanine + propionamide	4.8	3 3	.42[c] 0.60	.0
Propionamide	4.8	3 3	.00[c] 0.04	.0
Glycine + acetamide	3.5	1	.67	
Glycine	3.6	1	.02	
Glycine (0.5 *M*) + acetamide (0.5 *M*)	4.7[c]	1	.67	.0
Glycine (1.0 *M*)	4.2[c]	1	.06	
Proline + acetamide[d]	7.6	1	.62	
Proline	7.6	1	.0	
Proline + acetamide	4.4	1	.30	
Proline	4.5	1	.07	
Acetamide	4.4	1	.04	
Sarcosine·HCl + acetamide	3.4	3	.90	
Sarcosine·HCl	3.4	3	.0	
Sarcosine·HCl + acetamide	4.2	3	.71	
Sarcosine·HCl	4.2	3	.0	
Sarcosine·HCl + acetamide	7.6	3	.64	
Sarcosine·HCl + aceturic acid	7.6	3	.0	
Sarcosine·HCl + benzoylalanine	7.6	3	.0	
Sarcosine·HCl	7.6	3	.0	
Threonine + acetamide	4.2	3	.24	
Threonine	4.2	3	.04	
Alanylalanine + alanine	4.2	3	.17	
Alanylalanine (0.4 *M*)	4.2	3	.15	
ε-Aminocaproic acid + acetamide	3.4	3	.64	.14
ε-Aminocaproic acid	3.4	3	.52	.38
ε-Aminocaproic acid + acetamide	5.4	1 3	.75 0.95	.24 0.24
ε-Aminocaproic acid	4.9	1 3	.52 0.66	.39 0.58
ε-Aminocaproic acid + acetamide	2.4[e]	3	.64	.06
ε-Aminocaproic acid	2.4[e]	3	.12	.06

[a] Unless otherwise stated, the amino acid or amide alone was treated in 0.8 *M* solution. Amino acid + amide solutions were 0.4 *M* in regard to each reactant; the formaldehyde, 1.5 to 2.5 *M*. Except as noted, the solutions at *p*H 3.2–4.3 were buffered with approximately 0.5 *M* acetic acid or acetate; those at *p*H 4.4–7.6 with approximately 0.6 *M* phosphate. Reactions were performed at room temperature (approximately 23°). [b] Or amide-N when no basic nitrogen was present. [c] No buffer was used. [d] For the rate curve of this reaction see Fig. 1. [e] Oxalic acid (0.3 *M*) used as buffer.

(Table III). However, indications were obtained by other techniques that a condensation reaction involving alanine and acetamide did not occur appreciably below *p*H 1 and occurred only to a small extent above *p*H 11 (Table III).

A comparison of the rate and extent of the reaction occurring at *p*H 3–4 and *p*H 6–7 indicated that with amino acids and amides the neutral medium was the more favorable (Table I, Fig. 1). With amines and amides, however, condensation occurred better in acid solution. This difference was attributed to the rapid formation and stability of cyclic trimers of the amines and formaldehyde in alkaline solution (*cf.* footnote 14) and could be demonstrated by treating such trimers with acetamide at both *p*H levels. Amine–methylene–amide formation occurred at *p*H 4 but not at *p*H 8.3 (Table IV).

As expected, the condensation reaction was favored by high concentrations of the reactants

TABLE II

CONDENSATION REACTION OF FORMALDEHYDE WITH AMINES AND AMIDES[a]

Reactants	Molarity of Amine	Amide	Formaldehyde	Buffer	Final pH	Time, days	Formaldehyde bound, equivalents/basic N[b] Total	Irreversibly
Methylamine·HCl + acetamide	0.5	0.5	2.5	None	3.8	1	0.57[c]	0.0
Methylamine·HCl	1.0	..	2.5	None	3.0	1	.24[c]	
Dimethylamine·HCl + acetamide	0.45	.45	2.5	None	4.7	1 3	.31 0.35	
Dimethylamine·HCl	.9	..	2.5	None	5.0	1 3	.06 0.06	
n-Butylamine·HCl + acetamide	.25	.25	1.25	None	4.4	1 3	.58 0.70	.0 (3d)
n-Butylamine·HCl + propionamide	.25	.25	1.25	None	4.6	1 3	.58 0.70	
n-Butylamine·HCl	.5	..	1.25	None	3.9	3	.04	
n-Butylamine·HCl	.5	..	1.25	Acetic acid[d]	3.2	3	.00	
i-Butylamine + acetamide	.4	.4	2.0	Acetic acid[d]		3	.69	.12
i-Butylamine	.8	..	2.0	Acetic acid[d]	4.4	3	.79	.56
i-Butylamine	.8	..	2.0	Formic acid	3.8	3	.58	.45
i-Butylamine	.8	..	2.0	Butyric acid	4.9	3	.92	.67
i-Butylamine·HCl	.8	..	2.0	Acetic acid	2.5	3	.10	.0
Ethanolamine·HCl + acetamide	.43	.5	2.5	None	4.4	0.2 1 3	.63 0.70 0.70	.0 (1d)
Ethanolamine·HCl	.86	..	2.5	None	4.0	0.2 1 3	.0 0.0 0.0	.0 (1d)
Ethanolamine·HCl	.60	..	1.5	Acetic acid	2.4	1	.00	
Ethanolamine + acetamide	.95	1.0	2.4	Oxalic acid		1 5	.60 0.70	.. 0.05
Ethanolamine	.95	..	2.4	Oxalic acid		1 5	.05 0.25	.. 0.15
Ethanolamine + acetamide	.95	1.0	2.4	Acetic acid		1 3	.38 0.67	.0 0.22
Ethanolamine	.95	..	2.4	Acetic acid		1 3	.25 0.65	.15 0.49
Ethanolamine + acetamide	.25	0.25	1.25	Phosphate	8.0	1	.53	
Ethanolamine	.5	..	1.25	Phosphate	8.5	1	.25	.17
Ethanolamine + acetamide	.25	.25	1.25	Phosphate	5.9	1	.55	
Ethanolamine	.5	..	1.25	Phosphate	6.3	1	.22	.20
Ethanolamine + acetamide	.25	.25	1.25	Phosphate	6.8	1	.62	
Diethanolamine·HCl + acetamide	.43	.45	2.5	None		1 3	.06 0.06	
Diethanolamine·HCl	.85	..	2.5	None		1 3	.00 0.00	
1,4-Diaminobutane·2HCl + acetamide	.4	.4	2.0	Acetic acid		3	.62	.14
1,4-Diaminobutane·2HCl	.8	..	2.0	Acetic acid		3	.20	.20
Glycine ethyl ester·HCl + acetamide	.4	.4	2.0	Acetic acid	3.0	1 3	.26	.20
Glycine ethyl ester·HCl	.8	..	2.0	Acetic acid	3.0	1 3	.00 0.02	
Glycine ethyl ester·HCl + acetamide	.5	.5	2.5	None	3.6	1	.28	
Glycine ethyl ester·HCl	.5	.5	2.5	None	3.2	1	.00	
Acetamide	..	.8	2.0	Acetate	4.3	2 4	.06 0.11	
Acetamide	..	.8	1.5	Acetic acid	3.2	2 5	.10 0.20	
Acetamide	..	.7	1.8	Oxalic acid	2.0	1	.55	.0
Propionamide	..	.8	2.0	Acetate	4.0 4.8	1	.08 0.08	
Propionamide	..	.8	2.0	Acetic acid	3.3	3	.30	.0
Propionamide	..	.7	2.0	Oxalic acid	2.0	1	.63	.0

[a] Reactions performed at room temperature. [b] Or amide-N if no basic nitrogen is present. [c] Similar results were obtained when acetic acid was also present. Concerning the fixation of formaldehyde by methylamine hydrochloride, *cf.* footnote 14. [d] Similar results were obtained with formic and butyric acid.

(Table V). It reached equilibrium within twenty-four to forty-eight hours, at which time the formaldehyde bound corresponded usually to 60–100% of that equivalent to the amine or amide used. As final proof for the occurrence of the reaction, the formaldehyde condensation products of acetamide with alanine and proline were isolated and characterized.

The non-reactivity of secondary amides (—CO—NHR) for the condensation reaction as contrasted to the primary amides (—CO—NH_2) is significant (Table I).[16,17] Cross-linking has often been postulated as involving mainly the peptide linkage. In the light of the present findings, it would appear that the peptide bonds cannot be involved in the tanning reactions occurring at room temperature.

(16) Einhorn[11] found that primary and secondary amides differed also in their ability to add formaldehyde to form methylol groups.

(17) French and Edsall, "Adv. in Protein Chemistry," Vol. II, Academic Press, Inc., New York, N. Y., 1945, p. 277.

TABLE III

EFFECT OF EXTREMES OF *p*H ON ALANINE–ACETAMIDE–FORMALDEHYDE REACTION[a]

Alanine × 10^{-3} mole	Acetamide × 10^{-3} mole	Solvent	Final *p*H[b]	Apparent amino-N[c] × 10^{-3} mole	Formaldehyde bound × 10^{-3} moles
1.0	...	0.6 ml. 6 *N* HCl	0.85	1.0	0.0
1.0	1.0	0.6 ml. 6 *N* HCl	0.85	1.15	.63
...	1.0	0.6 ml. 6 *N* HCl	0.85	0.24	.52
1.0	...	0.6 ml. 2 *N* NaOH	11.3	.83	.01
1.0	1.0	0.6 ml. 2 *N* NaOH	11.1	.70	.49
...	1.0	0.6 ml. 0.33 *N* NaOH	11.45	.16	.58
1.0	...	0.6 ml. H_2O	4.7	.94	.01
1.0	1.0	0.6 ml. H_2O	4.7	.48	.57
...	1.0	0.6 ml. H_2O	4.5	.06	.02

[a] 24 hours at room temperature. All plus 0.5 ml. 7.5% formaldehyde (1.25 mM). [b] Measured after dilution to 10 ml. [c] See experimental part for discussion.

TABLE IV

USE OF CYCLIC TRIMERS OF METHYL- AND BUTYLAMINE AND FORMALDEHYDE FOR CONDENSATION REACTION WITH AMIDE

Reaction mixture	Final *p*H	Equiv. of formald. bound[a]
1,3,5-Tri*methyl*trimethylenetriamine (0.33)[b] + acetamide (1.0)	4.0	0.5[a]
1,3,5-Tri*methyl*trimethylenetriamine (0.33)[b]	4.0	0.11
1,3,5-Tri*methyl*trimethylenetriamine (0.33)[b] + acetamide	8.3	0.07[c]
1,3,5-Tri*methyl*trimethylenetriamine (0.33)[b]	8.3	0.0[c]
1,3,5-Tri*butyl*trimethylenetriamine (0.33) + acetamide (1.0)	5.0	0.55
1,3,5-Tri*butyl*trimethylenetriamine (0.33)[b]	5.0	0.13

[a] Stably in presence of dimedon at *p*H 4.6. [b] Figures in parentheses represent millimoles used. Each reaction mixture contained also 1.5 ml. 3 *M* acetic acid (*p*H 4 and 5) or phosphate buffer (*p*H 8.3). They were held for three days at room temperature. [c] To assure complete liberation of formaldehyde from 1,3,5-tri*methyl*trimethylenetriamine an aliquot of the diluted alkaline reaction mixture was held for 1 day in the *p*H 4.6 buffer before addition of the dimedon (*cf.* footnote 14).

TABLE V

EFFECT OF CONCENTRATION OF REACTANTS ON CROSS-LINKING REACTION (A); AND LACK OF EFFECT ON ACETAMIDE–FORMALDEHYDE (B); AND ALANINE–FORMALDEHYDE REACTION (C)[a]

	Molarity of					Formaldehyde bound, equivalents/basic N[b]		
	Alanine	Acetamide	Formaldehyde	Time, days	Final *p*H			
A:	0.14	0.14	1.4	3	3.4	0.17		
	.4	.4	1.5	2	3.4	.67		
	.4	.4	0.75	2	3.4	.44		
	.4	.4	0.5	3	3.4	.36		
B:	..	.8	1.5	2 5 12	3.4	.10	.20	.40
	..	.16	1.5	2 5 15	3.4	.08	.19	.50
C:	.8	..	1.5	5	7.6	.55		
	.16	..	1.5	5	7.6	.5		

[a] Reactions performed at room temperature, with acetic acid or phosphate as buffers. Alanine itself reacts at an appreciable rate with formaldehyde only at *p*H 7 or above. [b] Or amide-N if no basic N is present.

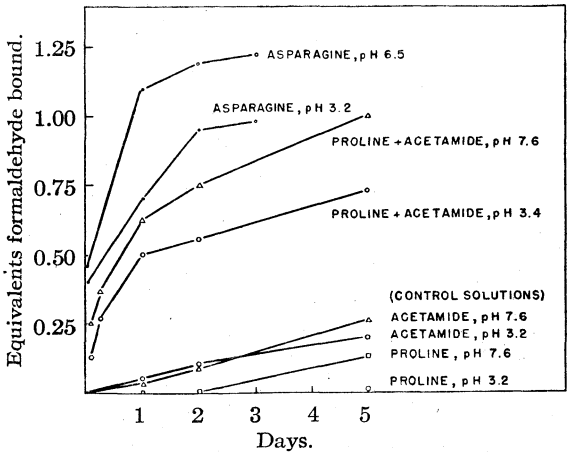


Fig. 1.—Rate of fixation of formaldehyde by various compounds at 23°: asparagine, 1 mM. in 3.5 ml. containing 2.5 mM. formaldehyde and approximately 0.5 molar acetate or phosphate buffer. For composition of other reaction mixtures, see Table I. The amount of unbound formaldehyde was determined by precipitation with dimedon.

The mechanism of Reaction (I) has not been clearly established. Like the Mannich reaction,[15] it is a condensation involving a primary or secondary base, formaldehyde, and a reactive hydrogen, furnished in this case by a primary amide group. It would appear probable that this occurs in two steps. Einhorn[11] believed that the amido-methylol compound formed first, but presented no conclusive evidence in support of this mechanism. However, addition of formaldehyde to the amide group in the absence of an amine proceeds much more slowly than the cross-linking reaction and thus probably does not represent an intermediate stage. This is further indicated by the inability of amido-methylol compounds to condense with the amines (see Experimental).

The alternate possibility is that the amine reacts first to give an aminomethylol (Reaction III) which then condenses with the amide (Reaction IV).

$$R{-}NH_2 + CH_2O \longrightarrow R{-}NHCH_2OH \quad (III)$$

$$R{-}NH{-}CH_2OH + NH_2{-}CO{-}R' \longrightarrow R{-}NH{-}CH_2{-}NH{-}CO{-}R' + H_2O \quad (IV)$$

In neutral and alkaline solution, amines are known to be transformed by formaldehyde to methylol and dimethylol compounds, but no evidence appears to be available that such reactions occur also at *p*H 3–4. Because of the lability of the amino–methylol linkage, the occurrence of this reaction cannot be demonstrated by the dimedon or Van Slyke amino nitrogen techniques.[18] That formaldehyde actually reacts with amino groups within a few hours at *p*H 3.6 or lower is indicated by (1) a fall in the *p*H of the reaction mixtures (Table VI)

(18) The *slow* decrease in the formaldehyde and amino nitrogen contents of amino acid–formaldehyde reaction mixtures[17] is evidence of secondary reactions, possibly of the Mannich type, rather than of the primary addition reaction.

TABLE VI

EFFECT OF FORMALDEHYDE ON SOLUTIONS OF AMINE HYDROCHLORIDES AT *p*H 3.6[a]

Amine	Drop of *p*H after addition of formaldehyde: Original *p*H	Final *p*H	Time until constant, min.	Equivalents of NaOH needed to titrate back to original *p*H
Methyl	3.6	1.2	120	0.170
Dimethyl	3.6	2.9	60	.0018
Butyl	3.6	2.5	60	.014
Ethanol	3.6	2.2	30	.029
Diethanol	3.6	3.1	10	.0014

[a] To 10 ml. of 1.5 *M* solutions of the amine hydrochlorides adjusted to *p*H 3.6 ± 0.1 were added 4 ml. of commercial 40% formalin (*p*H 3.6).

and (2) a change in optical rotation of solutions containing L-amino acids and formaldehyde. The rate of reaction (III), even in acid solution, appears to be sufficiently fast, compared to the cross-linking, to allow it to be the first step of the latter reaction.

While it is probable that in acid solution the equilibrium of Reaction III is greatly to the left, this may well be shifted by the occurrence of Reaction IV to permit the cross-linking to proceed to the observed extent. Changes in the optical rotation of reaction mixtures containing an optically inactive amide, an optically active amine, and formaldehyde lend independent support to the two-stage mechanism here proposed (see Experimental). The initial formation of the aminomethylol compound is also now favored as occurring during typical Mannich reactions.[15,19]

B. Experiments with Proteins or Macromolecular Model Compounds.—A second experimental approach consisted in studying the introduction, by means of formaldehyde, of simple amines, amides, or guanidines into proteins or other macromolecular materials rich in amide, amino, or guanidyl groups. The data generally support the findings obtained with the model systems. Gliadin and polyglutamine, both very rich in *amide groups*, bind in acid solution large amounts of ammonia, primary amines, or amino acids (Table VII). Imino acids appear to be bound only to a limited extent by gliadin and not above *p*H 2.0 by polyglutamine, although they were found to react readily with acetamide over a wide *p*H range (Table I). Since the resultant linkage was found to be relatively labile, the possibility exists that greater amounts of the secondary amines were actually bound by polyglutamine and gliadin than could be demonstrated after extensive periods of dialysis. It seems that in acid solution the amido–methylol linkage, though forming more slowly, is more stable than the methylene cross-links here described. This probably explains why in 50% acetic acid–formalin much more alanine is introduced into gliadin in two hours than after three days (Table VII).

When proteins or a tyrosine-formaldehyde polymer[20] rich in *amino groups* were treated with formaldehyde in the presence of acetamide, considerable amounts of this compound were introduced at room temperature over the range of *p*H 2–8 (Table VIII). As expected, this reaction did not occur appreciably, however, if most of the amino groups of the protein were blocked by acetylation.

The cross-linking of amino with guanidyl compounds by formaldehyde is demonstrated by the introduction, over the range of *p*H 4.2–8.5, of methylguanidine into proteins rich in amino groups (Table IX). On the other hand, the inability of amide and guanidyl groups to condense under similar conditions is shown with polyglutamine (Table VII) and salmine (Table VIII). Both of these latter conclusions were suggested but not conclusively demonstrated by the model experiments. The fixation of all low molecular compounds by proteins is usually accompanied by an analytically demonstrable increase in the amounts of formaldehyde bound over those bound under the same conditions in the absence of the added compounds.

A particular case of amine–amide interaction was studied in some detail, because of its special interest and possible practical importance. Swallen and Danehy[21,22] have described a remarkable catalytic effect of amines or ammonium ions on the reaction of formaldehyde with zein. When a 20% solution of zein in glacial acetic acid is treated with an equal volume of commercial formalin, a gel forms within a few minutes only if traces of ammonium ions or primary amines are added; otherwise, the mixture remains fluid for several hours.[23] Similar experiments have now been performed with gliadin. This protein also sets quickly to a gel only after the addition of small amounts (*e.g.*, 2 equivalents per 10^4 g.) of ammonia or primary amines. Commercial gliadin and a preparation made by a technique involving isoelectric fractionation from acetic acid solution behaved like zein in gelling slowly even without added amines, but gliadin carefully prepared from wheat gluten by fractionation with cold alcohol did not gel at all until an amine was added as "catalyst".[24] Gels formed in the presence of small amounts of "catalyst" were found to liquefy if the reaction mixture was held for one to three days at room temperature. In contrast permanent gels and insoluble products were obtained when greater amounts of amine had been added.

(19) Bachmann and Heisey, THIS JOURNAL, **68**, 2496 (1946).

(20) Obtained by treating tyrosine with formaldehyde in acid solution. The preparation used contained 4.8% amino nitrogen (Olcott, in preparation).

(21) Swallen, *Ind. Eng. Chem.*, **33**, 397 (1941).

(22) Swallen and Danehy, in Alexander, "Colloid Chemistry," Vol. VI, Chemical Catalog Co., New York, N. Y., 1946, p. 1140.

(23) The authors are indebted to J. P. Danehy, Corn Products Refining Co., for drawing their attention to this phenomenon.

(24) The same behavior was noted with "gliadin sulfate," the water-soluble fraction resulting from the sulfation of wheat gluten with concentrated sulfuric acid. This derivative contains acid sulfuric esters on the hydroxyl groups and sulfonic acid substituents on the phenolic groups of the protein [Reitz, Ferrel, Fraenkel-Conrat and Olcott, THIS JOURNAL, **68**, 1024 (1946)].

TABLE VII

FIXATION OF AMINES BY MACROMOLECULAR COMPOUNDS RICH IN AMIDE GROUPS THROUGH FORMALDEHYDE CONDENSATION[a]

Macromolecular compound	Additive	Final pH	Equivalents per 10^4 g. Bound additive[b]	Bound formaldehyde	Increased acid groups
Polyglutamine[c]	Ammonium chloride[d]	2.5	23	33	
	Methylamine·HCl[d]	2.6	18	17	
	Dimethylamine·HCl	3.2	0	8	
	Alanine·HCl	2.8	32	25	14[e]
	Sarcosine·HCl	2.0	10	4	3.4
	Proline·HCl	2.2	0	7	0
	Piperazine·2HCl	2.6	20	25	
	Methylguanidine·$^1/_2H_2SO_4$	3.2	0	3	
	Morpholine oxalate	4.2	20	23	
	Ammonium acetate	3.6	6	8	
	Methylamine	4.3	10	16	
	Alanine	3.3	28	24	6[e]
	Alanine	4.8	18	22	14
	Sarcosine	4.9	0	7	0
	Proline	3.3	0	3	0[e]
	Proline	4.8	0	1	0
	None	3.4	..	7	..
Gliadin	Ammonium chloride (2 hours)[g]	2.2	(22)		
	Ammonium acetate (2 hours)[g]	2.8	(9)		
	Alanine (2 hours)	2.6	(23)	15	14.6
	Alanine (3 days)	2.6	(3)		2.0
	Proline (2 hours)	2.6	(7)	6	2.3
	Proline (3 days)	2.6	(7)		2.3
	Amino ethyl sulfuric acid (7 days)	2.6	10.0[h]	21	
	None (2 hours)	2.5	..	4	..
	None (7 days)	2.5	..	20	..
Gliadin[i]	Ammonium chloride[g]	2.3	(17)		
	Ammonium acetate (30% insol.)	3.4	(7)		
	Amino ethyl sulfuric acid	2.9	9.8[h]		6.4
	Alanine	3.2	(9)		5.9
	Proline	3.2	(7)		2.0
	Alanine·HCl	2.2	(5)		2.1
	Sarcosine·HCl	2.2	(7)		0.0
	Piperazine·2HCl[g]	2.4	(9)		
	Ethylenediamine[g]	3.9	(2)		
	Ethylenediamine·2HCl[g]	2.1	(5)		

[a] Polyglutamine and gliadin contain 52 and 32 amide groups per 10^4 g., respectively. [b] Approximate values, obtained by Kjeldahl nitrogen analysis after thorough dialysis, except where otherwise noted. Nitrogen recoveries for gliadin were unreliable as a measure of the amounts of amine introduced since part of the protein became dialysable during the reaction. (Recovery in control samples consistently only 87%.) The uncertain values are in parentheses. [c] 5% solutions of the polyamide, 4% in regard to formaldehyde were treated for five days with 80 equivalents of the various amine salts or amino acids (per 10^4 g.), unless otherwise specified. The solutions contained 1.0–1.5 *M* acetic acid or acetate buffer. [d] In these cases gels formed within one and two days, respectively. When the reaction mixtures were made up five times more dilute, no gels formed, but only 2 and 0 equivalents of ammonia or methylamine were bound, respectively, and correspondingly small amounts of formaldehyde (2 and 1 equivalent). When the reactions were terminated before gelling occurred (after six and twenty-four hours, respectively), 8 and 5 equivalents of the amines were introduced, and 6 and 3 equivalents of formaldehyde. [e] Analyzed after many weeks of dialysis for the purpose of molecular weight determinations. [f] 10% gliadin in 50% glacial acetic acid–50% formalin mixture, with 32 equivalents of the additives. Reaction times indicated in parentheses. [g] Products largely insoluble. [h] Calculated from amount of sulfate sulfur introduced. [i] 4% gliadin, 8% formaldehyde, 0.6 *M* acetic acid, and 32 equivalents of the various amines were used. Reactions were allowed to proceed for four days at room temperature.

With regard to the nature of the amine, all primary amines used except α-aminoisobutyric acid, glucosamine, serine and threonine were effective. In equivalent amounts, the different amines caused gelling after varying time periods. Those acting most rapidly were: ammonia, glycine, alanine, arginine, ethanolamine, 2-aminoethylsulfuric acid and aniline. Glutamic and ε-amino-*n*-caproic acids, butylamine, hexadecylamine, semicarbazide, hydroxylamine and hydrazine acted more slowly. In contrast dimethylamine, diethanolamine, proline, hydroxyproline, sarcosine, benzoylalanine, N-mesyltyrosine, guanidine and urea did not favor gel formation. Piperazine

TABLE VIII

FIXATION OF ACETAMIDE BY MACROMOLECULAR COMPOUNDS CONTAINING AMINO OR GUANIDYL GROUPS THROUGH FORMALDEHYDE CONDENSATION[a]

Macromolecular compound	Reactive groups per 10^4 g.	Additive	Final *p*H	Equivalents bound per 10^4 g. Acetamide	Formaldehyde
Bovine serum albumin (BSA)	9.7 amino	Acetamide	1.4	1.9	
		Acetamide	2.1	7.4	
		Acetamide	3.2	6.2	
		Acetamide	4.2[b]	7.0	7
		Acetamide	4.8	5.9	
		Acetamide	7.4[c]	5.7	5
		Acetamide	11.0	1.5	
		None	4.2[c]		3
Amino-acetyl BSA	0.5 amino	Acetamide	7.4	1.4	0.6
Methylene-tyrosine polymer	34 amino	Acetamide	1.2	3.3	
		Acetamide	6.2	9.6	10
		None	6.2	...	3
Lysozyme	5 amino	Acetamide	5.0[b,d]	4.7	
		Acetamide	7.4[b,c]	1.7	
Insulin	5 amino	Acetamide	4.0	2.2	
		Acetamide	7.0	1.5[e]	
Salmine sulfate	38 guanidyl	Acetamide	4.2	1	2
		None	4.2	...	1

[a] 100 mg. protein and acetamide in approximately 1 ml. 4% formaldehyde, 0.4–0.8 *M* acetate or phosphate buffers, or 1 *N* and 0.1 *N* HCl for the first two experiments; held at room temperature for two or three days. Control experiments showed that no amide was introduced if the formaldehyde was omitted. [b] 8% formaldehyde was used in these experiments. [c] This reaction mixture gelled after addition of the formaldehyde. [d] Lysozyme remained water-soluble under these conditions, whereas gelation occurred and an insoluble product was obtained in the absence of acetamide. [e] Insulin dissolved during the course of the reaction with acetamide at *p*H 7 but not at *p*H 4, nor with other additives (Table IX).

TABLE IX

FIXATION OF METHYLGUANIDINE SULFATE (MGS) BY MACROMOLECULAR COMPOUNDS CONTAINING AMINO GROUPS THROUGH FORMALDEHYDE CONDENSATION[a]

Macromolecular compound	Amino groups per 10^4 g.	Additive	Final *p*H	Equivalents bound per 10^4 g. Methylguanidine (Kjeldahl)	(Colorimetric)	Formaldehyde
Bovine serum albumin (BSA)	9.7	MGS	2.7[b]	0	0.3	
		MGS	4.8	5.5	3.7	
		MGS	7.4[b]	5.5	3.3	
Amino-acetyl-BSA	0.5	MGS	4.8	0		
Methylene tyrosine polymer	34	MGS	3.2	4.5[c]		13
		MGS	4.7	24		60
		MGS	4.7	14[d]		29[d]
		MGS	8.5	23[c]		43
		None	6.2	...	...	3
β-Lactoglobulin	8.9	MGS	4.2	4.3	3.3	8
		MGS	7.6[e]	5.8	3.0	8
		None	7.6[e]	...	...	2
Insulin	5.0	MGS	4.0[f]		0.8	
		MGS	7.0[f]		1.3	

[a] Conditions and control experiments same as used in experiments listed on Table VIII (footnote *a*) but with methylguanidine sulfate instead of acetamide. For techniques and limitations of analytical methods see Experimental Part. [b] Gels form at *p*H 2.7 overnight, at *p*H 7.4 instantaneously upon addition of formaldehyde. [c] Residual amino nitrogen in those preparation, 22 and 5 equivalents, respectively. [d] Reaction time only five hours. [e] Reaction mixtures gel, then liquefy. [f] Protein did not dissolve in reaction mixture.

and N,N′-diphenyl-*p*-phenylenediamine led to rapid stable gelation; N-phenylglycine caused slow and non-permanent gelation. Hexamethylenetetramine acted somewhat more slowly than ammonia.

The gelling effect of ammonium chloride, which was studied in more detail, was not dependent upon the above conditions, but occurred also in more dilute acetic acid (10%) or formaldehyde (4%) solution, as well as in aqueous ethanol with or without added acetic acid, but not in alkaline alcoholic solutions. No gelling could be produced if ammonium chloride or an effective amine was added after the protein–formaldehyde reaction mixture had stood for three days. High concentrations of urea neither prevented gel formation nor redissolved the gel, once it had formed.

No definite information was available concerning the mechanism of these phenomena. A plausible explanation was suggested by the results of the model experiments discussed above. Both zein and gliadin contain a very great excess of amide over amino groups. For gliadin this ratio is about 40, in contrast to 1–2 for many typical proteins. Therefore little cross-linking between the two types of groups can occur in proteins like gliadin and zein. There is thus ample opportunity for small-molecular-weight amines to be bound through methylene bridges to the amide groups of the protein molecule. If these amines are bifunctional in nature, they may act as cross-linking agents between protein molecules, according to reaction V.

In agreement with this hypothesis, only primary

$$2R{-}CONH_2 + HCHO + R'NH_2 \longrightarrow RCONH{-}CH_2{-}NR'{-}CH_2{-}NH{-}COR + 2H_2O \quad (V)$$

amines or secondary diamines (*e. g.*, piperazine) are effective gelation catalysts.[25] When greater than "catalytic" amounts of the cross-linking amines were used, their introduction into the protein under the conditions of gelling was demonstrated analytically (Table VII).

The course of the gelation reaction is in accord with the results of the model experiments with acetamide and alanine. These have shown that, at *p*H 3–6, the cross-linking proceeds considerably faster than does the fixation of formaldehyde by the amide alone. In conformity, gliadin gels within a few minutes after addition of an effective amine. If excessive amounts of amine are avoided, many amide groups remain unaffected by the cross-linking reaction and, more slowly, are

(25) In confirming studies now in progress (footnote 5), it has been found that only those amines that cause gelation favor the formation of derivatives whose average molecular weight is increased over that of the proteins.

transformed into amido-methylol groups.[26] This probably contributes to liquefaction of the gels within twenty-four hours and explains the water solubility of the final products. Further, when alanine was used as the cross-linking agent, its fixation was found to be reversed during prolonged exposure to the 50% acetic acid–formalin reaction mixture. It appears probable, though it was not demonstrated, that ammonia may also be slowly released under such conditions. No re-solution was observed, however, if more extensive cross-linking had been produced through the addition of somewhat more of the amine (with ammonium chloride, 10–20% of the weight of the protein, instead of 1–2%). The gels then were stable and the products after isolation were insoluble in water, acetic acid, and 10 *M* urea solution.

The reaction mechanism postulated for the simple systems is also supported by the experiments with gliadin. Thus, if the amine or ammonia was added to the reaction mixture only after several days of standing, *i. e.*, after the amide groups had been transformed to amido-methylol groups, no gelation nor fixation of the amine occurred.

The behavior of gliadin (and zein[21,22]) is largely duplicated by that of polyglutamine, thus removing the possibility of protein groups other than the amide playing a role in this reaction. Under the same formaldehyde reaction conditions usually used with gliadin (50/50 glacial acetic acid and formalin), this polyamide, in 10% solution, gelled within thirty minutes if traces of ammonium chloride were present, but otherwise only after two to three days. Also, in 4–8% formaldehyde solutions containing as little as 3% of the polypeptide and 3% acetic acid, gels or precipitates were obtained only in the presence of small amounts of ammonium chloride or primary amines. As previously stated, the introduction of the amine or amino acid could be analytically demonstrated when greater than "catalytic" amounts were used (Table VII).

Discussion

The data presented show that the amino groups of proteins may readily condense with formaldehyde and amide or guanidyl groups under conditions of temperature and *p*H at which each type of compound, separately, binds no, or very little, formaldehyde in stable manner. The reaction of asparagine with formaldehyde represents an intramolecular condensation of this same type.[28]

Marvel, *et al.*,[29] have recently expressed the stimulating idea that urea in condensing and polymerizing with formaldehyde may act as an amino acid amide. On the basis of this hypothesis they studied the reaction of some amino acid amides with formaldehyde, and obtained polymers. In the light of the present findings, the primary reaction would appear to be a chain condensation of amino and amide through methylene groups. It does not appear probable that cyclic trimers are involved, as was suggested by these workers,[29] since the polymerization reaction proceeds only under conditions unfavorable for the formation, or even for the existence, of such trimers (Table IV, *cf.* footnote 14). Further, the amount of formaldehyde bound by the polymer was only slightly in excess of that equivalent to the glycine amide units, whereas 1.5 equivalents would be needed for the extensively cyclized and cross-linked structure postulated.[29]

In view of the many amino as well as amide and guanidine groups present in most proteins, and of the ease with which pairs of these can condense with formaldehyde, it appears probable that these reactions may play an important role both in the hardening and tanning action of formaldehyde and in its use in the preparation of vaccines and toxoids. The reaction further may supply a useful means of introducing a great variety of primary amines, amides, or guanidines stably into proteins. In the presence of an excess of a small molecular amide, the methylol-amino groups of the protein appear to condense preferentially with this instead of with protein amide groups. Thus cross-linking between protein groups may be largely forestalled and soluble derivatives obtained at a *p*H which favors the formation of insoluble coagula in the absence of the simple amide (Tables VIII and IX). On the other hand, bifunctional amines furnish cross-links in proteins deficient in amino but rich in amide groups, and bifunctional amides or guanidines may be expected to act similarly in proteins rich in amino but deficient in these types of groups.

Besides methylene condensations involving two nitrogenous groups, other reactions can occur which may contribute to the tanning action of formaldehyde. Mannich reactions involving aromatic and heterocyclic side chains and amino groups will be discussed in a subsequent publication. Similar reactions between basic groups, formaldehyde and reactive aliphatic methylene groups (*e. g.*, R—CH_2—COOH),[14] possibly account for the large amounts of formaldehyde bound irreversibly by proteins at elevated temperature.

(26) Proteins and model polymers rich in amide groups bind much formaldehyde (a) at elevated temperature in dilute acetic acid solution[27] and (b) at room temperature in alkaline solution (*p*H 11–12) (unpublished). The present data (Table VII) show that the reaction occurs at room temperature also at high formaldehyde concentration (20%) in 50% acetic acid, but not to a similar extent in more dilute solutions, unless amines or ammonium salts are present.

(27) Fraenkel-Conrat, Cooper and Olcott, THIS JOURNAL, **67**, 950 (1945).

(28) Levy and Silberman [*J. Biol. Chem.*, **118**, 723 (1937)] and others (*cf.* French and Edsall, footnote 17) have shown that a tetrahydropyrimidine ring is formed through condensation of formaldehyde with the amino and amide groups of asparagine. In contrast to Levy and Silberman's observations, we found that this reaction, like similar intermolecular condensations between amino acids and amides, was favored by a higher *p*H (*p*H 6.5 *vs.* 3.2) (*cf.* Fig. 1).

(29) Marvel, Elliott, Boettner and Yuska, THIS JOURNAL, **68**, 1681 (1946).

Experimental

Methods and Materials.—Free, plus labily bound, formaldehyde was determined by means of dimedon at *p*H 4.6[30]; total recoverable (*i. e.*, free and acid hydrolyzable) formaldehyde, by combined hydrolysis and distillation followed by colorimetric[31] or dimedon[30] analysis of the distillate. Irreversibly-bound formaldehyde was estimated by the difference between the amount originally added and that recoverable by acid hydrolysis from reaction mixtures. Other analytical methods used were the Kjeldahl procedure for total nitrogen, and the manometric Van Slyke[32] and colorimetric ninhydrin[33] methods for amino nitrogen. The Folin uric acid reagent was used for SH tests according to Anson.[34]

The introduction of amides into proteins was demonstrated by increases in amide-nitrogen content: 10–25 mg. of protein was autoclaved with 1.2 *N* sulfuric acid at 120 lb. for two hours; the solution was then neutralized, buffered with phosphate at *p*H 7.4, and the ammonia distilled off in a Kjeldahl apparatus. Recoveries of nitrogen from acetamide by this technique averaged 98.5%.

The introduction of methylguanidine led to appreciable increases in the non-dialyzable nitrogen, which served as an approximate measure of the extent of fixation of this compound. More specific and possibly more accurate were colorimetric analyses of the increases in chromogenic activity by the Sakaguchi method, as applied by Brand and Kassell.[35] These data, however, may be somewhat low, since indications were obtained that hydrolysis of methylol arginine peptides leads to a partial destruction of the chromogenic group.

The introduction of amines into proteins represented the greatest analytical problem. When a polyamide, such as polyglutamic acid, was treated with an excess of amine, sufficient amounts were introduced so that Kjeldahl analyses could be relied upon as proof for its fixation. However, when only 1–5 equivalents (per 10^4 g.) of amine were introduced into a protein, increments in the total nitrogen by about 1–3% could not be demonstrated with sufficient accuracy, particularly when the reaction was performed in acid solution and caused some protein degradation. Tyrosine was used in some experiments and its fixation was demonstrated colorimetrically; however, only one equivalent was bound by 10^4 g. gliadin (32 amide groups), probably because of the insolubility of tyrosine. The use of 2-aminoethylsulfuric acid proved more advantageous. Its introduction into gliadin was demonstrated by sulfate-sulfur analyses[36] and supported by nitrogen analyses. Finally, the acid groups introduced into proteins or polyglutamine through methylene condensation with amino acids were demonstrated by a dye method.[37] This method supplied the most clear-cut and trustworthy evidence concerning the relative non-reactivity of secondary, as compared to primary, amines (*viz.* amino acids).

The gliadin preparations were kindly furnished by D. K. Mecham; lysozyme, by G. Alderton and H. L. Fevold; β-lactoglobulin, by E. F. Jansen; edestin, by D. M. Greenberg; salmine sulfate and insulin, by the Eli Lilly Company. Polyglutamine was prepared as previously described.[27] Aminoacetyl serum albumin was prepared from commercial crystalline bovine serum albumin by acetylation with acetic anhydride in concentrated sodium acetate solution.[38]

(30) Yoe and Reid, *Ind. Eng. Chem., Anal. Ed.*, **13**, 238 (1941).
(31) MacFadyen, *J. Biol. Chem.*, **158**, 107 (1945).
(32) Van Slyke, *ibid.*, **8**, 425 (1929).
(33) Harding and MacLean, *ibid.*, **24**, 503 (1916).
(34) Anson, *J. Gen. Physiol.*, **25**, 355 (1941–42).
(35) Brand and Kassell, *J. Biol. Chem.*, **145**, 359 (1942).
(36) Mease, *J. Research Natl. Bur. Standards*, **13**, 617 (1934); *cf.* also 24.
(37) Fraenkel-Conrat and Cooper, *J. Biol. Chem.*, **154**, 239 (1944).
(38) Olcott and Fraenkel-Conrat, *Chem. Rev.*, **41**, 151 (1947).

Isolation of Amino Acid–Formaldehyde–Acetamide Condensation Products—N-(N-Acetamido-methylene)-alanine.—To 8.9 g. (0.1 mole) of alanine and 5.9 g. (0.1 mole) of acetamide dissolved in water, was added 30 ml. of commercial 40% formalin and water to 100 ml. After three days of standing at room temperature, 93 ml. of the solution was cooled and poured into a five-fold amount of chilled acetone. The precipitate was washed with acetone and dried *in vacuo* (9.4 g.) (59% yield). Recrystallization was effected by dissolving 1 g. in 13 ml. of ice water, and then adding 20 ml. of chilled ethanol. The compound decomposes above 180°.

Anal. Calcd. for $C_6H_{12}O_3N_2$: C, 45.0; H, 7.50; N, 17.5; HCHO, 18.7. Found: C, 44.9; H, 7.56; N, 17.5; HCHO, 18.4.

N-(N-Acetamidomethylene)-proline.—1.15 g. of proline and 0.59 g. of acetamide were dissolved in 2 ml. of 40% formalin. After two days at room temperature the reaction product was precipitated with acetone and repeatedly redissolved in a little water and reprecipitated with acetone. Crystallization occurred both in the oily, insoluble fraction and in the mother liquor; 700 mg. was isolated (38%). Partial decomposition of the product during recrystallization from cold water–acetone mixtures may account for the low recoveries (15% or less). But the unrecrystallized material appeared to be quite pure; m. p. 135–138° (dec.).

Anal. Calcd. for $C_8H_{14}O_3N_2$: C, 51.6; H, 7.43; N, 15.1; HCHO, 15.4. Found: C, 51.5; H, 7.55; N, 15.1; HCHO, 15.4.

Stability of Condensation Products.—The crystalline condensation products of alanine or proline with formaldehyde and acetamide were found to be comparatively stable in the presence of dimedon at *p*H 4.6. This made it possible to use the dimedon technique to determine the extent of hydrolysis that occurred in aqueous solutions of varying *p*H. The alanine derivative was also stable under the conditions used for Van Slyke manometric amino nitrogen analyses, so that the liberation of amino nitrogen could be used as an additional measure of the extent of hydrolysis. The data obtained by these methods are listed in Table X. It is evident that the stability optimum of the alanine derivative is more alkaline than that of the proline derivative.

TABLE X

ABILITY OF REACTION PRODUCTS IN AQUEOUS MEDIA

Medium, buffer and/or solutes	Conditions *p*H	Temp., °C.	Time, days	Extent of hydrolysis[a] of acetamide-formaldehyde condensation product of Alanine, %	Proline, %
0.2% Dimedon,	4.6	23	1	9	5
acetate	4.6	40	3	96	98
0.1 *M* Citric acid	2.0	23	1	36	18
0.5 *M* Acetic acid	3.4	23	1	28 (25)	14
Water	4.2	23	1	25 (16)	8
Phosphate	7.6	23	1	10 (14)	25
Borate	9.1	23	1	10 (10)	..
Phosphate	11.7	23	1	15 (8)	35
2.5 *M* Sodium nitrite in 2 *M* acetic acid (manometric Van Slyke)		23	3 min.	6	
10% Pyridine (colorimetric ninhydrin)		100	30 min.	97	

[a] Figures in parentheses are based on Van Slyke manometric amino nitrogen analyses; all other figures are derived from dimedon analyses for liberated formaldehyde.

The finding that formaldehyde and amino nitrogen are liberated to a similar extent indicates that under the conditions used hydrolysis occurs first between the amide and methylene group—a true reversal of the two-stage reaction mechanism (Reaction IV, followed by III). A primary breaking of the amino-methylene linkage would yield methylol acetamide which would not liberate much formaldehyde at room temperature and *p*H 3.4. (N-Methylol-acetamide was hydrolyzed to only 2.4% in twenty-four hours under such conditions.)

Failure to Achieve Condensation of Amido-methylol with Amino Groups.—In the hypothetical reaction

$$R—CONH—CH_2OH + R'—NH_2 \longrightarrow R—CONH—CH_2—NH—R' + H_2O$$

there would be no fixation of formaldehyde, but measurable loss in amino nitrogen. In one experiment, the amido-methylol compound was formed by adding 0.1 ml. of 0.1 *N* sodium hydroxide to a solution of 0.5 mM. of acetamide in 1 ml. of 8% formaldehyde (2.5 mM.). After one hour at room temperature, the solution was neutralized with 0.1 ml. of 0.1 *N* hydrochloric acid, buffered at approximately *p*H 3.4 with 0.2 ml. of 3 *N* acetic acid, and then to it was added 0.5 mM. of alanine. After three days of standing at room temperature, the mixture was diluted and analyzed. The reaction of the amide with formaldehyde approached completion (0.47 mM.), as expected,[11] but there was no loss in amino nitrogen, *i. e.*, no cross-linking had occurred with the alanine.

In another experiment N-methylolacetamide was isolated prior to the treatment with alanine[11]; 0.48 mM. of the oily preparation was mixed with 0.5 mM. of alanine and 1.25 ml. of 0.6 *M* acetic acid. A similar sample was made up to contain also 0.5 mM. of free formaldehyde. Neither sample, after a three day reaction period and dilution, showed a loss in amino nitrogen. Thus no cross-linking occurred between amido-methylol and amino or amino-methylol groups.

Changes in Optical Rotation of Amino Acid–Formaldehyde Solutions with and without Added Acetamide at *p*H 3–4. A.—L-Proline (2% solution) in 0.72 *M* acetic acid, $[\alpha]^{25}D$ −83°.

Upon addition of 3 ml. of 40% formaldehyde to 12 ml. of this solution, the *p*H dropped from 3.0 to 2.9 in one hour, then remained constant. $[\alpha]^{25}D$ after ten minutes, two and one-half hours and twenty hours, was −92, −94 and −94°, respectively.

Addition of 3 ml. of 40% formaldehyde to 12 ml. of 2% L-proline solution (as above) containing also 1.04% acetamide (one equivalent) caused the rotation to rise to −91.5° after five to one hundred and twenty minutes, but to drop within 19, 43 and 67 hours to −85, −80.5 and −78°.

B.—L-Leucine (2% solution in 0.72 *M* acetic acid), $[\alpha]^{25}D$ −6.2.

After addition of 3 ml. of 40% formaldehyde to 17 ml. of amino acid solution, $[\alpha]^{25}D$ was −4.2, −3.5 and −3.0°, after ten minutes, three hours and twenty-one hours, respectively.

C.—L-Cystine (1% solution in 0.36 *N* hydrochloric acid containing 1% glycine, *p*H 0.85), $[\alpha]^{25}D$ −230°.

After addition of 3 ml. of 40% formaldehyde to 12 ml. of above solution, $[\alpha]^{25}D$ −212 to −214° after five to one hundred and eighty minutes.

Addition of amounts of acetamide to the formaldehyde-containing solution, equivalent to the sum of the amino acids present, caused a change of rotation within one hour to $[\alpha]^{25}D$ −180°, and after three, sixteen and forty hours to −182, −190 and −194°, respectively.

Attempts to Demonstrate Condensation between Alanine, Formaldehyde, and Acetamide in Strongly Acid and Alkali Solution.—The change in rotation noted in the case of the L-cystine–formaldehyde reaction mixture of *p*H 0.85 when acetamide was added suggested that interaction of the amino-methylol and amide had occurred. It was attempted to establish this more firmly in a simpler system by using Van Slyke amino-nitrogen analyses on alanine–acetamide–formaldehyde reaction mixtures of similar *p*H. Parallel experiments were also performed in alkaline solution (*p*H 11).

At both *p*H levels, acetamide alone binds formaldehyde readily, so that the aldehyde analyses could not be used as evidence for cross-linking. Amino-nitrogen analyses, performed after dilution and neutralization, gave high and erratic results until the free and dimedon-reversibly bound formaldehyde was removed from the solution (by means of dimedon). The presence of ammonia, formed through incipient hydrolysis of the acetamide, detracted from the quantitative significance of the data.

One typical experiment is shown in Table III. It appeared that there is little, if any, cross-linking in acid solution in twenty-four hours, and little cross-linking at *p*H 11. The (irreversible) fixation of formaldehyde and loss of amino nitrogen of alanine alone under the latter conditions interferes with quantitative interpretation of the amino-nitrogen data on the alanine–acetamide reaction mixture.

Search for Methylene-Condensation Reactions Involving Thiols and Guanidines.—When thioglycol reacted with formaldehyde over the range of *p*H 4.3–7.6 with or without added alanine or acetamide, no more formaldehyde was bound than could be accounted for by the added nitrogenous compound, and no loss in chromogenic activity of the thiol occurred (Table XI). This is regarded as evidence that no R–S–CH_2–NH-R bonds were formed unless these were so labile as to be hydrolyzed during dilution and analysis (*cf.* footnote 13).

TABLE XI

FIXATION OF FORMALDEHYDE IN REACTION MIXTURES CONTAINING ALANINE OR ACETAMIDE WITH THIOGLYCOL OR METHYLGUANIDINE

Reactants	Final *p*H	Time, days	Formaldehyde bound, equivalents[a]	% Thiol disappeared
Alanine (1)[b] + thioglycol (1)	7.6	4	0.18	0
Alanine (1) + thioglycol (1)	4.6	3	.09	0
Alanine (1) + thioglycol (1)	1.4	3	.47	97
Alanine (1)	7.6	1	.22	..
Alanine (2)	4.3	4	.10	..
Alanine (1)	1.4	1	.00	..
Thioglycol (2)	7.6	4	.00	0
Thioglycol (2)	4.3	4	.00	
Thioglycol (2)	1.4	3	.50	99
Acetamide (1) + thioglycol (1)	7.6	4	.18	
	4.3	4	.08	
Acetamide (2)	4.3	4	.22	
Alanine (1) + methylguanidine (1)	4.3	4	1.34	
Methylguanidine (2)	4.3	4	1.26	
Methylguanidine (1)	4.3	4	0.65	
Acetamide (1) + methylguanidine (1)	4.3	4	0.75	
Alanine (0.5) + methylguanidine (0.5)	4.7	4	1.34	
Methylguanidine (0.5)	4.7	4	0.46	
Alanine (0.5)	4.8	4	0.10	

[a] In terms of alanine if present; otherwise in terms of the potential reactant present. [b] Figures in parentheses indicate millimoles used (in 2.5 ml. of reaction mixture containing usually 4–5 millimoles of formaldehyde).

At *p*H 1.5, the disappearance of one-half equivalent of formaldehyde for one of thioglycol suggests that it was transformed quantitatively to the methylene bis-(ethanol) thioether, (CH_2OH–$(CH)_2$–S–CH_2–S–$(CH_2)_2$–CH_2OH), both in the presence and the absence of alanine

(Table XI); the compound was not isolated. Armstrong and du Vigneaud[39] have recently described a method of synthesis of djenkolic acid from cysteine in strong hydrochloric acid, which represents an analogous reaction.

Methylguanidine sulfate binds formaldehyde by itself in solutions above *p*H 7 and below *p*H 5. However, much more formaldehyde is bound at *p*H 4.7 and 4.3 in the presence of alanine than in the presence of acetamide or in solutions of methylguanidine sulfate alone, which is regarded as evidence for cross-linking between guanidine and amino groups (Table XI). The formation of such cross-links was further indicated by the fixation, in the presence of formaldehyde, of methylguanidine residues by proteins or model substances rich in amino groups (Table IX).

Little, if any, cross-linking between guanidine and amide groups appears to occur in the experiments listed in Tables VII, VIII, and XI. This is borne out by a preparative experiment with methylguanidine sulfate. A mixture of 5 millimole each of this compound and acetamide in 2 ml. of 40% formalin was held at room temperature for three days and at 53° for three hours, then isolated and washed by repeated acetone precipitation. The final product contained 92% of the methylguanidine nitrogen and only approximately 0.1% amide of total N.

Polymerization of Glycine Amide with Formaldehyde.[29]—To 110.5 mg. of glycine amide hydrochloride (1 mM.), dissolved in 1 ml. of 3 *M* sodium acetate, was added 0.6 ml. of 7.5% formaldehyde (1.5 mM.). The reaction mixture solidified to a white gel within twenty-four hours. After two days of standing, the product was isolated by repeated cycles of trituration with water and centrifugation. The last washing was free from formaldehyde. The supernatant and washings were pooled; the insoluble polymer was dried (over sodium hydroxide flakes) from the frozen state.

The pooled solution (50 ml.) was at *p*H 4.8. It contained 0.435 mM. of glycine amide (by nitrogen analysis), and 0.525 mM. free formaldehyde (dimedon). The total formaldehyde in the solution represented 0.885 mM. From these results it may be calculated that the insoluble polymer contained 0.565 mM. glycine amide and 0.615 mM. of formaldehyde, *i. e.*, 1.09 equivalents of formaldehyde per glycine amide unit. Very similar results were obtained in two further experiments in one of which 2.0 equivalents of formaldehyde were used. In all experiments, the nitrogen recovery in the two fractions was only 96–97% (formaldehyde recovery 99–100%), and the reproducibility of Kjeldahl analyses on the polymer was poor. Dumas analyses gave a lower value (25.1%). C and H analyses performed on a preparation that had been dried at 100° in high vacuum and then permitted to equilibrate with laboratory air, were difficult to interpret because of the probable absorption of carbon dioxide by the basic polymer (C, 38.3; H, 6.86; N (Kjeldahl), 25.3–26.6; HCHO, 31.7; weight loss and regain, 12.1%). The dried polymer contained no acetate. It was insoluble in all solvents tried, including saturated lithium iodide, and 1,3-dichloropropanol, solvents for silk fibroin, and nylon, respectively.

Use of Cyclic Trimers (—NR—CH_2—)$_3$ in Condensation Reaction.—Cyclic trimers were prepared from formaldehyde and both methylamine and *n*-butylamine. When these compounds were held at *p*H 4 or 5 in the presence of acetamide, much formaldehyde was bound stably (to dimedon at *p*H 4.6), while in the absence of acetamide almost the entire formaldehyde was liberated and could be precipitated with dimedon (Table IV). When the trimer was held at *p*H 8.3, no interaction occurred with acetamide, and all formaldehyde could be precipitated with dimedon after dilution and one day of exposure to *p*H 4.6 acetate (*cf.* footnote 14).

Acknowledgments.—The authors are indebted to E. D. Ducay for untiring technical assistance. Carbon and hydrogen analyses were performed by L. M. White and G. E. Secor; Dumas-nitrogen, by G. Rose; arginine (guanidyl group) analyses, by J. W. Pence.

Summary

Simple primary and secondary amines react with formaldehyde and primary amides over the range of *p*H 3–8 within twenty-four to forty-eight hours at room temperature to give condensation products of the general structure: R—NR′—CH_2—NH—CO—R″. Representative compounds of this type have been isolated in pure form.

Evidence is presented that the primary reaction is the formation of methylol-amines, not methylol-amides.

N-Alkyl amides, including peptides (RNH—CO—R′), do not react in similar systems.

Simple amines also condense with formaldehyde and guanidines at *p*H 4–5, but amides and guanidines do not react under the same conditions.

Through methylene condensation reactions of these types, formaldehyde permits the introduction of simple amides or guanidines into proteins or macromolecular model substances rich in amino groups, and also permits the introduction of primary amines into proteins or model substances that are rich in amide groups.

Under suitable conditions, small amounts of ammonia or primary amines cause gelation of acid formaldehyde reaction mixtures of gliadin, zein, or polyglutamine, probably by introducing cross-links $\left(\text{—CH}_2\text{—N(R)—CH}_2\text{—}\right)$ between the numerous amide groups of these substances.

While not unequivocally demonstrated, it appears very probable that these cross-linking reactions between amino and primary amide or guanidyl groups contribute greatly to the tanning or hardening action of formaldehyde at room temperature and over the range of *p*H 2–9, on proteins of average composition.

(39) Armstrong and du Vigneaud, *J. Biol. Chem.*, **168**, 373 (1947).

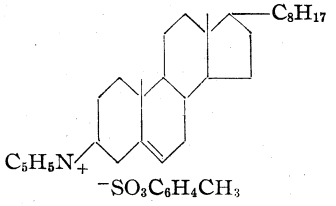
ALBANY, CALIF. RECEIVED SEPTEMBER 24, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

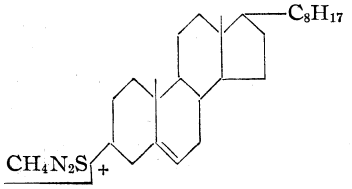
Preparation, Structure and Configuration of Some Salts Derived from Δ^6-*i*-Cholestadiene and *i*-Cholesten-6-one[1a]

BY L. CARROLL KING

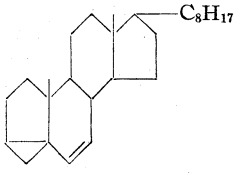
In a recent paper from this Laboratory[1b] it was demonstrated that *i*-cholesteryl methyl ether reacted with pyridine and *p*-toluenesulfonic acid to give cholesterylpyridinium tosylate (I) and with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give cholesterylisothiuronium tosylate (II). This type of reaction has now been applied



I



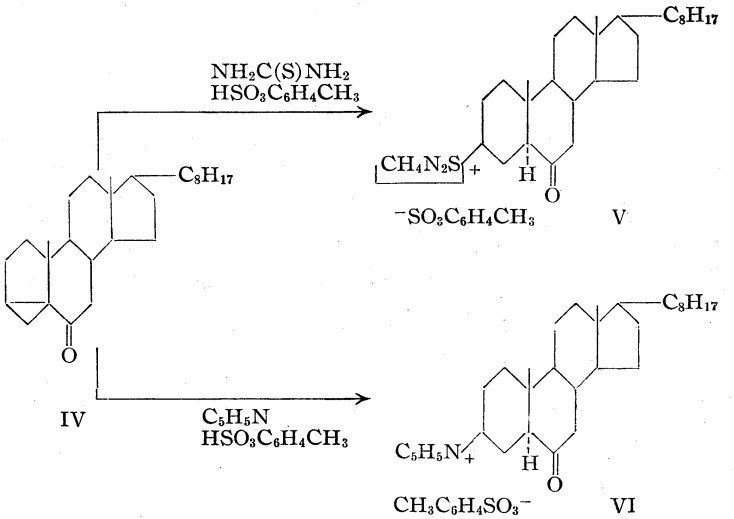
II



III

to two other molecules having the *i*-steroid structure.

The Δ^6-*i*-cholestadiene (III) described by Riegel[2] when it reacted with thiourea and *p*-toluenesulfonic acid in alcoholic solution gave compound II, identical with the corresponding substance obtained from similar treatment of *i*-cholesteryl methyl ether.[1b] Compound III, unlike *i*-cholesteryl methyl ether,[1b] would not react with pyridine and *p*-toluenesulfonic acid to give I.



IV V VI

i-Cholesten-6-one (IV) reacted with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give 6-ketocholestanylisothiuronium tosylate (V) and with pyridine and *p*-toluenesulfonic acid to give 6-ketocholestanylpyridinium tosylate (VI).[3] These reactions may be formulated as shown.

When *i*-cholesteryl ethers react with reagents such as the halogen acids, or acetic acid containing a trace of sulfuric acid,[4] or with various alcohols in the presence of acids,[5] the products are invariably 3-β-substituted derivatives.[6] It was shown by Riegel[2] that in acidic media nucleophilic reagents reacted with Δ^6-*i*-cholestadiene at position 3 to give derivatives with the β-configuration. In view of these observations the cholesterylisothiuronium tosylate (II) described in this paper and in ref. 1 should be a 3-β-substituted compound. By a similar argument the cholesterylpyridinium tosylate I (described in ref. 1) should be a 3-β-substituted compound.

Wallis and co-workers[9] reported that *i*-cholesten-6-one (IV) reacted with dilute sulfuric acid to give 3-β-hydroxy-6-ketocholestane and with hydrochloric acid or hydrobromic acid to give a 3-α-halo-6-ketocholestane. Now the corrected configurations of the 3-substituted cholestyl and cholesteryl halides[6] can be directly related to the 3-halo-derivatives of

(1a) Presented before the Organic Division of the American Chemical Society, Chicago meeting, April, 1948.

(1b) King, Dodson and Subluskey, THIS JOURNAL, **70**, 1176 (1948).

(2) Riegel, Hager and Zenitz, *ibid.*, **68**, 2562 (1946).

(3) Isolated only as the iodide.

(4) Benyon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); 406 (1937); Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

(5) The acid catalyzed conversion of *i*-cholesteryl methyl ether to the normal cholesteryl ether, isopropyl or *t*-butyl ether, according to the nature of the alcohol used as solvent, was reported by E. W. Meyer, Ph.D. Thesis, Northwestern University, 1943, p. 55 and pp. 96–101. A similar reaction wherein *i*-cholesteryl methyl ether is converted to normal ethers was recently reported by McKennis, *ibid.*, **69**, 2565 (1947); *J. Biol. Chem.*, **172**, 313 (1948). See also Hey and Hook, British Patent 591,955 [*C. A.*, **42**, 1028 (1948)].

(6) Previous to 1937 an incorrect formulation for the configuration of the 3-halogen substituted steroids existed. This inconsistency was apparent in the papers of Marker and co-workers, THIS JOURNAL, **59**, 619 (1937), and was corrected by Bergman, *Helv. Chim. Acta* **20**, 600 (1937). Recent papers by Shoppee[7] and by Dodson and Riegel[8] have reviewed the corrected formulation of cholesteryl and cholestyl halides in detail.

(7) Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946).

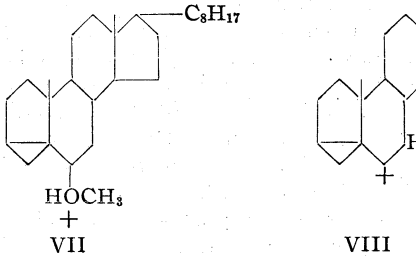
(8) Dodson and Riegel, *J. Org. Chem.*, **3**, 424 (1948).

(9) Ford, Chakravorty and Wallis, THIS JOURNAL, **60**, 413 (1938); Ladenburg, Chakravorty and Wallis, *ibid.*, **61**, 3483 (1938); Heilbron, Hodges and Spring, *J. Chem. Soc.*, 759 (1938).

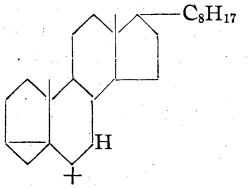
6-ketocholestane. In view of this the compounds formulated as 3-α-halo-6-ketocholestanes by Wallis and co-workers and by Heilbron and co-workers,[9] should be 3-β-halo-6-ketocholestanes.[10] Since all these known reactions of *i*-cholesten-6-one with nucleophilic groups of the type HX result in 3-substitution with β-configuration, it seems likely that compounds V and VI described in this paper are 3-β-substituted-6-ketocholestanes.

In the formation of compounds I, II, V and VI, it seems evident that a proton is first added to the *i*-steroid with formation of an intermediate such as VII, VIII or IX. The intermediate so formed then is attacked at the 3-position by the nucleophilic group. Thus *i*-cholesteryl methyl ether could form VII, compound III could form VIII, and compound IV could form IX. VII could then react with the appropriate reagents to give I or II, VIII could form II, and IX could react with the appropriate reagents to form V or VI.

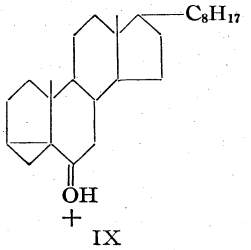
Our failure to obtain I from III is due to the limited availability of protons in pyridine solution so that VIII is not formed under these conditions.



VII



VIII



IX

In each of the reactions reported in this paper and in ref. 1 a change in the ionic nature of the solution takes place as the reaction proceeds. Hence it is possible to make a kinetic study of these reactions by electrical conductivity methods. Such a study is in progress in this Laboratory.

Experimental[11]

Δ^6-*i*-Cholestadiene.—This substance was prepared according to the directions of Riegel, Hager and Zenitz.[2] The use of chromatography on alumina was absolutely necessary to accomplish purification; m. p. 72.5–73°, $[\alpha]^{22}D$ −45.8° in chloroform.

***i*-Cholestene-6-one.**—This substance was prepared according to the direction of Windaus and Dalmer[12]; m. p. 95–97°, $[\alpha]^{22}D$ 47.9° in chloroform.

Cholesterylisothiuronium Tosylate (II).—A solution consisting of 0.50 g. of Δ^6-*i*-cholestadiene (III), 0.50 g. of *p*-toluenesulfonic acid monohydrate and 1.0 g. of thiourea in 20 cc. of methanol was refluxed for five hours. The methanol was partially removed and the product isolated as described in a previous paper[1]; yield 0.74 g. (88%), m. p. 234–235°, $[\alpha]^{22}D$ −27.4° in pyridine.

Attempted Preparation of Cholesterylpyridinium Tosylate (I) from Δ^6-*i*-Cholestadiene (III).—A solution consisting of 0.50 g. of III, 0.50 g. of *p*-toluenesulfonic acid monohydrate and 3.0 cc. of pyridine was refluxed for five hours. No product corresponding to I was obtained, but III was recovered unchanged. A twenty-hour heating period gave similar results.

6-Ketocholestanylisothiuronium Tosylate (V).—A solution consisting of 1.0 g. of *i*-cholesten-6-one (IV), 2 g. of thiourea and 1.0 g. of *p*-toluenesulfonic acid monohydrate in 20 cc. of methanol was refluxed for two hours and then allowed to stand overnight. The methanol was then removed by evaporation and the product thoroughly washed with water. The compound was crystallized from absolute alcohol; yield 1.5 g. (90%), m. p. 204–206°, $[\alpha]^{21}D$ −18.8° in chloroform.

Anal. Calcd. for $C_{35}H_{56}N_2S_2O_4$: C, 66.41; H, 8.91; N, 4.43. Found: C, 66.07; H, 8.47; N, 4.10.

This substance is insoluble in water and soluble in alcohol. It forms a very stable gel in water–alcohol solution.

6-Ketocholestanylpyridinium Iodide (VI).—A solution of 0.5 g. of *i*-cholesten-6-one, and 0.5 g. of *p*-toluenesulfonic acid in 3 cc. of pyridine was refluxed for twelve hours, then heated on the steam-bath for twenty-four hours, cooled and diluted with ether. The solid material which separated was taken up in absolute alcohol and hydroiodic acid was added. The crystalline solid which separated weighed 0.58 g. (75%) and melted at 285–295°. After crystallization from alcohol the melting point was 293–296°; $[\alpha]^{21}D$ 5.5° in chloroform.

Anal. Calcd. for $C_{32}H_{50}ONI$: C, 64.93; H, 8.51; N, 2.36. Found: C, 64.46; H, 8.43; N, 2.75.

Summary

Cholesterylisothiuronium tosylate was prepared from Δ^6-*i*-cholestadiene. Cholesterylpyridinium tosylate could not be prepared from this substance.

i-Cholesten-6-one reacted with thiourea and *p*-toluenesulfonic acid to give 6-ketocholestanylisothiuronium tosylate, and with pyridine and *p*-toluenesulfonic acid to give 6-ketocholestanylpyridinium tosylate.

A consideration of the reactions and steric relations involved indicates these compounds are all 3-β-substituted cholesteryl or cholestyl derivatives.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 20, 1948

(10) In the paper by Dodson and Riegel[8] the corrected configuration of this class of compounds is considered in detail.

(11) All rotations were determined with 100–105 mg. of sample in 3.0 cc. of solvent using a 1-dm. tube of 2.5 cc. capacity. All melting points were observed on a Fisher–Johns melting point block.

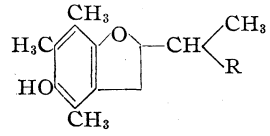
(12) Windaus and Dalmer, *Ber.*, **52**, 162 (1919).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

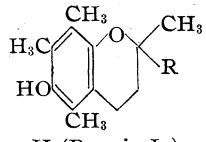
Vitamin E. XLVI.[1] Conversion of 4,6,7-Trimethylcoumaran-3-one into Some Homologs of 2-Isopropyl-4,6,7-trimethyl-5-hydroxycoumaran

BY LEE IRVIN SMITH AND GERALD A. BOYACK[2]

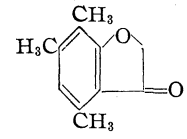
2-(2′-Alkyl)-4,6,7-trimethyl-5-hydroxycoumarans, I, are of interest because these substances are isomeric with, and closely related to, the 2,2-dialkyl-5,7,8-trimethyl-6-hydroxychromans, the structural type of the tocopherols, for example, α-tocopherol, II.



Ia, R = CH_3
b, R = n-C_5H_{11}
c, R = $C_{16}H_{31}$ (4,8,12-trimethyltridecyl)



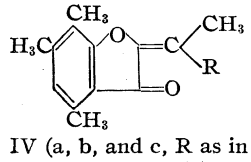
II (R as in Ic)



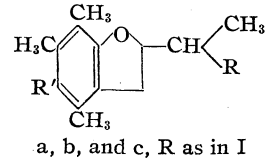
III

In an earlier paper[3] a method for the synthesis of 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran (Ia) was described in which the last step involved introduction of the hydroxyl group by replacement of a bromine atom at position 5. Since the steps in this synthesis involved rather accessible intermediates and simple reactions, it was of interest to investigate the generality of the method for synthesis of higher homologs of I, with a view of ultimately synthesizing the coumaran Ic isomeric with α-tocopherol II. The model experiments were successful, and led to the synthesis of Ib but when applied to the synthesis of Ic, the synthesis failed because the last step was unsuccessful.

Methyl *n*-amyl ketone was condensed with 4,6,7-trimethylcoumaran-3-one, III, to give 2-(2′-heptylidene)-4,6,7-trimethylcoumaran-3-one, IVb, which was catalytically reduced in the presence of Raney nickel to 2-(2′-heptyl)-4,6,7-trimethylcoumaran Vb. The coumaran Vb was converted to the bromo compound VIb by bromination, and the bromo compound was converted into the Grignard reagent VIIb, which was oxidized to the bromomagnesium phenolate VIIIb. The salt, when hydrolyzed, gave the coumaran, Ib. Although the synthesis was successful, serious difficulties were encountered. Thus, neither Vb nor VIb could be obtained in pure form. Hydrogenation of IVb under a variety of conditions did not lead to a product from which pure Vb could be isolated. The crude bromo compound VIb, prepared from impure Vb, contained approximately 4% of halogen which was precipitated by action of alcoholic silver nitrate, and which was not removed by action of activated alumina or of hydrogen in the presence of a palladium catalyst.



IV (a, b, and c, R as in I)



a, b, and c, R as in I

V, R′ = H
VI, R′ = Br
VII, R′ = MgBr
VIII, R′ = OMgBr

This route to the coumaran Ib having proved successful, attention was turned to the synthesis of Ic. The coumaranone III condensed with 6,10,14-trimethylpentadecanone-2 in the presence of zinc chloride to produce IVc. Catalytic reduction of IVc failed to yield a product from which pure Vc could be isolated. However bromination of the impure Vc gave a product which when chromatographed on alumina, yielded pure VIc. When the bromo compound VIc was subjected successively to the action of magnesium and oxygen, the product was a red oil from which no Ic could be isolated.

The ultraviolet absorption spectra of several of these compounds are given in Figs. 1, 2 and 3. The spectra of the coumaran-3-ones IVa, b and c (Fig. 1) are very similar; likewise the spectra of the bromocoumarans VIa and c (Fig. 2) are very similar. The spectra of the hydroxycoumarans Ia and b are very similar to that of 2,4,6,7-tetramethyl-5-hydroxycoumaran.[4]

Experimental Part[5]

2,3,5-Trimethylphenoxyacetic Acid.—The following modification of the procedure previously reported[3] was found to give higher yields and more uniform results. A mixture of 2,3,5-trimethylphenol (68 g.), potassium carbonate (69 g.), ethyl bromoacetate (92 g.), and acetone (150 cc.) was refluxed for seventy-two hours—a necessary period of time if good yields are to be obtained. Water (200 cc.) was added, acetone was removed by distillation, and the oily suspension was extracted with ether. The solvent was removed and the oily residue was mixed with a solution of sodium (10 g.) in ethanol (200 cc., 95% —not dry ethanol, as specified in the earlier report). When the vigorous reaction subsided, more ethanol (300 cc., 95%) was added, the mixture was heated for five minutes, and the solid was removed. Hydrochloric acid was added slowly to a stirred suspension of the solid

(1) XLV, THIS JOURNAL, **66**, 1526 (1944).

(2) Abstracted from a thesis by Gerald A. Boyack presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

(3) Smith, King, Guss and Nichols, THIS JOURNAL, **65**, 1594 (1943).

(4) Webb, Smith, Bastedo, Ungnade, Prichard, Hoehn, Wawzonek, Opie and Austin, *J. Org. Chem.*, **4**, 389 (1939).

(5) Microanalyses by R. Amidon, Mrs. R. A. Barnes, J. Kerns, P. Morgan and S. Sundet.

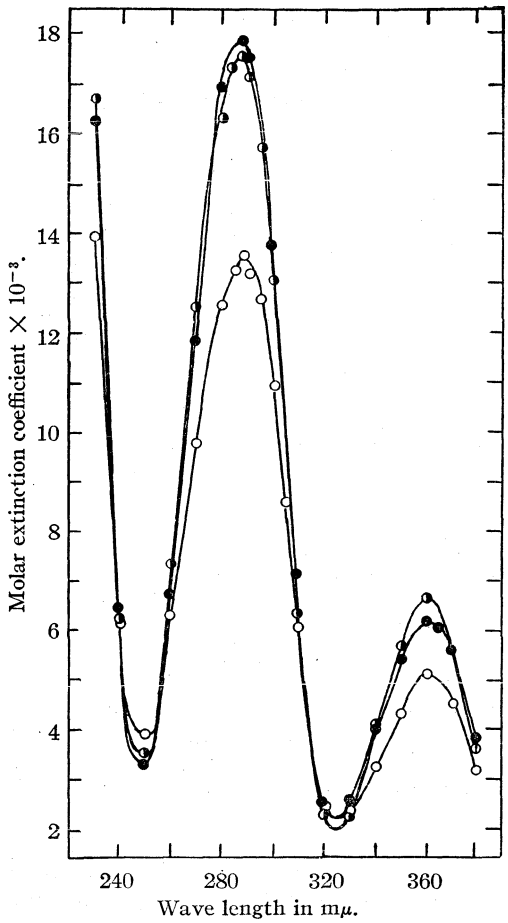


Fig. 1.—Absorption spectra: O, 2-(6′,10′,14′-trimethyl-2′-pentadecylidene)-4,6,7-trimethylcoumaran-3-one: ◑, 2-(2′-heptyl)-4,6,7-trimethylcoumaran-3-one: ●, 2-isopropyl-4,6,7-trimethylcoumaran-3-one: solvent, 95% ethanol.[3]

in warm water, and then the suspension was cooled and the solid (m. p. 129–131°) was removed and crystallized from benzene, when it melted at 130° and weighed 75 g. The alcoholic mother liquors were refluxed for ten hours, alcohol was removed by distillation, and water was added. The cooled solution was extracted with ether (extract discarded) and acidified with hydrochloric acid. The solid was removed and crystallized from benzene, when it melted at 127° and weighed 9.3 g. The total yield, 84.3 g., represents 86%.

4,6,7-Trimethylcoumaran-3-one, III.—The above phenoxyacetic acid (20 g.) was added, with shaking, to sulfuric acid at 90°. The cherry-red solution was heated for ten minutes at 90° and then poured into water (7000 cc.). The solid was removed, washed well with water, and the moist material was recrystallized from methanol, when it weighed 13.4 g. (76%) and melted at 89–91°. This procedure is superior to that previously reported,[3] although it must be followed exactly, otherwise the results are erratic and frequently the sole product will be an impure material of unknown structure, melting at 155–175°.

2-(2′-Heptylidene)-4,6,7-trimethylcoumaran-3-one, IVb.—A mixture of methyl *n*-amyl ketone[6] (44.1 g.) and zinc chloride (100 g., powdered, freshly fused) was stirred and heated on a steam-bath while a solution of III (13.6 g.) in methyl *n*-amyl ketone (44.1 g.) was slowly added (five hours), after which the mixture was heated and stirred for twenty-four hours. The mixture was poured into ice and water (500 g.) and the emulsion was filtered. The layers were separated and the aqueous

(6) Marvel and Johnson, "Org. Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 351.

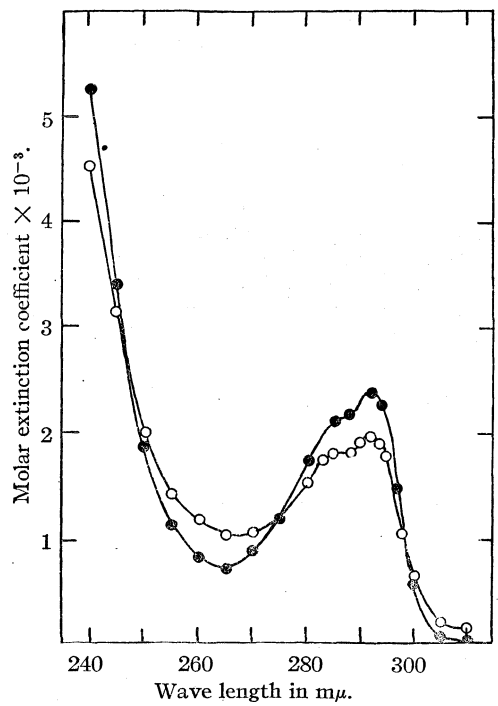


Fig. 2.—Absorption spectra: O, 2-(6′,10′,14′-trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-bromo-coumaran: ●, 2-isopropyl-4,6,7-trimethyl-5-bromocoumaran[3]; solvent, absolute ethanol.

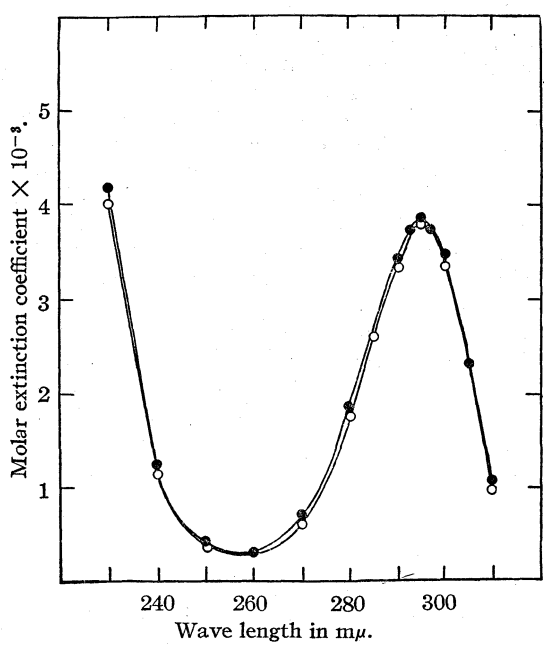


Fig. 3.—Absorption spectra: O, 2-(2′-heptyl)-4,6,7-trimethyl-5-hydroxycoumaran; ●, 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran[3]; solvent, 95% ethanol.

layer was extracted with ether. The combined organic solutions were washed with water and dried over sodium sulfate, and the solvent was removed. Excess ketone was removed by heating the residue at 100° under 25 mm. pressure, and the residual material was distilled molecularly from a pot-still under 0.0001 mm. With the bath temperature at 130–160°, a yellow oil (14.8 g., $n^{25}D$ 1.5576) distilled. Redistilled twice under the same conditions, the oil weighed 9.65 g. (46%), had $n^{25}D$ 1.5614, and gave the U. V. spectrum shown in Fig. 1.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.36; H, 8.88. Found: C, 79.61; H, 8.62.

2-Isobutylidene-4,6,7-trimethylcoumaran-3-one, melting at 81.5–82.5° after crystallization three times from petroleum ether (b. p. 40–70°), was prepared in the same way, substituting butanone-2 for methyl *n*-amyl ketone.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.43; H, 7.79.

2-(2′-Heptyl)-4,6,7-trimethylcoumaran Vb.—A solution of the coumarone IVb (3.6 g.) in dry ethanol (4 cc.) was subjected to the action of hydrogen in the presence of Raney nickel catalyst at 225° for four hours, under an initial hydrogen pressure of 3500 lb. The catalyst and the solvent were removed, and the residue was distilled molecularly from a pot-still under 0.001 mm. at a bath temperature of 75–80°. The pale yellow oil weighed 2.78 g. and had $n^{25}D$ 1.5045. It was still quite impure, but was nevertheless used for the next step.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 79.32; H, 10.19.

No better results were obtained when the reduction was carried out (a) as above, but at 250° for four and one-half hours; (b) as above, but at 200° for four hours and an initial hydrogen pressure of 3000 lb.; (c) as above, at 225° for five hours and an initial pressure of 3600 lb.; (d) as above, but in the presence of a small amount of sodium hydroxide; (e) using copper chromium oxide catalyst; (f) by the Clemmensen method. Neither fractional distillation nor chromatography was effective in producing pure Vb from any of these products.

2-(2′-Heptyl)-4,6,7-trimethyl-5-bromocoumaran VIb.—The above impure Vb (2.8 g.) was dissolved in chloroform (5 cc.) and brominated by slow addition of a solution of bromine (1.9 g.) in chloroform (5 cc.). The solution remained colorless until nearly all of the bromine had been added; there was a copious evolution of hydrogen bromide. The solvent was removed and the residue was distilled in a pot-still at 120–135° bath temperature and under 0.001 mm. The distillate (2.73 g., active Br, 4.0%) was dissolved in benzene (10 cc., thiophene-free) and shaken with hydrogen under 35 lb. in the presence of a palladium–barium carbonate catalyst for three and one-half hours. After removal of the catalyst and solvent, the residue was dissolved in petroleum ether (20 cc.) and the solution was passed through a 5 × 0.5-cm. column of alumina (Brockman). Additional petroleum ether (20 cc.) was passed through the column, the solvent was removed from the combined solutions and the residue was distilled as before. The yellow oil distilled at a bath temperature of 100–110°, weighed 1.7 g., had $n^{25}D$ 1.5334, and contained 2.3% of active bromine. It was not analyzed, but was used directly in the next step.

2-(2′-Heptyl)-4,6,7-trimethyl-5-hydroxycoumaran, Ib.—The above impure bromo compound (1.68 g.) and cyclohexyl bromide (1.61 g.) were dissolved in ether (10 cc.). A portion (2.5 cc.) of a solution of ethyl bromide (1.62 g.) in dry ether (10 cc.) was added to magnesium (1.08 g.) covered with boiling ether, and as the magnesium dissolved, the solution containing VIb, together with more (5 cc.) of the solution of ethyl bromide, were added over a period of two and one-half hours, with stirring. The remainder of the solution of ethyl bromide was then slowly added, and the whole was refluxed for two hours. The mixture was then cooled to −15° and dry oxygen was bubbled through it for two hours. The green solid was decomposed by addition of hydrochloric acid, the ether layer was removed, washed with water and dried. The solvent was removed and the residue was molecularly distilled from a pot-still under 0.001 mm. At 120° (bath) a yellow oil (0.43 g.) distilled; at 150° a waxy solid (0.40 g.) sublimed. The solid was dissolved in petroleum ether and the solution was cooled to −70°. The solid was removed by centrifugation and crystallized twice from petroleum ether. It was then dissolved in methanol and water was added slowly; the dark oil was removed by centrifugation and then addition of more water brought about deposition of a solid. This was removed and crystallized from petroleum ether, when it melted at 72–75°. The Folin–Denis test was strongly positive. The U. V. spectrum is shown in Fig. 3.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.51.

6,10,14-Trimethylpentadecanone-2.—Phytol (24 g.) in purified ethyl acetate[7] (200 cc.) was ozonized (4% O_3 in O_2) at −5° and the ozonide was reductively decomposed. The ketone (14.4 g., 67%) boiled at 120–122° (1 mm.) and had $n^{25}D$ 1.4441.[8]

2-(6′,10′,14′-Trimethyl-2′-pentadecylidene)-4,6,7-trimethylcoumaran-3-one IVc.—The coumaranone III (1.81 g.), the above ketone (27.6 g.) and zinc chloride (10 g. freshly fused and powdered) were heated on the steam-bath for twenty-four hours, with stirring during the first hour. The mixture was dissolved in chloroform, the solution was washed with water, dried over sodium sulfate, and the solvent was removed. Excess ketone was removed by distillation from a pot-still at 150° (bath temperature) under a pressure of 0.1 mm. The recovered ketone (19.6 g.) was heated with more III (1.29 g.) and zinc chloride (10 g.) and the mixture was processed as before. Again the recovered ketone (16.1 g.) was heated with III (1.06 g.) and zinc chloride and the mixture was similarly processed. The dark oils remaining after removal of excess ketone were combined and distilled and redistilled from a pot-still under 0.001 mm. The yellow oil distilling at 175–185° (bath temperature) weighed 3.5 g. (40%) and had $n^{25}D$ 1.5140. The U. V. spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.33; H, 11.14.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethylcoumaran Vc.—The above coumaranone IVc (1 g.) in ethanol was subjected to the action of hydrogen for four hours in the presence of Raney nickel catalyst at 250° under an initial hydrogen pressure of 3600 lb. The catalyst was removed by centrifugation, the solvent was removed by distillation, and the residue was distilled from a pot-still under 0.001 mm. at a bath temperature of 160–190°. The pale yellow oil weighed 0.85 g. and had $n^{25}D$ 1.5036; analysis showed that it was not pure Vc, though it was sufficiently pure for use in the next step.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 81.66; H, 12.41.

The hydrogenation did not always proceed uniformly; in an experiment duplicating the one described above, the product had $n^{25}D$ 1.4886 and also was not pure Vc.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-bromocoumaran VIc.—The above impure coumaran (0.72 g.) in carbon tetrachloride (10 cc.) was brominated by dropwise addition of a solution of bromine (0.312 g.) in carbon tetrachloride (2 cc.). The solution remained colorless until about two-thirds of the bromine was added, after which it became orange. The solution was washed successively with aqueous sodium bicarbonate and aqueous sodium bisulfite, dried, and the solvent was removed. The residue was distilled from a pot-still under 0.001 mm. The yellow oil distilling at 165–210° (bath temperature) weighed 0.72 g. It was dissolved in petroleum ether (30 cc., b. p. 40–70°) and passed through a 20 × 0.5-cm. column filled with alumina (Brockmann). Additional petroleum ether (30 cc.) was passed through

(7) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 364.

(8) Smith and Sprung, THIS JOURNAL, **65**, 1271 (1943).

the column. The solvent was removed from the combined solutions and the residue was distilled under 0.001 mm. as before. It weighed 0.42 g., had $n^{25}D$ 1.5059, and gave the U. V. spectrum shown in Fig. 2.

Anal. Calcd. for $C_{29}H_{48}OBr$: C, 70.56; H, 10.00. Found: C, 70.54; H, 9.83.

The bromocoumaran VIc (0.33 g.) and cyclohexyl bromide (0.22 g.) in ether (10 cc.) was stirred with magnesium (0.163 g.) while the magnesium was reacting with ethyl bromide (0.21 g.) in ether (10 cc.). The procedure and processing of the reaction mixture were carried out as described above in the preparation of Ib. The crude product was distilled from a pot-still at 170–200° (bath temperature) under 0.001 mm.; the orange distillate weighed 0.25 g. It gave a positive Folin–Denis test, and contained a trace of halogen. A solution of the oil in petroleum ether (30 cc.) was passed through a column of alumina (Brockmann); the column was washed with additional petroleum ether and the combined organic solutions were evaporated. The residue was distilled as before. The distillate (about 0.1 g.) gave an absorption spectrum in the U. V. which in no way resembled those of Ia and Ib. The column of alumina was eluted with ethanol, but very little material was present in the eluate and this material, likewise, was not a hydroxycoumaran.

Summary

1. Three ketones—methyl ethyl ketone, methyl *n*-amyl ketone, and "phytol" ketone—have been condensed with 4,6,7-trimethylcoumaran-3-one (III) to give the 2-alkylidene coumarones.

2. The alkylidene coumarones from the last two ketones were reduced to the coumarans, and the latter were brominated in the 5-position.

3. The 5-bromocoumaran thus obtained from methyl *n*-amyl ketone was converted to a Grignard reagent, and the latter was oxidized, producing the 5-hydroxycoumaran. Conversion of the 5-bromocoumaran derived from phytol ketone into the analogous 5-hydroxycoumaran was not achieved.

4. Curves are given showing the absorption spectra in the ultraviolet of several of the intermediates and final products.

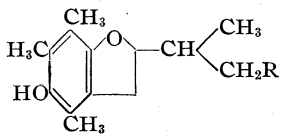
MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 2, 1948

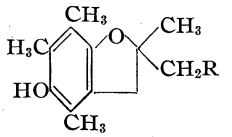
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Vitamin E. XLVII.[1] The Coumaran Isomer of α-Tocopherol

BY LEE IRVIN SMITH AND GERALD A. BOYACK[2]

Early in the history of the work upon the structure and synthesis of α-tocopherol, there was some discussion as to whether the vitamin was best represented as a coumaran, I, or as the isomeric chroman, II.[3]





I, R = $C_{15}H_{31}$ = 3,7,11-trimethyldodecyl. II, R = $C_{15}H_{31}$

Although the structure was definitely settled in favor of II,[4] a synthesis of the isomeric coumaran I would be of some interest, in view of the vitamin E activity of many compounds related to II. This paper describes a successful synthesis of I and one of its homologs X (R = *n*-$C_{13}H_{27}$). The coumaran I was obtained as a yellow oil and, although it showed vitamin E activity, the activity was only about 5% of that of α-tocopherol.

(1) Smith and Boyack, XLVI, THIS JOURNAL, **70**, 2687 (1948).

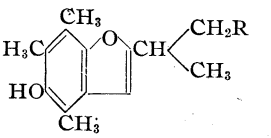
(2) Abstracted from a thesis by Gerald A. Boyack presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

(3) (a) Bergel, Todd and Work, *J. Chem. Soc.*, 253 (1938); (b) Karrer, Salomon and Fritzsche, *Helv. Chim. Acta*, **21**, 309 (1938); (c) Karrer, Fritzsche, Ringier and Salomon, *ibid.*, **21**, 520 (1938); (d) Fernholz, THIS JOURNAL, **60**, 700 (1938); (e) John, *Z. physiol. Chem.*, **252**, 222 (1938).

(4) (a) John, Dietzel, Günther and Emte, *Naturwiss.*, **26**, 366 (1938); (b) Karrer, Escher, Fritsche, Keller, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 939 (1938); (c) Smith, Ungnade and Prichard, *Science*, **88**, 37 (1938); (d) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941); (e) Smith, Ruoff and Wawzonek, *J. Org. Chem.*, **6**, 236 (1941); (f) Smith and King, THIS JOURNAL, **65**, 441 (1943).

The synthetic route to I involved the sequence of compounds III to VII (R as in formula I): the coumaron VII was then catalytically reduced to I.

III, $RCH_2C(CH_3)=CHCH_2OH$
IV, $RCH_2CH(CH_3)CH_2CH_2OH$
V, $RCH_2CH(CH_3)CH=CH_2$
VI, $RCH_2CH(CH_3)R'$
VIa, R′ = COOH
VIb, R′ = COCl
VIc, R′ = $COCH_3$
VId, R′ = $COCH_2COCH_3$



VII

Phytol (III) was catalytically reduced to dihydrophytol (IV) and the latter was converted to the stearate. When the crude stearate was pyrolyzed, phytene-1 (V) resulted. Although phytene-1 had been reported twice previously[5] no proof that the double bond is terminal has ever been given. The phytene-1 prepared in the present work had the proper iodine number and its reaction with perbenzoic acid was very slow—much slower than the rate with which oleic acid reacts, and slower even than the reaction of undecylene-1, indicating in this phytene the absence of a disubstituted double bond. Finally, ozonolysis of phytene-1 followed by oxidative decomposition of the ozonide, led to apophytoic acid VIa. The acid was converted into the acid chloride VIb and from this the methyl ketone VIc was prepared by action of dimethylcadmium.[6] A solid derivative of the methyl ketone VIc was not obtained; both the

(5) (a) Willstätter and Hocheder, *Ann.*, **354**, 255 (1907); (b) Willstätter, Mayer and Huni, *ibid.*, **378**, 91 (1911); (c) Karrer, Helfenstein and Widmer, *Helv. Chim. Acta*, **11**, 1201 (1928).

(6) Cason and Prout, THIS JOURNAL, **66**, 46 (1944).

semicarbazone and the 3,5-dinitrophenylhydrazone were liquids.

When the methyl ketone VIc reacted with ethyl acetate in the presence of sodamide, the diketone VId resulted. This gave a red color with ferric chloride, but no solid derivative was obtained; although VId formed a copper derivative, this was a liquid. Condensation between methyl apophytate and acetone in the presence of sodamide, which likewise would lead to VId, was unsuccessful—the chief product was apophytoic acid.

When a mixture of the diketone VId, trimethylquinone, and sodium ethoxide was allowed to stand for a week, the coumaron VII was obtained as a dark oil. The coumaron was characterized by analysis and by the U.V. absorption spectrum (Fig. 1), which exhibited maxima at the same wave lengths as shown by the spectrum of 2,4,6,7-tetramethyl-5-hydroxycoumaron.[7] The coumaron VII was reduced by action of hydrogen at 68° in the presence of a palladium catalyst; the product was the coumaran I, characterized by analysis, by conversion to a solid allophanate melting at 176–180° (m. p. of the allophanate of α-tocopherol, 158–160°)[8] and by the U. V. absorption spectrum (Fig. 1) which was quite similar to that of the simple isopropyl homolog (I, R = H).[1] The absorption spectrum of I was similar to that of α-tocopherol.[9] Curiously enough, the absorption spectrum of the allophanate of I was somewhat different from that of α-tocopheryl allophanate[10] but was almost identical with that of β-tocopheryl allophanate.[3a] The coumaran I was assayed biologically for Vitamin E activity[11] and the results showed that I possessed about 5% of the activity of *dl*-α-tocopherol. This is somewhat surprising, in view of the comparable activity of many compounds much less closely related structurally to α-tocopherol than I is, and in view of the fact that α-tocopherylamine is about as active as is α-tocopherol itself. It thus appears that the size of the ring—5 or 6—is a critical factor for vitamin E activity.

Before the experiments described above were undertaken, many model experiments were carried out. The route to the coumarans was based upon the work of Smith and Kaiser,[12] who added the enolate of acetylisobutyrylmethane to trimethylquinone and converted the resulting phenylated diketone, by action of hydrochloric acid, into a mixture of two 2-alkyl-4,6,7-trimethyl-5-hydroxy-

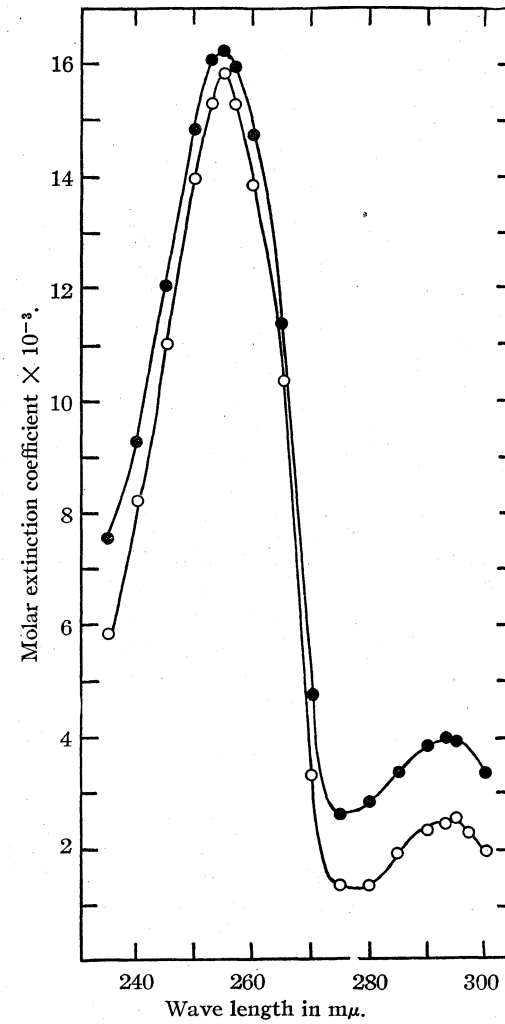


Fig. 1.—Absorption spectra: ○, 2-(6′,10′,14′-trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaron; ●, 2-tridecyl-4,6,7-trimethyl-5-hydroxycoumaran: solvent, 95% ethanol.

coumarons—the 2-methyl and the 2-isopropyl. This situation always arises when the starting diketone is unsymmetrical and the two alkyl groups have molecular weights close together; moreover, the resulting coumarons are separated only with great difficulty. Because of these facts, Smith and King[4f] in their synthesis of 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran (I, R = H) used the symmetrical diisobutyrylmethane as the starting diketone and so obtained only one coumaron. However, application of King's synthesis to the preparation of I offered formidable difficulties, for preparation of the intermediates necessary for conversion to the proper diketone involved many steps from the most accessible material, phytol. All of these intermediates, as well as the final product of the Claisen condensation, are liquids with very high boiling points, extremely difficult to purify. Consequently, if the approach to the synthesis of I could be made via Kaiser's method, the

(7) Webb, Smith, Bastedo, Ungnade, Prichard, Hoehn, Wawzonek, Opie and Austin, *J. Org. Chem.*, **4**, 389 (1939).

(8) Evans, Emerson and Emerson, *J. Biol. Chem.*, **113**, 319 (1936).

(9) Ref. 7; also Emerson, Emerson, Mohammed and Evans, *J. Biol. Chem.*, **122**, 99 (1937).

(10) John, *Naturwiss.*, **26**, 449 (1938).

(11) These assays were carried out by Dr. Paul D. Boyer and Mr. E. Liebe, of the Division of Agricultural Biochemistry, University of Minnesota, to whom the authors are greatly indebted. The method was that of K. E. Mason (*Biol. Symp.*, **12**, 1947). The minimum fertility dose (100% "litter efficiency") of I was between 15.0 and 17.5 mg.; in concurrent assays, the minimum fertility dose of *dl*-α-tocopherol was 0.75 mg.

(12) Smith and Kaiser, THIS JOURNAL, **62**, 133 (1940).

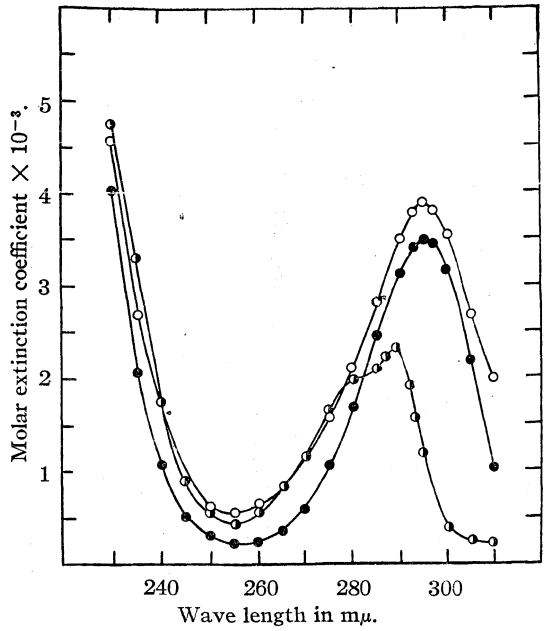
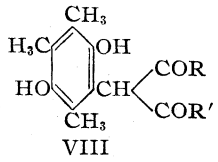
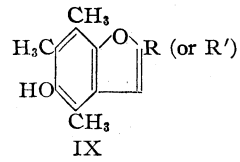


Fig. 2.—Absorption spectra: O, 2-(6′,10′,14′-trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaran: ●, 2-tridecyl-4,6,7-trimethyl-5-hydroxycoumaran: ◑, 2-(6′,10′,14′ - trimethyl - 2′ - pentadecyl) - 4,6,7 - trimethyl-5-hydroxycoumaran allophanate: solvent, 95% ethanol.

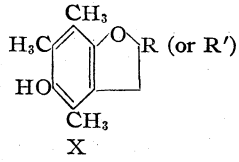
synthetic problems would be much simplified. Since the phenylated diketone VIII is an intermediate, the point of cleavage of this diketone during the ring closure determines the nature of the alkyl group in the 2-position of the coumaron



VIII



IX



X

IX. Kutz and Adkins[13] have shown that, when an acetylacylmethane CH_3COCH_2COR, is hydrolyzed by action of alkali, cleavage on the acetyl side of the molecule is promoted by increasing length and complexity of the group R. Therefore it appeared that if the group R in the diketone were large, the synthesis would lead to a mixture of coumarons in which the simpler 2-methylcoumaron would constitute but a minor proportion. If so, separation of the two coumarons should not offer much difficulty because the simple 2-methylcoumaron is quite volatile with steam. These expectations were fully justified; when myristoylacetylmethane was added to trimethylquinone and the resulting phenylated diketone was converted into coumarons, about three moles of IX, R = n-$C_{13}H_{27}$, were formed for every mole of IX, R = CH_3. The two coumarons were readily separated for IX, R = CH_3, is quite volatile with steam whereas IX, R = n-$C_{13}H_{27}$, is only slightly so. In the synthesis of I, none of the simple 2-methylcoumaron was obtained; ring closure led entirely to VII (R as in I).

The route to IX, R = n-$C_{13}H_{27}$, involved the same sequence of reactions that was used for synthesis of I. Myristoyl chloride was converted into pentadecanone-2 by reaction with dimethylcadmium.[6] In this reaction, a considerable amount of dimyristoylmethane was also formed. Pentadecanone-2 was converted into heptadecandione-2,4 by condensation with ethyl acetate in the presence of sodamide, in yields slightly better than those obtained when metallic sodium was used.[14] The diketone existed 100% in the enolic form, a finding in accord with the results of Weygand and Baumgartel[15] that the amount of enolic form at equilibrium in an acetylacylmethane increases with the length of the acyl group. Only poor yields of the diketone, accompanied by much myristic acid, were obtained when methyl myristate was condensed with acetone in the presence of sodium hydride according to the procedure of Hansley,[16] who stated that the diketone was produced in good yields. Condensation of the diketone with trimethyl quinone in the presence of sodium ethoxide, according to the procedure of King,[4f] offered no difficulty although a considerable amount of the diketone was recovered unchanged. Conversion of the phenylated diketone VIII to coumarons was effected by action of boiling dilute sodium hydroxide, although during the reaction air had to be carefully excluded. The phenylated diketone VIII was unaffected by hot hydrochloric acid, in contradistinction to the lower homologs, which are converted to coumarons by this reagent.[12] The coumaron IX (R = n-$C_{13}H_{27}$) was reduced to the corresponding coumaron (X, R = n-$C_{13}H_{27}$) by the action of hydrogen in the presence of a palladium catalyst.[17] Raney nickel catalyst under conditions of high temperature and pressure was without effect upon IX; this catalyst has been found effective for reduction of the lower homologs of IX.[18]

The melting points of the coumaran IX (R = n-$C_{13}H_{27}$) and the corresponding coumaran X are close together and a mixture of the two compounds does not show a depressed melting point. Nor does elementary analysis serve to distinguish between them. However, the absorption spectra in the ultraviolet are quite different for the two

(13) Kutz and Adkins, THIS JOURNAL, **52**, 4036 (1930).

(14) Morgan and Holmes, *J. Chem. Soc.*, 2891 (1925).

(15) Weygand and Baumgartel, *Ber.*, **62**, 574 (1929).

(16) Hansley, U. S. Patent 2,218,026 (1940).

(17) Bergel, Jacob, Todd and Work, *J. Chem. Soc.*, 1375 (1938).

(18) Ref. 4f; also Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, **4**, 305 (1939).

compounds; the curves are given in Figs. 1 and 2. The curve for this coumaran is very similar to those reported for other known 2-alkylcoumarans.[7]

Experimental Part[19]

Dihydrophytol IV.—Phytol (III, 200 g.)[20] was subjected to the action of hydrogen at 175° for one hour in the presence of Raney nickel catalyst, and under an initial hydrogen pressure of 2800 lb. The catalyst was removed and the product was distilled. The fraction boiling at 164–166° (0.01 mm.) did not decolorize bromine in carbon tetrachloride; it weighed 176 g. (85%) and had $n^{20}D$ 1.4520.[21]

Phytene-1 (V).—Dihydrophytol (166 g.) was heated at 125° (bath temperature) with stearoyl chloride (180 g.) for three hours. The cooled mixture was washed twice with double its volume of cold (10°) methanol. The crude liquid ester (329 g., free from chlorine) was pyrolyzed by dropping it slowly into a distilling flask immersed in a bath at 420°. The solid distillate (318 g.) was heated at 160° (bath temperature) under 0.01 mm. until there was no further distillate (phytene-1). The residue was washed with cold methanol to remove stearic acid, and was then distilled from a pot still at 340–380°. The olefin in the distillate was removed at 160° under 0.01 mm. as before, and the two olefin fractions (130 g.) were combined and allowed to stand over sodium for four days, with removal of the gelatinous material each day. The material was then distilled; the fraction boiling at 120–127° (0.01 mm.) weighed 86 g. (55%) and had $n^{25}D$ 1.4430.

Anal. Calcd. for $C_{20}H_{40}$: C, 85.63; H, 14.37; iodine number, 90.8. Found: C, 85.47; H, 14.09; iodine number, 91.4.[22] In three hours at 25° phytene-1 reacted with perbenzoic acid to the extent of 34.5%; under the same conditions, undecylene-1 and oleic acid gave the respective values of 44% at 100%.[23]

Apophytoic Acid (VIa).—Phytene-1 (V, 28 g.) in petroleum ether (200 cc., b. p. 28–38°, washed with sulfuric acid and dried over sodium) was ozonized at −50 to −40° by passing through the solution a stream of ozone–oxygen (0.4% O_3)[24] until approximately a third of the ozone was coming through unabsorbed. The solution was added to a stirred suspension of silver oxide (from silver nitrate, 46 g. and 1 *N* sodium hydroxide, 250 cc.) in aqueous sodium hydroxide (220 cc., 5%) at 95°. Petroleum ether distilled rapidly, and after all this solvent was removed, the mixture was stirred and heated on the steam-bath for eight hours. Chloroform (100 cc.) was added to the cooled and stirred suspension, which was then slowly acidified with nitric acid (80 cc.). The chloroform layer was removed, washed with water, dried over sodium sulfate, and the solvent was removed by distillation. The residues (28.3, 28.6 and 27.5 g.) from three such runs were combined and distilled from a Clarke flask under 0.01 mm. A low boiling fraction (6 g., odor of butyric acid) and an intermediate fraction (16 g., neutral), were followed at 175–185° by a fraction of apophytoic acid (51 g., 57%) having $n^{25}D$ 1.4489.

Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; neut. equiv., 298. Found: C, 76.57; H, 12.80; neut. equiv., 297.

The methyl ester (49.8 g., 98%) prepared from the acid (48 g.) by action of diazomethane (from 25 g., nitrosomethylurea) in ether (100 cc.) boiled at 125–133° (0.01 mm.) and formed a neutral liquid.

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90. Found: C, 76.97; H, 12.83.

Apophytoyl Chloride (VIb).—The acid VIa (27 g.) was refluxed in thionyl chloride (53.5 g.) for one hour. Excess thionyl chloride was removed at 120° (bath temperature) under 20 mm., and the residual acid chloride was distilled under 0.01 mm. It boiled at 165–170° and weighed 23.2 g. (81%).

Anal. Calcd. for $C_{19}H_{37}OCl$: C, 72.01; H, 11.77; Cl, 11.2. Found: C, 72.86; H, 12.30; Cl (Volhard), 10.7.

3,7,11,15-Tetramethylhexadecanone-2 (VIc).—A Grignard reagent was prepared by passing a current of methyl bromide into a stirred suspension of magnesium (3.58 g.) in ether (200 cc.) until the metal dissolved completely. To this solution, cadmium chloride (14.8 g., dried at 100° and powdered) was added all at once and the mixture was stirred and refluxed for ten minutes. Ether was removed by distillation until a mush of solid remained, then dry benzene (100 cc., thiophene-free) was added and distillation was continued until the temperature of the vapors reached 70°. More benzene (100 cc.) was added, the mixture was heated to the boiling point, and apophytoyl chloride (VIb, 23 g.) was added to the refluxing suspension as rapidly as the exothermic reaction would permit. The mixture was stirred and refluxed for thirty minutes longer, and was then poured over ice and acidified with hydrochloric acid until most of the solid dissolved. The organic layer was removed, and the aqueous layer was extracted with benzene. The combined organic layers were washed with water until the washings were neutral. The solution was dried over sodium sulfate and the solvent was removed by a flash distillation at 150°. The residue, distilled under 0.01 mm. gave a fraction boiling at 180–185° (11.1 g.) which had $n^{25}D$ 1.4453.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.01; H, 13.60. Found: C, 80.87; H, 13.71.

Additional ketone (1.3 g.) slightly less pure, was obtained by heating the residue from the above distillation in a pot still under 0.001 mm. at 130° (bath temperature). The total yield of ketone was 12.4 g. (58%). The residue remaining after removal of all the ketone, when distilled from a pot still at 210° (bath temperature) under 0.001 mm. gave a yellow oil (3 g.) having $n^{25}D$ 1.4650. It gave a red color with ferric chloride. This was probably a mixture of the 1,3-diketone $RCH_2CH(CH_3)COCH_2COCH(CH_3)CH_2R$ and the aldol product of the ketone, $RCH_2C(CH_3)=CHCOCH(CH_3)CH_2R$.

Anal. Calcd. for $C_{39}H_{76}O_2$ (diketone): C, 81.87; H, 13.28. Calcd. for $C_{40}H_{78}O$ (aldol): C, 83.56; H, 13.68. Found: C, 82.83; H, 13.36.

The semicarbazone of VIc, distilled from a pot still at 145° (bath temperature) under 0.001 mm., was a viscous oil having $n^{25}D$ 1.4713 and which could not be induced to crystallize. Likewise, the 2,4-dinitrophenylhydrazone of VIc was a viscous red oil, insoluble in ethanol (VIc was quite soluble in ethanol).

5,9,13,17-Tetramethyloctadecandione-2,4 (VId).—Small pieces of sodium were added to liquid ammonia (100 cc.) until the blue color was permanent, whereupon a small crystal of ferric chloride was added and air was drawn through the solution until the blue color disappeared. Then sodium (3.42 g.) was added and the mixture was stirred until the blue solution became a gray suspension. The ammonia was allowed to evaporate, being replaced by dry ether so that the volume remained constant. The ketone VIc (11 g.) in dry ether (30 cc.) was added and the mixture was refluxed for twenty minutes, then dry ethyl acetate (32.2 g.) was added slowly (ten minutes). The mixture first became very viscous, even though more ether (50 cc.) was added, but soon became thin enough to stir. It was stirred for seven hours at room temperature and then poured over ice and acidified (congo red) with hydrochloric acid. The organic layer was removed, combined with an ether extract of the aqueous layer, and dried over sodium

(19) Microanalyses by R. Amidon, Jay S. Buckley and S. Sundet.

(20) The authors are greatly indebted to Dr. R. T. Major, of Merck and Co., Inc., for a generous supply of phytol.

(21) (a) Kuhn and Sugmoine, *Helv. Chim. Acta*, **12**, 916 (1929), report 1.4538; (b) Willstätter, *et al.*, ref. 5b, report 1.45213.

(22) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green & Co., New York, N. Y., 1936, p. 212.

(23) Determinations by Mr. Tom Lee of the Division of Analytical Chemistry for which the authors are greatly indebted.

(24) The capacity of the transformer available; presumably higher concentrations would be equally effective.

sulfate. The solvent was removed and the residue, when distilled under 0.01 mm. gave a distillate (7.3 g., 58%) boiling at 150–153° and having $n^{25}D$ 1.4630.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 78.05; H, 12.51. Found: C, 77.85; H, 12.54.

The diketone gave a red color with alcoholic ferric chloride: when a solution of the diketone in a little methanol was shaken with warm aqueous cupric acetate, a blue oil separated. All attempts to crystallize this blue oil were unsuccessful.

When the enolate of acetone (19.1 g.) was prepared in liquid ammonia, essentially as described above, and brought into reaction with methyl apophytoate (49 g.) a product (59.7 g.) was obtained which, after distillation, had $n^{25}D$ 1.4500, and which consisted essentially of apophytoic acid, VIa.

Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; neut. equiv., 298. Found: C, 76.82; H, 13.09; neut. equiv., 313.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaron (VII).—A solution of the diketone VId (6.64 g.) in dry ethanol (10 cc.) was added to a solution of sodium (0.376 g.) in dry ethanol (50 cc.). The solution was stirred at room temperature for fifteen minutes, then was cooled to 15° and to it was slowly (one hour) added a solution trimethylquinone[25] (2.94 g.) in dry ethanol (30 cc.). The air in the flask was replaced by dry nitrogen and the flask was tightly stoppered and allowed to stand at room temperature for six and one-half days. The reaction mixture was poured onto ice, acidified with hydrochloric acid, and extracted three times with ether (100-cc. portions). The combined extracts were thoroughly washed with water and dried over sodium sulfate. The solvent was removed and the oil was subjected to distillation with steam; the distillate contained no organic material (*i. e.*, no IX, R = CH_3). The residue was taken up in ether, the solution was dried, the solvent was removed in a current of nitrogen. A red oil (1.76 g. unchanged VId) was removed from the product by distillation from a pot still under 0.001 mm. at a bath temperature of 130°. The residual oil from this distillation was stirred with petroleum ether (100 cc., b. p. 60–68°) and an insoluble black powder (1.12 g.) was removed. The solvent was removed in a current of nitrogen and the oil was distilled from a pot still under 0.001 mm. As the temperature of the bath was gradually raised, a dark oil (1.26 g.) distilled, followed by the coumaron VII (1.43 g., 21%) at 180°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.25; H, 11.08.

The absorption spectrum in the ultraviolet is shown in Fig. 1.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaran (I).—The coumaron VII (100 mg.) in acetic acid (15 cc.) was subjected for four hours to the action of hydrogen at 68° under a pressure of 20 lb. and in the presence of palladium–charcoal catalyst (10%). The catalyst was removed by centrifugation and the solvent was removed under reduced pressure (5 mm.) at 70°. The residual light brown oil weighed 92 mg.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.56; H, 11.76. The absorption spectrum in the ultraviolet is shown in Fig. 2.

Allophanate.—A stream of cyanic acid was passed for ten minutes through a solution of the coumaran I (90 mg.) in dry benzene (5 cc., thiophene-free). The solution was set aside in a refrigerator for six and one-half days. The solid was removed and washed with hot benzene; the filtrate and benzene washings were combined and the solvent was removed in a stream of nitrogen. The gummy residue was crystallized from methanol, when it weighed 45 mg. and melted at 160–174°. Recrystallized twice more from methanol, the substance melted at 176–180°.

Anal. Calcd. for $C_{31}H_{52}O_4N_2$: C, 72.05; H, 10.15. Found: C, 72.35; H, 10.37.

The absorption spectrum in the ultraviolet is shown in Fig. 2.

Pentadecanone-2.—This was prepared exactly as described above (for compound VIc) from magnesium (20.4 g.), methyl bromide, cadmium chloride (83.5 g.) and myristoyl chloride (104 g., b. p. 154–160° at 10 mm.). The product was distilled under 3 mm. pressure; the fraction (59.8 g., 63%) boiling at 122–135° solidified on cooling and then melted at 35–39°.[26] The semicarbazone melted at 124–125°.[27] Considerable residue remained after removal of the ketone; this was distilled from a pot still under 0.001 mm. at a bath temperature of 240°. The distillate, recrystallized from dry ethanol, gave 1.3 g. of dimyristoylmethane, melting at 62–63°.

Anal. Calcd. for $C_{29}H_{56}O_2$: C, 79.75; H, 12.92. Found: C, 79.49; H, 12.93.

The copper derivative, recrystallized from dry ethanol, melted at 101–102°.

Heptadecandione-2,4.—This was prepared as described above (for VId) from sodium (17.75 g.), liquid ammonia, pentadecanone-2 (58 g.), and ethyl acetate (55.5 g.). Cupric acetate dihydrate (50 g.) in water (500 cc.) was added to a solution of the crude product in warm methanol, the copper derivative was removed, washed with water, triturated with warm ethanol and the suspension was cooled and filtered. A small portion of the copper compound, crystallized from dry ethanol, was blue-gray and melted at 118–119°. The copper compound, suspended in petroleum ether (b. p. 40–70°), was shaken with dilute sulfuric acid until the solid disappeared. The organic layer was removed, washed thoroughly with water, and the solvent was removed by distillation. The residue (41.5 g., 60%) melted at 43–45°. The diketone gave a cherry-red color with alcoholic ferric chloride, and the enol content, determined by the method of Cooper and Barnes[28] was 98%. Condensation of methyl myristate (24.2 g.) in petroleum ether (200 cc., b. p. 100–140°) with acetone (2.9 g.) in the presence of sodium hydride (2.4 g.) gave only small amounts (5–8 g.) of the diketone, which was impure (m. p. 41–48°, enol content, 53%). The bulk of the condensation product was myristic acid.

3-(2′,5′-Dihydroxy-3′,4′,6′-trimethylphenyl)-heptadecandione-2,4 (VIII, R = CH_3; R′ = n-$C_{13}H_{27}$).—A solution of heptadecandione-2,4 (14.8 g.) in dry ethanol (50 cc.) was added, with stirring and some cooling (20°) to sodium methoxide (from sodium, 1.15 g.) in ethanol (50 cc.). Trimethylquinone (7.5 g.) in dry ethanol (25 cc.) was slowly (one and one-half hours) added to the cooled (15–20°) solution of the enolate. The solution was stirred for two hours at room temperature, then cooled (0°) and acidified with iced hydrochloric acid and extracted three times with ether. The combined extracts were washed with water, filtered, and the solvent was removed. The oily residue was dissolved in warm methanol and the solution, when cooled, deposited 9.5 g. of material melting at 40–70°. This material, recrystallized first from petroleum ether and then from methanol, weighed 3 g. (14%) and melted at 90–91°. The analytical sample, crystallized twice from petroleum ether and three times from methanol, melted at 95–96°.

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.44; H, 10.23.

Heptadecandione-2,4 (6.3 g., m. p. 43–45°) was recovered by recrystallization from methanol of the residue obtained when all the mother liquors from the above purification were combined and evaporated.

(25) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 138 (1939).

(26) Dreger, Keim, Miles, Shedlovsky and Ross, *Ind. Eng. Chem.*, **36**, 610 (1944), report the m. p. as 40.5°.

(27) (a) Baumgarten, *Ber.*, **76**, 213 (1943), reported the m. p. as 124–125°; (b) Pickard and Kenyon, *Proc. Chem. Soc.*, **27**, 312 (1911), reported 126.5°.

(28) Cooper and Barnes, *Ind. Eng. Chem., Anal. Ed.*, **10**, 379 (1938).

2-*n*-Tridecyl-4,6,7-trimethyl-5-hydroxycoumaron (IX, R = *n*-$C_{13}H_{27}$).—The diketone VIII (560 mg.) was warmed on the steam-bath for one hour with aqueous sodium hydroxide (1 *N*, 20 cc.) in an atmosphere of nitrogen. (When air was allowed to come into contact with the reaction mixture, the product was a red oil which could not be crystallized.) The cooled mixture was acidified with hydrochloric acid and then steam-distilled. From the distillate there was obtained 51 mg. (20%) of 2-methyl-4,6,7-trimethyl-5-hydroxycoumaron (IX, R = CH_3), m. p. and mixed m. p., 136–137°. The residual oil in the distillation flask solidified on cooling; it was removed and crystallized from methanol, when it weighed 260 mg. (54%) and melted at 101–102°. The analytical sample, crystallized from methanol, melted at 102–104°.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.41; H, 11.04.

The absorption spectrum in the ultraviolet is shown in Fig. 1. The diketone VIII (430 mg.) was recovered unchanged after 500 mg. of it was boiled with hydrochloric acid (10 cc.) and ethanol (2 cc.) for seven hours; likewise, action of hydrogen chloride in refluxing acetic acid (10 cc.) for one hour upon the diketone (500 mg.) did not bring about ring closure; the recovery of diketone was 275 mg.

2-*n*-Tridecyl-4,6,7-trimethyl-5-hydroxycoumaran (X, R = *n*-$C_{13}H_{27}$).—The coumaron IX (75 mg.) in acetic acid (10 cc.) was shaken with hydrogen at 46° and under a pressure of 20 lb. for four hours in the presence of a palladium–charcoal catalyst. The solvent was removed under reduced pressure at 40°; the residue was dissolved in methanol and the catalyst was removed by centrifugation. The solution, when concentrated and cooled, deposited a white solid melting at 93–94°. When mixed with the coumaran (m. p. 102–104°), the substance also melted at 93–94°.

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.76; H, 11.22.

The absorption spectrum in the ultraviolet is shown in Fig. 2. The coumaron IX (360 mg.) in dry ethanol (10 cc.) was heated on the steam-bath for fifteen minutes with Raney nickel catalyst. The catalyst was removed, fresh catalyst was added, and the mixture was subjected to the action of hydrogen for one hour at 125° and 1600 lb. The product weighed 230 mg. and melted at 101–103°. This material, subjected to the same conditions as before, but at 140°, gave a product which melted at 97–99°, alone or when mixed with known IX. The absorption spectrum in the ultraviolet indicated that no reduction had occurred.

Summary

1. The coumaran 2-(6′,10′,14′-trimethyl-2′-pentadecyl) - 4,6,7 - trimethyl - 5 - hydroxycoumaran, I, an isomer of α-tocopherol, II, has been synthesized. The coumaran has been characterized by its absorption spectrum, by conversion into an allophanate melting at 176–180° and by the absorption spectrum of the latter. Although I differs from II only in the size of the hetero ring, I has only about 5% as much vitamin E activity as II.

2. The synthesis of Smith and King, whereby 2-isopropyl-5-hydroxycoumaran and homologs are produced, has been modified in such a way that the more accessible unsymmetrical acetylacylmethanes may be used instead of the symmetrical diketones. When the R of the acyl group has a relatively high molecular weight, the coumaron with the higher alkyl group is formed exclusively or in preponderant amounts; if two coumarons are formed, the simple one may be removed from the reaction product by steam distillation. In this way, 2-*n*-tridecyl-4,6,7-trimethyl-5-hydroxycoumaron (IX) R = *n*-$C_{13}H_{27}$, has been prepared and separated from 2,4,6,7-tetramethyl-5-hydroxycoumaron (IX, R = CH_3), formed in the same reaction. The coumaron IX (R = *n*-$C_{13}H_{27}$) has been reduced to the corresponding coumaran X (R = *n*-$C_{13}H_{27}$).

3. The absorption spectra of a number of intermediates in the above syntheses have been determined.

MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 2, 1948

[A JOINT CONTRIBUTION FROM THE RESEARCH LABORATORY, DODGE & OLCOTT, INC., AND THE INSECTICIDE FELLOWSHIP, MELLON INSTITUTE]

Preparation and Cyclization of Certain Insecticidally Active α-Acetyl-δ-keto Esters

BY HERMAN WACHS AND OSCAR F. HEDENBURG

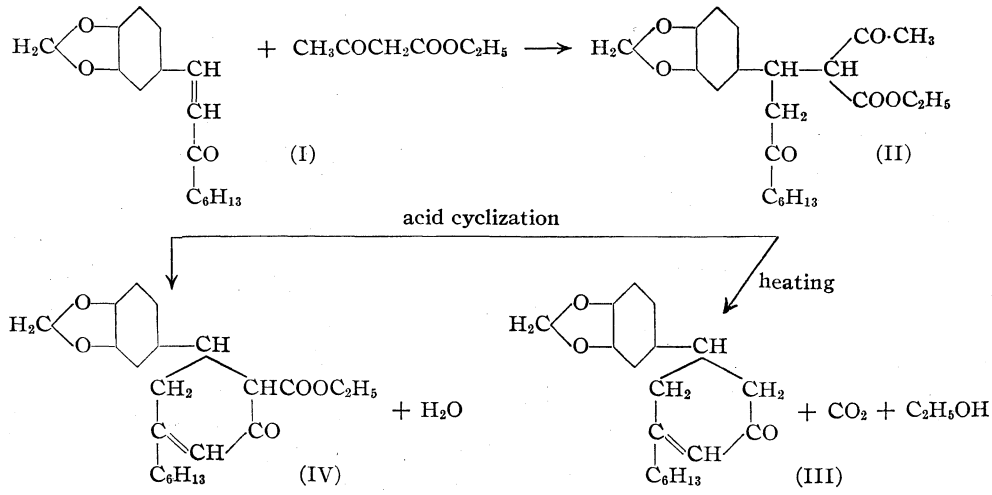
The condensation of ethyl acetoacetate with hexyl 3,4-methylenedioxystyryl ketone[1] at room temperature yields a mixture having high insecticidal activity. When allowed to crystallize, 3-hexyl - 5 - (3,4 - methylenedioxyphenyl) - 2 - cyclohexene-1-one (III) is obtained, which has been found to have the same insecticidal activity as the original mixture or the remaining mother liquor. This mother liquor contains resinous material and approximately 50% of 3-hexyl-5-(3,4-methylenedioxyphenyl) - 6 - carbethoxy - 2 - cyclohexene - 1 - one (IV). Proceeding on the assumption that the resinous portion was of little activity, it appeared desirable to devise a method by which the above ester (IV) could be obtained as the main product. The present paper describes the procedure developed to accomplish this purpose. This procedure also made it possible to obtain esters other than ethyl esters and to compare their relative effectiveness. The work was expanded to include compounds containing the furfuryl group in the 3 position of the cyclohexenone ring.

It was assumed that a Michael addition[2] takes place intermediate to the formation of the cyclohexenone ring. Taking advantage of the fact that such addition reactions are reversible,[3] by employing a large excess of ethyl acetoacetate and by

(1) Hedenburg and Wachs, THIS JOURNAL, **70**, 2216 (1948).

(2) Michael, *J. prakt. Chem.*, **35**, 351 (1887).

(3) Ingold and Powell, *J. Chem. Soc.*, 1976–82 (1921).



working at a temperature of +5° we obtained α-acetyl-β-(3,4-methylenedioxyphenyl)-δ-ketoethyl undecylate (II) from hexyl 3,4-methylenedioxystyryl ketone (I), in a yield of 65%. Compound (II) was a white crystalline solid melting at 149°; above its melting point it yielded ethyl alcohol, carbon dioxide and the cyclohexenone (III) in stoichiometric proportions.

When compound (II) was refluxed in benzene solution in the presence of a small quantity of toluene sulfonic acid or trichloroacetic acid, until no more water would distil over with the benzene, one molecular equivalent of water collected in the water trap, indicating that cyclization had taken place with a minimum of decomposition of the ester group. Only traces of liberated carbon dioxide were observed. The product was a light-colored, viscous liquid, which dissolved in most of the common organic solvents; it would not crystallize on cooling to −30° and could not be distilled *in vacuo* without decomposition; the saponification value indicated the presence of more than 90% of ester. On saponification, partial resinification occurred, but it was possible to isolate a good yield of crystals, which were identical with the decarboxylated cyclohexenone (III).

Hexyl 3,4-methylendioxystyryl ketone was also condensed with butyl, octyl, benzyl and allyl acetoacetates in an analogous manner and the corresponding α-acetyl-δ-keto esters were obtained in pure form. Upon cyclization by the aid of trichloroacetic or toluene sulfonic acid, the resulting allyl and butyl compounds had an insecticidal activity equal to that of the ethyl compound; the octyl and benzyl compounds were definitely inferior.

By the condensation of furfural with methyl isobutyl ketone, furylidene isobutyl ketone was prepared. It was condensed with ethyl acetoacetate and with butyl acetoacetate at 5° and the α-acetyl-δ-keto esters were isolated and purified. Upon cyclization the insecticidal activity was found to be poor.

The Table I summarizes certain characteristics of the products.

TABLE I

PROPERTIES OF SUBSTITUTED α-ACETYL-δ-KETO ESTERS

Ketone used	Aceto-acetate used	Melting point of α-acetyl-δ-keto ester, °C.	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
Hexyl-	Ethyl	149	$C_{22}H_{30}O_6$	67.67	67.92	7.75	7.55
3,4-me-	Allyl	134	$C_{23}H_{30}O_6$	68.64	68.41	7.51	7.30
thylene	Butyl	131	$C_{24}H_{34}O_6$	68.87	68.69	8.19	8.01
dioxy-	Octyl	133	$C_{28}H_{42}O_6$	70.85	70.67	8.92	8.62
styryl	Benzyl	138	$C_{27}H_{32}O_6$	71.71	71.81	7.12	7.34
Furylidene	Ethyl	116	$C_{17}H_{24}O_5$	66.28	66.41	7.84	7.51
isobutyl	Butyl	98	$C_{19}H_{28}O_5$	67.84	67.96	8.39	8.77

Experimental

α-Acetyl-β-3,4-methylenedioxyphenyl-δ-keto-ethyl Undecylate (II).—Metallic sodium (5.7 g., 0.25 mole) was dissolved in 150 cc. of anhydrous ethyl alcohol, 97 g. of ethyl acetoacetate was added, the solution cooled to 5° and, during one hour, a solution of 65 g. (0.25 mole) of hexyl 3,4-methylendioxystyryl ketone in 65 g. of benzene was added under agitation. The temperature was kept at 5 to 7° during the addition. The mixture was then agitated for an additional two hours and allowed to stand overnight at a temperature of 5 to 7°. It was neutralized with dilute hydrochloric acid under cooling, then warmed on the steam-bath to allow the benzene solution of the reaction product to separate. The benzene solution was drawn off and allowed to crystallize in an ice-box. The crystals were filtered off and washed with benzene. The dry crystals weighed 252 g. After recrystallization from benzene they melted at 149°.

Cyclization of (II).—A solution of 25 g. of (II) in 75 g. of benzene was refluxed in the presence of 1.5 g. of trichloroacetic acid or toluenesulfonic acid until no more water would distil over. The residue in the flask was neutralized with sodium carbonate solution, the benzene solution dried and filtered, the solvent distilled and the product dried *in vacuo*. It was a light colored viscous oil, the saponification value indicating about 90% of the ester, IV.

Furylidenemethyl Isobutyl Ketone.—Methyl isobutyl ketone (60 g.) was dissolved in 96 g. of methanol, 15 g. of a 20% aqueous solution of sodium hydroxide was added, and to this mixture 57.5 g. of freshly distilled furfural was added over a period of 0.5 hour under agitation at a temperature of 18 to 20°. The agitation was continued for two hours at the same temperature. The mixture was allowed to stand overnight. Water, 100 cc., and 100 cc. of benzene were added and the mixture neutralized with acetic acid. The benzene solution was separated, the solvent removed, and the remainder distilled *in vacuo*.

The final product distilled at 108° at 1.4 mm. It was a yellowish oil which darkened rather rapidly.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 73.97; H, 7.84.

The melting points and the analyses of other α-acetyl-δ-keto esters, similarly prepared, are given in Table I. In each case, saponification indicated about 90% of the cyclic ester in the crude cyclized product.

Summary

The preparation of 3,4-methylenedioxyphenyl substituted α-acetyl-δ-keto esters in pure form and in good yield is outlined. A method of their cyclization which yields cyclohexenone esters of high insecticidal activity with a minimum of splitting of the ester group is described.

Furyl substituted α-acetyl-δ-keto esters were prepared and cyclized to cyclohexenone esters and were found to be of much lower insecticidal activity than the 3,4-methylenedioxyphenyl substituted products.

BAYONNE, NEW JERSEY
PITTSBURGH, PA.

RECEIVED[4] MARCH 17, 1948

(4) Original manuscript received October 31, 1947.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED, HUNGARY]

Synthetic and Degradative Studies in the Isoquinoline Series. III

BY V. BRUCKNER, G. FODOR, J. KOVÁCS AND J. KISS

In previous communications[1,2] the structure of different 1,3-dimethyl-6,7-dialkoxy- and aralkoxyisoquinolines (Ia-If), of 1-benzyl-3-methyl-6,7-methylenedioxyisoquinoline (II), synthesized by us,[3,4] was established by exhaustive methylation followed by oxidation. In all cases investigated by us, degradation gives rise either to metahemipinic acid (IIIa), or to hydrastic acid (IIIb). To complete our first paper,[1] the structure of 1,3-dimethyl-6,7-methylenedioxyisoquinoline[5] (Ig) is now ascertained, by preparing it from the 6,7-dihydroxy derivative Ia of known structure.[1] Ring closure of α-(3,4-disubstituted phenyl)-β-acylaminopropanols to the isoquinolines takes place, consequently, in all cases studied by us in *m,p*-position to the alkoxy groups, to form 6,7-disubstituted 3-methylisoquinolines, independently of the substituents.

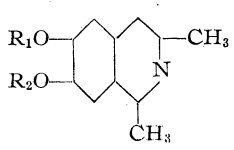
Pfeiffer, *et al.*,[6] obtained from brasiline a compound and suggested for its structure IV 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline by analogy with the structure of the compound obtained by them from hematoxyline. They attempted to confirm its constitution by synthesis from α-(3,4-dimethoxyphenyl)-β-(2′-carbethoxy-oxy-4′-methoxybenzoylamino)-propanol. Ring closure yielded only a small amount of an oily phenolic isoquinoline; its picrate was, however, not identical with that of the compound obtained from brasiline. Ring closure of the amorphous α-(3,4-dimethoxyphenyl)-β-(2′,4′-dimethoxybenzoylamino)-propanol led to a crystalline isoquinoline isomer, but which was not identical with the methyl ether of the compound from brasiline. Therefore they assign structure V, 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-7,8-dimethoxyisoquinoline, to the synthetic isoquinoline.

The present work was undertaken to synthesize through crystalline, well-defined intermediates the same phenolic isoquinoline whose picrate was described by Pfeiffer, *et al.*[6] As the structure of this synthetic compound and of its isomer have not been confirmed by degradation, it seemed desirable to carry out the oxidative degradation of the former.

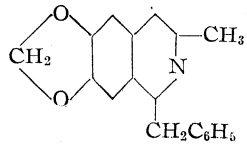
We started with the stereoisomeric α-(3,4-dimethoxyphenyl)-β-aminopropanols. One of these (m. p. 128°) was prepared according to Bruckner[5]; another (m. p. 138°) according to Iwamoto and Hartung.[7] 2-Benzyloxy-4-methoxybenzoic acid was prepared from β-resorcylic acid *via* methyl 2-hydroxy-4-methoxybenzoate and methyl 2-benzyloxy-4-methoxybenzoate. On condensation of 2-benzyloxy-4-methoxybenzoyl chloride with the aminopropanol (m. p. 138°) the amide VI is formed; on ring closure it yielded smoothly the corresponding isoquinoline derivative (benzyl ether of IV). The stereoisomeric aminopropanol gave on a similar treatment the identical isoquinoline. The benzyloxyisoquinoline derivative afforded on hydrogenolysis (Pd charcoal) the crystalline hydroxyisoquinoline IV in nearly quantitative yield. Its picrate shows m. p. 275°; its methyl ether prepared by diazomethane, m. p. 144°; its methyl ether picrate, m. p. 231–232°. The same data are recorded by Pfeiffer, *et al.*[6], for the compound formulated by them as V (*cf.* table of m. p.'s), they are consequently identical, whereas the product obtained from brasiline is different.

As a degradative approach to the structure of this phenolic isoquinoline we have chosen the oxidation with alkaline permanganate. Metahemipinic acid alone could be detected as a fragment, identified by its m. p., analysis and conversion into its ethylimide (m. p. 228°). For the synthetic hydroxyisoquinoline derivative the structure 1-

(1) Bruckner, Kovács and Kovács, *Ber.*, **77**, 610 (1944).
(2) Bruckner, Kovács and Nagy, *ibid.*, **77**, 710 (1944).
(3) Bruckner and Fodor, *Ber.*, **71**, 541 (1938).
(4) Bruckner and Krámli, *J. prakt. Chem.*, [2] **145**, 291 (1936).
(5) Bruckner, *Ann.*, **518**, 235 (1935).
(6) Pfeiffer, Breitbach and Scholl, *J. prakt. Chem.*, [2] **154**, 157 (1940).
(7) Iwamoto and Hartung, *J. Org. Chem.*, **9**, 513 (1944).

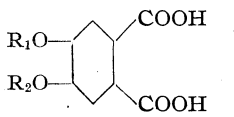


I



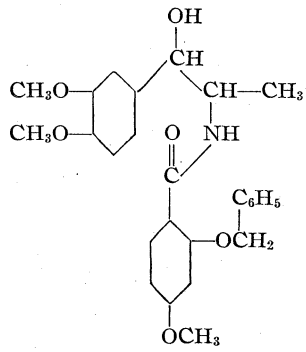
II

$R_1 = R_2 = H$/a/
$R_1 = R_2 = CH_3$/b/
$R_1 = R_2 = C_2H_5$/c/
$R_1 = R_2 = C_6H_5CH_2$/d/
$R_1 = CH_3$; $R_2 = C_2H_5$/e/
$R_1 = CH_3$; $R_2 = C_6H_5CH_2$/f/
$R_1 + R_2 = CH_2$/g/

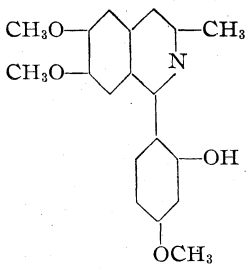


III

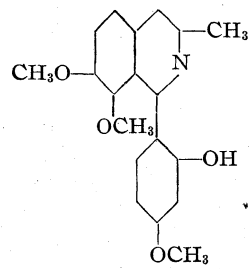
$R_1 = R_2 = CH_3$/a/
$R_1 + R_2 = CH_2$/b/



VI



IV



V

(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV is thus proved; its formulation as the 7,8-dimethoxyisoquinoline derivative V suggested by Pfeiffer, *et al.*[6], is evidently erroneous, the ring closure taking place in these cases also in *m,p*-position to the alkoxy groups.

Moreover, as the product obtained from brasiline is not identical with 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV, it remains to decide whether the difference is to be found in the isoquinoline nucleus or in the radical attached at position 1.

TABLE I

MELTING POINTS OF THE ISOQUINOLINES, °C.

Compound	From brasiline, °C.	Synthesized, °C. By Pfeiffer	By us
Phenolic isoquinoline	188–189	.....	143–144
Picrate	224–225	272–275	274–276
Methyl ether	110	144–145	142–144
Methyl ether picrate	212–215	233–235	232–235

Experimental

1,3-Dimethyl-6,7-methylenedioxyisoquinoline (Ig).—A mixture of 0.6 g. (0.003 mole) of 1,3-dimethyl-6,7-dihydroxyisoquinoline (Ia) in 60 ml. of ethanol, 0.18 g. (0.0078 atom) of sodium in 5 ml. of ethanol and 1.26 g. (0.004 mole) of methylene iodide was refluxed for six hours. The non-phenolic part was isolated in the usual manner: yield, 0.28 g. of Ig, m. p. 144°, alone and mixed with an authentic specimen.[5]

α-(3,4-Dimethoxyphenyl-) β-aminopropanol. A. From O-Methylisoeugenol-ψ-nitrosite the free base was obtained (m. p. 128°). **B. From α-Isonitroso-3,4-dimethoxypropiophenone,**[8] principally by the same method as recorded by Iwamoto and Hartung[7] the base, m. p. 138°, resulted.

Methyl 2-Hydroxy-4-methoxybenzoate.—Fifteen and five tenths grams (0.1 mole) of β-resorcylic acid was dissolved in a solution of 16.8 g. (0.3 mole) of potassium hydroxide in 100 ml. of water; then 20 ml. (0.2 mole) of dimethyl sulfate added under stirring. The mixture was heated one hour on the steam-bath. The aqueous layer was decanted, the ester dissolved in 50 ml. of ether, washed with water, dried and the solvent removed. The brown oily residue was dissolved in 40 ml. of methanol, 20 ml. of concentrated sulfuric acid added and refluxed for two hours, then cooled with an ice–salt mixture, the separated crystals filtered, washed with water until neutral; yield 11 g. (59%) of colorless plates, m. p. 50–52°.[9]

2-Benzyloxy-4-methoxybenzoic Acid.—A mixture from 2.3 g. (0.1 atom) of sodium in 100 ml. of ethanol, 18 g. (0.1 mole) of the ester obtained above and 13 ml. (0.1 mole) of benzyl chloride was refluxed for twelve hours, and the resulting solution of the benzylated ester boiled with 6 g. (0.11 mole) of potassium hydroxide in 20 ml. of water for saponification. The benzylated acid was isolated by the usual manner: yield 12 g. (47%). Recrystallization from 40 ml. of ethanol yielded 9.5 g. of colorless prisms, m. p. 103°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.47. Found: C, 69.61; H, 5.51.

α-(3,4-Dimethoxyphenyl)-β-(2′-benzyloxy-4′-methoxybenzoyl-amino)-propanol (VI).—Nine and a half grams (0.037 mole) of the foregoing acid was suspended in 20 ml. of toluene, treated with 16 ml. of thionyl chloride, heated on a water-bath at 35–40°, until hydrogen chloride evolved. The thionyl chloride was removed *in vacuo*, the remainder dissolved in 50 ml. of hot absolute toluene. The crude product is satisfactorily pure for use in acylation process. Twenty-one and three-tenths grams (0.1 mole) of the aminopropanol above (m. p. 138°) was dissolved in 500 ml. of boiling anhydrous toluene, and there was added, drop by drop under vigorous stirring, the toluenic solution of 2-benzyloxy-4-methoxybenzoyl chloride prepared above. The hydrochloride of the aminopropanol separates instantaneously. The mixture was then refluxed for fifteen minutes and filtered hot: yield 13 g. (0.052 mole) of aminopropanol hydrochloride. The filtrate (washed twice with 100 ml. of 2 *N* hydrochloric acid, then with 100 ml. of 2 *N* sodium hydroxide and finally with water) was dried and concentrated to 180 ml. On cooling, the amide separated as colorless needles: yield 15.1 g. (91%), m. p. 139–140°.

Anal. Calcd. for $C_{26}H_{29}O_6N$: C, 69.16; H, 6.47. Found: C, 68.96; H, 6.26.

1-(2′-Benzyloxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (Benzyl Ether of IV). A.—Fourteen and a half grams (0.032 mole) of the amide VI was dissolved in 300 ml. of hot toluene, then 15 ml. of phosphoryl chloride added on heating and occasional stirring. The mixture was refluxed for an hour, the isoquinoline salt formed being partly precipitated during this time. The reaction mixture was allowed to cool, then exhaustively extracted with one liter of water, cleared with charcoal, filtered and made alkaline with 5 *N* potassium hydroxide. The separating oily free base solidifies on standing in the ice-box overnight. The crude product was washed with water and dried, yield 10 g. (75%) of a yellow microcrystalline powder. On recrystallization from 180 ml. of

(8) Karg, *Arch. Pharm.*, **282**, 49 (1944).
(9) Mutschler, *Ann.*, **185**, 222 (1877).

alcohol–water (1:8), delicate needles, m. p. 83–84°, resulted. The hydrochloride prepared by the customary method forms a yellowish green crystalline powder, m. p. 221–222°.

Anal. Calcd. for $C_{26}H_{25}O_4N \cdot HCl$: C, 69.10; H, 5.79. Found: C, 69.10; H, 5.88.

B.—From 0.4 g. (0.002 mole) of the aminopropanol (m. p. 128°) in 15 ml. of toluene and 0.16 g. (0.0006 mole) of acid chloride—in the manner described above—0.3 g. of an amorphous amide was obtained which could be converted without further purification into the isoquinoline derivative. It yielded 0.2 g. of snow white clusters of crystals, m. p. 68°, which rises on recrystallization to 81°, alone and in admixture with the specimen obtained under A (its hydrochloride melted alone and mixed with that of A at 219–221°).

1-(2′-Hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline. IV.—Fifteen grams (0.033 mole) of the benzyloxyisoquinoline in 300 ml. of anhydrous ethanol absorbed 825 ml. of hydrogen (Pd charcoal) (calcd. for 1 mole H per mole, 809 ml.). The yellowish green crude product (10.75 g.) was recrystallized from aqueous ethanol to give 7.25 g. of delicate needles, m. p. 143–144°. This, together with a further crop (3.1 g.) of needles of the same m. p., yielded 10.35 g. (96%), equally soluble in cold dilute alkali and acid.

Anal. Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.88. Found: C, 69.48; H, 5.38.

The free base was converted into the **hydrochloride,** forming yellowish needles, m. p. 271°.

Anal. Calcd. for $C_{19}H_{19}O_4N \cdot HCl$: C, 62.89; H, 5.56. Found: C, 62.64; H, 5.62.

Picrate.—Yellowish microcrystals, m. p. 274–276° (dec.). Pfeiffer, *et al.*,[6] recorded 274–275° (dec.).

Anal. Calcd. for $C_{25}H_{22}O_{11}N_4$: C, 54.13; H, 4.00. Found: C, 54.25; H, 3.95.

1-(2′,4′-Dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (Methyl Ether of IV).—Twenty-six-hundredth gram (0.001 mole) of the phenolic isoquinoline IV dissolved in 10 ml. of anhydrous methanol was methylated by means of a 0.5 *N* ethereal diazomethane solution, until the yellowish color of the latter did not disappear: colorless plates, m. p. 144°. Pfeiffer[6] recorded m. p. 143–144°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24. Found: C, 70.42; H, 6.19.

Picrate.—Yellow plates, m. p. 231–232° (dec.). Pfeiffer[6] recorded m. p. 232–235°.

Anal. Calcd. for $C_{26}H_{24}O_{11}N_4$: C, 54.91; H, 4.26. Found: C, 55.01; H, 4.33.

Degradation of IV to Metahemipinic Acid.—Seven and twenty-four-hundredth grams (0.022 mole) of IV and 3 g. (0.075 mole) of sodium hydroxide were dissolved in 1.1 liter of hot water, then 50 g. of potassium permanganate in one liter of hot water was added by dropping within ten minutes under vigorous stirring and heating on the steam-bath, the solution becoming after twenty minutes nearly colorless. The hygroscopic solid residue of the solution was treated twenty-four hours continuously in a Soxhlet extractor with ethanol, the solvent removed *in vacuo* to give 1.5 g. of a yellowish crystalline mass. This was dissolved in 10 ml. of water, cleared with charcoal, filtered and then acidified (nitric acid) to congo. After the solution has been neutralized with ammonia, the lead salts were precipitated by means of lead acetate at *p*H 7–8, separated in the centrifuge, washed with a small amount of water. The acid was liberated with hydrogen sulfide, the filtrate concentrated to 3 ml. and allowed to stand overnight in an ice-box; 72 mg. of brief needles was obtained, which melted alone and in admixture with metahemipinic acid at 175–177°. For the analysis it was twice recrystallized from water.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.45. Found: C, 52.66; H, 4.34.

Further identification was made converting 26 mg. of the acid into its ethylimide on treatment with 1 ml. of 25% aqueous ethylamine. The water was then evaporated the remainder sublimed *in vacuo*, and 23 mg. of crystals obtained. Recrystallization afforded colorless long needles, m. p. 228°.[10] The ethyl imide of hemipinic acid shows m. p. 93°.[11]

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.25; H, 5.57. Found: C, 61.50; H, 5.59.

Acknowledgment.—The authors are grateful to Dr. D. Varsányi and Dr. T. Horváth for their assistance in preparing some of the compounds and to Dr. M. Kovács Oskolás for the microanalyses.

Summary

The ring closure of α-(3,4-dialkoxyphenyl)-resp. (3,4-methylenedioxyphenyl)-β-acylaminopropanols takes place in all cases investigated in *m,p*-position to the alkoxy groups, to form 6,7-disubstituted 3-methylisoquinolines. This is supported by a study of the oxidative degradation even in the case of 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV first obtained as picrate by Pfeiffer, *et al.*,[6] and described erroneously as a 7,8-dimethoxyisoquinoline derivative V. Consequently, the structure of the isomeric compound, obtained by Pfeiffer, *et al.*, from brasiline, and formulated as IV, becomes doubtful.

SZEGED, HUNGARY RECEIVED JANUARY 7, 1948

(10) Goldschmiedt, *Monatsh.*, **9**, 722 (1888)

(11) Freund and Heim, *Ber.*, **23**, 2906 (1890).

[COMMUNICATION NO. 1179 FROM THE KODAK RESEARCH LABORATORIES]

Investigation of the Properties of Cellulose Oxidized by Nitrogen Dioxide. VI. The Effect of Alkali on the Celluronic Acids[1]

BY P. A. MCGEE, W. F. FOWLER, JR., C. C. UNRUH AND W. O. KENYON

The initial investigations[2] of the action of nitrogen dioxide on cellulose showed that the resulting celluronic acids are alkali-soluble when the carboxyl content is sufficiently great. The celluronic acids undergo further reaction in alkaline solution which complicates the application of the copper number determination or direct determination of carboxyl groups by alkaline titration.[3] The reducing values obtained by copper number determinations were exceptionally high. It appeared probable that the reducing groups were not present to such an extent in the celluronic acids, but were generated by decomposition under the severe conditions of high *p*H and temperatures used in the determinations. Attempts to prepare sodium celluronate solutions, even at *p*H values only slightly above 7, showed that whenever solution was effected, concomitant degradation had occurred. The calcium acetate and carbon dioxide evolution methods which operate at *p*H values below 7 were chosen for carboxyl determinations to avoid the degradation which appeared to accompany the direct determination by alkaline titration.[2,3]

The evidence accumulated to date indicates that free carboxyl groups in celluronic acids are substantially contained in uronic acid units. The carboxyl values by carbon dioxide evolutions are at least as high as the values from potentiometric titration or the calcium acetate method.[4] Aside from carboxyl groups which should not produce alkali-instability in celluronic acids, oxidation of hydroxyl groups could form aldehyde or ketone groups or an enediol structure by isomerization of the latter. Aldehyde groups in simple organic compounds are attacked rapidly—sometimes almost explosively—by nitrogen dioxide; hence, their presence in substantial amounts in celluronic acids is doubtful. Ketone groups in certain compounds are less readily attacked[5] by this oxidant and such groups may be present in this oxidized cellulose.

The concept of the roles of keto or ene-diol groups as a source of alkali-sensitivity in carbohydrates and oxidized celluloses is not new and has been used recently to explain the alkaline fission of cellulose oxidized by periodates.[6]

Though the presence of ketone groups has earlier been considered as the cause of alkaline breakdown of celluronic acids, this communication represents the first systematic attempt to determine such groups by direct chemical methods. Quantitative data on degradation by alkali are included.

Experimental

Materials.—Celluronic acids were prepared by treating oven-dried 500-second cotton linters (ground to 100 mesh) with carbon tetrachloride solutions of nitrogen tetroxide for various periods of time to produce the desired degree of oxidation. Products containing substantial amounts of combined nitrogen were prepared by treating the cellulose with anhydrous nitric acid in the nitrogen tetroxide–carbon tetrachloride solutions. Details of these techniques and purification of the reagents have been given previously.

Published methods were used to obtain the alginic acid and simpler reference materials.[4] The samples of periodate-oxidized cellulose were obtained by the method of Jackson and Hudson[7] as modified by Davidson.[8]

Analyses of the celluronic acid employed are shown in Table I.

TABLE I

ANALYSES OF VARIOUS CELLURONIC ACIDS AND ALGINIC ACID

Oxidation time, hours	% N dry basis[b]	% COOR (dry basis) Calcium acetate[c]	Uronic acid[d]	Potentiometric titration[e]	% carbonyl[f] by weight
1	0.29	5.14	8.26	5.06	0.57
2	.34	6.34	9.26	6.06	0.65
4	.41	10.69	13.24	10.47	1.18
8	.46	14.30	17.12	13.97	1.45
16	.27	18.73	21.78	19.16	1.70
63	.06	19.59	22.31	19.44	..[g]
1[a]	4.82	0.73	14.45	0.73	
4[a]	2.46	8.26	14.86	7.93	
8[a]	1.75	12.15	19.04	11.98	
12[a]	0.63	17.41	23.03	17.69	
Alginic acid		22.15	...	...	−0.47

[a] Oxidations in presence of anhydrous HNO_3, ref. 6. [b] deVarda method. [c] Ref. 1. [d] Ref. 3. [e] This paper. [f] Method of Ref. 9. [g] Calcium salt highly swollen, gelatinous and difficult to handle.

Carbonyl determinations by the older methods common to organic chemistry operate at high *p*H values and are not applicable to alkali-sensitive oxidized celluloses. The recent method of Meesook and Purves[9] is particularly applicable and

(1) Presented before the Cellulose Division at the Chicago Meeting of the American Chemical Society, April, 1948.

(2) Yackel and Kenyon, THIS JOURNAL, **64**, 121–127 (1942).

(3) Unruh and Kenyon, *ibid.*, **64**, 127–131 (1942).

(4) Kenyon, *et al.*, *ibid.*, **69**, 342–354 (1947).

(5) Fowler, Unruh, McGee and Kenyon, *ibid.*, **69**, 1636–1640 (1947).

(6) Ivanov and Kaversneva, *Uspekhi Khimii*, **13** (4), 281–293 (1944).

(7) Jackson and Hudson, THIS JOURNAL, **60**, 989 (1938).

(8) Davidson, *J. Textile Inst.*, **32**, T109–31 (1941).

(9) Meesook and Purves, *Paper Trade J.*, **123**, 35 (1946).

was employed, for it gives reliable results at *p*H values below 7 where the celluronic acids are stable. The data are given in Table I. Accurate carboxyl values are necessary for the calculation of carbonyl content.

Purves states that carboxyl values tend to be low when oxycelluloses react with the calcium acetate solution at *p*H values below 6.3. The effects of the *p*H of the calcium acetate solution upon the carboxyl values were examined using alginic acid and celluronic acid, as shown in Table II.

TABLE II

EFFECT OF *p*H ON CALCIUM ACETATE CARBOXYL

Polyuronide	*p*H of calcium acetate solution	Carboxyl, %
Alginic acid	6.4	21.36
Alginic acid	6.5	21.41
Alginic acid	5.3	(1) 22.04
		(2) 22.04
Celluronic acid	6.5	(1) 20.21
		(2) 20.17
Celluronic acid	5.4	(1) 20.22
		(2) 20.22

Since higher values were not obtained on these materials, when the *p*H of the calcium acetate–uronic acid reaction mixture was adjusted to between 6.3 and 7.0, this adjustment was omitted.

Dilution of the calcium acetate solution to raise the equilibrium *p*H has been recommended[10] to force the reaction with the oxidized cellulose nearer to completion. Table III shows the effect of greater and less dilution than the 50 ml. of water employed in our calcium acetate method.

TABLE III

EFFECT OF DILUTION ON THE CALCIUM ACETATE DETERMINATION OF CARBOXYL

Celluronic acid, 0.50 g.; 0.5 *N* calcium acetate, 30.0 ml.; reaction time two hours

H_2O, ml.	Aliquot titrated, ml.	0.1123 *N* NaOH used, ml.	% COOH (dry basis)	Deviation, %
500	198.70	6.23	18.92	+0.48
100	48.76	6.21	18.87	+0.21
50	30.00	6.20	18.83	0.00
25	20.63	6.12	18.58	−1.33
0	11.25	6.07	18.34	−2.60

Dilution caused a 3% change in the apparent carboxyl values over the full range studied. However, dilution of our standard analytical mixture by a factor of 10, *i. e.*, from 50 to 500 ml., caused a change of only 0.5% in carboxyl value. This deviation is probably less than the precision obtained in sampling solid products from heterogeneous oxidation systems.

Potentiometric titrations were run by the following general method with such minor changes as are noted. One (1.000) gram (moist basis) of the celluronic acid suspended in 100 ml. of 1 *N* sodium bromide, with mechanical agitation, was titrated with small increments of 0.1 *N* sodium hydroxide to the desired *p*H. Since most of the maximum *p*H values desired were over 9.5, a special lithium glass "Type E" Beckman glass electrode was used with the Laboratory Model G Beckman *p*H meter. The suspended celluronic acids usually dissolved at the high *p*H values. The solutions were allowed to stand, usually at room temperature, for the desired times, then titrated to the original *p*H with hydrochloric acid of exactly the same normality as the alkali used. The extra amounts of alkali consumed were determined from the titration curves, as indicated in Fig. 1. These amounts, hereinafter referred to as the alkali consumption, are defined as the amount, *y*, in the complete titration curve shown. All results are calculated to the dry basis.

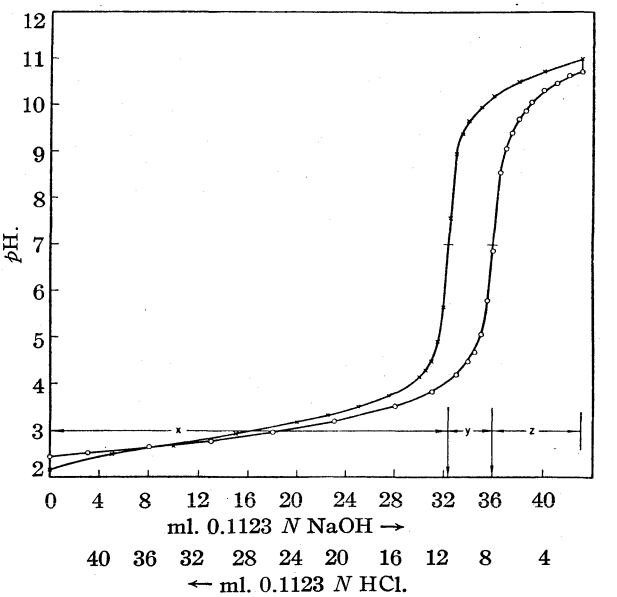


Fig. 1.—Potentiometric titration of a 1-g. sample of a sixteen-hour oxidized cellulose showing acidity developed in two hours at *p*H 11: X, titration with NaOH; O, back titration with HCl; ×, ml. alkali to reach equivalence in initial titration (zero time); Z, ml. acid to reach equivalence in final titration (two hours time); Y, ml. extra alkali consumed at *p*H 11 in two hours.

Air was not excluded during the action of alkali on the celluronic acids, but this was not a factor in the decomposition, as shown by the data of Table IV.

Kinetics data for determining the mechanism by which celluronic acids are acted upon by hydroxyl ion were obtained by a modified procedure. The celluronic acid was titrated with 0.1 *N* sodium hydroxide to a *p*H value representing the maximum desired in the experiment. These data were plotted and the resulting "master" titration curve was used for reading off the volumes of standard alkali necessary to produce definite *p*H values with a standard weight of sample. Samples of the same celluronic acid were suspended in 1 *N* so-

(10) Davidson and Nevell, *Shirley Inst. Mem.*, **21**, 85–99 (1947).

Table IV

Acidity Developed in Celluronic Acids at *p*H 11 in Two Hours Under Different Atmospheres

Basis: 1.0000 g. anhydrous celluronic acid

Oxidation time, hours	*y* in ml. 0.1123 *N* NaOH	*y* in mole NaOH × 10^4	Atmosphere
4	2.42	2.72	Nitrogen
16	3.84	4.31	Nitrogen
63	8.25	9.25	Nitrogen
4	2.50	2.82	Air
16	4.35	4.87	Air
63	8.24	9.24	Air

dium bromide solution, and the amounts of alkali added very rapidly to produce solutions (or suspensions) at the *p*H desired. This procedure minimizes the decomposition encountered while bringing the solutions to the proper high *p*H of the experiment. After two hours at room temperature, the samples were titrated rapidly with 0.1 *N* hydrochloric acid to a *p*H of 7.0. Calculation of extra alkali consumption was done as explained in Fig. 1. For a more meaningful comparison between samples of different degrees of oxidation, the ratio, *R*, between moles of extra alkali consumed and initial moles of alkali needed for equivalence is used in this paper.

Results and Discussion

The oxidation of the number six carbon atom in the anhydro-glucose unit of cellulose by nitrogen dioxide is essentially complete at the end of twenty-four hours reaction time under the experimental conditions used in preparing these particular samples. However, it is obvious that a secondary oxidation continues. While the calcium acetate, uronic acid, and titrated carboxyl values of Table I have about reached their maxima at the end of twenty-four hours reaction time, the data of Fig. 2 show that the extra moles of alkal. consumed continued to increase beyond this time of oxidation. A sample which has been oxidized for sixty-three hours consumed roughly twice as much extra alkali as that consumed by a sample having a sixteen-hour oxidation.

The celluronic acids contain small amounts of nitrogen presumably combined as nitrate groups. It is well known[11] that cellulose nitrates decompose intramolecularly in alkali with reduction of nitrate nitrogen to nitrite and oxidation of the cellulose molecule to simple organic acids. The data of Table V show that this is not the mechanism of alkali consumption by celluronic acids, since the consumption increases (column 4) and the nitrogen content decreases (column 2) with increase in time of oxidation.

Table V

Acidity Developed in Celluronic Acids of Various Nitrogen Contents at *p*H 11 in Two Hours

Basis: 1.0000 g. anhydrous celluronic acid

Oxidation time, hours	Nitrogen, %	*y* in ml. 0.1123 *N* NaOH	*y* in moles NaOH × 10^4
1	4.82	1.53	1.72
4	2.46	2.74	3.08
8	1.73	4.22	4.74
12	0.63	5.19	5.83
1	.29	1.65	1.86
4	.41	3.06	3.45
8	.46	3.99	4.48
16	.27	5.27	5.86

The alkali consumption is not due to oxidation of the alkaline solutions by atmospheric oxygen (Table IV). Dissolved oxygen is present but its role is believed to be negligible in this instance.

Typical curves of the generation of acidity as measured by alkali consumption are shown in Fig. 3, using the celluronic acid resulting from sixteen hours oxidation with nitrogen dioxide. Curve A shows that consumption during initial alkaline decomposition at *p*H 11 is nearly linear with respect to time. Extended reaction at *p*H 12 indicates that the consumption may approach completion at very long reaction times.

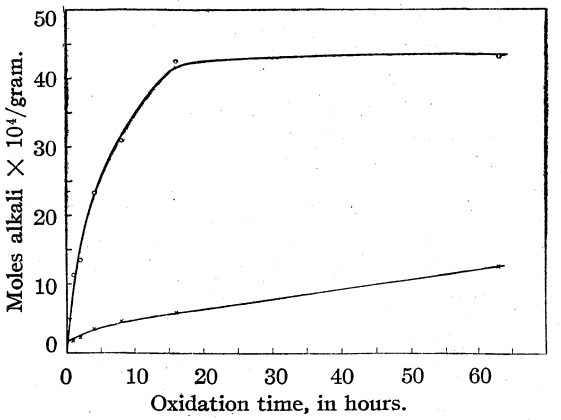


Fig. 2.—Relation between oxidation time and consumption of alkali in two hours at *p*H 11: O, initial equivalence; ×, extra moles alkali.

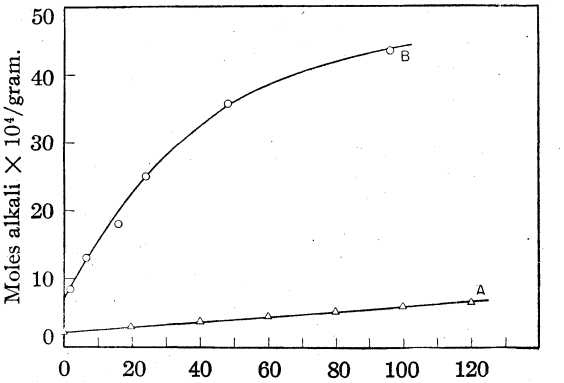


Fig. 3.—Rate of alkali consumption at high *p*H: plot A at *p*H 11; plot B at *p*H 12.

(11) Kenyon and Gray, This Journal, **58**, 1422 (1936).

Three celluronic acids of diverse oxidation history (*i. e.*, one-, four- and sixteen-hour oxidation, Table I) were each treated with alkali for two hours at several *p*H values greater than 7. The log of alkali consumption expressed as R was a linear function of *p*OH of the solution (Fig. 4). The equation for these curves is

$$\log R = -B[p\mathrm{OH}] + \log A \qquad (1)$$

where $-B$ is the slope of each curve and $\log A$ is the log R intercept. Equation (1) converts to

$$R = A[\mathrm{OH}^-]^B \qquad (2)$$

The constants A and B for these three celluronic acids are given in Table VI.

TABLE VI

CONSTANTS RELATING HYDROXYL-ION DEPENDENCY OF ACIDITY GENERATED BY CELLURONIC ACIDS AT *p*H 7

Oxidation time, hours	A	B
1	3.72	0.50
4	1.21	.34
16	1.31	.33

Thus, the catalyst in the generation of extra acidity at high *p*H appears to be hydroxyl ion. When a *p*H of 7 is exceeded, the celluronic acids begin to decompose even before dissolving.

The evidence thus accumulated indicates that the extensive oxidation of the primary hydroxyls of cellulose by nitrogen dioxide to form carboxyl groups is accompanied by some oxidation at another position forming an alkali-labile linkage. Systematic consideration will show that a variety of structures are theoretically capable of formation by oxidizing one or more positions in the anhydroglucose unit.[12] Oxidation of the glucoside links should be considered, as nitrogen dioxide is a powerful oxidant for simple ethers. All the possible resulting structures could not be examined, but data on a few typical ones are shown in Table VII.

TABLE VII

ACIDITY DEVELOPED IN REFERENCE SUBSTANCES AT ELEVATED *p*H (DRY BASIS)

Substance	*p*H max.	Time at *p*H max., hours	—% COOH— Theory	Potentiom. titra.	Extra moles alk. consumed per gram
Potassium acid saccharate	10.93	2	18.14	18.20	3.5×10^{-5}
D-Galacturonic acid monohydrate	10.92	2	21.22	20.41	6.6×10^{-5}
L-Ascorbic acid	11.12	2	25.56	25.42	1.07×10^{-3}
L-Ascorbic acid	11.04	48	25.56	25.42	7.80×10^{-3}
L-Ascorbic acid	11.20	96	25.56	25.42	8.15×10^{-3}
Tartaric acid	10.92	2	60.00	58.91	1.1×10^{-5}
D-Gluconic acid	10.98	2	22.96	24.76	6.0×10^{-5}
D-Glucono-γ-lactone	11.00	2	25.30	24.22	6.2×10^{-5}
Periodic acid-oxidized cellulose	12.00	64			5.79×10^{-3}

(12) Unruh and Kenyon, *Textile Research J.*, **16**, 1–12 (1946).

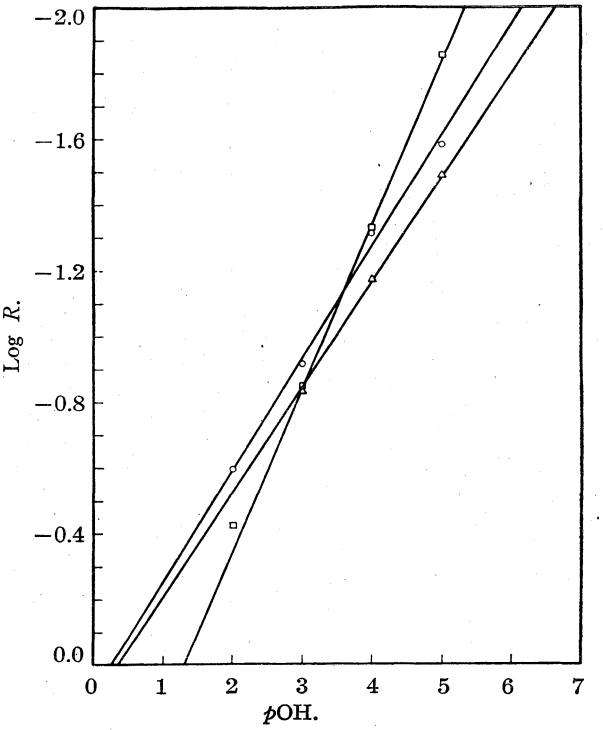


Fig. 4.—Relation between log of ratio of extra and initial moles alkali needed for equivalence and *p*OH: △, sixteen-hour oxidation; O, four-hour oxidation; □, one-hour oxidation.

Though the number of possible compounds or structures resulting from oxidation of the glucose unit is large, these compounds must contain, in addition to unreacted hydroxyls, one or more of the three following groups, *i. e.*, carboxyl (ester or lactone), ketone (ene-diol) or aldehyde (enol). Carboxylic acids typified by saccharic, gluconic and tartaric did not generate significant acidity in alkali. The slow hydrolysis of lactones is not the source of the acidity, for glucono-γ-lactone opened completely and was titrated as the free acid as the *p*H was raised. It is doubtful whether generation of acidity is due to a slow hydrolysis of ester groups. The saponification of esters is the the classical illustration of a bimolecular reaction. Mathematical analysis of the acidity generated at constant time as a function of alkali concentration (Fig. 4) did not fit the second-order kinetics.[13] Galacturonic acid generated only little acidity even though an aldehyde group is present. Periodate cellulose known to contain a high percentage of aldehyde groups, generated much acidity but as previously stated, aldehyde groups are so vigorously oxidized by nitrogen dioxide that their presence in celluronic acids must be considered with reserve.

Ketone groups appear the most probable source of alkali-lability. Measurement of their presence by the methyl hydroxylamine method

(13) We wish to thank Dr. L. K. J. Tong, of these Laboratories, for this analysis.

of Purves indicated small but significant amounts as shown in Table I. A celluronic acid from a sixteen-hour oxidation appeared to possess 1.7% of carbonyl group by weight, or about one carbonyl for each ten of the original glucose units. Analyses of the data indicate a possible mechanism by which extra alkali is consumed. Extrapolation of Fig. 3, Plot B, to infinite time indicates that a total of about 50×10^{-4} mole of alkali would finally be neutralized. The same sample contains approximately 6×10^{-4} mole of carbonyl per gram (Table I). If this is in the form of a keto-glucuronic acid, it may be calculated that there are 37.3×10^{-4} mole of carbonyl per gram. Therefore, one mole of keto-glucuronic acid unit consumes 1.34 moles of alkali. *l*-Ascorbic acid (Table VII) will ultimately consume approximately 80×10^{-4} mole of alkali per gram, or about 1.41 moles per mole.

Figure 5 shows that the relation between the carbonyl content and the extra alkali consumption in two hours of the various celluronic acid is linear, the slope being 1.02. The small positive intercept of the experimental curve (plotted by a least-squares analysis of the data) lies within the experimental error of the measurements.

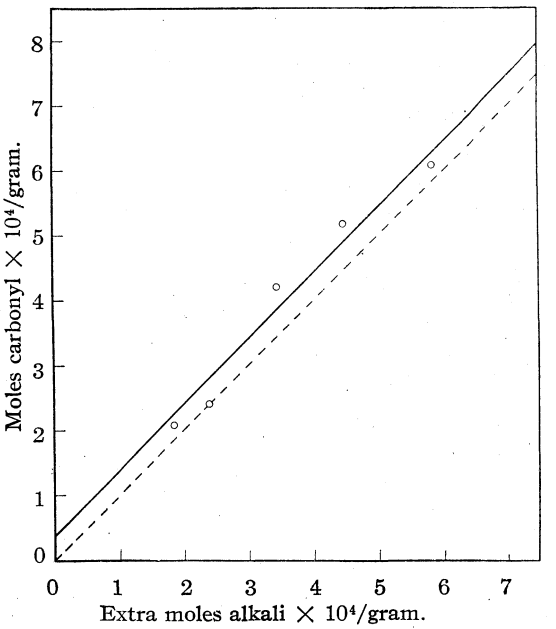
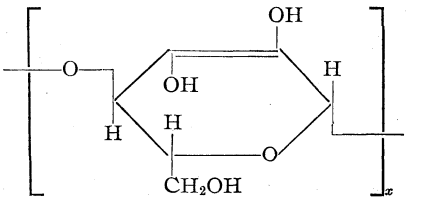


Fig. 5.—Relation between moles of carbonyl and extra moles of alkali consumed in two hours by various celluronic acids: solid line is experimental, broken line is exact equimolar relation.

This equimolar relationship would be greatly exceeded at longer reaction times in the alkali and at high *p*H values. Figure 3, Plot B, shows that several times as much alkali is consumed at about 100 hours as that consumed at two hours.

Evans and his collaborators[14] have explained the steps by which both simple sugars and glycosides are acted upon by alkali. Ivanov and Kaversneva[6] have applied these findings to the reaction of various oxidized celluloses with aqueous alkaline solutions so as to arrive at satisfactory mechanisms for explaining the changes in physical properties resulting from treatment of cellulose with several different oxidizing agents. They ascribed the increase in fluidity of oxidized celluloses after treatment with alkali to the shift of the keto form of different oxidized carbon atoms to the enols which render the glycosidic link unstable. Applying this concept to celluronic acids, the presence of a ketone group would constitute a weak point[15] in the chain as indicated by the enol structure shown.



Evans has shown that such enediols in simpler carbohydrates are ruptured by alkali, the generated aldehyde groups enolize, then the adjacent glucoside groups become alkali-labile. In an analogous manner, the units of celluronic acids containing ketone groups are readily split by alkali and the groups so split as well as the lower polyuronic acid fragments may undergo fission into reducing and acidic fragments. In other words, once the alkaline scission is initiated it continues, thus producing degradation far more extensive than indicated by the initial ketone content. Such fission along the chain would account for the extreme decrease in viscosity often observed even in lightly oxidized celluloses.[16] Davidson,[17] using oxidized celluloses prepared by a number of methods other than those involving the use of nitrogen dioxide, has demonstrated that the decrease in viscosities of nitrated oxidized celluloses in cuprammonium is not necessarily due to oxidative fission of the cellulose, but may be ascribed to the scission of alkali-sensitive links in the oxidized celluloses. The alkali-sensitivity of the periodic acid-oxidized celluloses appears to be related to the instability of the glyoxal and/or erythrose units (aldehyde groups).

Pacsu[18] has postulated that periodate-oxidized celluloses are reacted upn by alkaline solutions in the manner of an inner Cannizzaro reaction, supporting the theory in a qualitative way by showing that alkali reacted with such an oxidized cellulose to generate acidity. Since Davidson[8] has

(14) Evans and Benoy, THIS JOURNAL, **52**, 294 (1930); Evans and Hockett, *ibid.*, **53**, 4384 (1931); Gehman, Kreider and Evans, *ibid.*, **58**, 2388 (1936).

(15) Staudinger [*Ber.*, **72**, 1709 (1939)] has postulated such "defective" celluloses with carboxyl instead of carbonyl units.

(16) We wish to thank Dr. D. D. Reynolds, of these Laboratories, for criticism helpful in arriving at these conclusions.

(17) Davidson, *J. Textile Inst.*, **32**, 132–148 (1941); **32**, T109–131, (1931); **29**, T195–218 (1938).

(18) Pacsu, *Textile Research J.*, No. 10, **15**, 354 (1945).

demonstrated that a variety of breakdown products (such as formaldehyde and carbon dioxide) are produced during this type of cellulose oxidation, indicating that the oxidizing agent is not confined in its action to oxidation at the number two and three carbon atoms of the anhydro-glucose unit, this hypothesis may be viewed with some reserve. Head[19] recently has shown that in both mono- and polysaccharides, dialdehydes are converted to carboxyl slowly in the presence of dilute alkali.

The criticisms of Davidson and Purves on the calcium acetate method for carboxyl determination do not appear valid when the method is used for celluronic acids.

While this paper was being prepared, an investigation appeared of the structure of celluronic acids by absorption spectra.[20] The data indicate large contents of carboxyl groups with possibly a small carbonyl group content. These results agree with our chemical findings.

(19) Head, *Shirley Inst. Mem.*, **21**, 11 (1947).

(20) Rowen, Hunt and Plyler, *J. Research Natl. Bur. Standards*, **39**, 133–140 (1947).

Summary

1. Potentiometric investigations show that celluronic acids degrade in alkaline solutions to generate acidity.

2. Small amounts of carbonyl groups appear to be present in the celluronic acids.

3. The acidity generated in alkaline solution at a constant reaction time appears directly related to the carbonyl group content and is an exponential function of the alkali concentration.

4. The ketone groups are believed to enolize in alkali, the enediols split as in simple carbohydrates, the adjacent glucoside links hydrolyze and an extensive alkaline degradation is thus initiated which continues along the chain producing reducing and acidic substances.

ROCHESTER 4, NEW YORK RECEIVED FEBRUARY 24, 1948

[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY OF LOUISIANA STATE UNIVERSITY]

The Migration of Acetyl and Benzoyl Groups in *o*-Aminophenol

BY ARTHUR L. LEROSEN AND EDGAR D. SMITH

A considerable amount of experimental data has been collected on the general subject of acyl migrations in *o*-aminophenols since interest was first drawn to this problem by Stieglitz[1] in 1898. The great majority of this work has been published by Raiford and co-workers[2–4] and has indicated that when two different acyl groups, derived from carboxylic acids, are introduced into an *o*-aminophenol generally the same acyl derivative is obtained regardless of the order of introduction. On hydrolysis the heavier acyl group has usually been found on nitrogen.

No satisfactory general explanation has been given for all the phenomena observed in the acylation or hydrolysis of these compounds. The best discussion to date, in the opinion of the authors, was that of Bell,[5] and this work has generally been neglected by other workers in this field.

The present work was undertaken because it seemed probable that it would be possible to give an adequate explanation of these acyl migrations in terms of a combination of the theory of resonance and inductive effects. Accordingly a general theory was derived for these reactions and was found to agree in many respects with the data found in the literature. Nevertheless there were discrepancies and these were of such a nature that a reëxamination of the reported data was advisable, especially since at present new and powerful aids to this study are available in the form of absorbtion spectroscopy for the determination of structure, and chromatographic techniques for the quantitative analysis of mixtures.

It is premature to present the details of our theories of acyl migrations here, but three resulting conclusions are important: first, no migration should be complete, but instead there should be a reversible equilibrium; second, in the acetyl–benzoyl migration the N-acetyl isomer should predominate; and third, if a "migration" occurs in acylation, the opposite migration should be observed during hydrolysis. There are no conclusive data on this first point in the literature, Raiford found only one product in the acetyl–benzoyl mixed acyl derivative, while Bell reported the formation of different isomers, depending on the acylation sequence. Bell based his conclusions on mixed melting point data. Both of these men reported that hydrolysis yielded only *o*-benzoylaminophenol.

The experiments here were concerned with the determination of the nature of the acylation product when acetyl and benzoyl groups were introduced into *o*-aminophenol in different sequence. The method was to prepare the crude derivatives by acylation with the corresponding anhydrides in pyridine solution, and to separate the product into its constituents chromatographically. The determination of structure was accomplished by comparison with spectroscopic curves determined for all of the possible mono- and diacyl deriva-

(1) Julius Stieglitz, *Am. Chem. J.*, **21**, 111 (1898).

(2) L. C. Raiford, THIS JOURNAL, **41**, 2068 (1919).

(3) L. C. Raiford and J. R. Couture, *ibid.*, **46**, 2305 (1924); **44**, 1792 (1922).

(4) L. C. Raiford and H. P. Lankelma, *ibid.*, **47**, 1111 (1925).

(5) Frank Bell, *J. Chem. Soc.*, 2966 (1931).

tives of *p*-aminophenol using acetyl and benzoyl groups.

Our experimental results show that two mixed diacyl derivatives are present in both crude products which, however, are predominantly N-acetyl-O-benzoyl and N-benzoyl-O-acetyl depending on the acylation sequence. Acetylation of *o*-benzoylaminophenol gave 91% of the unrearranged N-acetyl-O-benzoyl derivative, while benzoylation of *o*-acetylaminophenol gave 62% of the unrearranged isomer. Both of the pure mixed diacyl derivatives were isolated in their pure form for the first time and their physical properties and relative stabilities under the influence of several factors were studied.

Solution of either of the isomeric mixed diacyls in alcohol or pyridine produced equilibrium mixtures containing 85 and 77% of the more stable N-acetyl-O-benzoyl form, respectively. Water and heat also served to isomerize these diacyls, while benzene, hexane, acetone, ethyl ether and dioxane were much less effective, if not inert, in this respect. It seems probable that this is a case of general acid and base catalysis.[6]

The absorption curves of the derivatives studied are shown in Fig. 1. It will be noted that the total area under the curves roughly indicates the number of phenyl groups in the molecule, while whenever a N-benzoyl structure is present, one of the peaks (previously superimposed) shifts to longer wave lengths. No attempt will be made here to interpret these curves in terms of theory, but it may be indicated that they offer a good possibility of interpreting the peaks in terms of the contributions of the different resonating structures. The spectra for the mixed diacyls were determined in hexane to avoid the isomerization which occurred in alcohol and these curves are shown in the figure. The absorption spectra of the other acyl derivatives of *o*-aminophenol are not shown since there was no essential change from the spectra found in alcohol. The wave lengths and molar extinction coefficient in both of these solvents is, however, included in the tabulation shown in Table V.

The analytical data are summarized in Tables I through IV below. Table I shows the analyses obtained on the crude products of the acylations in pyridine solution, and also the analysis of these two products after a single recrystallization from alcohol.

Table I

Analysis of Ortho Mixed Diacyls

Sample description	Reaction yield, %	Product analysis[a] %NA[b]	%NB[c]	% Recovery
Crude NB	98	38	62	91
Crude NB	98	37	63	94
Crude NA	84	91	9	94
Crude NA from 50% alc.	..	93	7	94
Crude NB from 50% alc.	..	82	18	95

[a] Analyses based on amount of sample recovered by elution of the bands with acetone. [b] N-acetyl-O-benzoyl-*o*-aminophenol. [c] N-benzoyl-O-acetyl-*o*-aminophenol.

(6) L. P. Hammett, "Physical Organic Chemistry," 1st ed., McGraw-Hill Book Co., New York, N. Y., 1940, pp. 215–227.

Table II shows the analyses found on the residual products obtained by dissolving mixed diacyl samples of varying composition in a few ml. of alcohol and then evaporating off the solvent under vacuum. It will be seen from this table that the isomerizations in alcohol were complete for all except the pure N-benzoyl-O-acetyl isomer. No explanation can be given here for the peculiar behavior of this isomer, but it may be significant that the sample recovery in these runs was consistently low.

Table II

Analysis of Alcohol Isomerization Products

Sample description	Standing time, hr.	Product analysis[a] %NA[b]	%NB[c]	% Recovery
Pure NA	0	85	15	107
91% NA	0	83	17	87
38% NA	0	84	16	89
38% NA	0	85	15	93
Pure NB	0	57	43	...
Pure NB	2	71	29	87
Pure NB	3.5	72	28	85

[a] Analyses based on amount of sample recovered by elution of the bands with acetone. [b] N-acetyl-O-benzoyl-*o*-aminophenol. [c] N-benzoyl-O-acetyl-*o*-aminophenol.

Table III shows the results of similarly dissolving the mixed diacyls in pyridine and then evaporating off the solvent under vacuum after allowing the solutions to stand for the length of time indicated. It will be seen that the isomerizations were slightly less rapid than those obtained in alcohol, and that the equilibrium mixture formed had a slightly different composition.

Table III

Analysis of Pyridine Isomerization Products

Sample description	Standing time, hr.	Product analysis[a] %NA[b]	%NB[c]	% Recovery
Pure NA	6	77	23	98
Pure NA	0	86	14	106
91% NA	3	77	23	95
38% NA	3	75	25	94
Pure NB	6	77	23	98
Pure NB	0	81	29	94

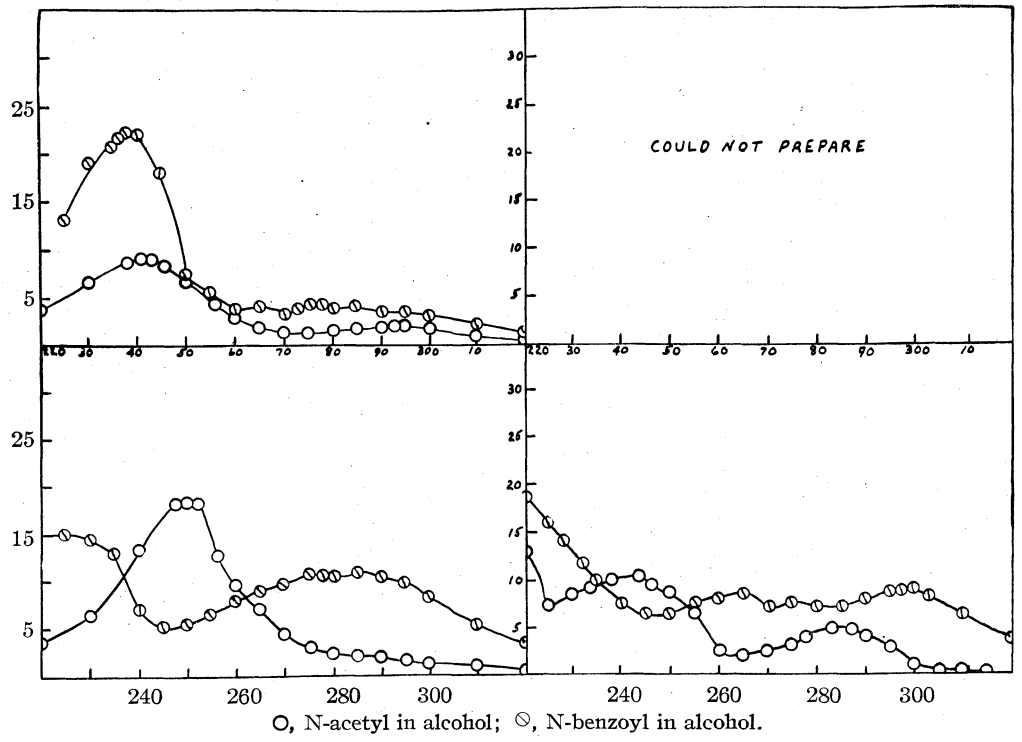
[a] Analyses based on amount of sample eluted by acetone. [b] N-acetyl-O-benzoyl-*o*-aminophenol. [c] N-benzoyl-O-acetyl-*o*-aminophenol.

Table IV shows the results of heating the two pure isomers for varying lengths of time at two different temperatures near their melting point. While the results of these runs are inconclusive since equilibrium was not reached in either of these runs, it appears that, as expected, the N-acetyl-O-benzoyl compound isomerized much more slowly than its isomeride.

In conclusion, it seems that the predictions of theory have been verified for the first two of the possibilities mentioned above, and that the con-

Para series: O, O-acetyl in alcohol; ⊘, O-benzoyl in alcohol.

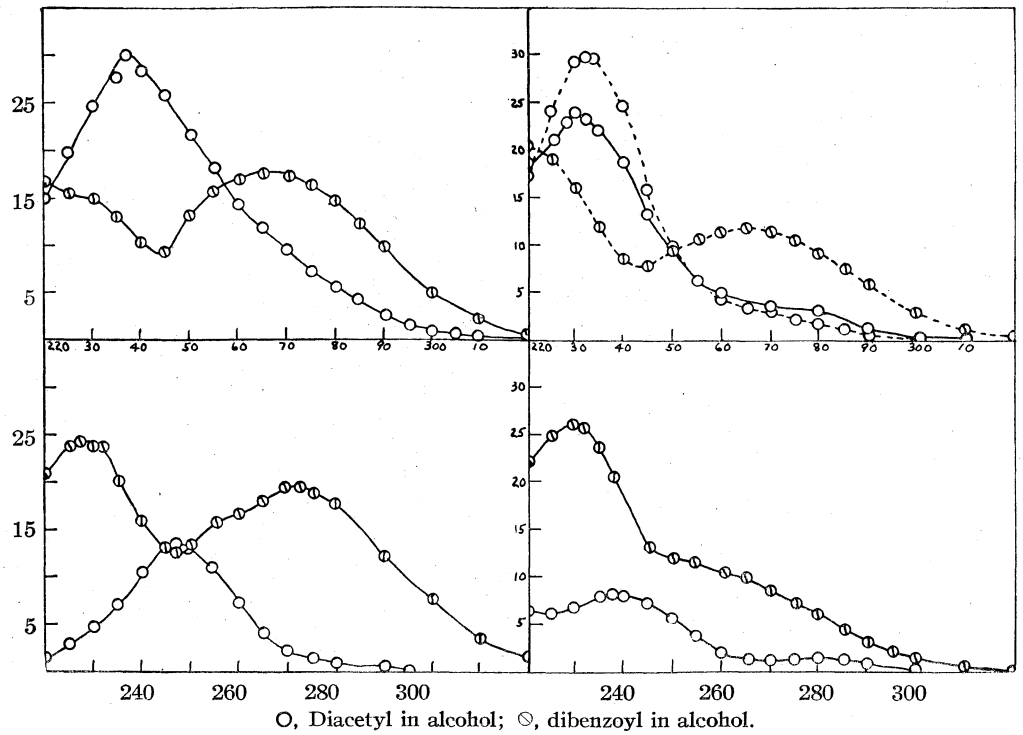
Ortho series: Could not prepare.



O, N-acetyl in alcohol; ⊘, N-benzoyl in alcohol.

O, N-Acetyl-O-benzoyl in alcohol; ⊘, N-benzoyl-O-acetyl in alcohol.

O—O, Alcohol equilibrium mixture: O---O, N-acetyl-O-benzoyl in hexane; ⊘---⊘, N-benzoyl-O-acetyl in hexane.



O, Diacetyl in alcohol; ⊘, dibenzoyl in alcohol.

Fig. 1.—Ultraviolet absorption spectra of acyl derivatives of *o*-aminophenol and *p*-aminophenol. The ordinate is the molecular extinction coefficient (ϵ) $\times 10^{-3}$, and the abscissa is the wave length in millimicrons.

Table IV

Effect of Heat on Pure Mixed Diacyls

Sample description	Temp., °C.	Standing time, hr.	Product analysis[a] %NA[b]	%NB[c]
Pure NA	140	2	69	31
Pure NB	140	2	59	41
Pure NA	132	70	61	39
Pure NB	132	70	54	46

[a] Analyses based on amount of sample recovered by elution with acetone. [b] N-acetyl-O-benzoyl-*o*-aminophenol. [c] N-benzoyl-O-acetyl-*o*-aminophenol.

flicting results obtained by Raiford and Bell may be explained as being due to the use of alcohol as a recrystallization solvent by the former. In such a case isomerization would occur, leading to the isolation of the predominant isomer, in this instance the N-acetyl-O-benzoyl compound. It now seems desirable to reëxamine much of the past work in this field in the light of these facts. We are continuing this study at present.

Experimental

Preparation of Compounds.—The acyl derivatives studied are listed in Table V. Except as noted in the table, they were prepared by heating a pyridine solution of the aminophenol with a 10% excess of the acid anhydride for about thirty minutes on a steam-bath. The product was isolated by cooling the solution and pouring it into ice water. With the exception of the mixed *o*-acyl derivatives the products were purified by crystallization from alcohol.

Table V

Acyl Derivatives Studied

Compound	Melting point, °C. (cor.) Found	Literature	Ultraviolet abs. maxima λ	$\epsilon^f \times 10^{-3}$
p-Aminophenyl-benzoate[a]	153–155	153[7]	239	22.5
p-Aminophenyl-acetate[b]	70–72	75[8]	241	9.2
p-Acetylamino-phenol	166	166[9]	250	18.5
p-Diacetylamino-phenol	150	152[10]	247	13.5
p-Benzoylamino-phenol	214–216	227,[7] 205[11]	225	15.0
		215,[12] 227[13]	285	11.0
p-Dibenzoyl-aminophenol	233–235	235[14]	228	24.2
			271	19.5
N-Benzoyl-O-acetyl-*p*-aminophenol	172–174	171[15]	220	18.0
			268	18.0
N-Acetyl-O-benzoyl-*p*-aminophenol	167–169	167,[13] 171[15]	237	30.0
o-Acetylamino-phenol	203–204	201–204[16]	242	10.5
	207–208[c]		284	5.0
			235[d]	6.9
			283[d]	3.0
o-Diacetylamino-phenol[e]	124–125	124–125[17]	238	8.0
			240[d]	12.0
o-Benzoylamino-phenol	170–171	168[18]	265	8.4
			296	8.6
			222[d]	17.8
			295[d]	8.0
o-Dibenzoyl-aminophenol	183–185	182–185[19]	230	26.0
			229[d]	30.0
			266[d]	12.5
N-Benzoyl-O-acetyl-*o*-aminophenol	138–140	134–138[2]	230	23.9[g]
		125–127[5]	220[d]	20.3
			265[d]	12.5
N-acetyl-O-benzoyl-*o*-aminophenol	139–141	134–138[2]	230	23.9[g]
		132–135[5]	232[d]	30.0

[a] Prepared by reduction of corresponding nitro compound with $SnCl_2$. [b] Prepared by method of Galatis[8] except that tar formation and resultant necessity of vacuum distillation was eliminated by the addition of a few crystals of hydroquinone and sodium bisulfite before neutralizing the acid hydrolysis mixture with sodium bicarbonate. [c] This high melting compound was prepared during an attempted acetylation of benzylidine *o*-aminophenol. It gave the same spectra as, and raised the melting point of, the 204° compound. [d] Refers to the absorption maxima found in hexane. All other absorption data were taken in alcohol. [e] The usual acylation method gave a mixture of mono and diacetyl derivatives which proved very difficult to separate. This compound was therefore prepared by heating the usual mixture of reactants under reflux for one and one-half hours, and then evaporating pyridine solution until crystals separated. [f] Molar extinction coefficient. [g] Alcohol equilibrium mixture.

Isolation and Purification of Mixed *o*-Acyl Derivatives.—It was found impractical to purify the mixed diacyl derivatives of the ortho series by recrystallization procedures since, in alcohol, isomerizations occurred, while in the other solvents tried the solubilities of the two isomers were too similar. These crude products were therefore chromatographed from benzene solution on a column of 1:1 silicic acid and Cellite using a 1.5% solution of acetone in benzene as the developing agent. The adsorbate zones were located by streaking the column first with a 3% solution of *p*-methoxybenzenediazonium fluoroborate, and then with a 5% solution of potassium hydroxide in methanol. This combination produced a distinct orange color with both isomeric mixed diacyls which could be further intensified by a third streaking with 6 *M* hydrochloric acid which caused the orange color to change to a deep red. The streaked areas were cut away, the column divided into the two sections containing the acyl derivatives, and the pure isomers recovered by eluting them from the adsorbent with acetone. (Determination of the ultraviolet absorption spectra of the two materials in hexane showed that the top zone was the N-acetyl-O-benzoyl derivative.)

Analysis of Diacyl Mixtures.—The crude mixture of isomers was chromatographically separated as outlined above, but, before eluting, the two portions of the adsorbent containing the pure isomers were powdered and dried under vacuum to remove any solvent which might absorb in the ultraviolet. The isomers were then eluted with

(7) H. Hübner, *Ann.*, **210**, 378 (1882).
(8) L. Galatis, *Ber.*, **59**, 850 (1926).
(9) A. Lumière, *et al.*, *Bull. soc. chim.*, [3] **33**, 785 (1905).
(10) Beilstein, "Handbuch der organischen Chemie," Vol. IV, xiii, 1930, p. 464.
(11) A. W. Smith, *Ber.*, **24**, 4042 (1891).
(12) F. Reverdin and E. Delétra, *ibid.*, **39**, 125 (1906).
(13) J. B. Tingle and L. F. Williams, *Am. Chem. J.*, **37**, 51 (1907).
(14) Beilstein, ref. 10, p. 470.
(15) F. Reverdin, *Ber.*, **39**, 3793 (1906).
(16) Beilstein, ref. 10, p. 370.
(17) E. Bamberger, *Ber.*, **36**, 2050 (1904).
(18) Beilstein, ref. 10, p. 372.
(19) Beilstein, ref. 10, p. 373.

absolute alcohol and the resulting solutions quantitatively determined by comparing their ultraviolet absorption at 230 millimicrons with that found for 0.01 *M* solutions of the mixed acyls.

Determination of Ultraviolet Absorption Curves.—All ultraviolet absorption data shown in Table V were taken on a Beckmann Ultra Violet Spectrophotometer, Model DU. Hundredth molar solutions of each acyl derivative were made up, and these solutions diluted as became necessary by pipetting a 1-ml. aliquot and diluting to 10 ml. No attempt was made to calibrate the volumetric flasks or pipets used.

In hexane solution, due to the extreme insolubility of the acyl derivatives, it was necessary to determine the spectra of the saturated solutions of the compounds in this solvent. The concentrations of these solutions were found by pipetting a 10-ml. aliquot, evaporating to dryness under vacuum, and taking up the residue in 10 ml. of absolute alcohol. The concentration of this alcohol solution, and hence that of the hexane solution, was then determined by comparing its ultraviolet absorption intensity at 230 millimicrons with that of an alcohol solution of known concentration.

Summary

1. In the benzoylation of N-acetyl-*o*-aminophenol and the acetylation of N-benzoyl-*o*-aminophenol, mixtures of the two possible isomers were obtained showing that a partial rearrangement occurred in each case. These mixtures were quantitatively separated by chromatography, and the identity of the two isomers established by comparison of their ultraviolet absorption spectra with that of the corresponding derivative of *p*-aminophenol.

2. It has been shown that alcohol, pyridine, water and heat cause either pure mixed diacyl derivative to isomerize to yield an equilibrium mixture of the two isomers. In alcohol and in pyridine solutions an equilibrium mixture containing 85 and 77%, respectively, of the N-acetyl-O-benzoyl form was obtained. It was pointed out that this isomerization in alcohol probably accounts for the conflicting results reported by Raiford and by Bell.

3. In the light of the above facts it seems desirable to reëxamine much of the past work in this field.

BATON ROUGE, LOUISIANA RECEIVED MARCH 1, 1948

[CONTRIBUTION NO. 149 FROM THE GOODYEAR TIRE AND RUBBER CO. RESEARCH LABORATORY]

Synthesis of Multichain Polymers and Investigation of their Viscosities[1]

BY JOHN R. SCHAEFGEN AND PAUL J. FLORY

Polymerizations in which the structural units are combined in other than strictly linear sequences generally yield gelled, insoluble products owing to the eventual formation of infinite network structures. Established exceptions are so few that thermoplasticity and solubility have sometimes been regarded as exclusive characteristics of linear polymers. On the other hand, non-linear structures have been postulated on various occasions for some of the thermoplastic vinyl polymers,[2,3] and it has been recognized,[4] in principle at least, that monomer units may be assembled in non-linear patterns which do not lead to network formation and the manifestations of gelation resulting therefrom. Chain transfer with previously formed polymer molecules in vinyl polymerizations doubtless leads to some degree of branching without producing network structures.[5-7] However, the extent of such branching, like the cross-linking produced in diene polymers, is not easily measured or controlled.

Effects of departure from linear structure on physical properties of non-gelled polymers have been the subject of frequent speculation, but little information of a quantitative nature is available as a result of the difficulty of isolating the non-linearity variable. In the first place, the extent of branching or of cross-linking (prior to gelation) in the polymer as a whole usually is difficult to estimate quantitatively. Secondly, such reactions ordinarily occur in a random manner such that the co-existing polymer molecules vary widely in degree of non-linearity, ranging from linear to highly branched structures. Finally, random cross-linking and branching reactions usually broaden the molecular weight distribution, sometimes severely; consequently, alteration of the molecular weight distribution, rather than non-linearity, may be primarily responsible for the effects observed.

In the present investigation a convenient general procedure for synthesizing non-linear condensation polymers of controlled structure has been demonstrated. The principle employed here involves the co-reaction of an A—B type monomer, *e.g.*, an amino acid or hydroxy acid, with a small proportion of a multifunctional reactant of the type RA_b or RB_b where R is a *b*-valent radical and A and B are co-reacting functional groups; such multifunctional reactants may be, for example, a polyamine or a polybasic acid. Polymers so produced can be represented by the formulas

$$R[-A(B-A)_{\overline{y}}-]_b \text{ or } R[-B(A-B)_{\overline{y}}-]_b$$

(1) Presented before the High Polymer Forum at the New York Meeting of the American Chemical Society, September, 1947.

(2) G. V. Schulz, *Z. physik. Chem.*, **B44**, 227 (1939); H. Staudinger and G. V. Schulz, *Ber.*, **68**, 2320 (1935); H. Staudinger and J. Schneiders, *Ann.*, **541**, 151 (1939).

(3) H. Mark and R. Raff, "High Polymeric Reactions," Interscience Publishers, Inc., New York, N. Y., 1941, pp. 191, 219, *et seq.*

(4) H. W. Melville, *Trans. Faraday Soc.*, **40**, 217 (1944).

(5) P. J. Flory, THIS JOURNAL, **59**, 241 (1937).

(6) P. J. Flory, *ibid.*, **69**, 2893 (1947).

(7) R. B. Carlin and N. E. Shakespeare, *ibid.*, **68**, 876 (1946).

These "multichain" polymer molecules are therefore composed of b chains, of average length $\bar{y}$ units each, radiating from the central radical R. It is to be noted that network formation is precluded so long as the terminal groups A, or B as the case may be, cannot co-react. Also, the degree of branching is fixed according to the functionality of the central unit. The average length, $\bar{y}$, of the chains is controlled by the proportion of multifunctional unit employed; it is also dependent on the extent of condensation, which, however, ordinarily is carried very nearly to completion.

The multichain polymers employed in the present investigation were prepared from ϵ-caprolactam (instead of the corresponding amino acid) using either a tetrabasic or an octabasic carboxylic acid as the multifunctional reactant. For comparison, monochain and dichain ϵ-caproamide polymers (stearic and sebacic acid, respectively, were used as the "multifunctional" reactant) have been prepared as well. Thus, the various polymers for which data are reported herein can be represented by the formula

$$R\{—CO[—NH(CH_2)_5CO—]_{\bar{y}}\ OH\}_b$$

where $b = 1, 2, 4$, or 8, $\bar{y}$ being varied in each case by manipulating the proportion of the multifunctional reactant. Cyclohexanone-tetrapropionic acid[8] and the analogous octabasic acid, dicyclohexanone-octapropionic acid[9] were used in preparing the tetrachain and octachain polymers, respectively.

Theoretical

Stoichiometric Relationships. The Number Average Molecular Weight.—Let Q represent the number of equivalents of the multifunctional reactant, RA_b, that reacts with one mole of A—B monomer. If the reaction were carried to completion, no unreacted B groups remaining, there would be obtained Q/b moles of polymer molecules, each molecule having b chains. Since it is never possible to carry the condensation process to absolute completion, a small fraction of the B groups will remain unreacted, and each unreacted B group will subtend a linear chain. Letting L represent the number of equivalents of unreacted groups per mole of A—B monomer, there will be L moles of linear molecules and Q/b moles of multichain molecules in the polymer. The ratio of L to Q/b depends on the degree of completion of the reaction and is very small if the reaction is carried reasonably near to completion. (In the examples discussed below, A = COOH and B = NH_2; the proportion L of the latter remaining unreacted in the polymer can be determined by titration of the free amino groups.)

As a consequence of the assumed equal reactivity of the carboxyl groups dealt with here, the average number, $\bar{y}$, of monomer units subtended by an A group of a multifunctional unit will equal the number attached to the terminal unit of a linear chain. Therefore $\bar{y}$ will equal the total number of monomer units excluding those with unreacted B groups, divided by the total number of chains, or

$$\bar{y} = (1 - L)/(Q + L) \qquad (1)$$

Letting y_L represent the average number of units in a linear molecule (including the terminal unit bearing the unreacted B group)

$$\bar{y}_L = \bar{y} + 1 = (Q + 1)/(Q + L) \qquad (2)$$

The number average molecular weights of the linear molecules ($\overline{M}_{n,L}$) and of the multichain molecules ($\overline{M}_{n,Q}$) are therefore

$$\overline{M}_{n,L} = m\bar{y}_L = m(Q + 1)/(Q + L) \qquad (3)$$

and

$$\overline{M}_{n,Q} = b(m\bar{y} + m_b) = b[m(1 - L)/(Q + L) + m_b] \qquad (4)$$

where m is the molecular weight of an A—B structural unit and m_b is the molecular weight of the multifunctional unit divided by b. The number average molecular weight ($\overline{M}_n$) of the entire polymer containing L moles of linear molecules and Q/b moles of multichain molecules can now be expressed as

$$\overline{M}_n = \frac{LM_{n,L} + (Q/b)M_{n,Q}}{L + (Q/b)} = \frac{(Qm_b + m)}{(Q/b) + L} \qquad (5)$$

It can be shown further that w_L, the weight fraction of linear molecules present in the mixture, is given by

$$w_L = L/\left\{L + Q\left[1 + \left(\frac{m_b}{m} - 1\right)\left(\frac{Q + L}{Q + 1}\right)\right]\right\} \qquad (6)$$

which reduces to

$$w_L = L/(Q + L) \qquad (7)$$

when Q and L are both small or when m_b is similar in magnitude to m. This relationship will be used in the next section (see equation 25) in deriving the expression for the weight average molecular weight of a mixture of multichain and linear molecules.

Molecular Size Distribution. The Weight Average Molecular Weight.—Schulz[10] has derived approximate relationships expressing the molecular weight distribution in polymers composed of a fixed number of chains of random length. His molecular weight distribution relationships were derived for the purpose of treating vinyl polymers believed to be branched. Since branching in vinyl polymers must necessarily be random, his relationships actually are of little value for the purpose intended, except in the $b = 2$ case representing polymers resulting from diradical chain growth in two directions. Schulz's approximate relationships may be applied to multichain polymers of the present type, provided the chain length is sufficiently great; at low chain lengths the approximations employed by

(8) Bruson and Riener, THIS JOURNAL **64**, 2850 (1942).

(9) J. R. Schaefgen and P. J. Flory, *ibid.*, **70**, 2823 (1948).

(10) G. V. Schulz, *Z. physik. Chem.*, **B43**, 25 (1939).

Schulz became invalid. Instead of these approximate equations, we have preferred to use exact relationships, the derivation of which is set forth below. They are as easily applied as the approximate forms of Schulz.

Let p represent the fraction of the A groups which have undergone reaction, *i. e.*

$$p = (1 - L)/(1 + Q) \tag{8}$$

If the A groups of the multifunctional units and those of the bifunctional units can be assumed to be equally reactive, p represents the probability that any given A group has condensed with a B group, since condensation polymerization reactions are known to proceed in a random manner.[11] The probability that a given multichain molecule possesses exactly x_1 bifunctional units in the first chain, x_2 in the second, etc., will be given by

$$Px_1x_2\cdots x_b = p^{x_1}p^{x_2}\cdots p^{x_b}\,(1 - p)^b \tag{9}$$

Let x represent the total number of structural units, counting the multifunctional constituent as a single unit. Then

$$x_1 + x_2 + \cdots + x_b + 1 = x \tag{10}$$

and

$$P_{x_1x_2\cdots x_b} = p^{x-1}\,(1 - p)^b \tag{11}$$

All combinations of the x's consistent with equation (10), the individual values of the x's ranging from 0 to x_b, are equally probable. It is to be noted that a given combination is specified by $b - 1$ of the x's, the remaining one being defined by equation (10) above. The number of ways the $x - 1$ units may be distributed over the b chains is given, therefore, by the combinatory factor

$$(x + b - 2)!/(b - 1)!(x - 1)!$$

which represents the number of combinations of $(x - 1) + (b - 1)$ elements (allowing for the permissible zero values) taken $b - 1$ at a time. Hence, the probability that a given multichain molecule contains $x - 1$ bifunctional units arranged in any manner is given by

$$P_{x,b} = (1 - p)^b p^{x-1}(x + b - 2)!/(b - 1)!(x - 1)! \tag{12}$$

$P_{x,b}$ represents the mole fraction of x-mers among the multichain molecules.

In order to obtain the weight fraction distribution and to deduce the weight average degree of polymerization, the summations

$$\sum_{x=1}^{\infty} xP_{x,b} \text{ and } \sum_{x=1}^{\infty} x^2P_{x,b}$$

must be evaluated.

$$\sum_{x=1}^{\infty} xP_{x,b} \equiv \sum_{x=2}^{\infty}(x - 1)P_{x,b} + \sum_{x=1}^{\infty} P_{x,b} \tag{13}$$

Substituting from equation (12)

$$\sum_{x=1}^{\infty} xP_{x,b} = \sum_{x=2}^{\infty}(1 - p)^b\, p^{x-1}\,\frac{(x + b - 2)!}{(x - 2)!(b - 1)!} + \sum_{x=1}^{\infty} P_{x,b}$$

Shifting limits in the first summation on the right, there is obtained

$$\sum_{x=1}^{\infty} xP_{x,b} = bp/(1 - p)\sum_{x=1}^{\infty} P_{x,b+1} + \sum_{x=1}^{\infty} P_{x,b}$$

Since

$$\sum_{x=1}^{\infty} P_{x,b+1} = \sum_{x=1}^{\infty} P_{x,b} = 1$$

$$\sum_{x=1}^{\infty} xP_{x,b} = (bp + 1 - p)/(1 - p) \tag{14}$$

Replacing x^2 with $(x - 2)(x - 1) + 3x - 2$ in the summations over $x^2P_{x,b}$ and proceeding similarly, there is obtained

$$\sum_{x=1}^{\infty} x^2P_{x,b} = \frac{p^2(b - 1)^2 + (3b - 2)p + 1}{(1 - p)^2} \tag{15}$$

The weight fraction distribution is given by

$$w_x = xP_{x,b}\Big/\sum_{x=1}^{\infty} xP_{x,b}$$

which on substituting from equation (14) reduces to

$$w_x = \left[\frac{(1 - p)^{b+1}}{(bp + 1 - p)}\right](p^{x-1})\,\frac{x(x + b - 2)!}{(b - 1)!(x - 1)!} \tag{16}$$

The corresponding weight fraction distribution expression derived by Schulz,[10] when expressed in the present symbols, is

$$w_x = (-\ln p)^{b+1}\, p^x(x^b/b!) \tag{17}$$

which approximates equation (16) when p is near unity (high *average* molecular weight) except for small values of x, since

$$-\ln p \cong (1 - p)$$
$$p^x \cong p^{x-1}$$
$$x^b/b! \cong \frac{x(x + b - 2)!}{(bp + 1 - p)(b - 1)!(x - 1)!}$$

The molecular weight distribution is narrower the greater the number b of chains. The dependence of the molecular weight distribution on b is illustrated in the curves published by Schulz,[10] which are qualitatively similar to the corresponding curves calculated from our equation (16).

The number and weight average degrees of polymerization, respectively, derived from the mole fraction size distribution as given by equation (12) are

$$\bar{x}_n = \sum_{x=1}^{\infty} xP_{x,b}\Big/\sum_{x=1}^{\infty} P_{x,b} = (bp + 1 - p)/(1 - p) \tag{18}$$

and

$$\bar{x}_w = \sum_{x=1}^{\infty} x^2P_{x,b}\Big/\sum_{x=1}^{\infty} xP_{x,b} = \frac{(b - 1)^2p^2 + (3b - 2)p + 1}{(bp + 1 - p)(1 - p)} \tag{19}$$

Substituting for p from equation (8) reduces the expression for the number average to

$$\bar{x}_n = 1 + \frac{b\,(1 - L)}{Q + L} \tag{20}$$

(11) P. J. Flory, THIS JOURNAL, **61**, 3334 (1939); **64**, 2205 (1942).

The ratio of the weight to number average degree of polymerization is

$$\frac{\bar{x}_w}{\bar{x}_n} = \frac{(b-1)^2p^2 + (3b-2)\,p + 1}{(bp + 1 - p)^2} \qquad (21)$$

Substituting from Equation (8) for p

$$\bar{x}_w/\bar{x}_n = 1 + \frac{b(1-L)(1+Q)}{[b(1-L) + (Q+L)]^2} \qquad (22)$$

For small values of Q and L, this equation reduces approximately to

$$\bar{x}_w/\bar{x}_n \cong 1 + 1/b \qquad (23)$$

which is the result obtained by Schulz. The narrowing of the molecular weight distribution with increase in b is reflected in the approach of this ratio to unity.

Equation (23) is too coarse an approximation on the one hand and (22) is unnecessarily cumbersome on the other. An intermediate approximation, which can be used with negligible error when $L << 1$ and $Q^2 << (b^2 + 2bQ)$, is the following

$$\bar{x}_w/\bar{x}_n = 1 + (1+Q)/(b+2Q) \qquad (24)$$

For a mixture of Q/b multichain polymer molecules with L linear polymer molecules the expression for the weight average molecular weight is[12] (see equations 3, 4, 7, and 24)

$$\overline{M}_w = w_L\,\overline{M}_{w,L} + w_Q\overline{M}_{w,Q} = w_L\overline{M}_{n,L}\,(\bar{x}_w/\bar{x}_n)_1 + (1 - w_L)\,\overline{M}_{n,Q}\,(\bar{x}_w/\bar{x}_n)_b \qquad (25a)$$

$$\cong \frac{L}{(Q+L)}\,\frac{m(1+Q)}{(Q+L)}\left[1 + \frac{(1+Q)}{(1+2Q)}\right] + \frac{Qb}{(Q+L)}\left[\frac{m(1-L)}{(Q+L)} + m_b\right]\left[1 + \frac{(1+Q)}{(b+2Q)}\right] \qquad (25b)$$

Since the first term in equation (25b) is small, $(1 + Q)$ can be set equal to unity therein. The second term can be simplified since $L(m_b - m)$ is small in comparison with m. Then

$$\overline{M}_w \cong 2\,mL/(Q+L)^2 + [Qb/(Q+L)^2](m + m_bQ)[1 + (1+Q)/(b+2Q)] \qquad (26)$$

The Viscosity Average Molecular Weight.—Interpretation of dilute solution viscosities requires evaluation of the viscosity average molecular weight[13] defined as

$$\overline{M}_v = \left[\sum_{x=1}^{\infty} w_x M_x^a\right]^{1/a} \qquad (27)$$

where a is a constant which usually is in the range of 0.6 to 0.9. Substituting from equation (16) for w_x and replacing M_x with xm

$$\overline{M}_v^a = m^a\left\{\frac{(1-p)^{b+1}}{[p(b-1)+1]p}\right\}\sum_{x=1}^{\infty}\left\{\left[(x+b-2)(x+b-3)\cdots(x+1)\right]x^{2+a}\,p^x/(b-1)!\right\}$$

Employing the ratio of $\overline{M}_v$ to $\overline{M}_n$, the latter being the product of m and x_n as expressed by equation (18), and expanding the products of the summation

$$(\overline{M}_v/\overline{M}_n)^a = \left[\frac{1-p}{p(b-1)+1}\right]^a \left\{\frac{(1-p)^{b+1}}{p[p(b-1)+1]}\right\}\sum_{x=1}^{\infty}\left\{\left[x^{b+a} + (1/2)(b-1)(b-2)x^{b-1+a} + (1/24)(b-1)(b-2)(3b^2 - 13b + 12)x^{b-2+a} + \cdots\right]p^x/(b-1)!\right\}$$

The summation is made up of terms of the form

$$S_m = \sum_{x=1}^{\infty} p^x\,x^{m+a}$$

where m is a positive integer. Replacing the summation by an integral and setting $y = -x \ln p$

$$S_m = (-1/\ln p)^{m+a+1}\int_0^{\infty} e^{-y}\,y^{m+a}\,dy = (-1/\ln p)^{m+a+1}\;\Gamma(m+a+1) = (-1/\ln p)^{m+a+1}\,[(m+a)(m+a-1)\cdots(1+a)\,\Gamma(1+a)]$$

Substituting this evaluation of S_m in the previous equation, the ratio of the viscosity average to the number average may be expressed conveniently as

$$(\overline{M}_v/\overline{M}_n) = (C/b)[(1/b!)(a+b)(a+b-1)\cdots(a+1)\Gamma(a+1)]^{1/a} \qquad (28)$$

where

$$C = \left(\frac{1-p}{-\ln p}\right)\left[\frac{b}{p(b-1)+1}\right]\left\{\left(\frac{1-p}{-\ln p}\right)^{b+1}\left[\frac{b}{p^2(b-1)+p}\right]\left[1 + \frac{(b-1)(b-2)(-\ln p)}{2(b+a)} + \frac{(b-1)(b-2)(3b^2-13b+12)(-\ln p)^2}{24(b+a)(b+a-1)} + \cdots\right]\right\}^{1/a} \qquad (29)$$

The series in brackets converges rapidly when

$$-b \ln p < 1$$

When, in addition to this condition, p is not less than about 0.8, C differs inappreciably from unity. To illustrate for $a = 0.8$, $b = 8$, and $p = 0.8$, C as calculated from equation (29) has a value of 1.03 (making a suitable estimation of the values of the unexpanded terms). For all higher values of p (and/or lower values of b), C is closer to unity. Within the limit of error introduced on replacing summations by integrals, C may therefore be set equal to unity in equation (28).

Experimental

Materials.—ϵ-Caprolactam was prepared from cyclohexanoneoxime by a Beckmann rearrangement[14] in 77% yield. The product was distilled at reduced pressure and then crystallized from acetone to a constant freezing point of 68.7–68.8°, determined by a cooling curve.

Stearic Acid.—A commercial grade was crystallized once from acetone and then several times from alcohol; m. p. 71–72°[15]; neutral equivalent 284, calcd. 284.5.

Sebacic Acid.—An Eastman Kodak Co. product was crystallized several times from distilled water; m. p. 128.5–130°, uncor.; neut. equiv. 101, calcd. 101.1.

(12) The subscript b on the ratio $(\bar{x}_n/\bar{x}_w)_b$ in equation (25a) refers to the value of b for the multichain molecules. The subscript "1" must be used for the co-existing linear species.

(13) P. J. Flory, THIS JOURNAL, **65**, 372 (1943).

(14) P. Schlack, U. S. Patent 2,313,026 (1943).

(15) All melting points are corrected for stem exposure unless marked "uncor."

2,2,6,6-Tetra-(β-carboxyethyl)-cyclohexanone (cyclohexanonetetrapropionic acid) was prepared by the method of Bruson.[8] Attempts to convert this acid or its nitrile to cyclohexane-tetrapropionic acid by the Clemmensen method were uniformly unsuccessful. The acid after several crystallizations from water melted at 182.5–184.5°, although one sample prepared by acid hydrolysis of the tetranitrile melted at 195–197°. However, mixed melting points showed that this sample was identical with the lower melting material indicating the existence of allotropic forms. The neutral equivalent was 96.6, calcd. 96.6. A sample of this acid when heated to 253° for three hours in an argon atmosphere turned black and tarry and underwent extensive decomposition with the liberation of gaseous products. When the acid was mixed with three times its weight of ε-caprolactam and initially polymerized at 200° (see section on Method of Polymerization), little decomposition occurred on further heating at 253° for a period of three hours, thus indicating that the amide is considerably more stable than the free acid.

bis-[3,3,5,5-Tetra-(β-carboxyethyl)-4-ketocyclohexyl] (Dicyclohexanoneoctacarboxylic Acid).—The preparation of this acid from *p,p'*-diphenol is described elsewhere.[9] Material melting at 274–277° and having a neutral equivalent of 96.6 to 96.8 (calcd. 96.4) was used in making polymers.

Method of Polymerization.—The polymerizations were carried out in two steps. In the first step weighed amounts of ε-caprolactam and the multifunctional coreactant together with a small amount of distilled water (*ca.* 17 mole per cent.) were polymerized[16] in a sealed tube at a temperature of about 200° until a low molecular weight polymer was produced (four hours or more). The tube was alternately evacuated and filled with argon or nitrogen (containing in either case less than 0.01% of oxygen) several times before sealing. In the second step the white brittle polymer produced in the first step was heated in an inert gas atmosphere at 253° (diphenyl vapor-bath) alternately at atmospheric pressure and at reduced pressure (down to 15 mm.) until the melt viscosity became constant, or for a period of from six to seven hours (see section on results). The distillate in each polymerization was collected and analyzed for evolved ε-caprolactam. The amount of ε-caprolactam used in the calculation of the polymer composition was corrected accordingly.

The apparatus used in the second step was essentially that described previously[17] except that the side-arm attached to the vertical polymerization tube sloped downward. This facilitated the complete removal of the unreacted ε-caprolactam. The trap in which the distillate was collected was cooled in an ice-bath.

Melt Viscosity.—The melt viscosities of the polymers were determined by the method previously described.[17] It was found convenient to use viscometers with two bulbs (or four marks in the case of the straight tube type) using the lower bulb to measure the changing viscosity as the reaction proceeded and saving the clean upper bulb to determine the final viscosity. Melt viscosities were ordinarily taken at the end of a given cycle, a cycle consisting of a fifteen-minute period of heating at reduced pressure followed by a fifteen-minute period at atmospheric pressure during which time the inert gas was bubbled through the molten polymer. When two consecutive viscosity determinations gave values within 5% of each other the reaction was assumed to be substantially complete and a final viscosity was determined. In preparing the higher molecular weight polymers, the heating period at 253° was prolonged to six or seven hours which was several times the length of time required for the lower molecular weight polymers to reach maximum viscosity. After this length of time the reaction was assumed to be complete, and a final viscosity was taken.

Solution Viscosities.—Relative viscosities of the polymer solutions in concentrated sulfuric acid were measured at 25.0 (±0.1°) using a Ubbelohde number 2 suspended level viscometer. The efflux time of the solutions was of the order of two minutes or more, making the kinetic energy correction negligible. The density of the solution was equal to that of the solvent within the experimental error.

Solutions were prepared by shaking a suspension of the finely divided polymer in ordinary commercial concentrated sulfuric acid until solution was complete, and making up to volume. To obtain polymer samples in a form which would dissolve readily, the brittle lower molecular weight polymers were ground in a steel mortar, whereas samples of the tough higher molecular weight polymers were drilled out from a solid plug thereof with a one-half inch drill. Concentrations were suitably chosen to obtain relative viscosities in the range 1.15 to 1.25. Values of $(\ln \eta_r)/c$, where c is expressed in g./100 cc. solution, calculated from relative viscosities in this range differed by 3% or less from the infinite dilution values, and were therefore accepted as intrinsic viscosities (*i. e.*, $(\ln \eta r)/c$ at $c = 0$)[18] without extrapolation. In a few representative cases the change of $(\ln \eta_r)/c$ with concentration was measured. Solutions for these experiments were made up either individually or by dilution of a more concentrated solution.

The observation of Matthes[19] that degradation of the polymer in concentrated sulfuric acid solution at room temperature is negligible within a twenty-four hour period was confirmed.

Amine Titer.—The amino end-group concentration in a polymer was determined by titrating a 50-ml. sample of a 6% by weight solution of the polymer in *m*-cresol with standard 0.1 *N* *p*-toluenesulfonic acid solution using thymolsulfonphthalein as an indicator. The solutions were prepared by shaking and gently warming the finely divided polymer suspension in *m*-cresol until solution was effected. The *m*-cresol (1500 ml.) used for these titrations was distilled at reduced pressure from sulfuric acid (5 ml.) and zinc dust (5 g.), and then redistilled from barium oxide (10 g.) to give a water-white neutral product. The amino group concentration is expressed as equivalents per mole of ε-caprolactam in the polymer. This value is equal to L, the equivalents of linear molecules present in the polymer per mole of ε-caprolactam.

Melting Points.—Polymer melting points were measured[20] on the heated stage of a microscope, plane polarized light being used for illumination. One Polaroid film was located between the light source and the sample, and another was placed in the objective of the microscope. With the Polaroids at right angles to each other, the crystalline portions of the sample were seen as light areas against a dark background. As the temperature of the stage was gradually increased, a range of temperature was reached in which the light areas disappeared into the dark background. This range of temperature is recorded as the melting point.

Results

Calculations and Errors.—Viscosity, molecular weight, and melting point data for monochain, dichain, tetrachain, and octachain polymers ($b = 1$, 2, 4, and 8) are recorded in Tables I, II, III, and IV, respectively. The quantities Q and L, defined earlier, were calculated in each case from the data in columns 1 and 2, and from the amine titer. The weight fraction of linear molecules, w_L, was calculated using equation (7). The number average, M_n, and weight average, M_w, molecular weights were calculated using equations (5) and (26), respectively. All poly-

(16) W. E. Hanford, U. S. Patent 2,241,322 (1941).

(17) P. J. Flory, THIS JOURNAL, **62**, 1057 (1940).

(18) E. O. Kraemer, *Ind. Eng. Chem.*, **30**, 1200 (1938).

(19) A. Matthes, *J. prakt. Chem.*, **162**, 245 (1943).

(20) Unpublished work of H. R. Mighton of this Laboratory. See R. D. Evans, H. R. Mighton and P. J. Flory, *J. Chem. Phys.*, **15**, 685 (1947).

TABLE I

MONOCHAIN POLYMERS

ϵ-Caprolactam, g.	Stearic acid, g.	$Q \times 10^2$	$L \times 10^4$	η^a	$[\eta]^b$	M. p., °C.	$\bar{M}_n$	$\bar{M}_w$
18.72	3.12	6.64	6.1	1.38	0.212	213–217	1,970	3,820
17.17	2.094	4.86	3.4	2.40	.248	212–216	2,600	5,090
18.87	1.445	3.05	6.0	10.0	.343	215–221	3,920	7,730
27.72	1.211	1.74	5.8	43.4	.516	219–221	6,560	13,000
28.98	0.982	1.36	5.7	103	.612	221–226	8,240	16,400
27.34	0.626	0.912	6.6	401	.804	221–225	11,860	23,600
28.07	0.498	0.707	10.0	615	.914	220–222	14,300	28,400

[a] Melt viscosity in poises at 253°. [b] Intrinsic viscosity in concentrated sulfuric acid at 25°.

TABLE II

DICHAIN POLYMERS

ϵ-Caprolactam, g.	Sebacic acid, g.	$Q \times 10^2$	$L \times 10^4$	η^a	$[\eta]^b$	M. p., °C.	$\bar{M}_n$	$\bar{M}_w$
18.57	2.203	13.30	0.44	1.25	0.171	203–205	1,900	2,880
19.04	1.405	8.27	4.0	2.72	.235	211–213	2,910	4,390
18.85	1.055	6.27	3.6	5.00	.281	213–215	3,770	5,690
18.20	1.010	6.22	2.5	5.82	.291	209–214	3,810	5,750
18.44	0.802	4.88	3.2	11.4	.350	214–216	4,780	7,200
18.97	.699	4.13	1.6	13.7	.381	212–217	5,650	8,490
18.73	.599	3.58	7.0	23.8	.427	214–218	6,280	9,550
18.72	.500	2.99	6.0	44.9	.496	214–220	7,500	11,400
19.00	.488	2.88	3.7	44.5	.496	218–222	7,850	11,900
17.00	.366	2.41	5.5	143	.627	217–220	9,170	14,100
18.08	.255	1.58	5.8	460	.800	218–222	13,500	20,800
15.72	.181	1.29	6.2	735	.908	220–223	16,200	25,000
17.56	.162	1.03	4.8	1650	1.085	221–225	20,200	31,200
17.73	.116	0.734	13.8	3130	1.313	221–227	22,600	37,100

[a] Melt viscosity in poises at 253°. [b] Intrinsic viscosity in concentrated sulfuric acid at 25°.

TABLE III

TETRACHAIN POLYMERS

ϵ-Caprolactam, g.	Tetrabasic acid, g.	$Q \times 10^2$	$L \times 10^4$	η^a	$[\eta]^b$	M. p., °C.	$\bar{M}_n$	$\bar{M}_w$	$w_L \times 10^2$
25.62	4.745	21.69	18	1.84	0.177	187–188	2,390	3,110	0.82
26.44	2.754	12.20	7.2	3.75	.233	205–207	3,970	5,150	0.58
14.39	1.322	10.76	12	5.46	.289	207–209	4,400	5,720	1.1
28.26	1.968	8.15	8.6	8.20	.287	210–212	5,700	7,350	1.0
25.54	1.446	6.63	7.7	16.4	.390	214–217	6,890	8,900	1.2
16.56	0.642	4.54	8.6	39.3	.459	216–218	9,620	12,600	1.8
28.77	1.089	4.43	8.8	43.5	.469	215–219	9,820	12,900	1.9
27.03	0.864	3.74	7.0	99.3	.550	219–222	11,600	15,200	1.8
28.67	.598	2.44	6.8	390	.649	221–225	17,000	22,800	2.7
28.85	.509	2.07	8.2	589	.750	222–224	19,200	26,200	3.8
17.28	.316	2.14	9.2	859	.923	220–223	18,400	25,200	4.1

[a] Melt viscosity in poises at 253°. [b] Intrinsic viscosity in concentrated sulfuric acid at 25°.

TABLE IV

OCTACHAIN POLYMERS

ϵ-Caprolactam, g.	Octabasic acid, g.	$Q \times 10^2$	$L \times 10^4$	η^a	$[\eta]^b$	M. p., °C.	$\bar{M}_n$	$\bar{M}_w$	$w_L \times 10^2$
4.98	1.0348	24.4	18	2.76	0.171	183–184	4,230	5,070	0.73
8.67	0.9913	13.4	9.3	6.00	.268	202–203	7,130	8,450	0.69
9.21	.5750	7.32	8.4	24.2	.420	214–216	12,000	14,600	1.1
8.93	.3313	4.35	6.1	126	.597	219–222	19,400	23,800	1.4
14.06	.3762	3.14	6.0	358	.806	221–222	25,700	32,400	1.9

[a] Melt viscosity in poises at 253°. [b] Intrinsic viscosity in concentrated sulfuric acid at 25°.

merizations were carried very nearly to completion, as shown by the low values obtained for w_L (Tables III and IV), hence the final polymers contained a preponderant number of multichain molecules.

The preceding deductions of structure and the formulas for the computation of molecular weights are based on literal application of stoichiometric considerations. Deviations from these idealized conditions doubtless occur owing to side reactions. These include oxidation, thermal decomposition, anhydride and imide formation.

Oxidation was minimized by carrying out the polymerizations in an argon or nitrogen atmosphere containing, in either case, less than 0.01% of oxygen. However, some oxidation occurred, especially in the higher molecular weight polymers for which the heating period at 253° was prolonged over a six to seven hour period. Small amounts of oxygen were also introduced during the melt viscosity measurements. Such oxidation as occurred presumably lowered the molecular weight by oxidative cleavage of the polymer chain. The magnitude of this effect is difficult to ascertain, but it is believed to have been small compared to the other side reactions mentioned; its effect was therefore neglected.

The most likely reaction to occur in thermal decomposition is decarboxylation. In support of this conclusion, the distillate in some of the polymerizations was found to be slightly acidic. To investigate the magnitude of the decomposition the number of carboxyl end-groups in a given polymer was determined by the method of Waltz and Taylor.[21] The results (Table V) show that loss of carbon dioxide does occur, but that in no case is the magnitude of the deviation between the observed value and that calculated from stoichiometric relationships greater than 9%. The fact that the major part of the octabasic acid used in a polymer could be recovered unchanged by hydrolysis is further proof that decomposition was slight. Loss of carbon dioxide, especially from the multichain molecule, would lower the degree of branching but would leave the molecular weight essentially unchanged since as b decreases $\bar{y}$ increases (see equation 4). The molecules which are formed may, for example, contain an average of 7.5 branches instead of eight.

TABLE V

CARBOXYL END-GROUP TITRATION OF MULTICHAIN POLYMERS IN BENZYL ALCOHOL AT 155°

Polymer	Equiv. COOH/g. polymer Calcd. × 10^4	Found × 10^4	% error
Tetrachain	1.87	1.85	1.1
Tetrachain	2.34	2.17	7.8
Tetrachain	4.04	4.10	1.5
Octachain	18.0	16.5	8.5
Octachain	10.7	10.1	5.9
Octachain	6.15	5.65	8.9
Octachain	3.76	3.48	8.0
Octachain	2.75	2.56	7.4

(21) J. E. Waltz and G. B. Taylor, *Anal. Chem.*, **19**, 448 (1947).

When the study of octachain polymers was extended to include polymers of higher molecular weight than reported herein, the melt viscosity of a given polymer continued to rise slowly on prolonged heating without seeming to approach a limit, and polymers of very high viscosity gave evidence of being partially gelled. This may have been due to the gradual formation of a small number of anhydride and/or imide linkages. All the polymers reported in this paper, however, were completely soluble and gave no evidence of gelation. It is quite possible, however, that a small number of such anhydride and/or imide linkages (short of gelation) were formed.

Furthermore it was found impossible to remove the last traces of monomeric ϵ-caprolactam from the polymer, owing to the occurrence of interchange reactions which constantly evolve small quantities of ϵ-caprolactam. This error would tend to make the observed viscosity low. Small amounts (*ca.* 0.15 g. in 16 g. of polymer) of a high melting (m. p. > 295°) sublimate which analyzed correctly for ϵ-caprolactam were also formed. The material is undoubtedly di-ϵ-caprolactam, a fourteen-membered ring compound.

Data reported here were obtained under conditions chosen with the object of minimizing errors arising from these various sources. While the results may nevertheless be vitiated by them to some extent, these errors are doubtless inconsequential insofar as the conclusions regarding the effects of branching are concerned.

Melt Viscosity.—It has been shown previously[17] that the viscosities of molten polyesters can be represented precisely by the equation

$$\log \eta = A + C\overline{M}_w^{1/2}$$

Graphs of the logarithm of the melt viscosity as a function of the weight average molecular weight for multichain polymers are shown in Fig. 1. The relationships are linear over the range of molecular weight considered just as in the case of polyesters, and the effect of branching is noticeable only in the octachain polymers. The equations for the lines are

$$b = 1, 2 \text{ or } 4 \quad \log_{10} \eta = 2.6 \times 10^{-2} \overline{M}_w^{1/2} - 1.32$$

$$b = 8 \quad \log_{10} \eta = 2.0 \times 10^{-2} \overline{M}_w^{1/2} - 1.00$$

The values of C are similar to those obtained for polyesters.[17,22] If the logarithm of the melt viscosity is plotted as a function of the square root of the number average molecular weight, individual linear relationships are obtained for each series of polymers.

Solution Viscosity.—The change of relative viscosity (η_r) with concentration for representative linear and multichain polymers was determined in sulfuric acid and in *m*-cresol solution. The function $(\ln \eta_r)/c$ was plotted against concen-

(22) W. O. Baker, C. S. Fuller and J. H. Heiss, THIS JOURNAL, **63**, 2142 (1941).

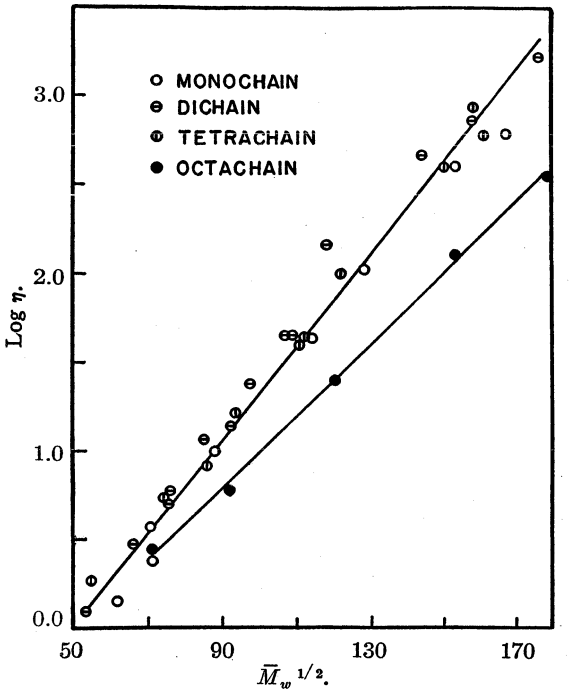


Fig. 1.—Relationships between melt viscosity and weight average molecular weight.

TABLE VI

THE CHANGE OF $(\ln \eta_r)/c$ WITH CONCENTRATION FOR SELECTED LINEAR AND MULTICHAIN POLYMERS

Branching	$[\eta]$	$d[(\ln \eta_r)/c]/dc$	$(\ln \eta_r)/c$ at $\eta_r \cong 1.2$	Error in %
(1) in sulfuric acid solution				
Linear $b = 2$	0.393	-29×10^{-3}	0.381	3.1
Tetrachain	.401	-26×10^{-3}	.390	2.7
Octachain	.428	-21×10^{-3}	.421	1.6
Octachain	.608	-16×10^{-3}	.603	0.8
Octachain	.828	-102×10^{-3}	.809	2.3
(2) in *m*-cresol solution				
Linear $b = 1$	.553	-31×10^{-3}	.542	2.0
Linear $b = 2$	.556	-37×10^{-3}	.542	2.5
Tetrachain	.541	-35×10^{-3}	.528	2.4
Octachain	.755	-103×10^{-3}	.730	3.3

tration and the slope and intercept, corresponding to the intrinsic viscosity, $[\eta]$, were determined. Values of the slopes, intrinsic viscosities, and the error involved in calculating the "intrinsic viscosity" from the relative viscosity at $\eta_r \cong 1.2$ are shown in Table VII. The data fail to show a definite correlation of the slope with the degree of branching.

Intrinsic viscosities of linear polymers generally depend on molecular weight according to a relationship of the form

$$[\eta] = K\bar{M}_v^a \qquad (30)$$

where $\bar{M}_v$ is the viscosity average molecular weight and K and a are constants for a given polymeric series. According to equation (28) the ratio $\bar{M}_v/\bar{M}_n$ is practically independent of molecular weight for a given value of b. Hence, if equation (30) can be applied to the multichain polymers, plots of log $[\eta]$ *vs.* $\bar{M}_n$ for polymers having the same b value should be linear. That this is the case over the molecular weight ranges investigated is shown in Fig. 2. The effect of branching is to lower the intrinsic viscosity at fixed *number average* molecular weight.

Treatment of the data by the method of least squares yields the following empirical relationships[23] corresponding to equation (30):

$b = 1$ $\log_{10}[\eta] = 0.764\ (\pm 0.016) \log_{10} \bar{M}_n - 3.20$ (31)

$b = 2$ $\log_{10}[\eta] = 0.794\ (\pm 0.018) \log_{10} \bar{M}_n - 3.38$ (32)

$b = 4$ $\log_{10}[\eta] = 0.736\ (\pm 0.084) \log_{10} \bar{M}_n - 3.26$ (33)

$b = 8$ $\log_{10}[\eta] = 0.857\ (\pm 0.027) \log_{10} \bar{M}_n - 3.87$ (34)

Within the experimental error, the slopes for the first three cases ($b = 1$, 2, or 4) are the same.

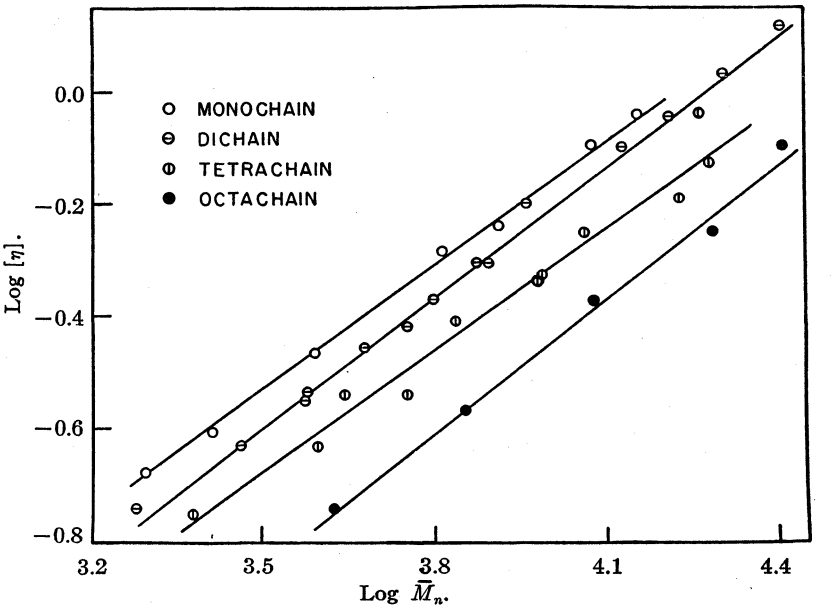


Fig. 2.—Relationships between intrinsic viscosity and number average molecular weight.

Matthes,[19] working with low molecular weight (400 to 5,000) poly-ε-caproamides, obtained values of $a = 0.67$ and $K = 12 \times 10^{-4}$ from measurements of molecular weight by end-group analysis and intrinsic viscosities in sulfuric acid. Staudin-

(23) The errors in the slopes shown in parentheses in equations (31) to (34) were estimated as $2\Delta y/(x_r - x_1)$ where x_1y_1, x_2y_2, ... x_ry_r are experimental points fitted by the equation $y = ax + b$ and Δy is the standard error in y.

ger and Schnell[24] carried out similar measurements (viscosities in *m*-cresol) over a wider range of molecular weights (1300 to 20,000), from which they concluded that the exponent a becomes equal to unity at higher molecular weights. In each case the measurements were carried out on precipitated polymers; consequently, the degree of heterogeneity of their samples cannot be appraised. Within the experimental uncertainties indicated by the scattering of the data, however, their results fit the line drawn through the points for linear polymers in Fig. 2. The values $a = 0.72$ and $K = 11 \times 10^{-4}$ obtained by Taylor[25] for poly-hexamethyleneadipamide polymers are similar in magnitude to our values for linear poly-ε-caproamide polymers.

A part, at least, of the apparent influence of the degree of branching b on the intrinsic viscosity–*number average* molecular weight relationship arises from the dependence of the molecular weight distribution on b. This effect of molecular weight distribution may be eliminated by converting the molecular weights to *viscosity averages*, using for this purpose equation (28) and the values of a obtained from the above empirical equations representing the log $[\eta]$ *vs.* $\overline{M}_n$ plots. Taking $a = 0.78$ for $b = 1$, 2 or 4 and $a = 0.86$ for $b = 8$, the ratios of $\overline{M}_v$ to $\overline{M}_n$ deduced from equation (28) for $b = 1$, 2, 4 and 8, respectively, are 1.90, 1.45, 1.22 and 1.12. If the rather trivial allowance which should be made for the small proportions of linear molecules is neglected, the number average molecular weights given in Tables I, II, III and IV may be converted to viscosity averages through the use of these respective factors.

A log–log plot of intrinsic viscosities *vs.* viscosity average molecular weights is shown in Fig. 3. Within the experimental error the data for polymers in which $b = 1$, 2, and 4 all fall on the same straight line, while the data for polymers in which $b = 8$ fall on a somewhat lower line. Thus the effect of branching on dilute solution viscosity becomes noticeable only in the octachain polymer series, a result paralleling the melt viscosity behavior.

Melting Points.—An increase in branching at the same molecular weight lowers the melting point (*cf.* Tables I, II, III, IV), and the relative amount of the depression of the melting point by branching depends on the molecular weight, decreasing as the molecular weight increases. In each case the melting points of the high molecular weight polymers ($\overline{M}_n$ = 20,000 or more) approach a constant value of about 225°.

Discussion

The results which have been presented demonstrate the feasibility of the scheme outlined in the introduction for preparing polymers with controlled degrees of branching. The principle should be capable of numerous extensions. We have found, for example, that polyacrylic acids may be employed as the multifunctional centers. Some of the products obtained in this manner are of much higher molecular weight than those herein reported, and they likewise exhibit the characteristics of ungelled materials. It should be noted that since the degree of polymerization of the polyacrylic acid molecules is non-uniform, b in this case is not constant.

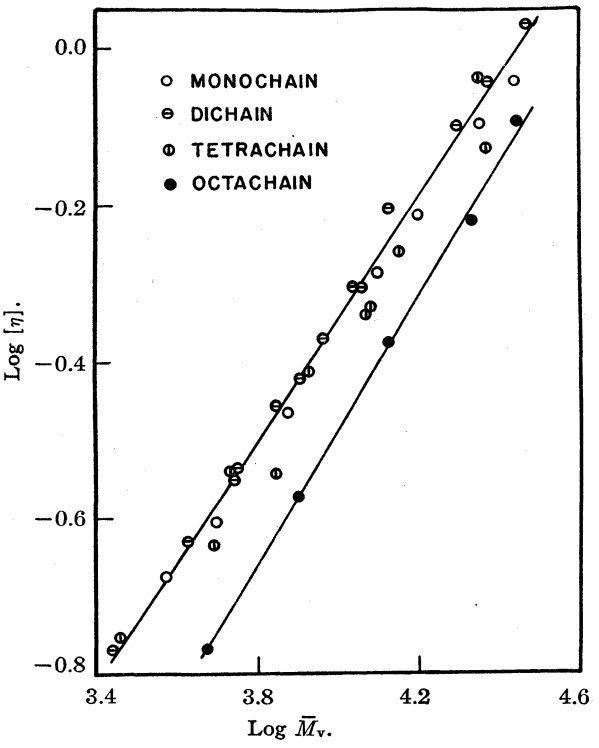


Fig. 3.—Relationships between intrinsic viscosity and viscosity average molecular weight.

In place of a polymerizable lactam, an amino acid, N-carboxyamino acid anhydride, hydroxy acid, or lactone may be employed in the preparation of multichain polymers and, similarly, other types of multifunctional reactants can be used (*e. g.*, polyamines or polyhydric alcohols). In any case, it is essential that the reactants be so chosen that all terminal groups of multichain molecules be of such a character that they cannot condense with any terminal groups (or other functional groups) of other multichain molecules.

The essential difference between multichain polymer molecules and the various non-linear polymers, obtained for example by polymerizing polybasic acids and glycols (or polyhydric alcohols and dibasic acids[26]) or by introducing cross linkages subsequent to the polymerization[27] is that

(24) H. Staudinger and H. Schnell, *Die Makromolekulare Chemie*, **1**, 36 (1947).

(25) G. B. Taylor, THIS JOURNAL, **69**, 635 (1947).

(26) L. L. Weil, W. H. Stockmayer and C. O. Beckmann, Abstracts of Papers, Atlantic City Meeting of the American Chemical Society, April, 1946, p. 38P.

(27) W. O. Baker, THIS JOURNAL, **69**, 1125 (1947).

the molecules of the former are uniformly branched whereas those of the latter vary widely in their degree of branching or cross-linking. As a result of this difference, the latter molecules may join together to form infinite networks and gelation may be observed. Multichain polymers are incapable (barring side reactions) of yielding network structures and gelation therefore is not observed. Thus the present observations on multichain polymers lend further support to the hypothesis that gelation is the direct consequence of infinite network formation, that is, non-linearity of polymer molecules does not of itself cause gelation to occur.

The observed effects of branching on both melt and solution viscosities are smaller than might have been expected according to various speculations on this subject. Only in the case of the octachain polymers does the influence of branching (at a given molecular weight) become noticeable within the range and precision of the present experiments. It should be emphasized, however, that the influence of non-linearity may become more pronounced at much higher molecular weights. (This behavior is indicated by the melt viscosity results.)

The intrinsic viscosity probably reflects as a first approximation the effective volume of the polymer particle including the solvent which in effect flows with the particle.[28,29,30] Increase in branching at a fixed molecular weight should therefore be expected to decrease the intrinsic viscosity, in accordance with observation. This decrease, however, is much smaller than would be expected according to the change in effective volume predicted from consideration of random chain configuration.

The present results show that the intrinsic viscosity is not determined, even in rough approximation, by the length of the longest chain of the structure, as Staudinger has contended. Thus, Staudinger's[31] use of the deviation of the intrinsic viscosity from the value normally expected for a linear polymer as a direct measure of the degree of branching is wholly unjustified.

The effect of branching on melting points is small except in the low molecular weight region where the relatively large proportion of the multifunctional unit is probably primarily responsible for the observed effect because of its inability to enter the crystallites.

Note Added in Proof.—Recently Melville and Youngson[32] have reported the synthesis of branched polyesters in which the degree of branching is allegedly the same in all molecules. Their method consists in treating a polyhydric alcohol such as pentaerythritol with polymeric ethylene adipate. Contrary to the contentions of these authors, the ester interchange process whereby these multifunctional reactants are incorporated into the polymer can be counted upon to introduce the polyalcohols at random, giving rise to a statistical array of molecular species in which the number of branching units per molecule is zero, one, two, etc. Evidence that this is so is afforded by the inference that gelation[33] occurs on further polymerization.

The addition of a multifunctional reactant (RA_b) to a polymerizing system derived from A—A and B—B type bifunctional reactants leads to structural differences in the resultant polymer which must be clearly differentiated from those occurring in a system containing A—B units exclusively. Uniformity of molecular pattern is impossible to achieve in polymerizations of the former type owing to the capacity of the reactants to unite variable numbers of the multifunctional reactant in the same molecule, and owing to the inherent random nature of the reactions involved (including ester or amide interchange). In experiments not reported here[34] we have investigated the influence of our tetrabasic acid on the polymerization of a diamine with a dibasic acid, a system analogous to those investigated by Melville and Youngson. In contrast to the polymerizations reported in this paper, such a system is highly susceptible to gelation. Gel points are in satisfactory agreement with statistical theory,[33] which again substantiates the random nature of these reactions.

Summary

A general method for the synthesis of branched chain polymers, in which all chains in a given molecule are united at a central multifunctional unit, has been demonstrated. Four series of polymers have been prepared in which the number of chains subtended by the central unit is one, two, four and eight, respectively.

The logarithm of the melt viscosity for a given series of polymers varies linearly with the square root of the weight average molecular weight; $[\eta]$ is proportional to M^a.

The effect of branching in the melt viscosity and in the intrinsic viscosity relationships becomes noticeable only when the amount of branching becomes large, that is, when the branching unit functionality is increased to eight.

AKRON, OHIO RECEIVED DECEMBER 29, 1947

(28) W. Kuhn, *Kolloid Z.*, **68**, 2 (1934).

(29) W. Kuhn and H. Kuhn, *Helv. Chim. Acta*, **26**, 1394 (1943).

(30) P. Debye and A. M. Bueche, *J. Chem. Phys.*, **16**, 573 (1948).

(31) H. Staudinger and G. V. Schulz, *Ber.*, **68**, 2320 (1935); H. Staudinger and K. Fischer, *J. prakt. Chem.*, **157**, 19, 158 (1940–1941); H. Staudinger and O. Nuss, *ibid.*, **157**, 283 (1941); H. Staudinger and Fr. Berndt, *Die Makromolekulare Chemie*, **1**, 22, 36 (1947).

(32) H. W. Melville and G. W. Youngson, *Nature*, **161**, 803 (1948).

(33) P. J. Flory, THIS JOURNAL, **63**, 3083, 3091, 3096 (1941); *J. Phys. Chem.*, **46**, 132 (1942).

(34) Unpublished work of F. S. Leutner, This Laboratory.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Specific Refractive Increment of Some Purified Proteins

BY GERTRUDE E. PERLMANN[1] AND L. G. LONGSWORTH

A quantitative interpretation of the electrophoretic patterns of protein mixtures obtained with the aid of the Tiselius method is based, in part, on a knowledge of the specific refraction of the proteins to be analyzed. Since the patterns are recorded at 0.5° and since no precise refractive index measurements of proteins at this temperature are available, an investigation has been made of the specific refractive increment of some purified proteins. A differential prism method, developed in this Laboratory,[2] has been used in conjunction with the optical equipment of the electrophoresis apparatus. This permits data to be obtained under the same conditions as those encountered in the routine electrophoretic analysis of protein mixtures. The results of this investigation are presented in this report.

Experimental

The proteins that have been studied in this research are listed in Table I. The egg albumin and β-lactoglobulin were prepared in this Laboratory; the bovine serum albumin was obtained from the Armour Company, Chicago, and the samples of human serum albumin and γ-globulin were kindly supplied by the Department of Physical Chemistry, Harvard Medical School.[3] In the case of egg albumin the purification procedure, including three recrystallizations, was that used by Sørensen and Høyrup[4] whereas β-lactoglobulin was prepared by a modification of Palmer's method[5] and was recrystallized four times. The modification consists of the removal of casein by the addition of solid ammonium sulfate to 40% saturation. The ammonium sulfate concentration of the filtrate was then increased to 55% saturation, the precipitate discarded and the β-lactoglobulin prepared from the filtrate.

Except for the egg albumin, which was kept as a paste in a concentrated ammonium sulfate solution, all of the protein samples were stored at 2° as dry powders until used. Salt-free solutions of the albumins were prepared by dialysis against distilled water. In the case of the protein solutions containing neutral or buffer salts, a sample was dissolved in the appropriate electrolyte solution and then dialyzed against this solution.

The concentrations of all of the protein solutions, except those dissolved in the sodium diethylbarbiturate buffers, have been determined from nitrogen analysis of weighed portions by the Pregl micro Kjeldahl method with the precautions recommended by Chibnall.[6] The factors for conversion of these results to a dry weight basis have been determined as follows. In the case of the albumins, weighed portions of a salt-free isoelectric solution were used for both the nitrogen and dry weight determinations. The dried residue presumably consisted entirely of protein. In the case of γ-globulin, an isoelectric solution in aqueous sodium chloride was used and correction for the weight of the salt in the residue was made with the aid of the assumption that this was the same as in a mass of the dialysate equal to that desiccated. The factor for the β-lactoglobulin was obtained from a nitrogen determination on a desiccated sample of the solid protein, thus eliminating any uncertainty as to correction for salt in the residue.

TABLE I

NITROGEN CONTENT OF THE PURIFIED PROTEINS

		Egg albumin	Bovine serum albumin	Human serum albumin	β-Lactoglobulin	Human γ-globulin
1	Method of desiccation	100° *in vacuo*	110° in air	110° in air	110° in air	110° in air
2	Percentage of nitrogen	15.72	16.05	15.95	15.53	15.9
3	Nitrogen factor	6.36	6.23[a]	6.27	6.44	6.29
4	References to nitrogen content	4, 6	7	7, 8	6, 9	7, 8

[a] The same value is obtained with water-dialyzed and electrodialyzed samples.

Under the conditions of desiccation given in line 1 of Table I, it was found that the dried residue attained a constant weight in twenty-four hours. The resulting nitrogen factor, line 3, is in good agreement with the best values found in the literature, references to which are indicated in line 4.

The determination of the protein concentration in the presence of the barbiturate buffer will be described later in this paper.

All weight concentrations have been converted to a volume basis, *i. e.*, gram protein per 100 ml. solution, with the aid of the density data in the "International Critical Tables"[10] and in Svedberg and Pedersen's "The Ultracentrifuge."[11] In estimating the density of a given solution the specific volumes of the components have been taken as additive. Moreover, all of the proteins of Table I have been assumed to have the specific volume, 0.741, of the "average protein" as given by Svedberg.[12]

Results

Effect of Protein Concentration in Salt-Free Solutions.—As the results presented in Table II indicate, the specific refractive increment, $k = (n_{\text{solution}} - n_{\text{solvent}})/p$, of a protein is independent of its concentration, p, over a wide range of this variable, if the concentration is expressed on a volume scale, *e. g.*, g./100 ml. solution. The results in Table II, and also those in Fig. 1 below, indicate that, although the specific refractive increment varies with the protein, this variation is

(1) Commonwealth Fund Fellow, 1945–1947.

(2) Longsworth, *Ind. Eng. Chem., Anal. Ed.*, **18**, 219 (1946).

(3) The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

(4) Sørensen and Høyrup, *Compt. rend. lab. Carlsberg*, **12**, 1 (1915–1917).

(5) Bull and Currie, THIS JOURNAL, **68**, 742 (1946).

(6) Chibnall, Rees and Williams, *Biochem. J.*, **37**, 354 (1943).

(7) Brand, Kassel and Saidel, *J. Clin. Invest.*, **23**, 437 (1944).

(8) Cohn, Strong, Hughes, Jr., Mulford, Ashworth, Melin and Taylor, THIS JOURNAL, **68**, 459 (1946).

(9) Brand, Saidel, Goldwater, Kassel and Ryan, *ibid.*, **67**, 1524 (1945).

(10) "International Critical Tables," Vol. III, McGraw-Hill Book Co., Inc., New York, N. Y., 1928.

(11) Svedberg and Pedersen, "The Ultracentrifuge," Oxford University Press, 1940, p. 446, app. III.

(12) Svedberg and Pedersen, "The Ultracentrifuge," Oxford University Press, London, 1940, p. 445, app. II.

small. These results confirm and extend those of Adair and Robinson[13] and others.

TABLE II

EFFECT OF PROTEIN CONCENTRATION ON THE SPECIFIC REFRACTIVE INCREMENT IN SALT-FREE SOLUTIONS

Protein	Protein concn., p, g./100 ml.	Specific refractive increment, $k \times 10^6$ at 0.5°
Egg albumin, pH 4.95	1.614	1874
	3.200	1877
	4.026	1878
	6.451	1877
		Av. 1876
Bovine serum albumin, pH 5.05	3.766	1906
	4.740	1902
	5.631	1906
	10.099	1897
		Av. 1901
Human serum albumin, pH 4.85	1.777	1886
	3.456	1887
	5.188	1888
	7.683	1887
		Av. 1887

Effect of Temperature on the Specific Refractive Increment.—Since the differential prism method can readily be adapted for work over a range of temperature, selected solutions have been studied at 0.5, 5, 10, 15, 20 and 25°.

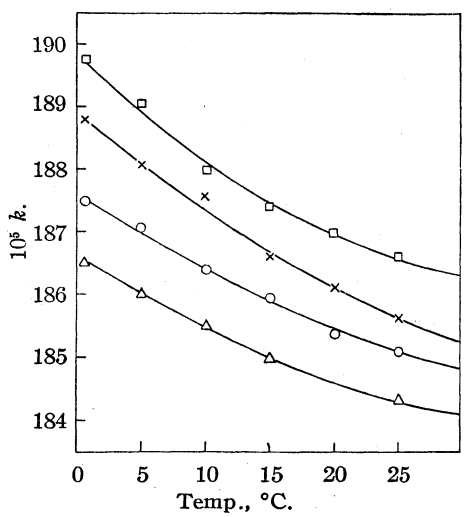


Fig. 1.—Effect of temperature on the specific refractive increment of proteins: □, bovine serum albumin; ×, human serum albumin; O, egg albumin; △, β-lactoglobulin.

These results are presented in Fig. 1 for the three albumins and β-lactoglobulin. Here the specific refractive increment, k, is plotted as ordinate against the temperature as abscissa. Contrary to the general impression, the effect of temperature on the refractive increment is not negligible for most proteins although it is smaller than that observed in the case of salts. This is shown in Table III, which also includes the results that have been obtained on some low molecular weight materials having electrical properties between those of salts and proteins. Of the substances investigated only γ-globulin had a negligible temperature coefficient.

TABLE III

COMPARISON OF THE EFFECT OF TEMPERATURE ON THE SPECIFIC REFRACTIVE INCREMENT, k, OF PROTEINS WITH ITS EFFECT ON OTHER SUBSTANCES

Substance	$k_0 \times 10^6$	$(k_0 - k_{25}) \times 10^6$
Sodium chloride		+171
Potassium chloride		+100
Glycine, alanine		+ 80
Arginine hydrochloride		+ 79
Glycylglycine		+ 80
Bovine serum albumin	1901	+ 32
Human serum albumin	1887	+ 33
Egg albumin	1876	+ 25
β-Lactoglobulin	1865	+ 23
Human γ-globulin	1875	0

The Specific Refraction at Different Wave Lengths.—Although most of the refractive index measurements have been made at λ = 5780 Å., the mean value of the mercury yellow doublet that is isolated with the Wratten filter number 22, a few solutions have also been studied at other wave lengths. In these measurements a cadmium–mercury lamp of the H4 type is used without a filter, the cell is filled with a fairly concentrated protein solution and, with the aid of the cylindrical lens attachment, the spectral lines are observed directly in the focus of the schlieren camera. With the yellow line as reference the displacements of other lines are measured and the corresponding values of $k_\lambda - k_{5780}$ computed. In Fig. 2, values of $(k_\lambda - k_{5780})/k_{5780}$ are plotted as ordinate against the reciprocal of the square of the wave length as

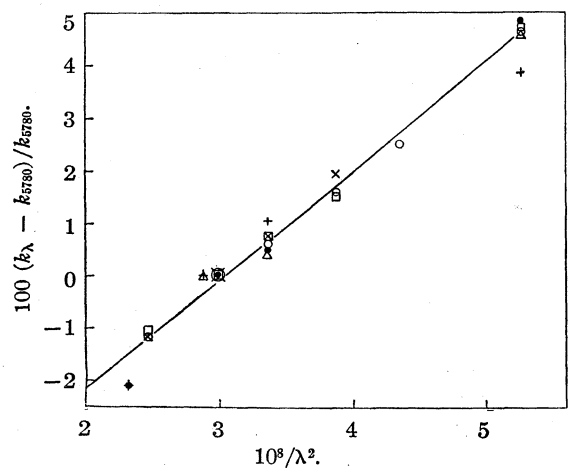


Fig. 2.—Effect of wave length on the specific refraction: □, bovine serum albumin; ×, human serum albumin; O, egg albumin; △, β-lactoglobulin; +, horse serum albumin; ●, horse serum globulin.

(13) Adair and Robinson, *Biochem. J.*, **24**, 993 (1930).

abscissa. As will be seen in the figure, all of the points, including those for horse serum albumin and globulin, and β-lactoglobulin taken from the work of Pedersen and Andersson,[14,15] can be adequately represented by a single straight line. Although the specific refraction varies somewhat with the nature of the protein it thus appears that the dispersion is essentially the same for all the proteins that have been studied. Since the slope of the line in Fig. 2 is 0.1946 the relation $k_\lambda = k_{5780}\,(0.940 + 2.00 \times 10^6/\lambda^2)$, where λ is in ångström units, may be used to obtain the specific refraction at any (visible) wave length.

The Specific Refraction of Sodium Proteinates.—The protein solutions employed in an electrophoretic analysis are usually prepared by dialysis against an appropriate buffer solution. The proteins are then present as charged particles in a solution of buffer ions whose composition is given, as a first approximation, by the Donnan equations. If the *p*H of the solution is above the isoelectric *p*H of the protein and if, as is usually the case, sodium buffer salts are employed, the protein is present as a sodium proteinate whose specific refraction differs from that of the isoelectric protein. Moreover, in addition to the acquisition of a net charge the protein may also bind some of the buffer salt. In order to distinguish between the effect of the charge and of bound salt it is essential to determine the refraction of sodium proteinate in the absence of buffer salts for comparison with the values obtained in their presence. Consequently the specific refractions of salt-free isoelectric protein solutions, to which small amounts of sodium hydroxide have been added, were determined with the results given in Table IV.

TABLE IV

EFFECT OF CHARGE ON THE SPECIFIC REFRACTIVE INCREMENT OF CRYSTALLINE EGG ALBUMIN AND BOVINE SERUM ALBUMIN

1 Moles NaOH × 10^5 per 1 g. protein	2 *p*H	3 *p*	4 Δ*n*	5 $k' \times 10^6$	6 *a*
		Egg albumin			
00.00	4.95	6.451	0.012106	1877	..
13.03	5.70	5.951	.011234	1888	45
19.28	6.20	5.739	.010868	1894	47
25.38	7.26	5.545	.010523	1898	44
32.67	8.7	5.334	.010187	1908	53
42.3	10.1	5.128	.00977	1904	36
44.6	10.5	5.025	.009593	1909	34
				Mean	44
		Bovine serum albumin			
00.00	5.02	4.740	0.009015	1902	..
19.59	7.22	4.340	.008329	1919	46
34.44	8.32	4.077	.007885	1934	49
53.68	10.10	3.782	.00735	1944	41
64.75	10.58	3.606	.007036	1951	40
72.97	10.72	3.525	.006978	1979	56
				Mean	46

In this table the quantity of alkali added is given in column 1 and the resulting *p*H of the solution in the next column. The protein concentration, column 3, is the value for the isoelectric solution after correction for the dilution due to the added alkali. If this is divided into the observed refractive increment, column 4, a specific refraction, k', column 5, is obtained that differs from the specific refraction k, of the isoelectric protein by an amount that is proportional to the net charge, e, of the protein, *i. e.*

$$k' = k(1 + ae)$$

Here the net charge is given by the values of column 1 since all of the added alkali reacts at the *p*H values studied. The computed values of the proportionality factor, a, column 6, are approximately constant and are essentially the same for the two proteins studied.

Refraction Measurements in Solutions in Sodium Chloride.—In view of the possibility that ions other than the hydrogen ion may be involved in the dissociation equilibria of the proteins, refraction measurements on these materials in solutions of the neutral salt, sodium chloride, have been made as an additional prerequisite to the study of proteins in buffer solutions. The results presented in Table V, where the specific refraction is taken as the difference, per unit concentration of protein, between the refractive indices of the equilibrated solutions, illustrate the two types of behavior that have been encountered. Thus the specific refraction of egg albumin is essentially independent of the concentration of the sodium chloride against which it has been dialyzed, whereas in the case of the bovine and human serum albumin small but significant changes occur. This is consistent with the findings of Scatchard and his associates[16] that these two materials bind some sodium chloride.

An additional feature of the bovine serum albumin used in this research also emerges from the data of Table V. Thus the k-values of 1923 and 1921 $\times 10^{-6}$ for the electrodialyzed solutions Nos. 11 and 13 differ significantly from that of 1902 $\times 10^{-6}$ for the water-dialyzed solution No. 6. If, however, water dialysis is used to remove the salt from solutions that have been equilibrated with aqueous sodium chloride, solutions Nos. 10 and 15, the values obtained, 1919 and 1920 $\times 10^{-6}$, then agree well with those for the solutions prepared by electrodialysis. The origin of these effects is obscure but, together with the observed constancy of the nitrogen factor, suggests the presence in the bovine serum albumin of a volatile, poorly refracting contaminant that is removed by electro- and saline dialysis but not by the or-

(14) Pedersen, *Biochem. J.*, **30**, 961 (1936).
(15) McFarlane, *ibid.*, **29**, 407 (1935).
(16) Scatchard, Batchelder and Brown, THIS JOURNAL, **68**, 2320 (1946).

TABLE V

EFFECT OF SODIUM CHLORIDE ON THE SPECIFIC REFRACTIVE INCREMENT OF CRYSTALLINE EGG ALBUMIN, BOVINE SERUM ALBUMIN AND HUMAN SERUM ALBUMIN

Soln. no.	Protein	Solution prepared by	*p*H	*p*	$k \times 10^6$
1	Egg albumin	Dialysis *vs.* H_2O	5.31	3.154	1869
2		Dialysis *vs.* 0.1 *M* NaCl	5.47	3.555	1874
3		Electrodialysis	4.74	3.187	1869
4		Dialysis *vs.* H_2O	4.95	3.199	1876
5		Dialysis *vs.* 0.5 *M* NaCl	5.38	3.604	1869
6	Bovine serum albumin	Dialysis *vs.* H_2O	5.05	4.740	1902
7		Dialysis *vs.* 0.1 *M* NaCl	5.35	5.219	1932
8		Dialysis *vs.* 0.5 *M* NaCl	5.31	4.634	1948
9		Dialysis *vs.* 0.1 *M* NaCl		3.495	1938
10		Dialysis of soln. No. 9 *vs.* H_2O		4.539	1919
11		Electrodialysis	5.25	2.223	1923
12		Electrodialysis + dialysis *vs.* 0.1 *M* NaCl	5.37	4.103	1943
13		Electrodialysis		4.891	1921
14		Electrodialysis + dialysis *vs.* 0.1 *M* NaCl		5.438	1941
15		Dialysis of soln. No. 14 *vs.* H_2O		6.424	1920
16	Human serum albumin	Dialysis *vs.* H_2O	4.85	3.424	1887
17		Dialysis *vs.* 0.5 *M* NaCl	5.26	2.262	1918

dinary water dialysis. Alcohol or decanol as the contaminant might satisfy these requirements.

Refraction Measurements in Buffer Solutions.—In the following interpretation of the refraction measurements in buffer solutions the assumptions have been made (a) that the refractions due to the various components are additive, (b) that the net charge on the protein may be obtained from the titration curve and (c) that the buffer electrolyte concentrations are given by the first term in the expansion of the Donnan equation. With the aid of these assumptions, together with the measured refractive increment, Δn-obsd., of the protein solution and that, $\Delta n'$-obsd., of the buffer solution against which it has been equilibrated, the specific refraction of the sodium proteinate has been computed as will be described in connection with Table VI. In that table, the concentrations, in equivalents per liter, of the buffer electrolytes in the dialysate, the *p*H of the protein solution in equilibrium therewith and the protein are given in the first four lines. The protein concentrations in line 5 marked with an asterisk were obtained by mixing weighed amounts of the buffer solution and the protein. Corrections were made not only for moisture content of the protein but also, by rapid weighing of the Cellophane bag and its contents before and after dialysis, for the rather large volume changes that occur during this process. In the case of the concentrations marked with a dagger a weighed sample of the equilibrated protein solution was dialyzed salt-free, transferred quantitatively to a volumetric flask and nitrogen determinations were made on weighed portions of this salt-free solution. It will be noted that the two methods of analysis lead to closely agreeing results for the specific refraction in the one instance where a comparison is possible, *i. e.*, columns III and IV of Table VI. In the phosphate buffers the protein concentration was obtained in the conventional manner since these buffer salts do not interfere with the nitrogen determination.

The sources of the values for the net charge, line 6 of Table VI, are given as footnotes whereas the equivalent concentration of the sodium proteinate, line 7, is simply $C_{NaP} = -10pe$. In the case of the diethylbarbiturate buffers the electrolyte concentrations in the protein solutions, lines 8 and 9, are given by the relations[17]

$$C_{NaR} = C'_{NaR} - {}^1/_2 C_{NaP} \text{ and } C_{HR} = C'_{HR}$$

whereas for the phosphate buffers[18]

$$C_{NaR} = C'_{NaR}\,(1 - 5C_{NaP}) \text{ and } C_{HR} = C'_{HR}\,(1 - 2.5C_{NaP})$$

Owing to small variations of the equivalent refraction with concentration and also to the difficulties of preparing some of the buffer salts for weighing, deviations of as much as 1×10^{-5} in the measured refractive increments of the buffer solutions from those computed by means of the relation

$$\Delta n' = K_{NaR} C'_{NaR} + K_{HR} C'_{HR}$$

have been observed. Here K is the equivalent refraction and, for the computations of Table VI, has been assigned the following values: sodium diethylbarbiturate, 0.04055; diethylbarbituric acid, 0.02905; Na_2HPO_4, 0.01502; and NaH_2PO_4, 0.0172. Correction for the deviations has been made by adding to the observed increment for the protein solution the small difference between the computed and observed increments for the buffer solution. The corrected values of the refractive index increment for the protein solutions are given in line 10 of Table VI.

The contribution of the buffer electrolytes to the

(17) Longsworth, *J. Phys. and Coll. Chem.*, **51**, 171 (1947).

(18) Svensson, *Arkiv. Kemi, Mineral. o. Geol.*, **22A**, No. 10, 27 (1946).

TABLE VI

THE SPECIFIC REFRACTIONS OF PROTEINS IN BUFFER SOLUTIONS

BSA = bovine serum albumin. HSA = human serum albumin. EA = egg albumin. LG = lactoglobulin.

		I	II	III	IV	V	VI	VII	VIII	IX	X
		R = diethylbarbiturate						R = $NaHPO_4^-$			
1	C′(NaR)	0.025	0.050	0.1	0.1	0.1	0.1	0.128	0.134	0.134	0.128
2	C′(HR)	0.005	0.01	0.02	0.02	0.02	0.02	0.008	0.008	0.008	0.008
3	pH	8.56	8.59	8.60	8.60	8.60	8.60	7.67	7.71	7.74	7.68
4	Protein	BSA	BSA	BSA	BSA	EA	LG	BSA	HSA	EA	LG
5	p − g./100 ml. soln.	2.010*	2.056*	1.9193*	5.024†	1.8115†	2.695†	3.4977	2.9943	2.3565	2.8324
6	$-e$	0.00038[a]	0.00038[a]	0.00038[a]	0.00038[a]	0.00032[a]	0.00051[b]	0.00027[a]	0.00027[c]	0.00027_5[a]	0.00043[b]
7	C(NaP) = $-10pe$	.00764	.00781	.00729	.01909	.00580	.01374	.00944	.00808	.00648	.01218
8	C(NaR)	.02118	.0461	.0963	.0905	.0971	.0931	.1220	.1286	.1297	.1202
9	C(HR)	.005	.01	.02	.02	.02	.02	.0078	.0078	.0079	.0078
10	Δn(obsd. − corr.)	.004986	.006323	.008291	.014179	.008087	.009800	.008665	.007767	.006520	.007297
11	Δn(NaR + HR)	.001004	.002160	.004486	.004251	.004518	.004356	.001966	.002066	.002084	.001939
12	Δn(NaP)	.003982	.004163	.003805	.009928	.003569	.005444	.006699	.005701	.004436	.005358
13	k(NaP)	.001981	.002025	.001982	.001976	.001970	.002020	.001915	.001904	.001882	.001892
14	k(NaP) $\mu \rightarrow 0$	$.001935$	$.001935$	$.001935$	$.001935$	.001902	.001909	$.001923$	.00191	$.001899$	$.001901$

[a] Interpolated from data of Table IV. [b] From Cannan, Palmer and Kibrick, *J. Biol. Chem.*, **142**, 803 (1942). [c] Cohn, Strong, Hughes and Blanchard, see Edsall, *Annals N. Y. Acad. Sci.*, **47**, 223 (1946).

increment of the protein solution is given by the relation

$$\Delta n(\text{NaR} + \text{HR}) = K_{\text{NaR}}C_{\text{NaR}} + K_{\text{HR}}C_{\text{HR}}$$

line 11 of Table VI, and the difference

$$\Delta n(\text{NaP}) = \Delta n - \Delta n(\text{NaR} + \text{HR})$$

line 12, divided by the protein concentration is the specific refraction of the sodium proteinate, line 13. For comparison, the values of k for the sodium proteinates in the absence of salt have been interpolated from the data of Table IV for the pH values of Table VI and are given in the last line of that table. It will be noted that the specific increment in the phosphate buffer is essentially the same as in the absence of salt whereas in the presence of the diethylbarbiturate it is significantly greater. Although several explanations for this observation could be advanced an attractive one is that this large organic ion is bound by the protein.

Comparison with Previous Work.—As a test of the validity of the differential prism method used in this research two of the salt solutions studied by Hölemann and his associates[19,20] have been prepared and their refractive increments determined over a sufficient range of temperature and wave length to permit a direct comparison with their results. At 25° and λ = 5876 Å., the increments for 1.6692 molal sodium chloride and 1.2983 molal potassium chloride are 0.015385 and 0.011906, respectively, and are in agreement with the values of 0.01538 and 0.01190 reported by Hölemann. Additional evidence that the precision of our refractive index measurements is about $\pm 1 \times 10^{-5}$ is afforded by the following fact. At 0.5° and λ = 5780, the refractions of the solutions of potassium chloride recently used in diffusion studies[21] follow, with an average deviation of $\pm 7 \times 10^{-6}$, the simple relation, $\Delta n/C = 0.011405 - 0.00100\sqrt{C}$, over the concentration range studied, *i. e.*, 0.1 to 1.0 normal.

(19) Hölemann and Kohner, *Z. physik. Chem.*, **B13**, 338 (1931).

(20) Shibata and Hölemann, *ibid.*, **13**, 347 (1931).

(21) Longsworth, THIS JOURNAL, **69**, 2510 (1947).

In the case of the specific refractions of proteins, however, the precision of the results is limited by the uncertainty in the protein concentration. As Armstrong, Budka, Morrison and Hasson have shown,[22] the presence of lipid in the protein renders particularly difficult the concentration determination. In the present research this source of error has been reduced by restricting our studies to proteins that contain minimal amounts of lipid and by controlling the nitrogen determinations with dry weight measurements. In spite of these precautions, however, in unfavorable cases the uncertainty in the protein concentration may amount to as much as one per cent. In some instances this is sufficient to mask the variation of the specific refraction from one protein to another or between different preparations of the same protein.

It is of interest that at 20° our values of the specific refraction of human albumin, 1862×10^{-6}, Fig. 1, and γ-globulin, 1875×10^{-6}, agree well with those, 186×10^{-5} and 188×10^{-5}, reported by Armstrong and associates. In the case of β-lactoglobulin, Pedersen reports[14] 1809×10^{-6} and 1812×10^{-6} as the specific refraction, at 20° and λ = 5799 Å., of two different preparations. In these measurements he used nitrogen factors of 6.61 and 6.55, respectively, that were obtained from nitrogen and dry weight determinations on aliquots of a solution of the protein in 0.5 molar sodium chloride. When analyzed similarly, our preparation of this protein gave a factor of 6.62, in essential agreement with Pedersen's values. However, when analyzed, as described earlier in this paper, in such a manner as to eliminate the uncertainty concerning the amount of salt in the dried residue, the nitrogen factor is 6.44. Correction of Pedersen's refraction data to this new factor gives $10^6 k$ = 1858 and 1843, in satisfactory agreement with our value of 1846 at 20°.

The authors are glad to acknowledge their indebtedness to D. A. MacInnes of these Laborato-

(22) Armstrong, Budka, Morrison and Hasson, *ibid.*, **69**, 1747 (1947).

ries for his interest in this research and for suggestions in the preparation of this paper.

Summary

With the aid of a hollow, prismatic cell and the optical equipment of the Tiselius electrophoresis apparatus, the refractive index increments of solutions of some purified proteins have been measured as a function of the protein concentration, the temperature, and the wave length of the incident light. The changes in the specific refractive increment that occur on titration of the protein with alkali, in the presence of neutral salts and after equilibration with buffers have also been determined. Such data are necessary for a quantitative interpretation of the electrophoretic patterns of proteins.

NEW YORK, N. Y. RECEIVED APRIL 22, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION]

Equilibrium of Iron–Carbon–Silicon and of Iron–Carbon–Manganese Alloys with Mixtures of Methane and Hydrogen at 1000°

BY RODNEY P. SMITH

Measurements of the equilibrium of iron–carbon alloys with mixtures of methane and hydrogen have been reported in an earlier paper.[1] Since most commercial steels contain various amounts of alloying elements, it is of considerable importance to know the effect of these additional elements on this equilibrium. Accordingly measurements were made of the carbon content of iron–silicon alloys containing up to 15% silicon and of iron–manganese alloys containing up to 15% manganese equilibrated at 1000°, with methane–hydrogen atmospheres of known composition. At this temperature the crystal structure of the silicon alloys may be either face-centered cubic (austenite or gamma iron) or body-centered cubic (ferrite or alpha iron) depending on the concentration of carbon and silicon. For these alloys measurements were made in the region in which austenite is stable and in the region in which ferrite is stable and an estimate is given of the phase boundaries in a portion of the isothermal section of the iron–silicon–carbon system. At 1000° the structure of the manganese alloys is austenitic at all compositions investigated. For the iron–manganese–carbon system an estimate is given of the position of the phase boundaries of the austenite–austenite+graphite and a portion of the austenite–austenite+carbide fields.

Experimental

The experimental procedure was similar to that previously described.[1] The dimensions of the samples used were about 1 × 1 × 0.4 cm. For each gas mixture a number of samples of either series of alloys and a sample of electrolytic iron were equilibrated simultaneously. The carbon content of samples containing more than 0.05% carbon were analyzed by the usual combustion method; those with less than 0.05% carbon by the low pressure combustion method described by Gurry and Trigg.[2] The silicon alloys were either milled or broken up in a steel mortar prior to combustion; the manganese alloys were burned without milling, 0.5 to 1.0 g. of Bureau of Standards sample 55b, 0.010% C, being added to start combustion.

The gas composition for each set of samples was derived from the carbon content of the electrolytic iron and the equilibrium data previously published[1] rather than from the analysis of the primary hydrogen–methane mixture and the flowmeter constants. This method has the following advantages: (1) an accurate knowledge of the composition of the primary hydrogen–methane mixture is not required; (2) it is not necessary to make corrections for the small deviations (less than ±1°) from 1000° of the furnace temperature. The minimum equilibration period was one week; that this time was sufficient was established by comparison of the analysis of the electrolytic iron, equilibrated together with a typical set of alloy samples using a primary mixture of known composition, with the results for pure iron–carbon alloys previously published.[1]

The silicon alloys of composition within the range 1.2 to 5.0% Si were commercial quality steels,[3] those between 7.0 and 15.0% Si were prepared from a high-grade ferrosilicon and electrolytic iron. Analysis of a sample of electrolytic iron and of the alloys containing 1.2 to 5.0% Si before and after equilibration with respect to carbon indicated a silicon pick up from the silica furnace tube of 0.02 to 0.06%. The results were not corrected for this small change in silicon content since its effect on the carbon concentration is nearly balanced by that of the manganese present in these alloys.

The manganese alloys were of commercial quality,[4] produced in a 250 lb. arc furnace. Since an alundum furnace tube was used in the equilibration of these alloys with respect to carbon, there was no change in their silicon content. There was, however, a small change in manganese content, that of the electrolytic iron increasing by 0.25%, that of the 14.67% Mn decreasing by 0.41%, the change in the other samples being nearly linear with the manganese content.

Results—Silicon Alloys

Equilibrium with Austenite.—The left portion of Table I gives the carbon content of the austenitic silicon alloys equilibrated with several CH_4–H_2 mixtures containing from 0.14 to 0.86% methane. The marked effect of silicon on this

(1) R. P. Smith, THIS JOURNAL, **68**, 1163 (1946).

(2) R. W. Gurry and H. Trigg, *Ind. Eng. Chem., Anal. Ed.*, **16**, 248 (1944).

(3) Analysis, C, 0.05–0.07; Mn, 0.2–0.3; P, 0.005–0.01; S, 0.01–0.02.

(4)

ANALYSES				
Mn	C	P	S	Si
3.92	1.50	0.015	0.014	0.03
6.48	1.64	.023	.011	.01
9.10	0.30	.040	.008	.19
12.87	0.94	.043	.010	.11
14.67	1.33	.040	.007	.09

TABLE I

CARBON CONTENT OF IRON–SILICON ALLOYS EQUILIBRATED WITH CH_4–H_2 MIXTURES AT 1000°: $r_1 = p_{CH_4}/p_{H_2}^2$, WHERE p IS IN ATMOSPHERES

Initial Si content weight per cent.	0	1.23	2.10	3.41	4.39	5.00	7.8	10.3	15.6
				Final carbon content, weight per cet.					
$r_1 \times 10^3$		Austenite				Ferrite			
1.42	0.308	0.261	0.223	0.023		0.016			
1.40	.306			.021		.016	0.009	0.003	0.003
3.24	.666	.572	.485	.394		.039			
3.08	.638					.036	.017	.006	.003
5.31	.995						.028	.011	.006
5.56	1.032	.880	.764	.619		.383			
8.45	1.390						.048	.020	.004
8.65	1.412	1.218	1.080	.866	.729	.658			

equilibrium is shown better in Fig. 1, in which the weight per cent. carbon at equilibrium at 1000°, for various gas ratios, $r_1 = p_{CH_4}/p_{H_2}^2$ is plotted against the weight per cent. silicon. For a given gas ratio the decrease in carbon for each per cent. increase in silicon is roughly 10% of the carbon content of pure iron. The activity of dissolved carbon is proportional to r_1, thus each line for a given value of r_1 represents an iso-activity line, with respect to carbon.

Austenite, Austenite + Graphite Boundary.—At the gas ratio, $r_1 = 0.00950$, the gas phase is in equilibrium with graphite.[1] Therefore the iso-activity line for $r_1 = 0.00950$ gives the boundary of the single phase austenite field and the two phase austenite + graphite field. This boundary, line FB in Fig. 1, was determined by extrapolating curves of r_1, plotted against weight per cent carbon for each silicon alloy to $r_1 = 0.0095$. It may be noted that the decrease caused by silicon in the solubility of graphite in gamma iron is similar to that found by Herty and Royer,[5] in the case of liquid iron (see Fig. 2). The solubility of graphite in austenitic silicon alloys as given in Fig. 1 is somewhat higher than that given by Charpy and Cornu-Thenard,[6] and considerably higher than that given by Becker.[7] The solubility of graphite in pure iron given by Becker is lower than the value given by more recent determinations and it is probable that his values for the silicon steels are also low.

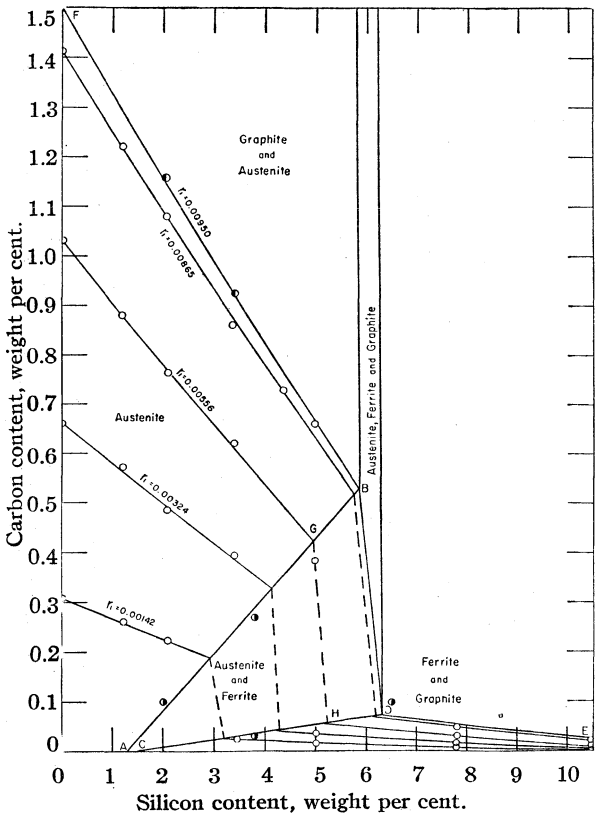


Fig. 1.—A portion of the iron–carbon–silicon equilibrium diagram at 1000°: O, experimental; ◐, extrapolated; ◑, "Alloys of Iron and Silicon"[12]; $r_1 = p_{CH_4}/p_{H_2}^2$.

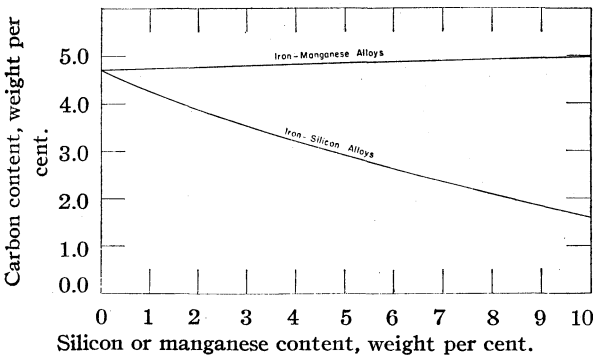


Fig. 2.—Effect of silicon and manganese on the solubility of graphite in iron at 1300° as given by Herty and Royer.[5]

Equilibrium with Ferrite.—The right portion of Table I gives the carbon content of the ferritic silicon alloys equilibrated with several CH_4–H_2 mixtures. These results are shown graphically in Figs. 1 and 5. The consistency of these results

(5) C. H. Herty and M. B. Royer, U. S. Bureau Mines, R. I. 3230 (1934).

(6) G. Charpy and A. Cornu-Thenard, *J. Iron Steel Inst.*, **91**, 276 (1915).

(7) M. L. Becker, *ibid.*, **112**, 239 (1925).

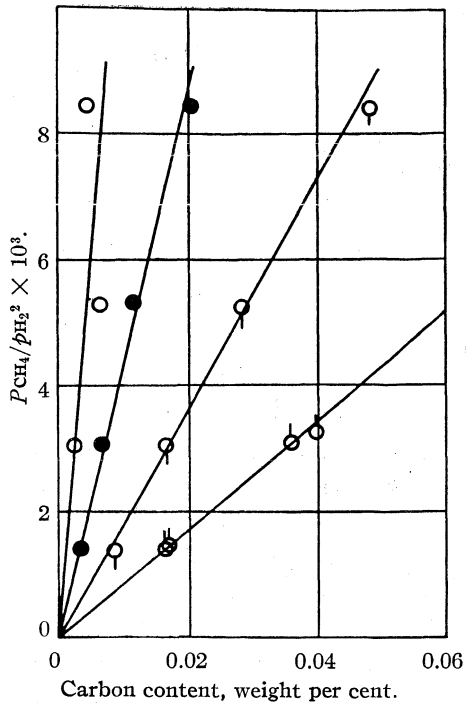


Fig. 3.—Carbon content of ferrite in relation to $p_{CH_4}/p_{H_2}^2$: ♂, 5.0% Si; ♀, 7.8% Si; ●, 10.3% Si; O, 15.6% Si.

may be illustrated better in the following manner. The activity of carbon is proportional to r_1, and its activity coefficient is inversely proportional to $\%C/r_1$ where $\%C$ is the weight per cent. carbon of a sample equilibrated with a gas whose $p_{CH_4}/p_{H_2}^2$ ratio is r_1. Since the carbon content of ferrite is always less than 0.08 weight per cent. it is reasonable to assume that, for a given silicon alloy, the activity coefficient of carbon is independent of the carbon concentration. The validity of this assumption is illustrated in Fig. 3 in which r_1 is plotted against weight per cent. carbon for the alloys containing 5.0, 7.8, 10.3 or 15.6% Si; the points fall on straight lines, within the experimental error, demonstrating that the system conforms to Henry's law, or the activity coefficient of carbon in these alloys does not change with the carbon concentration. The activity coefficient of carbon does, however, change appreciably with the silicon content for the range of concentration of 0 to 15% Si. In general log $\%C/r_1$, rather than $\%C/r_1$, will be a nearly linear function of %Si; thus if $\log \frac{\%C}{r_1}$ is plotted against weight per cent. silicon all points should fall on the same curve which will be either straight or nearly so. Fig. 4 shows such a plot; except for results for the alloy containing 15.6% silicon all the points fall on a straight line with ±10%. The curves of Fig. 5 represent smoothed results calculated from the straight line of Fig. 4 for the experimental values of r_1.

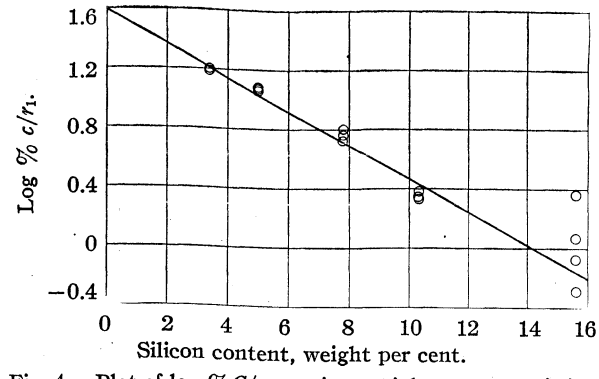


Fig. 4.—Plot of log $\%C/r_1$, against weight per cent. of silicon; $r_1 = p_{CH_4}/p_{H_2}^2$, % C = weight per cent. carbon.

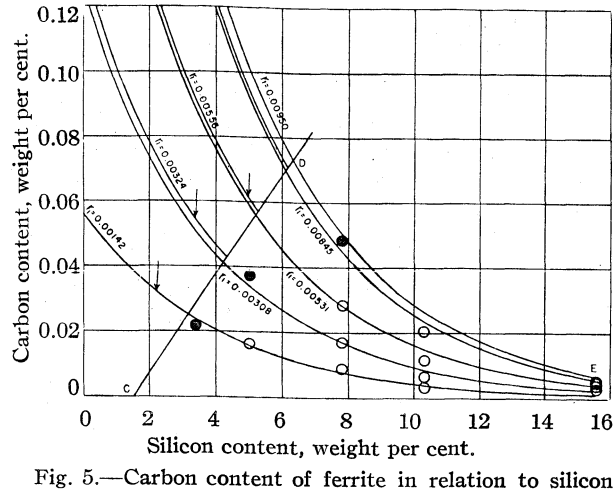


Fig. 5.—Carbon content of ferrite in relation to silicon content for various values of r_1 at 1000°: curves calculated from straight line of Fig. 4; O, ●, experimental points.

Extrapolation of the straight line, Fig. 4 to zero per cent. silicon allows the calculation of the hypothetical carbon content of alpha iron at 1000° for any given value of r_1; the corresponding carbon content of gamma iron is known,[1] thus a distribution coefficient for carbon between alpha iron and gamma iron may be calculated. The distribution coefficient, K, may be defined as

$$K = a_1/a_2 = \gamma_1 C_1/\gamma_2 C_2 \cong \gamma_1 C_1/C_2 \qquad (1)$$

where a_1 is the activity of carbon in gamma iron, when its concentration is C_1 weight per cent., a_2 is the activity of carbon in alpha iron, when its concentration is C_2 weight per cent., γ_1 and γ_2 are the activity coefficients of carbon in gamma iron and alpha iron, respectively. The standard state in each case is chosen so that the activity is equal to the weight per cent. when the latter approaches zero. The value of K at 1000° may then be compared with values calculated from the data of Smith[1] (at 800 and 1000°) and of Mehl and Wells[8] for the temperature range 723 to 849° and those of Adcock[9] at 1490° by the relation

(8) Robert Mehl and Cyril Wells, *Trans. Am. Inst. Mining Met. Engrs.*, **125**, 429 (1937).

(9) Frank Adcock, *J. Iron Steel Inst.*, **135**, 281 (1937).

$$\Delta H = -4.575 \, d \log K/(d1/T) \qquad (2)$$

where ΔH is the heat of transfer of carbon from alpha iron to gamma iron and T is the absolute temperature.

Since C_2 is always small, it is assumed that $\gamma_2 = 1$; γ_1 at 800 and 1000° may be determined from the deviation from Henry's law of the solid solution of carbon in gamma iron.[1] Within the experimental error γ_1 is the same at 800 and 1000° and in the calculation of K it is assumed to be independent of temperature. Fig. 6 shows a plot of log a_1/C_2 against $1/T$. The straight line through the points calculated from the data of Smith,[1] Mehl and Wells[8] and Adcock[9] gives 0.916 for log a_1/C_2 at 1000°. The value calculated from the equilibrium of CH_4–H_2 mixtures with austenite and the extrapolated value for ferrite, Fig. 4, is 0.826. Considering the uncertainties in each method of calculation, the agreement is satisfactory. The heat of transfer of carbon from alpha iron to gamma iron determined by equation (2) is −15,600 cal. per gram atom.[10] It may be noted that the quantity $RT \ln (3N_1/N_2)$ where N_1 and N_2 are the equilibrium atom fractions of carbon in gamma iron and alpha iron, respectively, which is considered constant with temperature by Zener,[11] varies from 9000 to 5400 cal. per mole for the temperature range 800 to 1490°.

Ferrite, Ferrite + Graphite Boundary.—The solubility of graphite in silicon ferrite, line DE, Figs. 1 and 5, was determined from the straight line of Fig. 4 and $r_1 = 0.0095$, the value for equilibrium of the gas phase with graphite.[1]

Ferrite, Ferrite + Austenite Boundary.—For the binary iron–silicon system the limit of the ferrite field at 1000° is 1.5% silicon.[12–14] This locates one terminus, C, in Fig. 1, of the boundary between the ferrite and the ferrite + austenite fields, line CD Fig. 1, for the three component system. Other points on this boundary, may be estimated in the following manner. In Fig. 5 the circles represent experimental data when the solid phase is ferrite, the vertical arrows indicate samples whose carbon content is too great for the solid phase to be ferrite for the particular value of r_1. The boundary between the ferrite and the ferrite + austenite fields lies at compositions to the right of those represented by the vertical arrows and to the left of the solid circles and is best represented by the straight line, CD Fig. 5, starting at 1.5%Si, 0%C, and which averages the difference in composition of points known to be in the ferrite field and those known to be in the austenite or austenite + ferrite fields. The other terminus of this boundary line is given by the intersection of line CD, Fig. 5, with the curve for $r_1 = 0.0095$. This intersection gives the composition for one corner of the three phase, austenite, ferrite, graphite, triangle. The position of the boundary is in fair accord with the best estimate from previous results.[12]

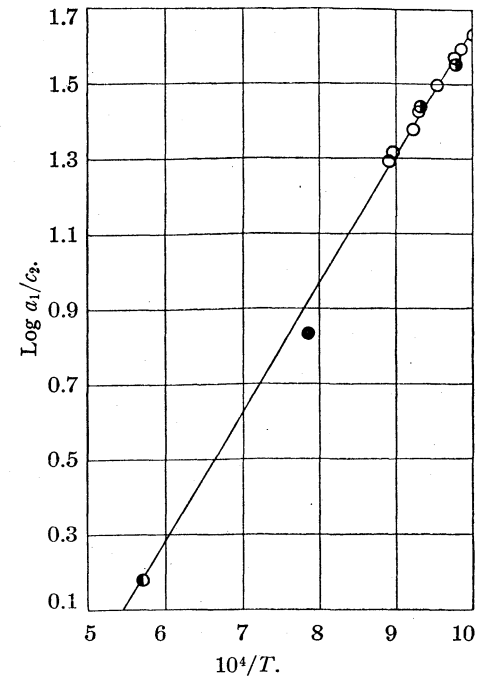


Fig. 6.—Plot of log a_1/C_2 against $10^4/T$: ◑, Smith[1]; ●, extrapolation of data for silicon alloys; ○, Smith,[1] Mehl and Wells[8]; ◐, Adcock.

Austenite, Austenite + Ferrite Boundary.—One terminus of this boundary, line AB, Fig. 1, is at 0%C, 1.3%Si.[12–14] A second point on this boundary may be estimated in the following manner. The carbon content, 0.383%C of the 5.0% silicon sample for $r_1 = 0.00556$ is below that of the smooth curve through the other points, Fig. 1, in the austenite field by an amount considerably greater than the probable experimental error. It is therefore reasonable to assume that this point lies in the austenite + ferrite field. The composition of ferrite at the ferrite, ferrite + austenite boundary in equilibrium with the gas mixture $r_1 = 0.00556$ is 0.057%C and 5.25%Si. The gross composition of all mixtures of ferrite and austenite in equilibrium with a gas of this composition will lie on a straight line, GH Fig. 1 (an isoactivity line with respect to carbon), through these two points. The intersection, G Fig. 1, of this straight line with the curve, $r_1 = 0.00556$, through the points in the austenite field gives a second point on the austenite, austenite + ferrite boundary. From these data the boundary may be represented by a straight line through points A and G, the other terminus will be at the intersection of this line with the austenite–graphite boundary. Although

(10) This result is in good agreement with the value −15,900 cal. given by the difference in heat of solution of graphite in alpha iron and gamma iron.[1]

(11) C. Zener, *Trans. Am. Inst. Mining Metal Engrs.*, **167**, 513 (1946).

(12) Greiner, Marsh and Stoughton, "Alloys of Iron and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1933.

(13) R. L. Rickett and N. C. Fick, *Trans. Am. Inst. Mining Met. Engrs.*, **167**, 346 (1946).

(14) C. Zener, *ibid.*, **167**, 354 (1946).

the location of this boundary depends mainly on a single experimental point, it agrees well with previous estimates,[12] especially in the range 1.3 to 4% silicon.

The Activity of Carbon Relative to Graphite.—The activity, a_c, of carbon relative to graphite is given by the equation

$$a_c = p_{CH_4}/p_{H_2}^2 K_3 = r_1/K_3 = r_1/0.0095 \quad (3)$$

where K_3 is the equilibrium constant for the reaction $2H_2 + C$ (graphite) $= CH_4$.[1] Table II gives values of a_c at 1000° for austenitic silicon alloys interpolated to even values of the concentration of carbon and silicon.

TABLE II

THE ACTIVITY OF CARBON, RELATIVE TO GRAPHITE IN AUSTENITIC IRON SILICON ALLOYS AT 1000°

	%Si				
%C	0.2	0.4	0.6	0.8	1.0
0	0.097	0.195	0.301	0.424	0.563
1	.107	.226	.358	.507	.674
2	.127	.267	.427	.607	.810
3	.157	.334	.533	.762	
4	.197	.415	.662	.945	

Values of a_c for ferritic silicon alloys may be calculated from the equation of the straight line in Fig. 4 and the equilibrium constant K_3 by the equation

$$-\log a_c = 1.60 - 0.113\ (\%Si) + \log K_3/\%C \quad (4)$$

where 1.60 is the intercept of the straight line at zero silicon and −0.113 is its slope.

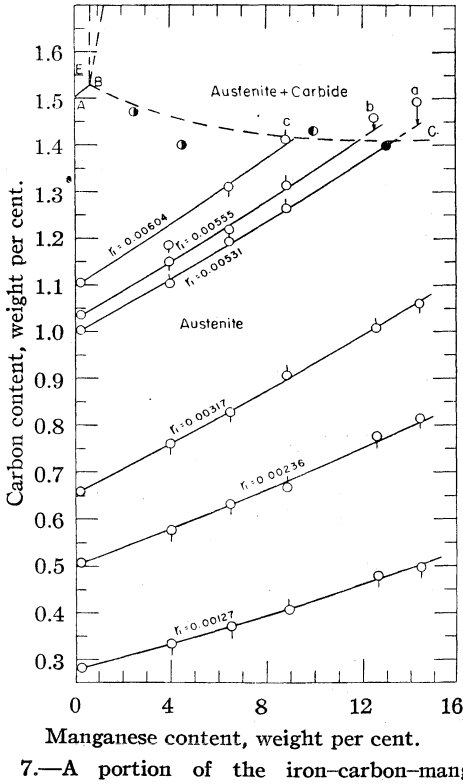


Fig. 7.—A portion of the iron–carbon–manganese equilibrium diagram at 1000°: ♁, equilibrium by carburization; ♀, equilibrium by decarburization; ◑, Gensamer[15]; ◐, Eckel and Krivobok[16]; ●, Wells and Walters[17]; $r_1 = p_{CH_4}/p_{H_2}^2$.

Results—Manganese Alloys

Equilibrium with Austenite.—The experimental results for equilibrium of CH_4–H_2 mixtures with iron–manganese alloys containing from 0 to 15% Mn, are given in Table III and shown graphically in Fig. 7. For a given gas atmosphere the carbon content increases markedly with increase in manganese. A similar, but less pronounced, effect has been observed in the case of the solubility of carbon in liquid iron–manganese alloys[5] (see Fig. 2).

TABLE III

CARBON CONTENT OF IRON–MANGANESE ALLOYS EQUILIBRATED WITH CH_4–H_2 MIXTURES AT 1000°

$r_1 = p_{CH_4}/p_{H_2}^2$ where p is in Atmospheres

	Initial manganese, weight Mn per 100 g. of Fe + Mn					
	0	4.04	6.54	8.95	12.69	14.52
$r_1 \times 10^3$	Final carbon content, weight per cent.					
1.27	0.277	0.333	0.371	0.406	0.478	0.495
2.36	.501	.576	.632	.667	.775	.815
3.17	.653	.760	.827	.906	1.009	1.061
5.31	.996	1.102	1.193	1.264		1.493
5.55	1.029	1.148	1.219	1.313	1.458[a]	
6.04	1.096	1.184	1.312	1.413		
9.45	1.496	1.861				

[a] Microscopic examination of a polished sample indicated carbide at temperature.

The consistency of these results may be illustrated better by a plot suggested by the semi-empirical equation

$$\log r_1/N_2 + 1.86\ (1 - N_2)^2 = kN_3\ (1 - N_2) + I \quad (5)$$

where N_2 and N_3 are the atom fractions of carbon and manganese respectively at equilibrium with a gas atmosphere whose $p_{CH_4}/p_{H_2}^2$ ratio is r_1; k and I are constants. If this relation is valid all the experimental points should fall on one straight line when the left side of equation (5) is plotted against $N_3\ (1 - N_2)$. Such a plot is shown in Fig. 8, and

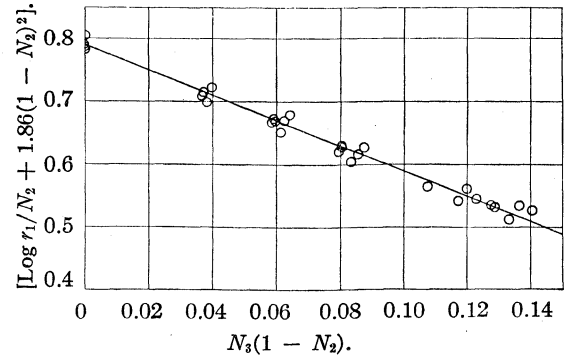


Fig. 8.—Plot of $\log r_1/N_2 + 1.86\ (1 - N_2)^2$ against $N_3\ (1 - N_2)$: $r_1 = p_{CH_4}/p_{H_2}^2$; N_2 = atom fraction of carbon; N_3 = atom fraction of manganese.

since there is no consistent deviation from a straight line it would appear that equation (5) is valid in this system within the experimental error. The greater number of the points fall on the straight line within ±5%. The slope of this line (k) is −2.05 and the intercept, I, at $N_3 (1 - N_2) = 0$ is 0.792.

Austenite, Graphite + Austenite Boundary.—It has been shown that equation (5) is valid, within the experimental error, for $r_1 = 0.0013$ to 0.006 and it is not unreasonable to assume that it also holds for $r_1 = 0.0095$, the value for equilibrium with graphite.[1] The concentration of carbon at this boundary when $N_3 = 0$ given by equation (5) is 1.47 weight per cent. A better estimate of this value, determined from a consideration of several investigations, is 1.50 weight per cent. carbon.[1] The boundary, line AB, Fig. 7, is drawn parallel to the line given by equation (5) but higher in carbon by 0.03 weight per cent. The other terminus of this line will be its intersection with the line representing the austenite, austenite + carbide boundary.

Austenite, Austenite + Carbide Boundary.—The limiting solubility of carbide in pure iron–manganese alloys has been determined by microscopic examination of quenched samples for 2.5 and 4.5% Mn alloys by Gensamer,[15] for a 10% Mn alloy of Eckel and Krivobok,[16] and for a 13% Mn alloy by Wells and Waters[17]; also for commercial quality alloys of the same range of composition by Bain, Davenport and Waring.[18] These two sets of measurements do not agree too well as to the carbide solubility but do give the same general form for the solubility curve at a given temperature. Since manganese forms an orthorhombic carbide, Mn_3C, which is isomorphous with cementite, Fe_3C, and apparently forms a continuous series of solid solutions with it,[19] it is to be expected that the extension of the solubility curve to zero Mn will intersect the carbon axis at the composition of gamma iron in equilibrium with cementite, E, Fig. 7. The boundary, line BC Fig. 7, is estimated from these data. While our equilibrium data are not sufficiently extensive to establish this boundary it may be shown that they are consistent with it. Point a, Fig. 7, has a carbon content considerably higher than that indicated by the smooth curve through the points in the austenite field and may be assumed therefore to be in the austenite + carbide field, and the boundary at 14.3% Mn must lie below 1.44%C (extension of the austenite curve to 14.3% Mn, indicated by arrow). Likewise at 12.5% Mn, point b, the boundary lies at a carbon content below 1.43%C.[20] Within the experimental error, point c, 8.84% Mn, 1.413%C, is on the smooth curve through the points for $r_1 = 0.00604$ and is therefore considered to be in the austenite field. Thus the boundary for 9 to 15% Mn lies between 1.40 and 1.43% carbon, which is consistent with the boundary as determined from microscopic examination of quenched alloys.

Activity of Carbon Relative to Graphite.—The activity, a_c, of carbon relative to graphite in austenitic iron manganese alloys is given in Table IV. The method of calculation was identical with that described for austenitic silicon alloys.

TABLE IV

THE ACTIVITY OF CARBON, RELATIVE TO GRAPHITE, IN AUSTENITIC IRON–MANGANESE ALLOYS AT 1000°

	% Mn					
%C	0.2	0.4	0.6	0.8	1.0	1.2
0	0.097	0.195	0.301	0.424	0.563	0.720
2	.085	.175	.277	.391	.521	.665
4	.078	.161	.253	.358	.479	.616
6	.071	.148	.233	.328	.441	.569
8	.065	.137	.214	303	.405	.526
10	.060	.127	.198	.280	.373	.484
12	.055	.117	.183	.258	.347	.445
14	.050	.107	.167	.237	.318	.408

Summary

The carbon content of several iron–silicon alloys (1.2 to 15% Si) and of a number of iron–manganese alloys (4.0 to 14.5% Mn) in equilibrium with various mixtures of methane and hydrogen of known composition at 1000° has been determined. For the silicon alloys the measurements cover both the region in which the crystal structure is face-centered cubic (austenite) and body-centered cubic (ferrite).

The activity of carbon, relative to graphite, is given for each system.

An estimate is given of the phase boundaries in a portion of each of the two three component systems. The phase boundaries determined by equilibrium measurements are in good agreement with those determined by others by microscopic methods.

KEARNY, N. J. RECEIVED MARCH 30, 1948

(15) M. Gensamer, *Trans. Am. Soc. for Steel Treating*, **21**, 1028 (1933).

(16) John Eckel and V. N. Krivobok, *ibid.*, **21**, 846 (1933).

(17) Cyril Wells and Francis Walters, Jr., *ibid.*, **21**, 830 (1933).

(18) E. C. Bain, E. S. Davenport and W. S. N. Waring, *Trans. Am. Inst. Mining Met. Engrs.*, **100**, 228 (1932).

(19) J. B. Austin, *Trans. Am. Soc. Metals*, **38**, 28 (1947).

(20) The presence of carbide in this sample was confirmed by microscopic examination.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

The Chemical Isolation of Samarium from Lanthanide Mixtures[1]

BY A. F. CLIFFORD AND H. C. BEACHELL

In efforts to separate the rare earth elements from each other a number of workers have successfully reduced from solution and isolated the elements europium[2] and ytterbium[3] in the divalent state. Samarium, however, has proved to be much more difficult to reduce in solution, although Marsh[4] has reported preparation of samarous compounds by dissolution of samarium amalgam in dilute acid and also by the simultaneous reduction of samaric and europic compounds in the presence of sulfate to precipitate the divalent ions. However, Marsh apparently found the reduction of samarium directly to the divalent state in the absence of europium to be extremely difficult.

In order to utilize the well-characterized divalency of samarium in its separation, it was proposed to employ a non-aqueous solvent to slow up the reoxidation of the divalent samarium by hydrogen ion. Inasmuch as the rare earth trichlorides are fairly soluble in ethanol and the dichlorides, like barium chloride, are reasonably insoluble, the chlorides were selected as the most likely to lead to a successful reduction. Most other rare earth salts were automatically ruled out because of insufficient alcohol-solubility in the trivalent state (fluorides, sulfates, acetates, etc.) or excessive solubility in the divalent state (iodides, etc.).

Experimental and Discussion

Preliminary experiments were carried out with a dilute solution of pure samarium trichloride (hydrated salt) (in which only faint traces of europium were detectable spectroscopically) in absolute ethanol containing a few drops of aqueous 12 *N* hydrochloric acid. It was found that when pieces of zinc, manganese, aluminum (in the presence of mercuric chloride), beryllium, thorium (which contained considerable carbide) and magnesium were added, although all reacted vigorously, only on the magnesium was there evidence of production of samarous chloride, $SaCl_2$. On the magnesium a deep red solid material formed, turning brown and disappearing when the acid became exhausted. Attempts to use calcium lithium and sodium were unsuccessful.

Identification of the substance as samarous chloride was based on its color,[5] its solubility in water to give momentarily a Bordeaux red solution,[6] its metathesis by aqueous sulfuric acid to a water-insoluble orange sulfate,[7] which was slowly dissolved and destroyed by aqueous acids, and by its metathesis by alcoholic ammonium or sodium hydroxide to a green compound,[8] insoluble in ethanol but soluble in the polar solvent formamide (with decomposition), as would be expected of a pseudo-alkaline earth hydroxide. Samarous chloride was observed to dissolve in formamide to yield momentarily a deep green solution. Since the formamide had not been especially purified, this was probably samarous hydroxide or some basic samarous salt. Also, by metathesis with aqueous solutions of the appropriate alkali salts, were prepared the fluoride (deep brownish or purplish red, water insoluble), the citrate (orange, insoluble in, but unstable to, water) and the carbonate (brownish-orange, water-insoluble). These preparations show that the green compound which Holleck[8] reported as being either "carbonate or hydroxide" was in fact the hydroxide.

Metathesis of samarous chloride with ethanolic hydrogen peroxide or formic acid or aqueous oxalate or iodate resulted in immediate oxidation of the samarous ion, in the last case with reduction of the iodate to iodine.

It was found possible to obtain an unstable orange suspension of samarous sulfate, $SaSO_4$, by treating aqueous samarium chloride containing 5–10% ethanol with magnesium and a little sulfuric acid or better by treating a solution of samaric chloride and magnesium sulfate in 1:1 aqueous methanol with magnesium and a little hydrochloric acid. This approach had the dual disadvantage of the instability of the divalent sulfate and the low solubility of the trivalent sulfate.

It was observed also that samarous sulfate was produced by magnesium amalgam in neutral or slightly acid aqueous sulfate solutions. Likewise magnesium amalgam produced samarous chloride in neutral ethanolic chloride solutions. Both reactions, however, were complicated by simultaneous precipitation of trivalent hydroxides. Thorium amalgam had no effect on an ethanol solution from which magnesium amalgam would precipitate samarous chloride.

It was decided that the optimum conditions for reduction could be obtained by using a 50–50 mixture of dioxane with ethanol saturated with strontium and barium chlorides. (The reduction was found to be successful also in acetone and isopropanol.)

Using commercial didymium chloride or chloride prepared from didymium carbonate—both being chlorides of the mixed rare earths minus cerium in the proportion in which they occur in monazite) containing about 3% samarium, and the ethanol–dioxane solvent described above, a saturated solution of the trichlorides was made. To this were added magnesium and sufficient aqueous 12 *N* hydrochloric acid to give a vigorous reaction on warming gently. When the magnesium was completely coated with red samarous chloride the mixture was cooled to allow the magnesium to settle and the liquor decanted. The product was washed with 1:2 ethanol–acetone saturated with alkaline earth chlorides (found to destroy the samarous chloride less rapidly than ethanol–dioxane). The process was repeated several times with fresh magnesium, replenishing the acid as required. From time to time it was necessary to boil the solution to near dryness and redissolve to get rid of the accumulated water. The process was brought to a halt when the magnesium content rose to the point where mixed magnesium–rare earth chlorides began to crystallize out. (This series of salts

(1) From a thesis presented by A. F. Clifford to the faculty of the University of Delaware in partial fulfilment of the requirements for the M. S. degree, September, 1947.

(2) Yost, Russell and Garner, "The Rare Earth Elements and Their Compounds," John Wiley and Sons, Inc., New York, N. Y., 1947; Yntema, THIS JOURNAL, **52**, 2782 (1930); Jantsch, Alber and Grubitsch, *Monatsh.*, **53–54**, 305 (1929); McCoy, THIS JOURNAL., **57**, 1756 (1935); **58**, 1577 (1936); **58**, 2279 (1936); W. Pearce, master's thesis, University of Illinois, 1931 (quoted by Yost, Russell and Garner, p. 65).

(3) Ball and Yntema, THIS JOURNAL, **52**, 4246 (1930); Marsh, *J. Chem. Soc.*, 1367 (1937); Pearce, Naeser and Hopkins, *Trans. Electrochem. Soc.*, **69**, 557 (1936).

(4) Marsh, *J. Chem. Soc.*, 531 (1943).

(5) Matignon and Cazes, *Ann. chim. phys.*, [8] **8**, 417 (1906).

(6) Yost, Russell and Garner, ref. 2.

(7) Jantsch and Skalla, *Z. anorg. allgem. Chem.*, **193**, 391 (1930).

(8) Holleck, *Atti X° congr. intern. chim.*, **2**, 671 (1938).

apparently has minimum solubilities in alcohol for the lightest rare earths.) The collected product in dilute hydrochloric acid solution was analyzed spectrophotometrically for samarium and neodymium. By comparison of the two values, the samarium content was found to have been increased from 3 to about 30% of the total rare earths. A reprocessing of the product further increased the samarium content (on the same basis) to 74%.

Using ethanol without dioxane and bubbling in hydrogen chloride gas instead of using the aqueous acid, the reduction was repeated with somewhat better separation. Too high a hydrogen chloride concentration was found to prevent the formation of samarous chloride, but when only sufficient gas was present to cause gentle evolution of hydrogen from the magnesium, samarous chloride formed readily on the metal. Using the didymium chloride previously described, after a short initial period of reaction, a suspension of particles of free samarous chloride began to appear. The free samarous chloride thus formed was stable in the medium and could be readily centrifuged down. One batch of solid samarous chloride was observed to be apparently unchanged after being in contact with this liquid for twenty-four hours. It was possible to wash the free salt with acetone without much oxidation, but not with ethanol. This product was of greater purity, as regards rare earths, than that of the previous run, the first product in this case having better than 55% samarium as compared with 30% in the former case.

It was found that addition of dioxane under these conditions resulted in an orange-colored product much more sensitive to hydrogen chloride concentration. The use of dioxane in the anhydrous method was therefore considered undesirable.

It was attempted to reduce samarium out of similar solutions containing all the rare earths in their ratio in monazite sand (cerium about 48%, samarium 1–2%). The material used contained considerable iron. Neither hydrous nor anhydrous reduction was successful. However, when the material was freed from iron and the ethanolic solution diluted with more than an equal volume of dioxane, the hydrous method did give a reduced samarium compound. The compound obtained, however, was not the expected red chloride but the green hydroxide, even with fairly large quantities of hydrochloric acid. That this compound was the hydroxide, or at least a basic salt, was strongly indicated by the fact that it was metathesized by ethanolic hydrogen chloride to the red samarous chloride. Furthermore, it had previously been observed that in solutions containing too much water for formation of samarous chloride, a very thin film of greenish material formed on the surface of the reacting magnesium where presumably the hydrogen ion concentration was depleted.

No reduction was obtained from these solutions by the anhydrous method even with iron-free material. This particular reaction is probably of no use as a separation method due to the tendency of the trichlorides to crystallize out of the dioxane solution, but may be of use as a qualitative test.

Specific tests on more concentrated samarium solutions showed that the presence of iron in small quantity, although apparently making reduction more difficult, did not completely prevent reduction. Much more harmful was the presence of platinum. Reduction was never obtained in a solution which had contained platinum even after repeated reduction by magnesium and centrifuging out of the platinum metal. Apparently very minute traces of platinum (presumably under these conditions colloidal metal) catalyzed the reverse reaction, the oxidation of samarous by hydrogen ion, faster than the samarium could be reduced. The effect of colloidal metals on similar reductions has already been noted by Marsh.

The specificity of magnesium (E_0 = 2.3 v.) in the reaction and the inability of thorium (E_0 = *ca.* 2.0 v.) to perform the reduction seem to place the normal oxidation potential for the samarous–samaric couple in ethanolic chloride solution between 1.9 and 2.3 v.

Compared with Laitinen's[9] experimental result of 1.15 v. for the ytterbous–ytterbic couple (for which Latimer[10] estimated 0.6 volt) a potential around 2 v. is much more likely than Latimer's estimate of 0.8 v. The extreme sensitivity to even the small hydrogen-ion concentration in absolute ethanol would appear to support the evidence for this high potential. It should be noted that this is somewhat greater than the normal reduction potential which would be deduced from the first wave of Noddack and Bruckl's[11] polarographic reduction of aqueous samarium sulfate—E_0 = 1.72 v.

Considering the relative reduction potentials of samarium, ytterbium, and europium, it becomes apparent that the first batch of samarium reduced should carry with it all the europium and ytterbium in the solution in the same way as their concentration by sulfate precipitation has been reported by Marsh, thus affording a very convenient means of concentrating these elements to the point where they can be separated from the samarium by the methods already reported in the literature. It is highly possible that thulous chloride, $TmCl_2$, can be prepared from thulium concentrates in the same way.

Acknowledgments.—We should like to express our gratitude to the Wolff–Alport Chemical Corp. of New York, and especially to the Lindsay Light and Chemical Company of Chicago for their very generous contributions of rare earth concentrates for this research.

Summary

Samarium has been separated from the other rare earth elements (except europium and ytterbium) by reduction of ethanolic solutions of rare earth trichlorides with magnesium and hydrochloric acid (aqueous or anhydrous), yielding red samarium dichloride, $SaCl_2$. Using aqueous hydrochloric acid and diluting largely with dioxane, even from very low samarium concentrations green samarous hydroxide is produced directly instead. This reaction may be of significance for qualitative detection of samarium. By metathesis of the dichloride, the sulfate (previously prepared), the hydroxide, citrate, carbonate and fluoride (new compounds), all water-insoluble, have been prepared. The poisoning effect of iron and particularly platinum on the reduction has been noted. In neutral ethanolic solution, samarous chloride was precipitated by magnesium amalgam. The reaction, however, was complicated by hydroxide precipitates. In neutral aqueous sulfate solution, samarous sulfate was likewise precipitated by magnesium amalgam, with the same complications. Addition of a little methanol in the last case aided the reaction. The potential for the samarous–samaric couple in ethanolic chloride solutions has been placed in the region of 1.9–2.3 v.

NEWARK, DELAWARE RECEIVED FEBRUARY 18, 1948

(9) Laitinen, THIS JOURNAL, **64**, 1133 (1942); Laitinen and Taebel, *Ind. Eng. Chem., Anal. Ed.*, **13**, 825 (1941).

(10) Latimer, "Oxidation Potentials," Prentice–Hall, Inc., New York, N. Y., 1938.

(11) Noddack and Bruckl, *Angew Chem.*, **50**, 362 (1937).

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Long Range Enzymatic Action on Films of Antigen

BY ALEXANDRE ROTHEN

The work reported here deals with the mode of action of two proteolytic enzymes, trypsin and pepsin, as well as that of the specific enzyme capable of depolymerizing the polysaccharide from Type III pneumococcus. This is a logical continuation of work previously published[1] on reactions between films of antigen and antibody molecules, where it was shown that specific forces between antigen and antibody seemed to extend considerably in space. In these experiments antigenic protein films were spread on water from which they were transferred onto polished metal slides. The slides were then coated with blankets of various inert materials and finally a drop of dilute solution of the corresponding immune serum was spread over each blanket. After the slide was washed, specific adsorption of antibody could be detected, the amount of which decreased regularly with the increase in thickness of the blanket. The probability that the antibody molecules reached the antigenic layers by diffusing through the blanket was for several reasons considered to be remote. The conclusion was therefore reached that the antibody molecules might actually be held on top of the slide by specific forces extending through the thickness of the blanket.

The analogy between immunological and enzymatic reactions naturally led to the question whether enzymes might not also exert their action through a blanket. In this case the interaction would be of such a nature as to bring about the breakdown of substrate molecules. Therefore, the film technique was extended to investigate possible long range enzymatic action.

When a slide covered with one or many monolayers of protein antigen is treated with a homologous immune serum, a specific adsorption of antibody occurs. However, no such adsorption takes place if the layers have been first treated for a few seconds with a pepsin or trypsin solution at the proper *p*H. Similarly, a monomolecular layer of the polysaccharide from Type III pneumococcus will adsorb a considerable thickness of homologous antibody but is no longer able to do so after being treated briefly with a solution of the enzyme which depolymerizes the polysaccharide. Thus the immunological reaction occurring between films of antigen and antibody molecules may be utilized as a very convenient and highly sensitive detector of enzymatic action.

The experiments devised to detect a long range enzymatic action were very simple. The antigenic layers—bovine albumin or polysaccharide from Type III pneumococcus—were deposited on a metal slide and coated with a screen of inert material, such as barium stearate or formvar (a formaldehyde polyvinyl polymer). A drop of the appropriate enzyme solution was then spread on the screen and allowed to remain for five to ten minutes. After the enzyme solution was washed off, the slides were treated directly with homologous antibody and the increase in thickness which followed was compared to that obtained on a screen of similar thickness when no enzyme treatment had been applied. (Advantage is thus taken of the long range interaction between antigenic films and antibody molecules to disclose a possible long range enzymatic action on the antigen films.) A far more satisfactory method, however, was to dissolve away the blanket after the enzyme treatment, and then to apply the antiserum directly on to the antigenic layers. It was found possible to remove formvar films with ethylene dichloride without impairing the immunological reactivity of either the protein antigen films or the adsorbed polysaccharide molecules underneath. The removal of the barium stearate screens was more difficult to carry out and was always accompanied by a partial loss of the immunological reactivity of the layers.

The experiments showed indeed, as reported in two preliminary notes,[2] that enzymatic action takes place in spite of an intervening blanket and that this action does not appear to result from actual diffusion of the enzyme molecules through the blanket. If our conclusions are correct it means that no intimate contact between substrate and enzyme molecules is necessary for the enzymatic action to proceed. This is of fundamental importance from a physical as well as from a biological point of view.

Experimental

The technique used in this work is essentially the same as that described in the preceding paper[1] dealing with immunological reactions. The thickness of transferred or adsorbed films was determined optically by measuring the change that occurs in the ellipticity of polarized light after reflection from a film coated slide. The instrument developed for this purpose is the ellipsometer, which is characterized by a half shadow end-point made possible by reference films deposited on the slides to serve as optical gage.[3] Previous papers[1-3] should be consulted for the description of this instrument as well as for the experimental details concerning the preparation of the optical gages and their conditioning with uranyl acetate, the spreading of films and their transfer onto metal slides, the deposition of the blankets or screens, the treatment with antisera, the washing of the slides, and the optical measurement of the film thickness.

Enzymes.—Crystalline pepsin and crystalline trypsin in concentrations of 0.04% with respect to protein were used, unless otherwise stated. The samples of crystalline trypsin contained 60% magnesium sulfate. Pepsin was

(1) A. Rothen, *J. Biol. Chem.*, **168**, 75 (1947).

(2) A. Rothen, *ibid.*, **163**, 345 (1946); **167**, 299 (1947).

(3) A. Rothen, *Rev. Sci. Instruments*, **16**, 26 (1945).

dissolved in 0.02 *M* hydrochloric acid and trypsin in a veronal buffer *p*H 7.5 (0.05 *M*). The solution containing the depolymerase for the polysaccharide was of unknown concentration but a range of dilutions from one to five were used.[4] The medium was a phosphate buffer *p*H 7.2.

Antisera.—Antisera were diluted 0.1 with a phosphate buffer *p*H 7.2 containing 1% sodium chloride as described previously. Rabbit antibovine albumin sera and rabbit and horse antipneumococcus Type III sera were used.

Bovine Albumin Films—Antibovine Albumin Rabbit Sera. Pepsin Action.—Two to six unfolded monolayers of bovine albumin were transferred onto slides covered with an uranyl conditioned optical gage of one and three (or two and four) monolayers of barium stearate. A drop of pepsin solution deposited on the layers for one minute brought about a decrease in thickness from 8 to 30 Å. depending on the number of monolayers of bovine albumin. No increment in thickness occurred after subsequent treatment with homologous antiserum, which demonstrated that the remaining unfolded antigen films had been completely inactivated by the enzyme. A solution of 0.02 *M* hydrochloric acid alone could detach in one minute all layers transferred onto a slide except the first two. In this case, however, these remaining layers were not inactivated, as was indicated by an increase in thickness of 60 Å. after homologous antiserum treatment. When a blanket of one double layer of barium stearate about 50 Å. thick was deposited on two transferred double layers of bovine albumin, no change in thickness resulted from pepsin treatment and no adsorption of antibody occurred on subsequent antiserum treatment. If a drop of 0.002 *M* hydrochloric acid was substituted for the pepsin–hydrochloric acid solution, the antiserum treatment produced an increment of 40 Å. Similarly, slides with three double layers of bovine albumin coated with two double layers of barium stearate exhibited significant differences between those treated with hydrochloric acid alone and those treated with pepsin. A layer of antibody about 40 Å. thick could be adsorbed on the hydrochloric acid treated slide, but no change or even a considerable decrease in thickness occurred on the pepsin treated slides.

These experiments demonstrate that pepsin solutions are capable of destroying, through at least two double layers of barium stearate, the specific capacity of bovine albumin layers to react with antibody molecules. The fact, however, that the acid medium used for dissolving the pepsin is by itself capable of detaching some of the antigenic layers from the slides, made this enzyme unsuitable for a systematic research on account of the difficulty in differentiating the true enzymatic action from that of the medium.

Trypsin Action.—Trypsin proved an ideal enzyme to investigate, since a veronal buffer at neutral *p*H, in which the enzyme is most active, does not remove multilayers of protein from the metal slides except in one case which will be discussed later.

Conditioned slides covered with one, two or three double layers of bovine albumin were treated for three minutes with trypsin. A decrease in thickness of about 9 Å. occurred when there was one and a decrease of about 18 Å. when there was more than one double layer of bovine albumin. No significant increase in thickness followed antiserum treatment. No change in thickness and no inactivation resulted from treating the slides with the buffer alone.

When one to three double layers of bovine albumin were coated with one double layer of barium stearate, no change in thickness followed trypsin treatment. There was an increase of 9 to 17 Å. when the blanket consisted of two or more double layers of barium stearate. Subsequent treatment with a homologous antiserum caused the removal of most of the stearate layers except when there was only one underlying double layer of bovine albumin, in which case no change or a very slight decrease of a few Å. units was observed.

The results showed that in spite of a blanket as thick as five double layers of barium stearate, the trypsin molecules were capable of undermining the architecture of two or three double layers of bovine albumin underneath. The anchorage of the blanket was weakened to such an extent that the barium stearate molecules were washed away by the antiserum treatment. It appears as if the foundations upon which the structure of the layers of barium stearate were built had disintegrated under trypsin action. No such removal of the blanket took place after serum treatment if the slides were not submitted to trypsin action.

It was shown in a preceding article[1] that conditioning deposited layers of bovine albumin with uranyl acetate reduced the amount of antibody which could subsequently be adsorbed. In an analogous way, trypsin action on antigenic layers of bovine albumin is considerably reduced by conditioning. For example, inactivation of conditioned multilayers of bovine albumin does not occur following a two-minute trypsin treatment. The results obtained on inactivation by trypsin of three conditioned double layers of bovine albumin through intermediate blankets of barium stearate are summarized in Table I.

TABLE I

TEN MINUTE TRYPSIN ACTION THROUGH BLANKETS OF BARIUM STEARATE MULTILAYERS ON THREE CONDITIONED DOUBLE LAYERS OF BOVINE ALBUMIN (U BOV ⇵)$_3$ DEPOSITED ON A GAGE OF BARIUM STEARATE

The figures in the table stand for the increase in Å. units observed after treatment with antiserum

	Blanket, number of monolayers of barium stearate					
	0	1	2	4	6	10
Trypsin treatment	40[a]	70	30	15	18	10
No trypsin treatment	135	110	100	85	60	25

[a] 10 Å. in 20′.

There was one conditioning treatment after each "round trip" (⇵) deposition but none after the last one. The system of layers can be represented by the symbol (U bov ⇵)$_3$ where U stands for one uranyl conditioning. The trypsin solution was left for ten minutes on the slides. If we compare the figures of the two horizontal rows it appears that a significant difference in the thickness of the adsorbed layers of antibody, between the slides treated with trypsin and the slides not so treated, is still noticeable with blankets up to three double layers of barium stearate ($\simeq$150 Å.). These experiments indicate that the range of action of trypsin extends at least as far as the distances at which interaction between antigenic layers and antibody molecules can be demonstrated. By the very nature of the test, it cannot be said whether this action extends even farther. Uranyl conditioning between the deposited antigenic layers produced such a stabilizing influence that, in spite of the enzyme treatment, the blanket of barium stearate was never removed by the antiserum treatment. This stabilizing action of the uranyl ions may be twofold, first, in restricting the disintegrating effects set up in the bovine albumin layers by the enzyme, second, in holding together the fragments of the broken down molecules of the layers in such a way as to offer still a firm anchorage for the molecules of the blanket.

Obviously, in order to evaluate the maximum thickness of blankets through which trypsin molecules can act, the blanket should be removed after the enzyme treatment and prior to the deposition of the antiserum. It will be seen later than this can be accomplished easily with blankets of formvar. The removal of the blankets of barium stearate without impairing the optical gage of barium stearate underlying the antigenic layers proved a more

(4) I am very much indebted to Dr. M. Kunitz for the samples of crystalline trypsin, and to Dr. O. T. Avery for the depolymerase solution.

delicate task. The problem was solved by using an optical gage of one and three, or three and five monolayers of octadecylamine instead of barium stearate. The slides were conditioned by uranyl acetate as usual. To remove the barium stearate blankets the slides were first treated with a citrate buffer *p*H 3.6 (0.057 *M*) for a minute or so to liberate the free stearic acid which was then leached off with ethylene dichloride or benzene. The optical gage of octadecylamine was unaffected by virtue of the insolubility of the salt of the amine in organic solvents.

Some experiments were made with blankets of octadecylamine which could be removed without affecting an optical gage of barium stearate layers. The blankets of amine were removed by treating the slides with a dilute solution of ammonia (0.01%) and then with benzene. Thus by taking advantage of the large difference in solubility in organic solvents between the salt of the acid and the free base (or between the free acid and the salt of the amine) it was possible to remove a blanket made of barium stearate without affecting an amine optical gage and vice versa.

The influence of blankets of octadecylamine on trypsin action have been summarized in Table II.

TABLE II

SIX MINUTE TRYPSIN ACTION THROUGH BLANKETS OF OCTADECYLAMINE COVERING MULTILAYERS OF BOVINE ALBUMIN DEPOSITED ON CONDITIONED BARIUM STEARATE GAGES

The figures represent the increment in Å. units observed after treatment with the immune serum, following removal of the blanket. The subtitles "buf." and "try." indicate whether the slides were submitted to "buffer" or "trypsin" before the dissolution of the blanket. The duration of the "trypsin" or "buffer" treatment was six minutes. The letter R indicates that the blanket was detached by the trypsin treatment.

Blanket, number of double layers of octadecylamine	Number of bovine albumin double layers (⇃↾) 1 Buf.	1 Try.	2 Buf.	2 Try.	3 Buf.	3 Try.
0	60	0	120	0	185	0
1	57	25		17		
2	38	38		17		
3	34	36		18		
4		37		48		R0
5			59	58		R0
6				54		
7			58			18
8				58	73	46
10					67	67 or less

In all these experiments the blankets were dissolved before the application of the antiserum. It is shown in the table that the removal of the screen sufficiently disrupted the system of multilayers of bovine albumin so that even without enzyme treatment the thickness of the antibody layer which could subsequently be adsorbed was considerably reduced. The thickness of the antibody layer dropped from 185 to 73 Å. in the case of three double layers of antigen. The difference, however, between "buffer" and "trypsin" treated slides is sufficiently large to permit definite conclusions to be drawn. A screen of two double layers of octadecylamine completely protects one underlying double layer of bovine albumin. Five double layers of octadecylamine are necessary when there are two double layers of bovine albumin underneath. Finally, a blanket as thick as ten double layers was needed to protect three double layers of bovine albumin. It also appears that with two double layers of bovine albumin, whether the blanket had been one, two, or three double layers thick, the thickness of antibody adsorbed was about 17 Å. This probably results from the fact that the first antigenic layer directly attached to the gage is more resistant toward trypsin than the others. Indeed, without a blanket, multilayers were nearly completely inactivated in a few seconds; there remained, however, a small but definite power for adsorbing specific antibody, corresponding roughly to that of one single layer. Even after a three-minute trypsin treatment a specific increment of antibody of 10 Å. could still be observed. Complete inactivation occurred, however, in a few seconds if the slides coated with a conditioned gage were first covered with one single or one double layer of egg albumin before the deposition of the bovine albumin layers. This procedure thus ensured a more uniform sensitivity of the bovine albumin multilayers toward trypsin and it is for this reason that it has been used in nearly all the following experiments.

Some of the results obtained with screens of barium stearate have been summarized in Table III.

TABLE III

SIX MINUTE TRYPSIN ACTION THROUGH BLANKETS OF BARIUM STEARATE COVERING MULTILAYERS OF BOVINE ALBUMIN DEPOSITED ON CONDITIONED GAGES OF ONE AND THREE LAYERS OF OCTADECYLAMINE

All slides after deposition of the blanket were treated for six minutes with a trypsin solution (active) or a solution of trypsin which had been brought to a boil for a few minutes (inactivated). After dissolving the blankets, the slides were treated with the antiserum. The figures stand for the increments observed in Å units. The letter R indicates when the blanket was removed by trypsin treatment. "ov" and "bov" stand for ovalbumin and bovine albumin, respectively.

System of antigenic layers	Enzyme treatment	Blanket, number of double layers of barium stearate 1	2	3	4	5
ov ↑ bov ↑	Active	25				
	Inactivated		45			
ov ↑ bov(↑)$_2$	Active	15	26			
	Inactivated		46			
ov ↑ bov(↑)$_3$	Active	0	2			
	Inactivated		57			
ov ↑ bov(↑)$_4$	Active	0	0	0	0	0
ov ↑ bov(↑)$_5$	Active	0	0	R	R	R
ov ⇃↾ bov ↑	Active	10				
ov ⇃↾ bov(↑)$_2$	Active	0	0	8		
ov ⇃↾ bov(↑)$_3$	Active	0	0	0		
ov ⇃↾ bov(⇃↾)	Active	0	18	36	42	45
	Inactivated		48			
ov ⇃↾ bov(⇃↾)$_2$	Active	0	0	0		10
	Inactivated			86		
ov ⇃↾ bov(⇃↾)$_3$	Active	0	0	0	0	0

As in the experiments of Table II, the removal of the blanket produced partial inactivation (see Fig. 4 of ref. 1). The table shows that the greater the number of layers of bovine albumin the thicker the blanket needed for protection. It also appears that the mode of deposition of the antigenic layers is of importance. Inactivation could occur through blankets of greater thickness when the bovine albumin layers were deposited on the way up (↑↑)$_n$ by successive emersions than when they were deposited by successive immersions and emersions (⇃↾)$_n$. The depositions by emersion were accomplished by immersing the slides into the tray before the protein had been spread. In the deposition by successive immersion and emersion the protein film was spread before immersing the slides. With the antigenic system ov ⇃↾ bov (↑)$_6$, complete inactivation occurred through twenty double layers of barium stearate and twenty-five double layers were needed to ensure complete protection. This very

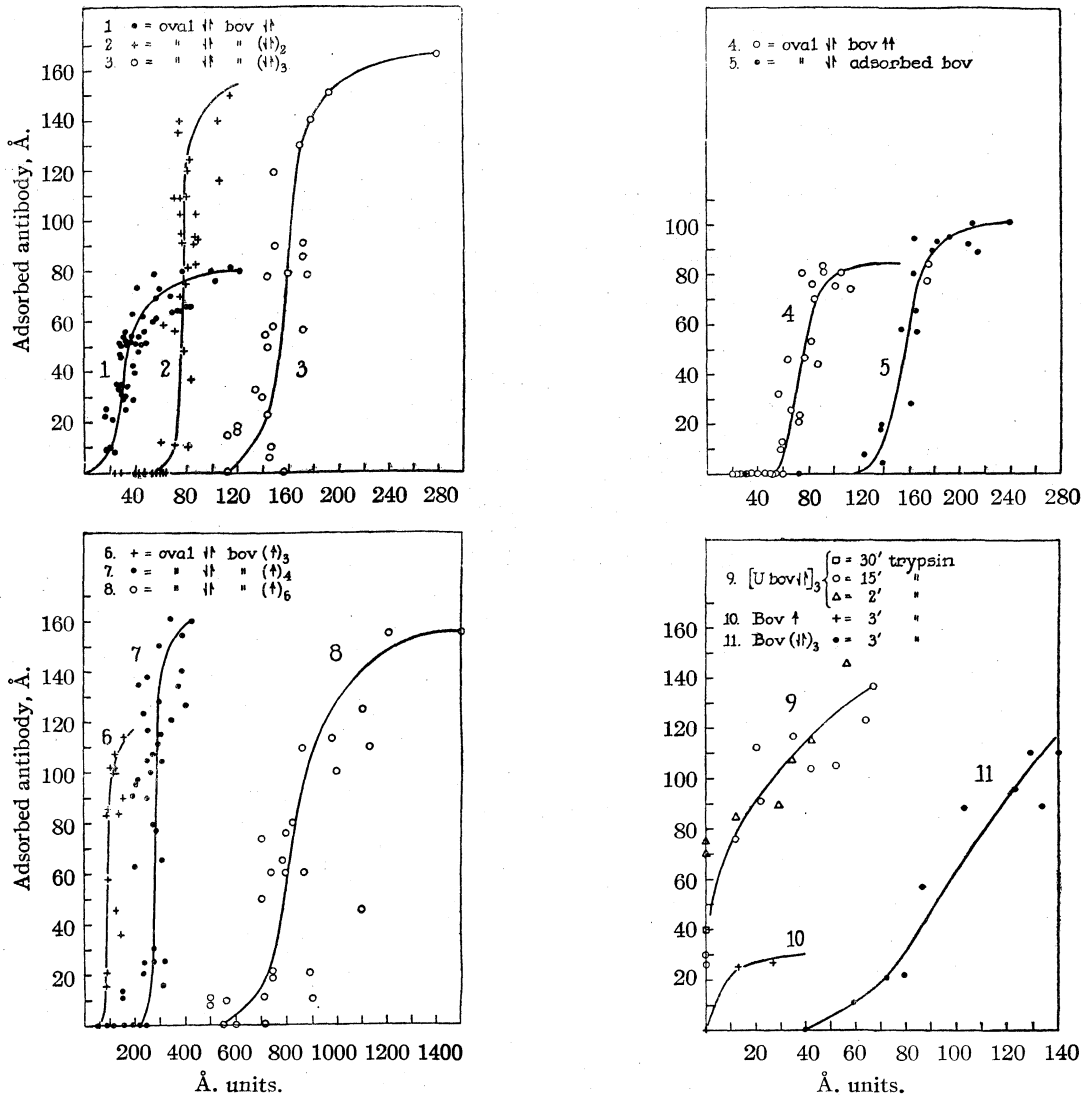


Fig. 1.—Inactivation of films of bovine albumin by trypsin through intervening blankets of formvar.

fundamental difference in the behavior of "up" and "down-up" layers will appear even more strikingly in the results obtained with blankets of formvar described in the next section.

Formvar Blankets.—Blankets of barium stearate or octadecylamine were not entirely satisfactory for two reasons, first the removal of the blankets produced a certain amount of inactivation, second the blankets were often removed by the enzyme treatment when there were three double layers of antigen underneath. Such disadvantages were not encountered with formvar blankets.

All the results obtained with screens of formvar have been summarized in Fig. 1. The abscissas give the thickness in ångström units of the formvar blankets present during the trypsin treatments and the ordinates, the amount of antibody adsorbed after removal of the blanket.

The conditions required for reproducibility of the results are very rigorous and traces of impurity appear to play an important role. Variations in results were more apt to occur between experiments carried out on different days than between results obtained with slides treated simultaneously. Experiments with one or two monolayers were more consistent than similar experiments made with multilayers. In other words, the phenomenon of coöperation between successive layers is very sensitive to small variations in experimental conditions.

Figure 1 summarizes experiments made with one, two and three double layers of bovine albumin deposited by the "down-up" process or the "up" process on slides covered with a conditioned gage of three and five layers of barium stearate plus one double layer of egg albumin. The abscissas show the thickness of the blanket of formvar upon which the trypsin solution was deposited, and the ordinates, the thickness of antibody specifically adsorbed after removal of the screen with ethylene dichloride. It is evident from the curves that the thickness of a formvar blanket needed for protection against trypsin action increases with the number of bovine albumin layers, in harmony with what was found with blankets of barium stearate and octadecylamine. A blanket of formvar about 180 Å. thick is necessary to protect three double layers of bovine albumin whereas for one double layer of bovine albumin 70 Å only will suffice. It is to be noted that all curves rise very sharply ($\partial y/\partial x \rightarrow \infty$) at a critical thickness of blanket.

Time Factor.—In all these experiments, the trypsin solution was left on the blankets for ten minutes. The time factor was investigated wtih the system ov ⇵ bov

$(\Updownarrow)_2$. It was found that essentially the same curve was obtained whether the enzyme solution stayed for five minutes or fifteen minutes on the slides. The amount of specifically adsorbed antibody, however, was only 35 Å. instead of 80 to 85 Å. if the trypsin solution was left for four hours on a blanket 160 Å. thick deposited on one double layer of egg albumin plus one double layer of bovine albumin.

When the layers of bovine albumin were deposited on the way "up" curves 4, 6, 7, 8 and 10 of Fig. 1 were obtained. It is evident from comparing the results presented in Fig. 1, that the mode of deposition of the antigen layers has a tremendous effect on the thickness of the blanket needed for protection. A blanket of 100 Å. is sufficient to protect the antigenic pile ov $\Updownarrow$ bov $(\Updownarrow)_2$, but the protective thickness has to be increased to about 260 Å. when the antigenic pile has the structure ov $\Updownarrow$ bov $(\uparrow\uparrow)_2$. The total thickness of the protein layers was the same in both cases.

A formvar blanket 600 Å. thick offered practically no protection at all for six layers of bovine albumin deposited on the way up and the impressive thickness of 1,000 Å. was necessary to keep the protein layers completely active. It was, therefore, of importance to determine whether or not a system of "up" layers without blankets was much more labile toward trypsin action than a system of "down-up" layers. If this were so, it could be argued that the difference in behavior of the two types of systems toward trypsin in the presence of a blanket was due to a small amount of trypsin which might have diffused through the blanket and would be capable of inactivating the "up" layers and not the "down-up" layers on account of difference in stability. The inactivation of the two types of multilayers without blanket, was therefore investigated as a function of the concentration of the trypsin solutions. The experiments were carried out at 4° for the following reasons. It was observed that at room temperature (20°) the veronal buffer was by itself capable of removing the equivalent of three to four layers of an "up" system of multilayers, but none at all if the layers had been built up by the "down-up" process. At 4°, however, the veronal buffer did not remove any of the layers of either system. It is of importance to note that a system of six "up" layers once coated with a formvar blanket does not lose any thickness following a veronal buffer treatment of ten minutes at room temperature. In other words, unfolded bovine albumin molecules cannot diffuse through a formvar blanket. The results which have been summarized in Table IV show that a system of "up" layers is inactivated slightly faster than a system of "down-up" layers, but this small difference cannot account for the large difference in the thickness of formvar blankets needed for protection against trypsin action.

TABLE IV

INACTIVATION OF MULTILAYERS OF BOVINE ALBUMIN BY TRYPSIN

Figures in columns 2 and 3 represent the thickness in Å. units of adsorbed antibody after treatment of the multilayers by trypsin solutions at 4° for ten minutes.

Concentration trypsin mg. per cc.	ov $\Updownarrow$ + bov $(\uparrow)_6$	ov $\Updownarrow$ + bov $(\Updownarrow)_3$
0.4	0	0
.008	48	66
.004	80	95
.0008	160	160

The case represented by curve 5 of Fig. 1 is particularly interesting. All the bovine albumin films described so far were formed on a water surface and then transferred onto the slides. Bovine albumin molecules, however, can be adsorbed directly by depositing a drop of solution on the metal slides. In this case whatever unfolding of the molecules takes place is not complete, since the average thickness of an adsorbed layer was consistently found to be between 17 and 18 Å. This thickness is equal to that of two monolayers of unfolded molecules. The thickness of the blanket needed for protection, however, was about 180 Å., twice the thickness necessary to protect two "up" layers.

Conditioning of the antigen layers with uranyl acetate greatly diminished the thickness of the blankets in formvar needed for protection, as is plainly shown in curves 9 and 11 of Fig. 1. Fifty ångströms of formvar offer no protection for three double layers of bovine albumin, but ensure nearly total protection for the system of layers (U bov $\Updownarrow)_3$.

Curve 10 shows that a blanket of formvar as thin as 20 Å. completely protected against inactivation one monolayer of bovine albumin deposited on the way "up."

Since the thickness of a blanket needed for protection increases with the number of layers of bovine albumin underneath, it was of interest to determine whether a thicker blanket was also needed if layers of egg albumin were substituted for some of the bovine albumin layers. As it will be seen later trypsin acted upon egg albumin layers just as easily as upon bovine layers in destroying their property of reacting with immune sera. The following systems of layers were deposited on conditioned gages of barium stearate: (ov $(\Updownarrow)_2$ bov $\Updownarrow$), (ov $(\Updownarrow)_4$ bov $\Updownarrow$) and (ov $\Updownarrow$ bov $\Updownarrow$ ov $\Updownarrow$). The curve of inactivation as a function of the thickness of the screen was very much the same for all three systems and intermediate between curves 1 and 3 of Fig. 1.

Polyvinyl Chloride Blankets.—A few experiments carried out with blankets of polyvinyl chloride indicated that the screening action was analogous to that offered by blankets of formvar.

Metallic Blankets.—Metallic blankets of gold were deposited by evaporation in high vacuum directly onto transferred films of bovine albumin. It was found, however, that a thin blanket of gold 20 Å. thick evaporated onto three double layers of bovine albumin prevented any specific adsorption of homologous antibody. (In the case of the polysaccharide from pneumococcus Type III, a specific adsorption of antibody still occurred through 50 Å. of gold.) It was impossible to remove the gold once it was evaporated on the protein layers. Thus slides coated with bovine albumin layers and a blanket of gold obviously could not be used to detect any trypsin action through the blanket because of the lack of means to determine whether or not inactivation had occurred. Of all the methods tested to detect trypsin action through metallic blankets the one most satisfactory was as follows. Gold films were deposited by evaporation *in vacuo* on clean microscope slides. Thin films of formvar were then deposited on top of the gold by dipping the slide into a solution of formvar in ethylene dichloride. When the formvar film was detached from the slide and floated on a water surface, the gold film adhered to the formvar, with the result that the gilded face of the formvar film was in contact with the water surface. Such gilded blankets were transferred from the water surface onto the antigenic films coating a metallic slide in such a manner that the gilded surface was on top. Trypsin solution was deposited on the gilded blanket for ten minutes. After washing off the enzyme solution the slides were treated with a strong jet of ethylene dichloride which dissolved the formvar and removed the gold at the same time. If the blanket was transferred with the gilded face in contact with the antigenic layers, the gold could not be removed by ethylene dichloride treatment. It was observed that a blanket consisting of a formvar film 130 to 200 Å. thick, plus a gold film 40 to 60 Å. thick, offered complete protection against trypsin to six "up" layers of bovine albumin. Partial protection was ensured if the gold film was ≃30 Å. thick, and with no gold, as it has been shown above, complete inactivation still occurred with films of formvar as thick as 600 Å.

Ovalbumin and Antiovalbumin Rabbit Sera

The inactivation of ovalbumin films by trypsin was not studied extensively, because the amount of rabbit anti-

body which can be specifically adsorbed is independent of the number of deposited ovalbumin layers (1) and, therefore, does not afford a sensitive indication of inactivation. Some of the results are presented in Table V, which shows that a blanket of 70 Å. of formvar offers ample protection for two as well as for four double layers of ovalbumin.

TABLE V

TRYPSIN ACTION THROUGH BLANKETS OF FORMVAR COATING MULTILAYERS OF OVALBUMIN

The protein layers were deposited on conditioned gages of two and four layers of barium stearate. The blankets of formvar were dissolved in ethylene dichloride before treatment with the antiserum. The figures in the last column represent the thickness of the adsorbed antibody layer in Å. units.

Protein films	Thickness formvar blanket, Å.	Trypsin treatment, min.	Antiovalbumin rabbit serum treatment
ov(⇵)$_2$	96	0	23
ov(⇵)$_2$	71	5	18
ov(⇵)$_4$	50	5	11
ov(⇵)$_4$	74	5	18
bov ⇵ ov(⇵)$_2$	64	5	0
bov ⇵ ov(⇵)$_4$	60	5	0
bov ⇵ ov(⇵)$_4$	51	0	20

It should be noted, however, that if the ovalbumin layers were deposited on one double layer of bovine albumin complete inactivation occurred in spite of a screen of 64 Å. This would seem to indicate that a layer of ovalbumin anchored directly on the barium stearate gage is much more resistant to trypsin action than if it is anchored on a double layer of bovine albumin. As mentioned earlier, an analogous situation was encountered with films of bovine albumin.

Action of the Specific Enzyme Hydrolyzing the Polysaccharide from Type III Pneumococcus

The interaction between polysaccharide from Type III pneumococcus and homologous rabbit antibody through blankets of various kinds was described in the previously mentioned article.[1] In the present experiments horse as well as rabbit antisera were used, and interesting differences were brought to light.

The polysaccharide was adsorbed by placing a drop of solution on the slide, as described previously. The layer of polysaccharide, whether adsorbed on a conditioned gage of octadecylamine or on barium stearate, was about 5 Å. thick. When, however, the octadecylamine gage was not conditioned the adsorbed layer was 12 to 15 Å. thick, but the amount of antibody which could be specifically adsorbed was independent of the thickness of the layer of polysaccharide.

Horse Antipneumococcus Sera.—The thickness of the layer of horse antibody specifically adsorbed by the polysaccharide was about 70 Å. Reproducible results were difficult to obtain, values as large as 80 Å. and as low as 30 Å. were occasionally observed. The thickness was not dependent on the nature of the underlying gage, barium stearate or octadecylamine, nor did the coating of the gage with one double layer of protein prior to the adsorption of the polysaccharide influence the results. These findings are in direct contrast to the events observed with rabbit sera where it was found that a layer of antibody about 300 Å. thick could be adsorbed if the polysaccharide was anchored on an amine gage whereas the increment was only 120 Å. if the polysaccharide was on a barium stearate gage. No increment was observed following treatment with an antiserum against Type I pneumococcus or upon treatment of an adsorbed layer of polysaccharide from Type I with a Type III antiserum.

When a drop of a solution of the depolymerase was left for ten minutes on a polysaccharide layer adsorbed on a barium stearate gage or on a barium stearate gage coated with one double layer of protein, complete inactivation of the polysaccharide occurred. The increment observed after treatment with an antiserum was from 0 to 10 Å. If, however, the polysaccharide was adsorbed on an amine gage or an amine gage coated with one double layer of protein, little or no inactivation resulted from the enzyme treatment, the thickness of the subsequently adsorbed layer of antibody being 30 to 60 Å. In other words, the anchorage of the polysaccharide was such that the enzyme was ineffective. It could be argued that the amine by itself acted as an inhibitor for the enzyme. This assumption is disproved by the fact that if a blanket of octadecylamine is deposited on top of a polysaccharide adsorbed on a barium stearate gage, complete inactivation occurred through a blanket of at least one double layer of amine. It was also found that if one double layer of barium stearate was deposited on top of an amine gage prior to the adsorption of the polysaccharide, the enzyme was then capable of inactivating the polysaccharide just as well as if there had not been any amine layer underneath. Thus the direct anchorage of the polysaccharide to the amine is necessary to prevent the enzymatic action.

Rabbit Antipneumococcus Sera.—On account of the thick layers of rabbit antibody which could be adsorbed on a polysaccharide layer from Type III pneumococcus, this system was particularly suited for investigating the screening effect of blankets on the action of the depolymerase. The results have been summarized in Fig. 2, where the abscissa represents the thickness of the formvar or barium stearate blanket which was removed prior to the antiserum treatment. The curve shows that a blanket of about 180 Å. is necessary to protect the polysaccharide whether it was adsorbed on an amine or barium stearate gage. Also, a blanket of barium stearate has the same screening effect as that of an equivalent thickness of formvar. The same curve of inactivation was obtained whether the slides were treated for ten or twenty minutes with the enzyme solution. With no blanket present the enzyme produced complete inactivation when the polysaccharide was adsorbed on a barium stearate gage, but on an octa-

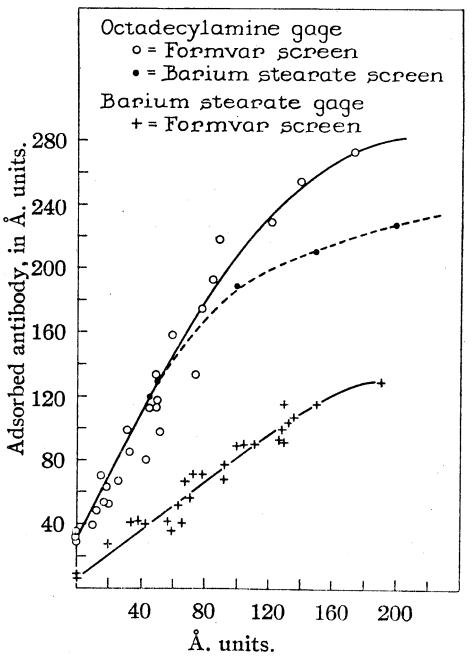


Fig. 2.—Inactivation of polysaccharide from Type III pneumococcus through intervening blankets.

decylamine base enough activity of the polysaccharide remained to produce an increment of 30 to 40 Å. of antibody, the same thickness found when horse serum was used. These experiments show that the enzyme is capable of altering the polysaccharide adsorbed on an amine layer to a much greater extent than the results with the horse serum indicated. The large increment of rabbit antibody adsorbed only a polysaccharide layer anchored to an octadecylamine gage results probably from a delicate adjustment between the structures of the antigen and the antibody. The small increment observed with the horse antiserum under similar conditions indicates that the horse antibody molecules do not respond to the whole antigenic pattern of the polysaccharide permitting the specific fixation of thick layers of antibody, but only to that part of the pattern responsible for short range action.

The enzyme is apparently capable of destroying the "fine" structure of the polysaccharide adsorbed on amine gage but cannot disrupt the whole of the pattern responsible for the specific reaction.

Discussion

All the data presented indicate that pepsin and trypsin, as well as the enzyme depolymerizing the polysaccharide from Type III pneumococcus can act through various blankets made of formvar, polyvinyl chloride, barium stearate and octadecylamine. The question of fundamental importance to answer is: Do the enzyme molecules come in contact with the antigenic layers underneath, or do they act at a distance through the blanket by some mechanism yet unknown? A similar question was raised in the previous study on immunological reaction where it was concluded that the mesh of the fabric of blankets similar to those used in the present experiments did not appear large enough to permit the diffusion of the antibody molecules, and that all available evidence tended to indicate that long range action operated between antigenic layers located on one side of the blanket and antibody molecules adsorbed on the other side.

In the case of enzymatic action, one should keep in mind that a single enzyme molecule diffusing through a blanket might damage an extensive area of the antigenic film. It should also be remembered that the size of a trypsin molecule ($M \simeq$ 30,000) is considerably smaller than that of a rabbit antibody molecule ($M \simeq$ 180,000), and that nothing is known about the size of the enzyme depolymerizing the polysaccharide except that it is a non-dialyzable protein molecule.

However, the results obtained with trypsin acting on multilayers of bovine albumin layers through blankets of formvar offer the strongest kind of evidence against diffusion of the enzyme through the blanket. It was shown that the thickness of the blanket needed for protection against trypsin action increased with the number of underlying bovine albumin layers, and that the thickness needed to protect three double layers of bovine albumin was nearly three times that needed for one double layer. It was shown also that the mode of deposition of the layers $(\downarrow\uparrow)_n$ or $(\uparrow\uparrow)_n$ was just as important as their total number. A much thicker screen was needed to protect a system of layers deposited upwards $(\uparrow\uparrow)_n$ than a system of the same total thickness deposited by a round trip process $(\downarrow\uparrow)_n$. It is an amazing fact that a blanket 600 Å. thick offered no appreciable protection to six monolayers deposited upwards, a total thickness of only 48 Å. There is no reason to believe that the permeability of the blanket should depend on the number or mode of deposition of the antigenic layers underneath, especially when the fact is considered that the blanket can be made first on a clean glass slide, floated on water and transferred as one single unit onto the antigenic layers. If the enzyme molecules do actually diffuse through the blanket, they must then diffuse faster or slower depending on the mode of deposition and number of the antigenic layers underneath, a process which in itself would involve a long range action. The fact that the enzymatic action is to a certain extent independent of the time, the same degree of inactivation occurring after ten or twenty minutes in the case of the enzyme depolymerizing the polysaccharide, or after five or ten minutes with trypsin, speaks against a diffusion process. Curve 9 of Fig. 1 indicates that the amount of inactivation of uranyl conditioned layers of bovine albumin through blankets of formvar is the same after two or fifteen minutes. With no screen present, however, the thickness of the adsorbed layer of antibody for slides treated for two minutes with trypsin was more than twice the thickness obtained with slides treated for fifteen minutes. It may be that in the absence of a blanket, the trypsin molecules diffuse slowly through the disintegrating layers and are able to inactivate each layer in turn whereas no diffusion of enzyme molecules could take place through the blanket.

Slides covered with protein multilayers are hydrophilic; they become hydrophobic when the layers are coated with a formvar blanket and are still hydrophobic after trypsin treatment. One must assume, nevertheless, that water and buffer ions must diffuse through the blanket and that the range of action of trypsin molecules should depend on the diffusibility of the buffer ions. It is a fact that trypsin in a phosphate buffer acts at markedly longer distances than in a veronal buffer. There was no appreciable difference in the action of trypsin whether the formvar blankets were formed directly on top of the antigenic layers or whether they were transferred as one unit from a water surface. There was, however, a difference in the shielding action if the blankets were made in two steps, either by forming a blanket directly on the slide and then transferring a second blanket on top of it from a water surface, or by successively transferring two blankets from a water surface. When the antigenic layers consisted of six "up" layers, a screen of formvar 500 Å. thick made in two steps was adequate to protect the system from trypsin action. A considerable amount of inactivation still occurred with a "two step"

blanket 300 Å. thick. This difference in the behavior of the two types of blankets may be due to a diminished permeability to the buffer ions when the blankets have been made in two steps.

It has sometimes been questioned whether, during the treatment of the slides with enzyme solution or antisera, the different layers stay in their original position or whether these are sufficiently mobile to be displaced. Previously mentioned experiments showed that successively deposited layers remain in their order of deposition. It may be added that some of the experiments on the enzymatic action on the polysaccharide from Type III pneumococcus point to the same interpretation. The enzyme can completely inactivate the polysaccharide molecules adsorbed on a stearate layer deposited on an octadecylamine base. The inactivation is incomplete if the polysaccharide is adsorbed directly on an amine base. Consequently the polysaccharide stays on the barium stearate layer and does not diffuse downward toward the amine layer or vice versa the amine base does not migrate upwards. Also the fact that a blanket of amine, deposited on the polysaccharide adsorbed on a barium stearate base, does not prevent inactivation by the enzyme demonstrates that the polysaccharide molecules stay anchored on the stearate and are not displaced when the blanket of amine is deposited on top of them.

It was shown in the study on interaction between films of antigen and antibody molecules that the amount of specific adsorption in the presence of a blanket was practically independent of the nature of the blanket. In the case of the action of the enzyme on the polysaccharide from Type III pneumococcus, a barium stearate blanket has the same protective effect as that of a formvar blanket of equivalent thickness. A different condition prevails when trypsin acts on multilayers of bovine albumin. Inactivation occurs through a larger thickness of barium stearate than of formvar. The interaction between antigenic layers and trypsin is so strong that very often, as we have seen, the blanket of barium stearate is removed following enzyme or serum treatment. When the interaction is diminished by conditioning with uranyl acetate in between the deposition of the antigenic layers, the blankets of barium stearate are never removed and it was shown (Table II) that trypsin acts at least through six, possibly ten, monolayers of barium stearate blanketing three double layers of bovine albumin deposited by the round trip process. In contrast, a blanket of formvar 60 Å. thick entirely cuts off trypsin action on similarly treated layers of bovine albumin.

It has been suggested that the metal slides onto which the layers were deposited have such rough surfaces on a molecular scale, that the results observed might be artifacts due to the valley-mountain profile of the slide. It is known, however, from electron micrographs that an ordinary microscope glass slide has a remarkably smooth surface. Therefore, some glass slides were coated by evaporation *in vacuo* with a film of chromium or gold thick enough to ensure metallic reflection. The same experiments were carried out using these slides and identical results were obtained.

The evidence just presented would indicate that the enzyme does not penetrate the blanket. Nevertheless, the effect of the enzyme does extend through the blanket and this fact should be considered in connection with theories of enzymatic action. The general mechanisms of enzymatic action postulated so far can be classified in two groups. One group assumes an intermediate complex between enzyme and substrate. The existence of such complexes has been demonstrated in the case of peroxidase and catalase by Chance.[5] In the second group, the reaction proceeds from inactivation by collision and by taking a quantum of the energy liberated during the reaction.[6]

It would be very difficult to explain our results on the basis of either type of mechanism if contact between our substrate films and enzyme does not really occur. In the case of proteolytic enzymes, enzymatic activity does not seem to be located in a prosthetic group, but results from steric architecture of the whole molecule. The following experiments, which show that trypsin as well as pepsin requires the native configuration of its molecules to retain enzymatic activity, are in harmony with this view. One or two monolayers of unfolded trypsin deposited on a slide are incapable of inactivating subsequently transferred layers of bovine albumin, even if a drop of a buffer solution at *p*H 7.5 is deposited on the slide for ten minutes. Similar results are obtained if trypsin films are transferred on top of the antigenic films; no inactivation occurs. Unfolding of the enzyme molecule should not abolish its activity altogether if the origin of the enzymatic activity resided in a prosthetic group. Thus this activity must originate from an extensive portion of the active molecule.

One plausible explanation of the long range action at present would appear to be through some resonance phenomenon perhaps involving a characteristic frequency of the substrate and of the enzyme. Appropriate tuning could then result by correspondence in the frequency and polarization of the vibrations, and the vibrations set up in the substrate layers could break down certain bonds characterizing the antigenic pattern. This interpretation has already been proposed by Chaudhury,[7] but is carried one step further. If such hypothetical resonators are extended, and as we have seen the evidence is in favor of an extended "active" part of the enzyme molecule, it is conceivable that resonance may occur at distances of an entirely different order of magnitude from

(5) B. Chance, *J. Biol. Chem.*, **151**, 553 (1943); *Acta Chem. Scandinavica*, **I**, 236 (1947).

(6) G. Medwedew, *Enzymologia*, **2**, 53 (1937).

(7) A. K. R. Chaudhury, *Curr. Sci.*, **14**, 261 (1945).

those involved when small molecules or individual atoms are considered. Resonance might occur in spite of intermediate blankets, no immediate contact being necessary between substrate and enzyme. It might also be conceived that, depending among other things on the frequency involved, certain vibrations would be better transmitted than others by the intermediate blankets. Some types of blankets may have a stronger specific adsorption than others for the particular frequencies involved. The experiments made with blankets of evaporated gold show that such blankets are extremely efficient in preventing enzymatic as well as immunological reactions.

Thus, long range enzymatic action through a resonance phenomenon could be an explanation of the observed facts. If, as the presented data seem to indicate, long range enzymatic action occurs between films of antigen, or adsorbed molecules of antigens, and enzyme molecules, it would seem also likely that the same mechanism could apply to a substrate in solution and should be considered in a discussion of any theory of enzymatic action.[8]

Also it is important to note that in these experiments one is not justified in considering the behavior of single molecules of the substrate independently. The effect of the number and mode of deposition of monolayers of bovine albumin on its range of action is already an indication that considerable interaction takes place between the layers and presumably between the molecules within one single layer. The phenomenon of long range action could be considered as due to the cooperation of a group of molecules. Coöperation phenomena may play a role in biological processes, the degree of coöperation possibly determining the distance at which an enzyme may act. Finally, the possibility of enzymatic action through a thin cell membrane offers a new vista on physiological events.

(8) It is interesting in this connection to mention an article by Vlasow, *J. Physics, U. S. S. R.*, **9**, 25 (1945). The author shows that when considering large polyatomic systems one cannot neglect weak forces of interaction at long distances and that "these interactions reveal new dynamic properties of polyatomic systems, putting the problem of the transition from 'micro' to 'macro' anew." When collective interaction is taken into account, then follows according to the author "the presence and spontaneous origin of eigen frequencies in polyatomic systems." It is worth mentioning that in 1939 Langmuir, *Proc. Phys. Soc.*, **51**, 592 (1939), considered the possible importance of vibrations for the specificity of protein molecules.

Most of the data presented in this work were obtained with the able assistance of Miss Marjorie Hanson. I am indebted to her for her help in the preparation of this article. My thanks go also to Dr. Lyman C. Craig who read with care the manuscript and offered valuable criticism.

Summary

Multilayers of bovine albumin were submitted to the action of trypsin, and films of polysaccharide from Type III pneumococcus to that of a specific depolymerase. In both cases, following enzymatic action, the layers were altered to such a degree that they became incapable of specifically adsorbing homologous antibody. It was observed that blankets of barium stearate, of a plastic polymer (Formvar), and of polyvinyl chloride polymers deposited on the layers did not prevent enzymatic action from occurring when the enzyme solution was deposited on the blanket. The thickness of the blanket necessary to prevent any enzymatic action varied within a wide range depending on the number and mode of deposition of the underlying layers. It seemed unlikely that the enzyme molecules penetrated the blanket and the assumption was made that enzymatic action took place at a distance, the enzyme and substrate molecules being actually separated by an intervening blanket.

NEW YORK, N. Y. RECEIVED FEBRUARY 10, 1948

[CONTRIBUTION FROM EASTMAN KODAK COMPANY]

The Determination of Primary Hydroxyl Groups in Cellulose Acetate by Tosylation and Iodination

BY CARL J. MALM, LEO J. TANGHE AND BARBARA C. LAIRD

A study was undertaken of the amounts of primary and secondary hydroxyl groups in various samples of cellulose acetate to determine whether any difference could be detected depending on the history of the sample.

The method of tosylation and iodination for the determination of primary hydroxyl groups in glucose and its derivatives depends on (a) complete tosylation of primary hydroxyl groups and partial or complete tosylation of secondary hydroxyl groups, and (b) subsequent replacement of all primary tosyl groups by iodine and no reaction of secondary tosyl groups. These reactions have been applied to a commercial cellulose acetate by Purves and co-workers,[1,2] who found that slightly more than one third of the hydroxyl groups were primary. Their work indicated that the method should be suitable for comparing the amounts of primary hydroxyl in various samples.

This method, with minor modifications, was used, and the samples chosen for comparison in the

(1) F. B. Cramer and C. B. Purves, THIS JOURNAL, **61**, 3458 (1939).

(2) T. S. Gardner and C. B. Purves, *ibid.*, **64**, 1539 (1942).

TABLE I

STARTING MATERIALS

Sample		% acetyl	Hydroxyl per g. u.	Approximate % primary hydroxyl found
A	Acetylated and hydrolyzed with moderate amount of H_2SO_4	40.4	0.48	33
B	Same as A	31.6	1.27	25
C	Acetylated and hydrolyzed with $ZnCl_2$ and HCl	40.0	0.52	28
D	Acetylated with a large amount of H_2SO_4; combined sulfate split off with $MgCO_3$ and acetone	41.4	.38	60
E	From a sample similar to B, by tritylating, acetylating and detritylating	40.3	.49	33
F	Same as A	39.6	.57	33
G	Same as A	32.3	1.22	25
H	From A, deacetylated with 14% NH_4OH	None	3.00	33

present work are listed in Table I. These included cellulose acetates made by differing techniques, which possibly could affect the proportions of primary hydroxyl groups. They were tosylated with *p*-toluenesulfonyl (tosyl) chloride in the presence of pyridine for varying lengths of time (Fig. 1). The tosylated products were iodinated in acetonylacetone solution with sodium iodide, and the results obtained on the first five samples are given in Table II, from which the following points merit consideration:

1. Upon iodination of the tosylated samples, increasing amounts of iodine were introduced as the time of tosylation was extended. By determining the point at which the reaction slowed down, an approximate value for the amount of primary hydroxyl could be obtained. The estimated percentages of primary hydroxyl in the various samples are given in the last column of Table I.

2. The samples showed variations in the per cent. of primary hydroxyl groups as measured by this method. Samples A and E were in qualitative agreement with the results of Gardner and Purves,[2] but sample C, made with zinc chloride, contained slightly less, and sample D, made with a large amount of sulfuric acid catalyst, contained considerably more primary hydroxyl groups.

3. Sample E, made through the trityl derivative to contain substantially all primary hydroxyl groups, actually contained no more than sample A, made by commercial methods. This is indicative of migration of acetyl groups from secondary to primary hydroxyl during the detritylation step. Note that the tosylation time curves of samples A and E were almost identical (Fig. 1).

4. In sample D the amount of tosyl reached a maximum after eight hours. Also, in the last two samples of this tosylation time series the molecular amount of iodine introduced exceeded the amount of tosyl present.

This behavior was traced to the displacement of tosyl by chlorine during tosylation, and of chlorine by iodine during iodination. Qualitative analysis[3] of the iodinated samples showed only a trace of chlorine, and the amount of iodine introduced was always less than the sum of tosyl and chlorine. Comparison of the degree of iodine substitution in Samples D-1 through D-6, Table II, where the chlorine is neglected, and in Table III, where it is taken into account, shows that the introduction of chlorine during tosylation does not

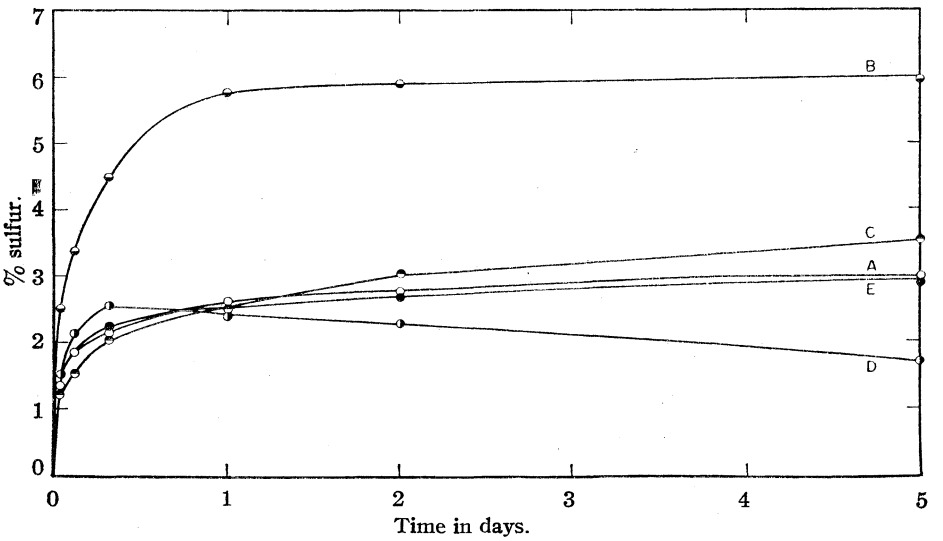


Fig. 1.—Tosylation of different samples of cellulose acetate.

(3) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 115.

TABLE II

TOSYLATION AND IODINATION OF VARIOUS SAMPLES OF CELLULOSE ACETATE

Sample	Tosylation Time, hours	Tosylation S, %	Tosylation Tosyl per g. u.	Iodination (6 hr.) I, %	Iodination (6 hr.) Iodine per g. u.	Ratio of iodine per g. u. to original OH per g. u.
A-1	1	1.35	0.121	4.69	0.104	0.22
A-2	3	1.85	.170	6.25	.141	.29
A-3	8	2.14	.200	6.81	.156	.32
A-4	24	2.63	.252	7.08	.167	.35
A-5	48	2.77	.267	7.54	.179	.37
A-6	120	2.99	.292	8.12	.194	.40
B-1	1	2.51	.209	8.20	.167	.13
B-2	3	3.38	.295	10.00	.212	.16
B-3	8	4.49	.420	10.94	.248	.19
B-4	24	5.78	.587	14.59	.354	.27
B-5	48	5.90	.604	...	...	..
B-6	120	5.93	.608	...	...	..
C-1	1	1.20	.106	3.92	.086	.17
C-2	3	1.53	.138	4.98	.111	.21
C-3	8	2.05	.189	4.56	.127	.24
C-4	24	2.51	.237	6.63	.148	.28
C-5	48	3.04	.296	6.45	.155	.30
C-6	120	3.54	.355	7.04	.174	.33
D-1	1	1.53	.140	5.99	.136	.36
D-2	3	2.13	.202	8.63	.200	.53
D-3	8	2.55	.245	9.24	.218	.57
D-4	24	2.43	.234	9.78	.230	.61
D-5	48	2.28	.218	9.93	.231	.61
D-6	120	1.71	.159	9.68	.227	.60
E-1	1	1.29	.115	5.09	.112	.23
E-2	3	1.84	.169	6.56	.148	.30
E-3	8	2.20	.205	7.16	.164	.33
E-4	24	2.55	.243	7.52	.176	.35
E-5	48	2.73	.263	7.75	.183	.36
E-6	120	2.84	.275	8.03	.190	.38

materially affect the subsequent iodination. However, in Table III and subsequent tables, the chlorine was taken into account and assumed to be replaced by iodine.

TABLE III

TOSYLATION AND IODINATION OF CELLULOSE ACETATE

Sample D; 41.4% acetyl; 2.62 acetyls per g. u.

Sample	Chlorination % Cl	Chlorination Chlorine per g. u.	Iodination (6 hr.) % I	Iodination (6 hr.) Iodine[a] per g. u.	Ratio of iodine per g. u. to original OH per g. u.
D-1	0.09	0.008	5.99	0.136	0.36
D-2	.09	.008	8.63	.200	.53
D-3	.37	.032	9.24	.220	.57
D-4	.80	.070	9.78	.238	.62
D-5	1.04	.090	9.93	.242	.63
D-6	1.89	.160	9.68	.237	.62

[a] Based on replacement of all the chlorine and part of the tosyl.

To obtain further evidence for the replacement of chlorine by iodine during iodination, a sample high in chlorine was prepared by treating a tosylated cellulose acetate with pyridine hydrochloride.[1] This was iodinated along with the original tosylated sample and comparable amounts of iodine were introduced to each.

The increasing amounts of iodine introduced throughout the tosylation time series were disturbing. However, when the procedure described by Gardner and Purves[2] was exactly followed using sample F, the same increase in iodine content was again observed. Small amounts of chlorine were found in the products even with short time of tosylation. The minimum amount of chlorine was introduced when the tosylation was carried out at 0°.

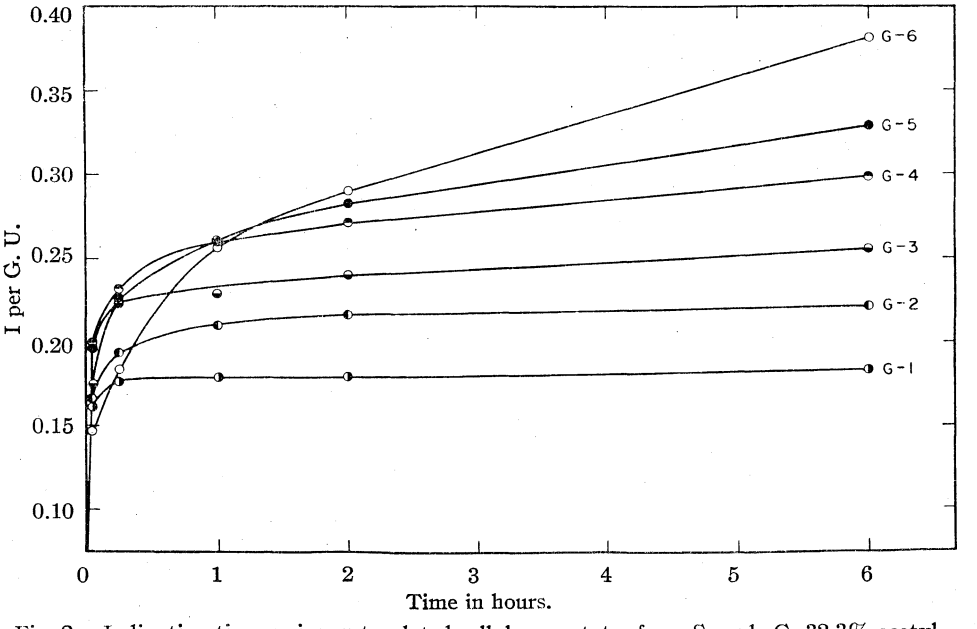


Fig. 2.—Iodination time series on tosylated cellulose acetates from Sample G, 32.3% acetyl.

TABLE IV

TOSYLATION AND IODINATION OF CELLULOSE ACETATE

Sample F; 39.6% acetyl; 2.434 acetyls per g. u.

Sample	Time, hours	Temp., °C.	Ratio TsCl: cellulose ester	S, %	Tosyl per g. u.	Cl, %	Chlorine per g. u.	Iodination (2 hr.) I, %	Iodination (2 hr.) Iodine per g. u.
F-1	1	20	13.1:1	1.66	0.149	0.12	0.009	5.7	0.127
F-2	3	20	13.1:1	2.20	.203	.16	.013	7.2	.165
F-3	8	20	13.1:1	2.54	.239	.16	.014	7.7	.179
F-4	24	20	13.1:1	3.08	.298	.23	.021	7.8	.188
F-5	48	20	13.1:1	3.43	.339	.34	.031	8.1	.199
F-6	120	20	13.1:1	4.01	.409	.79	.074	8.4	.217
F-7	48	0	13.1:1	3.14	.306	.13	.011	8.1	.193
F-8	48	20	6.6:1	3.21	.315	.43	.038	7.9	.192
F-9	48	20	3.3:1	2.61	.247	.36	.031	7.8	.184
F-10	48	20	1.7:1	1.96	.179	.20	.017	6.8	.154

TABLE V

IODINATION OF TOSYLATED CELLULOSE ACETATE

Samples from Table IV

Sample	Tosyl per g. u.	Iodination Time, min.	Iodination I, %	Iodination Iodine per g. u.
F-2-1	0.203	15	7.1	0.163
F-2-2		30	7.1	.163
F-2-3		60	7.2 7.2	.165
F-2-4		120	7.2	.165
F-2-5		360	7.2 7.3	.166
F-3-1	.239	5	7.5	.175
F-3-2		15	7.7	.179
F-3-3		30	7.4	.173
F-3-4		60	7.8	.182
F-3-5		120	7.5	.175
F-3-6		240	7.6	.177
F-4-1	.298	15	7.6	.183
F-4-2		30	7.7	.185
F-4-3		60	7.8	.188
F-4-4		120	7.8	.188
F-4-5		240	8.3	.199
F-4-6		360	8.4	.201
F-5-1	.339	15	7.0	.173
F-5-2		30	7.5	.185
F-5-3		60	7.8	.192
F-5-4		120	8.2	.202
F-5-5		240	8.7	.214
F-5-6		420	8.7	.214
F-6-1	.409	15	6.0	.156
F-6-2		30	6.8	.178
F-6-3		60	7.5	.195
F-6-4		120	8.2	.214
F-6-5		240	8.8	.228
F-6-6		480	9.0	.233

Even including samples where variations were also made in the temperatures and the amount of tosyl chloride, the amount of iodine introduced on iodination increased with the amount of tosyl present.

Iodination time series were then carried out on some of the samples of Table IV and the results are presented in Table V. Upon iodination of a sample low in tosyl, a constant amount of iodine was introduced as the time of iodination was extended; but with increased amounts of tosyl in the sample, the amount of iodine increased considerably as the time of iodination was extended.

This behavior was even more pronounced when tosylation and iodination time series were carried out on sample G, containing 32.3% acetyl (Tables VI and VII, and Fig. 2). Increased amounts of sodium iodide in the iodination of the last sample of this series were not helpful in obtaining a sharper break in the iodination reaction.

TABLE VI

TOSYLATION OF CELLULOSE ACETATE

Sample G; 32.3% acetyl; 1.78 acetyls per g. u.; temp. 25°; ratio TsCl:cellulose ester 5.6:1

Sample	Time, hours	S, %	Tosyl per g. u.	Cl, %	Chlorine per g. u.
G-1	1	3.03	0.265	0.19	0.015
G-2	3	4.10	.379	.12	.010
G-3	8	5.04	.492	.23	.020
G-4	24	6.45	.690	.35	.034
G-5	48	6.94	.770	.59	.059
G-6	120	7.52	.878	.89	.093

The upward drift in the amount of iodine introduced as the times of tosylation and iodination were extended suggested that secondary hydroxyl groups were slowly reacting. Although the original work of Oldham and Rutherford[4] contained several examples of the non-reactivity of tosyl groups on secondary hydroxyls, a review of the more recent literature showed several instances of their reactivity. Levene and Raymond[5] treated xylose derivatives tosylated in the 3-position (*i. e.*, on secondary hydroxyl groups) with sodium iodide and found a slow iodination at 110°. Hess[6] degraded tritosyl starch to a tritosyl glucose derivative into which he was able to introduce two atoms of iodine with sodium iodide at 130°. Levene[7] replaced all three tosyl groups in tritosylglycerol by this method. Tetratosyl erythritol

(4) J. W. H. Oldham and J. K. Rutherford, THIS JOURNAL, **54**, 366 (1932).

(5) P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933).

(6) K. Hess, O. Littman and R. Pfleger, *Ann.*, **507**, 55 (1933).

(7) P. A. Levene and C. L. Mehltretter, *Enzymologia*, **4**, II, 232 (1937).

TABLE VII

IODINATION OF TOSYLATED CELLULOSE ACETATE

(Samples from Table VI)

Sample	Tosyl per g. u.	Iodination: Ratio NaI: sample	Iodination: Time, min.	Iodination: I, %	Iodine per g. u.
G-1-1	0.265	1:1	5	7.8	0.168
G-1-2			15	8.6	.185
G-1-3			60	8.7	.188
G-1-4			120	8.7	.188
G-1-5			360	8.9	.192
G-2-1	.379	1:1	5	7.3	.166
G-2-2			15	8.5	.193
G-2-3			60	9.3	.210
G-2-4			120	9.6	.217
G-2-5			360	9.8	.221
G-3-1	.492	1:1	5	8.1	.196
G-3-2			15	9.3	.224
G-3-3			60	9.5	.228
G-3-4			120	10.0	.240
G-3-5			360	10.7	.256
G-4-1	.690	1:1	5	7.5	.200
G-4-2			15	8.7	.232
G-4-3			60	9.8	.260
G-4-4			120	10.3	.272
G-4-5			360	11.3	.298
G-5-1	.770	1:1	5	6.2	.174
G-5-2			15	8.1	.226
G-5-3			60	9.4	.261
G-5-4			120	10.2	.283
G-5-5			360	11.9	.328
G-6-1	.878	1:1	5	4.9	.147
G-6-2			15	6.4	.191
G-6-3			60	8.7	.257
G-6-4			120	9.9	.291
G-6-5			360	13.1	.381
G-6-6	.878	2:1	5	5.7	.170
G-6-7			5	7.7	.228
G-6-8			60	10.3	.303
G-6-9			120	11.4	.333
G-6-10			360	13.8	.400
G-6-11	.878	5:1	5	6.4	.191
G-6-12			15	8.0	.237
G-6-13			60	11.1	.325
G-6-14			120	13.5	.392

showed irregular behavior,[8] losing all of its tosyl groups with the formation of butadiene. Tosylates of certain simple secondary alcohols, such as isopropyl-*p*-toluenesulfonate showed considerable reactivity toward sodium iodide even at room temperature.[9] Hockett and co-workers[10] applied the reaction to a sorbitol derivative tosylated at positions 2 and 5 (*i. e.*, on secondary hydroxyl groups). In solvents such as acetone, acetonylacetone or acetic anhydride at 120–140°, one of the tosyl groups was replaced with iodine.

(8) R. S. Tipson and L. H. Cretcher, *J. Org. Chem.*, **8**, 96 (1943).

(9) R. S. Tipson, M. A. Clapp and L. H. Cretcher, *ibid.*, **12**, 133 (1947).

(10) R. C. Hockett, H. G. Fletcher, E. L. Sheffield and R. M. Goepp, THIS JOURNAL, **68**, 927 (1946).

Accordingly, the tosylation and iodination reactions were applied to cellulose itself where the introduction of more than one iodine per glucose unit would be clear evidence for the participation of secondary hydroxyl groups.

Previous investigators[11] have found it necessary to use an active cellulose and to avoid high temperature in the tosylation reaction. Cellulose regenerated from the acetate was chosen for this work because of its reactivity. Even then but little tosyl was introduced without suitable conditioning of the cellulose. Pretreatment with aqueous pyridine gave a starting material which reacted with tosyl chloride at room temperature to yield a soluble product containing 1.5 to 1.8 tosyl groups per glucose unit. At steam-bath temperature according to the directions of Honeyman[12] products were obtained containing large amounts of nitrogen and chlorine. At 0° less than one tosyl per glucose unit was introduced and the product failed to dissolve in the reaction mixture. Successful iodinations could be carried out, however, in acetonylacetone suspension. The results on tosylation of regenerated cellulose are given in Table VIII, and on iodination of the tosylated products in Tables IX and X.

TABLE VIII

TOSYLATION OF CELLULOSE

Sample	Ratio TsCl: Cell	Time, hours	Temp., °C.	S, %	Tosyl per g. u.	Cl, %	Chlorine per g. u.
H-1	7:1	16	R. T.	12.58	1.62	0.28	0.03
H-2	7:1	46	R. T.	13.25	1.87	0.58	.07
H-3	7:1	168	R. T.	12.95	1.80	2.58	.32
H-4	4:1	48	R. T.	12.20	1.50	0.67	.08
H-5	6:1	4	0	3.58	0.22	.11	.01
H-6	6:1	7	0	3.90	.24	.31	.02
H-7	6:1	24	0	5.31	.36	.38	.02
H-8	6:1	48	0	6.50	.48	.48	.03

Where excess tosyl had been introduced, slightly more than one iodine per glucose unit was introduced when the time of iodination was extended. Two possible explanations for the increase in iodine content beyond one iodine per glucose unit, other than replacement of secondary tosyl groups by iodine, have come to our attention[13] and have been investigated.

An increase in weight per cent. iodine could result from the loss of tosyl without entrance of iodine. Gardner and Purves[2] found that no tosyl was lost which was not replaced by iodine, and occasional analyses of our iodinated products showed the required amount of tosyl remaining. To investigate this point more fully, sulfur and iodine analyses were made on samples from two iodination time series (Table X), and the degrees of iodine and tosyl substitution were calculated.

(11) A review of earlier work is given by C. J. Malm and C. R. Fordyce in "Cellulose and its Derivatives," Emil Ott, Editor, Interscience Publishers, Inc., New York, N. Y., 1943, p. 702.

(12) J. Honeyman, *J. Chem. Soc.*, 168 (1947).

(13) E. Heuser, private communication.

TABLE IX

IODINATION OF TOSYLATED CELLULOSE

Samples from Table VIII

Sample	Ratio NaI:Sample	Time, min.	I, %	Iodine per g. u.[a]
H-1-1	1:1	15	29.2	0.87
H-1-2		30	32.4	0.95
H-1-3		60	34.8	1.01
H-1-4		120	38.2	1.10
H-1-5		360	41.2	1.18
H-1-6	2:1	15	34.9	1.02
H-1-7		30	35.3	1.03
H-1-8		60	35.4	1.03
H-1-9		120	37.2	1.08
H-1-10		360	41.1	1.18
H-2-1	1:1	60	25.8	0.86
H-2-2		120	30.4	1.00
H-2-3		360	36.1	1.17
H-3-1	1:1	360	35.1	1.21
H-4-1	1:1	5	26.1	0.74
H-4-2		15	31.7	0.89
H-4-3		30	34.8	0.98
H-4-4		60	35.5	1.00
H-4-5		120	37.3	1.03
H-5-1	1:1	5	10.5	0.16
H-5-2		15	11.7	.17
H-5-3		30	10.0	.15
H-5-4		60	11.6	.17
H-5-5		120	12.3	.18
H-8-1	1:1	5	14.0	.25
H-8-2		15	16.3	.29
H-8-3		30	18.5	.33
H-8-4		60	18.6	.33
H-8-5		120	19.0	.34

[a] Not corrected for loss of tosyl.

TABLE X

LOSS OF TOSYL ON PROLONGED IODINATION OF TOSYLATED CELLULOSE

Ratio of NaI: Sample 2:1

Sample	Time, min.	I, %	Iodine per g. u.[a]	S, %		Tosyl per g. u.	Tosyl lost per g. u.
H-2-4	5	24.1	0.78	8.4	8.1	1.06	0.10
H-2-5	15	30.0	0.97	7.2	7.1	0.91	.06
H-2-6	30	33.0	1.04	6.5	6.3	.80	.10
H-2-7	60	35.0	1.13		6.3	.81	None
H-2-8	120	37.4	1.04	4.7	4.3	.50	.40
H-2-9	360	42.2	1.19	3.9	3.7	.43	.38
H-2-10[b]	5	27.8	0.89		7.5	.95	.10
H-2-11	30	32.0	1.04		6.9	.90	None
H-2-12	60	35.8	1.15		6.2	.79	None
H-2-13	120	37.0	1.14		5.5	.67	.13
H-2-14	360	40.2	1.14		4.1	.46	.34

[a] Corrected for loss of tosyl. [b] Samples H-2-10 to H-2-14 were soaked overnight in 0.1 *N* sodium thiosulfate to remove any absorbed iodine.

When the time of iodination was one hour or less the loss of tosyl was negligible, but as the time of iodination was extended to six hours, there was a considerable loss of tosyl without entrance of iodine. Hence, the degree of iodine substitution of samples iodinated for six hours, calculated on iodine content alone (as in Table IX), is slightly high, but even when it is corrected for the amount of tosyl lost, is still slightly more than 1.00 per glucose unit. A similar correction should apply to six-hour iodinations of samples derived from cellulose acetate, since the iodine substitutions were calculated from iodine content alone, assuming no loss of tosyl without entrance of iodine.

Absorbed iodine would likewise contribute to high iodine content of the products. Extraction of iodinated samples with dilute sodium thiosulfate solution has been used[14] to remove absorbed iodine. Typical iodinated products reported herein were soaked overnight in 0.1 *N* sodium thiosulfate, and a loss of 0.6–0.8% iodine was observed. No iodine was lost, however, on refluxing the products for one hour with ethyl alcohol or with carbon tetrachloride.

In Table X, iodination time series without (Samples H-2-4 to H-2-9) and with (Samples H-2-10 to H-2-14) thiosulfate extraction gave comparable results.

The gradual increase in iodine content beyond one per glucose unit is interpreted as a slow replacement of secondary tosyl groups by iodine. This situation closely parallels that observed in a study of cellulose trityl ether[15] where slightly more than one trityl group per glucose unit could be introduced under extended reaction conditions.

Trityl derivatives were prepared from cellulose acetate sample F to determine the amount of primary hydroxyl to compare with the results of tosylation and iodination. About one-third of the hydroxyl groups could be tritylated, the exact amount of trityl introduced depending on the reaction conditions.

When applied to samples lower in acetyl, tritylation indicated slightly more primary hydroxyl than tosylation and iodination. In the preparation of sample E, about one-third of the hydroxyl groups in cellulose acetate, 31.0% acetyl, could be tritylated. In the tosylation and iodination of similar materials, samples B and G, only about 25% of the original hydroxyl groups could be readily replaced with iodine.

The results herein reported show that the tosylation and iodination method does not fulfil the conditions required for the exact determination of primary hydroxyl groups in cellulose acetate. All primary hydroxyl groups must be tosylated. However, large amounts of secondary tosyl groups are objectionable, since they interfere with the subsequent iodination, and in the iodination step the iodine content does not level off satisfactorily with the time of reaction. On samples low in tosyl where all of the primary hydroxyl groups may not have been tosylated the iodine levels off but at

(14) G. E. Murray and C. B. Purves, THIS JOURNAL, **62**, 3194 (1940).

(15) W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.*, **65**, 2449 (1943).

too low a level. It was possible, however, by maintaining identical reaction conditions throughout, to determine the approximate primary hydroxyl content and to detect differences from sample to sample depending on their past histories. Especially noteworthy was the sample (D) of cellulose acetate prepared using a large amount of sulfuric acid catalyst, with subsequent removal of combined sulfate groups at the completion of the esterification. In this sample, approximately 60% of the hydroxyl groups were primary, indicating a preferential reactivity of the primary hydroxyl groups of cellulose toward the sulfuric acid catalyst during the esterification process.[16]

Experimental

Starting Materials.—Samples A, B, F and G, Table I, were made by commercial methods using sulfuric acid as the catalyst, both for the acetylation and the subsequent hydrolysis. The amount of acetyl in the products was controlled by the time of hydrolysis.

Sample C, Table I, was made by acetylation of cotton linters using acetic anhydride and zinc chloride catalyst. The amount of zinc chloride used was equal to the weight of the cellulose. In addition, 20 ml. of concentrated hydrochloric acid was added per pound of cellulose to aid the esterification. At the completion of the esterification of the cellulose, water was added to hydrolyze the product to the desired acetyl content.

Sample D, Table I, was made by acetylation of cotton linters using acetic anhydride and a comparatively large amount of sulfuric acid (28% of the weight of the cellulose). With this large amount of catalyst, good cooling was necessary to prevent excessive rise in temperature. The esterification was complete after a reaction time of one-half hour, as indicated by absence of fiber and grain. At this point an amount of magnesium carbonate was added, equivalent to three-fourths of the sulfuric acid catalyst. After stirring fifteen minutes at 100° F. the reaction mixture was diluted with half its volume of acetone, and the mixing was continued for one hour at the same temperature. The magnesium carbonate and the acetone aided the removal of combined sulfate without hydrolysis of acetyl. The product was then precipitated and washed in water.

Sample E, Table I, was prepared in three steps, by tritylation, acetylation, and detritylation of cellulose acetate according to the details immediately following:

1. **Tritylation.**—Twenty grams of cellulose acetate (31.0% acetyl; 1.68 acetyl groups per glucose unit) was dissolved in 100 ml. of anhydrous pyridine and 30 g. of triphenylchloromethane was added. The reaction mixture was heated at 70° for sixteen hours, at which time it was diluted with acetone, precipitated and washed in alcohol. The yield was 25.8 g. of a white, fluffy product containing 22.1% acetyl.[17] When several similar products were combined and tritylated again with fresh reagents, there was a slight increase in the amount of trityl introduced.

Anal. Calcd. for tritylation of one-third of the available hydroxyl groups (1.68 acetyl and 0.44 trityl per glucose unit): acetyl, 21.2; trityl, 31.6. Found: acetyl, 21.4; trityl, 31.4, 32.0.[15]

2. **Acetylation.**—Forty grams of the above product was dissolved in 200 ml. of anhydrous pyridine, and 40 ml. of acetic anhydride was added. After seventy-two hours at 50° the reaction mixture was diluted with 200 ml. of methanol. Considerable heat was evolved, indicating an excess of acetic anhydride. The product was precipitated and washed in alcohol, yielding 43.1 g. of a white, fluffy product.

Anal. Calcd. for complete acetylation of remaining hydroxyl groups (2.56 acetyl and 0.44 trityl per glucose unit): acetyl, 29.2; trityl 28.5. Found: acetyl, 29.4, 29.5; trityl, 27.8, 28.2.

3. **Detritylation.**—Ten grams of the above product (2.56 acetyl and 0.44 trityl per glucose unit) was dissolved in 70 ml. of acetic acid. A mixture of 14 ml. of acetic acid and 7 ml. of concentrated hydrochloric acid was added with stirring. Upon standing two hours at room temperature, crystals of triphenylcarbinol had separated out. The reaction mixture was diluted with 25 ml. of acetone and the product was precipitated and washed in methanol. The dried product was redissolved in acetone and precipitated in methanol to ensure complete removal of triphenylcarbinol. The yield was 6.3 g. of a white, fluffy product.

Anal. Calcd. for 2.56 acetyl per glucose unit: acetyl, 40.8. Found: acetyl, 40.2, 40.3; trityl, absent.

The above material represents sample E, Table I. It displayed the same solubilities in organic solvents as commercial cellulose acetate of comparable acetyl content, such as sample A, Table I.

Sample H, Table I, was prepared by the deacetylation of sample A by treatment with 14% ammonium hydroxide for two days at room temperature. The product remained in suspension throughout the process and retained the flaky appearance of the cellulose ester. The viscosity at 25° of the regenerated cellulose was 14 centipoises when dissolved in 2.5% concentration in cuprammonium solution.

Tosylation of Cellulose Acetate.—All tosylations were carried out at room temperature or lower with the cellulose acetate dissolved in anhydrous pyridine.

For the samples of Table II, the cellulose acetate was dissolved in 10 parts of pyridine and 2 g. of tosyl chloride per gram of cellulose acetate was added. After stirring for a few minutes to dissolve the latter, the bottles were placed in the 25 ± 0.1° bath. At the times indicated samples were diluted with acetone and precipitated and washed in alcohol. The tosylated products[18] acquired a slight color after a long time of reaction, but were all obtained in a fluffy, fibrous texture.

When small amounts of chlorine were found[19] in the tosylated materials measures were taken to eliminate or minimize this side-reaction. The tosyl chloride was dissolved in pyridine and the solution was cooled before it was added to the solution of the cellulose ester. Various samples of tosyl chloride were compared, and one sample was recrystallized from cyclohexane before use. These measures were without avail, although lowering of the reaction temperature to 0° did decrease the amount of chlorine entering.

In repeating the experiment of Gardner and Purves[2] a sample of cellulose acetate of comparable acetyl content was selected and all details were modified to conform to their experimental conditions. The results are given in samples F-1 through F-6, Table IV, and in Fig. 2. In the remaining samples of Table IV, variations were made in the temperature and in the amount of tosyl chloride.

In an attempt to eliminate the introduction of chlorine, some experiments were made with *p*-toluenesulfonic anhydride as the tosylating agent. This material was prepared from the acid and thionyl chloride, and melted

(16) C. J. Malm, L. J. Tanghe and B. C. Laird, *Ind. Eng. Chem.*, **38**, 77 (1946).

(17) Acetyl analyses were carried out by the Eberstadt method as described by L. B. Genung and R. Mallatt, *Ind. Eng. Chem., Anal. Ed.*, **13**, 369 (1941).

(18) Sulfur analyses were carried out by the Parr bomb or by the method described by C. J. Malm and L. J. Tanghe, *Ind. Eng. Chem., Anal. Ed.*, **14**, 940 (1942).

(19) The chlorine determinations were carried out by a saponification procedure developed in this Laboratory by Dr. J. W. Mench. This has been found adaptable to small amounts of chlorine in cellulose esters and has given results in agreement with a standard combustion method.

at 128°, in good agreement with the literature.[20] A tosylation reaction was carried out in pyridine solution using four parts of the anhydride to one part of cellulose acetate (Sample A, Table I). When only 0.30% sulfur was found in the product after a reaction time of twenty-four hours on the steam-bath, this method was abandoned.

Tosylation of Regenerated Cellulose.—When dried regenerated cellulose was treated with tosyl chloride in pyridine suspension, only a small amount of sulfur was introduced after several days of reaction at room temperature.

For activation, 30 g. of regenerated cellulose (Sample H, Table I) was tumbled overnight with 450 g. of pyridine and 150 g. of water. The water was then displaced by four changes of anhydrous pyridine, the cellulose being pressed out on a Buchner funnel with a sheet of rubber after each treatment.

To obtain samples H-1, H-2 and H-3, Table VIII, the cellulose, wet with pyridine, was divided into three parts of 48 g. each. To each was added 100 ml. of pyridine and 70 g. of tosyl chloride, and the mixtures were tumbled at room temperature for the times indicated. Sample H-1 gave a reaction dope with considerable grain. As the reaction time was extended the grain diminished, and was absent from sample H-3. In each case the reaction mixture was diluted with an equal part of pyridine and the product precipitated and washed in alcohol. The products were all light tan in color and fluffy in texture.

In order to obtain samples with lower amounts of tosyl and to minimize the introduction of chlorine, a reaction time series was carried out at 0°. The regenerated cellulose was activated in the same way, and the mixture was stirred continuously throughout the reaction (Samples H-5 through H-8, Table VIII). Less than one tosyl group per glucose unit was introduced under these conditions, and the cellulose failed to dissolve. The products were washed in alcohol and were unchanged in appearance from the starting material.

Iodination of Tosylated Cellulose Derivatives.—After a few trials using acetone at 100° in sealed tubes as the solvent for the iodination, this solvent was abandoned in favor of acetonylacetone.[2]

Where iodination time series were not taken, 1 g. of the tosylated sample and 1 g. of sodium iodide were dissolved in 30 ml. of acetonylacetone and heated in the electric oven at 120 ± 2°. In Table II the reaction time was six hours, and in Table IV, two hours, with occasional stirring. Crystallization of sodium *p*-toluenesulfonate took place during the course of the reaction. The products were isolated by precipitation and washing in distilled water.

A yellow color was always indicative of a large amount of iodine in the product. Most of these iodinated products were fluffy in texture and isolated in good yield. However, iodinated derivatives of Samples B-5 and B-6, Table II were too powdery to be isolated after iodination for six hours.

The iodinated derivatives of tosyl cellulose (Table IX) were isolated in poor yield when the time of iodination was extended to six hours. With shorter times of iodination, good yields were obtained on these products.

For the iodination time series 2.5 g. of tosylated derivative was dissolved in 75 ml. of acetonylacetone and heated in an oil-bath to 120 ± 1.0° in a three-necked flask fitted with thermometer and stirrer. After the solution had come to temperature 2.5 g. of sodium iodide was added. Approximately 15-ml. portions were pipetted out at the indicated intervals, and the products were precipitated and washed in distilled water.

All the tosylated derivatives except the cellulose *p*-toluenesulfonates containing less than one tosyl per glucose unit were soluble in hot acetonylacetone. Satisfactory iodinations were achieved in insoluble derivatives by carrying out the reaction in suspension.

Chlorination of Tosylated Cellulose Acetate.—Sample F-9, Table IV, was treated on the steam-bath with an equal weight of pyridine hydrochloride in pyridine solution. A large portion of the tosyl was replaced by chlorine, yielding a product containing 2.7% chlorine. Upon iodination, a product was obtained with 7.1% iodine, the chlorine having undergone the same displacement reaction as the tosyl.

Summary

The method of tosylation and iodination did not give exact results in the determination of primary hydroxyl in cellulose and cellulose acetate; since as the reaction conditions in both the tosylation and iodination steps were extended, increasing amounts of primary hydroxyl were indicated.

In view of these difficulties the reaction conditions must be standardized in comparing the amounts of primary hydroxyl in different samples of cellulose acetate.

Different proportions of primary hydroxyl were found in samples of cellulose acetate depending on their methods of preparation.

The introduction of slightly more than one iodine per glucose unit into tosylated cellulose indicated a slow participation of secondary hydroxyl in the tosylation–iodination reaction.

ROCHESTER, N. Y. RECEIVED MARCH 17, 1948

(20) A. L. Bernouilli and H. Stauffer, *Helv. Chim. Acta*, **23**, 627 (1940).

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

The Influence of Substituents on the Course of Addition of Maleic Anhydride to Diarylethylenes

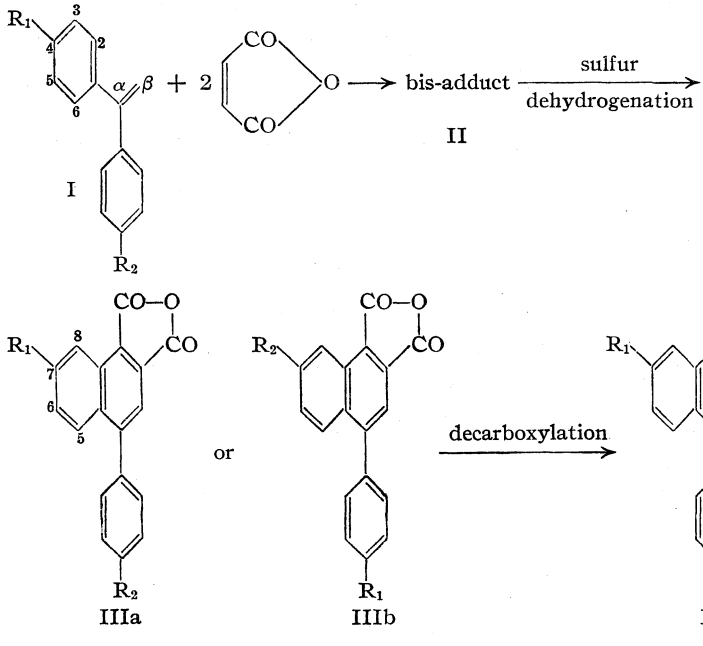
BY FELIX BERGMANN AND JACOB SZMUSZKOWICZ[1]

When an unsymmetrical diarylethylene of the general formula I is subjected to a Wagner–Jauregg type addition of maleic anhydride,[2] the reaction can lead to two isomeric products (IIIa or IIIb). However, as indicated in our earlier paper[3] and elaborated upon in the present investigation, only a single product is obtained in every case.[4] Proof of the structure of the addition product was obtained either by degradation of the aromatic anhydrides III to simple naphthalene derivatives, which could be synthesized in an unequivocal way or identified by exclusion of the isomeric structure, or by spectrographical analysis.[5]

TABLE I

FORMATION OF 4-ARYLNAPHTHALENE-1,2-DICARBOXYLIC ACID ANHYDRIDES (III)

	Ethylene used (I)		Aromatic anhydride (III)		
	R_1 =	R_2 =	R_1 =	R_2 =	Proof of structure
1	Phenyl	H	Phenyl	H	By exclusion
2	CH_3	H	H	CH_3	By independent synthesis
3	C_2H_5	H	H	C_2H_5	By spectroscopic analogy
4	$(CH_3)_2CH$	H	H	$(CH_3)_2CH$	By spectroscopic analogy
5	$(CH_3)_3C$	H	H	$(CH_3)_3C$	By spectroscopic analogy
6	OCH_3	H	OCH_3	H	By independent synthesis
7	OCH_3 (and OCH_3 at C_5)	H	OCH_3 (and OCH_3 at C_6)	H	By spectrographical analysis
8	F	H	H	F	By independent synthesis
9	Cl	H	H	Cl	By independent synthesis
10	Br	H	H	Br	By analogy
11	F	CH_3	(F	CH_3?)	None



Our results, which are summarized in Table I, enable us to divide all the aromatic substituents investigated into two classes: (a) substituents which promote participation of the substituted ring in the addition reaction (methoxyl, phenyl); (b) substituents which prevent participation of the substituted ring (halogen, alkyl).

For a full understanding of this classification we have to take into consideration that a substituent of group b does not interfere *per se* with the successful addition to the substituted ring. Thus, although in the unsymmetrical halogenated ethylenes (I,8 and 9) the substituted ring is excluded from reaction, the symmetrical dihalogenated derivatives (I,13 and 14) react very smoothly with maleic anhydride and the same is true for the di-(*p*-tolyl)-ethylene (I,12). Therefore in the unsymmetrically substituted ethylenes very accurately balanced electronic effects must result from the presence of two different aromatic rings.

If methoxyl and chlorine are taken as representatives of the two groups, it appears probable that the reaction starts by electrophilic attack of maleic anhydride to the β-carbon atom of the side chain. This attack is favored by the +T − effect of methoxyl and hindered by the −I − effect of chlorine (as compared to the unsubstituted ring), the effects being transmitted through the whole

(1) Part of a thesis submitted to the Hebrew University, Jerusalem, 1947.

(2) Wagner-Jauregg, *Ber.*, **63**, 3218 (1930); *Ann.*, **491**, 1 (1931).

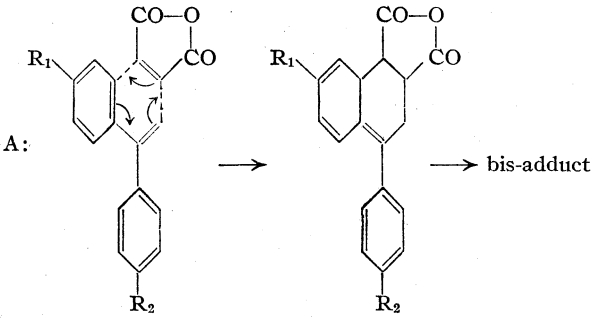
(3) F. Bergmann, J. Szmuszkowicz and Fawaz, THIS JOURNAL, **69**, 1773 (1947).

(4) About the possible exception from this rule of the *t*-butyl derivative I,5 see Experimental Part.

(5) Hirschberg and Jones, *Can. J. Res.*, in press.

conjugated system to the β-carbon atom. However, in electrophilic substitutions methyl usually behaves like methoxyl, whereas in the reaction under discussion the alkyls parallel the halogen group. This apparent contradiction can, however, be solved easily, if it is realized that the reaction involves a two-step addition to the β-carbon and the ortho position. If the first addition is electrophilic, the second step must be nucleophilic in character, so that the reacting system can pass through a complete electronic cycle, in which all electron shifts occur simultaneously (scheme A).

A:



The course of the reaction is therefore dependent on the electronic influence of a given substituent upon both the β- and ortho-position. If we assume that a substituent would—at least qualitatively—exert a similar influence on the diphenylvinyl system as it does on an isolated benzene ring, we can make use of Hammett's σ-constants for an estimate of the electronic shifts to be expected.[6] The pertinent figures are given in Table II and show very clearly, that an increased positive charge in the 2-position is at least as important as an increased electron density at the β-carbon atom. This is borne out especially by example I,1. The *p*-phenyl group has such a small positive σ-value, that no prediction can be made on this base. However the large positive δ-value for the *m*-position, directs addition toward the substituted ring. The figures of Table II thus support the reaction scheme A, as formulated above, and make it very probable that all Diels–Alder reactions follow a similar "polar" pattern.

An interesting case is represented by the dimethoxy compound I,7. Superficially both positions involved in the cyclization bear a negative charge and thus addition should be directed to the unsubstituted ring. However, the Wagner–Jauregg reaction involves a simultaneous addition of the dienophil at both the β-carbon and the *o*-position, and it is clear that the two methoxyl groups cannot resonate at the same time to produce a negative charge on their respective para positions and that the more extended conjugated systems associated with the 4-methoxyl is favored for resonance. Therefore, the 5-methoxyl can exert only its inductive effect. Although the I-effect of an aromatic methoxyl upon its para position cannot be determined separately, we have tried to estimate the electronic displacements in I,7 in the following way:

The β-carbon atom is under the *p*-effect of the resonating C_4-methoxyl ($\sigma = -0.268$) and the *m*-effect of the C_5-methoxyl ($\sigma = +0.115$). Assuming additivity of the two effects, we come to an over-all value of $\sigma_\beta = -0.153$. For the 2-position in the ring we have the *m*-effect of the resonating C_4-methoxyl, which certainly is $> +0.115$ and the purely inductive *p*-effect of the C_5-methoxyl, which is unknown, but certainly smaller than the *m*-effect (compare the values for *m*- and *p*-chlorine, *m*- and *p*-bromine), so that the increase of the meta-inductive effect of the C_4-methoxyl would be approximately balanced by the decrease of the para-inductive effect of the C_5-methoxyl. We assume σ_{ortho} to be approximately $2 \times 0.115 = +0.230$. Conditions in the 4,5-dimethoxylated ring are thus very favorable for the addition of maleic anhydride according to scheme A.

The symmetrically substituted diarylethylenes represent a different case. In general, resonance and coplanarity between the ring and the vinyl group in styrene is increased by the introduction of a second ring as in I. If both aromatic systems are identical, the symmetry of resonance favors the Wagner–Jauregg addition so much, that adversary electronic effects of individual substituents are overcome. If the two rings are not identical, any small difference in resonance energy is enlarged by the fact that only one aromatic group can be coplanar with the vinyl group at a time, whilst the other one is twisted out of the plane.[7]

The reaction scheme, as developed here, permits several predictions to be made about the course the reaction will take, if a single substituent is introduced in I into a *m*-position. This aspect of the problem is now under investigation.

TABLE II

σ-VALUES FOR *m*- AND *p*-SUBSTITUENTS

Substituent	σ-Value for *p*-Position	σ-Value for *m*-Position
Group a: Methoxyl	−0.268	+0.115
Phenyl	+ .009	+ .218
Group b: Fluorine	+ .062	+ .337
Chlorine	+ .227	+ .373
Bromine	+ .232	+ .391
Methyl	− .170	− .069

Experimental Part[8]

A. Preparation of Diarylethylenes (I)

Three methods are available for the synthesis of 1,1-diarylethylenes: (a) interaction of ethyl acetate with two moles of a Grignard compound (applicable only for cases with identical aryls); (b) reaction of an acetophenone with an arylmagnesium halide; (c) reaction of a benzophenone with methylmagnesium iodide.

Method (c) gives the best yields (nearly quantitative), but method (b) is often more economical inasmuch as a number of different diarylethylenes can be prepared from

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 188.

(7) R. N. Jones, THIS JOURNAL, **65**, 1818 (1943); F. Bergmann and Israelashvili, *ibid.*, **68**, 1 (1946).

(8) All m. p.'s are uncorrected.

the same acetophenone, whereas with method (c) a special synthetic route is required for every individual ethylene. The yields in reaction (a) are usually low, and this method is of little preparative value.

I,3: *p*-Ethyldiphenylethylene (I, $R_1 = C_2H_5$, $R_2 = H$).—*p*-Ethylbenzophenone was originally described by Söllscher.[9] The yield is reported as 75%. Norris and Blake,[10] however, found it necessary to purify the ketone, obtained "in the usual way," by four fractionations. We have observed that the Perrier modification[11] gave a 70% yield of a product of excellent purity. The reaction proceeded at room temperature and was completed by heating to 80° for one hour; b. p. 130–135° (0.5 mm.). The crude carbinol obtained from *p*-ethylbenzophenone and methylmagnesium iodide, was dehydrated by heating to 150° for one hour. Distillation yielded 85% of pure *p*-ethyldiphenylethylene; b. p. 118–120° (0.2 mm.); $n^{27.5}D$ 1.5864.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.3; H, 7.7. Found: C, 91.9; H, 7.8.

I,4: *p*-Isopropyldiphenylethylene (I, $R_1 = CH(CH_3)_2$; $R_2 = H$).—*p*-Isopropylbenzophenone was prepared in 80% yield by Smith[9b] from cuminyl chloride and benzene. We applied again the Perrier technique. The benzoyl chloride–aluminum chloride complex reacted with isopropylbenzene at 0°; the reaction was completed at +15°. The ketone was obtained in 79% yield, b. p. 145–148° (0.1 mm.).

The Grignard reaction with methylmagnesium iodide was carried out as before. *p*-Isopropyldiphenylethylene boils at 122–123° (0.1 mm.); yield 86%; $n^{17}D$ 1.5823.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.9; H, 8.1. Found: C, 92.1; H, 8.0.

I,5: *p*-*t*-Butyldiphenylethylene (I, $R_1 = C(CH_3)_3$; $R_2 = H$).—*p*-*t*-Butylbenzophenone was prepared by adding *t*-butylbenzene (60 g.) to the Perrier complex, prepared from benzoyl chloride (75 g.) and aluminum chloride (70 g.) in carbon disulfide (350 cc.) at +5°. The main reaction proceeded at room temperature and was completed by heating on a water-bath for one half-hour: yield 53%; b. p. 132–134° (0.1 mm.); $n^{25}D$ 1.5725.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 85.3; H, 7.9.

The ethylene I,5 was prepared according to method (c). Dehydration of the intermediary tertiary carbinol was effected by heating to 150° for one hour: yield 95%; b. p. 123° (0.1 mm.); $n^{27}D$ 1.5767.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.5; H, 8.5. Found: C, 91.2; H, 8.7.

I,8: *p*-Fluorodiphenylethylene (I, $R_1 = F$; $R_2 = H$).—*p*-Fluorobenzophenone was obtained by Dunlop and Gardner[12] in 66% yield from benzoyl chloride and fluorobenzene. The Perrier technique yielded in this case only 45% of the ketone; b. p. 110–115° (0.4 mm.); m. p. 48°. The Grignard reaction with methylmagnesium iodide was carried out as before and yielded 96% of the ethylene I,8. It possesses a b. p. of 105–110° (0.3 mm.) and shows a strong blue fluorescence; $n^{19}D$ 1.5840.

Anal. Calcd. for $C_{14}H_{11}F$: C, 84.8; H, 5.6. Found: C, 84.7; H, 5.8.

I,9: *p*-Chlorodiphenylethylene (I, $R_1 = Cl$; $R_2 = H$) was prepared according to Bergmann and Bondi.[13]

I,10: *p*-Bromodiphenylethylene[14] (I, $R_1 = Br$; $R_2 = H$) was prepared according to method (b) in 67% yield.

I,11: 1-(*p*-Tolyl)-1-(*p*-fluorophenyl)-ethylene (I, $R_1 = CH_3$; $R_2 = F$) was obtained from *p*-methylacetophenone and *p*-fluorophenylmagnesium bromide in 40% yield as a clear yellow oil of b. p. 141–142° (0.03 mm.); $n^{27.5}D$ 1.5738.

Anal. Calcd. for $C_{15}H_{13}F$: C, 84.9; H, 6.1. Found: C, 85.1; H, 6.1.

I,12: 1,1-Di-(*p*-tolyl)-ethylene (I, $R_1 = R_2 = CH_3$) was prepared in an unspecified yield by Anschütz and Hilbert[15] according to method (a). Repetition of their experiment gave only an 18% yield of the required ethylene. However, application of method (b) yielded the di-(*p*-tolyl)-ethylene in 58% yield, m. p. 60–61°.

I,13: 1,1-Di-(*p*-chlorophenyl)-ethylene[13] (I, $R_1 = R_2 = Cl$) was prepared according to method (b) from *p*-chloroacetophenone and *p*-chlorophenylmagnesium iodide in 73% yield, m. p. 91°.

I,14: 1,1-Di-(*p*-fluorophenyl)-ethylene (I, $R_1 = R_2 = F$).[16]—Method (a) yielded about 15% of this ethylene. As the preparation of *p,p'*-difluorobenzophenone according to Coates and Sutton is very tedious, we prepared the ethylene from *p*-fluoroacetophenone[17] and *p*-fluorophenylmagnesium bromide in 63% yield; b. p. 150–160° (30 mm.); m. p. 46°.

II. Condensation with Maleic Anhydride—Formation of bis-Adducts (II)

The formation of the bis-adducts (II) was carried out as before.[3] The optimal temperature had to be determined in each individual case, as the success of the condensation of the ethylenes I with maleic anhydride depends on narrowly defined temperature limits. When halogen was present in the ethylene, the bis-adduct always crystallized.[18] Among the alkyl-substituted ethylenes, only the mono- and di-tolyl derivative allowed the isolation of crystalline bis-adducts. In all other cases, the products were too soluble to permit crystallization. They were therefore dissolved in ethanol and precipitated by water as brownish powders. These crude, amorphous materials were purified by dissolution in sodium hydroxide and reprecipitation with hydrochloric acid. The white powders, so obtained, were then dried in an oven at 50–70° and used directly for the next step.

The properties of the bis-adducts (II) are summarized in Table II.

III. Dehydrogenation of bis-Adducts

All the aromatic anhydrides (III) were prepared by sulfur dehydrogenation of the bis-adducts. Details of these reactions together with the properties of the dehydrogenation products are given in Table III. Under the heading "Temperature of Dehydrogenation" two figures are given: The lower one designates the temperature at which the evolution of hydrogen sulfide started. The reaction mixture was usually kept at this temperature for ten to fifteen minutes. Thereafter the mixture was heated for five minutes to a temperature determined by the higher figure in the table, in order to complete the reaction. All the aromatic anhydrides are intensely yellow, beautifully crystalline substances, with a blue to violet fluorescence. When their alcoholic solutions were kept for some days, however, the color faded gradually due to the opening of the anhydride ring. The "dichloro" derivative (III,13) was so hygroscopic, that it could not be obtained in an anhydrous form, but rather as the semihydrate of the free dicarboxylic acid.

We have reported already in our first paper,[3] that some of the aromatic anhydrides are dimorphic, *e. g.*, the 4,7-diphenyl derivative (III, R_1 = phenyl; $R_2 = H$). We have observed now a further case of dimorphism: the fluoro derivative (III,8) crystallizes from acetic acid as

(9) Söllscher, *Ber.*, **15**, 1680 (1882); (b) see also Smith, *ibid.*, **24**, 4025 (1891); (c) Vorländer, *ibid.*, **44**, 2455 (1911).

(10) Norris and Blake, THIS JOURNAL, **50**, 1808 (1928).

(11) See Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., Boston, Mass., 1941, p. 192.

(12) Dunlop and Gardner, THIS JOURNAL, **55**, 1665 (1933); see also Kopal, *Rec. trav. chim.*, **34**, 157 (1915).

(13) E. Bergmann and Bondi, *Ber.*, **64**, 1468 (1931).

(14) Stoermer and Simon, *ibid.*, **37**, 4163 (1904).

(15) Anschütz and Hilbert, *ibid.*, **57**, 1697 (1924).

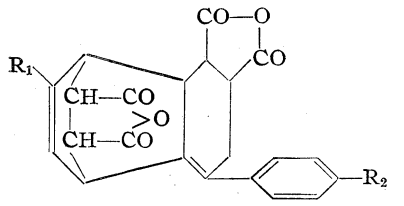
(16) Coates and Sutton, *J. Chem. Soc.*, 567 (1942).

(17) Renoll, THIS JOURNAL, **68**, 1160 (1946).

(18) In these cases, the crude melt was dissolved in ethanol and left for twenty-four hours. In the case of di-(*p*-fluorophenyl)-ethylene (I, $R_1 = R_2 = F$), the bis-adduct crystallized already in the hot melt and was isolated by treatment with methanol.

TABLE III

BIS-ADDUCTS (II)



No.	R_1	R_2	Ratio: e/m[a]	Optimal reaction temp., °C.	Time, hr.	Yield, %	M. p., °C.	Solvent[b]	Crystal form[c]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2	H	CH_3	1:5	150–160	4	80	238–239	A	s. n.	$C_{23}H_{18}O_6$	70.8	70.6	4.6	4.5
3	H	C_2H_5	1:8	150	3	(80)[d]	Amorph.							
4	H	$(CH_3)_2CH$	1:5	150	3	(75)	Amorph.							
5	H	$(CH_3)_3C$	1:5	135	3	(90)	Amorph.							
8	H	F	1:8	150–160	3½	25	302–303	B	t. c.	$C_{22}H_{15}O_6F$	67.0	67.2	3.8	4.1
9	H	Cl	1:5	150	3	60	275–277	C	s. n.	$C_{22}H_{15}O_6Cl$	64.4	64.1	3.7	3.8
11	F	CH_3	1:7	140–150	3	(75)[d]	Sirupy							
12	CH_3	CH_3	1:5	140–150	2	28	238–239	D	f. h. p.	$C_{24}H_{20}O_6$	71.3	71.5	5.0	5.0
13	Cl	Cl	1:10	170–180	1	44	303–305	B	h. c.	$C_{22}H_{14}O_6Cl_2$	59.5	59.7	3.2	3.5
14	F	F	1:7	140–150	3	22	347–348	E	t. r.	$C_{22}H_{14}O_6F_2$	64.1	64.4	3.4	3.7

[a] e/m = ethylene/maleic anhydride. [b] A = butyl acetate; B = acetic anhydride; C = acetic–acid + acetic anhydride; D = butyl acetate + toluene; E = acetic anhydride + butyl acetate. [c] s. n. = short needles; t. c. = triangular columns; f. h. p. = flat hexagonal prisms; h. c. = hexagonal columns; t. r. = thin rods. [d] Because of the amorphous condition of the products, no exact yield can be stated.

a mixture of elongated rods (main form), and prisms (a very small portion) both of m. p. 179° (no depression upon mixing!). The two forms were separated mechanically and recrystallized from acetic acid.

The methyl derivative III,2 formed a mixture of brownish rods of m. p. 183–184°, and pale yellow needles of m. p. 186–187°. The m. p. of a mixture of both forms was 183–184°. Analysis showed that the second form contains half a molecule of water.

The amorphous bis-adduct II,5 gave, upon dehydrogenation, a mixture of two (isomeric ?) anhydrides (III, 5a and b), which again were separated mechanically. The main form crystallized from petroleum ether as yellow blocks of m. p. 158–159°. The second isomer, which was obtained only in a small amount, formed thin rods when recrystallized from the same solvent, m. p. 184–185°. Absorption spectra of the two products give no indication, as to whether they possess isomeric structures.[5]

IV. Decarboxylation

For decarboxylation, the anhydrides were either mixed directly with barium hydroxide (5 parts) and copper bronze (1.5 parts) and subjected to heating (method A) or a dioxane solution of the anhydride was added dropwise to a warm aqueous solution of barium hydroxide, the precipitated salt washed and dried, and then mixed with copper bronze (1.5 parts) (method B).

The degradation of III,2 (III, R_1 = H; R_2 = CH_3) has already been described.[3] The higher alkyl homologs of this compound gave only oils, which upon nitration gave amorphous and non-crystallizable nitro derivatives, unsuitable for comparison. In these cases, therefore, assignment of a certain structure depends entirely on spectrographical evidence.[5] 4-(*p*-Chlorophenyl)-naphthalene-1,2-dicarboxylic acid anhydride (III,9; R_1 = H; R_2 = Cl) was decarboxylated according to method A at 320°. The clear, colorless oil, 1-(*p*-chlorophenyl)-naphthalene (IV,9), could not be induced to crystallization or converted into a crystalline picrate. It was therefore nitrated directly by heating its acetic acid solution with one equivalent of fuming nitric acid to 60° for thirty seconds and pouring on ice. The yellow oil, so obtained, was dissolved in alcohol. The filtered solution, upon cooling, deposited yellow prismatic rods of m. p. 119°.

Anal. Calcd. for $C_{16}H_{10}O_2NCl$: C, 67.8; H, 3.5; N, 4.9. Found: C, 67.7; H, 3.7; N, 5.1.

An authentic sample of IV,9 was prepared in the following manner. To a Grignard solution, prepared from *p*-chloroiodobenzene (18.5 g.), magnesium (2.2 g.) ether (40 cc.) and benzene (40 cc.), was added at 0° a solution of tetralone (10 g.) in benzene (25 cc.). The mixture was refluxed for four hours and then decomposed in the usual way. The crude reaction product was dehydrated by heating to 150° for one hour in the presence of an equal weight of sodium bisulfate. Distillation gave a colorless oil of b. p. 150–152° (0.2 mm.). This product represents 1-(*p*-chlorophenyl)-3,4-dihydronaphthalene; yield 45%.

Anal. Calcd. for $C_{16}H_{13}Cl$: C, 80.0; H, 5.4. Found: C, 80.0; H, 5.6.

The dihydronaphthalene derivative was dehydrogenated with sulfur at 190 → 270° and the product distilled over copper bronze. 1-(*p*-Chlorophenyl)-naphthalene (IV,9) was obtained in quantitative yield; b. p. 151–153° (0.4 mm.).

Anal. Calcd. for $C_{16}H_{11}Cl$: C, 80.7; H, 4.6. Found: C, 80.9; H, 4.9.

Nitration in acetic acid, under the same conditions as described before, gave a mononitro derivative, which crystallized from ethanol in yellow prismatic rods, m. p. 121–122°; mixed m. p. with the above nitro derivative, 119°.

Both nitro compounds were converted by reduction with tin and hydrochloric acid in ethanol into the corresponding amine, which was acetylated directly by acetic anhydride. Water precipitated the crude acetamino derivative, which was recrystallized from dilute acetic acid; short rods of m. p. 215–216°. The mixed m. p. of both acetamino compounds showed no depression.

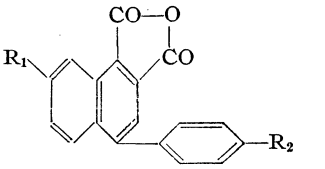
Anal. Calcd. for $C_{18}H_{14}ONCl$: C, 73.2; H, 4.7. Found: C, 73.5; H, 4.9.

4-(*p*-Fluorophenyl)-naphthalene-1,2-dicarboxylic acid anhydride (III,8) was decarboxylated according to method B at 320°. The colorless oil (IV,8), obtained in 27% yield, could not be induced to crystallize and was therefore nitrated directly in the same manner as described before. The nitration product, x(4?)-nitro-1-(*p*-fluorophenyl)-naphthalene, crystallized from ethanol in long yellow blocks of m. p. 104°.

Anal. Calcd. for $C_{16}H_{10}O_2NF$: N, 5.2. Found: N, 5.2.

TABLE IV

DERIVATIVES OF 4-PHENYLNAPHTHALENE-1,2-DICARBOXYLIC ACID ANHYDRIDE (III)



No.	R_1	R_2	Temp. of dehydrogenation, °C.	Range of sublimation temperature, °C.	Mm.	Yield, %	M. p., °C.	Solvent[a]	Crystal form[b]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2	H	CH_3[c]	240 → 270	270–320	0.2	88	183–184	a. a.	b. p.	$C_{19}H_{12}O_3$	79.2	79.4	4.2	4.5
3	H	C_2H_5	240 → 280	250–280	.4	75	162–163	a. a.	l. y. r.	$C_{20}H_{14}O_3$	79.5	79.3	4.6	4.8
4	H	$(CH_3)_2CH$	240 → 280	250–280	.4	Small	132–133	p. e.	t. y. p.	$C_{21}H_{16}O_3$	79.7	79.9	5.1	5.2
5a	H	$(CH_3)_3C$	280	250–300	.2	87	158–159	p. e.	y. p. b.	$C_{22}H_{18}O_3$	80.0	80.2	5.5	5.7
5b	[$(CH_3)_3C$	H ?]	280	250–300	.2	Very small	184–185	p. e.	b. y. r.	$C_{22}H_{18}O_3$	80.0	80.1	5.5	5.8
8	H	F[d]	265 → 300	250–280	.4	50	179	a. a.	y. n.	$C_{18}H_9O_3F$	74.0	74.1	3.1	3.1
9	H	Cl	270 → 300	240–280	.2	67	186–187	a. a.	e. y. r.	$C_{18}H_9O_3Cl$	70.1	70.0	2.9	3.0
11	F	CH_3	275 → 320	300–340	.4	40	195–196	a. a.	e. y. r.	$C_{19}H_{11}O_3F$	74.5	74.3	3.6	3.9
12	CH_3	CH_3	240 → 275	250–280	.5	100	182–183	a. a.	p. y. r.	$C_{20}H_{14}O_3$	79.5	79.3	4.6	4.7
13	Cl	Cl	280 → 310	280–310	.15	50	196–197	a. a.	l. b. p. r.	$C_{18}H_{10}O_4Cl_2 \cdot {}^1/_2H_2O$	58.4	58.7	3.0	2.8
14	F	F	340	280–310	.8	Small	209	a. a.	p. l.	$C_{18}H_8O_3F_2$	69.7	69.4	2.6	2.9

[a] a. a. = acetic acid; p. e. = petroleum ether. [b] b. p. = brown prisms; l. y. r. = long yellow rods; t. y. p. = thin yellow plates; y. p. b. = yellow prismatic blocks; b. y. r. = bright yellow rods; y. n. = yellow needles; e. y. r. = elongated yellow rods; p. y. r. = pointed yellow rods; b. p. r. = light-brown prismatic rods; p. l. = prismatic leaflets. [c] This substance was already described in the first paper of this series.[3] The purest sample, now obtained, melts four degrees higher than before. On working with larger amounts, we obtained a second form; yellow needles of m. p. 186–187° (from acetic acid). Analysis shows this form to be a semihydrate of the anhydride III,2. *Anal.* Calcd. for $C_{19}H_{12}O_3 \cdot {}^1/_2H_2O$: C, 76.8; H, 4.4. Found: C, 77.1; H, 4.6. [d] This anhydride appeared in two crystalline modifications of identical m. p. (see Experimental).

An authentic sample of IV,8 was prepared as in the foregoing case by interaction of tetralone with *p*-fluorophenyl magnesium bromide. 1-(*p*-Fluorophenyl)-3,4-dihydronaphthalene distilled at 120–125° (0.05 mm.) as a nearly colorless oil. It was obtained in 69% yield.

Anal. Calcd. for $C_{16}H_{13}F$: C, 85.7; H, 5.8. Found: C, 85.9; H, 6.0.

Dehydrogenation with sulfur proceeded at 200 → 220°. The product was distilled twice over copper bronze, b. p. 116–118° (0.04 mm.). This sample of 1-(*p*-fluorophenyl)-naphthalene (IV,8) formed a light yellow oil, which crystallized very slowly on standing; from methanol as colorless plates of m. p. 71–72°; yield, quantitative.

Anal. Calcd. for $C_{16}H_{11}F$: C, 86.5; H, 5.0. Found: C, 86.7; H, 4.8.

An acetic acid solution of IVa was heated with one equivalent of fuming nitric acid to 50° for ten seconds and the mixture poured onto ice. The nitro derivative crystallized from ethanol in yellow blocks of m. p. 104–105°, not depressed by admixture of the above nitration product.

Acknowledgment.—The authors wish to thank Prof. L. P. Hammett for his advice and criticism in the theoretical discussion of this investigation.

Summary

Unsymmetrically substituted 1,1-diarylethylenes react with maleic anhydride to yield only one of the two possible isomeric addition products. Substituents can be arranged in two groups: (a) substituents which promote addition to the substituted ring (methoxyl, phenyl); (b) substituents which prevent addition to the substituted ring (halogen, alkyl).

These effects are explained by the electronic influence of substituents on a meta and para position, applying Hammett's σ-values. The reaction mechanism is represented by an electronic cycle, involving electrophilic attack on the β-carbon atom and nucleophilic attack on the ortho position of the diarylethylene.

Symmetrically substituted diarylethylenes undergo the reaction even if they contain substituents of group b.

REHOVOTH, PALESTINE RECEIVED MARCH 12, 1948

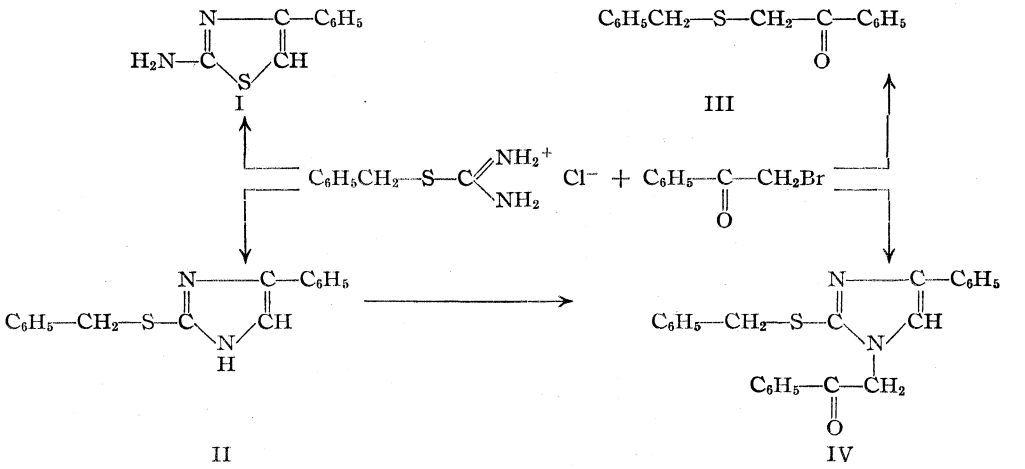
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

The Reaction of S-Benzylisothiourea with Phenacyl Bromide

BY R. M. DODSON

Although thiourea[1] has been used very extensively in the synthesis of heterocyclic compounds the use of S-alkylisothioureas for this purpose has been rather limited. Wheeler[2] and co-workers have used S-methyl- and S-ethylisothioureas in the synthesis of 2-alkylthiopyrimidines. Deck and Dains[3] have used a number of substituted S-methylisothioureas in the synthesis of various heterocyclic rings, but in their syntheses the methylthio group was eliminated. The purpose of this investigation was to extend the use of S-alkylisothioureas to the preparation of alkylthioimidazoles.

It is well known that thiourea reacts with α-haloketones to form 2-aminothiazoles.[1a] This reaction illustrates the preferential alkylation of the thio group in thiourea with alkyl halides. If, however, the thio group is first protected by alkylation, reaction of the S-alkylisothiourea with an α-haloketone should lead to the formation of an alkylthioimidazole. Kunckell[4] has demonstrated that α-haloketones will react with amidines to form imidazoles, and S-alkylisothioureas are merely readily available amidines.



The first attempted preparation of 2-benzylthio-4(5)-phenylimidazole (II) was made by heating equivalent amounts of S-benzylisothiourea hydrochloride and phenacyl bromide over a free flame until a clear melt was obtained. From this reaction 2-amino-4-phenylthiazole (I) rather than the expected imidazole was isolated. The benzyl group was eliminated, and the product was identical with that obtained from the reaction of thiourea with phenacyl bromide.

Condensation of equivalent amounts of S-benzylisothiourea hydrochloride and phenacyl bromide in alcohol in the presence of sodium bicarbonate formed 2-benzylthio-4(5)-phenylimidazole (II) in moderate yield (38%). The product was accompanied by smaller amounts of benzyl phenacyl sulfide (III) and 1-phenacyl-2-benzylthio-4-phenylimidazole (IV). The benzyl phenacyl sulfide (III) was formed concurrently with 2-benzylthio-4(5)-phenylimidazole (II) by the cleavage of the S-benzylisothiourea to benzyl mercaptan, followed by condensation of the mercaptan with phenacyl bromide. The 1-phenacyl-2-benzylthio-4-phenylimidazole (IV)[5,6] was formed by the further reaction of the 2-benzylthio-4(5)-phenylimidazole with phenacyl bromide. The relative quantities of these substances produced in the reaction depended on the conditions. Thus, in 50% aqueous alcohol, cleavage of the S-benzylisothiourea led to the formation of much (50%) benzyl phenacyl sulfide (III), but the 2-benzylthio-4(5)-phenylimidazole (II) (33%) was not alkylated. In absolute alcohol, on the other hand, most of the imidazole was alkylated to 1-phenacyl-2-benzylthio-4-phenylimidazole (IV). When potassium hydroxide was substituted for sodium bicarbonate, cleavage of the S-benzylisothiourea predominated and benzyl phenacyl sulfide (III) was formed in very good yield (81%). The 1-

(1) (a) V. Traumann, *Ann.*, **249**, 31 (1888); (b) M. Jackman, A. J. Bergman and S. Archer, THIS JOURNAL, **70**, 497 (1948); (c) R. Anschütz and H. Geldermann, *Ann.*, **261**, 129 (1891).

(2) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(3) J. F. Deck and F. B. Dains, THIS JOURNAL, **55**, 4986 (1933).

(4) F. Kunckell, *Ber.*, **34**, 637 (1901).

(5) It is realized that this compound could be alternately formulated as 1-phenacyl-2-benzylthio-5-phenylimidazole. Structure IV is preferred by the author because Pyman and co-workers have found that 4(5)-phenylimidazole, on treatment with methyl sulfate, yields 1-methyl-4-phenylimidazole and 1-methyl-5-phenylimidazole in the proportions of 4.8 to 1.

(6) C. E. Hazeldine, F. L. Pyman and J. Winchester, *J. Chem. Soc.*, **125**, 1431 (1924).

phenacyl-2-benzylthio-4-phenylimidazole (IV) was best prepared (73%) by heating an alcoholic solution of one mole of S-benzylisothiourea hydrochloride and two moles of phenacyl bromide under reflux with sodium bicarbonate. The concurrent formation of benzyl phenacyl sulfide (III) and the further reaction of the imidazole with phenacyl bromide satisfactorily explain the moderate yield of 2-benzylthio-4(5)-phenylimidazole obtained.

The formation of 2-amino-4-phenylthiazole on fusion of S-benzylisothiourea hydrochloride with phenacyl bromide introduced the possibility that compound II was 2-benzylamino-4-phenylthiazole, formed by the migration of the benzyl group. This necessitated a proof of structure of the compound. On treatment with acetyl iodide[7] the 2-benzylthio-4(5)-phenylimidazole (II) was cleaved to 2-thiol-4(5)-phenylimidazole, identical with the compound previously prepared by Clemo and coworkers.[8]

Experimental[9]

2-Amino-4-phenylthiazole (I).—A dry mixture of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride, m. p. 172–175°, and 5.00 g. (0.025 mole) of phenacyl bromide was cautiously heated over a free flame until molten. The reaction was stopped when the solution started to boil. The resulting melt was cooled and extracted with 100 ml. of dilute (1:10) hydrochloric acid. The acid extract was decanted through a filter, and the excess acid was neutralized with sodium bicarbonate. The precipitate was separated by filtration and crystallized from benzene. From this reaction 1.57 g. (36%) of 2-amino-4-phenylthiazole, m. p. 149.5–150°, was obtained.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.34; H, 4.58. Found: C, 61.55; H, 4.67.

The acetyl derivative, prepared by the action of acetic anhydride, melted at 212.5°. 2-Amino-4-phenylthiazole and its acetyl derivative are reported to melt at 151–152° and 214–214.5°, respectively.[10]

2-Amino-4-phenylthiazole was also formed in the same yield when the mixture of S-benzylisothiourea hydrochloride and phenacyl bromide were heated under vacuum in an oil-bath at 150–160° until distillation of volatile material ceased.

2-Benzylthio-4(5)-phenylimidazole (II).—A solution of phenacyl bromide in 100 ml. of chloroform, prepared by the bromination of 30.0 g. (0.25 mole) of acetophenone, was added to a solution of 51.0 g. (0.25 mole) of S-benzylisothiourea hydrochloride in 300 ml. of 84% ethyl alcohol. To this combined solution 84.0 g. (1.0 mole) of sodium bicarbonate was added slowly and the suspension heated under reflux for three hours. The solvent was then distilled from the reaction mixture. The residue was treated with 300 ml. of warm water and heated on the steam-bath until all of the inorganic salts had dissolved. The suspension was cooled and decanted through a filter. The product was washed a second time with warm water and dried. It was next treated with 100 ml. of boiling benzene; all lumps were broken; the resulting suspension was cooled in ice, and the product was separated by filtration. The process was repeated with 50 ml. of benzene and the product finally washed on the filter with two 25-ml. portions of cold benzene. From this reaction 25.1 g. (37.7%) of 2-benzylthio-4(5)-phenylimidazole, m. p. 173–177°, was obtained. One crystallization of the compound from alcohol raised its melting point to 176.5–177.5°.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.01; H, 5.38; N, 10.23.

The picrate was prepared in boiling alcohol, m. p. 145–145.5°.

Anal. Calcd. for $C_{22}H_{17}N_5O_7S$: C, 53.33; H, 3.46. Found: C, 53.59; H, 3.52.

The benzene mother liquors from the above preparation were thoroughly shaken with 150 ml. of dilute (1:6) hydrochloric acid. The hydrochloride was separated by filtration and washed on the filter with 100 ml. of water, 100 ml. of ether, and finally 30 ml. of water, then crystallized from alcohol. A solution of this salt in alcohol was made basic with ammonium hydroxide, heated to boiling, diluted with water until slightly cloudy, then cooled. The product was separated by filtration and washed on the filter with 20 ml. of 70% ethyl alcohol. In this way 7.2 g. (15% based on the phenacyl bromide consumed) of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 141.5–143°, was obtained. Crystallization of the compound from alcohol raised its melting point to 143–143.5°.

Anal. Calcd. for $C_{24}H_{20}N_2OS$: C, 74.95; H, 5.24. Found: C, 74.96; H, 5.36.

The organic mother liquors from the filtration of the above hydrochloride were distilled and the residue was crystallized from 95% alcohol. Very crude benzyl phenacyl sulfide (18.2 g.), m. p. 64–76°, was obtained. Repeated crystallizations from alcohol failed to give a pure product. Crystallization from a mixture of benzene and petroleum ether (b. p. 60–70°) gave 11.2 g. (18.5%) of benzyl phenacyl sulfide, m. p. 87.5–88°. A mixture with an authentic sample of benzyl phenacyl sulfide showed no depression of melting point.

From the above benzene and petroleum ether mother liquors a small quantity (1.6 g.) of dibenzyl disulfide, m. p. 69.5–70° was isolated. For purposes of identification this was oxidized to benzyl benzylthiolsulfonate ("dibenzyl disulfoxide"), m. p. 106.5–107°. The reported melting points of these compounds are 72 and 108°, respectively.[11]

Benzyl Phenacyl Sulfide (III).—To a boiling solution of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride and 5.00 g. (0.025 mole) of phenacyl bromide in 50 ml. of ethyl alcohol was added a solution of 3.50 g. (0.0625 mole) of potassium hydroxide in 20 ml. of ethyl alcohol. The resulting suspension was heated under reflux for two hours. It was then cooled to 5°, and the product separated by filtration. The product was washed on the filter with 10 ml. of cold alcohol, then suspended in warm water and stirred thoroughly to free it from potassium bromide and potassium chloride, then again separated from the solution by filtration. From this reaction 4.90 g. (81%) of benzyl phenacyl sulfide, m. p. 86–87°, was obtained. Crystallization of the compound from alcohol raised its melting point to 87.5–88.5°. Oxidation with potassium permanganate gave benzyl phenacyl sulfone, m. p. 112°. The reported melting points of benzyl phenacyl sulfide and benzyl phenacyl sulfone are 89° and 113°, respectively.[12]

1-Phenacyl-2-benzylthio-4-phenylimidazole (IV).—To a solution of 5.10 g. (0.025 mole) of S-benzylisothiourea hydrochloride and 10.00 g. (0.050 mole) of phenacyl bromide in 50 ml. of absolute alcohol was added 8.4 g. (0.10 mole) of sodium bicarbonate. The resulting suspension was heated under reflux for two and one-half hours with periodic shaking, then diluted with water. The product was separated by filtration, powdered, and treated with 200 ml. of ether. The resulting suspension on filtration yielded 5.33 g. of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 139–143°. The ether mother liquors were next extracted with 75 ml. of dilute (1:2)

(7) E. L. Gustus and P. G. Stevens, THIS JOURNAL, **55**, 378 (1933).

(8) G. R. Clemo, T. Holmes and G. C. Leitch, *J. Chem. Soc.*, 753 (1938).

(9) Microanalyses by Messrs. Roger Amidon, Jay Buckley, and William Hunter. All melting points were taken on a Fisher–Johns melting-point apparatus.

(10) R. M. Dodson and L. C. King, THIS JOURNAL, **67**, 2242 (1945).

(11) E. Fromm and J. de Seixas Palma, *Ber.*, **39**, 3308, 3317 (1906)

(12) C. Wahl, *ibid.*, **55**, 1449 (1922).

hydrochloric acid, and the insoluble hydrochloride treated according to the directions given above. An additional 1.68 g. of 1-phenacyl-2-benzylthio-4-phenylimidazole, m. p. 136–139°, was obtained. The total yield of crude product was 7.01 g. or 73%. One crystallization from dilute alcohol gave 6.37 g. of material, m. p. 141.5–142.5°. A mixture with the previously prepared sample showed no depression of melting point. This same product can be made in 78% yield by alkylating 2-benzylthio-4(5)-phenylimidazole with phenacyl bromide in alcohol in the presence of sodium bicarbonate.

The picrate of 1-phenacyl-2-benzylthio-4-phenylimidazole was prepared by mixing the base and picric acid in hot alcohol, m. p. 169–171°.

Anal. Calcd. for $C_{30}H_{23}N_5O_8S$: C, 58.72; H, 3.78. Found: C, 58.90; H, 3.74.

2-Thiol-4(5)-phenylimidazole.—Red phosphorus (3.7 g.) was added to 15 g. of iodine in 25 ml. of glacial acetic acid, and the resulting suspension was heated under reflux for twenty minutes. Then 3.00 g. of 2-benzylthio-4(5)-phenylimidazole was added and the solution was heated under reflux for three and one-half hours. The solution was filtered to free it from phosphorus, decolorized with sodium bisulfite, diluted with two volumes of water, and neutralized with ammonium hydroxide. The resulting suspension was cooled in ice, and the product was separated from the solution by filtration. To free the 2-thiol-4(5)-phenylimidazole from starting material, it was dissolved in 50 ml. of 10% sodium hydroxide solution. After separating the insoluble 2-benzylthio-4(5)-phenylimidazole (0.34 g., m. p. 172–175°), the filtrate was neutralized with 8 ml. of glacial acetic acid, and cooled. On filtration 1.13 g. (64% on the basis of the starting material consumed) of 2-thiol-4(5)-phenylimidazole, m. p. 249–255°, was obtained. Crystallization of the compound from a mixture of acetone and benzene raised its melting point to 261–262°. The picrate, formed in absolute alcohol, crystallized as garnet-red prisms, m. p. 178–179° (dec.). For further identification of 2-thiol-4(5)-phenylimidazole was oxidized with dilute nitric acid to 4(5)-phenylimidazole, m. p. 130–131°; 4(5)-phenylimidazole nitrate, m. p. 167–167.5° (dec.). These physical constants agree well with those previously recorded for these compounds.[8,13]

Summary

1. It has been shown that the reaction of S-benzylisothiourea with phenacyl bromide can form any one of four products, 2-amino-4-phenylthiazole, benzyl phenacyl sulfide, 2-benzylthio-4-(5)-phenylimidazole and 1-phenacyl-2-benzylthio-4-phenylimidazole, depending upon the conditions of the reaction.

2. The 2-benzylthio-4(5)-phenylimidazole was cleaved to the known 2-thiol-4(5)-phenylimidazole by the action of acetyl iodide.

(13) R. L. Grant and F. L. Pyman, *J. Chem. Soc.*, **119**, 1893 (1921).

MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 16, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Synthesis of Some Substituted 2-Thiouracils

BY HENRY GILMAN AND H. SMITH BROADBENT

Considerable interest has developed within the last few years in the treatment of hyperthyroid disturbances by chemical means.[1] Among the most effective substances employed have been 2-thiouracil and some of its derivatives. In the course of a study of the chemotherapeutic properties of several types of nitrogen and sulfur containing compounds, it was decided, therefore, to synthesize several derivatives of 2-thiouracil for examination.

The 6-substituted-2-thiouracils were prepared by the usual method of condensing β-oxo esters with thiourea in the presence of sodium ethoxide.

Three different methods were employed in the preparation of the necessary β-oxo esters. They were the alkylation of ethyl acetoacetate, the Claisen condensation of esters, and the carbethoxylation of ketones with ethyl carbonate.

By alkylating sodio ethyl acetoacetate with γ-diethylaminopropyl chloride and with γ-diethylaminopropyl β-chloroethyl sulfide, the respective β-oxo esters, 1-diethylamino-4-carbethoxyhexanone-5 and 1-(γ-diethylaminopropylmercapto)-3-carbethoxypentanone-4, were prepared, isolated, and some of their important physical constants determined as well as those of some of their precursor compounds.

We were unable to condense successfully these two complex β-oxo esters with thiourea to form 2-thiouracils by the usual procedures. Only polymeric, gummy residues, quite unlike the probable properties of the expected compounds, were obtained. Anderson, *et al.*,[2] report the formation of unidentified by-products in considerable amount in preparing some of the longer chain (butyl, *n*-amyl, *n*-hexyl) 6-substituted-2-thiouracils. The yields in these condensations are not high at best.

The α-, β-, and γ-pyridoylacetates were prepared by the Claisen condensation of the pyridinecarboxylic acid esters and ethyl acetate. Although these β-oxo esters have been reported heretofore,[3,4,5,6] it was found possible to prepare the first two of them in greatly improved yields by a suitable modification of the Claisen condensation procedure using benzene as a diluent. The preparation of the necessary sodium ethoxide *in situ* in benzene suspension also obviates the necessity of preparing fresh, anhydrous, solid sodium ethoxide for the condensation as is usually done. The isolation of pure liquid ethyl picolinoylacetate does not appear to have been done. Pinner[3] isolated it as its sodium salt; Burrus and Powell[4] obtained it as

(1) Roblin, *Chem. Rev.*, **38**, 255 (1946).

(2) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(3) Pinner, *Ber.*, **34**, 4237 (1901).

(4) Burrus and Powell, THIS JOURNAL, **67**, 1468 (1945).

(5) Bloom, Breslow and Hauser, *ibid.*, **67**, 2207 (1945).

(6) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948).

TABLE I

2-THIOURACIL DERIVATIVES

Compound	Procedure	M. p., °C.[a]	Yield, %	Recrystallized from	Formula	Analyses, % N Calcd.	N Fd.	S Calcd.	S Fd.
6-(α-Pyridyl)-2-thiouracil	A	291–294 dec.	29	Gl. AcOH	$C_9H_7ON_3S$	20.48	20.70		
6-(β-Pyridyl)-2-thiouracil[b]	A	296–298 dec.	38	Gl. AcOH	$C_9H_7ON_3S$	20.48	20.42		
6-(γ-Pyridyl)-2-thiouracil	A	355–358 dec.	50	[d]	$C_9H_7ON_3S$			15.62	15.73
6-(*p*-Methoxylphenyl)-2-thiouracil[c]	A	285–288 dec.	31	Gl. AcOH	$C_{11}H_{10}O_2N_2S$	11.96	12.10		
6-(α-Thienyl)-2-thiouracil	A	293–296 dec.	30.5	Gl. AcOH	$C_8H_6ON_2S_2$	13.3	13.6		
2-(γ-Diethylaminopropyl-mercapto)-4-hydroxy-6-methylpyrimidine	B	B. p. 183–188° (0.4 mm.)	82	.....	$C_{12}H_{21}ON_3S$	16.46	16.65		
2-(*p*-Nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine	B	220–221	89	Dioxane–water	$C_{12}H_{11}O_3N_3S$			11.56	11.32
2-(*p*-Nitrophenethylmercapto)-4-hydroxy-6-methylpyrimidine	B	Softens 222 Melts 224–226 dec.	62	Dioxane–propanol	$C_{13}H_{13}O_3N_3S$			11.01	11.08

[a] All melting points were taken on a Berl–Kullman block. [b] Two years after this work was completed the preparation of this compound was reported by others.[6,8] The first group gives its melting point as 296–298°. The second gives *ca.* 291°. [c] Two years after this work was completed, the preparation of this compound was reported by others[6] who report its melting point as 226–227°, a value we were unable to substantiate. [d] Insoluble in all ordinary organic solvents. It was purified by dissolving it in alkali, filtering, reprecipitating with acetic acid, and washing with water.

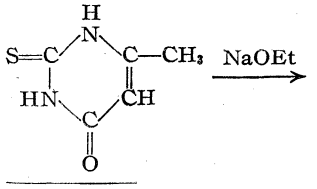
its hydrochloride; however, it was found possible to distil the free base with little decomposition and isolate the slightly impure liquid, which can be kept for a long time with very little change.

The method of Camps[7] has usually been used in esterifying the pyridinecarboxylic acids. He reports yields of 90, 90 and 91%, respectively, for the α-, β- and γ-isomers; however, later workers have not been able to duplicate his yields. Burrus and Powell[4] obtained yields of 61 and 30% of the β- and γ-isomers, respectively, by Camps' method. We were able to prepare ethyl nicotinate in 72% yield by Camps' method. By employing a different esterification procedure, ethyl isonicotinate was conveniently secured in 61.4% yield.

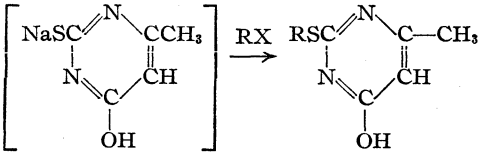
The 6-pyridyl-2-thiouracils (see table) are very high melting solids, quite insoluble in organic solvents. In fact, the γ-isomer is almost completely insoluble in acetic acid, nitrobenzene, carbitol, aniline, pyridine, quinaldine, tri-*n*-butyl phosphate, and all common solvents at their boiling temperatures; however, all three of them are readily soluble in strong acids and bases.

Ethyl *p*-anisoylacetate and ethyl β-(2-thienyl)-oxopropionate were prepared by the carbethoxylation with ethyl carbonate and sodamide of the corresponding ketones. The former tends to decompose on distilling even at low pressures.

Mercapto derivatives of 6-methyl-2-thiouracil were prepared as follows



(7) Camps, *Arch. Pharm.*, **240**, 346 (1902).



Neither *o*- nor *p*-nitrobromobenzene were found to be sufficiently reactive to undergo metathesis in our hands with a suspension of the sodium salt of the thiouracil in absolute ethanol, although they will readily condense with ordinary sodium mercaptides under such conditions. With 2,4-dinitrochlorobenzene a very insoluble product was secured; however, its isolation in a pure form was not accomplished.

γ-Diethylaminopropyl chloride, *p*-nitrobenzyl chloride and *p*-nitrophenethyl bromide, all substituted aliphatic halides, condensed easily with the sodium salt of 6-methyl-2-thiouracil forming the corresponding mercapto derivatives.

The attempted preparation of 2-(*p*-aminobenzylmercapto)-4-hydroxy-6-methylpyrimidine and 2-(*p*-aminophenethylmercapto)-4-hydroxy-6-methylpyrimidine by the catalytic reduction of their corresponding nitro compounds over Raney nickel catalyst resulted in the formation of resinous polymers containing less than the required amount of sulfur in both cases. The correct amount of hydrogen was absorbed for complete reduction of the nitro groups and then hydrogenation ceased. Johnson and Bailey[9] report that 2-ethylmercapto-4-hydroxy-5-ethyl-6-methylpyrimidine slowly reacts with aniline in ethanolic solution forming 2-anilino-4-hydroxy-5-ethyl-6-methylpyrimidine. It appears probable, therefore,

(8) Jackman, Bergman and Archer, THIS JOURNAL, **70**, 497 (1948).

(9) Johnson and Bailey, *ibid.*, **35**, 1010 (1913).

that the desired aminoaralkylmercaptouracils were first formed on reduction, but later polymerized forming the anilino linkage with adjacent molecules to some extent.

The pharmacological results are to be published elsewhere, and the authors are grateful to Parke, Davis and Company for arranging for the tests.

Experimental

1-Diethylamino-4-carbethoxyhexanone-5.—Sodio ethyl acetoacetate, 0.22 mole, was prepared in 80 ml. of absolute ethanol, and the mixture was gently refluxed while 30 g. (0.2 mole) of γ-diethylaminopropyl chloride was added dropwise over a two-hour period. After six hours of refluxing it was cooled, and filtered free of 10.6 g. of sodium chloride (11.6 g. theoretical).

After the bulk of the ethanol was distilled from the filtrate, the residue was poured into water and extracted with ether. From the aqueous layer considerable polymeric gum, likely arising from quaternization of the γ-diethylaminopropyl chloride, was obtained on evaporation. After drying the ether extract and evaporating the solvent, the residue was distilled through a ten-inch Vigreux column. The principal fraction amounted to 23 g. boiling at 116–129° (1 mm.). On refractionation 17.8 g. (36.5%) of product was collected at 107–109° (0.5 mm.): $n^{20}D$ 1.4514; d^{20}_4 0.956; $M^{20}D$ calcd. 69.06 (keto) 70.10 (enol); $M^{20}D$ obs. 69.0.

On another 0.35-mole run using freshly distilled γ-diethylaminopropyl chloride about 60% of it was added all at once to the refluxing sodio acetoacetic ester solution, and two hours later the remainder was added. After twenty hours of refluxing, the mixture was worked up as before. The residue on distillation gave 53.6 g. (63%) of clear, colorless product at 100–107° (largely at 104–105°) (0.4 mm.): $n^{20}D$ 1.4509.

Anal. Calcd. for $C_{13}H_{26}O_3N$: N, 5.73. Found: N, 5.57.

1-(γ-Diethylaminopropylmercapto)-3-carbethoxypentanone-4.—γ-Diethylaminopropyl β-chloroethyl sulfide was prepared according to the directions of Gilman and Tolman.[10] From 91 g. (1.17 moles) of β-hydroxyethanethiol and 174.5 g. (1.17 moles) of γ-diethylaminopropyl chloride, 191.5 g. (86%) of γ-diethylaminopropyl β-hydroxyethyl sulfide boiling at 105° (1.1 mm.) was obtained. Some physical constants which have not been determined heretofore are: $n^{20}D$ 1.4957; d^{20}_4 0.9830; M_D calcd. 57.3, found 56.8. This was converted to the corresponding chloro compound with thionyl chloride giving 53.5 g. (57%) of product boiling at 84–95° (0.3–0.4 mm.) (bath 112–132°). The constants, which have not been determined heretofore, are: $n^{20}D$ 1.4890; d^{20}_4 1.000; $M^{20}D$ calcd. 60.7, found 60.5. It was conveniently stored as its hydrochloride and recovered as the free base, just prior to use. The freshly distilled γ-diethylaminopropyl β-chloroethyl sulfide, 22.6 g. (0.108 mole) was added dropwise with stirring over a five-hour period to a refluxing solution of 0.12 mole of sodio ethyl acetoacetate in absolute ethanol. Upon working up the product and two fractionations 11 g. (33.5%) of the desired β-oxo ester was obtained boiling at 147–150° (0.4 mm.): $n^{20}D$ 1.4811; d^{20}_4 1.005; $M^{20}D$ calcd. 85.2 (keto), 86.3 (enol), found 86.0.

Anal. Calcd. for $C_{15}H_{29}O_3NS$: S, 10.6. Found: S, 10.8.

Ethyl Picolinoylacetate.—This ester was prepared according to the method of Gilman, Tolman and Massie,[11] who did not, however, isolate the product but hydrolyzed it directly to the ketone *in situ*.

To 13.8 g. (0.6 atom) of sodium sand in 550 ml. dry benzene, 27.6 g. (0.6 mole) of absolute ethanol was added dropwise at such a rate as to promote gentle reflux until all the sodium had reacted. Then a mixture of 60.4 g. (0.4 mole) of ethyl picolinate[12] and 70.4 g. (0.8 mole) of dry ethyl acetate was slowly run into the refluxing suspension. After the addition was complete, the thick sludge was filtered. The precipitate was dissolved in water, treated with an excess of acetic acid, and the liberated ester extracted with ether, dried, and distilled. One portion weighing 24.4 g. was collected at 115–120° (0.4 mm.), $n^{20}D$ 1.5181, and another weighing 29.9 g. at 122–124° (0.5 mm.), $n^{20}D$ 1.5184, d^{20}_4 1.1639, M_D obs. 50.37; M_D calcd. 50.37.[13] Both portions were red when first collected, but soon changed to a straw color on standing; total yield, 54.3 g. (70%).

The identity of the product was established by refluxing a 0.01-mole portion with an equivalent of phenylhydrazine in 10 ml. of ethanol containing a few drops of acetic acid as a catalyst. On cooling, yellow needles of 1-phenyl-3-(α-pyridyl)-pyrazolone-5 melting at 177–178° were obtained: yield, 2 g. (85%) (reported,[3] 179°).

Ethyl Nicotinate.—One hundred grams (0.813 mole) of nicotinic acid was warmed on the steam-bath with a mixture of 250 ml. ethanol and 125 ml. concd. sulfuric acid until all the solid dissolved. After cooling the mixture was poured into 2 kg. of cracked ice and 350 g. of potassium carbonate, then filtered. The filtrate was saturated with sodium carbonate and extracted with ether. On evaporation of the ether the residue yielded on distillation, 88 g. (72%) of colorless, liquid ester boiling at 107–108° (16 mm.).

Ethyl Nicotinoylacetate.—A suspension of 0.75 mole of sodium ethoxide was prepared in 690 ml. of benzene in the manner described above. To this a mixture of 88 g. (1.0 mole) of anhydrous ethyl acetate and 75.5 g. (0.5 mole) of ethyl nicotinate was added slowly under reflux. After twelve hours of refluxing the liquid became clear. The benzene was distilled off on the steam-bath and the residual gum hydrolyzed with an excess of dilute acetic acid. After adding an excess of potassium carbonate, the ester was extracted with ether, dried and distilled. The product was collected as 64.5 g. (67%) of pale, slightly straw-colored oil boiling at 121–123° (0.4 mm.) (reported, by other modifications of the Claisen condensation: 37%[4] as the hydrochloride, and 58%[5]).

Ethyl Isonicotinate.—Isonicotinic acid was prepared by oxidizing 200 g. (2.15 mole) of γ-picoline (technical grade) in 3 l. of water with a total of 680 g. (4.30 mole) of potassium permanganate added portionwise (the reaction easily becomes violent.) A yield of 155 g. (59%) of pure acid was obtained from the acidified filtrate without reworking the mother liquors.

One hundred and forty grams (1.14 moles) of isonicotinic acid suspended in 980 ml. of absolute ethanol was cooled to 0° while dry hydrogen chloride was bubbled in until the solution was saturated. Then with the gas still being slowly passed in, it was refluxed until the solid all dissolved. The excess ethanol was removed under reduced pressure, the solid dissolved in water, cooled and treated with an excess of saturated sodium carbonate solution, filtered and extracted with ether. On distillation 105.5 g. (61.4%) of clear, colorless ester was obtained boiling at 105–108° (16–17 mm.) (reported[4]: 30% yield by the method of Camps).

Ethyl Isonicotinoylacetate.—The technique used in this preparation was parallel to that used in synthesizing the β-pyridoyl isomer. From 0.5 mole of ethyl isonicotinate 66.4 g. (69%) was obtained boiling at 118–120° (0.4 mm.), m. p. 53–55° (reported[5]: m. p. 54°, in 85% yield by another technique).

(10) Gilman and Tolman, THIS JOURNAL, **67**, 1847 (1945).

(11) Gilman, Tolman and Massie, *ibid.*, **68**, 2399 (1946).

(12) Kindly supplied by S. P. Massie of these laboratories.

(13) The calculated value will vary a great deal depending on the numerical contribution to the total molecular refraction assigned to the pyridine moeity of the molecule. The calculated value shown was obtained using the atomic and structural factors given in Gilman, "Organic Chemistry," Vol. II, 2nd ed., John Wiley and Sons, New York, 1943, p. 1751, and considering the contributions of the three double bonds in pyridine as equal to 3 × 1.73 = 5.19. The close agreement is undoubtedly fortuitous under the circumstances.

Ethyl *p*-Anisoylacetate.—To sodamide prepared from 9.2 g. (0.4 atom) of sodium in 250 ml. of liquid ammonia 30 g. (0.2 mole) of *p*-methoxyacetophenone dissolved in 100 ml. of dry ether was added with vigorous stirring. The excess ammonia was evaporated off and replaced with ether. Under reflux 47.2 g. (0.4 mole) of ethyl carbonate was then added. After stirring the fluid grayish black suspension under reflux for five hours, a semi-solid mass resulted which was hydrolyzed with acetic acid and extracted with ether. After drying and evaporating the solvent, the residue was distilled with some decomposition giving 11.9 g. (26.8%) of clear, viscous oil at 155–158° (0.6–0.7 mm.) (reported,[14] boiling point 180–190° (10–12 mm.) with decomposition, prepared by another method).

The identity of the ester, prepared by this method for the first time, was established by refluxing a small portion in ethanol with hydroxylamine hydrochloride. Long, slender, white needles of 3-(*p*-methoxyphenyl)-isoxazolone-5 were obtained melting at 140–141° (reported,[15] 143°).

Ethyl *β*-(2-Thienyl)-*β*-oxopropionate.—According to the procedure of Levine and Hauser,[12] 0.4 mole of 2-acetothienone was carbethoxylated in the presence of sodamide. A yield of 33.3 g. (84%) of viscous, oily ester distilling at 121–123° (0.4–0.5 mm.) was obtained (reported,[16] 48% yield boiling at 150–153° (5 mm.)).

6-(α-Pyridyl)-2-thiouracil. Procedure A.—The procedure used was substantially that of Anderson, *et al.*[2] Thiourea, 3.8 g. (0.05 mole), and 8.95 g. (0.05 mole) of ethyl picolinoylacetate were added to 0.1 mole of sodium ethoxide in ethanol. Almost immediately a precipitate began to form. After refluxing overnight, the solvent was removed under reduced pressure, the residue taken up in water, filtered, and acidified with acetic acid. The precipitate was filtered off, dried and recrystallized from 200 ml. of glacial acetic acid. Three grams (29%) of hard, well formed crystals with a faint greenish cast was obtained. They melted with slight decomposition at 291–294°. The procedure followed in preparing the other 6-substituted-2-thiouracils was analogous.

2-(γ-Diethylaminopropylmercapto)-4-hydroxy-6-methylpyrimidine. Procedure B.—A suspension of the sodium salt of 6-methyl-2-thiouracil was prepared by digesting 7.1 g. (0.05 mole) of the thiouracil in a solution of 0.05 mole of sodium ethoxide in 50 ml. of ethanol at reflux temperature for two hours. Then 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride in 25 ml. of ethanol was added, and the mixture was stirred under reflux for six hours. The cooled mixture was filtered free of sodium chloride and the solvent evaporated. On distillation 10.5 g. (82.4%) of a colorless, very viscous oil, almost a glass, was obtained boiling at 183–188° (0.4 mm.). It was very soluble in ethanol, insoluble in water and ligroin, and sparingly soluble in ether. We were not successful in obtaining a crystalline hydrochloride.

The other two compounds prepared by this method (procedure B) were themselves insoluble in ethanol; consequently, the reaction mixture slurry was exhaustively washed with water to remove inorganic substituents and the residue recrystallized to constant melting point (see Table I).

Catalytic Reduction of 2-(*p*-Nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine and its Next Higher Homolog.—Ten grams (0.036 mole) of the former compound suspended in 200 ml. dioxane with 2–3 g. Raney nickel catalyst was shaken under 4 atm. pressure of hydrogen. The calculated amount of hydrogen for complete reduction of the nitro group was absorbed in five hours, then the uptake of hydrogen ceased. After filtering and removing the solvent under reduced pressure, a hard, red glass softening gradually above 110° was obtained. It was ground to a resinous, yellow powder and dried *in vacuo* at 110° for analysis.

Anal. Calcd. for $C_{12}H_{13}ON_3S$: S, 12.69. Found: S, 10.83.

From a similar treatment of the next higher homolog, the phenethyl derivative, an orange vitreous mass, insoluble in ether and ethanol, was obtained which could not be crystallized. It melted *ca.* 55–70°. This polymeric material also gave a low analysis for sulfur.

Anal. Calcd. for $C_{13}H_{15}ON_3S$: S, 12.27. Found: S, 11.17.

Summary

1. Some new derivatives of 2-thiouracil have been prepared for evaluation as antithyroid agents.

2. Two new *β*-oxo esters have been isolated and improved techniques for the preparation of some others and their precursory starting materials have been described.

3. Catalytic reduction of 2-(*p*-nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine and its next higher homolog was found to initiate a complex reaction yielding polymeric substances.

AMES, IOWA RECEIVED MAY 7, 1948

(14) Wahl and Silberzweig, *Bull. soc. chim.*, [4] **11**, 27 (1912).
(15) Wahl, *Compt. rend.*, **148**, 353 (1909).
(16) Levine and Hauser, THIS JOURNAL, **66**, 1769 (1944).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXII. Piperazinium Salts for Utilization in Identification of Organic Acids

BY M. PRIGOT AND C. B. POLLARD

In previous papers[1,2] from this Laboratory certain piperazinium salts were reported for utilization in identification of organic acids. The present paper describes an improved method of preparation, and data concerning thirty-six new piperazinium salts are shown in Table I.

Experimental

The respective acid was dissolved in anhydrous ether or propanol-2 in a Waring blendor. The calculated amount of piperazine was added as 1 *M* piperazine in propanol-2 during vigorous stirring. The precipitate was suction filtered, added to fresh ether or propanol-2, stirred again in a Waring blendor, refiltered and dried in a desiccator over phosphorus pentoxide before physical constants were determined. For purposes of qualitative analysis plate drying is usually sufficient. Acids which were quite insoluble in ether or propanol-2 were dissolved in water before addition of piperazine. This necessitated evaporation on a steam-bath to recover the piperazinium salts.

Melting points are corrected and were determined by use of a bronze block, preheated to within 5° of the m. p.

Neutral equivalents were determined by dissolving the salt in 50% aqueous propanol-2 and titrating with 0.1 *N*

(1) Pollard and Adelson, THIS JOURNAL, **56**, 150 (1934).
(2) Pollard, Adelson and Bain, *ibid.*, **56**, 1759 (1934).

TABLE I

DATA CONCERNING PIPERAZINIUM SALTS DERIVED FROM VARIOUS ORGANIC ACIDS

Acids, common name of acid	Yield, %	Piperazinium salts: Melting point, °C. cor.	Neutral equivalents Calcd.	Neutral equivalents Found	Nitrogen, % Calcd.	Nitrogen, % Found
o-Benzoylbenzoic	78	186.2–186.6	287	289	4.88	4.79
o-Bromobenzoic	90	227–230 dec.	244	241	5.74	5.87
m-Bromobenzoic	74	169–171	244	250	5.74	5.52
p-Bromobenzoic	49	224–226	244	240	5.74	5.75
α-Bromopropionic	73	195 dec.	196	192	7.14	6.96
Dichloroacetic[b]	62	181 dec.	343.9	339.7	8.15	8.22
n-Capric	49	92.5–93.5	215	219	6.50	6.51
n-Caprylic	32	97.5–98.0	187	184	7.48	7.51
o-Chlorobenzoic	81	217–218 dec.	200	194	7.02	6.93
p-Chlorobenzoic	67	219–220 dec.	200	199	7.02	6.76
trans-Cinnamic	92	206 dec.	191	190	7.33	7.46
Citric	100	141–142	139	137	10.1	10.4
Ethoxyacetic	73	120–121	147	145	9.55	9.60
p-Ethoxybenzoic	76	176.2–177.0 dec.	209	211	6.70	6.10
Fumaric	98	240 dec.	101	105	13.9	13.5
α-Furoic	94	234–236 dec.	155	160	9.03	8.84
Gallic	84	209.0–209.7 dec.	213	[a]	6.57	6.57
Hippuric	82	182–184 dec.	222	222	12.6	12.0
Lauric	77	92.0–92.5	243	243	5.76	5.86
Maleic	92	148	101	102	13.85	13.43
Methoxyacetic	80	155.7–156.4	133	132	10.52	10.41
o-Methoxybenzoic	92	190.4–191.4	195	196	7.18	7.03
m-Methoxybenzoic	89	136.9–138.5 dec.	195	202	7.18	7.26
α-Naphthoic	48	131.5–139.0 dec.	215	216	6.51	6.45
β-Naphthoic	89	194.0–195.0 dec.	215	217	6.51	6.46
p-Nitrocinnamic	90	247.9–248.7 dec.	232	232	11.86	11.59
p-Nitrophenylacetic	96	205.5–205.9 dec.	224	225	12.49	12.39
4-Nitrophthalic	96	201.5–204.5 dec.	149	149	14.14	13.7
Pelargonic	60	95.1–96.2	201	198	7.03	6.96
Phenoxyacetic	84	183.7–184.2 dec.	195	195	7.18	6.94
o-Phthalic[b]	91	187–188	139	139	6.69	6.73
Isophthalic	77	251.7–252.2 dec.	126	126	11.2	11.1
Terephthalic	52	Dec. above 350	126	127	11.2	10.9
d-Tartaric	86	248–254	118	117	11.9	11.2
meso-Tartaric	87	140–141	118	119	11.9	11.5
p-Toluic	79	203.0–203.3	179	181	7.82	7.61

[a] Solution too dark to titrate. [b] Previously prepared by Pollard, Adelson and Hampton, but not reported.

sodium hydroxide using either thymolphthalein or Orange II as indicator.

By the method employed the following acids failed to give salts which are of practical value for qualitative organic analysis: α-bromo-*n*-butyric, anthraquinone-β-sulfonic, barbituric, 2-chloropropionic, 2,5-dichlorobenzenesulfonic, 2,4-dichlorophenoxyacetic, diethylacetic, diphenylacetic, erucic, glycine, *p*-hydroxybenzoic, iodoacetic, itaconic, levulinic, *dl*-methylethylacetic, mucic, 1-naphthol-4-sulfonic, sulfosalicylic, thioglycolic, and trimesic.

Summary

Thirty-six new piperazinium salts which may be utilized for the identification of organic acids are reported.

Twenty organic acids which failed to give suitable derivatives are listed.

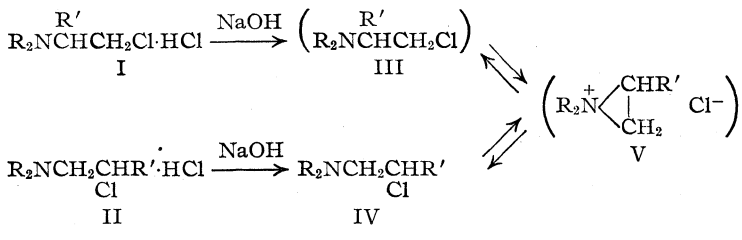
GAINESVILLE, FLORIDA RECEIVED APRIL 10, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Ring Enlargement by Rearrangement of the 1,2-Aminochloroalkyl Group; Rearrangement of 1-Ethyl-2-chloromethylpyrrolidine to 1-Ethyl-3-chloropiperidine

BY REYNOLD C. FUSON AND CHARLES L. ZIRKLE[1]

Recently it has been found that 1,2-aminochloroalkanes undergo a rearrangement[2] analogous to that of 2-chloroisopropyl sulfides.[3] In all examples thus far studied, the amines liberated from the isomeric 1,2-aminochloroalkane hydrochlorides (I and II) are identical and possess the normal structure (IV).[2b,c,d,4] This rearrangement of



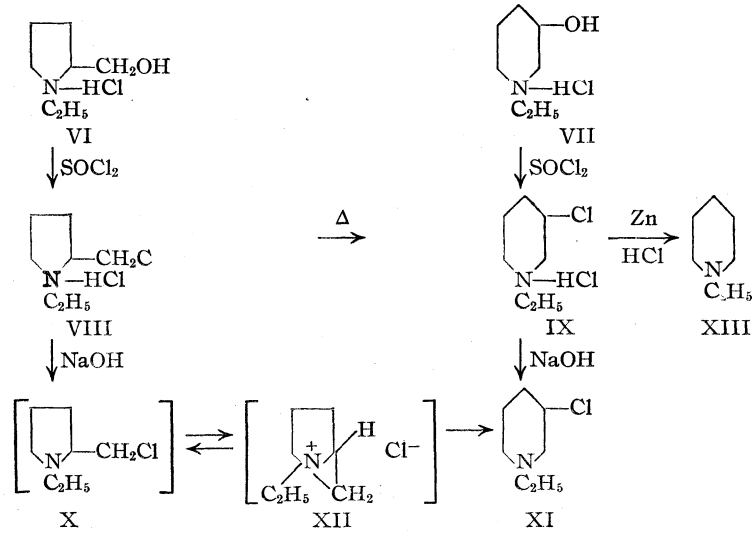
I III V

II IV

chloro amines of structure I is believed to occur through the cyclic imonium chloride intermediate (V). It has been shown that ethyleneimonium salts of this type are formed in other reactions of 2-haloalkylamines.[5]

This behavior of 2-chloroalkylamines suggested the interesting possibility that 1-alkyl-2-chloromethyl cyclic imines—compounds in which the chlorine is in the 2-position to a cyclic tertiary amino group—by a similar rearrangement might undergo ring enlargement, providing a route to 1-alkyl-3-chloro cyclic imines having one more carbon in the ring. We have accomplished such a ring enlargement by rearrangement of 1-ethyl-2-chloromethylpyrrolidine hydrochloride (VIII) to 1-ethyl-3-chloropiperidine (XI).

It was found that when 1-ethyl-2-chloromethylpyrrolidine hydrochloride (VIII), prepared from the corresponding amino alcohol hydrochloride (VI) by treatment with thionyl chloride, was treated with alkali, the free base obtained was not the pyrrolidine derivative (X) but the isomeric 1-ethyl-3-chloropiperidine(XI). Presumably the 1-ethyl-2-chloromethylpyrrolidine (X) underwent rearrangement as rapidly as it was formed, the cyclic imonium salt (XII) being the intermediate. That the chloromethyl pyrrolidine (X) did not rearrange when in the form of its hydrochloride (VIII) was demonstrated by the fact that the picrate formed from the salt was different from that obtained from the free amine. The picrate of the distilled amine was identical with that prepared from the crude base, indicating that no change in the chloro amine occurred during distillation. The chloropiperidine (XI), prepared from 1-ethyl-3-hydroxypiperidine hydrochloride (VII), did not rearrange when liberated from its salt (IX). The free amine after being distilled formed a picrate identical with



that from the original piperidine hydrochloride and that of the free base obtained from the chloromethylpyrrolidine hydrochloride (VIII). For additional proof that the amine isolated from the isomeric chloro amine salts was the piperidine derivative, 1-ethyl-3-chloropiperidine hydrochloride (IX) was converted to 1-ethylpiperidine (XIII) by means of zinc and hydrogen chloride in glacial acetic acid.

(1) Smith, Kline and French Laboratories Walter G. Karr Fellow 1947–1948.

(2) (a) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947); **69**, 2454 (1947); (b) Schultz and Sprague, *ibid.*, **70**, 48 (1948); (c) Brode and Hill, *ibid.*, **69**, 724 (1947); (d) Kerwin, Ullyot, Fuson and Zirkle, *ibid.*, **69**, 2961 (1947); (e) Ross, *ibid.*, **69**, 2982 (1947).

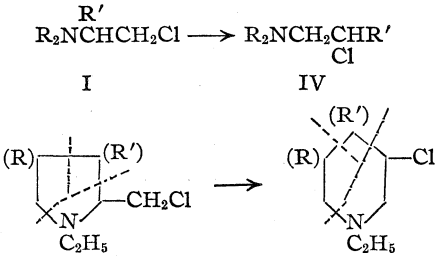
(3) Fuson, Price and Burness, *J. Org. Chem.*, **11**, 475 (1946).

(4) Schultz and Sprague (ref. 2b) reported that 2-dimethylamino-1-chloropropane did not rearrange immediately when liberated from its hydrochloride at room temperature, but did change to the isomeric 1-dimethyl-2-chloropropane upon distillation.

(5) (a) Gilman and Phillips, *Science*, **103**, 409 (1946); (b) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946); (c) Golumbic and Bergmann, *ibid.*, **11**, 536 (1946); (d) Fruton and Bergmann, *ibid.*, **11**, 543 (1946); (e) Golumbic, Stahmann and Bergmann, *ibid.*, **11**, 550 (1946); (f) Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947); (g) Bartlett, Davis, Ross and Swain, *ibid.*, **69**, 2977 (1947); (h) Cohen, Van Artsdalen and Harris, *ibid.*, **70**, 281 (1948).

The experiments described above indicate that 1-ethyl-2-chloromethylpyrrolidine is stable in the form of its hydrochloride (VIII). In fact, this salt sublimed without change at temperatures below its melting point. The picrate formed from the sublimed hydrochloride was identical with that obtained from the original chloromethylpyrrolidine hydrochloride. At temperatures above its melting point, however, the pyrrolidine salt rearranged to 1-ethyl-3-chloropiperidine hydrochloride. This property has been found to be general for 1,2-aminochloroalkane hydrochlorides of type I.[2a,b,c,d] Upon rapid heating the pyrrolidine salt (VIII) melted at 165–170°, solidified, and remelted at 193.5–194.0°. When the temperature was raised slowly the isomeric hydrochlorides and a mixture of the two salts had the same melting point (193.5–194.9°), although the picrates prepared from the hydrochlorides differ in melting point.

The direction of rearrangement in this isomeric pair of cyclic chloro imines is that observed in other 1,2-aminochloroalkanes, *i. e.*



However, in some of their reactions, *e. g.*, hydrolysis and alkylation,[2a,b,c,d,e] the 2-chloro-*n*-propylamines (IV, R = CH_3) sometimes yield products containing the isopropylamino group—a change which is the reverse of that found in the isomerization of these chloro amines. Undoubtedly the ease and direction of rearrangement is determined by the steric and polar nature of both the intermediate cyclic imonium ion and the attacking nucleophilic agent. When the latter is chloride ion, the product appears to be that of structure IV exclusively.

Work is now in progress to determine whether other 1-alkyl-2-chloromethyl cyclic imines also undergo this rearrangement.

Experimental

1-Ethyl-2-hydroxymethylpyrrolidine.—This amino alcohol was prepared by the synthesis of Signaigo and Adkins.[6a] Hydrogenation[7] of 1,2-dicarbethoxypyrrole[6b] over Raney nickel in dry methanol at 70° and 1500 lb. pressure gave a 95% yield of 1,2-dicarbethoxypyrrolidine[6a]; b. p. 133–135° (8 mm.) (Signaigo and Adkins reported 133–134° (8 mm.)). The latter (33.6 g., 0.156 mole) in absolute ethanol upon hydrogenation at 250° and 100 atm. in the presence of 10 g. of copper chromite yielded 6.3 g. (31%) of 1-ethyl-2-hydroxymethylpyrrolidine; b. p. 78–79° (17 mm.); $n^{23}D$ 1.4659 (reported: b. p. 82–84° (24 mm.); $n^{25}D$ 1.4662). The hydrochloride, prepared by saturating a dry toluene solution of the amine with hydrogen chloride, separated as an oil which resisted all attempts at recrystallization. The benzoate hydrochloride of the amino alcohol separated as an oil when a mixture of the alcohol and an equimolar amount of benzoyl chloride in dry toluene was heated for an hour on the steam-bath. On standing overnight in the ice-box the oil solidified as waxy needles but all attempts to recrystallize the solid failed. A picrate was formed by adding a concentrated solution of the benzoate hydrochloride to a saturated aqueous solution of picric acid; m. p. 170.5–171.5° after two recrystallizations from acetone.

Anal. Calcd. for $C_{20}H_{22}O_9N_4$: C, 51.95; H, 4.80; N, 12.12. Found: C, 51.68; H, 4.62; N, 12.16.

1-Ethyl-3-hydroxypiperidine.—By the method of Paul,[8] diethyltetrahydrofurfurylamine[8] was converted to 1-ethyl-3-hydroxypiperidine in 43% yield; $n^{23}D$ 1.4744. The benzoate hydrochloride melted at 198–199° (203–204° (cor.)) (Paul reported a boiling point of 97–98° (21 mm.); $n^{23}D$ 1.47427; benzoate hydrochloride, m. p. 204°). A benzoate picrate was prepared as described above for comparison with that of 1-ethyl-2-hydroxymethylpyrrolidine. The yellow crystals recrystallized from acetone melted at 181.5–182.5°.

Anal. Calcd. for $C_{20}H_{22}O_9N_4$: N, 12.12. Found: N, 12.08.

The amino alcohol formed a hydrochloride (VII) which melted at 157–158° after recrystallization from ethyl acetate–ethanol.

Anal. Calcd. for $C_7H_{16}ONCl$: C, 50.75; H, 9.74; N, 8.46. Found: C, 50.93; H, 9.64; N, 8.26.

1-Ethyl-2-chloromethylpyrrolidine Hydrochloride (VIII).—To a flask equipped with a mechanical stirrer and a condenser fitted with a calcium chloride tube was added 4.0 g. (0.031 mole) of 1-ethyl-2-hydroxymethylpyrrolidine in 25 ml. of dry chloroform. The flask was immersed in an ice–salt-bath and the solution saturated with dry hydrogen chloride to form the salt of the amino alcohol (VI). With stirring 4.8 g. (0.040 mole) of thionyl chloride in a few milliliters of chloroform was added dropwise to the cold solution of amine hydrochloride. After all the thionyl chloride was added the mixture was stirred for thirty minutes at room temperature, then refluxed for one hour. The dark crystalline product after removal of solvent was triturated with acetone and collected on a filter. Two recrystallizations of the slightly discolored solid from acetone–ethanol gave 3.2 g. (56%) of the chloro amine hydrochloride. When the bath temperature was raised rapidly (20° per minute), the hydrochloride melted at 165–170°, solidified, and remelted at 193.5–194.0° (rate of heating, two degrees per minute). When the temperature was raised slowly, the sample contracted without melting at 165° and melted at 193.5–194.0°. A mixture melting point with 1-ethyl-3-chloropiperidine hydrochloride (IX) showed no depression. These observations indicate that upon heating the two isomeric salts rearrange to the same compound.

Anal. Calcd. for $C_7H_{15}NCl_2$: C, 45.66; H, 8.21; N, 7.61; Cl, 38.52. Found: C, 45.56; H, 7.86; N, 7.45; Cl, 38.56.

A picrate prepared by adding a concentrated solution of the chloro amine hydrochloride to a saturated aqueous solution of picric acid was recrystallized from ethanol; m. p. 128.5–129.5°.

Anal. Calcd. for $C_{13}H_{17}O_7N_4Cl$: C, 41.44; H, 4.55; N, 14.87; Cl, 9.41. Found: C, 41.59; H, 4.45; N, 14.73; Cl, 9.43.

The pyrrolidine hydrochloride sublimed without change at 90° (2 mm.). The picrate prepared from the sublimed salt was identical with that obtained from the hydrochloride before sublimation.

Evaporation of the acetone with which the crude 1-ethyl-2-chloromethylpyrrolidine hydrochloride was washed

(6) (a) Signaigo and Adkins, THIS JOURNAL, **58**, 709 (1936); (b) **58**, 1122 (1936).

(7) The hydrogenations were performed by Mr. David J. Wallace.

(8) Paul, *Bull. soc. chim.*, **12**, 830 (1945).

yielded a dark water-soluble oil which formed a picrate (1.4 g.) when added to saturated aqueous picric acid solution. After repeated crystallizations from ethanol the picrate (0.4 g.) melted at 163.5–164.5°. The analytical values for this compound are in close agreement with those calculated for the picrate of 1-methyl-2-chloromethylpyrrolidine.

Anal. Calcd. for $C_{12}H_{15}O_7N_4Cl$: C, 39.73; H, 4.14; N, 15.45; Cl, 9.77. Found: C, 39.91; H, 3.99; N, 15.32; Cl, 9.79.

It is possible that the 1-ethyl-2-hydroxymethylpyrrolidine from which the corresponding chloro compound was prepared contained a small amount of 1-methyl-2-hydroxymethylpyrrolidine which would form the 1-methyl chloro compound upon treatment with thionyl chloride. Some of the N-methyl alcohol would be formed along with the N-ethyl alcohol if, upon hydrogenation of 1,2-dicarbethoxypyrrolidine, the 1-carbethoxy group were reduced to a methyl group instead of being removed by hydrogenolysis and replaced by an ethyl group from the ethanol present to form 1-ethyl-2-hydroxymethylpyrrolidine. Contamination of the latter compound by the 1-methyl alcohol would explain the fact that a pure crystalline hydrochloride and benzoate hydrochloride could not be obtained from 1-ethyl-2-hydroxymethylpyrrolidine.

If the unknown chloro amine is 1-methyl-2-chloromethylpyrrolidine, it was thought that the free base probably would rearrange to 1-methyl-3-chloropiperidine. An attempt to demonstrate this gave inconclusive results. The picrate of the unknown amine (0.3 g.) was treated with 20% sodium hydroxide and the free base separated by extraction with several small portions of chloroform. The combined extracts were dried for three hours over anhydrous calcium sulfate, filtered, and saturated with hydrogen chloride. Evaporation of the solvent left a crystalline residue of amine hydrochloride which formed a picrate (0.2 g.) when added to picric acid solution. After recrystallization from ethanol the picrate melted at 148–150°. Four additional crystallizations raised the melting point to 156–159°. A mixture melting point with the original unknown picrate (m. p. 163.5–164.5°) showed no depression. Evidently the picrate of the free base was a mixture, possibly of the unrearranged chloromethylpyrrolidine and 1-methyl-3-chloropiperidine picrates. An insufficient amount of material prevented further investigation of the unknown chloro amine.

1-Ethyl-3-chloropiperidine Hydrochloride (IX).—To a suspension of 5.0 g. (0.030 mole) of 1-ethyl-3-hydroxypiperidine hydrochloride (VII) in 50 ml. of dry toluene was added 3.7 g. (0.031 mole) of thionyl chloride. The mixture was refluxed for three hours during which time the solid disappeared and two layers formed. Removal of the toluene at the water-pump left a dark solid residue which, after recrystallization from ethyl acetate–ethanol (activated carbon), gave 4.8 g. (87%) of slightly discolored crystals. After two additional crystallizations the 1-ethyl-3-chloropiperidine hydrochloride melted at 193.5–194.0°. A mixture of this salt with 1-ethyl-2-chloromethylpyrrolidine hydrochloride showed no depression in melting point. The picrate prepared from the hydrochloride melted at 159–160° after recrystallization from ethanol (Paul[9] reported a melting point of 156–157°).

The Free Amine from 1-Ethyl-2-chloromethylpyrrolidine Hydrochloride.—An ice-cold solution of 1.5 g. of the chloro amine hydrochloride (VIII) in 3 ml. of water was treated with 0.5 g. of sodium hydroxide in 2 ml. of water. The liberated amine was removed by extraction with three 5-ml. portions of chloroform. A small sample of the combined extracts was withdrawn immediately, the solvent evaporated rapidly under an air stream, and the residue added to a saturated aqueous solution of picric acid. The picrate after recrystallization from ethanol melted at 159–160° and showed no depression in melting point when mixed with that obtained from 1-ethyl-3-chloropiperidine hydrochloride, indicating that 1-ethyl-2-chloromethylpyrrolidine, when liberated from its salt, rearranges at room temperature to the piperidine isomer. The remainder of the chloroform solution of the free base was dried overnight over anhydrous calcium sulfate. After removal of the solvent the chloro amine (0.8 g.) distilled at 75–76° (20 mm.); $n^{20}D$ 1.4676 (reported for 1-ethyl-3-chloropiperidine:[9] b. p. 75° (20 mm.); $n^{19.5}D$ 1.46807). The picrate of the distilled amine was identical with that of the crude amine.

The Free Amine from 1-Ethyl-3-chloropiperidine Hydrochloride.—The chloro amine hydrochloride was treated with sodium hydroxide as described above. The isolated base distilled at 74–76° (20 mm.); $n^{20}D$ 1.4678. These constants agree well with those of the free amine from 1-ethyl-2-chloromethyl pyrrolidine hydrochloride. The picrate of the distilled amine was identical with that prepared from 1-ethyl-3-chloropiperidine hydrochloride, indicating that no rearrangement occurred during the liberation and distillation of the chloro amine.

Treatment of 1-Ethyl-3-chloropiperidine Hydrochloride with Zinc and Hydrogen Chloride.—To 1.5 g. of the chloro amine hydrochloride dissolved in glacial acetic acid was added 15 g. of zinc dust. The mixture was saturated with hydrogen chloride and heated on the steam-bath. Every two to three hours the solution was resaturated with hydrogen chloride. After all of the zinc was in solution another 15 g. of the metal was added and the process repeated. The reaction mixture was made strongly basic with sodium hydroxide and steam distilled into hydrochloric acid, the condenser outlet being kept slightly below the surface of the acid in the receiver. After evaporation of the distillate on the steam-bath, the residue of amine hydrochloride was treated with concentrated sodium hydroxide and the liberated base extracted with chloroform. The extract was dried overnight over anhydrous calcium sulfate. Removal of the solvent and distillation of the residue through a narrow 5-cm. Vigreux column yielded 0.4 g. of 1-ethylpiperidine, b. p. 129–130°.[10] About 0.4 g. of high-boiling material remained in the distillation flask. The picrate of the piperidine melted at 167–168°[10] and showed no depression when mixed with an authentic sample of 1-ethylpiperidine picrate.

Summary

1-Ethyl-2-chloromethylpyrrolidine, when liberated from its hydrochloride, undergoes ring enlargement by a rearrangement similar to that observed in other 1,2-aminochloroalkanes, to form 1-ethyl-3-chloropiperidine. The transformation probably occurs through an ethyleneimonium ion intermediate.

URBANA, ILLINOIS RECEIVED APRIL 14, 1948

(9) Paul, *Compt. rend.*, **221**, 412 (1945).

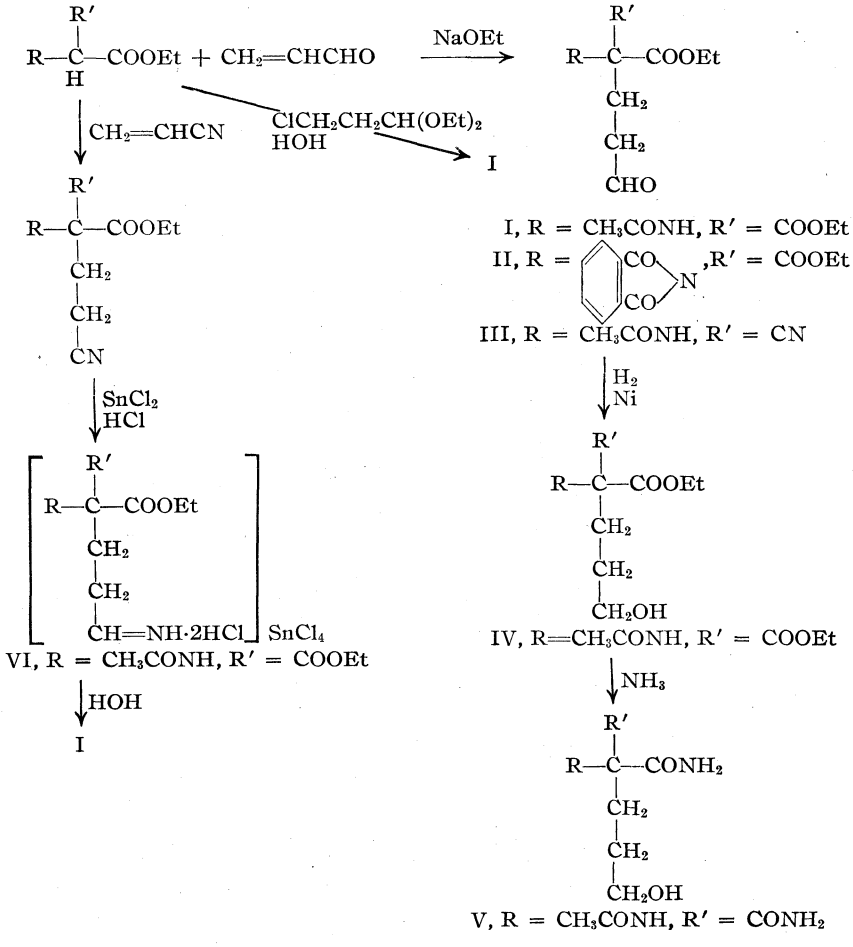
(10) Evans, *J. Chem. Soc.*, **71**, 524 (1897), reported a boiling point of 128°; picrate, m. p. 167.5°.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

1,4-Addition Reactions. I. The Addition of Acylamidomalonates to Acrolein[1a]

BY OWEN A. MOE AND DONALD T. WARNER

The 1,4-addition reactions between malonate systems and α,β-unsaturated aldehydes have not been reported. Instead, under the conditions employed, a Knoevenagel condensation occurs and the reaction involves a 1,2-addition. However, the latter reaction requires two α-hydrogen atoms for completion (addition followed by loss of water) whereas the former reaction requires only one α-hydrogen atom. Since both reactions, 1,2-addition and 1,4-addition, are reversible, it appeared that a 1,4-addition reaction of acrolein might be realized provided the addend possessed only one, but sufficiently reactive, α-hydrogen atom.



This paper describes the successful 1,4-addition of three such compounds (ethyl acetamidomalonate, ethyl phthalimidomalonate and ethyl acetamidocyanoacetate) to acrolein. The products, obtained in excellent yields, have structures I, II and III, respectively.

(1a) Paper No. 89, Journal Series, Research Laboratories, General Mills, Inc.

The 1,4-addition of ethyl acetamidomalonate to acrolein proceeded smoothly in an alcoholic solution in the presence of catalytic quantities of sodium ethoxide. Because of the exothermic character of the reaction, the acrolein was added at a slow rate to a stirred suspension of ethyl acetamidomalonate. Concentration of the neutralized solution yielded γ-acetamido-γ,γ-dicarbethoxybutyraldehyde I as a straw-colored, viscous oil. The action of phenylhydrazine on either the original reaction mixture or the viscous oil yielded the crystalline phenylhydrazone of compound I in 65–85% yield. The 1,4-addition of ethyl acetamidomalonate to acrolein also proceeded smoothly in the absence of alcohol when benzene was used as the solvent and the phenylhydrazone was obtained in 87% yield directly from the reaction mixture.

The reaction between ethyl phthalimidomalonate and acrolein yielded γ,γ-dicarbethoxy-γ-phthalimidobutyraldehyde II which was characterized as the phenylhydrazone and the 2,4-dinitrophenylhydrazone. Ethyl acetamidocyanoacetate yielded a crystalline adduct (γ-acetamido-γ-carbethoxy-γ-cyanobutyraldehyde) which was characterized as the crystalline 2,4-dinitrophenylhydrazone.

The structure of the aldehydo compound I was proved by two different syntheses. The first method involved the alkylation of ethyl acetamidomalonate with β-chloropropionaldehyde diethylacetal. Hydrolysis of the product with dilute acid gave compound I. In the second synthesis, ethyl α-acetamido-α-carbethoxy-γ-cyanobutyrate[1] was reduced by the action of stannous chloride and hydrogen chloride.[2] The resulting crystalline complex was readily hydrolyzed with warm water to I. As a by-product there resulted a crystalline compound melting at 181–182°. The an-

(1) Albertson and Archer, THIS JOURNAL, **67**, 2043 (1945).

(2) (a) Stephen, *J. Chem. Soc.*, **127**, 1874 (1925); (b) Williams, THIS JOURNAL, **61**, 2248 (1939).

alysis indicated that this compound was ethyl α-acetamido-α-carbethoxy-γ-carbamylbutyrate.

The aldehydo compound I, subjected to hydrogenation in the presence of Raney nickel, gave the crystalline carbinol IV which was characterized as the 3,5-dinitrobenzoate and the *p*-nitrobenzoate. Action of concentrated ammonia upon IV yielded the diamido compound V which in turn yielded a *p*-nitrobenzoate.

Experimental[3]

The 1,4-Addition of Ethyl Acetamidomalonate to Acrolein. A. In Alcohol.—A mixture containing ethyl acetamidomalonate[4] (87.4 g.), sodium (0.1 g.) and absolute ethanol (200 cc.) was chilled in an ice-bath to 3° to produce a thin slurry. Acrolein (25.9 g.) was added dropwise with stirring over a period of seventy-five minutes while the reaction temperature was maintained at 3–7°. A clear, light yellow solution resulted after an additional hour of stirring. The reaction mixture was allowed to stand for an additional ninety minutes at 3° and then the catalyst was neutralized with glacial acetic acid (0.35 g.). The total volume of the reaction mixture was 290 cc. A portion (135 cc.) of the reaction mixture was treated with 4 g. of acetic acid and 22 g. of phenylhydrazine. After warming to 50° the solution was diluted with 7 cc. of water and cooled overnight. The crystalline product was collected by filtration and dried. The phenylhydrazone (44 g.) thus obtained melted at 135–137°. The filtrate was diluted with water and an additional quantity (6.4 g.) of the phenylhydrazone was obtained. After crystallization from aqueous ethanol the phenylhydrazone melted at 140–141°.

Anal. Calcd. for $C_{18}H_{25}O_5N_2$: C, 59.5; H, 6.94; N, 11.58. Found: C, 59.8; H, 7.17; N, 11.41.

B. In Benzene.—Ethyl acetamidomalonate (217 g.) was suspended in benzene (330 cc.) containing a catalytic amount of sodium methoxide (0.5 g.). The resulting reaction mixture was cooled in a water-bath at 19°. Acrolein (68.5 cc.) dissolved in benzene (70 cc.) was added dropwise at a moderate rate. The temperature increased rapidly to 35°. Following the addition of the acrolein the reaction mixture was stirred for an additional two hours and filtered. The clear, yellow filtrate was treated with 24 cc. of glacial acetic acid and 120 g. of phenylhydrazine. After warming to 50° the resulting orange-colored solution was set aside for a period of two days. The crystalline derivative was collected by filtration and washed with 150 cc. of benzene. It was further decolorized by suspension in 250 cc. of benzene, filtered and dried *in vacuo*. The yield of the phenylhydrazone of the aldehydo compound I was 315.1 g. (87%) melting at 140–141°. The crystals were nearly white in color.

Reduction of γ-Acetamido-γ,γ-dicarbethoxybutyraldehyde.—The crude aldehydo compound (46.9 g.) was dissolved in ethanol and Raney nickel catalyst (4.8 g.) was added. The resulting mixture (290 cc.) was hydrogenated for two and one-half hours at a temperature of 85–95° and an initial pressure of 1700 pounds. After cooling, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Benzene was added to the residual oil and the solution was again concentrated. This procedure was repeated three times in order to complete removal of the alcohol. Then ether was added and the carbinol IV crystallized from the ether solution. After drying the crystalline product weighed 14.2 g. and melted at 75–77°. Evaporation of the ethereal filtrate yielded additional quantities of the carbinol IV. Purification by recrystallization from ether increased the melting point to 80–81°.

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.36; H, 7.74; N, 5.09. Found: C, 52.62; H, 8.15; N, 5.30.

The 3,5-dinitrobenzoate and the *p*-nitrobenzoate were prepared in the usual manner and after purification melted at 151–152° and 79–80°, respectively.

Anal. Calcd. for $C_{19}H_{23}O_{11}N_3$: C, 48.6; H, 4.95; N, 8.96. Found: C, 48.86; H, 5.40; N, 9.06. Calcd. for $C_{19}H_{24}O_9N_2$: N, 6.61. Found: N, 6.78.

The carbinol IV, ethyl α-acetamido-α-carbethoxy-δ-hydroxyvalerate, was converted to α-acetamido-α-carbamyl-δ-hydroxyvaleramide by treatment with a concentrated ammonia solution (saturated at 0°). The diamido compound V thus obtained melted at 170–171° after recrystallization from ethanol.

Anal. Calcd. for $C_8H_{15}O_4N_3$: C, 44.22; H, 6.96; N, 19.34. Found: C, 44.15; H, 6.91; N, 19.33.

The *p*-nitrobenzoate of the diamido compound V was prepared in the usual manner and it melted at 242–243° with decomposition.

Anal. Calcd. for $C_{15}H_{18}O_7N_4$: N, 15.30. Found: N, 15.25.

Preparation of γ,γ-Dicarbethoxy-γ-Phthalimidobutyraldehyde.—An alcoholic solution containing 90 cc. of absolute ethanol and 60 mg. of sodium was mixed with 20.4 g. of ethyl phthalimidomalonate, and the resulting reaction mixture was cooled to 5°. Acrolein (4.7 cc.) was added dropwise and the temperature of the reaction mixture increased to 20°. After the addition of the acrolein was complete, the reaction mixture was neutralized by the addition of 0.5 cc. of glacial acetic acid, and a nearly colorless solution resulted. The alcoholic solution of the aldehydo compound II was used directly for the preparation of the phenylhydrazone and the 2,4-dinitrophenylhydrazone which melted at 150–151° and 167–168°, respectively.

Anal. Calcd. for $C_{24}H_{25}O_6N_3$: C, 63.84; H, 5.58. Found: C, 64.08; H, 5.89. Calcd. for $C_{24}H_{23}O_{10}N_5$: C, 53.24; H, 4.29; N, 12.94. Found: C, 53.13; H, 4.12; N, 13.15.

Preparation of γ-Acetamido-γ-carbethoxy-γ-cyanobutyraldehyde.—An alcoholic solution containing 60 cc. of absolute ethanol and 50 mg. of sodium was mixed with 17 g. of ethyl acetamidocyanoacetate and the resulting suspension was cooled in a water-bath. Acrolein (7.5 cc.) was added dropwise, and after the addition was complete the reaction was stirred for two hours and finally neutralized with the requisite quantity of glacial acetic acid. The reaction mixture was filtered, and the filtrate was placed in the refrigerator for a period of twenty-four hours when a copious quantity of needle-like crystals was noted. The crystalline product was collected by filtration and dried. The yield of the crude aldehydo compound III was 15 g. melting at 106–109°. Purification by crystallization from 95% ethanol increased the melting point to 113.5–114.5°.

Anal. Calcd. for $C_{10}H_{14}O_4N_2$: C, 53.56; H, 6.29; N, 12.50. Found: C, 53.10; H, 5.93; N, 12.20.

The 2,4-dinitrophenylhydrazone prepared in the conventional manner melted at 196–197° after purification.

Anal. Calcd. for $C_{16}H_{18}O_7N_6$: C, 47.29; H, 4.46; N, 20.69. Found: C, 47.52; H, 4.44; N, 20.86.

When the above addition reaction was carried out using benzene as the reaction diluent, the aldehydo compound III was obtained in 82% yield and melted at 111–112.5°.

Alkylation of Ethyl Acetamidomalonate with β-Chloropropionaldehyde Diethylacetal.—Ethyl acetamidomalonate (10.9 g.) was added to an alcoholic sodium ethoxide solution containing 1.15 g. of sodium and 100 cc. of absolute ethanol. The above reaction mixture was heated to the reflux temperature and β-chloropropionaldehyde diethylacetal[5] (8.3 g.) was added over a ten-minute period. The reflux temperature was maintained for a period of twenty-four hours. The reaction mixture had developed a light orange color. The precipitated sodium chloride was removed after cooling, and the filtrate was concentrated under reduced pressure. The residual oil was clari-

(3) Micro analyses by Mr. Harold Boyd and Miss Katherine Tellor.

(4) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944).

(5) Witzemann, Evans, Hess and Schroeder, "Organic Syntheses," **11**, 26 (1931).

fied by filtration, and the product thus obtained weighed 11.35 g. and was insoluble in water. A portion (5.2 g.) of the above crude diethylacetal of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde was suspended in 15 cc. of water and 3.5 cc. of 1 *N* sulfuric acid was added. The resulting reaction mixture was warmed over a steam-bath for five to six minutes with vigorous swirling. The insoluble acetal hydrolyzed rapidly to yield a clear, light yellow solution. This solution was treated with 0.5 g. of sodium acetate and concentrated *in vacuo* to a volume of 11 cc. The addition of 33 cc. of ethanol caused an immediate precipitate which was removed by filtration and proved to be inorganic. The clear filtrate was mixed with one cc. of acetic acid and 4.8 cc. of phenylhydrazine. The resulting reaction mixture was heated to 55° and after cooling and diluting with water a crystalline product (0.4 g.) was collected by filtration. The filtrate was further diluted with water and yielded an additional crop of crystals (0.53 g.). The crude phenylhydrazone of the aldehydo compound I thus obtained melted at 128–132° and after crystallization from dilute ethanol it melted at 138–140°. The melting point was not depressed when mixed with the phenylhydrazone prepared by the first method.

Reduction of Ethyl α-Acetamido-α-carbethoxy-γ-cyanobutyrate.—The ethyl α-acetamido-α-carbethoxy-γ-cyanobutyrate was prepared in accordance with the directions given by Albertson and Archer.[1]

Anhydrous stannous chloride (41.6 g.) was suspended in anhydrous ether (320 cc.) and anhydrous hydrogen chloride was passed into the reaction mixture until the formation of two layers was noted. The substituted cyanobutyrate (26.8 g.) was dissolved in 125 cc. of chloroform and the resulting solution was added slowly over a ninety-minute period as the reaction mixture was stirred, and dry hydrogen chloride was passed in for four hours with vigorous stirring. The introduction of the hydrogen chloride was then interrupted; however, the stirring was continued overnight. The following day the introduction of hydrogen chloride was continued for an additional period of eighteen hours at which time a few crystals had appeared. The reaction mixture was then permitted to stand at room temperature for a period of five days. After this total reaction time of one week the aldimine complex had precipitated as a white crystalline product. The complex was collected by filtration, washed with ether and dried *in vacuo* (weight, 65 g.). The odor of hydrogen chloride was noted. A portion of the above complex VI (15 g.) was mixed with 100 cc. of water and warmed to 50°. The clear, aqueous solution which resulted was extracted twice with 100 cc. portions of chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate. After filtration the chloroform was removed by distillation *in vacuo* and a viscous oil remained which partially crystallized on standing. This residue was dissolved in a small quantity of ethanol, and a few drops of acetic acid were added together with a slight excess of phenylhydrazine. The resulting reaction mixture was warmed on a steam-bath and after cooling and diluting with water a crystalline product was obtained. The crude phenylhydrazone of the aldehydo compound I melted at 133–137°. After crystallization from dilute ethanol it melted at 138–140°.

The above aqueous solution was again extracted with chloroform. After drying, the chloroform was removed under reduced pressure and a crystalline residue remained. This crude product melted at 135–155° and after crystallization from dilute ethanol it melted at 181–182°. The analysis of this product indicated that it was probably ethyl α-acetamido-α-carbethoxy-γ-carbamylbutyrate.

Anal. Calcd. for $C_{12}H_{20}O_6N_2$: C, 49.97; H, 6.99; N, 9.72. Found: C, 49.84; H, 7.07; N, 9.58.

Summary

1. The 1,4-addition of acylamidomalonates such as ethyl acetamidomalonate, ethyl phthalimidomalonate and ethyl acetamidocyanoacetate to acrolein has been reported.

2. The resulting aldehydo compounds have been characterized as the phenylhydrazones.

3. The structure of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde (resulting from the 1,4-addition of ethyl acetamidomalonate to acrolein) has been proved by two independent synthetic routes.

MINNEAPOLIS, MINN. RECEIVED MARCH 24, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

Amino Acids. I. New Syntheses of DL-Tryptophan, DL-Ornithine and DL-Glutamic Acid*

BY DONALD T. WARNER AND OWEN A. MOE

Several syntheses for DL-tryptophan have been reported.[1] Most of these methods employ gramine as the starting material. A different approach was recently disclosed by Hegedus[2] wherein acetoacetic ester was used as the starting material. The present report concerns a new and convenient synthesis of DL-tryptophan employing the phenylhydrazone III of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde I.[3]

The phenylhydrazone III readily underwent cyclization to yield IV, the same product as that obtained by the reaction between gramine and ethyl acetamidomalonate.[1a] The cyclized product IV was converted to DL-tryptophan in the usual way[1a]; the over-all yield based on III was 50%.

Recently, Albertson and Archer[4] published an excellent synthesis of DL-ornithine monohydrochloride in which the cyanoethylation product of ethyl acetamidomalonate was used as an intermediate. The synthesis of DL-ornithine monohydrochloride reported in the present paper involves the phenylhydrazone III as an intermediate. Reduction of III in the presence of Raney nickel gave β-

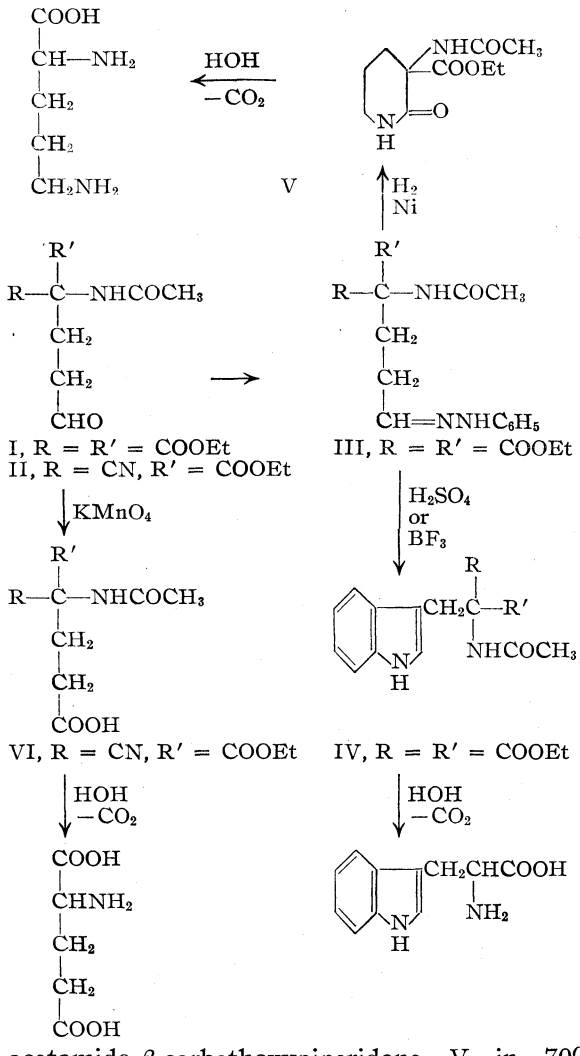
(*) Paper No. 90, Journal Series, Research Laboratories, General Mills, Inc.

(1) (a) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944); (b) Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944); **67**, 36 (1945); (c) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); (d) Elks, Elliott and Hems, *J. Chem. Soc.*, 624, 626, 629 (1944).

(2) Hegedus, *Helv. Chim. Acta*, **29**, 1499 (1946).

(3) Moe and Warner, THIS JOURNAL, **70**, 2763 (1948).

(4) Albertson and Archer, *ibid.*, **67**, 2043 (1945).



acetamido-β-carbethoxypiperidone V in 70% yield. This piperidone V is the same product as that obtained by the reduction of ethyl α-acetamido-α-carbethoxy-γ-cyanobutyrate in the presence of Raney nickel. Hydrolysis of V essentially as described by Albertson and Archer[4] yielded DL-ornithine monohydrochloride in nearly quantitative yield.

Glutamic acid has been synthesized by the 1,4-addition of phthalimidomalonic and acetamidomalonic esters to methyl acrylate[5,6] and acrylonitrile.[4] In the present work, oxidation by permanganate of γ-acetamido-γ-carbethoxy-γ-cyanobutyraldehyde yielded γ-acetamido-γ-carbethoxy-γ-cyanobutyric acid VI which was converted to DL-glutamic acid by the action of concentrated hydrochloric acid.

Experimental[7]

Cyclization of III Using Sulfuric Acid as Catalyst.—The phenylhydrazone III (50 g.) was mixed with 300 cc. of water containing 14 cc. of concentrated sulfuric acid. The reaction mixture was heated to the reflux temperature with very vigorous stirring. The phenylhydrazone liquefied at the reflux temperature, and after approximately one hour the suspended liquid had solidified. The reflux temperature was maintained for a period of four and one-half hours. After cooling, the solid reaction product was then mixed with water in a Waring blendor, collected, washed with water and dried *in vacuo*. The yield of product melting at 145–149° was 42.5 g. (approximately 90%). Recrystallization from aqueous ethanol (50–50) gave 35 g. (73%) of product IV melting at 156–157°.

Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.44; H, 6.40; N, 8.01. Found: C, 62.55; H, 6.51; N, 8.05.

Cyclization of III in absolute ethanol using sulfuric acid as the catalyst gave the cyclized product in 40–50% yield. When the cyclization reaction was carried out in 50 volume per cent. aqueous ethanol the yield of IV was 55–65%.

Ethyl α-acetamido-α-carbethoxy-β-(3-indole)-propionate was also prepared by the reaction between gramine and ethyl acetamidomalonate, as described by Howe, Zambito, Snyder and Tishler.[1c] The resulting product melted at 157–158° and no depression in the mixed melting point was observed with the above described sample.

Cyclization of the Phenylhydrazone III Using Boron Trifluoride[8] as the Catalyst.—To a suspension of the phenylhydrazone III (36.3 g.) in 100 cc. of glacial acetic acid there was added with swirling boron trifluoride etherate (14.2 g.) and the resulting reaction mixture was heated cautiously in an oil-bath. The reflux temperature was maintained for a period of thirty minutes. A copious precipitate of the boron trifluoride–ammonia complex was noted and after cooling was removed by filtration. Water was added to the filtrate to yield a slight turbidity, and the mixture was cooled in the refrigerator overnight. The precipitated product (amorphous in appearance) was collected and dried *in vacuo*. The dry product weighed 13.8 g. (40%) and melted at 137–142°. Recrystallization from 50 volume per cent. aqueous ethanol yielded 8.8 g. (25%) melting at 153–155°.

DL-Tryptophan.—The hydrolysis and decarboxylation of the cyclized product IV to yield DL-tryptophan (m. p. 281–283°) were carried out as described by Snyder and Smith.[1a]

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.70; H, 6.01.

Preparation of Piperidone V.—The phenylhydrazone III (54.48 g.) was suspended in 350 cc. of 95% ethanol and reduced in the presence of Raney nickel catalyst at 1400 pounds of hydrogen at 100°. After approximately six hours, the reduction was complete. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual pasty solid (amine odor) was suspended in 250 ml. of ether. The suspended solid had the appearance of shiny leaflets.

After cooling, the piperidone V was collected by filtration and dried *in vacuo*. The yield of the white crystalline product was 24.1 g. (70%) melting at 136.5–138°. The melting point was not depressed when mixed with the piperidone prepared as described by Albertson and Archer.[4]

DL-Ornithine Monohydrochloride.—The piperidone V was converted to DL-ornithine monohydrochloride (m. p. 218°) by refluxing with concentrated hydrochloric acid as described in the literature.[4] The dipicrate (m. p. 196°) and the dibenzoate (ornithuric acid) (m. p. 186°) of ornithine were prepared.

Permanganate Oxidation of γ-Acetamido-γ-carbethoxy-γ-cyanobutyraldehyde, II.—Crude γ-acetamido-γ-carbethoxy-γ-cyanobutyraldehyde II (22.6 g., m. p. 109–112°) was dissolved in 400 cc. of water. The resulting solution was cooled to 8° and a solution of potassium permanganate (10.6 g. of permanganate in 400 cc. of water) was added in portions. The temperature was maintained at 8–12° and the *p*H at approximately 8. When the oxidation was complete, the reaction mixture

(5) Marvel and Stoddard, *J. Org. Chem.*, **3**, 198 (1938).

(6) Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945).

(7) Micro analyses by Mr. Harold Boyd and Miss Katherine Tellor.

(8) Snyder and Smith, THIS JOURNAL, **65**, 2452 (1945).

was allowed to stand at room temperature overnight. After removal of the manganese dioxide, the solution was acidified with 10 cc. of concentrated hydrochloric acid. Concentration *in vacuo* to a volume of approximately 100 cc. yielded a turbid emulsion. After saturation with sodium chloride the reaction mixture was extracted with two 100-cc. portions of ethyl acetate. After drying over anhydrous sodium sulfate the ethyl acetate was removed by distillation. The solid residue was macerated with ether, and filtration yielded 15.9 g. of a white solid. Purification by crystallization from ethyl acetate yielded the γ-acetamido-γ-carbethoxy-γ-cyanobutyric acid melting at 154–154.5°.

Anal. Calcd. for $C_{10}H_{14}O_5N_2$: C, 49.99; H, 5.87; N, 11.66; neut. equiv., 240. Found: C, 49.68; H, 6.06; N, 11.55; neut. equiv., 241.7.

DL-Glutamic Acid.—The γ-acetamido-γ-carbethoxy-γ-cyanobutyric acid (5 g.) was mixed with 25 cc. of concentrated hydrochloric acid. The resulting reaction mixture was refluxed for a period of sixteen hours and then concentrated *in vacuo*. The residual solid was dissolved in 12 cc. of water. After filtration the filtrate was neutralized by addition of 10% aqueous sodium hydroxide solution to a *p*H of 3.2. When cooled, the resulting solution yielded a crystalline product (2.3 g.) which melted at 193–194° with decomposition after drying *in vacuo*. The melting point was not depressed when mixed with an authentic sample. The N-benzoyl derivative was prepared and it melted at 156–157.5°.

Summary

1. New syntheses of DL-tryptophan, DL-ornithine and DL-glutamic acid have been reported.

2. These amino acids result from the aldehydo intermediates prepared by the 1,4-addition of acylamidomalonates to acrolein.

MINNEAPOLIS, MINNESOTA RECEIVED MARCH 24, 1948

[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY, EMERYVILLE, CALIFORNIA]

Some Free Radical Reactions of Hydrogen Chloride

BY JOHN H. RALEY, FREDERICK F. RUST AND WILLIAM E. VAUGHAN

Although the chain addition of hydrogen bromide to ethylenic linkages is readily brought about by peroxides (the well known Kharasch "peroxide effect")[1] or actinic radiation,[2] it has been generally recognized that the analogous reaction with hydrogen chloride is much less likely. In fact, at the time the present study was begun, there was no report of a free radical hydrogen chloride–olefin combination.[3]

In this paper the vapor phase addition of hydrogen chloride to ethylene, as initiated by ultraviolet light or di-*t*-butyl peroxide, is described. Evidence for the corresponding, but much slower, reaction with propylene, is presented. Hydrogen chloride sensitizes the vapor phase decomposition of di-*t*-alkyl peroxides. This reaction, apparently a chain process involving chlorine atoms, is related to the photochlorination of di-*t*-butyl peroxide which is also described.

Experimental

Photochemical Experiments.—The cell was a fused quartz cylinder (22 mm. o.d. × 150 mm.) provided with plane windows. The body of the cell was wrapped with metal foil and jacketed by an aluminum pipe which was heated electrically. A thermocouple imbedded in the foil gave an approximate measure of the reaction temperature.

The light source was a hydrogen discharge tube of the Kistiakowsky type[4] (Hanovia Mfg. Co.) operated from a 2.5-kw. transformer. Since mercury vapor (from the vacuum line) could be present in the cell, radiation absorbable by this element was excluded to prevent the occurrence of mercury-sensitized reactions. The filter was a quartz cylinder dimensionally identical with the cell, containing carbon dioxide saturated with mercury vapor at room temperature. Ethylene absorbs appreciably only below the quartz region[5] but continuous absorption by hydrogen chloride begins at about 2500 Å. and increases rapidly below 2200 Å.[6]

The pressure change was measured with a quartz spiral manometer[7] sealed to the cell. After irradiation, the cell contents were transferred directly to a bulb by means of a Toepler pump, measured, and subsequently analyzed mass spectrometrically.

Experiments with Di-*t*-alkyl Peroxides.—The closed system apparatus used has been described in an earlier communication.[8] For certain experiments the 500-cc. reaction vessel was packed with 2-mm. Pyrex rods to effect an increase in the surface:volume ratio from 0.61 to 7.0 cm.$^{-1}$.

After reaction, the vessel contents were condensed with Dry Ice–acetone and the volatile products, excepting a portion of the dissolved ethyl chloride, pumped into a sample bulb for mass spectrometric analysis. The cold trap contents were dissolved in water containing a little isopropyl alcohol and aliquots taken for carbonyl[9] and chloride ion (Volhard) determinations.

Larger scale runs with a flow type apparatus provided material for product identification. This apparatus also has been described previously.[10] Because of the complexity of the effluent, particularly when the peroxide content of the feed was high, product yields could be determined only very roughly. However, isobutylene chlorohydrin was isolated (in *ca.* 10% yield) from the products of both the di-*t*-butyl peroxide–hydrogen chloride and di-*t*-butyl peroxide–hydrogen chloride–ethylene re-

(1) For literature review, see Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

(2) Vaughan, Rust and Evans, *J. Org. Chem.*, **7**, 477 (1942).

(3) In a recent patent (U. S. 2,418,832, April 15, 1947), Hanford and Harmon report the preparation of a homologous series of primary alkyl chlorides by a high pressure reaction between ethylene and hydrogen chloride. Catalysts employed include oxygen, peroxides, and lead tetraphenyl. This work was presented as Paper No. 57 before the Organic Division of the American Chemical Society, 113th National Meeting, Chicago, Ill., April 19–23, 1948.

(4) Kistiakowsky, *Rev. Sci. Instruments*, **2**, 549 (1931).

(5) Noyes and Leighton, "The Photochemistry of Gases," Reinhold Publishing Corp., New York, N. Y., 1941, p. 331; also, Price, *Phys. Rev.*, **47**, 444 (1935).

(6) H. Trivedi, *Proc. Nat. Acad. Sci. India*, **6**, 18 (1936).

(7) Vaughan, *Rev. Sci. Instruments*, **18**, 192 (1947).

(8) Raley, Rust and Vaughan, THIS JOURNAL, **70**, 88 (1948).

(9) This procedure, based on reaction with hydroxylamine hydrochloride, is a modification of the method of Marasco (*Ind. Eng. Chem.*, **18**, 701 (1926)), and is described in "Methyl Ethyl Ketone, Its Uses and Data on Its Properties," Shell Chemical Co., San Francisco, Calif., 1938, p. 45.

(10) Rust, Seubold and Vaughan, THIS JOURNAL, **70**, 95 (1948).

actions (b. p. 126.6–126.7°, $n^{20}D$ 1.4375, acidimetric equivalent weight, 114; literature or theoretical values for $(CH_3)_2COHCH_2Cl$, respectively, 126.6–128.8°, 1.4388, and 108.5). The product from the di-*t*-butyl peroxide–hydrogen chloride–propylene reaction contained small amounts of both *n*- and isopropyl chlorides, as shown by infrared absorption analysis.

Materials.—The various gases used in the static apparatus were taken from commercial cylinders (stated purity more than 99% except hydrogen chloride (97.5%)), redistilled under high vacuum (collection of middle one-third), out-gassed, and stored in glass bulbs. For the flow experiments no purification was made. Di-*t*-butyl and di-*t*-amyl peroxides were purified in the manner described previously.[8]

Photochlorination of Di-*t*-butyl Peroxide.—Chlorine (2.0 moles) was bubbled through a sintered glass plate into di-*t*-butyl peroxide (3.0 moles) at a rate which maintained the temperature at 30-40°. A 500-watt projection lamp adjacent to the Pyrex reaction flask served as the source of radiation. The product was water-washed, dried, and fractionated under reduced pressure. The monochloride (b. p. 55° (20 mm.), f. p. −31°, $n^{20}D$ 1.4211, Cl, 19.7% (theory, 19.62%)) was obtained in 42.5% yield based on input chlorine. The dichloride fraction, probably consisting of three possible isomers, boiled at 55-70° at 4-5 mm.; $n^{20}D$ 1.4454, Cl, 33.3% (theory, 32.96%).

Photo-addition of Hydrogen Chloride to Ethylene.—The effect of radiation from the hydrogen lamp on hydrogen chloride–ethylene mixtures at two temperatures is illustrated in Fig. 1. It will be noted that there is no appreciable "dark" reaction. Ethyl chloride is the only significant product detected mass spectrometrically, and the composition after illumination agrees, within the analytical error, with that calculated from the pressure decrease on the assumption that only the addition reaction occurs. For example, at 26° the composition by analysis was 13 ± 1% C_2H_5Cl and 41 ± 2% C_2H_4, while that calculated was 14.5% C_2H_5Cl and 42.2% C_2H_4. The hydrogen and ethane contents were both 0.1% or less.

Since light absorption by hydrogen chloride leads to the production of chlorine and hydrogen atoms, the probable path of the reaction is

$$HCl + h\nu \longrightarrow H + Cl \quad (1)$$

$$Cl + C_2H_4 \longrightarrow CH_2ClCH_2 \quad (2)$$

$$CH_2ClCH_2 + HCl \longrightarrow CH_2ClCH_3 + Cl \quad (3)$$

Addition reactions such as

$$CH_2ClCH_2 + C_2H_4 \longrightarrow CH_2Cl(CH_2)_2CH_2 \quad (4)$$

are apparently much slower than (3) under the present conditions since higher molecular weight products were not detected.

The hydrogen atoms could also initiate a chain, *viz.*

$$H + HCl \longrightarrow H_2 + Cl, \text{ or} \quad (5)$$

$$H + C_2H_4 \longrightarrow CH_3CH_2 \quad (6)$$

$$CH_3CH_2 + HCl \longrightarrow C_2H_6 + Cl \quad (7)$$

and, from the yields of hydrogen and ethane the chain length is estimated to be at least 30 at room temperature.

In keeping with the characteristics of a chain process, the reaction is inhibited by oxygen and a number of other substances (Fig. 2). The pro-

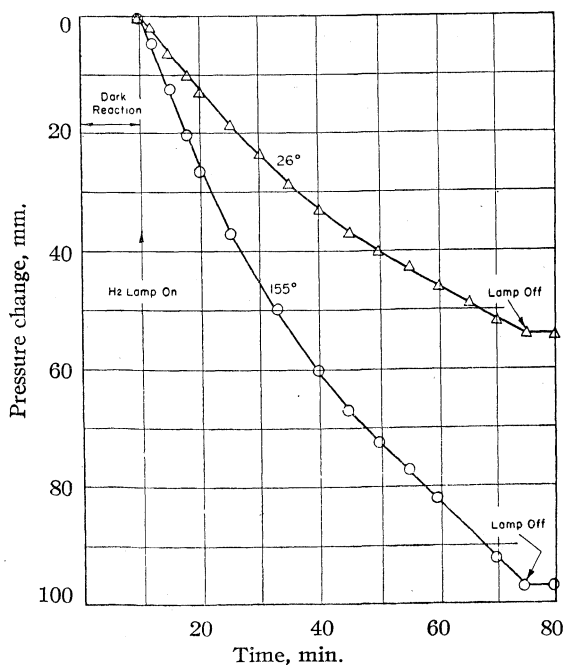


Fig. 1.—Photo-addition of hydrogen chloride to ethylene: (0.0116 mole/liter HCl, 0.0113 mole/liter C_2H_4).

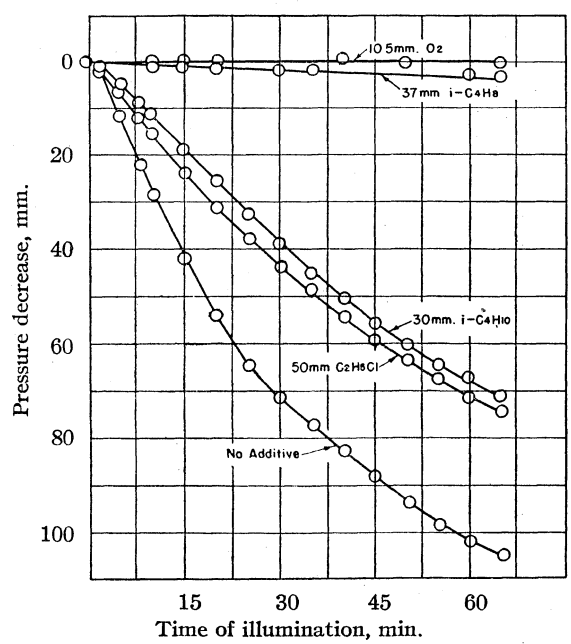


Fig. 2.—Effect of additives on the photochemical hydrogen chloride–ethylene reaction: temperature, 155°; HCl 309 mm.; C_2H_4, 300 mm.

nounced effect of small oxygen concentrations is attributed to the relatively rapid reaction

$$CH_2ClCH_2\cdot + O_2 \longrightarrow CH_2ClCH_2O_2\cdot \quad (8)$$

the peroxy radical being incapable of continuing the chain. Retardation by isobutylene is probably due to the reactions

$$Cl + (CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2\dot{C}CH_2Cl \quad (9)$$

$$\longrightarrow \dot{C}H_2C(CH_3){=}CH_2 + HCl \quad (10)$$

wherein, respectively, a tertiary or allylic radical, less able to abstract hydrogen from hydrogen chloride is produced. In the presence of isobutylene only a trace of ethyl chloride formed, the chief product being C_4 chloride(s). With isobutane as the additive, chlorine atom attack at the tertiary carbon–hydrogen bond is the most likely mode of interference. Since ethyl chloride is also a retardant, the reaction must be self-inhibiting. In this case the effect is apparently due to the formation of the $CH_3\dot{C}HCl$ radical which is less capable of metathetical reaction with hydrogen chloride than its isomer, $CH_2Cl\dot{C}H_2$. This difference in reactivity might be expected from the results of studies on the thermal chlorination of ethyl chloride.[11]

Peroxide-catalyzed Addition of Hydrogen Chloride to Olefins.—The reaction with ethylene, as initiated by a small amount of di-*t*-butyl peroxide, is illustrated in Fig. 3. A complete product analysis has not been made but ethyl chloride was identified again as a major component. A small amount of methane was also produced. In view of the known decomposition of di-*t*-butyl peroxide to *t*-butoxy and methyl radicals,[8,12] the initiation steps are probably

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot \quad (13)$$

$$(CH_3)_3CO\cdot + HCl \longrightarrow (CH_3)_3COH + Cl \quad (14)$$

$$(CH_3)_3CO\cdot \longrightarrow (CH_3)_2CO + CH_3 \quad (15)$$

$$CH_3 + HCl \longrightarrow CH_4 + Cl \quad (16)$$

The reaction has been carried out at 140–185° in both types of apparatus.

The analogous reaction with propylene is much slower. For example, at 155° a mixture of 200 mm. propylene, 200 mm. hydrogen chloride, and 13 mm. di-*t*-butyl peroxide undergoes a pressure decrease of only 10 mm. in sixty minutes. The hydrogen transfer step involving a secondary radical

$$CH_3\dot{C}HCH_2Cl + HCl \longrightarrow CH_3CH_2CH_2Cl + Cl \quad (17)$$

would be more endothermic than the corresponding process in the ethylene reaction, (3). Furthermore, allyl radical formation could occur by

$$Cl + CH_3CH{=}CH_2 \longrightarrow HCl + \dot{C}H_2C\dot{H}CH_2, \text{ or} \quad (18)$$

$$CH_3\dot{C}HCH_2Cl + CH_3CH{=}CH_2 \longrightarrow$$

$$CH_3CH_2CH_2Cl + \dot{C}H_2C\dot{H}CH_2 \quad (19)$$

Di-*t*-alkyl Peroxide–Hydrogen Chloride Reaction.—In addition to a simple dissociation into two *t*-alkoxy radicals, di-*t*-alkyl peroxides in the presence of a minor amount of hydrogen chloride undergo a sensitized decomposition (Fig. 4).

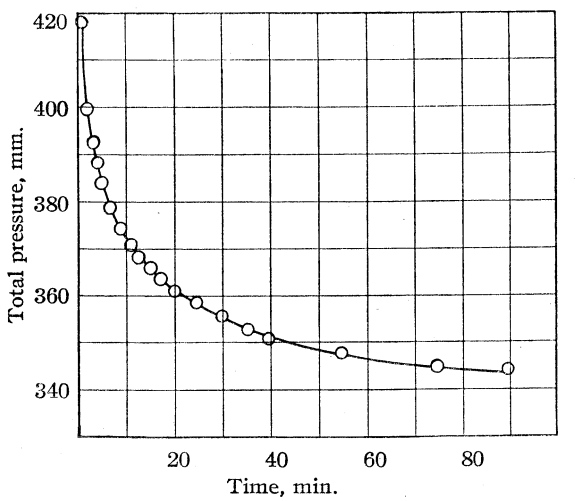


Fig. 3.—Di-*t*-butyl peroxide—catalyzed addition of hydrogen chloride to ethylene: 200.7 mm. HCl, 200.3 mm. C_2H_4, 10.5 mm. peroxide, 6.4 mm. nitrogen, temperature 154.7°.

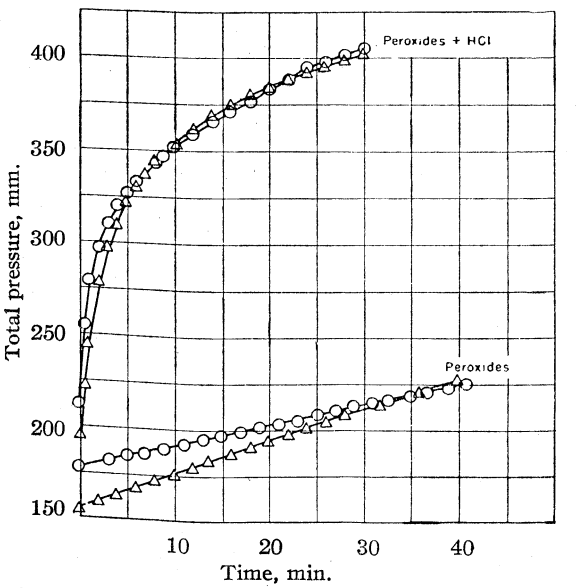


Fig. 4.—Effect of hydrogen chloride on di-*t*-alkyl peroxides: O, di-*t*-butyl peroxide (139.7(8)°) 173.4 mm. peroxide, 180 mm. peroxide + 27.6 mm. HCl; △, di-*t*-amyl peroxide (136.7(4)°) 149.2 mm. peroxide, 160 mm. peroxide + 30.8 mm. HCl.

(11) From the data of Rust and Vaughan (*J. Org. Chem.*, **6**, 479 (1941)), reaction (11) is known to be faster than (12):

$$Cl + CH_3CH_2Cl \longrightarrow HCl + CH_3\dot{C}HCl \quad (11)$$

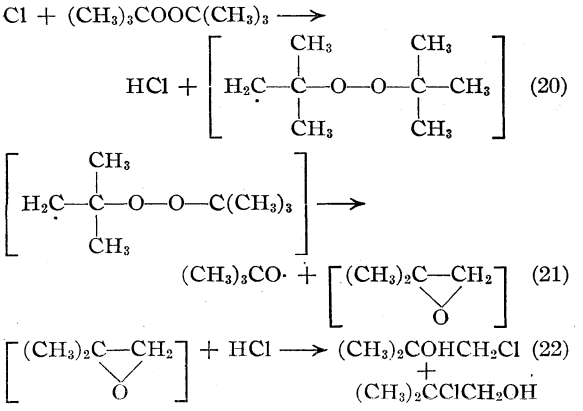
$$Cl + CH_3CH_2Cl \longrightarrow HCl + CH_2Cl\dot{C}H_2 \quad (12)$$

Therefore, the reverse of (11) might be expected to be slower than the reverse of (12).

(12) Milas and Surgenor, THIS JOURNAL, **68**, 205 (1946).

The major hydrocarbon product contains only half as many carbon atoms as that produced in the unsensitized reaction, and substantially less than two molecules of ketone are produced from each peroxide molecule decomposed. Additional products that appear in the case of di-*t*-butyl peroxide include isobutylene chlorohydrin and *t*-butyl chloride. This sensitized reaction is essentially homogeneous since the rate of pressure increase is unaffected by the presence of Pyrex rod packing. Furthermore, various compounds readily attacked by free radicals or atoms (ethylene, propylene, isobutane, etc.) have a retarding influence. These observations indicate a chain, the mechanism for which is postulated to be:

Steps (13) to (16) followed by



Evidence for the step involving chlorine atom attack on the peroxide comes from experiments on the photochlorination of the peroxide described elsewhere in this paper. The production of monochloride, $ClCH_2(CH_3)_2COOC(CH_3)_3$, by a photo reaction must certainly involve (20). Because of the lower temperature and the presence of molecular chlorine, however, the resultant radical does not decompose but instead forms the chloride. It is interesting to note the differing reactivities of chlorine atoms and methyl radicals toward the peroxide. In the vapor phase the latter apparently do not readily abstract hydrogen atoms from the peroxide since the thermal decomposition of this compound is not a chain reaction.[8] Although isobutylene oxide has not been isolated, the chlorohydrin, (22), is a recognized derivative.

The preponderance of ethane over methane observed in the sensitized decomposition of di-*t*-amyl peroxide is in agreement with earlier observations that *t*-amyloxy radicals yield acetone and ethyl radicals.[8,13] A partial product analysis for both peroxides is given in Table I. Carbonyl and methane yields are nearly equivalent for the di-*t*-butyl compound, as are the carbonyl and (methane + ethane) yields for the amyl analog. Products characteristic of the combination of two alkyl radicals (*i. e.*, butane from ethyl radicals) are unimportant. These data illustrate the predominance of (16) and the analogous ethyl radical reaction over other processes involving alkyl radicals. This is particularly interesting inasmuch as (16) is almost energetically neutral while the ethyl-hydrogen chloride reaction is somewhat endothermic. It is clear that (15) is more important than (14) although the exact ratio of these two reactions cannot be determined without knowledge of either the amount of alcohol produced or the fraction of input peroxide decomposed.

TABLE I

HYDROGEN CHLORIDE–DI-*t*-ALKYL PEROXIDE REACTIONS

Reaction time, 31 minutes

Produced, mm.	Di-*t*-butyl peroxide 139.8°	Di-*t*-amyl peroxide 136.7°
Carbonyl	114	135
CH_4	110	6.5
Ethane	...	124
Butane	...	1
Input, mm.		
Peroxide	180	160
HCl	28	31

Under comparable conditions hydrogen bromide has little effect on the decomposition of di-*t*-butyl peroxide. Although hydrogen bromide reacts readily with methyl radicals to produce methane, the resultant bromine atoms apparently are less capable of attacking the peroxide to continue the chain. This is in agreement with the observation that photobromination of the peroxide is more difficult than photochlorination.

Summary

The vapor phase addition of hydrogen chloride to ethylene can be initiated photochemically or by di-*t*-butyl peroxide. A free radical, chain mechanism is proposed and the influence of added inhibitors is interpreted in terms of this mechanism. Propylene reacts much more slowly.

Hydrogen chloride sensitizes the vapor phase decompositions of di-*t*-butyl and di-*t*-amyl peroxides. A chain mechanism involving chlorine atom attack on the peroxide is suggested for these reactions. The latter step is demonstrated by the photochlorination of di-*t*-butyl peroxide.

EMERYVILLE 8, CALIFORNIA RECEIVED MARCH 30, 1948

(13) Milas and Surgenor, THIS JOURNAL, **68**, 643 (1946).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MINNESOTA]

Coördination Compounds of Mercury. I

BY THOMAS D. O'BRIEN

Mercury exhibits a coördination number of 3 in such groups as $HgCl_3^-$ and a coördination number of 4 in $[Hg(CN)_4]^{-2}$ and $[HgCl_4]^{-2}$. Whereas this same type of ion exists for zinc and cadmium, the latter two elements also exhibit a coördination number of 6. The present study was undertaken to attempt to determine whether mercury also has a stable coördination number of 6.

There are several reports[1] of compound formation between ethylenediamine (en = ethylenediamine) and mercuric chloride, but the results are generally qualitative and usually contradictory. Sinha and Ray[2] report the preparation of Hg $py_6(ClO_4)_2$ in which the mercury seems to be 6-coordinate.

Experimental

The ethylenediamine was dehydrated according to the method of Putnam and Kobe[3] and the fraction boiling at 117° collected.

en $(HgCl_2)_2$.—Ten milliliters of a solution containing 3.0 g. (0.05 mole) of ethylenediamine was slowly added with stirring to 200 ml. of a solution containing 27.16 g. (0.1 mole) of mercuric chloride. After standing for two hours the precipitate was filtered and washed with water. The precipitate was then treated with a solution containing 0.2 mole of hydrochloric acid and allowed to stand, with intermittent stirring, for one hour. The very small amount of undissolved residue was filtered and to the clear filtrate was added a solution containing 0.1 mole of ethylenediamine. After standing two hours the precipitate was filtered and the above procedure repeated. The final precipitate was washed with successive portions of water, methanol, acetone and ether and then dried at 100° for two minutes. Prolonged heating at 100° causes decomposition.

Anal. Calcd. for en $(HgCl_2)_2$.: Hg, 66.5; Cl, 23.5. Found: Hg, 66.0; Cl, 23.3.

en $HgCl_2$.—Same procedure followed as described above except a 1:1 molar ratio of base to salt used.

Anal. Calcd. for en $HgCl_2$: Hg, 60.5; Cl, 21.4. Found: Hg, 60.2; Cl, 21.4.

The white precipitate of en $HgCl_2$ was dissolved in aqueous ethylenediamine and the solution was allowed to evaporate slowly at room temperature. The crystals that formed were washed with ether and dried to constant weight at 100°.

Anal. Calcd.: Cl, 21.4. Found: Cl, 21.3.

Hg en$_2$ SO_4 and [Hg en$_2$ $(H_2O)_2$]SO_4.—Mercuric sulfate was dissolved in excess ethylenediamine and the solution was allowed to evaporate slowly in a covered Petri dish. The large crystals that formed were removed, washed once with anhydrous ether and blotted well between layers of filter paper.

Anal. Calcd. [Hg en$_2$ $(H_2O)_2$]SO_4: Hg, 44.3; SO_4, 21.2. Found: Hg, 44.5; SO_4, 21.3.

The above compound is efflorescent, slowly losing water to the atmosphere at room temperature. When heated at 100° to constant weight (ten to twelve hours) or when dried over concentrated sulfuric acid the theoretical amount of water (7.98%) is lost, and stable [Hg en$_2$]-SO_4 results. Prolonged heating of this compound causes a slow decomposition.

Anal. Calcd. Hg en$_2$ SO_4: Hg, 48.2; SO_4, 23.0. Found: Hg, 48.2; SO_4, 23.3.

(en 2H)$_2$$HgCl_6$.—Some en $HgCl_2$ was dissolved in the smallest volume of *N* hydrochloric acid solution. To the clear solution was added an equal volume of concentrated hydrochloric acid. The crystals which formed were filtered and then redissolved in the smallest volume of water. Concentrated hydrochloric acid was again added and the crystals which formed were again filtered, redissolved and reprecipitated. After the final filtration the precipitate was washed with methanol, then acetone, and finally ether, then dried in an oven for three minutes at 100°. Longer drying causes no decomposition.

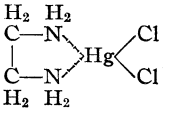
Anal. Calcd. (en 2H)$_2$$HgCl_6$: Hg, 37.3; Cl, 39.6; N, 10.42. Found: Hg, 37.2; Cl, 39.6; N, 10.44.

Cryoscopic Measurements.—The conventional freezing point lowering apparatus was used with a Beckman thermometer. When 0.238 g. of (en 2H)$_2$$HgCl_6$ was dissolved in 46.2 g. of water a freezing point lowering of 0.121° was observed. When 0.416 g. of the salt was dissolved in 45.6 g. of water a freezing point depression of 0.210° was observed.

Refractive Index.—To 100.00 cc. of a 0.1 *M* solution of mercuric chloride there was added 0.90 g. (0.015 mole) of ethylenediamine. The solution was shaken at intervals while digesting for one hour. A small portion of this was filtered and the refractive index of the clear filtrate determined on a Bausch and Lomb refractometer. The above procedure was repeated with separate solutions using increasing amounts of ethylenediamine. The refractive index values of portions of the mixtures were determined after standing for twenty-four hours, and five days, with no change in value. All values are averages of at least six different readings.

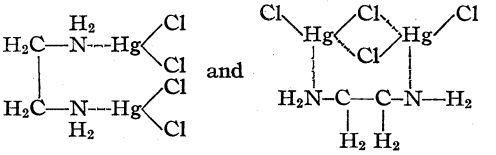
Discussion of Results

Results of the present study show that both en $HgCl_2$ (I) and en $(HgCl_2)_2$ (II) exist. A possible structure of (I) is shown in which the mercury is



(I)

4-coördinate. Two immediately apparent possible structures for (II) are:



(IIa) (IIb)

The mercury has a coördination number of three, in IIa and the mercury is 4-coördinate in IIb, the chloride bridges being analogous to those in the polymeric halides of aluminum and gold.

(1) (a) Schering, German Patent 12,095 (1901); (b) Siemssen, *Chem. Ztg.*, **36**, 214 (1912); (c) Ray and Dhar, *Trans. Chem. Soc.*, **103**, 3 (1913); (d) Tranke and Loewe, *Ber.*, **47**, 1908 (1914).

(2) Sinha and Ray, *J. Indian Chem. Soc.*, **20**, 32 (1943).

(3) Putnam and Kobe, *Trans. Electrochem. Soc.*, **74**, 610 (1938).

Both (I) and (II) are soluble in an excess of ethylenediamine. All attempts to isolate the soluble complex failed, because any solid substance separated from the solution evolved ethylenediamine to give (I). With the analogous sulfate, however, crystalline bis(aquo)bis(ethylenediamine)mercury(II) sulfate was isolated. This compound decomposed slowly at room temperature, and rapidly at 100°, to give the stable Hg en_2 SO_4.

The simple possibilities for the soluble ethylenediamine mercury chloride salt are (1) [Hg en_2 Cl_2,] (2) [Hg en_2 $(H_2O)_2$]Cl_2, and (3) [Hg en_3]Cl_2 (III), with the last one being favored because of the break in the refractive index curve (Fig. 1) at a 3:1 ratio of ethylenediamine to mercuric chloride. The break at the 1:2 ratio probably corresponds to the complete formation of (I). As more ethylenediamine is added it reacts completely with insoluble (I) to form equally insoluble (II), causing no change in the refractive index, which is the value for the pure solvent (for water, n_{28} 1.3321). The refractive index of the corresponding sulfate could not be determined because of the formation of insoluble basic salts when mercuric sulfate is put in water.

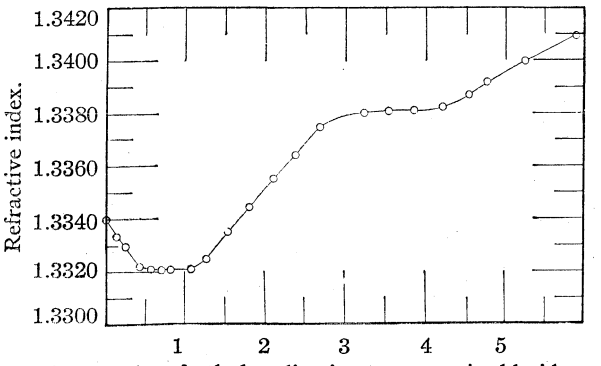


Fig. 1.—Change of refractive index of solution of ethylenediamine and mercuric chloride as concentration of ethylenediamine is increased.

Treatment of (I), (II) or (III) with an excess of concentrated hydrochloric acid produces a white crystalline substance, only slightly soluble in an excess of hydrochloric acid but easily soluble in water. The formula (en 2H)$_2$[$HgCl_6$] (IV) is assigned to the compound in accordance with the analogous copper salt.[4] Cryoscopic measurements indicate that when dissolved in water, (IV) completely dissociates into 2(en 2H+), 4 Cl^- and $HgCl_2$ (only very slightly dissociated). Using 1.86 as the freezing point constant of water, the two observed lowerings of 0.121° and 0.120° correspond to 6.8 and 6.7 particles, respectively, per mole of salt.

Any highly soluble chloride will cause the precipitation of (IV). Saturated solutions of copper, lithium, and cadmium chlorides when added to an aqueous solution of (IV) cause precipitation of the bis(ethylenediamine)hexachloromercury salt and not the metal hexachloromercury salt.

That the mercury to chloride bonds are more ionic than covalent is further supported by the non-availability of possible bonding orbitals for six coördination. Kimball[5] gives the following possibilities: d^2sp^3, d^4sp, d^5p, d^3p^3, d^3sp^2, d^5s and d^4p^2. As the 5d orbitals in mercury are filled, and as it is extremely doubtful if the 6d orbitals are available for covalent bonding, it appears as if the Hg–Cl bonds must be largely ionic in character.

Summary

1. The existence of Hg en Cl_2 and en$(HgCl_2)_2$ has been demonstrated.

2. The results indicate that mercury probably has a coördination number of 6 in the compound (en 2H)$_2$[$HgCl_6$] and that the [Hg en_2 $(H_2O)_2$]$^{+2}$, ion probably exists in solution, wherein the mercury is also 6-coördinate.

3. The new compounds Hg en_2 SO_4 and Hg en_2 $(H_2O)_2SO_4$ have been prepared.

MINNEAPOLIS, MINN. RECEIVED DECEMBER 9, 1947

(4) Jonassen, Crumpler and O'Brien, THIS JOURNAL, **67**, 1709 (1945).

(5) Kimball, *J. Chem. Phys.*, **8**, 188 (1940).

[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY, EMERYVILLE, CALIFORNIA]

The Isomerization of Cyclohexane and Methylcyclopentane in the Presence of Aluminum Halides. II. Equilibrium and Side Reactions

BY D. P. STEVENSON AND JANE H. MORGAN

Introduction

In the preceding paper with the same title, there were presented the results of a set of experiments designed to elucidate the nature of the catalysis of the interconversion of cyclohexane and methylcyclopentane. In the course of this work considerable data were acquired on the equilibrium constant of the isomerization reaction, as well as on the nature and relative rates of the side reactions which accompany the isomerization reaction. The equilibrium between cyclohexane and methylcyclopentane has been the subject of several previous investigations.[1] The results of the previous investigators are concordant with and confirmed by the present work. Despite the apparent duplication, it seems worth while to record our results in view of the very different and probably more reliable analytical methods at our disposal. In the equilibrium studies particular attention was devoted to the possible presence of the various cyclobutanes and cyclopropanes, isomeric with cyclohexane and methylcyclopentane, which have been reported to be formed by the action of moist aluminum bromide on cyclohexane.[2]

Paraffins, C_7 and C_8 naphthenes, and bicyclanes have been identified among the products of the side reactions accompanying the interconversion of cyclohexane and methylcyclopentane catalyzed by aluminum halides. It was of particular interest to determine whether or not cyclopentane accompanies the formation of the higher naphthenes as might be expected by analogy with formation of isobutane and hexanes in side reactions accompanying the interconversion of iso- and normal pentane.

Experimental

The experiments were carried out by the methods described in the preceding paper, using the materials therein described, with the exceptions noted below.

Purified aluminum bromide, ground to a fine powder in a dry box (dried by spreading Dry Ice on the bottom), was used after exposure to atmospheric moisture to assure catalytic activity. Cyclopentane was prepared by hydrogenation of carefully purified cyclopentadiene. The crude cyclopentane was fractionated in a high efficiency column and residual traces of cyclopentadiene and cyclopentene were removed by percolation through activated silica gel (Davco, 28–200 mesh) and shaking with a small portion of moist aluminum chloride. After the aluminum chloride treatment, the cyclopentane was subjected to a trap (room temperature) to trap (liquid nitrogen) vacuum distillation. The mass and infrared spectra of the final cyclopentane showed the presence of no detectable impurity.

In a number of the experiments the reaction product was separated from the catalyst by a high vacuum distillation. The reaction tube was opened with the contents chilled with liquid oxygen and connected to the vacuum system by means of a short length of rubber tubing. After evacuation, the pump was cut off from the manifold, and the liquid oxygen was transferred to a weighed trap affixed to the manifold by means of a standard taper joint. The reaction tube was permitted to warm slowly to room temperature. The distillation was stopped approximately five minutes after the reaction tube attained room temperature. The product so collected is defined as the volatile product.

The traps were constructed with a stopcock so that the samples could be stored while awaiting analysis without danger of loss of volatile components. The stopcocks were of the pressure type and were lubricated with a hydrocarbon insoluble grease compounded of mannitol, starch and anhydrous glycerol. A section of tubing packed with ascarite was interposed between the reaction tube and collecting trap to remove hydrogen halide and entrained catalyst.

The products of all experiments were examined with the mass spectrometer in order to determine the extent of the side reactions and the applicability of the infrared spectrophotometric method for determining methyl cyclopentane and cyclohexane. The products of the experiments in which the side reaction was excessive were subjected to analytical distillation to give three fractions, (1) boiling below 65°, (2) boiling from 65 to 85°, and (3) boiling above 85°. These fractions were analyzed with the mass spectrometer.

The results of the experiments on the cyclohexane–methylcyclopentane reaction at 27, 59 and 100°, are summarized in Tables I, II, and IIIa, and IIIb, respectively. The experiments with cyclopentane at 100° are described in Table IV.

In all the experiments on the reaction of the C_6 naphthenes with aluminum bromide the reacting system remained a clear, colorless solution. In the 60° experiments, the aluminum chloride retained its white, granular appearance. The aluminum chloride–C_6 naphthene system at 100° rapidly changed from a liquid–solid system to one of two liquid phases. The more dense phase acquired a very faint yellow color. Upon cooling to room temperature the more dense phase became very viscous, and white crystals precipitated from it very slowly. When the 100° reaction tubes were opened, the unfrozen film of the denser phase at the top of the tube became bright red very quickly and then slowly darkened until it became black. The non-volatile residues from the vacuum separation of the product of the 100° experiments were hydrolyzed in the cold (0°) with 6 *N* sodium hydroxide solution. From the resultant mixture a dark yellow to brown, viscous oil was recovered. The depth of color increased with time. This oil as first recovered was soluble in isoöctane, but from the isooctane solutions a brown, resinous substance slowly precipitated on standing in contact with air. It was found that a colorless oil could be recovered from the deeply colored oil by means of a high vacuum (10^{-4} mm.) distillation from a trap at room temperature to one at liquid nitrogen temperature.

The formation of two liquid phases from the solid–liquid system aluminum chloride–aromatic has been often described. However, the more dense phase formed when paraffins, olefins, or aromatics are the hydrocarbon components of the system is very deeply colored (orange to

(1) (a) Glasebrook and Lovell, THIS JOURNAL, **61**, 1717 (1939); (b) Schmidt, Hoog and Verheus, *Rec. trav. chim.*, **59**, 793 (1940); (c) Mizusima, Morino and Fujisiro, *J. Chem. Soc. Japan*, **62**, 587 (1941).

(2) Zelinsky and Turowa-Pollak, *Ber.*, **65**, 1171 (1932).

TABLE I

REACTION OF CYCLOHEXANE AND METHYLCYCLOPENTANE IN THE PRESENCE OF MOIST ALUMINUM BROMIDE AT 27.0 ± 0.5°

Expt. no.	Iden.	C_6H_{12} m. × 10^3	Al_2Br_6 m. × 10^3	Time, hr.	MCP/CH M. S.[a]	MCP/CH I. R.[b]	Mole % C_5H_{10}[c]	Mole % C_5H_{12}	Mole % C_6H_{14}[d]	Mole % C_7H_{14}[c]	Mole % C_8H_{16}[c]	Mole % $C_{12}H_{22}$[e]
1[h]	CH	46	1.38	24	[f]	0.048[g]	....	....	...	....	....	....
2[h]	MCP	44	1.25	24	...	.230[g]	....	....	...	....	....	....
3[h]	MCP	44	1.21	256	0.132	.112	<0.05	<0.03	0.4	0.05	0.05	0.2
4[h]	CH	46	1.16	256	.135	...	< .05	< .03	< .1	< .01	< .01	< .02
5[h]	MCP	44	0.94	313	.147	.150	< .05	< .03	.5	...	....	....
6[h]	CH	46	0.95	313	.109	...	< .05	< .03	< .1	< .01	< .01	< .01
7[h]	MCP	44	1.07	352	...	.113	....	....	...	....	....	....
8[h]	CH	46	0.88	352	.142	...	< .05	< .03	< .1	< .01	< .01	< .01
9[i]	CH	46	0.82	352	.136	.121	< .05	< .03	< .1	....	....	....
10[i]	MCP	44	0.85	352	.135	.146	< .05	< .03	< .1	....	....	....
				Average	0.134	0.129						
					±0.008	±0.016						
					0.132	±0.012						

[a] Mass spectrometric analysis. [b] Infrared analysis. [c] Calculated as naphthene. [d] Calculated as methylpentane. [e] Calculated as dicyclohexyl. [f] Dots (...) indicate not determined. [g] Omitted from average. [h] Products recovered by hydrolysis. [i] Product recovered by distillation. Analysis reported, that of all material boiling below 85°. Over 99.7%w of the hydrocarbon was recovered by the vacuum distillation and less than 1% of the recovered hydrocarbon boiled above 85°.

TABLE II

THE REACTION OF CYCLOHEXENE AND METHYLCYCLOPENTANE IN THE PRESENCE OF MOIST ALUMINUM CHLORIDE OR BROMIDE AT 59.0 ± 0.5°

Expt. no.	Iden.	C_6H_{12} m. × 10^3	Al_2Cl_6 m. × 10^3	Time, hr.	MCP/CH M. S.[a]	MCP/CH I. R.[b]	Mole % C_5H_{10}[c]	Mole % C_5H_{12}	Mole % C_6H_{14}[d]	Mole % C_7H_{14}[c]	Mole % C_8H_{16}[c]	Mole % $C_{12}H_{22}$[e]
11[h]	CH	46	2.5	256	0.255	0.246	<0.05	<0.04	0.2	0.04	0.04	0.65
12[h]	MCP	44	3.5	256	.252	.241	< .05	< .04	.3	0.05	.05	.71
13[h]	CH	46	2.4	282	.238	.232	< .05	< .04	.2	.03	[f]	...
14[h]	MCP	44	3.1	282	.230	.228	< .05	< .04	.2	.04	.06	.66
15[i]	MCP	44	2.7	330	.246	.249	< .05	< .04	.2	....	....	...
16[h]	CH	46	0.36[j]	119	.256	...	< .05	< .05	< .1	< .04	< .04	...
17[h]	CH	46	2.0	96	.230	...	< .05	< .05	< .1	< .04	< .04	...
				Average	0.244	0.239						
					±0.010	±0.080						

[a] through [i] see notes to Table I. [j] Aluminum bromide was used in this experiment.

TABLE IIIa

REACTION OF CYCLOHEXANE AND METHYLCYCLOPENTANE WITH ALUMINUM CHLORIDE AT 100.0 ± 1.0°

Expt.	Iden.	C_6H_{12} M. × 10^3	Al_2C_{16} M. × 10^3	Time, hr.	MCP/CH I. R.[b]	Mole, % C_5H_{10}	Mole, % C_5H_{12}	Mole, % C_6H_{14}	Mole, % C_7H_{14}	Mole, % C_6H_{16}	Mole, % C_9H_{18}
18[e]	CH	46	0.16	8.0	0.475	<0.05	0.1[a]	0.1	0.004	0.004	<0.003
19[e]	CH	46	.18	24.0	.485	< .05	.1[a]	0.5	.005	.010	< .003
20[e]	MCP	44	.17	24.0	.503	< .05	< .05[a]	1.0	.05	.10	[f]
21	CH	46	.22	24.0	.509	....	.....	...	....	....	.....
22	CH	46	.17	24.0	.514	....	.....	...	....	....	.....
23	MCP	44	.21	24.0	.530	....	.....	...	....	....	.....
					0.503 ± 0.015						

[a] C_4H_{10} found to be less than 0.5 mole %. [b,c,d] See notes of Table I. [e] Product recovered by distillation. Over 99.7%w hydrocarbon recovered. [f] See notes of Table I.

deep brown), so that the formation of a colorless aluminum chloride–hydrocarbon complex from the C_6 cyclanes is unexpected. In this regard it must be noted that the aluminum bromide–cyclopentane solutions at 100° give rise to two liquid phases and the more dense phase has a deep brown color.

Discussion

In discussing the methylcyclopentane–cyclohexane equilibrium, two related subjects must be considered along with the ratio of the pair of isomers. These are (1) the possibility of cyclopropane and cyclobutane isomers of C_6H_{12} being present in the system, but undetected due to inadequacy of the analytical methods, and (2) the effect of side reactions on the apparent equilibrium ratio.

It has been reported[2] that dimethylcyclobutanes were found in a low boiling fraction resulting from the action of moist aluminum bromide on cyclohexane at a temperature less than 100°. There

TABLE IIIb

REACTION OF CYCLOHEXANE AND METHYLCYCLOPENTANE WITH ALUMINUM CHLORIDE AT 100.0 ± 1.0°

Expt.	24[a]	25[a]	26	27[a]
C_6H_{12}	CH	MCP	CH	MCP
C_6H_{12} moles × 10^3	46	44	46	44
Time, hr.	33	33	8	8
Wt. % HC recovered	63.7	63.4	82.5	82.0
Al_2Cl_6 moles × 10^3	2.8	2.7	2.3	2.6
Compn. of recovered HC,[b] mole %				
C_3H_8	0.7	0.6	0.2	0.2
C_4H_{10}[c]	14.4	13.6	3.7	4.5
C_5H_{12}[c]	3.2	4.0	1.4	1.5
C_5H_{10}	< 0.1	< 0.1	< 0.05	< 0.05
C_6H_{14}[d]	11.7	9.5	8.1	7.5
C_6H_{12}	61.2	61.1	81.8	82.5
C_7H_{16}	< 0.1	< 0.1	< 0.1	< 0.1
C_7H_{14}	3.6	4.2	1.6	1.6
C_8H_{16}	4.9	6.6	2.6	2.4
C_9H_{18}	0.3	0.4	0.02	0.08
MCP/CH	0.50	0.49	0.50	0.48

[a] Composite of two identical, parallel runs. [b] Combined analytical distillation and mass spectrometric analysis. [c] Predominantly the "iso" isomer. [d] 2 MP, 3 MP, 2.3 M_2B, and 2.2 M_2B identified.

TABLE IV

REACTION OF CYCLOPENTANE WITH ALUMINUM BROMIDE AT 100°

Expt. no.	28	29	30	31	32
C_5H_{10} moles × 10^3	52.3	51.5	51.3	41.6	29.1
Al_2Br_6 moles × 10^3	1.08	1.05	1.00	0.97	1.12
Time, hr.	21	8.0	8.0	161	161
Wt. % volatile	97.4	99+	99+	93.6	94.8
Volatile product					
Mole % C_3H_8	<0.1[a]	....	....	....	....
C_4H_{10}	1.3	....	....	1.6	1.7
C_5H_{12}	3.0	0.14	0.16	2.3	2.2
C_5H_{10}	90.8	99+	99+	91.9	93.0
C_6H_{14}	0.4	<0.05	<0.05	0.1	0.1
C_6H_{12}	4.0	0.46	0.31	2.4	1.7
C_7H_{14}	0.2	0.03	0.03	0.5	0.3
C_8H_{16}	0.01	....	....	0.7	0.5
$C_{12}H_{22}$	....	....	....	0.5	0.5

[a] Mass spectrometric analysis of distillation cuts. Distillation data, 4.0 mole % <45°, 84.5 mole % 45–55°, 11.5 mole % >55°. Cut 2, 45–55°, contained 99.1 mole % C_5H_{10}.

are sound thermodynamic reasons for doubting the identification. From the strain energies suggested by Golmov,[3] the heat of isomerization of a cyclopentane to a cyclobutane or cyclopropane isomer may be calculated to be 31.5 ± 3 kcal./mole. If one takes as a very liberal estimate the corresponding entropy of isomerization to be 20 e.u. (cyclohexane → methylcyclopentane, ΔS° = 8.5 e.u.), the free energy of isomerization at 400°K. is found to be of the order of 20 to 25 kcal./mole. Such a free energy corresponds to an equilibrium ratio of the cyclopropane or cyclobutane isomer to the cyclopentane of less than 10^{-4}, *i.e.*, less than 0.01%.

(3) Golmov, *J. Gen. Chem. USSR*, **11**, No. 5–6, 405 (1940). Strain energies per CH_2 group, C_3 ring 11.4, C_4 ring 8.5, C_5 ring 0.5, C_6 and higher rings 0.0 kcal./mole.

It is unlikely that direct mass spectrometric or infrared spectrophotometric analysis would be capable of detecting less than 1% of the cyclopropane and cyclobutane isomers of C_6H_{12} in a mixture of cyclohexane and methylcyclopentane plus small quantities (<2%) hexanes and other paraffins and naphthenes, even if the spectra of the twelve isomers were available. Although the spectra of the C_6H_{12}, cyclopropanes, and cyclobutanes have not been measured, it may be predicted that their mass and infrared spectra are such that the two analytical methods will err in the same direction, namely, that the methylcyclopentane will be overestimated and the cyclohexane underestimated in proportion to the quantity of the other isomers in the system. From the estimate of the probable equilibrium concentration of these extra isomers it appears that the analytical error from this source should be negligibly small.

The experiments with cyclopentane were undertaken in part because there is good reason to believe that the presence of methylcyclobutane and the cyclopropane isomers of C_5H_{10} can be detected by means of the mass spectrometer, even though the mass spectra have not been measured. By analogy with the mass spectra of the C_6 and C_7 naphthenes[4] that have been measured, it may be concluded that the relative intensity of the ion $C_4H_7^+$ in the mass spectra of the C_5H_{10} cyclopropanes and methylcyclobutane should be much greater than the relative intensity of this ion in the mass spectrum of cyclopentane. Thus the evaluation of the relative intensity of this ion, $C_4H_7^+$, should provide a sensitive indication of the presence of isomers of cyclopentane.

After correction for the pentane and butane contribution to the mass spectrum of the low boiling (<45°) fraction of the product of experiment 28, Table IV, the residual intensity of the ion, $C_4H_7^+$, relative to that of the ion, $C_5H_{10}^+$, agreed with that characteristic of pure cyclopentane to better than 1%. This fact, combined with the known low boiling points of the isomers of cyclopentane, a conservative assumption concerning the relative intensity, $C_4H_7^+/C_5H_{10}^+$, in that mass spectra of the isomers of cyclopentane, and the analytical data given in the footnote to Table IV, lead to 0.006% as an upper limit to the concentration of isomers of cyclopentane in the product of experiment 28.

The agreement between the calculated and experimental estimates of the upper limit to the concentration of C_3 and C_4 cyclanes which may exist in such systems as those considered in this paper, may be taken as reasonable grounds for ignoring possible effects of such isomers on the accuracy of the determination of the methylcyclopentane–cyclohexane ratios.

(4) The substances which have been studied include methylcyclopentane, cyclohexane, methylcyclohexane, ethylcyclopentane, four of the five dimethylcyclopentanes and a mixture of dimethylcyclohexanes (hydrogenated commercial xylene).

The effect of irreversible side reactions on the apparent equilibrium ratio of a pair of reversibly interconvertible substances has been considered by Bates.[5] His equation (8) for the limiting ($t = \infty$) ratio of B/A for the reacting system (1)

(1a) $A \underset{kb_1}{\overset{ka_1}{\rightleftharpoons}} B$, K eq $= \frac{B}{A} = \frac{ka_1}{kb_1}$

(1b) $A \xrightarrow{ka_2}$ Products

(1c) $B \xrightarrow{kb_2}$ Products

may be transformed to the form

$$(2) \qquad \left(\frac{B}{A}\right)_{t=\infty} = \frac{K_{eq}}{2}\left[\theta + \sqrt{\theta^2 + \frac{4}{K_{eq}}}\right]$$

where $\theta = 1 - 1/K_{eq} + (ka_2 - kb_2)/ka_1$. The term $(ka_2 - kb_2)/ka_1$, of the parameter θ, is particularly convenient for estimating the effect of the irreversible side reactions on the apparent equilibrium ratio, $(B/A)_{t=\infty}$. It has been found useful to prepare a graph of $(B/A)_{t=\infty}$ a function of $(ka_2 - kb_2)/ka_1$, for various values of K_{eq}.

Bates has pointed out that if $ka_2 = 0$ and $kb_2 = 0$, his equation (8) reduces to $(B/A)_{t=\infty} = K_{eq}$. However, the much less stringent condition, $ka_2 = kb_2$, is also a sufficient condition for the equality of the apparent equilibrium ratio, $(B/A)_{t=\infty}$, and the true equilibrium constant for the reversible reaction. In fact, examination of our equation (2) reveals that the important condition, necessary for the equality of $(B/A)_{t=\infty}$ and K_{eq} is that the ratio of the difference between the rates of the irreversible side reactions to the rate of the forward step of the reversible reaction be small compared with $1 - (1/Ke)$.

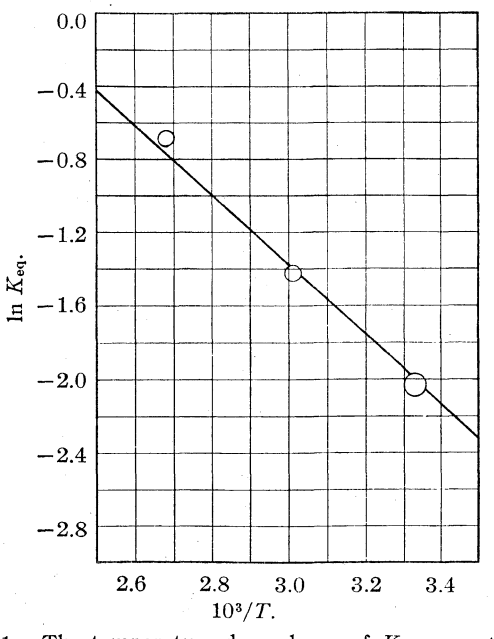


Fig. 1.—The temperature dependence of K_{eq} = methylcyclopentane/cyclohexane.

(5) Bates, THIS JOURNAL, **68**, 511 (1946).

For the experiments described in Tables I, II, and IIIa, it is apparent that the extent of the irreversible side reactions accompanying the C_6H_{12} isomerization must have had a negligible effect on the ratio of methylcyclopentane to cyclohexane. However, this is not the case for the experiments of Table IIIb. If it is assumed that the kinetics of the reactions of cyclohexane and methylcyclopentane may be represented by the differential equations corresponding to equations (1a), (1b), and (1c), experiments 26 and 27 (Table IIIb) lead to $ka_2 = 0.025$ hr.$^{-1}$, while experiments 24 and 25 give $ka_2 + kb_2 = 0.015$ hr.$^{-1}$. Experiments 18 and 19 in the presence to $^1/_{16}$ the quantity of catalyst present in experiments 24 through 26 indicate ka_1 $\left(\text{CH} \xrightarrow{ka_1} \text{MCP}\right)$ to be of the order of 0.1 hr.$^{-1}$. Thus for experiments 24 through 26 $(ka_2 - kb_2)/ka_1 < 0.02/16 \times 0.1 \cong 0.013$, and $\theta - 1 + 1/Ke_2 < 0.01$, and the ratio of MCP/CH must differ from the equilibrium ratio by less than 0.5% as a result of the side reactions.

In view of the foregoing discussion, it is reasonable to assume that the MCP/CH ratios given in Tables I, II, and IIIa may be taken to be equal to the equilibrium constant for the reaction

Cyclohexane (liquid) $\rightleftharpoons$ Methylcyclopentane (liquid)

The three values of this equilibrium constant are shown on the usual ln K *vs.* $1/T$ plot in Fig. 1. The radii of the circles representing the experimental points are equal to the mean deviations of the individual determinations of the MCP/CH ratio from the averages shown in the tables referred to. The straight line shown on the graph, represented by the equation $\ln K = 4.31 - 1890/T$, is a least squares fit of published values of the equilibrium constant.[1] Our values of the equilibrium constant at 27 and 59° agree within their experimental error with the previous determinations. However, our value for the equilibrium constant at 100° is definitely higher than that indicated by previous determinations. A least squares treatment of our data yields the equation

$$\ln K = 4.814 - 2059/T$$

The heats of combustion of cyclohexane and methylcyclopentane have been measured by Moore and Parks,[6] from which one obtains $\Delta H_{298.1} = 3{,}930 \pm 35$ cal./mole. Aston[7] gives $S^\circ_{298.1}$ (liq. CH) = 48.73 e.u., and Ruehrwein and Huffman[8] found $S^\circ_{298.1}$ (liq. CH) = 48.84 e.u. Douslin and Huffman[9] have recently redetermined the entropy of methylcyclopentane and give $S^\circ_{298.1}$ (MCP liq.) = 59.22 e.u. From the data of these authors one then finds

(6) Moore and Parks, *ibid.*, **61**, 2561 (1939).
(7) Aston, Szasz and Fink, *ibid.*, **65**, 1135 (1943).
(8) Ruehrwein and Huffman, *ibid.*, **65**, 1620 (1943).
(9) Douslin and Huffman, *ibid.*, **68**, 173 (1946).

CH (liq.) = MCP (liq.) $\Delta H^\circ_{298.1} = 3{,}930 \pm 35$ cal./mole
$\Delta S^\circ_{298.1} = 10.44 \pm 0.3$ e. u.
$\Delta C^\circ_{p\,298.1} = 0.6$ cal./mole °K.

The values of ΔH°_{298} and ΔS°_{298} obtained from the equilibrium data are compared with the thermochemical and third law values in Table V.

TABLE V

THE HEAT AND ENTROPY OF THE REACTION CYCLOHEXANE (LIQUID) ⇄ METHYLCYCLOPENTANE (LIQUID) 25°

	Thermal[a]	Equil.[b]	Equil.[c]
$\Delta H^\circ_{298.1}$	3,930 ± 35	3,735	4,015 ± 550
$\Delta S^\circ_{298.1}$	10.44 ± 0.3	8.49	9.50 ± 1.1

[a] See text. [b] $\ln K = 4.31 - 1890/T$, from previous investigations. [c] $\ln K = 4.814 - 2059/T$, this investigation.

The values of ΔH and ΔS from the equilibrium data have been corrected from an average temperature of 65° to 25° by use of the value of ΔC_p for the reaction quoted above ($\Delta C_p = 0.6$). The values deduced from our data are in considerably better agreement with the thermal data than are those resulting from the averaging over-all previous work.

The assignment of the formula $C_{12}H_{22}$ to the primary high molecular weight product is based on previous identification of dicyclohexyl and dimethyl dicyclopentyl among the reaction products[10] and our observation of an ion of molecular weight 166 in the mass spectra of the products of a number of our experiments.

In view of the rapid coloration upon exposure to air of the non-volatile catalyst complex formed in the reactions at 100°, it seems likely that unsaturated hydrocarbons are present in the catalyst complex. That the "polymer" can act as a hydrogen donor is indicated by the observation that the total quantity of paraffins formed in experiments no. 26 and 27 exceeds one-half of the $C_{12}H_{12}$ lost as heavy ends.

Our inability to detect cyclopentane in the product of any of the experiments with cyclohexane and methylcyclopentane indicates that reactions between naphthenes, analogous to the well-known paraffin dismutation reactions, are slow.

The results of the experiments with cyclopentane (Table IV) show this substance is not inert to the action of the aluminum halides,[11] although it is considerably less reactive than the C_6 naphthenes. It was definitely surprising to find evidence (mass spectra) for the presence of $C_{12}H_{22}$ (dicyclohexyl, dimethyl dicyclopentyl, etc.) but none for the $C_{10}H_{18}$ (dicyclopentyl). However, the observation that the catalyst complex formed in the cyclopentane reaction is highly colored and similar in appearance to that formed by the action of aluminum halides on paraffins, while the catalyst complex formed from the C_6 naphthene is colorless (in absence of air) indicates that the reactions of the cyclopentane are in important respects different from those of the C_6 naphthenes.

In experiment no. 28 (Table IV) the cyclopentane used was not treated with moist aluminum chloride prior to use. Analyses indicated the sample to contain *ca.* 0.2% cyclopentadiene (ultraviolet) and *ca.* 0.1% cyclopentene (mass spectrometer). The much greater extent of reaction in this experiment than in the other experiments with cyclopentane which had been treated to remove last traces of unsaturates indicates that unsaturates are promoters of catalytic activity in aluminum bromide for reactions of cyclanes. Pines and Wackher[12] have shown that olefins are promoters of isomerization activity in the aluminum halides toward the butanes. Thus there is further evidence of the similarity between the catalysis of alkane and cyclane reactions in the presence of aluminum halides (see the preceding paper).

Summary

The equilibrium constant of the reaction

cyclohexane (liq.) ⇄ methylcyclopentane (liq.)

has been measured at 27, 59 and 100°. It is represented by $\ln K = 4.814 - 2059/T$, which corresponds to $\Delta H^\circ_{298.1} = 4015 \pm 550$ cal./mole and $\Delta S^\circ_{298.1} = 9.50 \pm 1.1$ e.u. in good agreement with thermochemical and cryogenic measurements.

Among the products of side reactions accompanying the equilibration in the presence of moist aluminum halides, there have been identified by mass spectrometric analysis, propane, butane, pentane, hexane, C_7, C_8, and C_9 naphthenes and C_{12} binaphthenes. No evidence could be found for the formation of cyclopentane or C_7 or higher alkanes.

Arguments against the formation of C_5 or C_6 cyclopropanes and cyclobutanes from cyclopentane or methylcyclopentane and cyclohexane are presented, and partial experimental confirmation of the arguments is reported.

It has been found that butane, pentane, hexane, C_6, C_7, and C_8 naphthenes and C_{12} binaphthene are formed by the action of moist aluminum bromide on cyclopentane at 100°.

RECEIVED MARCH 3, 1948

(10) Ipatieff and Komarewsky, THIS JOURNAL, **56**, 1926 (1934).

(11) Compare Cox, *Bull. soc. chim.*, [4] **37**, 1549 (1925).

(12) Pines and Wackher, THIS JOURNAL, **68**, 595 and 599 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, REED COLLEGE]

Nucleophilic Substitution in the Benzene Ring. I. Rates of Reactions of *p*-Substituted Bromobenzenes with Piperidine

BY J. F. BUNNETT AND ARNOLD LEVITT[1]

It has long been known that an ortho- or para-nitro group strongly activates the condensation of a halobenzene with a nucleophilic reagent such as the hydroxide ion, an alkoxide ion, a mercaptide ion, or an amine. Several other groups, such as carboxyl, nitroso, cyano, sulfonyl, acyl and carbalkoxyl groups, have similar ortho–para activating effects.

This activation has been extensively studied, and for various reactions there are available comparisons[2] of the relative activating effects of pairs of groups. From these comparisons it is plain that nitro is more strongly activating than the other important activating groups, but there isn't available any comparison of the relative activating effects of the several groups in a single sort of reaction under constant conditions.

In this paper we report rate constants for the reactions of some *p*-substituted bromobenzenes with piperidine in benzene at 99°. The rate constants found are recorded in Table I. The order of activation in this reaction we have thus found to be: $NO_2 \gg CH_3SO_2 > CN > CH_3CO$.

TABLE I

REACTIONS WITH PIPERIDINE

	k (liters moles^{-1} sec.$^{-1}$)
p-Bromonitrobenzene	64.5×10^{-7}
p-Bromophenyl methyl sulfone	3.40×10^{-7}
p-Bromobenzonitrile	1.98×10^{-7}
p-Bromoacetophenone	0.86×10^{-7}
p-Chloronitrobenzene	11.4×10^{-7}

The determination on *p*-chloronitrobenzene was made with the object of comparing the rate constant found for it with those to be determined for *p*-chlorobenzophenone and *p*-chlorobenzotrifluoride. Samples of the two latter compounds were available in the laboratory; both of them, however, proved to have an order of reactivity too low to allow determination of rate constants in the time available. In about three and one-half days, 3.4% of the chlorine of *p*-chlorobenzophenone was liberated as chloride ion; the corresponding figure for *p*-chlorobenzotrifluoride was 1.2%.

We have also studied the reactions of *p*-nitrobromobenzene and of *p*-bromophenyl methyl sulfone with sodium methoxide in methanol at 99°. Rate constants for these reactions are listed in Table II.

These values, along with those in Table I, show very clearly that the relative activating effects of groups in nucleophilic substitution reactions are influenced by the nature of the nucleophilic reagent and by the nature of the solvent. In the reaction with sodium methoxide the nitro compound reacts twenty-eight times as fast as the sulfone, while in the reaction with piperidine it reacts only nineteen times as fast.

TABLE II

REACTIONS WITH SODIUM METHOXIDE

	k (liters moles^{-1} sec.$^{-1}$)
p-Bromonitrobenzene	78.5×10^{-5}
p-Bromophenyl methyl sulfone	2.84×10^{-5}

Experimental

In the cases of *p*-nitrobromobenzene, *p*-bromoacetophenone and *p*-chloronitrobenzene, the commercial product was recrystallized to a satisfactory melting point. Commercial piperidine was redistilled, and middle fractions were used in this work. A highly purified sample of *p*-chlorobenzotrifluoride was generously furnished by Dr. A. F. Scott.

***p*-Bromobenzonitrile.**—To a solution of 20 g. of *p*-bromobenzamide in 120 ml. of tetrachloroethane, 32 g. of phosphorus pentachloride was added and the mixture was refluxed for several hours during which hydrogen chloride was evolved. The mixture was poured over ice, and the organic layer separated and steam-distilled. After removal of the tetrachloroethane, the distillate containing the nitrile was collected and filtered. The nitrile was recrystallized from petroleum ether; m. p. 110–112°[3]; yield, 7.4 g. (41%).

***p*-Bromophenyl Methyl Sulfone.**—The method of Oxley, Partridge, Robson and Short[4] was followed. From 50 g. of *p*-bromobenzenesulfonyl chloride, 16 g. (35%) of *p*-bromophenyl methyl sulfone, m. p. 102–103°,[5] were obtained.

***p*-Chlorobenzophenone.**—A sample, m. p. 74–75°,[6] was generously supplied to us by Mr. Herbert Hergert who prepared it by the method of Gomberg and Cone.[7]

Kinetic Measurements. A. Reactions with Piperidine.—For the study of a particular compound, four or five sealed Pyrex tubes with identical contents were prepared. Within each tube were 20 ml. of a thiophene-free benzene solution about 1.5 molar in piperidine and about 0.05 molar in the halogen compound. All four or five tubes were placed in the thermostat[8] at once; a drop in temperature ensued, and when the temperature had returned to 99°, one of the tubes was removed and cooled to 0°. The other tubes were

(1) Present address: Department of Chemistry, Oregon State College, Corvallis, Oregon.

(2) Mattaar, *Rec. trav. chim.*, **41**, 103 (1922); Todd and Shriner, THIS JOURNAL, **56**, 1382 (1934); Le Fèvre, *J. Chem. Soc.*, 810 (1931).

(3) Von Braun, *Ber.*, **37**, 2816 (1904), reported m. p. of *p*-bromobenzonitrile 113°.

(4) Oxley, Partridge, Robson and Short, *J. Chem. Soc.*, 767 (1946).

(5) Bourgeois and Abraham, *Rec. trav. chim.*, **30**, 407 (1911), *C. A.*, **6**, 623 (1912), reported m. p. of *p*-bromophenyl methyl sulfone 102–103°.

(6) Kollarits and Merz, "Beilstein," 4th ed., Vol. VII, p. 419, reported m. p. of *p*-chlorobenzophenone 75.5–76°.

(7) Gomberg and Cone, *Ber.*, **39**, 3278 (1906).

(8) A thermostat of the type described in Ostwald–Luther, "Physiko-chemischer Messungen," 5th ed., Leipzig, 1931, p. 121, was used, with water the boiling liquid. The bath temperature was 99 ± 0.5°.

removed at subsequent recorded times. The contents of the tubes were extracted with water and halide ion in the water extracts was determined by the Volhard method.

The percentage of reaction in the last tube removed varied from 75.3% (forty hours reaction time) in the case of *p*-nitrobromobenzene, to 7.0% (137.62 hours reaction time) in the case of *p*-bromoacetophenone.

Rate constants were determined from the equation[9]

$$kt = \frac{2.303}{b - 2a} \log_{10} \frac{(b - 2x)}{(a - x)} + C$$

where b is initial concentration of piperidine, a is initial concentration of the halogen compound, and x is concentration of the piperidinium halide product at time t (first tube removed from bath at $t = 0$). This mathematical expression is valid for the chemical equation

$$RX + 2C_5H_{10}NH \longrightarrow RNC_5H_{10} + C_5H_{10}NH_2X$$

When values of the term $2.303/(b - 2a) \log_{10} [(b - 2x)/(a - x)]$ were plotted against t, the points in every case fell virtually on a straight line.[10] Values of the slope were calculated by the Method of Zero Sum.[11]

B. Reactions with Sodium Methoxide.—The technique was generally the same as used for the reactions with piperidine. The same thermostat was used with temperature again 99 ± 0.5°. Each tube contained 0.00200 mole of the halogen compound (added as a solid) and 0.00200 mole of sodium methoxide in a total volume of 19.28 ml. When a tube was opened, its contents were added to 100 ml. of 50% methanol and unconsumed base was determined by titration with standard hydrochloric acid to the methyl red end-point. For one tube of each compound, this titration was followed by a conductimetric titration of halide ion, and it was observed that bromide liberated was equal to methoxide consumed in the case of the nitro and sulfone compounds.

Rate constants were calculated from the expression

$$1/(a - x) = kt + C$$

applicable to second order reactions in which the initial concentrations of both reactants are equal. Values of k were found by the Method of Zero Sum.[11]

Acknowledgment.—The authors are grateful for generous financial support by the Research Corporation which greatly aided the progress of this work.

Summary

1. Rate constants for the reactions of some *p*-substituted bromobenzenes with piperidine at 99° have been determined; comparison of them shows that for this reaction four groups stand in the following order of activating influence: $NO_2 \gg CH_3SO_2 > CN > CH_3CO$.

2. Rate constants for the reactions of *p*-bromonitrobenzene and of *p*-bromophenyl methyl sulfone with methanolic sodium methoxide at 99° have been determined.

3. The rate constant for the reaction of *p*-chloronitrobenzene with piperidine at 99° has been determined; *p*-chlorobenzotrifluoride and *p*-chlorobenzophenone reacted too slowly with piperidine to allow kinetic study of the reactions.

PORTLAND, OREGON RECEIVED JANUARY 7, 1948

(9) *Cf.* Rheinlander, *J. Chem. Soc.*, **123**, 3099 (1923).

(10) The average deviation of points from the straight line was in every case less than 3% of the difference between the first and last values plotted.

(11) Campbell, *Phil. Mag.*, **39**, 177 (1920); **47**, 816 (1924).

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Polysaccharide Aryl Carbamates[2]

BY IVAN A. WOLFF AND CARL E. RIST

Although aromatic isocyanates are regularly used for the characterization of a variety of alcohols, the reactions of these reagents with carbohydrates have not been extensively investigated. Carbanilates of several common sugars,[3] sugar alcohols,[4] glucosides,[5] and the 1-N-α-naphthyl carbamate of 2,3,4,5,6-0-pentamethyl-(*levo*)-sorbitol[6] have been prepared. Recently carbamate derivatives of cellulose and of partially esterified or etherified cellulose have been reported.[7]

This paper reports the preparation and some properties of the esters of corn starch, corn amylose and amylopectin with phenyl isocyanate and with α-naphthyl isocyanate. Tricarbanilates of waxy (glutinous) corn starch, white potato amy-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Manuscript presented before the Division of Sugar Chemistry and Technology of the American Chemical Society at Chicago, Illinois, April 19–23, 1948.

(3) Maquenne and Goodwin, *Bull. soc. chim.*, [3] **31**, 430 (1904).

(4) Tessmer, *Ber.*, **18**, 968 (1885).

(5) Jolles and Botrini, *Gazz. chim. ital.*, **65**, 1217 (1935); Wolfrom and Pletcher, THIS JOURNAL, **62**, 1151 (1940); Hearon, Hiatt and Fordyce, *ibid.*, **66**, 995 (1944); Hearon, *ibid.*, **70**, 297 (1948); Reeves, *ibid.*, **70**, 259 (1948).

(6) Wolfrom and Gardner, *ibid.*, **65**, 750 (1943).

(7) Hearon, Hiatt and Fordyce, *ibid.*, **65**, 829, 833 (1943); Dyer and McCormick, *ibid.*, **68**, 986 (1946); Hearon and Lobsitz, *ibid.*, **70**, 296 (1948).

lose and amylopectin, glycogen, corn torrefaction dextrin, dextran from *Leuconostoc mesenteroides*,[8] corn β-amylase limit dextrin[9] and Schardinger β-dextrin[10] were also prepared. The tricarbanilate esters were different from the aliphatic esters previously studied in that they could be prepared from starch granules which had no pretreatment. Their optical rotations were negative in pyridine and were related to the degree of branching of the polysaccharide used. Starch tricarbanilate could be separated into its linear and non-linear components by the selective solvent action of ethyl acetate.

Corn starch granules reacted rapidly with phenyl isocyanate at 100° in the presence of pyridine to give a trisubstituted product. Esterification was substantially complete after two hours, but a reaction period of twenty-four hours gave products whose solutions in organic solvents showed greater clarity. The yield of trisubstituted derivatives was quantitative. Waxy corn starch, the corn and white potato starch components, Schardinger β-dextrin and the β-amylase limit dextrin reacted in a similar fashion. Dextran was converted to its triester in the pyridine-phenyl isocyanate medium, although the material was never completely in solution. Corn torrefaction dextrin was quite resistant to carbanilation. After twenty-four hours at 100° only 3.67% nitrogen had been introduced. The dextrin was rendered more reactive by solution in water and reprecipitation in ethanol.

Trisubstitution occurred readily when α-naphthyl isocyanate reacted with corn amylose, amylopectin or previously pasted and dried starch. Reaction with starch granules was, however, slower than in the case of phenyl isocyanate. In the presence of an excess of α-naphthyl isocyanate over that needed for trisubstitution, only two groups per anhydroglucose unit were introduced in twenty-four hours at 100°.

All of the esters were white amorphous solids which fused over a considerable temperature range of 220–300° (see Table I). The Schardinger β-dextrin tricarbanilate melted at 214–215°.

In contrast with the high positive optical rotations of corn starch and its aliphatic esters and ethers the tricarbanilates of the whole starch, corn amylose, and amylopectin had a levorotation in pyridine (see Table I). Even more striking was the 20° difference in the rotations of the amylose and the amylopectin derivatives. Since it is now believed that corn amylose is linear while amylopectin is branched, this rotational difference indicated that correlation might be expected between the structure of a 1,4-linked anhydroglucose polymer and the optical rotation of its tricarbanilate

(8) Jeanes, Wilham and Miers, paper presented before the Division of Sugar Chemistry and Technology at the 112th meeting of the American Chemical Society, New York, N. Y., September 15–19, 1947.

(9) Hodge, Montgomery and Hilbert, *Cereal Chem.*, **25**, 19 (1948).

(10) McClenahan, Tilden and Hudson, THIS JOURNAL, **64**, 2139 (1942).

TABLE I

OPTICAL ROTATIONS AND MELTING RANGES OF POLYSACCHARIDE TRICARBANILATES

Tricarbanilate of	$[\alpha]^{25}D$, (C = 1), in Pyridine[a]	Morpholine	Melting range, °C.[b]
Corn amylose	−82.5°	− 7°	248; 259–265
Corn amylopectin	−62.0	− 4	250–260
Corn starch	−66.0	− 5	209; 222–262
Waxy corn starch	−61.0	− 3	250–260
White potato amylose	−82.5	− 7	245–265
White potato amylopectin	−61.0	− 6	245–260
Corn β-amylase limit dextrin	−35.0	+ 17	240–255
Glycogen	−31.5	+ 4	220; 240–260
Corn torrefaction dextrin	−46.0	+ 9	200; 226–245
Dextran	Insol.	+343	255; 288–298
Schardinger β-dextrin	+69.5	+ 22	214–215

[a] Values stated to the nearest 0.5°.

[b] Taken in capillary tubes. The first figure is the sintering point. Then the melting range is given.

in pyridine. This expectation was borne out in the series of compounds listed in Table I. The potato amylose and amylopectin derivatives had rotations equal to those of the corn starch fractions. Waxy corn starch tricarbanilate had the same rotation as the amylopectin derivative to which it is closely related in structure.[11] Glycogen and corn β-amylase limit dextrin, which are thought to be approximately equally branched[12] and more so than amylopectin, gave derivatives with nearly the same rotations, but less negative than those of amylopectin. Using similar reasoning it would appear that the water-soluble corn torrefaction dextrin, prepared in the absence of catalyst, was more highly branched than amylopectin, but less so than glycogen. The rotation of the Schardinger β-dextrin carbanilate was not directly comparable to the rotations of the higher molecular weight polysaccharides.

Since the dextran tricarbanilate was sufficiently soluble only in morpholine for reading its optical rotation, the rotations of the other derivatives in morpholine were measured for comparison. The accuracy of these last-mentioned rotations was low because of their very small value. An outstanding difference could be noted, however (Table I), between the rotations of the predominantly 1,4-linked polysaccharide derivatives taken as a group and the large dextrorotation of the dextran carbanilate which contained an abundance of 1,6-linkages.[13] This phenomenon is being investigated as a possible test for the presence of different types of glycoside linkages in polysaccharides.

The optical rotations of the tri-α-naphthyl carbamates of the starch, amylose and amylopec-

(11) Schopmeyer, Felton and Ford, *Ind. Eng. Chem.*, **35**, 1168 (1943).

(12) Meyer in "Advances in Colloid Science," ed. by E. O. Kraemer, Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1942, pp. 159, 175.

(13) Levi, Hawkins and Hibbert, THIS JOURNAL, **64**, 1959 (1942).

tin of corn were +40, +50 and +36°, respectively. These positive values were unexpected in view of the negative rotations of the corresponding phenyl derivatives. The spread between the amylose and amylopectin α-naphthylcarbamates, while not as great as between their carbanilates, was substantially more than in the case of the aliphatic acid triesters.

The tri-α-naphthylcarbamates were not completely soluble in any organic solvent tested. They were partially soluble in pyridine, dioxane and morpholine. All of the higher molecular weight tricarbanilates were most soluble in pyridine and morpholine, less so in acetone, ethyl acetate, 1,4-dioxane and cold diethyl Cellosolve, and insoluble in other common organic solvents. The torrefaction dextrin and Schardinger β-dextrin carbanilates were readily soluble in most of the solvents tested. The tricarbanilates were often more soluble in cold than in warm solvents. This was shown most strikingly by the corn amylose derivative, which was completely soluble in diethyl Cellosolve at room temperature, but precipitated immediately on slight warming. Cooling of the mixture caused prompt re-solution.

Fractionation of corn starch tricarbanilate into the corresponding amylose and amylopectin derivatives has been accomplished by the selective solvent action of ethyl acetate. The soluble portion of the ester, constituting from one-sixth to one-quarter of the original material, had a rotation that indicated it to be the amylose ester, from 65 to 80% pure. After removal of the carbanilino groups, the reconstituted fractions were titrated potentiometrically with iodine.[14] The soluble fraction sorbed from 139 to 158 mg. of iodine per gram while the insoluble portion sorbed 19 mg. per gram, thus substantiating the analyses on the basis of optical rotation. This is the first known instance of successful solvent fractionation of a starch ester into its linear and non-linear components.

The close agreement between the optical rotation data and the fraction purities obtained in the potentiometric iodine titration suggested the possible use of the former as an analytical tool in determining the amylose–amylopectin ratio in a mixture. The successful operation of this procedure on a fairly pure amylose sample and on a material of rather low amylose content (whole starch) has been demonstrated above. The principle has also been applied to a synthetic sample composed of a mixture of equal parts by weight of corn amylose tricarbanilate and amylopectin tricarbanilate. The rotation of this mixture was −72.0° (pyridine, $C = 1$) indicating an amylose content of 49%. This procedure might advantageously be applied in cases where only very small amounts of material are at hand since the weight of sample is more than tripled by reaction with phenyl isocyanate.

(14) Bates, French and Rundle, THIS JOURNAL, **65**, 142 (1943); Wilson, Schoch and Hudson, *ibid.*, **65**, 1380 (1943).

Further studies on the reactions of carbohydrate materials with mono- and polyfunctional isocyanates are in progress.

Experimental

Materials.—The corn starch used was a high-grade commercial product. The white potato and waxy corn starches were extracted from their natural source in the pilot plant of this Laboratory. Amylose and amylopectin were separated by the butanol precipitation procedure,[15] and the amylose was recrystallized until the iodine sorption was 190 mg./g. or higher.[14] β-Amylase limit dextrin was prepared from an aqueous solution of corn amylopectin by allowing wheat β-amylase to react with it for eighteen hours.[9] The dextrin was isolated by precipitation with ethanol. Dextran from *Leuconostoc mesenteroides* was a water-soluble product of high viscosity prepared by allowing the organism to act for twenty-four hours on a 10% sucrose solution.[8] Corn torrefaction dextrin was prepared by heating corn starch in the absence of a catalyst for six hours at 185°. The product was completely water-soluble. It was pretreated by homogenization of an 8% aqueous solution in a Waring Blendor, filtration, and then isolation of the dextrin by precipitation in ethanol. Schardinger β-dextrin was kindly furnished to us by Dr. T. J. Schoch. Glycogen, phenyl isocyanate, and α-naphthyl isocyanate were Eastman Kodak Co. white label chemicals, used without further purification. Commercial pyridine having a 2° boiling range was dried over solid sodium hydroxide and distilled before use.

General Methods of Preparing the Tricarbanilate Esters.—The reactions of corn starch, waxy corn starch, corn and potato amylose and amylopectin, corn torrefaction dextrin, and corn β-amylase limit dextrin with phenyl isocyanate were carried out as in the following typical preparation. Nitrogen analyses on the products agreed with the calculated value for a tricarbanilate (calcd. for $C_{27}H_{25}N_3O_8$: N, 8.09) within ±0.1%.

Ten grams (0.055 mole) of waxy corn starch (moisture 10.76%) was suspended in 150 ml. of dry pyridine. Distillation through a 6-inch Vigreux column was carried out with stirring until 75 ml. had distilled. The amount distilled was then replaced with dry pyridine. Forty grams of phenyl isocyanate (0.34 mole) was added, and reaction was carried out for twenty-four hours at 100°. The clear, light yellow, viscous mass was precipitated in ethanol, washed three times with ethanol, and then dried, giving 28.9 g. of product (theoretical yield for the tricarbanilate 28.6 g.).

The course of the reaction of corn starch granules with phenyl isocyanate is shown in the following data:

Reaction time	% N in ester
14 min.	3.37
28 min.	5.54
57 min.	7.36
1 hr. 49 min.	7.82
4 hr. 32 min.	8.03

After fifteen minutes the reaction mixture was very viscous. No gross changes in viscosity occurred after this time.

Dextran tricarbanilate was prepared as above, but a reaction period of forty-eight hours was used. The reaction mixture in this case was light tan and somewhat viscous, but was not free of solid material at any time during the period of reaction.

Glycogen tricarbanilate was prepared by reaction of glycogen with phenyl isocyanate for twenty-four hours. After that time the mixture was filtered through a coarse Pyrex fritted glass funnel and the residue, which was estimated at approximately 10% of the starting material, was discarded. This was probably largely impurities in the glycogen. The filtrate was poured into ethanol, where-

(15) Schoch, *ibid.*, **64**, 2957 (1942).

upon the glycogen tricarbanilate formed a very fine precipitate. This ester was washed twice with ethanol, once with water, and then dried.

In the preparation of Schardinger β-dextrin tricarbanilate a reaction period of six hours at 100° was used. The esterification mixture was poured into four volumes of absolute ethanol, giving a clear solution, which was then poured into an equal volume of water. Eighty-three per cent. of the theoretical amount of crude tricarbanilate, m. p. 162–175°, precipitated. The crude product was soluble in hot isopropyl alcohol and reprecipitated (as round, non-crystalline particles) on cooling. Two reprecipitations gave pure Schardinger β-dextrin tricarbanilate, melting at 214–215°.

Anal. Calcd. for $C_{189}H_{175}O_{56}N_{21}$: N, 8.09. Found: N, 8.02.

Preparation of α-Naphthylcarbamates.—Corn starch (5.6 g., air-dried) was dried azeotropically with pyridine and reacted for twenty-four hours at 100°, in 100 ml. of pyridine, with 28 g. of α-naphthyl isocyanate. The tan, opaque reaction mixture was poured into ethanol, giving 16.1 g. of α-naphthyl carbamate, containing 5.61% N; calcd. for the triester 6.28% N.

A 7% cornstarch paste was stirred in a Waring Blendor for fifteen minutes, and the starch was then precipitated in ethanol, washed with ethanol, and dried. This pretreated starch, when treated with α-naphthyl isocyanate as above, gave starch tri-α-naphthylcarbamate.

Anal. Calcd. for $C_{39}H_{31}N_3O_8$: N, 6.28. Found: N, 6.29.

Corn amylose and amylopectin tri-α-naphthylcarbamates were prepared in a fashion similar to that for the starch derivative.

Optical Rotations.—All optical rotations were taken at 1% concentration. When an ester was incompletely dispersed in the solvent or when the solution was too turbid to see through in the saccharimeter, the mixture was homogenized in a Waring Blendor. These blended solutions always showed improved clarity. Their concentrations were determined by evaporating 10-ml. aliquots to dryness.

Fractionation of Corn Starch Tricarbanilate.—Five grams of the tricarbanilate prepared from pretreated corn starch was stirred at room temperature for twenty-four hours with 150 ml. of ethyl acetate. The mixture was then centrifuged and the soluble and insoluble portions were individually precipitated with 50% ethanol, washed with water, and dried. The soluble fraction weighed 1.0 g., $[\alpha]^{25}D$ −78.5° (pyridine, C = 1). The insoluble fraction weighed 3.4 g., $[\alpha]^{25}D$ −66.0° (pyridine, C = 1).

Two grams of the ethyl acetate-insoluble fraction and 0.54 g. of the soluble fraction were refluxed for twelve hours in 100 ml. and 50 ml., respectively, of 1.2 *N* sodium methoxide in absolute methanol. The regenerated fractions were washed twice with absolute ethanol, once in ethanol containing a small amount of glacial acetic acid, once with 90% ethanol, twice more with absolute ethanol, and then were dried. The iodine sorption of the regenerated fractions was 19 mg./g. and 158 mg./g., respectively.

In another similar fractionation, 1.3 g. of soluble tricarbanilate was obtained, $[\alpha]^{25}D$ −75.0° (pyridine, C = 1). The recovered amylose from this material sorbed 139 mg. of iodine per gram.

A similar separation was effected with the tricarbanilate prepared from non-pretreated starch.

The use of trade names in this paper does not necessarily constitute endorsement of these products nor of the manufacturers thereof.

Acknowledgment.—We are indebted to B. K. Zoss and P. R. Watson for carrying out portions of the experimental work, to M. Austin and C. Wilham for certain of the polysaccharide raw materials, and to M. Wiele for the nitrogen analyses reported in this paper.

Summary

1. Tricarbanilates have been prepared of corn starch, corn amylose and amylopectin, potato amylose and amylopectin, waxy corn starch, dextran, glycogen, β-amylase limit dextrin, corn torrefaction dextrin and Schardinger β-dextrin.

2. Tri-α-naphthylcarbamates of corn starch, amylose and amylopectin were also prepared.

3. The melting characteristics, solubility behavior and optical rotations of these derivatives were given.

4. In contrast with the usual aliphatic acid anhydrides, phenyl isocyanate reacted in the presence of pyridine with non-pretreated starch granules to give a fully esterified product.

5. The wide variation of up to 20° between the specific rotations of the tricarbanilates of branched and unbranched polysaccharides suggests a means of differentiation of polysaccharides of different structural types.

6. The fractionation of starch tricarbanilate by the selective solvent action of ethyl acetate into the component amylose and amylopectin esters was successfully accomplished.

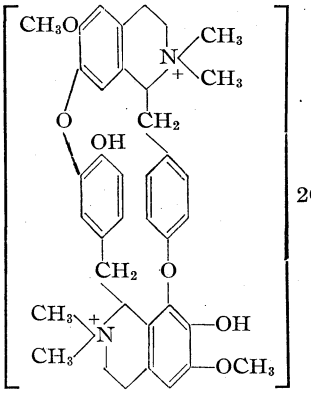
PEORIA, ILLINOIS RECEIVED APRIL 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Curariform Activity and Chemical Structure. II. Synthesis in the Benzyltetrahydroisoquinoline Series[1]

BY L. E. CRAIG AND D. S. TARBELL

One of the most effective of the curare alkaloids in causing paralysis of the peripheral nervous system (curariform paralysis) is *d*-tubocurarine chloride. This naturally occurring alkaloid was shown by King[2] to be of the bisbenzyltetrahydroisoquinoline type and to have structure I.



I

The present paper reports the syntheses of and the results of preliminary pharmacological tests on certain compounds analogous to half of the *d*-tubocurarine chloride molecule, that is, quaternary salts of benzyltetrahydroisoquinoline derivatives.

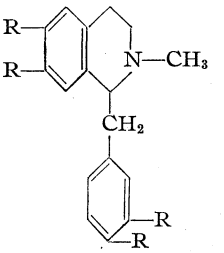
Numerous syntheses of laudanosine (II) have been reported in the literature. Pyman[3] treated tetrahydropapaverine with methyl iodide and obtained laudanosine hydroiodide in 5% yield, along with 21% of tetrahydropapaverine hydroiodide and 19% of laudanosine methiodide. Pictet and Finkelstein[4] prepared the methiodide of 3,4-dihydropapaverine, obtained from homoveratroylhomoveratrylamine by the Bischler–Napieralski reaction, converted it to the methochloride by stirring with silver chloride, and reduced the methochloride chemically with tin and hydrochloric acid. They obtained a 7% yield, based on the starting amide.

Several chemical reductions of N-methyl quaternary salts of papaverine have been reported,[5] in yields of 50–80%, but relatively long reaction periods were required and the necessary decomposition of the tin or zinc complex salts at the end of the reduction made the isolation of the product very inconvenient.

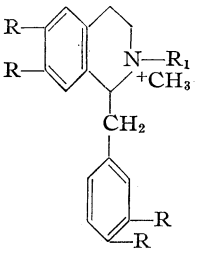
We have found that tetrahydropapaverine can be methylated to laudanosine very conveniently, and in excellent yield (89%), by the reductive methylation procedure,[6] using anhydrous formaldehyde in absolute alcohol, with Raney nickel and hydrogen under mild conditions.

N-Methyllaudanosinium iodide (III) and the previously unreported N-benzyllaudanosinium bromide (IV) were prepared by conventional methods.

The tetrahydropapaverine required for this synthesis was prepared by the hydrogenation of both papaverine and 3,4-dihydropapaverine, in the presence of Raney nickel, giving yields (greater than 80%) greatly improved over those reported in the literature.[7] A further advantage is that the 3,4-dihydropapaverine, which is very unstable, need not be isolated and purified after its formation by ring-closure of homoveratroylhomoveratrylamine, but may be hydrogenated in the crude form after transferring to the appropriate solvent.



(II) R = —OCH_3
(VII) R = —H



(III) R = —OCH_3, R_1 = CH_3
(IV) R = —OCH_3, R_1 = —$CH_2C_6H_5$
(VIII) R = —H, R_1 = —CH_3

A literature survey[8] on the types of compounds exhibiting curariform activity disclosed that certain compounds possessing a tertiary or quaternary nitrogen common to two saturated ring systems show marked curariform activity. Treatment of tetrahydropapaverine with formaldehyde gave such a compound, 2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine[9] (V), which was converted to the quaternary methiodide (VI) by treatment with methyl iodide.

(1) Aided by a Grant from the National Foundation for Infantile Paralysis. We are indebted to Dr. Virgil Boekelheide and R. Plato Schwartz, M.D., for their interest in this work.

(2) King, *J. Chem. Soc.*, 1381 (1935); 265 (1948).

(3) Pyman, *ibid.*, **95**, 1610 (1909).

(4) Pictet and Finkelstein, *Ber.*, **42**, 1979 (1909).

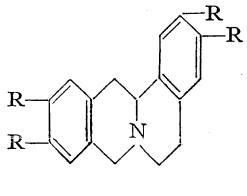
(5) (a) Awe and Unger, *ibid.*, **70**, 472 (1937); (b) Pictet and Athanasescu, *ibid.*, **33**, 2346 (1900); (c) Pyman and Reynolds, *J. Chem. Soc.*, **97**, 1320 (1910).

(6) For references related to the alkylation of aromatic and aliphatic amines with aldehydes and ketones, see (a) Clark, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1936), and (b) Emerson and Ringwald, *ibid.*, **63**, 2843 (1941), the last paper of a series.

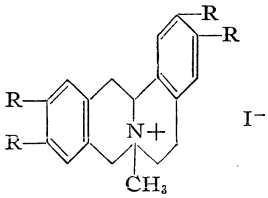
(7) (a) Späth and Burger, *Ber.*, **60**, 704 (1927), obtained a 62% yield by electrolytic reduction of papaverine. Pyman[3] obtained a 39% yield by reduction of papaverine with tin and hydrochloric acid. (b) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934), reduced dihydropapaverine catalytically with palladium in 63% yield.

(8) Craig, *Chem. Rev.*, **42**, 285 (1948).

(9) This compound has appeared in the literature under the following names: norcoralydine, tetrahydropalmatine, and 2,3,11,12-tetramethoxyberbine. The "Ring Index" name has been used in this paper for clarity.



(V) R = —OCH_3
(IX) R = —H



(VI) R = —OCH_3
(X) R = —H

The corresponding compounds without methoxyl groups were also prepared. 1-Benzyl-1,2,3,4-tetrahydroisoquinoline was prepared by catalytic hydrogenation (Raney nickel) of the 1-benzyl-3,4-dihydroisoquinoline formed in the Bischler–Napieralski synthesis. Here again the 3,4-dihydroisoquinoline was not isolated. Only chemical reductions have previously been reported.[10] The reductive methylation of the tetrahydroisoquinoline with formaldehyde gave 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII) in 66% yield. (VII) was converted into the quaternary methiodide (VIII).

Attempts to prepare 5,6,13,13a-tetrahydro-8-dibenzo(a,g)-quinolizine (IX) by treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde under both acidic and basic conditions were unsuccessful, but it was obtained by the method of Leithe[11] and converted to the quaternary methiodide (X).

Compounds III, IV, VI and VIII exhibited curare-like activity in mice, the two most effective, VI and VIII, being 1/70th to 1/75th as active as *d*-tubocurarine chloride. All four of the compounds showed vasodepression in dogs. Compounds V and X were convulsant poisons.[12]

Experimental[13]

Tetrahydropapaverine. A.—Ten grams of papaverine[14] in 250 cc. of ethanol was shaken with 1 g. of Raney nickel for four hours at 150° under hydrogen at 150 atm. The catalyst was removed by filtration and the filtrate reduced in volume to about 100 cc. An excess of dry hydrogen chloride gas was bubbled through the solution and ether added to precipitate the tetrahydropapaverine hydrochloride. Ten grams (89%) was obtained, m. p. 216–218°. The picrate after recrystallization from ethanol melted at 161–162°.[15]

B.—A 10-g. sample of homoveratroylhomoveratrylamine, prepared from the hydrazide of β-(3,4-dimethoxyphenyl)-propionic acid and homoveratric acid by the method of Schöpf and Salzer,[16] was treated with phosphorus oxychloride in thiophene-free benzene according to the method of Kindler and Peschke,[7b] all operations being carried out under an atmosphere of nitrogen rather than carbon dioxide. The chloroform extract of the dihydroisoquinoline was evaporated to dryness, and the residue taken up in 75 cc. of ethanol. The solution was shaken for five hours at about 70° under hydrogen at 3.5 atm. in the presence of about 0.5 g. of Raney nickel. After removing the catalyst by filtration, the solution was reduced in volume to about 50 cc. and an excess of dry hydrogen chloride gas introduced. The tetrahydropapaverine hydrochloride was recrystallized from ethanol–ether, 8.7 g. (79%) of very light tan needles being obtained, m. p. 216°. The picrate melted at 161–162°.[15]

Laudanosine (II).—A 2-g. sample of tetrahydropapaverine hydrochloride was converted to the free base and dissolved in 50 cc. of absolute ethanol. An excess of anhydrous formaldehyde was introduced into the solution by passing a stream of dry nitrogen over dry paraformaldehyde, heated in a flask immersed in an oil-bath at 180–190°, and then into the cooled solution. About 0.5 g. of Raney nickel was added, and the solution shaken at room temperature for three and one-half hours under hydrogen at a pressure of 2.5 atm. The catalyst was removed by filtration, the ethanol solution reduced in volume to about 25 cc., and an excess of dry hydrogen chloride introduced. On adding ether, an oil separated and slowly crystallized. The product was dissolved in water and the cooled solution made basic with dilute alkali. The white amorphous solid (1.7 g., 89%, m. p. 111–113°) melted at 114–115° after recrystallization from dilute ethanol. The picrate was obtained as yellow needles from ethanol, m. p. 173–175°.[17]

N-Methyllaudanosinium Iodide (III).—This product was obtained in 69% yield by refluxing a dry benzene solution (50 cc.) of 3 g. of laudanosine and 1.5 cc. of methyl iodide for three hours, m. p. 212–214° without further purification. A small sample recrystallized from ethanol–ether with charcoal treatment melted at 214–215°.[18] This product was shown by mixed melting point to be identical with a product obtained in 15% yield from the treatment of tetrahydropapaverine with methyl iodide.

Anal. Calcd. for $C_{22}H_{30}INO_4$: C, 52.91; H, 6.10. Found: C, 52.98; H, 6.09.

N-Benzyllaudanosinium Bromide (IV).—This product was obtained in essentially quantitative yield by refluxing a benzene solution (25 cc.) of 1.2 g. of laudanosine and 0.5 cc. of benzyl bromide for six hours. After recrystallization from absolute ethanol, tiny needles were obtained, m. p. 157–165° with decomposition. No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{28}H_{34}BrNO_4$: C, 63.63; H, 6.49. Found: C, 63.50; H, 6.10. These analytical values were obtained after several analyses in which carbon percentages were consistently low.

2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine (V).[19]—Five grams of tetrahydropapaverine hydrochloride in 40 cc. of water was heated on a steam-bath while 10 cc. of 35% formaldehyde was added in small portions over a period of thirty minutes. Heating was continued for an additional thirty minutes. After concentrating the solution and cooling, 5.2 g. of the crude hydrochloride was obtained. The product was dissolved in a small amount of water and the free base liberated by the addition of an excess of dilute alkali, giving 3.8 g. (83%), m. p. 158–159°.

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09. Found: C, 70.98; H, 6.93.

The hydrochloride, prepared by passing dry hydrogen chloride gas through an ether solution, melted at 234–237° with decomposition.[20]

(10) (a) Leithe, *Ber.*, **63**, 1498 (1930); (b) Forsyth, Kelly and Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(11) Leithe, *Ber.*, **63**, 2343 (1930).

(12) The authors are indebted to Drs. J. A. Shannon, C. R. Linegar and J. C. Burke of the Squibb Institute for Medical Research for the pharmacological tests on these compounds.

(13) All melting points are corrected; analyses by Mrs. G. L. Sauvage and Dr. Carl Tiedcke.

(14) Obtained as the hydrochloride from Mallinckrodt Chemical Co.

(15) Pyman[3] reported 217–219° as m. p. of the hydrochloride and 161–162° for the picrate.

(16) Schöpf and Salzer, *Ann.*, **544**, 1 (1940).

(17) Pictet and Anthanasescu[5b] reported 115° as m. p. for the free base, and 174° for the picrate.

(18) Pyman[3] reported a m. p. of 123–215°. Pictet and Athanasescu[5b] reported a m. p. of 215–217°.

(19) Pictet and Chou, *Ber.*, **49**, 370 (1916).

(20) (a) Hayworth, Koepfli and Perkin, *J. Chem. Soc.*, 548 (1927), reported a m. p. of 147° for the free base. (b) Feist, *Arch. Pharm.*, **245**, 627 (1907), reported a m. p. of 145°. Pictet and Chou[19] reported a m. p. of 157–158° for the free base, and 213° for the hydrochloride.

7-Methyl-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizinium Iodide (VI).—This quaternary salt was obtained in essentially quantitative yield by refluxing a solution of 2 g. of 2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine and 1 cc. of methyl iodide in 50 cc. of benzene for three and one-half hours. The tiny white needles which precipitated melted at 244–249°.[21] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{22}H_{28}INO_4$: C, 53.12; H, 5.67. Found: C, 52.75; H, 5.71.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline.—A 20-g. sample of N-(β-phenylethyl)-phenylacetamide[22] was converted to 1-benzyl-3,4-dihydroisoquinoline by treatment with phosphorus pentoxide in boiling tetralin according to the procedure of Späth, Berger and Kuntara.[23] The light yellow oil (10 g., 54%) was dissolved in 75 cc. of ethanol, 1 g. of Raney nickel added, and the solution shaken for three hours at 70° under hydrogen at 3.5 atm. The catalyst was removed by filtration and the filtrate concentrated to about 40 cc. An excess of dry hydrogen chloride gas was introduced and ether added to facilitate precipitation. The 8.8 g. of colorless crystals obtained represent a 75% yield in the hydrogenation. A small sample after recrystallization from ethanol–ether melted at 172–173°.[24]

1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII).—The free base from 3.3 g. of 1-benzyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was dissolved in 75 cc. of absolute ethanol and an excess of anhydrous formaldehyde introduced as above. About 0.5 g. of Raney nickel was added and the solution shaken for three hours at room temperature under hydrogen at 3.3 atm. The catalyst was removed by filtration and the ethanol removed by distillation, leaving 2.3 g. (66%) of very light yellow oil. The picrate was obtained as tiny yellow needles from ethanol, m. p. 166.5–167°.[25]

(21) Osada, *J. Pharm. Soc.*, No. 547, 711 (1927), reported a m. p. of 245°. Haworth, Koepfli and Perkin, *J. Chem. Soc.*, 2263 (1927), reported a m. p. of 266° for the β-isomer, 230° for the α-isomer. Robinson and Sugasawa, *ibid.*, 789 (1932), reported a m. p. of 215°.

(22) Prepared by the method of Decker, *Ann.*, **395**, 282 (1912).

(23) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(24) Leithe (ref. 10a) reported a m. p. of 173°.

(25) Forsyth, Kelly and Pymán (ref. 10b) reported a m. p. of 165–167°.

1-Benzyl-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (VIII).—A dry benzene solution (50 cc.) of 2.2 g. of 1-benzyl-2-methyl-1,2,2,4-tetrahydroisoquinoline and 2 cc. of methyl iodide was refluxed for three hours on a steam-bath. The light tan powder obtained on filtering the cooled reaction mixture amounted to 2.9 g. (83%). After recrystallization from absolute ethanol, 2.5 g. (72%) of tiny colorless needles were obtained, m. p. 242°.[26]

5,6,13,13a-Tetrahydro-8-dibenzo[a,g]quinolizine (IX).—Attempts to prepare 5,6,13,13a-tetrahydro-8-dibenzo-[a,g]quinolizine by treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde in the presence of hydrochloric acid, or of sodium bicarbonate, were unsuccessful. It was prepared in 38% yield by the method of Leithe,[11] m. p. of the free base 84–85°, m. p. of the hydrochloride 231–232°.

7-Methyl-5,6,13,13a-tetrahydro-8-dibenzo[a,g]quinolizinium Iodide (X).—A dry solution of 0.6 g. of 5,6,13,-13a-tetrahydro-8-dibenzo[a,g]quinolizine and 2 cc. of methyl iodide in 50 cc. of dry benzene was refluxed for four hours. The light tan precipitate which formed was collected by filtration and dried. The 0.8 g. of product after recrystallization from ethanol–ether with charcoal treatment gave 0.7 g. (73%) of very light tan powder, m. p. 198–202°.[27] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{18}H_{20}IN$: C, 57.30; H, 5.34. Found: C, 57.64; H, 5.36.

Summary

1-Benzyltetrahydroisoquinolines have been synthesized by improved methods. Quaternary salts of these compounds exhibited curare-like activity, the most effective being 1/75th as active as *d*-tubocurarine chloride.

(26) Leithe (ref. 10a) reported a m. p. of 242°. Freund and Bode, *Ber.*, **42**, 1763 (1909), reported a m. p. of 239–242°.

(27) Chakravarti, Haworth and Perkin, *J. Chem. Soc.*, 2275 (1927), reported a m. p. of 230–232° for the β-isomer, 212° for the α-isomer.

ROCHESTER, N. Y. RECEIVED APRIL 17, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Synthesis of Some Iodo-sugar Derivatives[1]

BY ALBERT L. RAYMOND AND ELMER F. SCHROEDER

The use of iodinated organic compounds as X-ray contrast agents in urography has become well established in recent years. However, the administration of such compounds by the intravenous route is attended by an element of danger because of occasional side effects. In a search for other suitable contrast agents of lower toxicity, a number of water soluble iodo-sugar derivatives have been prepared and subjected to preliminary tests. These include 6-iodo-6-desoxy-D-galactose (I), 6-iodo-6-desoxy-α-methyl-D-glucopyranoside (II), 6-iodo-6-desoxy-β-methyl-D-glucopyranoside (III) and 6-iodo-6-desoxy-1,4-sorbitan (IV).

The introduction of the iodine atom into the sugar residues was accomplished by the well-known procedure of Oldham and Rutherford[1a] by heating the corresponding 6-*p*-toluenesulfonyl (tosyl) derivative, suitably stabilized by substituent groups, with sodium iodide in acetone solution. Thus, 6-iodo-6-desoxy-D-galactose was obtained by the following series of reactions: 1,2,3,4-diisopropylidene-D-galactose[2] → 6-tosyl-1,2,3,4-diisopropylidene-D-galactose[3] → 6-iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose[4] → 6-iodo-6-desoxy-D-galactose. The final step in this series was carried out by hydrolysis of the diisopropyli-

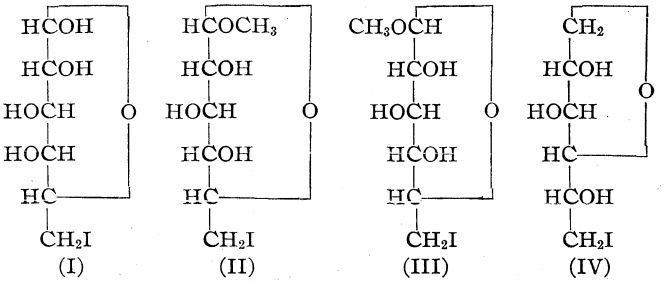
(1) Presented before the Division of Sugar Chemistry and Technology of the American Chemical Society at the Chicago meeting, April, 1948.

(1a) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(2) Van Grunenberg, Bredt and Freudenberg, *ibid.*, **60**, 1507 (1938).

(3) Freudenberg and Hixon, *Ber.*, **56**, 2119 (1923).

(4) Freudenberg and Raschig, *ibid.*, **60**, 1633 (1927).



dene derivative in 50% acetic acid. The iodogalactose was readily obtained in crystalline form by treatment with absolute ethanol, from which it separated in rectangular plates containing one molecule of ethanol. The anhydrous form resulted on recrystallization of the alcoholate from an acetic acid–methyl ethyl ketone mixture. It melted at 114–116° and rotated $[\alpha]^{25}D$ + 75.3° (three minutes) in water, decreasing to a constant $[\alpha]^{25}D$ + 66.9° in about five hours. The anhydrous form readily gave crystalline alcoholates also with methanol and 2-propanol. On treatment with phenylhydrazine, an insoluble phenylhydrazone was precipitated at room temperature.

6-Iodo-6-desoxy-α-methyl-D-glucopyranoside was recently prepared by Zief and Hockett[5] by deacetylation of 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside with hot aqueous–alcoholic hydrogen chloride. We obtained the same compound simply by treating α-methyl-D-glucopyranoside in pyridine with one mole of tosyl chloride, and after removal of the pyridine, heating the sirupy reaction product with sodium iodide in acetone solution. From the resulting digest, the iodo-glucoside was isolated directly in about 22% yield. Alternatively, the crude product from the iodide digestion may be converted by acetylation into 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside, which can then be catalytically deacetylated by means of sodium methoxide in methanol solution.[6] The fact that this deacetylation can be smoothly and practically quantitatively accomplished by no more than about 0.01 mole equivalent of sodium methoxide is rather surprising in view of the presence of the halogen atom. The 6-iodo-6-desoxy-α-methyl-D-glucopyranoside obtained by either procedure, after recrystallization from ethanol, melted at 146–147°, and rotated $[\alpha]^{25}D$ + 101.5° in water.

6-Iodo-6-desoxy-β-methyl-D-glucopyranoside was obtained in similar manner, by treatment of β-methyl-D-glucopyranoside hemihydrate with 1.5 mole equivalents of tosyl chloride in pyridine. However, in this case, when the sirupy tosylation product was heated with sodium iodide in acetone, the iodo-glucoside, which itself is easily soluble in warm acetone, separated from the hot reaction mixture presumably as an insoluble complex with sodium *p*-toluenesulfonate. This complex is probably analogous to those described by Watters, Hockett and Hudson[7] of certain β-methyl glycosides with potassium acetate. Treatment of the complex with an acetylating mixture yielded 6-iodo-6-desoxy-2,3,4-triacetyl-β-methyl-D-glucopyranoside, which on deacetylation with sodium methoxide gave the desired 6-iodo-6-desoxy-β-methyl-D-glucopyranoside in an over-all yield of 53%. The product separated from alcohol as needles melting at 157–158° and rotating $[\alpha]^{25}D$ −17° in water.

The synthesis of 6-iodo-6-desoxy-1,4-sorbitan, and several of its derivatives, is represented schematically. On treatment of 1,4-sorbitan (V) with tosyl chloride at low temperature, a 53% yield of 6-tosyl-1,4-sorbitan (VI) was obtained. This was condensed with benzaldehyde in the presence of hydrochloric acid or zinc chloride to give an excellent yield of 6-tosyl-2(3),5-benzylidene-1,4-sorbitan (VII), melting at 129.5–130.5° and rotating $[\alpha]^{25}D$ + 8.9° in water. As an alternative procedure, 1,4-sorbitan was condensed with benzaldehyde using zinc chloride as catalyst to give 2(3),5-benzylidene-1,4-sorbitan (VIII), melting at 154.5–155.5° and rotating $[\alpha]^{25}D$ + 17.7° in methanol,[8] which with tosyl chloride was converted almost quantitatively into 6-tosyl-2(3),5-benzylidene-1,4-sorbitan (VII) identical with the product obtained by benzalation of 6-tosyl-1,4-sorbitan. Treatment of the tosyl derivative with sodium iodide yielded 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan (IX) which was readily hydrolyzed by heating for ten minutes at 100° in aqueous–alcoholic 0.1 *N* sulfuric acid to give an 85% yield of 6-iodo-6-desoxy-1,4-sorbitan (IV), melting at 108–109° and rotating $[\alpha]^{25}D$ − 11.9° in water.

The assignment of the tosyl group, and consequently of the iodine atom, to the 6 position in these compounds follows from the Oldham–Rutherford rule[1a] that only tosyl groups attached to primary alcohol groups are readily replaceable by iodine on treatment with sodium iodide. The location of the benzylidene group has not been completely established. However, that one of the linkages is attached to position 5 is highly probable in view of the observation that, while 6-tosyl-1,4-sorbitan (VI) on treatment with sodium iodide decomposes with liberation of iodine, its benzylidene derivative (VII) reacts smoothly without evidence of decomposition. In our experience,[9] when 6-tosyl derivatives, having an unprotected secondary hydroxyl group in the adja-

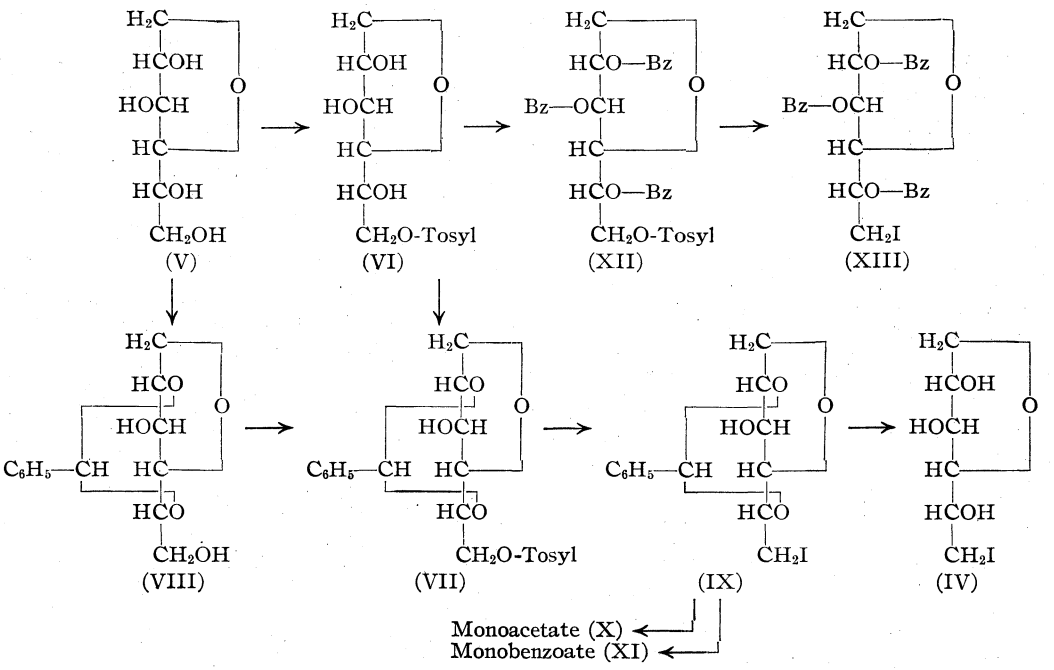
(5) Zief and Hockett, THIS JOURNAL, **67**, 1267 (1945).

(6) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

(7) Watters, Hockett and Hudson, THIS JOURNAL, **56**, 2199 (1934).

(8) Soltzberg, Goepp and Freudenberg, *ibid.*, **68**, 919 (1946), recently reported the preparation in small yield of two additional monobenzylidene-1,4-sorbitans by refluxing sorbitan with benzaldehyde without catalyst. That neither of these is identical with the product obtained by us is indicated by the reported constants (m. p. 136–140°, $[\alpha]D$ +33.72° in methanol for the first and m. p. 121–122° for the second).

(9) Unpublished results. See also Bell, Friedmann and Williamson, *J. Chem. Soc.*, 252 (1937).



cent 5 position, are heated with sodium iodide there is a greater or less tendency for liberation of free iodine to occur. This is not evident when the 5 position is blocked, either by a substituent group or, as in the case of the 6-tosyl-α- and β-methyl-D-glucopyranosides, by the presence of a pyranoid ring structure.

Several additional derivatives of 1,4-sorbitan were prepared during the course of this work. 6-Iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan (IX) gave a monoacetate (X) and a monobenzoate (XI). On treatment of crystalline 6-tosyl-1,4-sorbitan (VI) with excess benzoyl chloride, there was obtained 6-tosyl-2,3,5-tribenzoyl-1,4-sorbitan (XII) melting 106–107° and rotating $[\alpha]^{25}D$ +47.2° in chloroform,[10] converted by sodium iodide into 6-iodo-6-desoxy-2,3,5-tribenzoyl-1,4-sorbitan (XIII). The latter could not be debenzoylated without simultaneous loss of iodine.

The iodo-sugar derivatives (I-IV) are readily soluble in water to give colorless solutions. Thus 6-iodo-6-desoxy-D-galactose (I) and 6-iodo-6-desoxy-1,4-sorbitan (IV) dissolve at room temperature in their own weight of water. The two 6-iodomethyl-D-glucopyranosides are less soluble, dissolving in about two parts of water at 50°, but partially crystallizing out again on cooling. The β-form separates from water in needles, while the α-form produces rods frequently several centimeters long.

These compounds show a wide divergence in the firmness with which the iodine atom is held, as is shown in Table I. These data were obtained by dissolving equivalent amounts of the iodo-sugar derivatives (0.0013 mole) in 25 cc. of water, immersing for exactly thirty minutes in a boiling water-bath, then titrating the hydrogen iodide formed with standard alkali.

TABLE I

STABILITY OF IODO-SUGAR DERIVATIVES AT 100°

Compound	Cc. 0.01 *N* NaOH required	% Decomposition
I	2.20	1.66
II	0.10	0.07
III	0.18	0.13
IV	44.80	33.7

As would be expected, the stabilizing effect of the pyranoid ring is evident. The two iodomethyl-D-glucopyranosides (II and III), having a fixed ring structure, show only negligible decomposition; iodo-D-galactose (I), in which a ring shift is possible in solution, is somewhat less stable, while iodo-sorbitan (IV), having a free hydroxyl group adjacent to the iodine, is by far the least stable. At room temperature, aqueous solutions of the iodo-D-glucosides remain unchanged indefinitely, while solutions of iodo-D-galactose and iodo-sorbitan show evidence of acid liberation within several months and several weeks, respectively.

Pharmacological studies carried out on dogs have shown that 6-iodo-6-desoxy-D-galactose exhibits a fairly low acute toxicity, is concentrated rapidly by the kidneys, and yields satisfactory X-ray pictures of the kidney region. However, in view of the relatively low stability of the carbon–iodine linkage, the application to clinical use must await further study.

(10) After completion of our experimental work on this compound, Hockett, Conley, Yusem and Mason, THIS JOURNAL, **68**, 922 (1946), reported its preparation directly from 1,4-sorbitan without isolation of the intermediate 6-tosyl-1,4-sorbitan. However, the constants reported by these investigators are at considerable variance with those found by us (m. p. 161.5–163.0°, rotation +35.1° in chloroform).

Experimental

1,2,3,4-Diisopropylidene-D-galactose.—Crude diisopropylidene galactose was prepared by a modification of the method of Gruenenberg, Bredt and Freudenberg.[2] The principal changes introduced were in the substitution of sulfuric acid for the phosphoric acid–phosphorus pentoxide catalyst, and in a considerable reduction in the quantity of acetone used.

A mixture consisting of anhydrous D-galactose (200 g.), acetone (2500 cc.), powdered, fused zinc chloride (240 g.), and sulfuric acid (8 cc.), was stirred for four hours at room temperature. The reaction mixture was treated with a solution of 400 g. of sodium carbonate in 700 cc. of water, and vigorously stirred until the supernatant liquid became zinc-free. The precipitated salts were filtered off and washed with acetone. The filtrate, consisting of two liquid phases, was completely freed of acetone by distillation, and the crude diisopropylidene galactose, separating as a light-yellow upper layer, was taken up in ether, washed with water, and dried with sodium sulfate. After removal of the solvent, the yield of crude product was 260 g., or 90% of theory.

6-Tosyl-1,2,3,4-diisopropylidene-D-galactose.—The procedure of Freudenberg and Hixon[2] was somewhat modified for this preparation. A solution of 260 g. (1 mole) of crude diisopropylidene galactose in a mixture of 275 cc. of acetone and 175 cc. of pyridine was cooled in tap water. With stirring, 228 g. (1.2 moles) of tosyl chloride was added in portions over a period of one hour, the temperature being maintained below 45°. After standing overnight, the excess tosyl chloride was decomposed by the addition of 10 cc. of water. The reaction mixture was then poured into 2.5 liters of water, a sirupy product precipitating, which solidified on standing for several hours. This was filtered off, washed with water, and air-dried; yield, 360 g. The product was dissolved in 360 cc. of 2-propanol, and allowed to crystallize overnight at room temperature. After 360 cc. of Skellysolve C were gradually added with stirring, the crystals were filtered off and washed with Skellysolve C. The yield was 275 g. (66%) of product melting at 87–89°; reported,[3] 91–92°. If the product melts much below this point, it must be recrystallized before use in the subsequent reaction with sodium iodide.

6-Iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose.—The procedure of Freudenberg and Raschig[4] was somewhat modified for this preparation. A solution of 248 g. (0.6 mole) of 6-tosyl-1,2,3,4-diisopropylidene-D-galactose and 180 g. (1.2 moles) of sodium iodide in 1250 cc. of acetone was heated at 105–110° for thirty-six hours.[11] After removal of the precipitated sodium *p*-toluenesulfonate by filtration and washing with acetone, the filtrate was concentrated under reduced pressure. The residual sirup was stirred with 1 liter of water and a few crystals of sodium thiosulfate to destroy traces of free iodine. After several hours, the product solidified and was washed repeatedly with water. This crude material may be used directly, without drying, in the subsequent hydrolysis. If desired, it may be recrystallized from 250 cc. of methanol; yield, 190 g. (85%), melting at 69–71°; reported, 72°.[4]

6-Iodo-6-desoxy-D-galactose.—6-Iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose (275 g.) was dissolved in 800 cc. of glacial acetic acid, immersed in a boiling water-bath, and with frequent shaking, treated with 750 cc. of hot water added in 50-cc. portions over a period of one hour. Heating was continued for one hour longer, at which time hydrolysis was complete as shown by the fact that a 1-cc. test portion remained clear on dilution with 5 cc. of water. In some runs, an additional twenty or thirty minutes of heating was required to complete hydrolysis. The solution was cooled, treated briefly with Darco, and filtered through a layer of Celite. The filtrate was then concentrated to a thin sirup under reduced pressure at a temperature not exceeding 40°. Absolute ethanol (500 cc.) was added, and the solution again concentrated. On redissolving the sirupy residue again in 800 cc. of absolute ethanol, cooling and scratching, a voluminous mass of crystals rapidly separated. After standing in the cold overnight, the product was filtered off, washed with ethanol, and twice recrystallized from 1500 cc. of absolute ethanol. The 6-iodo-6-desoxy-D-galactose prepared in this manner crystallized with one molecule of ethanol. The yield of alcoholate was 196 g., or 78% of the theoretical; rectangular plates, melting at 105–106° (cor.); very soluble in water, moderately soluble in hot alcohol, ethyl acetate and acetone, insoluble in chloroform and benzene. The substance had an initial (three minutes) rotation of $[\alpha]^{25}D$ +84.7° (*c*, 6.08 in water), which decreased to a constant value of +57.6° in five hours. Calculated on the basis of the iodo-galactose content, the latter becomes $[\alpha]^{25}D$ +66.8° (*c*, 5.24), identical with the constant value later obtained for anhydrous iodogalactose itself.

Anal. Calcd. for $C_6H_{11}O_5I \cdot C_2H_5OH$: C, 28.58; H, 5.10; I, 37.76. Found: C, 28.30; H, 4.86; I, 37.75, 38.0.

The alcohol is held quite tenaciously, being only incompletely removed by heating at 61° for seventeen hours (1 mm.). Calcd.: C_2H_5OH, 13.71. Found: C_2H_5OH, 12.2. Attempts to obtain the anhydrous form of the iodo-galactose by recrystallization from ethanol under a variety of conditions of concentration and temperature resulted in recovery of the starting material. The following procedure, however, gave the anhydrous form in good yield. A quantity of 50 g. of the alcoholate was heated for five minutes in a boiling water-bath with 25 cc. of glacial acetic acid. To the hot solution was added 250 cc. of hot, freshly distilled, methyl ethyl ketone. On cooling, anhydrous 6-iodo-6-desoxy-D-galactose separated in the form of needles, which were filtered off and washed with methyl ethyl ketone. The yield was 35 g. of product melting sharply at 113–114° (cor.), and rotating $[\alpha]^{25}D$ +75.3° (three minutes, *c*, 5.68 in water), decreasing to a constant value of +66.9° in about five hours.

Anal. Calcd. for $C_6H_{11}O_5I$: C, 24.84; H, 3.82; I, 43.75. Found: C, 24.78, 24.51; H, 3.82, 3.78; I, 43.87, 43.70.

Phenylhydrazone of 6-Iodo-6-desoxy-D-galactose.—To a solution of 7 g. of phenylhydrazine in 75 cc. of 50% acetic acid were added 3 g. of 6-iodo-6-desoxy-D-galactose. A white precipitate began to form at once. After one hour at room temperature the product was filtered off, washed with water and cold alcohol, and dried; yield 3.8 g.; theory, 3.93 g. After two recrystallizations from 120 cc. of 95% ethanol, the product darkened at 126° and melted with vigorous decomposition at 136–137° (cor.); $[\alpha]^{25}D$ +34.3° (*c*, 5.40 in pyridine), showing no evidence of mutarotation, but developing a marked yellow color in the pyridine solution in thirty minutes; rectangular plates.

Anal. Calcd. for $C_{12}H_{17}O_4N_2I$: N, 7.37; I, 33.42. Found: N, 6.99, 7.01; I, 33.49.

6-Iodo-6-desoxy-α-methyl-D-glucopyranoside.—A solution of 300 g. (1.55 moles) of α-methyl-D-glucopyranoside in 1500 cc. of dry pyridine was cooled in tap water and treated by the portionwise addition of 318 g. (1.67 moles) of tosyl chloride, the temperature being held below 40°. After standing for one hour longer, most of the pyridine was removed by distillation under reduced pressure. The residual sirup was taken up in 300 cc. of warm water, cooled, and neutralized (brom thymol blue) by the addition of 5 *N* sodium hydroxide (360 cc. required). The solution was concentrated to dryness under reduced pressure, and the residual sirup (700 g.) dissolved in 1200 cc. of acetone, some insoluble products being removed by filtration. Sodium iodide (210 g.) was dissolved in the acetone solution, which was transferred to pressure flasks and heated for two hours at 100°. Sodium *p*-toluene-

(11) Freudenberg and Raschig[4] employed a temperature of 125° for thirty-six hours. In our hands, considerable decomposition occurred under these conditions. At 105–110° the reaction is complete in thirty-six hours, as indicated by the practically quantitative yield of sodium *p*-toluene-sulfonate.

sulfonate was removed by filtration, washed with acetone, and the filtrate concentrated to dryness. The sirupy residue was dissolved in 700 cc. of water, extracted several times with dichloromethane and the aqueous phase then concentrated under reduced pressure. When about 500 cc. of distillate had been collected, the desired product began to separate out, and crystallization was complete after standing for twenty-four hours in the cold. The product was filtered off and recrystallized twice from 100 cc. of 95% ethanol; yield, 100 g., 22%.

Anal. Calcd. for $C_7H_{13}O_5I$: C, 27.65; H, 4.31; I, 41.74. Found: C, 27.72, 27.94; H, 4.40, 4.61; I, 41.71, 41.62.

The 6-iodo-6-desoxy-α-methyl-D-glucopyranoside is obtained as long rods melting sharply at 146–147° (cor.) and rotating $[\alpha]^{25}D$ +101.5° (*c*, 5.00 in water). Zief and Hockett[5] found m. p. 136.9–137.4° and $[\alpha]D$ +93.9° in water. The product is readily soluble in water but crystallizes out of concentrated aqueous solution on cooling, easily soluble in warm alcohol and acetone, insoluble in chloroform and benzene.

As an alternative procedure, we found that if, as sometimes occurred, the 6-iodo-glucoside failed to crystallize in the final distillation previously described, the residue could be taken to complete dryness and acetylated by addition of 500 cc. of pyridine and 500 cc. of acetic anhydride. On treatment with much water, 6-iodo-6-desoxy-2,3,4-triacetyl-α-methyl-D-glucopyranoside separated. Recrystallization from 900 cc. of 95% ethanol yielded 165 g. of pure product melting at 149–150°; reported,[12] 150–151°. Deacetylation was conveniently carried out by suspending this material in 375 cc. of methanol, adding 40 cc. of 0.1 *N* sodium methoxide in methanol, and shaking for one hour. On concentrating to dryness, the 6-iodo-6-desoxy-α-methyl-D-glucopyranoside separated as a solid mass and was recrystallized from 125 cc. of 95% ethanol; yield, 100 g.; m. p. 146–147°. A mixed melting point with the product obtained by direct isolation showed no depression.

Preparation of β-Methyl-D-glucopyranoside *via* its Potassium Acetate Complex.—Watters, Hockett and Hudson[7] reported that certain β-methyl-D-glycosides form molecular complexes with potassium acetate, and suggested that this property might be useful in some cases in the separation of the α- and β-isomers. We have found that this method offers a fairly convenient means of preparing β-methyl-D-glucopyranoside in quantity directly from D-glucose.

Anhydrous glucose (500 g.) was added to 1000 g. of methanol containing 3% by weight of hydrogen chloride, previously heated to a boil in a flask fitted with a reflux condenser and a calcium chloride tube. With occasional shaking, the heating was continued for just one hour. The solution was cooled, seeded with α-methyl-D-glucopyranoside, and allowed to stand in the icebox overnight. The α-methyl-glucopyranoside (90 g.) was filtered off and the filtrate neutralized by addition of 80 g. of solid sodium bicarbonate. After removal of the salts, the filtrate was concentrated to a thick sirup under reduced pressure. The sirup was dissolved in 500 cc. of hot absolute ethanol, treated with a hot solution of 200 g. of potassium acetate in one liter of ethanol, and allowed to stand overnight in the cold. The voluminous precipitate consisting mainly of the addition complex between β-methyl-D-glucopyranoside and potassium acetate, was filtered off, washed with ethanol and acetone, and finally dried briefly by heating at 100° under reduced pressure; yield, 200 g.

To decompose the complex, the 200 g. of crude addition complex was dissolved in 600 cc. of hot methanol and treated with a hot solution of 110 g. of D-tartaric acid in 600 cc. of 95% ethanol. After one hour the precipitated potassium acid tartrate was filtered off through Celite, the filtrate concentrated to a thin sirup (230 cc.), seeded, and allowed to stand in the cold to complete crystallization. The β-methyl-D-glucopyranoside separating was recrystallized from 500 cc. of 95% ethanol; yield, 115 g., or 21%, melting at 104–106° (cor.), and rotating $[\alpha]^{25}D$ −32° (*c*, 5.72 in water). The product was obtained as the hemihydrate.[13]

6-Iodo-6-desoxy-β-methyl-D-glucopyranoside.—A solution of 100 g. (0.51 mole) of β-methyl-D-glucopyranoside hemihydrate in 100 cc. of dry pyridine was cooled in running tap water and treated by the dropwise addition of a solution of 146 g. (0.76 mole) of tosyl chloride in 100 cc. of dichloromethane. The addition required about thirty minutes, the temperature being held below 45°. After one hour, the reaction mixture was neutralized by the addition of sodium hydroxide (required, 200 cc. of 5.17 *N* solution), using brom thymol blue as external indicator. The solution was concentrated to dryness under reduced pressure, the temperature being raised to 100° toward the end of the distillation to remove water as completely as possible. The sirupy residue (295 g.), together with 100 g. of sodium iodide, was dissolved in 400 cc. of acetone and heated for two hours at 100° in pressure flasks. The voluminous precipitate was filtered off, washed with acetone and air dried. It weighed 285 g. and consisted of some sodium chloride and sodium *p*-toluenesulfonate, together with a large amount of what is, probably, an insoluble complex between sodium *p*-toluenesulfonate and 6-iodo-6-desoxy-β-methyl-D-glucopyranoside.

To break up the complex[14] the 285 g. of material was covered with 150 cc. of dry pyridine and 150 cc. of acetic anhydride. After standing overnight at room temperature, the mixture was poured into two liters of water. After a short time the precipitated 6-iodo-6-desoxy-2,3,4-triacetyl-β-methyl-D-glucopyranoside was filtered off, washed with water, and recrystallized from 150 cc. of 95% ethanol. The yield was 129 g. (59%) of product melting at 114–115°; reported[15] m. p., 114–115°.

Deacetylation was carried out by suspending the 129 g. of triacetate in 300 cc. of methanol, adding 30 cc. of 0.1 *N* sodium methoxide solution, and shaking occasionally for about one hour. The solution was concentrated to dryness under reduced pressure, the 6-iodo-6-desoxy-β-methyl-D-glucopyranoside separating out near the end of the distillation in practically quantitative yield. It was twice recrystallized from 250 cc. of 95% ethanol, giving 82 g. (90%) of pure product. It separated in the form of long colorless needles melting at 157–158° (cor.) with decomposition, and rotating $[\alpha]^{25}D$ −17° (*c*, 5.00 in water). It is readily soluble in warm water, but crystallizes from a concentrated (40%) aqueous solution on cooling; readily soluble in warm alcohol and acetone, insoluble in chloroform.

Anal. Calcd. for $C_7H_{13}O_5I$: C, 27.65; H, 4.31; I, 41.74. Found: C, 27.99, 27.76; H, 4.49, 4.57; I, 41.67, 41.91.

6-Tosyl-1,4-sorbitan.—A solution of 200 g. (1.22 moles) of 1,4-sorbitan[16] in 800 cc. of pyridine was cooled to −5° and treated during one hour with 232 g. (1.22 moles) of tosyl chloride. After standing for two hours, most of the pyridine was removed by distillation under reduced pressure. The sirupy residue (660 g.) was taken up in 800 cc. of 95% ethanol, cooled to −5°, and neutralized with a cold 4 *N* solution of sodium hydroxide in 50% ethanol, using brom thymol blue as internal indicator (required 322 cc., theory 304). The precipitated sodium chloride was filtered off, and the filtrate concentrated to dryness under reduced pressure, the bath temperature not exceeding 50°. The sirupy residue (520 g.) was dis-

(12) Helferich and Himmen, *Ber.*, **61**, 1825 (1928).

(13) Koenigs and Knorr, *ibid.*, **34**, 957 (1901).

(14) Because of contamination with excess sodium *p*-toluenesulfonate, it was not possible to obtain the complex in sufficient purity for analysis. However evidence for its existence is seen in the fact that although 6-iodo-6-desoxy-β-methyl-D-glucopyranoside itself is readily soluble in warm acetone, it does precipitate from the hot acetone during the course of the sodium iodide reaction.

(15) Compton, THIS JOURNAL, **60**, 395 (1938).

(16) To this monoanhydride of sorbitol, a product of the Atlas Powder Co., has recently been assigned the trivial name Arlitan by Soltzberg, Goepp and Freudenberg.[8]

solved, with vigorous shaking, in 200 cc. of dichloromethane. On addition of 800 cc. more of this solvent, and cooling, the 6-tosyl-1,4-sorbitan crystallized out as a voluminous, pasty mass. A further 700 cc. of dichloromethane was added to aid in the crystallization, and after standing in the cold for several hours, the material was filtered off and air dried (300 g.). After two recrystallizations from an equal weight of warm water, 207 g. (53%) of product were obtained; rods, melting at 110–111° (cor.) and rotating $[\alpha]^{25}D$ −3.2 (*c*, 4.96 in water); readily soluble in alcohol and acetone, insoluble in ether, petroleum ether, or chloroform. The product may also be recrystallized with little loss from about twelve parts of ethylene dichloride.

Anal. Calcd. for $C_{13}H_{18}O_7S$: C, 49.05; H, 5.70; S, 10.07. Found: C, 49.1, 48.9; H, 5.68, 5.71; S, 10.23.

The same product was also obtained directly from D-sorbitol by treating a pyridine solution of the latter with two molecular equivalents of tosyl chloride, and neutralizing the reaction mixture as previously described. The amount of alkali required to reach the brom thymol blue end-point indicated that one of the tosyl groups of the 1,6-ditosyl-sorbitol presumably formed in the tosylation had been hydrolyzed during the neutralization. By working up the mixture as indicated above, 6-tosyl-1,4-sorbitan was isolated in a yield of 15%.

2(3),5-Benzylidene-1,4-sorbitan.—A mixture of 400 cc. of benzaldehyde, 100 g. of 1,4-sorbitan, and 100 g. of powdered fused zinc chloride was stirred for four hours. The temperature rose to 40°, and nearly complete solution occurred in one hour. After standing overnight the reaction mixture was repeatedly washed with water and Skellysolve C. The residual sirup was dissolved in a small amount of ethanol, treated with 100 cc. of toluene and evaporated to dryness under reduced pressure. The semi-solid mass was covered with more toluene and allowed to stand overnight in the cold. The crystalline material was filtered off and recrystallized from twelve parts of ethyl acetate. The product separated as rods, melting at 154.5–155.5° (cor.), and rotating $[\alpha]^{25}D$ +17.7° (*c*, 4.52 in methyl alcohol). The yield was 32 g.; readily soluble in acetone and alcohol, insoluble in ether, chloroform and benzene.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.8, 61.9; H, 6.32, 6.22.

6-Tosyl-2(3),5-benzylidene-1,4-sorbitan. A. From 2(3),5-Benzylidene-1,4-sorbitan.—A solution of 10 g. (0.04 mole) of 2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was cooled to −5°, and treated in small portions with 8.5 g. (0.044 mole) of tosyl chloride. After several hours at room temperature, the excess tosyl chloride was decomposed by addition of 2 cc. of water. On pouring the reaction mixture into 200 cc. of water, the product crystallized out at once; yield of crude product, 14 g., or 87%. After two recrystallizations from 8 parts of methanol, the material was obtained as needles melting at 129.5–130.5° (cor.), and rotating $[\alpha]^{25}D$ +8.9° (*c*, 5.88 in chloroform); insoluble in petroleum ether, readily soluble in acetone, ethyl acetate and chloroform.

Anal. Calcd. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46; S, 7.89. Found: C, 59.1, 59.1; H, 5.36, 5.49; S, 8.24.

B. From 6-Tosyl-1,4-sorbitan.—A mixture of 100 g. of 6-tosyl-1,4-sorbitan, 100 cc. of water, 100 cc. of benzaldehyde, and 40 cc. of hydrochloric acid (sp. gr. 1.18) was vigorously stirred at room temperature for three hours. A crystalline precipitate began to form in about an hour. After standing overnight, the supernatant liquid was decanted, and the semi-solid residue shaken with 100 cc. of water and 300 cc. of Skellysolve C. The product was filtered off, suspended for a short time in dilute bicarbonate solution, then again filtered and washed with water and Skellysolve C. The crude yield was 116 g., or 91%. The crude material was dissolved in 1200 cc. of hot methanol in the presence of 2 g. of powdered calcium carbonate, and filtered. On cooling, 104 g. of pure material, melting at 129.5–130.5°, was obtained. A mixed melting point with the product prepared by method A showed no depression.

The same product was prepared in equally high yield, but less conveniently, by stirring a mixture of 100 g. of 6-tosyl-1,4-sorbitan, 400 cc. of benzaldehyde, and 100 g. of zinc chloride for four hours at room temperature, and isolating the product essentially as described previously.

6-Iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan.—A solution of 40 g. (0.1 mole) of 6-tosyl-2(3),5-benzylidene-1,4-sorbitan and 30 g. (0.2 mole) of sodium iodide in 250 cc. of acetone was heated for two hours at 100° in a pressure flask. The precipitated sodium *p*-toluenesulfonate was removed by filtration, washed with acetone, and the colorless filtrate evaporated to a sirup under reduced pressure. On addition of water, the product crystallized immediately. After two recrystallizations from 5 parts of 95% ethanol, 28.5 g. (80%) of product was obtained; needles, melting at 147–148° (cor.), and rotating $[\alpha]^{25}D$ +24.8° (*c*, 4.00 in chloroform). The substance is insoluble in water and petroleum ether, moderately soluble in alcohol and benzene, and very soluble in acetone, ether, ethyl acetate and chloroform.

Anal. Calcd. for $C_{13}H_{15}O_4I$: C, 43.11; H, 4.17; I, 35.04. Found: C, 42.8, 43.0; H, 4.02, 4.12; I, 35.10.

It is essential that the tosyl-benzylidene-sorbitan used in the reaction with sodium iodide be quite pure. If it is not, extensive decomposition takes place, benzaldehyde is formed, and little product results.

6-Iodo-6-desoxy-2(3),5-benzylidene-monoacetyl-1,4-sorbitan.—A cold solution of 10 g. of 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was treated with 9 g. of acetic anhydride. After several hours at room temperature, the reaction mixture was poured into ice water, crystallization occurring at once. The colorless product was twice recrystallized from 12 parts of ethanol in needles, melting at 126.5–127.5° (cor.), and rotating $[\alpha]^{25}D$ +40.4° (*c*, 3.16 in chloroform); yield, 10 g.

Anal. Calcd. for $C_{15}H_{17}O_5I$: C, 44.57; H, 4.24; I, 31.40. Found: C, 44.7, 44.4; H, 4.20, 4.31; I, 31.53.

6-Iodo-6-desoxy-2(3),5-benzylidene-monobenzoyl-1,4-sorbitan.—A cold solution of 10 g. of 6-iodo-6-desoxy-2(3),5-benzylidene-1,4-sorbitan in 50 cc. of pyridine was benzoylated with 11 g. of benzoyl chloride. After several hours at room temperature, the reaction mixture was poured into ice water, giving a solid product which was twice recrystallized from 25 parts of 95% ethanol in long colorless rods, melting at 139–141° (cor.), and rotating $[\alpha]^{25}D$ +73.8° (*c*, 4.84 in chloroform); yield, 12 g.

6-Iodo-6-desoxy-1,4-sorbitan.—A mixture of 50 g. of 6-iodo-6-desoxy-2,(3),5-benzylidene-1,4-sorbitan, 150 cc. of 95% ethanol, and 150 cc. of 0.2 *N* sulfuric acid, was immersed, under reflux condenser, in a boiling water-bath for just ten minutes. The homogeneous solution was rapidly cooled and extracted several times with 50-cc. portions of dichloromethane to remove benzaldehyde and unchanged starting material. The aqueous layer was neutralized with barium carbonate, filtered through Celite, and concentrated to dryness under reduced pressure, the bath temperature not exceeding 50°. The iodo-sorbitan crystallized out during the final stages of the distillation. Traces of water were removed by storing the flask containing the product in a desiccator overnight. The material was dissolved in 25 cc. of warm methanol, to which was then added 400 cc. of dichloromethane. On cooling and scratching, crystallization occurred. The product was filtered off and washed with dichloromethane, giving 28 g. of colorless product. An additional 4 g. was obtained by reworking the mother liquors; total yield, 32 g., or 85%. The material was recrystallized in excellent yield by dissolving in 25 cc. of methanol and adding 300 cc. of dichloromethane.

Anal. Calcd. for $C_6H_{11}O_4I$: C, 26.29; H, 4.05; I, 46.31. Found: C, 26.7, 26.1; H, 3.98, 4.07; I, 46.70.

6-Iodo-6-desoxy-1,4-sorbitan crystallizes in the form of 6-sided plates melting at 108–109° (cor.), and rotating $[\alpha]^{25}D$ −11.9° (*c*, 3.36 in water). It has a somewhat bitter taste, and is very soluble in water, alcohol and acetone, moderately soluble in hot ethyl acetate, and insoluble in ether, benzene and chloroform. It is rela-

tively unstable, showing signs of decomposition in several weeks when exposed to light, and in several months in the dark.

6-Tosyl-2,3,5-tribenzoyl-1,4-sorbitan.—To a solution of 10 g. (0.031 mole) of 6-tosyl-1,4-sorbitan in 100 cc. of pyridine, cooled in ice, was added 14.6 g. (0.10 mole) of benzoyl chloride. After standing twenty-four hours at room temperature, the reaction mixture was poured into water. The water layer was decanted from the sirupy product which precipitated. On stirring the sirup with 50 cc. of methanol, rapid crystallization occurred. After two recrystallizations from 10 parts of 95% ethanol, 18 g. (90% of theory) of colorless product was obtained in needles, melting at 106–107° (cor.),[10] and rotating $[\alpha]^{25}D$ +47.2° (*c*, 5.55 in chloroform), readily soluble in acetone, chloroform and benzene and insoluble in petroleum ether and water.

Anal. Calcd. for $C_{34}H_{30}O_{10}S$: C, 64.76; H, 4.80; S, 5.08. Found: C, 65.2, 64.5; H, 4.72, 4.76; S, 5.30.

6-Iodo-6-desoxy-2,3,5-tribenzoyl-1,4-sorbitan.—A solution of 19 g. (0.03 mole) of 6-tosyl-2,3,5-tribenzoyl-1,4-sorbitan and 9 g. (0.06 mole) of sodium iodide in 100 cc. of acetone was heated for one hour at 100° in a pressure flask. The precipitated sodium *p*-toluenesulfonate was filtered off, and the solvent removed from the filtrate. The residue solidified on addition of water, and was twice recrystallized from 600 cc. of 95% ethanol; yield, 15 g., 85%. The substance crystallized in plates melting at 151–153° (cor.) and rotating $[\alpha]^{25}D$ +5.1° (*c*, 2.92 in chloroform), insoluble in petroleum ether, ethyl ether and water and soluble in acetone, chloroform and benzene.

Anal. Calcd. for $C_{27}H_{23}O_7I$: C, 55.30; H, 3.95; I, 21.65. Found: C, 55.9, 55.2; H, 3.87, 3.87; I, 21.34.

Summary

1. A number of water soluble iodo-sugar derivatives have been prepared in order to study their utility as X-ray contrast agents in intravenous urography. These include 6-iodo-6-desoxy-D-galactose, 6-iodo-6-desoxy-α- and β-methyl-D-glucopyranosides, and 6-iodo-6-desoxy-1,4-sorbitan.

2. Several other new derivatives of 1,4-sorbitan have been synthesized.

3. β-Methyl-D-glucopyranoside has been prepared in 21% yield by treatment of glucose with methanolic hydrogen chloride, followed by isolation of the glucoside through its complex with potassium acetate.

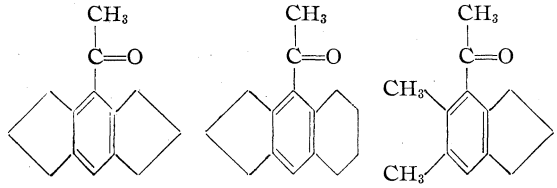
CHICAGO, ILLINOIS RECEIVED APRIL 12, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

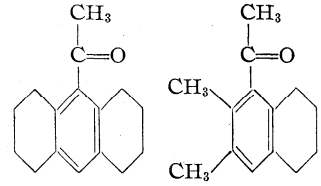
The Steric Effect of Methylene Groups. III

BY RICHARD T. ARNOLD AND PAUL N. CRAIG[1]

In an attempt to determine the relative steric influences of methylene groups in five- and six-membered rings, the following acetophenone derivatives have been prepared and examined.



(I) (II) (III)

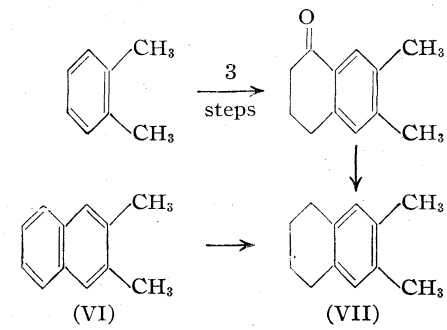


(IV) (V)

As reported earlier,[2] when treated with hypochlorite, acetohydrindacene (I) gives chloroform and 4-hydrindacenecarboxylic acid, whereas 9-acetoöctahydroanthracene (IV) gives a relatively stable trichloro ketone. The amount of methane evolved from methylmagnesium iodide (Zerewitinoff determination) decreases in the order IV > II > I. As a result of these observations and the values of carbonyl Raman frequencies, it was concluded that the steric hindrance around the carbonyl group decreases in the order IV > II > I.[2] Additional confirmatory evidence has now been obtained from observations on compounds III and V.

Of the above five ketones, only II is liquid; the others were readily purified by careful recrystallization. Tetrahydrobenz(f)indane, from which II is derived has now been prepared in a higher state of purity (m. p. 4°) and a sample of II obtained from this purer hydrocarbon has been reexamined.

6,7-Dimethyltetralin (VII) is obtained directly by catalytic reduction of 2,3-dimethylnaphthalene (m. p. 104°) in the presence of Raney nickel. The hydrocarbon so formed is essentially identical with that prepared from pure *o*-xylene.[3]



(VI) (VII)

It would appear that close approach to the cata-

(1) Du Pont fellow, 1947. Present address: Smith, Kline and French Company, Philadelphia, Pa.

(2) Arnold and Rondestvedt, THIS JOURNAL, **68**, 2176 (1946).

(3) Barnett and Sanders, *J. Chem. Soc.*, 434 (1933).

lyst of the benzenoid ring attached to the methyl groups in VI is sterically inhibited.[4]

Table I contains a summary of our observations of the action of methylmagnesium iodide on the ketones I–V.

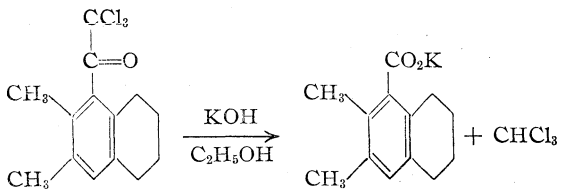
TABLE I

Compound	Action of CH_3MgI % Enolization[a]	% Addition
I	30	70
II	75[b]	25
III	93	9
IV	95	5
V	100	1.5

[a] The per cent. error is approximately ±2. [b] Reported earlier[2] as 62% on a less pure sample.

Ketones IV and V give well-defined trichloro derivatives when treated with sodium hypochlorite solutions. Compounds II and III gave complex mixtures of chlorinated ketones, chloroform and the corresponding aromatic acids.

By comparative studies it has been shown that alcoholic potassium hydroxide is much more effective than sodium hydroxide in bringing about the cleavage of hindered trichloromethyl ketones. Thus, 5-trichloroacetyl-6,7-dimethyltetralin is



relatively easily cleaved with alcoholic potassium hydroxide.

Experimental

6,7-Dimethyltetralin.—2,3-Dimethylnaphthalene (62.4 g.) was dissolved in ethanol (300 cc., 95%) and Raney nickel catalyst (4 g.) was added. Absorption of hydrogen (2 moles) was complete in one hour at 110° and a pressure of 1000 lb./sq. in. After removing the catalyst by filtration, the filtrate was fractionated directly to give 56.4 g. (89%) of 6,7-dimethyltetralin, b. p. 131–133 (20 mm.). Percolation through Alorco chromatographic alumina (80 mesh) gave a material having $n^{25}D$ 1.537.

Oxidation of 6,7-Dimethyltetralin.—A Carius tube was charged with 1.0 g. of the hydrocarbon (obtained from 2,3-dimethylnaphthalene) and nitric acid (15 cc. diluted 3 to 1 with water). This mixture was held at 165° for five hours. The solution was evaporated to dryness on a steam-bath; water (10 cc.) was added and the whole again evaporated to dryness. The residue was dissolved in ether and converted to its tetramethyl ester with diazomethane in the usual manner; m. p. 141–143°. When mixed with an authentic sample of the methyl ester of 1,2,4,5-benzenetetracarboxylic acid there was no depression of melting point.

5-Aceto-6,7-dimethyltetralin.—To 6,7-dimethyltetralin (22 g.) dissolved in carbon bisulfide (150 cc.) was added aluminum chloride (46 g.) at 0°. To this, acetic anhydride (17.3 g.) was added dropwise over a twenty-minute period. After one and three-quarters hours the reaction mixture was poured onto ice and hydrochloric acid. From the organic layer there was obtained the desired ketone; b. p. 150° (1 mm.); m. p. 50–52° (from 28–38° petroleum ether); yield 40%.

(4) Linstead and co-workers, THIS JOURNAL, **64**, 1985 (1942).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.28; H, 9.29.

5-Trichloroacetyl-6,7-dimethyltetralin.—One gram of the above ketone was treated with a solution of potassium hypochlorite prepared from commercial calcium hypochlorite (15 g. H.T.H. grade). After fifteen minutes the crude trichloro ketone was collected on a filter. Two recrystallizations from acetic acid and one from methanol gave a pure product; m. p. 57–58.5°.

Anal. Calcd. for $C_{14}H_{15}OCl_3$: C, 55.03; H, 4.95. Found: C, 55.10; H, 5.21.

6,7-Dimethyltetralin-5-carboxylic Acid.—The above described trichloro ketone (50 mg.) was heated under reflux for twenty minutes with ethanol (20 cc., 95%) and potassium hydroxide (4 pellets). After adding cold water (100 cc.), the solution was extracted with ether. Acidification of the aqueous phase gave the expected acid; m. p. 193–195°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.50; H, 8.13.

3,4-Dimethylphenyl-β-chloroethyl Ketone.—*o*-Xylene (53 g.) was added to a solution containing carbon bisulfide (600 cc.) and aluminum chloride (94 g.) at 0°. To this was added over a period of forty-five minutes, β-chloropropionyl chloride (69 g.) dissolved in carbon bisulfide (100 cc.). Stirring was continued for one hour at 0° and the solution was poured onto ice and hydrochloric acid. The organic layer was washed with dilute sodium hydroxide, dried with sodium sulfate and evaporated to dryness on a steam-bath. Dissolution of the residue in petroleum ether (b. p. 40–75°) gave a solution from which 82.5 g. (90%) of ketone was isolated at low temperature; m. p. 72–72.5°.

Anal. Calcd. for $C_{11}H_{13}OCl$: C, 67.18; H, 6.66. Found: C, 67.05; H, 6.53.

5,6-Dimethylhydrindanone-1.—The above described chloroketone (172 g.) was dissolved in sulfuric acid (1000 cc., sp. gr. 1.84), warmed on a steam-bath for three hours and then poured into 3.5 liters of ice and water. The brown product was recrystallized from petroleum ether (b. p. 60–68°) to give a yellowish-white product; m. p. 61–62°. This consisted of two isomers which were separated by one recrystallization from aqueous ethanol and two recrystallizations from petroleum ether. Only one pure ketone was isolated; m. p. 87–88°; yield 22 g.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.70; H, 7.54.

That this ketone had the assigned structure was established by its oxidation to 1,2,4,5-benzene tetracarboxylic acid.

The oxime of this ketone melted at 181–183°.

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.39; H, 7.49. Found: C, 75.10; H, 7.65.

5,6-Dimethylhydrindene.—A mixture of 5,6-dimethylhydrindanone-1 (17.0 g.), toluene (120 cc.), acetic acid (60 cc.), concentrated hydrochloric acid (200 cc.) and zinc (50 g. which had been amalgamated) was refluxed continuously for forty-three hours. Distillation of the toluene layer afforded 12 g. (77%) of the expected hydrocarbon, b. p. 115° (25 mm.), $n^{26.5}D$ 1.5314.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.14; H, 10.09.

4-Aceto-5,6-dimethylhydrindene.—The above hydrocarbon (8 g.) was acetylated at 0° in carbon bisulfide (200 cc.) with aluminum chloride (16 g.) and acetic anhydride (11.2 g.). The reaction was complete in thirty minutes. After distilling the crude ketone (b. p. 166–167° (25 mm.)) the material solidified. Recrystallization first from aqueous ethanol and then from petroleum ether gave a pure product; m. p. 43°; yield 42%.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.85; H, 8.73.

The oxime of this ketone was prepared from hydroxylamine in pyridine and absolute ethanol; m. p. 133–134°.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43. Found: C, 75.10; H, 8.65.

5,6-Dimethylhydrindene-4-carboxylic Acid.—The above ketone (35 mg.) was dissolved in methanol and treated with excess potassium hypochlorite at 60–65° for thirty minutes. At this time most of the methanol had evaporated. An ether extract of the solution upon evaporation deposited an oil containing much chlorine (Beilstein test). This oil was dissolved in methanol (15 cc.) to which potassium hydroxide (3 pellets) had been added and the solvent was evaporated on a steam-bath until the volume reached 3 cc. Addition of dilute hydrochloric acid precipitated the carboxylic acid; m. p. 169–170°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.36; H, 7.72.

Tetrahydrobenz[f]indane.—To a mixture containing phosphoric acid (165 g., 85%) and phosphorus pentoxide (165 g.) was added γ-(5-hydrindenyl)-butyric acid (68.5). After being heated at 100–120° for five minutes with good stirring, the solution was poured into water (1000 cc.). The crude product was extracted with benzene and the benzene solution was washed with dilute alkali and dried. Removal of the benzene and distillation in a sausage flask gave a crude ketone which solidified on standing. Two recrystallizations from petroleum ether (b. p. 40–75°) followed by recrystallization from aqueous alcohol gave 28 g. of 6,7-cyclopentene-1-tetralone; m. p. 38–39°.

Clemmensen reduction of this ketone gave pure tetrahydrobenz[f]indane; m. p. +4°. A sample prepared earlier in this Laboratory[5] melted at −3 to −5°.

Acetotetrahydrobenz(f)indane (V).—To tetrahydrobenz[f]indane (8 g., m. p. 4°) dissolved in carbon bisulfide (85 cc.) was added aluminum chloride (21 g.). Stirring was commenced and acetic anhydride (7.1 g.) was added over fifteen minutes. The entire reaction was carried out at 0° for one and three-quarters hours. After decomposition with ice and hydrochloric acid in the usual manner there was obtained a liquid ketone; wt. 6.8 g.; of b. p. 167–170° (1 mm.); $n^{25.5}D$ 1.5610. This material could not be induced to crystallize.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.17; H, 8.44.

Summary

1. Further evidence is presented to prove that the steric effect of methylene groups in five membered rings (*i. e.*, hydrindene) is smaller than that in corresponding six-membered rings (*i. e.*, tetralin).

(5) R. Barnes, Ph.D. Thesis, University of Minnesota, 1943.

MINNEAPOLIS, MINNESOTA RECEIVED APRIL 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Tri-α-naphthylboron as a Highly Hindered Reference Acid; a Case of Polymorphism Ascribed to Hindered Rotation[1]

BY HERBERT C. BROWN[2] AND SEI SUJISHI[2,3]

Earlier results[4] have shown that the relative base strengths of ammonia and a given series of primary, secondary, and tertiary amines (NH_3, RNH_2, R_2NH, R_3N) are dependent upon the reference acid used to compare them. Thus the sequence in strength observed with trimethylboron as the reference acid is $NH_3 < CH_3NH_2 < (CH_3)_2NH > (CH_3)_3N$. This sequence is altered to $NH_3 < CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$, when tri-*t*-butylboron is used as the reference acid. This change in sequence has been ascribed to the increase in the steric requirements of the reference acid.[4b]

According to this interpretation, a reference acid of even greater steric requirements than tri-*t*-butylboron should cause the observed sequence to approach the theoretically possible limit, $NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$. It was of interest to test this conclusion.

The selection for this purpose of a triarylboron with large steric requirements was dictated by a number of considerations. Tri-*t*-butylboron is a very weak reference acid for the amines under discussion, considerably weaker than trimethylboron itself.[4a] This weakness has been attributed to the large steric requirements of the three tertiary butyl groups. Further increase in the bulk of the alkyl groups would be expected to decrease the stability of the addition compounds with the amines to the point where it would be relatively difficult experimentally to make comparisons. The available evidence strongly suggests that the replacement of alkyl groups by aryl groups markedly increases the acid strength of the boron compounds.

For a number of reasons, tri-α-naphthylboron[5] (hereafter TNB) appeared especially promising in attaining the theoretical limit sequence. It was therefore decided to prepare the addition compounds of ammonia and the three methylamines with TNB and to compare their relative stabilities by a careful study of each system. Since the addition compounds were found to be highly dissociated at temperatures at which neither TNB nor the addition compound were sensibly volatile, the problem reduced itself to measuring and comparing the pressures exerted by the only volatile component of the system—the gaseous base.

$$(\alpha\text{-}C_{10}H_7)_3B{:}NR_3\ (\text{solid}) \rightleftharpoons (\alpha\text{-}C_{10}H_7)_3N\ (\text{solid}) + NR_3\ (\text{gas})$$

The observed pressures vary in the order $NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$ (*vide post*), and support the conclusion that the theoretical

(1) Studies in Stereochemistry. XII.

(2) Present address: Department of Chemistry, Purdue University.

(3) Ethyl Corporation Fellow at Wayne University, 1945–1947.

(4) (a) Brown, THIS JOURNAL, **67**, 374 (1945); (b) **67**, 378 (1945); (c) **67**, 1452 (1945); (d) Brown and Pearsall, *ibid.*, **67**, 1765 (1945).

(5) Krause and Nobbe, *Ber.*, **63**, 934 (1930).

limit sequence of base strength, $NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$, is actually under observation. In the course of these studies, some interesting and unusual instances of polymorphism were observed in the behavior of the addition compounds. It is suggested that these phenomena are the result of restricted rotation of the α-naphthyl groups in the addition compounds.

Observations

TNB was prepared by the action of α-naphthylmagnesium bromide on boron trifluoride etherate in benzene–ether solution. The product was isolated in the form of white crystals containing one mole of benzene per mole of TNB. Krause and Nobbe[5] report that TNB separates from benzene solution with two moles of benzene, but repeated experiments support the conclusion that the pure material obtained in the present study contains but one mole of benzene.

After a single recrystallization from benzene, the benzene of crystallization was removed under high vacuum at 150–160°. TNB was thus conveniently obtained in pure form in over-all yields of 50–60%.

The high degree of purity of the product is indicated by the following observations. It melts sharply at 206–207° (vacuum)[6] in contrast to the previously reported value[5] of 203–205°. Moreover, Krause and Nobbe report that the substance, although remarkably stable when compared to other triarylborons, showed significant signs of oxidation after several days of exposure to air; yet samples of TNB prepared by the present procedure show no noticeable change after exposures to laboratory air for more than one year. Finally, ultimate analyses for boron and acidimetric titrations of the compounds with a standard solution of sodium ethoxide in alcohol and phenolphthalein as indicator, yield results which point to purities of better than 99.8%.

$$(\alpha\text{-}C_{10}H_7)_3B + Na^+ OC_2H_5^- = Na^+[(\alpha\text{-}C_{10}H_7)_3B{:}OC_2H_5]^-$$

The titration of TNB with standard solutions of sodium methoxide, ethoxide, and isopropoxide in the corresponding alcohols proceeded very smoothly—the indicator, phenolphthalein, changed color sharply at the equivalence point. However, with sodium *t*-butoxide the end-point was indistinct and the indicator changed color considerably before the true stoichiometric quantity of base had been added. It therefore appears that the large steric requirements of the *t*-butoxide group produce a definite shift of the acid–base equilibrium toward the left.

$$(\alpha\text{-}C_{10}H_7)_3B + {}^-OC(CH_3)_3 \rightleftarrows [(\alpha\text{-}C_{10}H_7)_3B{:}OC(CH_3)_3]^-$$

Krause and Nobbe prepared their addition compounds by adding the base to a saturated solution of the triarylboron in ethyl ether. The addition compounds precipitated and were recovered on the filter. In order to avoid the possibility that the presence of traces of ether in the resulting compounds might affect the observed dissociation pressures, preparation of the substances in the absence of solvents was investigated.

Three methods were examined. In the first, a large excess of the liquified amine was contacted with the boron compound. After reaction was complete, the excess amine was removed under high vacuum. In the second method, the gaseous amine was passed over the solid boron compound. Absorption was very rapid and the reaction could be readily followed by noting the evolution of heat. Both methods yielded products whose composition satisfactorily agreed with the 1:1 compounds previously reported. However, the addition compounds possess a marked affinity for excess amine and it proved difficult to remove such excess amine to obtain samples as analytically pure as the studies required. Recourse was therefore had to the third procedure, which avoided this difficulty. In this method, the addition compounds were synthesized by bringing together carefully matched equivalent samples of the two components in the high vacuum apparatus used to study the dissociation pressures.

The products prepared by each of these three procedures appeared identical as regards analyses, melting points, and dissociation pressures. However, the last procedure proved so much more definite and convenient, that it was finally adopted for all preparations in the present study.

The melting points of the addition compounds showed an unusual behavior not reported by Krause and Nobbe. For example, ammonia–TNB, if heated slowly in a capillary tube, melted at 200–205°. However, if the tube were inserted in a bath at 170–172°, the substance melted, resolidified, and then remelted at the higher temperature. Monomethylamine–TNB likewise showed two melting points—a fugitive one at 150–155°, followed by resolidification, and the permanent one at 190–192°. Dimethylamine–TNB melted only at 193–196°; no other melting point was observed. All attempts to add trimethylamine to TNB by the three procedures described were unsuccessful.

Ammonia–TNB was then synthesized in the apparatus shown in Fig. 7 (attached to the main high vacuum apparatus) and the dissociation pressures measured over a range of temperatures. It

TABLE I

DISSOCIATION PRESSURE OF AMMONIA-TNB

Mole ratio Ammonia/TNB	Pressure, mm.	Mole ratio Ammonia/TNB	Pressure, mm.
A. Freshly prepared sample, at 40°		B. Heat-treated sample, at 130°	
0.30	4	0.20	4
.60	6	.40	4
.90	26	.50	4
.98	43	.98	5
1.00	62		

(6) All melting points were taken with capillary tubes of the usual dimensions. These tubes were evacuated and sealed after the samples had been introduced. The temperatures are corrected.

was observed that the pressure of the freshly prepared addition compound varied with the mole fraction of amine. The results of a typical experiment at 40° are summarized in Table I-A. The other amines behaved similarly.

The addition compounds were then synthesized by bringing the two components together with a slight constant deficiency of the base. It was hoped that in this way the observed pressures for the different bases would be made strictly comparable, and, moreover, that the effects of slight errors in the mole ratio of the two components would thereby be minimized. Under these conditions, the pressure of the system became sensibly constant within several minutes,[7] and the plot of log P *vs.* $1/T$ showed the expected linearity (Fig. 1).

New phenomena made their appearance at higher temperatures. The curve showed a definite deviation from linearity, and the observed pressures, particularly in the higher ranges (120° and above) declined noticeably with time. The decrease was very rapid at 140°. In one experiment at this temperature the pressure dropped from a value of 450 mm to 20 mm. within one hour. However, the rate of pressure decrease then diminished, and the pressure at this temperature became constant at a new low value, 10 mm., only after a period of twenty hours.

The behavior of the product obtained in this way was then investigated. A new series of pressure values at elevated temperatures were recorded. These values were much lower than the first series of measurements, they were easily reproducible, and yielded only the second series of pressure measurements, without evidence of any tendency to revert to the original high values.

In contrast to the original material, the dissociation pressures of which were highly dependent on the mole ratio of the components (Table I-A), the dissociation pressures of the heat-treated material were essentially independent of composition (Table I-B).

That these phenomena were not due to some irreversible change in the TNB component was demonstrated by a number of experiments. A sample of the heated compound was maintained at 130°. The gas evolved was pure ammonia; the amount corresponded exactly to the original quantity of ammonia used in the synthesis. The residual solid melted at 205–206° and caused no depression in melting point when mixed with a sample of the original material. Moreover, the product formed by recombining the recovered ammonia and TNB possessed the same characteristic high dissociation pressures as the original preparation and exhibited the same behavior on heating. It may therefore be concluded that the recovered TNB is chemically indistinguishable from the original material.

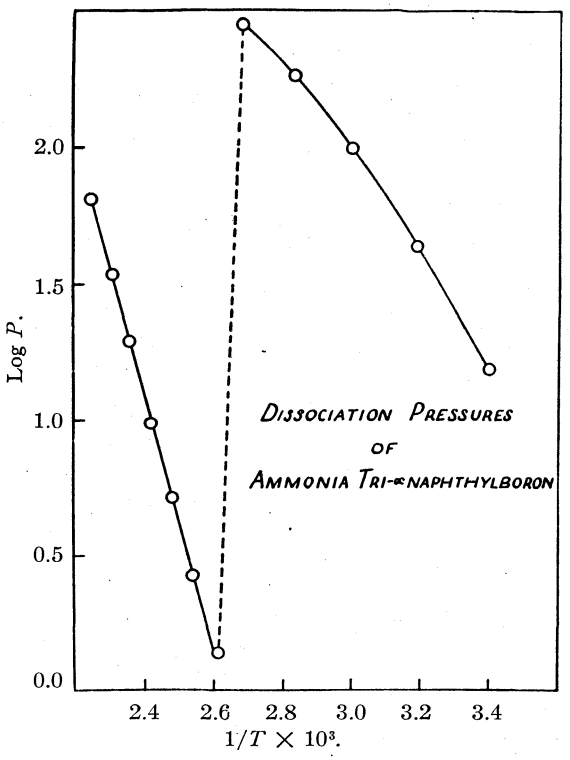


Fig. 1.—Dissociation pressures exhibited by a freshly prepared sample of ammonia-tri-α-naphthylboron as the temperature is raised.

The curves for the log P *vs.* $1/T$ plots of the corresponding monomethylamine and dimethylamine compounds with TNB showed the same general characteristics. The entire curve (*i. e.*, the two sections which describe the behavior of the freshly prepared substance and of the heat-altered product) for the methylamine compound lies above the curve for the ammonia derivative; the curve for dimethylamine is higher still.[8] Trimethylamine did not add to TNB under these conditions.

It was concluded that the observed pressures of the freshly prepared compounds are dependent not only on the mole fraction (particularly so in the region of equimolar ratios), but are also dependent upon time (particularly in the higher temperature ranges.) It was therefore decided that little could be gained by further refining the measurements of the variable pressures exhibited by these materials. Instead, attention was focused on the highly reproducible dissociation pressures exhibited by the addition compounds after prior heat treatment at 100–140°.

(7) Although the pressure of the system apparently reached an equilibrium value within several minutes, it was noted that the observed pressure tended to drift to lower values over periods of several hours duration. Moreover, samples of the addition compound which had been stored at room temperature for several weeks yielded considerably lower values of the dissociation pressure than freshly synthesized samples.

(8) The dissociation pressure curve definitely established the existence of two forms of the dimethylamine derivative. Failure to observe a "fugitive" melting point, as in the case of the other two addition compounds, is believed to be due to a more rapid transformation of the dimethylamine derivative near its melting point into the higher melting form.

TABLE II

DISSOCIATION PRESSURES OF THE HEAT ALTERED FORMS OF THE ADDITION COMPOUNDS OF TNB WITH AMINES

Ammonia, $\log P = -4762/T + 12.525$

Temp., °C.	110	120	130	140	150	160	170
Press., mm.	1.4	2.7	5.3	10.0	20.0	34.5	65.5

Methylamine, $\log P = -4666/T + 12.863$

Temp., °C.	103	110	119	130	140	150
Press., mm.	2.7	5.3	10.7	19.9	39.1	72.1

Dimethylamine, $\log P = -4296/T + 13.71$

Temp., °C.	50	60	70	80	90	100
Press., mm.	4.0	7.4	15.2	34.8	71.3	164

The observed dissociation pressures for the heat-treated products are listed in Table II, and the values are represented graphically in Fig. 2.

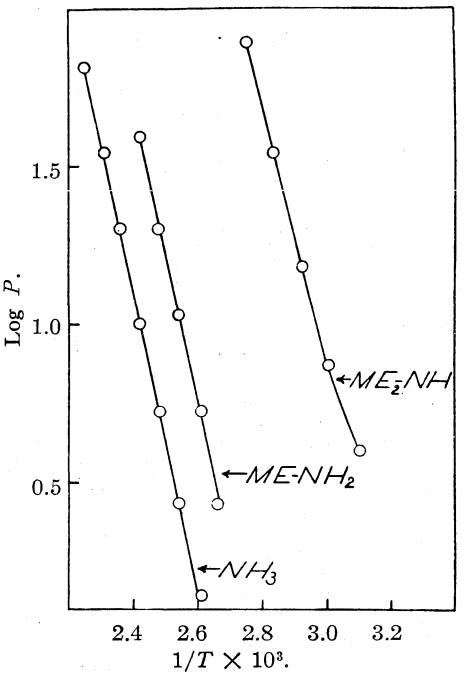


Fig. 2.—Dissociation pressures of the heat-treated ("stable") forms of the addition compounds of tri-α-naphthylboron with ammonia, methylamine and dimethylamine.

Discussion

In this investigation the pressure of the gaseous amine above a mixture of the solid TNB and solid addition compound has been taken as a measure of the stability of the latter.

$$(\alpha\text{-}C_{10}H_7)_3B{:}NR_3\ (\text{solid}) \rightleftharpoons (\alpha\text{-}C_{10}H_7)_3B\ (\text{solid}) + NR_3\ (\text{gas})$$

This interpretation of the data apparently ignores such complications as may be caused by the crystal lattice energies of the solid compounds. Fortunately, there are reasons for believing that the differences between the crystal lattice energies of TNB on the one hand and each of the addition compounds on the other are relatively small and sensibly constant.

First, TNB and the three addition compounds (the heat stable forms) all melt at approximately the same temperatures. This observation suggests that the stabilities of the crystal lattices are of the same order of magnitude. Second, the molecular dimensions of the amines used are quite small compared to the TNB component. It therefore appears probable that the attractive forces between individual molecules of the addition compounds are largely due to the TNB portion of the molecule. This suggests that the difference between the lattice energy of any given addition compound and that of TNB itself should not be large. Finally, the amine component is so small and must be buried so deeply within the relatively huge masses of the three α-naphthyl groups that the attractive forces between individual molecules of the addition compounds should not be markedly affected by the particular amine present. It therefore appears not unreasonable to assume that, in the present instances, the differences in the crystal lattice energies of the individual compounds are relatively small and their effects are relatively minor compared with the effects of F-strain.

If this assumption is valid, it may be concluded that the relative stabilities of the addition compounds decrease in the order, $NH_3 > CH_3NH_2 > (CH_3)_2NH > > (CH_3)_3N$, and the apparent strengths of the four bases decrease in the same order, $NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$. This is obviously the order predicted by the F-strain hypothesis for a reference acid with an exceedingly high F-strain factor.

There remain to be considered the phenomena observed in the course of preparing the addition compounds and measuring their dissociation pressures. It is suggested that these phenomena are due to the existence of two polymorphic forms of the solid addition compounds. Furthermore, the existence of these polymorphic forms is ascribed to the restricted rotation of the three α-naphthyl groups in the addition compounds about the carbon to boron bonds.

The observations requiring explanation may be briefly summarized as follows:

1. Solid TNB absorbs the gaseous bases with avidity to form only the lower melting, metastable form of the addition compound. For convenience, this substance will be referred to hereafter as the "metastable" form of the addition compound.

2. The metastable form of the addition compound is converted to another form, the "heat-altered" or "stable" form, slowly at room temperature and rapidly above 100°.

3. The dissociation pressures exhibited by the metastable form are much higher than those exhibited by the corresponding stable form.

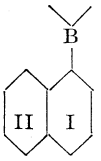
4. The dissociation pressures of the metastable form are strongly dependent upon the relative

mole ratios of the two components; the dissociation pressures of the stable form do not exhibit such dependence.

5. The dissociation pressures of the metastable form are dependent upon the age of the sample and decrease with time, slowly at room temperature and more rapidly at higher temperatures. The corresponding pressures of the stable form are not dependent upon these factors.

6. Removal of the base from either form of the addition compound yields apparently identical samples of TNB.

For the ensuing discussion it will be convenient to distinguish between the two fused rings of the α-naphthyl groups. Accordingly, that ring which is directly attached to the boron atom will be designated by the numeral I; the other by the numeral II.



Presumably, the boron atom in TNB will be similar to the boron atom in trimethylboron[9] with its three bonds coplanar, making equal angles of 120° with each other. For convenience this plane, defined by the three bonds of the boron atom, will be referred to simply as the plane of reference or reference plane of the molecule.

Examination of the Fisher–Hirschfelder model of TNB indicates that the three α-naphthyl groups can be arranged about the central boron atom in two different ways. In one of these arrangements, the three α-naphthyl groups are relatively symmetrically fixed, with the three II-rings all pointing in the same direction away from the reference plane (the "symmetrical" arrangement or form, Fig. 3). In the other possible form, one of the α-naphthyl groups is so fixed that its II-ring is pointed in a direction from the plane of reference opposite to that of the other two α-naphthyl groups (the "unsymmetrical" arrangement or form, Fig. 4).[10]

These two forms would be readily interconvertible were it possible to rotate one of the α-naphthyl rings about the boron-to-carbon bond through the reference plane. However, the model suggests that such a rotation would be difficult and would involve the simultaneous rotation of all three groups at a carefully controlled rate in order to effect the transformation without excessive distortion of the model.

Simplified line drawings of the two postulated forms of TNB are shown in Figs. 5 and 6. In

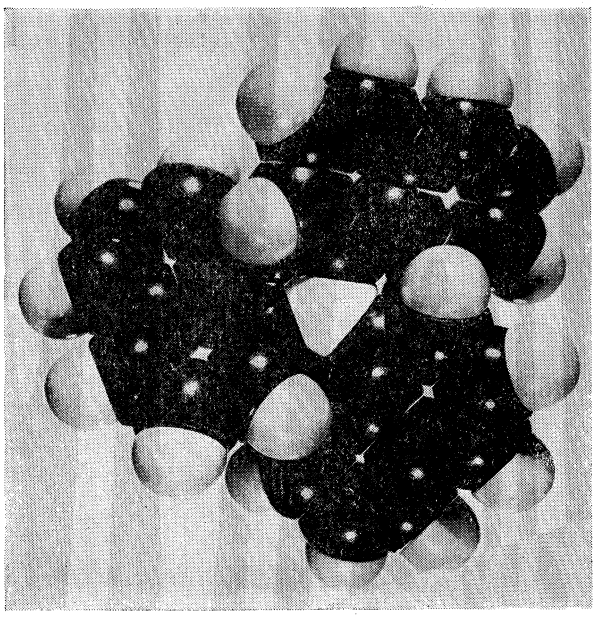


Fig. 3.—Molecular model of tri-α-naphthylboron–symmetrical arrangement.

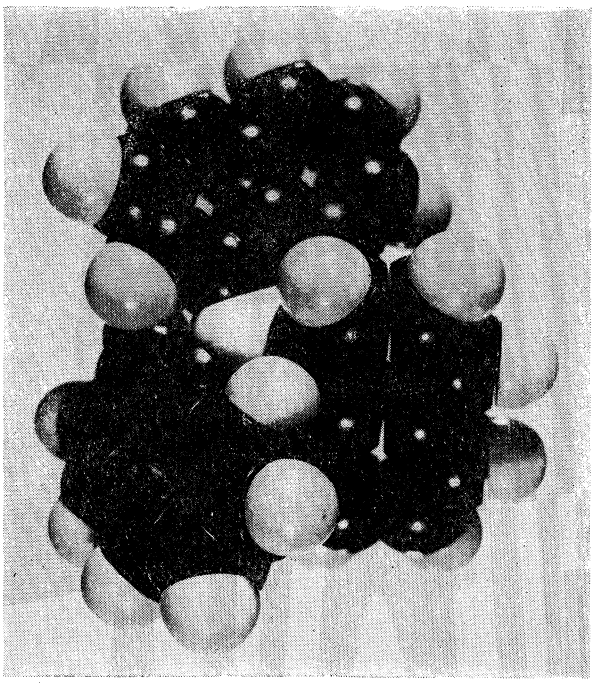


Fig. 4.—Molecular model of tri-α-naphthylboron–unsymmetrical arrangement.

(9) Levy and Brockway, THIS JOURNAL, **59**, 2085 (1947).

(10) It has been suggested already [Lewis, Magel and Lipkin, *ibid.*, **64**, 1774 (1942)] that triphenylmethyl and related compounds exist in two isomeric forms, one in which the three rings face in the same direction, similar to the blades of a propeller, the other containing one ring facing in a direction opposed to the other two. At first sight the isomerism proposed in the present paper may seem to be related to that proposed by G. N. Lewis. However, the latter is independent of the symmetry of the rings involved; the former could only be observed if the rings attached to the central atom were unsymmetrical, as with the α-naphthyl groups of the present investigation. Indeed, the consideration of the molecular models indicates that the large II-ring makes the type of isomerism proposed for triphenylmethyl impossible in the case of TNB.

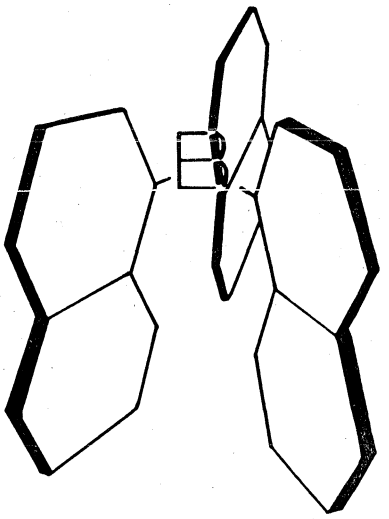


Fig. 5.—Symmetrical arrangement of tri-α-naphthylboron.

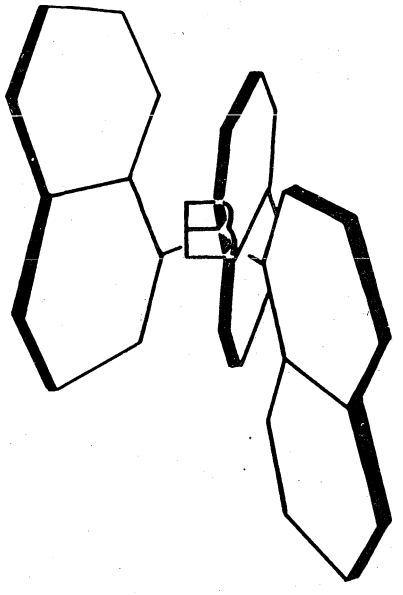


Fig. 6.—Unsymmetrical arrangement of tri-α-naphthylboron.

these figures the three α-naphthyl groups are represented with the plane of each ring lying perpendicular to the plane of reference of the molecule. It is highly probable that the three α-naphthyl groups are tilted to a greater or lesser degree from this idealized position, as indicated in Figs. 3 and 4. However, use of the idealized line drawings will facilitate the discussion without affecting the conclusions.

It is proposed that the unsymmetrical arrangement of TNB (Figs. 4 and 6) is the more stable of the two possible arrangements and that the crystalline TNB prepared in the present study consists of this unsymmetrical form. Addition of an amine to a molecule with this configuration could conceivably occur in two ways. The base could unite with the boron atom by approaching it either from above the reference plane, or from below. However, the latter path is considerably more hindered than the former. In approaching from below, the amine molecule must contend with two *peri* positions blocking the line of approach; from above, there is but one *peri* position in its path. It is therefore postulated that the base adds to the unsymmetrical form of TNB and that the addition occurs from above to give the less strained of the two possible configurations derived from the unsymmetrical form of TNB. It is further suggested that the projection of the one *peri* position of the inverted α-naphthyl group into the region occupied by the amine molecule leads to a condition of considerable strain—strain which is not present in the free TNB molecule. This strain is largely relieved by rotation of the offending α-naphthyl group so that all three *peri* positions lie below the reference plane, on the other side from the attached amine. The resulting addition compound is now configurationally related to the symmetrical arrangement of TNB and theoretically may be considered as being derived from this arrangement (Fig. 5) by addition to the boron atom from above the reference plane.

This hypothesis permits a simple interpretation of the observed phenomena. 1. Addition of the base to TNB yields the metastable or *strained* form of the addition compound.

2. The metastable or *strained* form is converted to the stable or *unstrained* form[11] slowly at room temperature, rapidly at 100°. Conversion requires rotation of one α-naphthyl group and involves an appreciable energy of activation.

3. The dissociation pressures of the metastable form are high because of the strain which results from projection of the *peri* position of the odd α-naphthyl group into the region occupied by the amine molecule. The stable form exhibits much lower dissociation pressures because the offending *peri* position has been moved below the plane of the molecule, away from the added amine. (In other words, the unsymmetrical form of TNB has a higher F-strain factor[4] than the symmetrical form.)

4. Addition of the amine to the unsymmetrical form of TNB is not accompanied by any marked changes in the configuration or in the size of the molecule. Therefore the metastable form of the addition compound and TNB form a series of solid solutions and the dissociation pressures depend on the mole ratio of the two substances. On the other hand, formation of the stable form is accompanied by a marked change in the molecular configuration and the crystal lattice of TNB (the more stable, unsymmetrical form) is no longer able to accommodate the molecules of the addition compound (stable form). Accordingly, solid solution phenomena no longer occur, and the dis-

(11) It probably would be more precise to describe it as "less strained" rather than "unstrained," since there must be considerable F-strain present even in the stable form.

sociation pressures are no longer dependent on mole ratio.

5. Transformation of the metastable form to the stable form, slow at room temperature and rapid at higher temperatures, in effect removes equimolar quantities of the two compounds (amine and TNB) from the reaction mixture. If the amine and TNB are not present in exactly equivalent amounts at the start, the slow transformation of the metastable to the stable form will bring about a gradual change in the mole ratio of "available" TNB and amine. The observed pressure will then show a gradual change with time.[12]

6. Removal by volatilization of the amine from the stable forms of the addition compounds requires elevated temperatures (100–140°) and proceeds relatively slowly. It is probable that the symmetrical form of TNB is the first product of the dissociation, but at the elevated temperatures used it must be rapidly converted into the more stable unsymmetrical form. It is therefore not too surprising that removal of the amine from the metastable form of the addition compound at relatively low temperatures and removal of the amine from the stable form at elevated temperatures yield samples of TNB that appear to be identical.

It should be possible either to isolate or to obtain some definite evidence on the existence of the symmetrical form of TNB by removing the base from the addition compound at relatively low temperatures by chemical means. An investigation of this problem is under way.

There remain to be considered certain discrepancies between the results of the present investigation and those previously reported by Krause and Nobbe.[5] These authors report that TNB is "moderately" soluble in ether. They prepared the compound by the action of α-naphthylmagnesium bromide on boron trifluoride in ether solution. After the reaction was complete, water was added. The ether layer was dried and *concentrated*, then poured into a crystallizing dish where a mass of fine crystalline needles separated. In the present investigation, addition of water to the Grignard reaction mixture caused an immediate precipitate of TNB. In order to avoid such precipitation it was necessary to add large quantities of benzene to the reaction mixture. Experiment revealed that the solubility of TNB thus obtained is relatively small, 1.6 g. per 100 ml. of ether at 25°, and is practically constant over a wide temperature range. In their preparations of triarylborons Krause and Nobbe report that they used one mole of Grignard reagent in a 1-liter reaction flask. Assuming yields similar to those we obtained, a quantity of ether from 3 to 5 liters should have been required to dissolve the product, instead of the concentration of the ether layer reported by the authors.

Krause and Nobbe prepared their amine addition compound by treating a solution of the triarylboron in ether with the base. The addition compounds precipitated immediately and were recovered by filtration. Although they do not report any details on the preparation of ammonia–TNB, presumably the technique was similar to that which they had used for other such compounds reported in their paper. In the present investigation, a saturated solution of TNB in anhydrous ether was treated with an equivalent quantity of ammonia in the same solvent. However, no precipitate was observed. At the end of several hours a small quantity of precipitate was noted, but the quantity was not increased by cooling the solution to the neighborhood of −80°. The precipitate was collected and tested—its dissociation pressures corresponded to the *stable* form of ammonia–TNB. The ether solution was allowed to stand for an additional ten days at room temperature. In the course of this time the quantity of crystalline precipitate continued to grow.

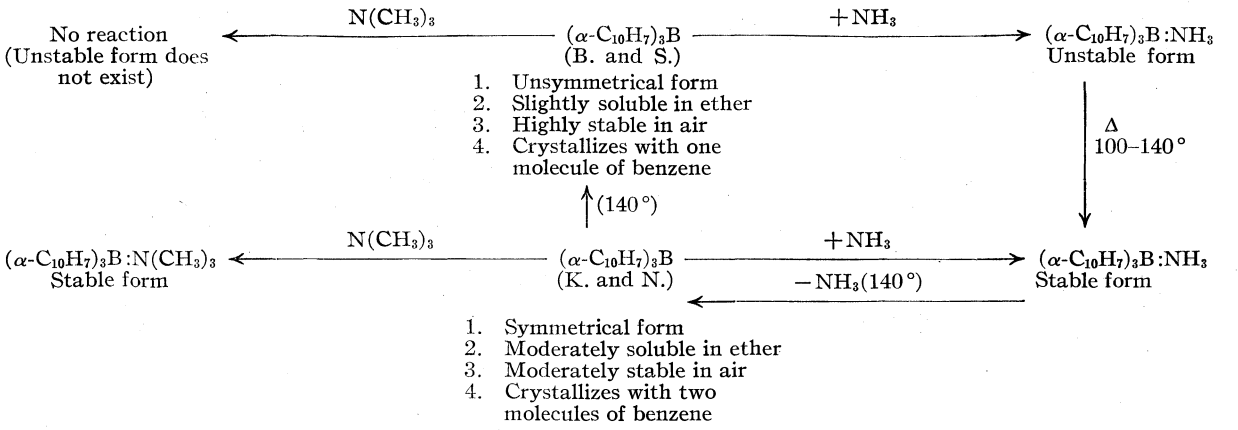
This experiment is of interest not only because of the discrepancy between our observations and those of Krause and Nobbe, but also because it suggests that the formation of the stable form of ammonia–TNB from the metastable form is a relatively slow process, even in solution at room temperature, so that the two forms of the addition compound are true geometrical isomers whose existence does not depend on crystal lattice forces. Further experimental studies along this line are underway.

Krause and Nobbe further report that trimethylamine–TNB precipitates immediately upon bringing the components together in ether solution. Even though they report that the compound is measurably dissociated at room temperature, their ability to make the two components unite is remarkable in view of our numerous failures along this line.

The relative instability toward oxidation of TNB reported by Krause and Nobbe may also be contrasted with the high stability shown by our product. The difference in the number of molecules of benzene of crystallization in the two investigations is also worthy of comment.

There is a possible explanation which could resolve these differences. If the product isolated by Krause and Nobbe were the symmetrical form of TNB, the higher reactivity of their product to-

(12) This point may be clarified by an illustration. Assume that the reaction mixture at the start of the experiment consists of one mole of TNB and 0.5 mole of ammonia. The dissociation pressure exhibited by this mixture at a suitable temperature, 40° for example, would be that of a solid solution of 0.5 mole fraction of TNB and ammonia–TNB (metastable form). If the temperature is maintained at 40°, the metastable form will slowly change over to the stable form. At the point where the change is 50% complete, the reaction mixture will consist of 0.25 mole of ammonia–TNB (stable form), 0.25 mole of ammonia–TNB (metastable form) and 0.5 mole of free TNB. Since the pressure of the stable form is negligible at 40°, the pressure exerted by the mixture would be that of a solid solution of 0.33 mole fraction of the addition compound and 0.67 mole fraction of the free boron component. It is obvious that it should be possible to use the observed dissociation pressure to analyze a given mixture of the two forms and to follow the rate of the transformation.



ward ammonia and trimethylamine could be understood. Moreover, the symmetrical form would presumably be the less stable of the two crystalline forms of TNB, so that its crystal lattice energy would be less than that of the unsymmetrical form and a higher solubility would be anticipated. Differences in the stability toward oxidation and in the number of molecules of benzene of crystallization between their product and ours would then offer no difficulty.

In this case the various interconversions and reactions could be interpreted as shown in the chart.

Several of the proposed transformations are, of course, highly hypothetical and require experimental verification. Experimental studies to resolve the discrepancies and difficulties raised by the present study are now under way.

Experimental Part

Preparation and Purification of Intermediates.—The preparation of ammonia and the methylamines in pure form has been previously described.[4] Other intermediates used were largely Eastman Kodak Company products and were purified by standard methods.

Preparation of TNB.—Because of the discrepancies between the product obtained in the present investigation and that obtained by Krause and Nobbe, the preparation of TNB will be described in detail.[5]

A standard 1-liter 3-necked flask, fitted by standard-taper glass joints to a condenser, gland-sealed stirrer, and dropping funnel, was used. In the flask were placed 24.3 g. (1 g. atom) of magnesium turnings and a crystal of iodine. The flask was flushed out with nitrogen and then gently heated until the iodine had partially sublimed. The flask and its contents were allowed to cool to room temperature and a mixture of 100 ml. of anhydrous ether and 10 ml. of α-bromonaphthalene (b. p. 143° at 14 mm.) was added. Meanwhile 130 ml. of α-bromonaphthalene (making a total of 1 mole) was dissolved in an additional 400 ml. of anhydrous ether. One-half of this solution was then slowly added through the dropping funnel at such a rate as to keep the ether gently refluxing. The reaction mixture became brown during the addition and toward the end of the addition the Grignard reagent began to separate. Benzene, 100 ml., was added to dissolve the Grignard reagent and the remainder of the ether–halide mixture added. A total of three hours was required to add the halide. The reaction mixture was then heated under reflux for a further period of one-half to one hour to ensure completion of the reaction.

The flask was next cooled in ice, the ice-bath removed, and a solution of 32 ml. (0.25 mole) of boron trifluoride–etherate (b. p. 125°) in 150 ml. of benzene was added to the Grignard reagent over a period of approximately one hour. After all of the reagent had been added, the reaction mixture was heated under gentle reflux for an additional hour. The reaction mixture was then forced under nitrogen pressure through a glass tube into a 2-liter flask filled with crushed ice and containing 50 ml. of concentrated hydrochloric acid. The upper organic layer was yellow in color and contained a small quantity of brownish solid suspended near the interface; the lower aqueous layer was greyish-brown in color.

No attempt was made to separate the layers at this stage. The flask was stoppered and put aside overnight to allow time for the crystallization of the benzene addition compound of TNB. The organic layer was then decanted from the aqueous layer and suspended solid. The solid was recovered on a Buchner funnel (without filter paper) by pouring the gelatinous aqueous layer and suspended solid into the funnel under slight suction. The brownish-appearing residue was washed repeatedly with water and then with alcohol. The crude product was dissolved in 300 ml. of refluxing benzene (nitrogen atmosphere) and quickly poured through a prewarmed Buchner funnel (with filter paper) into a 1-l. Erlenmeyer flask. White crystals immediately began to separate from the filtrate. The flask was stoppered and placed in a refrigerator overnight (6–8°).

The next day the bottom and walls of the flask were covered with an adhering crust of white large crystals. The supernatant liquid was poured off and the solid broken up with a stirring rod. The crystals were washed with several small portions of cold benzene and then transferred to a weighed flask and the adherent solvent removed by volatilization under high vacuum to constant weight.

In a typical preparation 63 g. of the pure product, $(\alpha\text{-}C_{10}H_7)_3B\cdot C_6H_6$, was obtained, a yield of 54% based on the boron trifluoride-etherate used.

The benzene of crystallization was removed by heating the flask and its contents to a temperature of 150–160° at pressures of less than one millimeter. After the flask had reached constant weight (weighings were made only after the flask and its contents had reached room temperature to avoid exposure of the hot triarylboron to oxygen), the product weighed 51.8 g. Thus the product lost 11.2 g. compared with 10.5 g. of benzene calculated for the 1:1 compound.

The product was analyzed for boron by treating it with hot concentrated sulfuric acid followed by distillation of the boron as methyl borate and titration as boric acid in the presence of mannitol.[13]

Calcd. for $C_{30}H_{21}B$: B, 2.71. Found: B, 2.75.

Titration of TNB.—G. N. Lewis[14] has frequently pointed out the similarity between the behavior of the "proton" acids and electron acceptors such as the trialkyl- and triarylborons. It was of interest to determine whether

(13) Fowler and Kraus, THIS JOURNAL, **62**, 1143 (1940).

(14) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

TNB could be analyzed by a standard base similar to more conventional acid analyses.

A standard solution of 0.04644 *M* TNB in benzene was prepared. Ten-ml. aliquots of this solution were titrated with approximately 0.06–0.10 *N* solutions of sodium alkoxide in the corresponding alcohol. Phenolphthalein was used as the indicator. The results are summarized in Table III.

TABLE III

TITRATIONS OF TNB WITH SODIUM ALKOXIDES

Base	Normality	Volume of base used		Volume of base calcd.	End-point
Sodium methoxide	0.1050	4.46	4.49	4.42	Sharp
Sodium ethoxide	.1075	4.31	4.32	4.32	Sharp
Sodium isopropoxide	.0880	5.34	5.29	5.29	Sharp
Sodium *t*-butoxide	.0593	7.68		7.83	Indistinct[a]

[a] End-point taken as very faint pink which persisted.

Solubility of TNB.—The solubilities were determined by placing in a vessel excess solid TNB and 50 ml. of solvent. The mixture was stirred at constant temperature (under nitrogen) for twenty-four hours. The excess solid was permitted to settle and 5 ml. of the supernatant liquid was pipetted out. The solvent was removed under vacuum and the solid determined by weighing. The results indicated a solubility per 100 ml. of solvent at 25° of 1.7 g. in ether, 0.2 g. in alcohol, 6.4 g. in benzene, and 5.0 g. in carbon tetrachloride. At −80° the solubility was 1.4 g. per 100 ml. of ether.

Preparation of Addition Compounds. (a) By Condensation of Excess Amine.—A large excess of the amine was liquefied in a tube immersed in a Dry Ice-bath. Sodium was used to remove traces of moisture. The amine was then permitted to volatilize from the sodium and condense in a second tube containing 2–3 g. of TNB. The liquid amine and suspended solid were allowed to remain in contact for two hours at 20–30° below the boiling point of the amine. At the time the cooling bath was removed and the excess amine permitted to volatilize away as the temperature rose to 25°. In these operations the product was at all times protected from the atmosphere. The last traces of excess amine were removed by pumping the material with a high vacuum pump. Periodic weighings of the product showed asymptotic approach to 1:1 addition over a period of several hours. Composition of the products was verified by Kjeldahl analyses for nitrogen. Ammonia, methylamine and dimethylamine all yielded well-defined addition compounds whose properties have been previously described. Trimethylamine showed no signs of reaction; even at −80° a stream of nitrogen rapidly removed all of the amine from a mixture of the liquid amine and solid TNB.

(b) **Reaction with a Stream of the Gaseous Base.**—In a typical experiment, a stream of ammonia was passed over a sample of 0.9030 g. of TNB contained in a boat. Considerable heat was evolved as the ammonia reached the solid and there was a sharp drop in pressure as the gas was absorbed. The slow stream was continued for one hour. The product gained 0.0401 g. Calculated gain for 1:1 addition is 0.0392 g. The properties of the product obtained in this way were identical with those obtained in the first method. Trimethylamine was not absorbed in a similar experiment involving this base.

(c) **By Reaction of Measured Quantities of the Components in the High Vacuum Apparatus.**—The apparatus shown in Fig. 7, attached to the usual high vacuum line, was used. A weighed quantity of TNB was introduced into the small bulb and the tube sealed. The tube was evacuated through the manometer (with the mercury lowered) and the float valve. A quantity of amine was then measured out as a gas in the high vacuum line and then condensed in the tube with liquid nitrogen. Mercury was then raised into the manometer and the equilibrium pressures developed at room temperature and above were measured on the manometer.

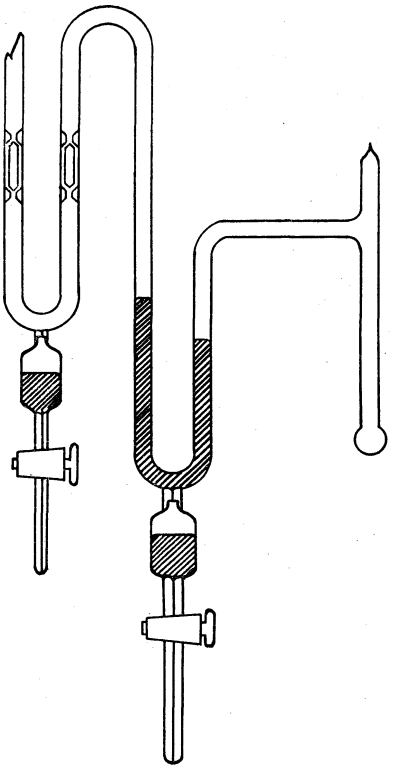


Fig. 7.—Apparatus for following the dissociation pressures of the addition compounds.

There was a remarkable difference in the time required for the equilibrium pressure to be reached. The ammonia derivative reached essentially stationary pressure values in five minutes; the monomethylamine derivative required approximately one hour; the dimethylamine compound required some five to twelve hours for the observed pressure to become sensibly constant. Over a period of some three months trimethylamine showed no signs of being absorbed.

(d) **By Reaction in Ether Solution.**—A solution of 2.04 g. of TNB in 250 ml. of anhydrous ether was mixed with 74.5 ml. of ether containing an equivalent quantity of ammonia. No precipitate was observed. A portion of the solution was cooled to approximately −80°, but no precipitate formed. Overnight a few crystals appeared. These were isolated and introduced into the high vacuum apparatus. They exhibited pressures corresponding to the stable form of ammonia-TNB[15] and analyzed for a 1:1 addition compound.

The solution was permitted to stand at room temperature (protected from the atmosphere) for nearly two weeks. In this time, additional crystals of the same appearance as those already isolated were observed to precipitate, the amount increasing daily. Unless it is assumed that the crystallization is an exceedingly slow process, in contradiction to the observation of Krause and Nobbe,[7] one can only conclude that the crystalline material is the result of a slow change occurring in the dissolved soluble addition compound (presumably the metastable form is isomerizing to the stable form).

Acknowledgment.—This investigation was made possible by Grants No. 710 and 776 from the Penrose Fund of the American Philosophical

(15) The observed pressures, 5.5 mm. at 130°, 16.5 mm. at 150° and 57.0 mm. at 170°, differed slightly from the pressures measured for the addition compound prepared by direct synthesis. The cause of the discrepancy is under investigation.

Society. In addition, the financial assistance afforded by two graduate fellowships supported by the Ethyl Corporation is gratefully acknowledged.

Summary

1. Tri-α-naphthylboron has been prepared and found to possess somewhat different properties from the product previously described in the literature.

2. Addition compounds of tri-α-naphthylboron with ammonia, methylamine and dimethylamine were prepared. Trimethylamine did not combine with tri-α-naphthylboron.

3. The dissociation pressures of the addition compounds indicate a relative stability in the order, $NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$. This order is the theoretical limit predicted for a reference acid with an exceedingly high F-strain factor.

4. The addition compounds exist in two polymorphic modifications. It is suggested that these modifications result from restricted rotation of the α-naphthyl groups in the addition compounds.

5. The hypothesis is advanced that the discrepancies between the properties of the tri-α-naphthylboron prepared in the present investigation and the tri-α-naphthylboron previously described may be due to the existence of two rotation isomers of the compound.

LAFAYETTE, INDIANA RECEIVED NOVEMBER 28, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Reaction of Hydrazine Hydrate on Nitro-Compounds and a New Route to Synthetic Oestrogens

BY HUANG-MINLON[1]

The reduction of nitrobenzaldehydes by alkaline treatment of the corresponding hydrazones is not successful.[2] The modified Wolff–Kishner reduction[3] has now been found to proceed normally, with the exception that nitro-groups are reduced simultaneously. *p*- or *m*-toluidine can be obtained by this method from *p*- or *m*-nitrobenzaldehyde, respectively, in good yield. The reduction of nitro compounds by hydrazine has been observed,[4] although a sealed tube or an autoclave was usually employed. The reduction by hydrazine of *p*- or *m*-nitrotoluene to the corresponding toluidines required reaction in a sealed tube at 130° for four hours.[5] In the present investigation, the reduction was found to proceed readily in refluxing diethylene glycol. *m*-Nitrotoluene can be reduced to *m*-toluidine in good yield in this way; alkali does not affect the course of the reduction. *p*-Toluidine is obtained from *p*-nitrotoluene in good yield only if alkali is absent; in the presence of alkali a dimeric product, 4,4′-diaminostilbene (I), is also formed. The action of alkali alone on *p*-nitrotoluene is known to yield a mixture of condensation products from which 4,4′-dinitrodibenzyl (II) and 4,4′-dinitrostilbene could be isolated (IV).[6] The initial products of the alkali treatment are believed to be nitroso dimeric compounds.[7] Consequently the formation of 4,4′-diaminostilbene from *p*-nitrotoluene undoubtedly proceeds through a nitro or nitroso dimeric product by reduction. The same diamino product in better yield can also be obtained from *p*-nitrobenzyl chloride by treatment with alkali and hydrazine hydrate.

4,4′-Dinitrostilbene (II) is readily reduced by hydrazine hydrate in the presence of alkali to 4,4′-diaminostilbene (I) (80% yield). If alkali is absent, the double bond is also saturated, and 4,4′-diaminodibenzyl (III) can be obtained in this way in 70% yield. Alkali also affects the reduction of 4,4′-dinitrodibenzyl (IV): Treatment with hydrazine alone yields 4,4′-diaminodibenzyl (III) in almost quantitative yield, whereas treatment with hydrazine and alkali yields 4,4′-diaminostilbene (I) in more than 90% yield. Since neither 4,4′-diaminostilbene (I) nor 4,4′-diaminodibenzyl (III) is affected by treatment with hydrazine, with or without alkali, the electron-attracting *p*-nitro group thus activates the methylene or methine group for the donation or acceptance of hydrogen.

Substitution of sulfonic acid groups in the 2,2′-positions does not alter the reaction (see chart, R = SO_3H).

p-Nitrophenylacetic acid can be converted to a dinitrodicarboxylic acid (m. p. 264–266°) by treatment with alkali in the presence of an oxidizing agent. This acid when treated with hydrazine gives 4,4′-diaminodibenzyl; reduction and decarboxylation both take place.

p-Nitropropylbenzene[8] on heating with hydrazine hydrate and alkali gives *meso* and racemic 4,4′-diamino-α,β-diethyldibenzyl (V) along with *p*-aminopropylbenzene. Both of these isomeric diamino compounds have been used by Carlisle and Crowfoot[9] for X-ray measurements but the methods of preparation have not been mentioned.

(1) On leave of absence from the National Research Institute of Chemistry, Academia Sinica.

(2) Lock and Stach, *Ber.*, **76**, 1252 (1943).

(3) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(4) Curtius, *J. prakt. Chem.*, **76**, 238, 281 (1907).

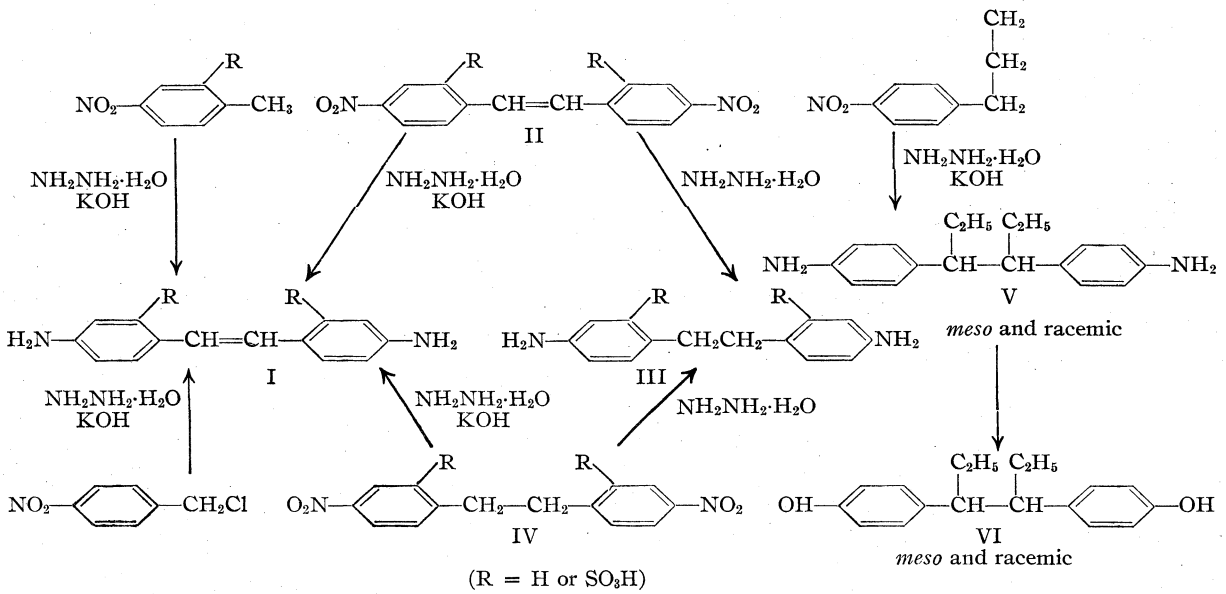
(5) Müller, *ibid.*, **111**, 278, 281 (1925).

(6) Fischer and Hepp, *Ber.*, **26**, 2231 (1893).

(7) Green, Davies and Horsfall, *J. Chem. Soc.*, **91**, 2076 (1907).

(8) Baddeley and Kenner, *J. Chem. Soc.*, 303 (1935); *cf.* Kondo and Uyeo, *Ber.*, **70**, 1087 (1937).

(9) Carlisle and Crowfoot, *J. Chem. Soc.*, 6 (1941).



Baker[10] prepared these compounds from *p*-propiopropionanilide in several steps.

The *meso* and racemic 4,4′-diamino-α,β-diethyldibenzyls on diazotization followed by heating with water give *meso*-4,4′-dihydroxy-α,β-diethyldibenzyl (VI) (hexestrol)[11] and its racemic isomer (isohexestrol),[12] respectively.

It is remarkable that *p*-nitrotoluene and 4-nitrotoluene-2-sulfonic acid on heating with hydrazine hydrate and alkali give the stilbene derivatives whereas *p*-nitropropylbenzene under the same conditions gives the isomeric dibenzyl derivatives.

Further work is in progress for the conversion of *p*-nitropropylbenzene into the corresponding dimeric nitro product to explore the possibilities of obtaining diethylstilbestrol and hexestrol by using hydrazine hydrate in the presence or absence of alkali, similar to the conversion of the dinitrostilbenes or dinitrodibenzyls into diaminostilbenes and diaminodibenzyls as shown in the chart, followed by diazotization.

I am indebted to Prof. L. F. Fieser for his encouragement in the pursuance of this investigation and to Mary Fieser for help in the preparation of this manuscript.

Experimental[13]

All the compounds were reduced by the following general methods with the variations described in the notes.

A mixture of nitro compounds, diethylene glycol and 85% hydrazine hydrate with or without addition of alkali hydroxide was refluxed for about half an hour and the condenser was then removed to allow the aqueous liquor to evaporate and the temperature of the reaction mixture to rise to about 200°. Refluxing at this temperature was continued until the dark colored solution became nearly colorless or light brown (one to three hours). The reaction mixture was cooled and diluted with water and the separated amino product was filtered or extracted with ether.

Note 1.—In reduction of alkali-sensitive compounds such as nitro aldehydes it is advisable to reflux the solution of starting material in diethylene glycol with hydrazine hydrate for about half an hour and then a concentrated aqueous soution of alkali hydroxide is added slowly through the condenser and after refluxing for about twenty minutes longer the aqueous liquor is evaporated as described above.

Note 2.—In cases where either the starting material or the reduced product is volatile a take-off adapter was used instead of removing the condenser to evaporate aqueous liquor.

Note 3.—In some cases a mixture of nitro compound, diethylene glycol and hydrazine hydrate was allowed to stand for a while and then alkali hydroxide in solid form or dissolved in a small amount of water was added.

Note 4.—In cases where the reduced product is acidic, such as amino sulfonic acids, the cooled and diluted reaction mixture was acidified with warm concentrated hydrochloric acid.

p-Toluidine.—(a) From *p*-nitrobenzaldehyde (Notes 1 and 2): *p*-Nitrobenzaldehyde (7.5 g.) dissolved in 100 cc. of diethylene glycol with addition of 15 cc. of hydrazine hydrate and 11 g. of potassium hydroxide gave 3.79 g. (70.8%) of *p*-toluidine, b. p. 116–117° at 53 mm., m. p. 44–45° not depressed with an authentic sample; acetyl compound, m. p. 148–149°, not depressed with N-acetyl-*p*-toluidine. A reduction made with 6.1 g. of *p*-nitrobenzaldehyde without addition of alkali hydroxide gave only 1.8 g. (41.3%) of *p*-toluidine.

(b) From *p*-nitrotoluene (Note 2): 13.7 g. of *p*-nitrotoluene, 200 cc. of diethylene glycol and 20 cc. of hydrazine hydrate (without addition of alkali) gave 9.55 g. (89.2%) of *p*-toluidine, b. p. 106–107° at 34 mm., m. p. 44–45°. Acetyl compound, m. p. 147–148°, not depressed with N-acetyl *p*-toluidine.

m-Toluidine.—(a) From *m*-nitrobenzaldehyde (Notes 1 and 2): 7.5 g. of *m*-nitrobenzaldehyde, 100 cc. of diethylene glycol, 15 cc. of hydrazine hydrate and 11 g. of potassium hydroxide gave 3.54 g. (66.6%) of *m*-toluidine, b. p. 118–119° at 53 mm., $n^{25}D$ 1.5659; acetyl compound, m. p. 67–68°, not depressed with N-acetyl-*m*-toluidine.

(10) Baker, THIS JOURNAL, **65**, 1572 (1943).

(11) For literature or review of syntheses of hexestrol, see Sisido and Nozaki, *ibid.*, **70**, 778 (1948); Solmssen, *Chem. Rev.*, **37**, 481 (1945).

(12) My thanks are due to Prof. E. C. Dodds, Dr. W. Lawson and Dr. C. W. Sondern for a sample of isohexestrol, to Dr. C. H. Carlisle for a sample of *meso*-4,4′-diamino-α,β-diethyldibenzyl, and to Dr. B. R. Baker for the samples of dipropionyl compounds of *meso* and racemic 4,4′-diamino-α,β-diethyldibenzyl.

(13) The microanalyses were carried out by Shirley Katz of this Laboratory.

(b) From *m*-nitrotoluene (Note 2): The reduction of 13.7 g. of *m*-nitrotoluene with 20 cc. of hydrazine hydrate in 200 cc. of diethylene glycol in absence and in presence of alkali gave 8.26 g. (77.2%) and 8.59 g. (80.3%), respectively, of *m*-toluidine b. p. 107–109° at 34 mm., $n^{25}D$ 1.5658; acetyl compound m. p. and mixed m. p. 67°.

4,4′-Diaminostilbene.—(a) From *p*-nitrotoluene (Note 3): On reduction of 13.7 g. of *p*-nitrotoluene in 200 cc. of diethylene glycol with 20 cc. of hydrazine hydrate and 22 g. of potassium hydroxide and extraction of the reaction product with ether there was obtained 3.1 g. (30%) of crystalline basic product separated from the ethereal solution, m. p. 223–225°. Recrystallization from acetone–alcohol gave pure product (short prisms), m. p. 226–228° not depressed by admixture with 4,4′-diaminostilbene prepared from 4,4′-dinitrostilbene.[14,15]

Anal. Calcd. for $C_{14}H_{14}N_2$: N, 13.32. Found: N, 13.71.

It furnished a dibenzal compound,[14] m. p. and mixed m. p. 253–254°. From the ethereal mother liquor, 3.17 g. of *p*-toluidine was obtained.

(b) From *p*-nitrobenzyl chloride: To a warm solution of 5 g. of *p*-nitrobenzyl chloride in 20 cc. of alcohol a solution of 1.8 g. of potassium hydroxide in 1.5 cc. of water and 8 cc. of alcohol was added dropwise at about 50°. After cooling to room temperature 120 cc. of diethylene glycol, 12 cc. of hydrazine hydrate and 8 g. of potassium hydroxide were added and the reaction mixture was treated as described for the general method. On extraction with ether and evaporation of the ethereal solution there was obtained 2.17 g. (70.5%) of crystalline product, m. p. 212–220°; 227–228° after recrystallization from alcohol, not depressed by admixture with 4,4′-diaminostilbene prepared from *p*-nitrotoluene and from 4,4′-dinitrostilbene.[15] It furnished a dibenzal compound, m. p. 253°.

(c) From 4,4′-dinitrostilbene: The reduction of 1 g. of 4,4′-dinitrostilbene (prepared from *p*-nitrobenzyl chloride[16]) in 40 cc. of diethylene glycol with 2.5 cc. of hydrazine hydrate and 2 g. of potassium hydroxide gave 0.62 g. (80.5%) of 4,4′-diaminostilbene, m. p. 227–228° (228–229° after recrystallization from alcohol) not depressed by admixture with the authentic samples from other sources.

(d) From 4,4′-dinitrodibenzyl: The reduction of 1 g. of 4,4′-dinitrodibenzyl (prepared from dibenzyl by nitration[17]) by the general procedure gave 0.72 g. (93.2%) of 4,4′-diaminostilbene, m. p. 222–224°, and 0.57 g. (74%) of once-recrystallized material, m. p. 228–229° (no depression in mixed m. p. with authentic samples). It gave the dibenzal compound, m. p. and mixed m. p. 252–254°.

4,4′-Diaminodibenzyl.—(a) From 4,4′-dinitrostilbene: On reduction of 2.7 g. of 4,4′-dinitrostilbene in 100 cc. of diethylene glycol with 4 cc. of hydrazine hydrate in absence of alkali there was obtained 1.5 g. (71%) of 4,4′-diaminodibenzyl, m. p. 135–136° (white glistening plates, m. p. 137–138°, recrystallized from dilute alcohol after treatment with charcoal), not depressed by admixture with the authentic sample prepared from 4,4′-dinitrodibenzyl by reduction with tin and hydrochloric acid.[18]

Anal. Calcd. for $C_{14}H_{16}N_2$: N, 13.20. Found: N, 13.41.

(b) From 4,4′-dinitrodibenzyl: The reduction of 1 g. of 4,4′-dinitrodibenzyl in absence of alkali as above gave 0.77 g. (99%) of 4,4′-diaminodibenzyl, m. p. 130–133°. Recrystallization from dilute alcohol (charcoal) gave 0.62 g. (79.5%) of pure product, m. p. 136–137°, not depressed by admixture with an authentic sample.

(c) From *p*-nitrophenylacetic acid: To a warm solution (40°) of 4.2 g. of *p*-nitrophenylacetic acid in 20 cc. of water containing a few drops of 30% sodium hydroxide solution a mixture of 10 g. of sodium hydroxide in 9 cc. of water and 25 cc. of sodium hypochlorite (5% available chlorine) was added slowly so that the temperature was not over 45°. After addition of the alkaline oxidizing agent, stirring was continued for three to five hours at 45–50°. The clear diluted solution was acidified with dilute hydrochloric acid and the separated yellowish white crystalline product was filtered (4.04 g.), melting at 258–261° (decomposing). After recrystallization from a large volume of acetic acid the melting point could be raised to 261–262° or 264–266°, depending on the rate of heating. Titration of this compound roughly indicated the presence of two carboxyl groups. Without further identification the dibasic acid (1 g.) was heated in 25 cc. of triethylene glycol with 4 cc. of hydrazine hydrate in absence of alkali (general method). Cooling and dilution of the reaction mixture gave 4,4′-diaminodibenzyl melting at 131–132°. On recrystallization from dilute alcohol, there was obtained 0.51 g. (white plates) of pure product, melting and mixed melting point 137–138°.

4,4′-Dinitrostilbene-2,2′-disulfonic Acid.—This was prepared according to Green and Wahl[19] with the following modifications.

To a warm solution (40–45°) of 5 g. of *p*-nitrotoluene-*o*-sulfonic acid[20] (recrystallized from acetone–benzene, m. p. 137–138°) in 30 cc. of diethylene glycol, a mixture of 50 cc. of sodium hypochlorite (5% available chlorine) and a solution of 6 g. of sodium hydroxide in 8 cc. of water was added slowly under stirring (inside temperature 45–55°). After addition stirring was continued and the temperature was kept at 50–55°. After about fifteen minutes the clear solution became turbid and fine yellow needles began to separate. After about twenty minutes the reaction was complete and the sodium hypochlorite was consumed (iodide starch paper). On cooling and filtration there was obtained 4.9 g. of the sodium salt of 4,4′-dinitrostilbene-2,2′-disulfonic acid which was converted to the free acid,[21] m. p. 266° after recrystallization from acetic acid.

Anal. Calcd. for $C_{14}H_{10}O_{10}N_2S_2$: N, 6.51. Found: N, 6.23.

4,4′-Diaminostilbene-2,2′-disulfonic Acid.—(a) From 4,4′-dinitrostilbene-2,2′-disulfonic acid (Note 4): One gram of 4,4′-dinitrostilbene-2,2′-disulfonic acid was treated with hydrazine hydrate and alkali as described in the preparation of 4,4′-diaminostilbene (c) and there was obtained 0.63 g. (73.3%) of diamino product (fine yellowish needles, m. p. over 300°) which appeared to be identical with 4,4′-diaminostilbene-2,2′-disulfonic acid[6,19,22] (prepared from the same starting material by reduction with tin and hydrochloric acid), from its crystal form, high melting point, solubility and decolorization of cold alkaline potassium permanganate solution.

Anal. Calcd. for $C_{14}H_{14}O_6N_2S_2$: N, 7.56. Found: N, 7.47.

(b) From 4,4′-dinitrodibenzyl-2,2′-disulfonic acid (Note 4): One gram of this starting material (prepared from *p*-nitrotoluene-*o*-sulfonic acid[19]) treated with hydrazine hydrate and alkali as above gave 0.58 g. (67.5%) of 4,4′-diaminostilbene-2,2′-disulfonic acid.

Titration: 96.01 mg. consumed 0.1 *N* sodium hydroxide 5.180 cc. Calcd. for $C_{14}H_{14}O_6N_2S_2$: 5.184 cc.

(c) From *p*-nitrotoluene-*o*-sulfonic acid (Note 4): 2.2 g. of this starting material with 20 cc. of diethylene glycol, 2.5 cc. of hydrazine hydrate and 3 g. of potassium hydroxide gave 0.5 g. (27%) of 4,4′-diaminostilbene-2,2′-disulfonic acid.

Titration: 152 mg. consumed 0.1 *N* sodium hydroxide 8.21 cc. Calcd. for $C_{14}H_{14}O_6N_2S_2$: 8.20 cc.

4,4′-Diaminodibenzyl-2,2′-disulfonic Acid.—(a) From 4,4′-dinitrodibenzyl-2,2′-disulfonic acid (Note 4): One gram of this starting material with 25 cc. of diethylene glycol and 4 cc. of hydrazine hydrate gave 0.63 g. (70%) of

(14) Ruggli and Lang, *Helv. Chim. Acta*, **19**, 996 (1936).
(15) Calvin and Buckles, THIS JOURNAL, **62**, 3326 (1940).
(16) Walden and Kernbaum, *Ber.*, **23**, 1959 (1890).
(17) Rinkenbach and Aaronson, THIS JOURNAL, **52**, 5041 (1930).
(18) Stelling and Fittig, *Ann.*, **137**, 262 (1866).
(19) Green and Wahl, *Ber.*, **30**, 3097 (1897).
(20) I am indebted to E. I. du Pont de Nemours and Company for this material.
(21) Ruggli and Welge, *Helv. Chim. Acta*, **15**, 576 (1932).
(22) Bender and Schultz, *Ber.*, **19**, 3235 (1886).

4,4′-diaminodibenzyl-2,2′-disulfonic acid (white pointed flat needles) which was found to be identical with an authentic sample prepared from the same starting material by reduction with tin and hydrochloric acid.[23]

Anal. Calcd. for $C_{14}H_{16}O_6N_2S_2$: N, 7.53. Found: N, 7.13. *Titration:* 99.03 mg. consumed 0.1 *N* sodium hydroxide 5.295 cc. Calcd. for $C_{14}H_{16}O_6N_2S_2$: 5.318 cc.

(b) From 4,4′-dinitrostilbene-2,2′-disulfonic acid (Note 4): 2 g. of 4,4′-dinitrostilbene-2,2′-disulfonic acid in 40 cc. of diethylene glycol with 8 cc. of hydrazine hydrate gave 0.8 g. (46.2%) of 4,4′-diaminodibenzyl-2,2′-disulfonic acid (white pointed flat needles).

Titration: 95.80 mg. consumed 0.1 *N* sodium hydroxide 5.12 cc. Calcd. for $C_{14}H_{16}O_6N_2S_2$: 5.14 cc.

4,4′-Diamino-α,β-diethyldibenzyl.—The reduction of 19.8 g. of *p*-nitropropylbenzene with 180 cc. of triethylene glycol, 30 g. of potassium hydroxide and 24 cc. of hydrazine hydrate gave 14 g. of dark oily product which was fractionally distilled.

Fraction I: 3.5 g. boiling at 86–87° at 4 mm., identical with *p*-aminopropylbenzene. It furnished an acetyl compound (plates), m. p. 95–96°.

Anal. Calcd. for $C_{11}H_{15}ON$: C, 74.53; H, 8.53; N, 7.90. Found: C, 74.68; H, 8.49; N, 8.03.

Fraction II: 5.1 g. boiling at 178–188° at 0.3 mm.; it solidified after standing. Recrystallization from a mixture of ether and petroleum ether (70–90°) and then from methanol gave about 2 g. of *meso*-4,4′-diamino-α,β-diethyldibenzyl (rhombic plates), m. p. 141–142°, not depressed by admixture with an authentic sample.[12]

The ether–petroleum ethereal mother liquor obtained above on concentration gave the racemic isomer in leaflets. Recrystallization from ether–petroleum ether gave 1.7 g., m. p. 97–98.5° (one sample recrystallized from methanol melting at 98–99°).

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.54; H, 9.01; N, 10.43. Found: (*meso* form) C, 80.68; H, 9.12; N, 10.63; (racemic form) C, 80.50; H, 8.82; N, 10.71.

Both *meso* and racemic isomers furnished the dipropionyl compounds melting at 264–266° (plates) and 217–218° (plates), respectively, mixed with authentic samples[12] (*meso* form m. p. 262–264°; racemic form 207–215°[10]) melted at 263–266° and 210–216°, respectively.

4,4′-Dihydroxy-α,β-diethyldibenzyl.—0.14 g. of *meso*-diamino compound, m. p. 141–142°, was dissolved in dilute sulfuric acid and diazotized with sodium nitrite. After standing at 2–5° about twenty minutes and pouring in portions into 300 cc. of boiling water, the crystalline dihydroxy compound separated on cooling, m. p. 174–178° (0.12 g.). Recrystallization from benzene gave pure product, m. p. 181–182°, not depressed by admixture with an authentic sample of hexestrol.

Diazotization of racemic diamino compound (m. p. 97–98°) under the same conditions as above gave the racemic or isohexestrol which after repeated recrystallization from ether–petroleum ether melted at 128–129°, not depressed by admixture with an authentic sample.[12]

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found (*meso* form): C, 80.18; H, 8.14. (racemic form): C, 80.04; H, 8.22.

(23) Ris and Simon, *Ber.*, **30**, 2618 (1897).

Summary

1. The modified Wolf–Kishner method has been adapted for the reduction of aromatic nitroaldehydes.

2. Nitrotoluenes have been converted to the corresponding dimeric amino products and toluidines by using hydrazine hydrate.

3. Both the 4,4′-dinitrostilbenes and the 4,4′-dinitrodibenzyls have been converted to the diaminostilbenes or diaminodibenzyls by the action of hydrazine hydrate. In all of these cases the presence of alkali was a determining factor with respect to the formation of dimeric products and the persistence or the reduction of the ethylenic linkage.

4. A new synthetic route for the preparation of hexestrol has been described.

CAMBRIDGE 38, MASSACHUSETTS RECEIVED APRIL 17, 1948

[CONTRIBUTION FROM ROHM & HAAS COMPANY]

Preparation of Acetals or Ketals from Vinyl-type Esters

BY W. J. CROXALL, F. J. GLAVIS AND H. T. NEHER

In the course of an investigation of the addition of alcohols to vinyl compounds, it was observed that when vinyl acetate is added to an excess of alcohol containing a small amount of mercury oxide and boron trifluoride, heat is evolved and an acetal and acetic acid are formed in high yields. Under similar conditions isopropenyl acetate gives a ketal and acetic acid. The over-all course of the reaction is

$$CH_2{=}CHOCOCH_3 + 2ROH \longrightarrow CH_3CH(OR)_2 + CH_3COOH$$

Mixtures of mercuric oxide and the complexes formed from boron trifluoride with alcohols, ethers or carboxylic acids were found to be the most active catalysts. With these, the reaction starts promptly and is so rapid that efficient cooling is required to prevent vigorous or even violent boiling. Mercuric sulfate is a slightly less active catalyst. With mercuric phosphate no appreciable reaction occurs at room temperature, but after the mixture is refluxed for two hours, some hemiacetal acetate is formed. Coffman[1] obtained the 1-acetoxyethyl ether of a glycolic ester when equi-molar quantities of vinyl acetate and the glycolic ester were refluxed in the presence of mercuric phosphate. Mercuric oxide alone is entirely inert as a catalyst at room or elevated temperatures. Boron trifluoride diethyl etherate alone induces no exothermic reaction, but when the reaction mixture is refluxed, acetal is produced in low yield, together with acetic ester, acetaldehyde and water. Presumably, the initial reaction in this case is an alcoholysis[2] after which some of the acetaldehyde undergoes acetal formation

$$CH_2{=}CHOCOCH_3 + ROH \longrightarrow CH_3CHO + CH_3COOR$$
$$CH_3CHO + 2ROH \longrightarrow CH_3CH(OR)_2 + H_2O$$

(1) Coffman, U. S. Patent 2,384,726 (1945).

(2) Herrmann and Deutsch, British Patent 314,646 (1929).

The course of the reaction is believed to be quite different when the mercuric oxide boron trifluoride catalysts are used. No acetaldehyde could be detected when dry reagents were used. When the mole ratio of alcohol to vinyl acetate is less than two, 1-alkoxyethyl acetate occurs as one of the products. This compound is believed to be an intermediate in the reaction. It is suggested that the reaction proceeds as follows

(a) $CH_2{=}CHOCOCH_3 + ROH \longrightarrow CH_3CH(OR)OCOCH_3$

(b) $CH_3CH(OR)OCOCH_3 + ROH \longrightarrow CH_3CH(OR)_2 + CH_3COOH$

The plausibility of reaction (b) was clearly demonstrated when butyl acetal was obtained in 81% yield by the action of 1-butoxyethyl acetate on *n*-butyl alcohol in the presence of mercury oxide and boron trifluoride. The 1-butoxyethyl acetate was prepared from *n*-butyl vinyl ether and acetic acid.[3]

The reaction offers a convenient method for preparing acetals and is especially useful for preparing ketals. It is applicable to primary and secondary alcohols. Ethylene glycol forms the cyclic acetal, 2-methyl-1,3-dioxolane. Tertiary alcohols do not give the acetals but undergo alcoholysis to acetaldehyde and the tertiary alkyl acetates. Phenol undergoes a vigorous reaction with vinyl acetate under the reaction conditions to give acetic acid and alkali soluble polymeric materials. The yields of acetals from primary alcohols are 80–90% as compared to a 38% yield from isopropyl alcohol. The best yields are obtained when the reaction is carried out under anhydrous conditions. In one experiment in which 98% ethanol and undistilled vinyl acetate were used with mercuric sulfate as a catalyst, the yield of acetal was 58%, as compared to 88% when anhydrous reagents were used. Ethyl acetate was isolated in this experiment, indicating that some alcoholysis also occurred. The ketal yields are lower than the yields of the corresponding acetals. Table I lists some of the acetals and ketals prepared by this method.

TABLE I

ACETALS AND KETALS PREPARED

Acetals (of acetaldehyde)	B. p., °C. (mm.)	Yield, %	$n^{20}D$
Methyl	62.5–64	84	1.3665[a]
Ethyl	103–104	88	1.3809[a]
Isopropyl	126.5	38	1.3890[b]
n-Butyl	74.5–76(14)	89	1.4080[4]
Allyl	148–149.5	85	1.4218[c]
2-Methyl-1,3-dioxolane	82–83.5	68	1.3970[d]
Ketals (of acetone)			
Ethyl	113–113.5	55	1.3891[e]
n-Butyl	64–64.5(3)	63	1.4120[f]
Allyl	61–62(26)	32	1.4262[c]
2,2-Dimethyl-1,3-dioxolane	91–92	49	1.3980[g]

[a] "Beilstein," I, 671–672. [b] Adkins and Adams, THIS JOURNAL, **50**, 182 (1928). [c] Hurd and Pollack, *ibid.*, **60**, 1907 (1938). [d] Clarke, *J. Chem. Soc.*, **101**, 1804(1912). [e] Claisen, *Ber.*, **31**, 1012 (1898). [f] *Anal.* Calcd. for $C_{11}H_{24}O_2$: C, 70.16; H, 12.84. Found: C, 70.01; H, 12.79. [g] Otto, THIS JOURNAL, **59**, 1591 (1937).

The substitution of mercaptans for alcohols in the reaction gave 2-alkylmercaptoethyl acetates instead of mercaptals. The yield was about 75% when mercuric sulfate or mercuric oxide and boron trifluoride etherate was used, as compared to a 99% yield with boron trifluoride etherate alone as the catalyst. A 10% yield of the same product was obtained when the reaction mixture was refluxed without catalyst.

Experimental

Materials.—The alcohols were dried when necessary in the usual manner and carefully fractionated. The vinyl acetate was fractionated and material of b. p. 72.5–73° used. The isopropenyl acetate was obtained from Tennessee Eastman Corporation and material of b. p. 96° used. *n*-Butyl mercaptan was fractionated and material of b. p. 97° used.

Preparation of Acetals and Ketals.—The following preparation of *n*-butyl acetal is representative of the method used. In a one-liter three-necked flask equipped with a mercury-sealed stirrer, thermometer, dropping funnel and reflux condenser, were placed 148 g. (2.0 moles) of *n*-butyl alcohol, 1 g. of red mercuric oxide and 1 ml. of boron trifluoride diethyl etherate. To this was added 86 g. (1.0 mole) of vinyl acetate over a period of ten minutes while maintaining the temperature below 55° by means of an ice-bath. The mixture was allowed to stir for one hour, after which it was poured into a suspension of 56 g. (0.5 mole) of sodium carbonate in 250 ml. of water. The upper oil layer was separated and dried over anhydrous potassium carbonate. The aqueous layer was acidified with concd. hydrochloric acid, extracted with ether, dried over anhydrous sodium sulfate and distilled to give 26 g. of acetic acid, b. p. 116.5–117°, $n^{20}D$ 1.3721.

The oil layer upon distillation through a one-foot glass helices packed column gave 153 g. (88.5%) of *n*-butyl acetal, b. p. 74.5–76° (14 mm.), $n^{20}D$ 1.4080.[4]

When the mercuric oxide was omitted in the above experiment, a small amount (3 g.) of acetaldehyde, 18 g. of *n*-butyl acetate and 50 g. of butyl acetal was obtained. The major portion of the reaction mixture consisted of the starting materials and butyl acetate.

Reaction of *t*-Butyl Alcohol with Vinyl Acetate.—From 296 g. (4 moles) of *t*-butyl alcohol, 2 g. of mercuric oxide, 4 g. of methanol boron trifluoride complex (1:1) and 344 g. (4 moles) of vinyl acetate, there was obtained 5 g. of material trapped in a Dry Ice receiver (b. p. around 0°, decolorized a solution of bromine in carbon tetrachloride; thought to be isobutylene); 76 g., b. p. up to 97°; 69 g. (15%) *t*-butyl acetate, b. p. 97–98°, $n^{24}D$ 1.3875; 70 g. higher boiling material (98–170°), and considerable polymeric residue. Attempts to fractionate the 98–170° cut gave no constant boiling fractions.

Preparation of 1-(*n*-Butoxy)-ethyl Acetate from *n*-Butyl Vinyl Ether.—To 120 g. (2 moles) of acetic acid and one drop of concd. sulfuric acid was added with stirring 208 g. (2 moles) of *n*-butyl vinyl ether. The temperature during the addition was maintained below 45° by cooling. Stirring was continued for one and one-half hours and 0.5 g. of sodium methoxide was added. Distillation gave 265 g. (82.8%) of 1-(*n*-butoxy)-ethyl acetate, b. p. 65° (14 mm.), $n^{20}D$ 1.4025.[5] The saponification equivalent determined for this compound was 158, the calculated value is 160.

Preparation of *n*-Butyl Acetal from 1-(*n*-Butoxy)-ethyl Acetate.—Two moles of *n*-butyl alcohol (148 g.), 3 g. red mercuric oxide and 2 ml. of methanol boron trifluoride

(3) Reppe, "Advances in Acetylene Chemistry," 1940, trans. by R. F. C., Office of Rubber Reserve, July 25, 1945.

(4) Connor, Elving and Steingiser, *Ind. Eng. Chem.*, **40**, 498 (1948).

(5) Hurd and Green, THIS JOURNAL, **63**, 2202 (1941).

(1:1) were placed in a one-liter flask. To this was added with rapid stirring, 320 g. (2 moles) of 1-(*n*-butoxy)-ethyl acetate over a period of fifty-five minutes. The temperature was maintained at 10–20° by means of an ice-bath. Stirring was continued for thirty minutes, the reaction mixture poured into a suspension of 106 g. (1.0 mole) of sodium carbonate in 150 ml. of water, the oil layer separated, dried over anhydrous potassium carbonate and distilled to give 295 g. (85%) of *n*-butyl acetal, b. p. 185–189°, $n^{20}D$ 1.4080.[4]

Preparation of 2-Butylmercaptoethyl Acetate.—Upon mixing 90 g. (1 mole) of *n*-butyl mercaptan, 43 g. (0.5 mole) of vinyl acetate and 0.5 ml. of boron trifluoride etherate, the temperature rose slowly to 62°. The mixture was allowed to stand overnight and 1 g. of sodium methoxide added. Distillation gave 75 g. (99% yield based on vinyl acetate) of 2-butylmercaptoethyl acetate, b. p. 72–75° (2 mm.), $n^{20}D$ 1.4616.

With mercuric sulfate as the catalyst instead of boron trifluoride etherate, the yield of the mercapto-ester was 76%; with no catalyst present the yield of this ester amounted to only 10%.

Summary

1. Acetals are produced in good yield by the reaction of vinyl acetate with primary aliphatic alcohols in the presence of an acidic mercury catalyst.

2. Ketals are produced in a similar manner from isopropenyl acetate.

3. It is suggested that the vinyl acetate and alcohol initially react to form a hemiacetal acetate, which subsequently reacts with alcohol to give an acetal and acetic acid.

PHILADELPHIA, PA. RECEIVED APRIL 1, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Some Diethylisopropoxyhalogenosilanes and their Hydrolysis Products[1]

BY PATRICK A. MCCUSKER AND CHARLES E. GREENE

Although a number of alkoxyfluorosilanes and some alkylalkoxychlorosilanes have been prepared, no alkylalkoxyfluorosilanes have been previously reported. In the course of the preparation of a compound of this type, some previously unreported organosilicon compounds were prepared and some observations made on the hydrolysis of diethylisopropoxyhalogenosilanes.[2]

Direct reaction of excess isopropyl alcohol and diethyldichlorosilane gave yields of only 20% of diethyldiisopropoxysilane while yields of 67% have been reported for the analogous preparation of dimethyldi-*n*-butoxysilane.[3] The lower yield of the isopropoxy compound may be attributed to the greater steric requirements of the isopropoxy group or to the general lower reactivity of the secondary alcohol compared to the primary. A low yield of diethylisopropoxyfluorosilane (22%) was obtained from the reaction of zinc fluoride on diethylisopropoxychlorosilane. This is probably due to a competing reaction in which both the alkoxy and chloro substituents are replaced by fluorine.

An aqueous suspension or a homogeneous solution of 0.04 molar diethylisopropoxyfluorosilane in a methanol–water mixture, maintained a hydrogen ion concentration of less than 10^{-4} mole per liter, as indicated by the basic color given by methyl orange which is unchanged on standing several days. Using phenolphthalein as an indicator, however, the suspension in water could be rapidly titrated to a stoichiometric end-point with 0.1 *N* base. A calculation of the concentration of hydrogen fluoride necessary to produce a hydrogen ion concentration of 10^{-4} mole per liter indicated that the hydrolysis came to equilibrium when less than 0.3% of the fluoride has been hydrolyzed in neutral water. At a somewhat lower hydrogen ion concentration, 10^{-10} mole per liter, hydrolysis proceeded to completion very rapidly.

On the hydrolysis of diethylisopropoxychlorosilane, with an equivalent amount of base, even in the presence of excess isopropyl alcohol, the alkoxy group split off and the cyclic trimer and tetramer were formed in high yield. [Diethyldiisopropoxysilane was found, however, to be stable in excess base.] Justification for the assignment of formulas to the two cyclic compounds is based on the analytical composition, molar refraction and molecular weight determination. The absence of any hydroxyl groups was further shown by the application of the Zerewitinoff reaction.

A marked difference in the action of sodium on the cyclic trimer and the cyclic tetramer was incidentally observed. The trimer on heating with sodium in the temperature range 150 to 245° evidently underwent a polymerization resulting in a marked increase in viscosity. The tetramer, on the other hand, was completely unaffected by long heating with finely divided sodium at 295°.

Experimental

The reaction apparatus used in this work consisted of a 1-liter, 3-necked flask equipped with stirrer and reflux condenser and protected from atmospheric moisture. All products were purified by fractional distillation through a total reflux, partial take-off column, 12 mm. inside diameter and 53″ in height, packed with 1/8″ glass helices. The column was operated at a reflux ratio of ten to one. Carbon and hydrogen analyses were made by Micro-Tech Laboratories, Skokie, Illinois, and hydrolyzable halogen was determined by titration of aqueous mixtures with standard base. Molar refractions were calculated from the bond refraction values of Warrick[4] and molecular

(1) This paper consists of a report of work done under contract with the Technical Command, Chemical Corps, U. S. Army.

(2) The authors wish to thank Dr. Charles C. Price for his helpful interest in this work.

(3) Sauer, THIS JOURNAL, **68**, 138 (1946).

(4) Warrick, *ibid.*, **68**, 2455 (1946).

weights were obtained from cryoscopic measurements in benzene.

Diethylisopropoxychlorosilane.[5]—Purified diethyldichlorosilane (1.75 moles) and 500 ml. of benzene were heated to reflux in the reaction flask. During a period of three hours, 1.75 moles of isopropyl alcohol was added dropwise to the refluxing mixture. During the first stages of the reaction a water-insoluble, combustible gas was given off in addition to the hydrogen chloride. The volume of the gas, presumably propylene, was measured and found to represent a loss of about 5 mole %. In a considerable number of preparations this same gas evolution was observed and appeared to be characteristic of the reaction under these conditions. After addition was complete the reaction mixture was fractionated in the 53″ column to give a 72% yield of diethylisopropoxychlorosilane. The properties of the purified compound are as follows: b. p. 155.5° at 750 mm., $n^{20}D$ 1.4123, d^{20}_4 0.9227, MR_D calcd. 49.2, obs. 48.7.

Anal. Calcd. for $C_7H_{17}OSiCl$: C, 46.6; H, 9.5; Cl, 19.6; mol. wt., 180.5. Found: C, 46.7; H, 9.5; Cl, 19.2; mol. wt., 182.

Diethyldiisopropoxysilane.—In the residue from the fractionation of diethylisopropoxychlorosilane there was found in all runs about 10 mole % of the diether. For purposes of characterization further amounts of this compound were prepared by addition of diethyldichlorosilane to excess isopropyl alcohol. Only a small yield (20%) was obtained in this manner. Sufficient product, however, was obtained for characterization. The compound was purified by fractional distillation and had the following properties: b. p. 174° at 750 mm.; $n^{20}D$ 1.4032; d^{20}_4 0.8423; MR_D calcd. 59.6, obs. 59.2.

Anal. Calcd. for $C_{10}H_{24}SiO_2$: C, 58.8; H, 11.8. Found: C, 58.8; H, 11.9.

The compound is a colorless liquid with a mild sweet odor, insoluble and non-reactive in water. Hydrolytic cleavage was found to occur very rapidly in aqueous acid but either slowly or not at all in aqueous base.

Diethylisopropoxyfluorosilane.—Diethylisopropoxychlorosilane (0.58 mole) in 250 ml. of benzene was placed in the reaction flask. Technical grade zinc fluoride (0.33 mole) dried by heating for one hour at 200°, was added slowly with stirring during one hour. The reaction was slow to start but exothermic enough to require cooling. The mixture was stirred for four hours and filtered. Fractional distillation of the filtrate gave the following fractions: Ten grams of diethyldifluorosilane, 12 g. (22% yield) of diethylisopropoxyfluorosilane, 12 g. of unreacted diethylisopropoxychlorosilane and 31 g. of unidentified residue. The purified diethylisopropoxyfluorosilane had the following properties: b. p. 127° at 750 mm., $n^{20}D$ 1.3803, d^{20}_4 0.8745, MR_D calcd. 43.5, obs. 43.5.

Anal. Calcd. for $C_7H_{17}OSiF$: C, 51.2; H, 10.4; F, 11.5. Found: C, 51.1; H, 10.6; F, 11.5.

(5) The authors acknowledge the assistance of Mr. O. C. Kohler in the preparation of this compound.

Cyclic Polysiloxanes.—Hydrolysis of diethylisopropoxychlorosilane was carried out under two sets of conditions. In procedure A, 50 g. (0.9 mole) of potassium hydroxide was added to 500 g. of isopropyl alcohol and the mixture heated until nearly all the solid had dissolved. Diethylisopropoxychlorosilane (0.83 mole) was added dropwise to the cold solution with agitation, while the temperature of the mixture was held below 20°. After addition was complete the potassium chloride was filtered off and the filtrate fractionated. The isopropyl alcohol which came off first gave a strongly acid reaction when dissolved in water indicating that an excess of base may not have been maintained in the reaction mixture. Distillation of the 84 g. of residue remaining after the removal of the alcohol gave 21 g. of hexaethylcyclotrisiloxane (25% yield) and 50 g. (59% yield) of octaethylcyclotetrasiloxane.

In procedure B a 20% aqueous sodium hydroxide solution containing 2.5 moles was placed in the reaction flask and 1 mole of diethylisopropoxychlorosilane added slowly under the surface of the solution with stirring. The temperature of the reaction mixture was held below 20°. The cloudy one-phase liquid was then extracted with three 50-ml. portions of ether and the combined extracts dried with anhydrous sodium sulfate. On distillation a 50-g. fraction of isopropyl alcohol was obtained. The higher boiling fraction yielded 28 g. (27% yield) of hexaethylcyclotrisiloxane, 12 g. (12% yield) of octaethylcyclotetrasiloxane and 29 g. of a high boiling residue.

The properties of the purified cyclic trimer from both procedures were as follow: b. p. 246° at 750 mm., 97° at 2 mm., $n^{20}D$ 1.4305, d^{20}_4 0.9560, MR_D calcd. 83.7, obs. 82.9.

Anal. Calcd. for $C_4H_{10}SiO_3$: C, 47.01; H, 9.86; mol. wt., 306. Found: C, 46.91; H, 10.04; mol. wt., 319.

The purified cyclic tetramer had the following properties: b. p. 295° at 750 mm., 134° at 2 mm.; $n^{20}D$ 1.4340, d^{20}_4 0.9625; MR_D calcd. 111.6, obs. 110.6.

Anal. Calcd. for $C_4H_{10}SiO_4$: C, 47.01; H, 9.86; mol. wt., 409. Found: C, 47.16, H. 9.83; mol. wt., 394.

Summary

1. Diethylisopropoxychlorosilane, diethylisopropoxyfluorosilane and diethyldiisopropoxysilane have been prepared and characterized.

2. The hydrolysis of the fluoro compound has been observed to proceed to only a very slight extent in neutral water but to go rapidly to completion in slightly basic solution.

3. Hydrolysis of diethylisopropoxychlorosilane in excess isopropyl alcohol, containing a nearly equivalent amount of potassium hydroxide, has been found to give high yields of cyclic trimer and tetramer. These cyclic polysiloxanes have been purified and characterized.

NOTRE DAME, IND. RECEIVED FEBRUARY 24, 1948

NOTES

Ribitol Pentaacetate

By W. W. Binkley[1] and M. L. Wolfrom

The acetates of the sugars and sugar alcohols are significant reference compounds especially in certain types of chromatographic techniques.[2] All of the acetates of the pentitols have been described in crystalline form save that of ribitol (synonym, adonitol). We wish to report herein the crystallization of such a derivative of this naturally occurring pentitol.

Experimental

A mixture of 2.00 g. of ribitol, 0.3 to 0.4 g. of freshly fused zinc chloride, and 20 ml. of acetic anhydride was surrounded with an ice- and water-bath and was stirred for sixteen hours. The temperature of the bath was allowed to rise gradually to 25° during this period. The reaction mixture was poured on 30 g. of finely crushed ice, was stirred for thirty minutes, and was adjusted to a *p*H of 6 with sodium bicarbonate. This solution was extracted with four 25-ml. portions of chloroform. Solvent removal from the dried extract yielded crystalline material; yield 4.78 g. Pure material was obtained on recrystallization from diethyl ether; yield 3.87 g., m. p. 51°. A further crop of less pure material (0.33 g.) was obtainable from the mother liquor on the addition of petroleum ether (b. p. 60–65°). The substance crystallized in elongated prisms that were soluble in benzene, chloroform, ethanol and diethyl ether.

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 13.80 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 49.62; H, 6.07; CH_3CO, 13.82 ml.

(1) Sugar Research Foundation Fellow of The Ohio State University Research Foundation (Project 190).

(2) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, This Journal, **67**, 527 (1945).

Department of Chemistry
The Ohio State University
Columbus, Ohio

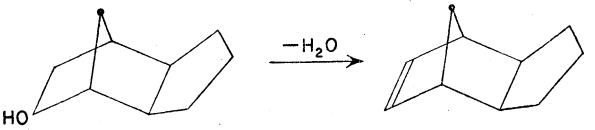
Received April 23, 1948

Dihydro-*exo*-dicyclopentadiene

By Herman A. Bruson[1] and Thomas W. Riener[1]

Recently Bartlett and Goldstein[2] showed that the hitherto rare *exo* isomer of dicyclopentadiene can be readily obtained by dehydrohalogenation of iodo-dihydro-*exo*-dicyclopentadiene[3] which may conveniently be prepared by warming ordinary *endo*-dicyclopentadiene with hydriodic acid.[3]

By dehydrating hydroxy-tetrahydro-*exo*-dicyclopentadiene[4] (I) with phosphoric acid we have obtained the corresponding dihydro-*exo*-dicyclopentadiene (II) in which the residual double bond is in the bridge endomethylene ring.



(I) (II)

This completes the series of isomeric dihydrodicyclopentadienes.

Experimental

Dihydro-*exo*-dicyclopentadiene.—A mixture of 15 g. of sirupy 85% phosphoric acid and 198 g. of hydroxytetrahydro-*exo*-dicyclopentadiene[4] which had twice been recrystallized from nitroethane to m. p. 53°, was stirred and heated in an oil-bath under a reflux condenser to which was attached a water separator device. After heating for about one hour at 150–230°, 40 cc. of oily liquid and 20 cc. of water had collected in the separator. The residual oil in the still flask was washed with water and distilled under reduced pressure to yield 40 g. of oil boiling at 80–95° (40 mm.). This was combined with the 40 cc. of oil distillate and the mixture redistilled. A fraction (68 g.) boiling at 89–93° (40 mm.) was thus secured. This was refractionated through an efficient packed column to yield 61 g. of colorless oil b. p. 89–91° (39 mm.) having $n^{25}D$ 1.4993; d^{25}_4 0.9571. It boiled at 182° (768 mm.).

Anal. Calcd. for $C_{10}H_{14}$: C, 89.55; H, 10.44. Found: C, 89.45; H, 10.43.

(1) Present address: Industrial Rayon Corporation, Cleveland, Ohio.

(2) Bartlett and Goldstein, This Journal, **69**, 2553 (1947).

(3) Previously referred to as iodo-dihydro-*nor*-dicyclopentadiene, Bruson and Riener, *ibid.*, **67**, 1179 (1945).

(4) Previously referred to as hydroxy-tetrahydro-*nor*-dicyclopentadiene, Bruson and Riener, *ibid.*, **67**, 727 (1945).

Resinous Products and
Chemical Company, Inc.
Philadelphia, Pa.

Received May 5, 1948

Addition of Organolithium Compounds to the Azomethine Linkage of γ-Picoline and 6-Methoxyquinoline

By Henry Gilman and H. Smith Broadbent[1]

In connection with some studies on compounds having possible physiological activity, occasion arose to prepare some "anil addition" compounds of γ-picoline and 6-methoxyquinoline.

At −80° *n*-butyllithium was found to be without observable action on γ-picoline in ether solution. Upon carbonation of the reaction mixture, γ-picoline and valeric acid were the only isolable products. At −10°, however, addition to the anil linkage is the predominant reaction yielding first the lithium salt of 2-*n*-butyl-4-methyl-1,2-dihydropyridine (not isolated) which upon acidification and air oxidation gave 2-*n*-butyl-4-methylpyridine.

Addition of α-thienyllithium to 6-methoxyquinoline at the reflux temperature of ether similarly yielded 2-(α-thienyl)-6-methoxyquinoline.

(1) Present address: Department of Chemistry, Brigham Young University, Provo, Utah.

Experimental

2-*n*-Butyl-4-methylpyridine.—Twenty-three grams (0.25 mole) of γ-picoline in 75 ml. of anhydrous ether was added dropwise with stirring to an equivalent amount of 0.94 molar butyllithium in ether, which was maintained at −10° in an ice–salt-bath. A yellow precipitate formed. After one and one-half hours stirring the mixture was carbonated by pouring jet-wise into a slurry of Dry Ice and ether. After the Dry Ice had evaporated, the mixture was extracted with 20% sodium hydroxide solution. On acidifying the alkaline extract only a very small amount of red gum was obtained from which a very small amount (*ca.* 10–20 mg.) of unidentified crystalline material, m. p. 148–150°, separated on cooling. The alkali-insoluble portion was a yellow oil, which was aerated to oxidize the dihydropyridine to the pyridine, dried over barium oxide and distilled. Five grams of the anil addition product was obtained boiling at 200–202° (740 mm.). A Siwoloboff boiling point determination gave reproducible values at 201–202°: $n^{20}D$ 1.4778; sp. gr.$^{27}_{27}$ 0.885.

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.50.

The picrate was prepared in boiling ethanol giving bright yellow crystals, melting at 88.5–90.5° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{16}H_{18}O_7N_4$: N, 14.8. Found: N, 14.9.

2-(α-Thienyl)-6-methoxyquinoline.—Thiophene, 30.3 g. (0.36 mole) in 100 ml. of anhydrous ether, was metalated with 0.3 mole of butyllithium in the conventional apparatus under a nitrogen atmosphere. Then 34 g. (0.214 mole) of 6-methoxyquinoline in 60 ml. of ether was added dropwise to the stirred α-thienyllithium at such a rate as to maintain reflux. A greenish-white precipitate formed. After stirring the mixture for one hour, it was hydrolyzed carefully with 200 ml. of water.

The ether phase was separated, mixed with 25 ml. of nitrobenzene to oxidize the dihydroquinoline, and distilled. A fraction (nitrobenzene, aniline, thiophene) was collected at 90–105° (18 mm.). Then 26 g. (a 75% recovery) of 6-methoxyquinoline was obtained boiling at 105–114° (18 mm.). (Its identity was checked by preparing its picrate and comparing the picrate prepared from an authentic sample of 6-methoxyquinoline. Both melted at 217–218°, with no depression on mixing.) A final fraction of 3.5 g. (6.8%) boiling 200–210° (18 mm.), was collected and crystallized from a benzene and ligroin mixture; melting point, 137–138.5°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.81. Found: N, 5.69.

A picrate of the product was prepared and recrystallized from ethanol. The melting point was 190.5–192°.

Anal. Calcd. for $C_{20}H_{14}O_8N_4S$: N, 11.9. Found: N, 11.75.

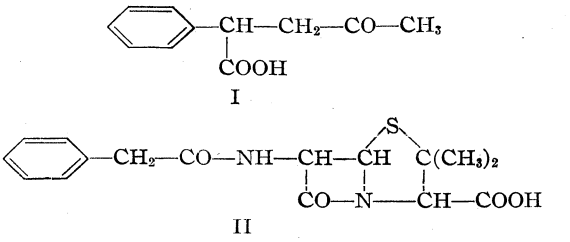
DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED MAY 7, 1948

α-Phenyl-levulinic Acid, a Product of the Alkaline Degradation of Penicillin G

BY M. W. GOLDBERG, WILLIAM R. SULLIVAN AND W. E. SCOTT

In the course of studies on the chemistry of penicillin G carried out in 1945, we encountered significant amounts of a degradation product which was readily identified as α-phenyl-levulinic acid (I). It was obtained from penicillin G, along with larger quantities of phenylacetic acid, by treatment with aqueous sodium hydroxide.



I

II

At that time no information was available to us concerning results of degradative studies carried out in other laboratories. Meanwhile, there have appeared several publications on the chemistry of penicillin[1] which discuss in survey form the experimental evidence that led to the general acceptance of formula II for penicillin G. These publications, while mentioning a great number of degradation products obtained from the various penicillins, do not contain any reference to α-phenyl-levulinic acid.

The accepted β-lactam formula for penicillin G (II) does not contain the carbon skeleton of α-phenyl-levulinic acid, and it is not readily apparent to us by what series of reactions this C-11 acid could be formed from it. The β-lactam structure is based upon such a wide variety of evidence that it seems necessary to conclude that our product is an artifact formed somehow by a reductive condensation of certain of the penicillin G degradation products. The mechanism, however, is obscure.

There is no question that the α-phenyl-levulinic acid isolated by us is actually formed from penicillin G. The preparation has been repeated several times during the past two and a half years, using sodium penicillin G of high purity, obtained by different methods from different lots of penicillin. The α-phenyl-levulinic acid has been isolated as such and in the form of its methyl ester and as the *p*-nitrophenylhydrazone, all of which have proved to be identical with authentic synthetic specimens.

Experimental

Isolation of α-Phenyl-levulinic acid.—Crystalline penicillin G sodium salt (2.694 g.), a composite of several pure samples obtained by a chromatographic process, was dissolved in 140 ml. of *N* sodium hydroxide which had been freed of dissolved oxygen by boiling in a stream of nitrogen. The solution was boiled under reflux for one hundred minutes, while nitrogen was passed into the mixture through a capillary. Ammonia was evolved. After cooling, the solution was acidified with sulfuric acid, saturated with sodium chloride, and extracted with ether. Removal of the solvent from the extract left 1.106 g. of a deep purple oil which was sublimed *in vacuo*. The fraction subliming between 75° and 129° (201 mg.) was recrystallized twice from ligroin and gave 54 mg. of an acid melting at 121–124°. This was combined with corresponding fractions from other experiments and recrystallized from *n*-hexane, which raised the melting point to 124–125.5°. The melting point of a mixture with a

(1) Committee on Medical Research, O. S. R. D., *Science*, **102**, 627 (1945); du Vigneaud and co-workers, *ibid.*, **104**, 431 (1946); Editorial Board of Monograph on the Chemistry of Penicillin, *ibid.*, **105**, 653 (1947); **106**, 503 (1947).

sample of synthetic α-phenyl-levulinic acid[2] was not depressed.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; neut. equiv., 192. Found: C, 68.39; H, 6.03; neut. equiv., 183, 186.

The *p*-nitrophenylhydrazone melted at 190.5–191.5° (cor.), and a mixture with a sample prepared from the synthetic acid was not depressed.

Anal. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.23; N, 12.84. Found: C, 62.00, 62.10; H, 5.13, 5.04; N, 12.87, 13.22.

Isolation as Methyl α-Phenyl-levulinate.—The material used in this experiment was crystalline penicillin G sodium salt obtained *via* the crystalline triethylamine salt. It was purified by repeated recrystallization from aqueous acetone and dried to constant weight *in vacuo* over phosphorus pentoxide. The preparation was acetone free. The minimum penicillin G content, as determined by the official FDA N-ethylpiperidine method, was 95%, and the potency ratio in the *Bacillus subtilis–Staphylococcus aureus* plate test was 0.98; $[\alpha]^{25}D$ +301° (c = 0.51 in water).

Anal. Calcd. for $C_{16}H_{17}N_2O_4SNa$: C, 53.92; H, 4.81. Found: C, 53.96; H, 5.15.

Nineteen grams (0.0533 mole) of this sodium penicillin G sample was dissolved in 950 cc. of 1 *N* sodium hydroxide previously heated to boiling under nitrogen. The solution was refluxed one hundred minutes under nitrogen, cooled, and extracted with ether. Evaporation of the ether extract left a red-brown residue weighing 0.25 g. The water layer was acidified with dilute sulfuric acid and extracted with ether. The ether layer was evaporated, leaving a semi-crystalline residue of 7.09 g. which was treated with an excess of freshly distilled diazomethane in ether. Removal of the solvent left a liquid residue of 7.50 g. which was distilled at 5 mm. to yield several fractions:

Fraction	Bath temp., °C.	Weight, g.	$n^{22}D$
1	Up to 119	3.80	1.5047
2	119–130	0.09	....
3	130–135	0.14	1.5058
4	135	0.18	1.5054
5	135–165	1.74	Crystalline
Residue		1.46	

The first four fractions consisted of methyl phenylacetate[3] and amounted to 4.21 g. (0.024 mole) or 45%.

Fraction 5 was suspended in petroleum ether and filtered. The crystals weighed 1.47 g. and melted at 66–68°. Recrystallization from *n*-butanol gave 1.18 g. melting at 68–70°, and a mixture with synthetic methyl α-phenyl-levulinate[4] melted at 68–70°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.80; H, 6.67.

The yield (1.47 g.) corresponded to 0.064 mole or 12% of the theoretically possible amount.

Direct Isolation as the *p*-Nitrophenylhydrazone.—The crystalline penicillin G sodium salt used in this experiment was purified in the manner described above. It was, however, derived from an entirely different lot. The minimum penicillin G content, as determined by the N-ethyl-piperidine method, was 94%, and the potency ratio in the *B. subtilis–S. aureus* plate test was 0.99; $[\alpha]^{26}D$ +302° (c = 0.49 in water).

Anal. Calcd. for $C_{16}H_{17}N_2O_4SNa$: C, 53.92; H, 4.81. Found: C, 53.84; H, 5.11.

Ten grams of this penicillin G sodium salt was treated with 500 ml. of boiling *N* sodium hydroxide as above. Concentration of the ether extract of the acidified reaction mixture gave 3.90 g. of a semi-crystalline red mass. A portion (2.90 g., corresponding to 7.436 g. of starting material) was heated to boiling with 100 ml. water and the solution filtered to remove some reddish resin. To the hot filtrate was added a hot solution prepared by heating 0.92 g. of *p*-nitrophenylhydrazine with 18 ml. of glacial acetic acid and 55 ml. of water and filtering. The mixture became cloudy at once, and crystals appeared on heating. After cooling in the ice-box, the product was filtered off and dried. It weighed 0.95 g. and melted at 171–173°. Two recrystallizations from dioxane–water mixtures raised the melting point to 186–188° and a further recrystallization from ethanol brought it up to 188–188.5°.

Anal. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.23. Found: C, 62.24; H, 5.58.

A mixture with an authentic sample of the synthetic *p*-nitrophenylhydrazone melted at 187.5–188.5°. Based on crude product, the yield was thus 0.14 mole per mole of penicillin G degraded.

We are indebted to Dr. Al Steyermark for the microanalyses, to Dr. E. G. Wollish for the penicillin G determinations, and to Mr. B. Tabenkin for the microbiological assays.

RESEARCH LABORATORIES
HOFFMANN–LA ROCHE, INC.
NUTLEY, NEW JERSEY

RECEIVED APRIL 12, 1948

(2) S. Ruhemann, *J. Chem. Soc.*, **85**, 1451 (1904).

(3) M. S. Kharasch, Henry C. McBray and N. H. Urry, *J. Org. Chem.*, **10**, 394 (1945), report $n^{20}D$ 1.5073.

(4) A. Weltner, *Ber.*, **18**, 790 (1885).

Aminative Reduction of Ketones

BY L. HASKELBERG

Aminative hydrogenation has been used widely to convert ketones to primary amines

$$>C{=}O \xrightarrow[NH_3]{H_2\ cat.} >CH{-}NH_2$$

This paper reports a number of such conversions using ethanolic ammonia, hydrogen at about atmospheric pressure and Raney nickel. Included in this study are ketones containing an ω-diethylamino group and α,β-unsaturated ketones. The products were isolated by fractionation of the mixture, after removal of the catalyst. In most cases a higher boiling constituent, according to the analysis secondary amine, was isolated also.

For details of the experiments, see Table I.

The following general observations appear pertinent.

β-Phenylisopropylamine has been synthesized by reduction of phenylacetone oxime[1] or by interaction of the ketone itself with ammonium formate.[2] Aminative hydrogenation of phenylacetone at ordinary temperature and pressure appears to be a simpler procedure; it gives a yield of 85%.

Catalytic hydrogenation of benzalacetone and furfuralacetone leads to saturation of the C=C bond and replacement of the carbonyl group by $CHNH_2$. β-Ionone (I), too, absorbed the amount of hydrogen required for these two reactions, leading to a dihydroionylamine. By analogy, one should assign it formula (II); this structure would be in accord with the observation of Kandel[3] that catalytic hydrogenation of β-ionone (I) reduces first the carbonyl group to a secondary hydroxyl and then attacks the (exocyclic) α,β-double bond, leading to (III).

(1) Hey, *J. Chem. Soc.*, 18 (1930); Hartung and Munch, THIS JOURNAL, **53**, 1878 (1931); Jaeger and van Dijk, *C. A.*, **37**, 621 (1943).

(2) Magidson and Garkusha, *C. A.*, **35**, 5868 (1941); **38**, 4963 (1944).

(3) Kandel, Thesis, Paris, 1938.

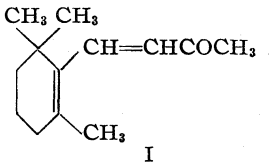
TABLE I

AMINATIVE HYDROGENATION OF KETONES[a]

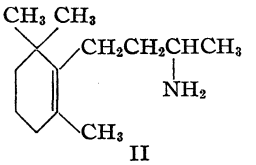
Carbonyl compound	Wt., g.	Moles	NH_3 sol.,[b] cc.	Cat.,[c] g.	Product	Yield, %	B. p., °C.	B. p., Mm.	% N Calcd.	% N Found
Phenylacetone[d]	118	0.89	400	22	$C_9H_{13}N$[e]	85	80	10	10.4	10.1
Benzalacetone[f]	29.2	.21	400	5	$C_{10}H_{15}N$[g]	67	80	4	9.4	9.4
Furfuralacetone[h]	100	.74	300	7	$C_8H_{13}ON$[i]	50	190	760[i]	10.0	10.3
β-Ionone[k]	130 (I)	.67	400	5	$C_{13}H_{25}N$[l]	93	78	0.3[m]	7.2	7.2
Diethylamino-acetone[n]	25.4	.20	100	5	$C_7H_{18}N_2$[o]	65	154	760[p]		
4-Diethylamino-2-butanone[q]	14.3	.10	100	1.5	$C_8H_{20}N_2$[r]	72	70	10		
5-Diethylamino-2-pentanone	15.7	.10	150	15	$C_9H_{22}N_2$[s]	85	196–198	755	17.8	17.9

[a] Hydrogen pressure at 1 atm. or slightly above; temperature at 20° or slightly above. [b] 17% NH_3 in ethanol. [c] Raney nickel. [d] "Organic Syntheses," Coll. Vol. II, p. 487; Bobranskii and Drabik, *C. A.*, **36**, 2531 (1942). [e] Hydrochloride, m. p. 146°. By-product: 10.2 g. (8%) bis-(1-phenylpropyl-2)-amine, $C_{18}H_{23}N$, b. p. 154° (2 mm.). Calcd.: N, 5.5. Found: N, 5.5. [f] B. p. 153° (25 mm.). [g] Previously prepared by reduction of the oxime (Harries and de Osa, *Ber.*, **36**, 2999 (1903); Bargellini, Beilstein, **12**, 1165) or phenylhydrazone [Schlenk, *J. prakt. Chem.*, **78**, 57 (1908)] of benzalacetone. Hydrochloride, from ethyl acetate, m. p. 148°. [h] Leuck and Cejka, "Organic Syntheses," Coll. Vol. I, p. 283. See also *Chem. Zentr.*, **103**, II, 2183 (1932). [i] $n^{28}D$ 1.4730. Calcd.: C, 69.0; H, 9.3; mol. wt., 139. Found: C, 68.5; H, 9.4; mol. wt., 142. By-product, 18 g. (19%) of di-(1-α-furylbutyl-3)-amine, $C_{16}H_{23}O_2N$, b. p. 128° (0.05 mm.), $n^{29}D$ 1.4942. Calcd: C, 73.5; H, 8.8; N, 5.4. Found: C, 74.0; H, 8.3; N, 5.0. [j] B. p. 102° (25 mm.). [k] B. p. 100–102° (2 mm.). [l] $n^{27}D$ 1.4800. Calcd.: C, 80.0; H, 12.8; mol. wt., 195. Found: C, 79.9; H, 12.6; mol. wt., 185. Hydrochloride, m. p. 212°, very soluble in water; chloroplatinate, m. p. 216° (dec.); picrate (from 60% ethanol), m. p. 176°. [m] B. p. 115° (30 mm.). [n] Stoermer and Dzimski, *Ber.*, **28**, 2220 (1895). [o] By-product, 1.4 g. of bis-(3-diethylaminopropyl)-2-amine, $C_{14}H_{33}N_3$, b. p. 150° (20 mm.). Calcd.: N, 17.3. Found: N, 17.3. [p] B. p. 70° (20 mm.). [q] Mannich, *Arch. Pharm.*, **255**, 261 (1917); Sohl and Shriner, THIS JOURNAL, **55**, 3828 (1933); Emerson, *ibid.*, **60**, 2023 (1938); **65**, 471 (1943); du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 56 (1937); Tuda, Hukusima and Oguri, *C. A.*, **36**, 3154 (1942). Yield, 60%, b. p. 80° (18 mm.), $n^{16}D$ 1.463, d^{24}_4 0.863. [r] d^{20}_{20} 0.826; $n^{18}D$ 1.4430. By-product, 1.1 g. of bis-(4-diethylaminobutyl-2)-amine, $C_{16}H_{37}N_3$, b. p. 152–155° (22 mm.). Calcd.: N, 15.5. Found: N, 15.5. [s] d^{20}_4 0.8296, $n^{20}D$ 1.4442. Calcd.: C, 68.3; H, 13.9. Found: C, 68.0; H, 14.0. Chloroaurate, m. p. 157°, lit. 155°. By-product, small amount of bis-(5-diethylaminopentyl-2)-amine, $C_{18}H_{41}N_3$, b. p. 152° (3 mm.). Calcd.: N, 14.0. Found: N, 14.6.

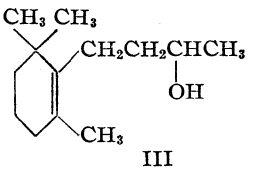
No exact proof of formula (II), however, has so far been obtained.



I



II



III

The amines of the general formula $(C_2H_5)_2N(CH_2)_nCH(NH_2)CH_3$ are usually prepared by reduction of the corresponding ketoximes.[4] It has been found that they can be obtained directly from the ketones by catalytic hydrogenation in presence of ammonia under fairly mild conditions.[5] In the case of 5-diethylamino-2-aminopentane (from 5-diethylamino-2-pentanone), the product was characterized by its known[6] chloroaurate; it is believed that the products obtained from 4-diethylamino-2-butanone and diethylaminoacetone are, analogously, 4-diethylamino-2-aminobutane and 3-diethylamino-2-aminopropane, respectively.

In each of the three cases, a higher-boiling by-product was observed in small quantities, which analyzed for the corresponding secondary amine $[(C_2H_5)_2N(CH_2)_nCH(CH_3)]_2NH$. For $n = 3$, the structure was proved by conversion into 5-diethylamino-2-aminopentane according to Grigorowski, Margolina and Magidsson[7] with 40% yield. Assignment of the analogous structures in the other two cases appears justified.

(4) (a) Magidson and Grigorowsky, *Ber.*, **69**, 401 (1936); (b) Magidson, Grigorovsky, Melnikov and Klein, *Prom. Org. Khimji*, 596 (1936); Knunyantz, Chelintzev and Osetroua Russian Patent 35,837 [*C. A.*, **29**, 8007 (1936)]; Grigorowki Russian Patent 48,203 [*Chem. Zentr.*, **108**, II, 472 (1937)]; (c) Breslow, *et. al.*, THIS JOURNAL, **66**, 1921 (1944).

(5) Breslow, Walker, Yost, Shivers and Hauser [THIS JOURNAL, **68**, 100 (1946)] carried out this reaction under high pressure.

(6) Knunjanz, Toptschijew and Tschelinzew, *Chem. Zentr.*, **106**, I, 1896 (1935).

(7) Grigorowski, Margolina and Magidsson, *ibid.*, **109**, II, 768 (1938).

WEIZMANN INSTITUTE OF SCIENCE
DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL

RECEIVED JANUARY 2, 1947

The Reaction of Benzyl Bromide with Ethyl α-Acetoxyacetoacetate

BY NATHAN GREEN AND F. B. LAFORGE

Dimroth and Schweitzer[1] have described the preparation of ethyl α-acetoxyacetoacetate and state that the sodium derivative reacts with halogen compounds, giving substitution products. The resulting compounds were not further investigated, however.

The present investigation is a study of the reaction of benzyl bromide with the sodium derivative of ethyl α-acetoxyacetoacetate, and of the behavior of the product.

The reaction with benzyl bromide proceeded normally, giving ethyl α-acetoxy-α-benzylaceto-

(1) Dimroth and Schweitzer, *Ber.*, **56**, 1381 (1923).

acetate. An acetyl determination on the product showed two acetyl groups. Attempted ketone cleavage with sodium ethylate, or even with cold dilute aqueous barium hydroxide, removed two acetyl groups and gave β-phenyllactic acid as the end-product. The reaction had therefore proceeded exclusively in the sense of the acid cleavage with simultaneous saponification of the acetoxy group. Attempts at acid hydrolysis were also unsuccessful, where the compound showed great resistance to this treatment.

It is probable that the reaction of halides with α-acetoxyacetoacetates may be generally useful in the preparation of α-hydroxy acids.

Experimental Part

Ethyl α-Acetoxyacetoacetate.[1]—Eighty-four grams of ethyl acetoacetate (0.65 mole) was dissolved in 320 ml. of benzene, and 88 g. of lead tetraacetate (0.6 mole calculated on a 100% basis) was added in several small portions with stirring, the temperature being kept below 35°. The mixture was stirred for one-half hour after the last addition, and then ice-water was added and the layers were separated. The benzene solution was washed with ice water and sodium bicarbonate solution, dried, and distilled from a modified Claisen flask. Forty-one grams (34%) of product was obtained boiling at 125–127° at 17.5 mm., $n^{25}D$ 1.4280.

The compound distills as a pale yellow liquid, which becomes colorless upon standing. It readily reduces Fehling solution in the cold. *Anal.* Calcd. for $C_8H_{12}O_5$: C_2H_5O, 23.9. Found: C_2H_5O, 23.8.

Ethyl α-Acetoxy-α-benzylacetoacetate.—Two and four-tenths grams (0.1 mole) of sodium hydride was placed in a nitrogen-swept flask with 100 ml. of dioxane, and 18.8 g. (0.1 mole) of the acetoxy compound in 40 ml. dioxane was added dropwise to the stirred mixture over a period of thirty minutes. After an additional thirty minutes 17.1 g. (0.1 mole) of benzyl bromide was added slowly, and the mixture was then refluxed for one and a half hours. The reaction mixture was poured into 1 liter of water containing sufficient acetic acid to neutralize the alkali. The heavy oil which separated was extracted twice with ether, and the ethereal solution was washed with water and then with saturated sodium chloride solution. The solution was dried, the solvent removed, and the product distilled from a modified Claisen flask. The yield was 18.6 g. (67%) of product boiling at 118–122° at 0.5 mm., $n^{25}D$ 1.4916.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52; C_2H_5O, 16.2; $2CH_3CO$, 30.9. Found: C, 64.02; H, 6.72; C_2H_5O, 16.0; CH_3CO, 26.7.

Hydrolysis of Ethyl α-Acetoxy-α-benzylacetoacetate.—The compound was unchanged by refluxing with water for one hour. Refluxing with glacial acetic acid containing a little concentrated hydrochloric acid also failed to hydrolyze the compound. Although some carbon dioxide was evolved by the process, the starting material was recovered almost quantitatively. The same was true when the compound was refluxed with 20% sulfuric acid. The products of these experiments were identified, by boiling points, refractive indices and ethoxyl analyses, as the original material.

Hydrolysis with Sodium Ethylate.—Five and one-half grams (0.02 mole) of ethyl α-acetoxy-α-benzylacetoacetate was added to 2 g. of sodium dissolved in 35 ml. of ethanol and the solution was refluxed for one hour. Most of the alcohol was removed under diminished pressure, and the residue was acidified to congo red with dilute hydrochloric acid. The solution was then saturated with sodium chloride and extracted several times with ether. On evaporation of the solvent on the steam-bath and subsequently under reduced pressure, 3.3 g. of crystalline material was obtained, which was recrystallized from benzene. The product melted at 95–96°, neutralization equivalent 166, and was identified as β-phenyllactic acid.[2]

Hydrolysis with Barium Hydroxide.—Five and one-half grams of ethyl α-acetoxy-α-benzylacetoacetate was added to 250 ml. of a 2.5% aqueous solution of barium hydroxide, and the suspension was shaken for forty-eight hours. Carbon dioxide was then passed into the solution to remove the excess alkali. After the barium carbonate had been filtered off, most of the water was removed under reduced pressure. On addition of ethanol, 5.8 g. of crude barium salt of β-phenyllactic acid was obtained.

(2) *Ber.*, **42** [4], 4892 (1909).

U. S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH ADMINISTRATION
BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
BELTSVILLE, MARYLAND
RECEIVED MAY 17, 1948

Preparation of 1,2-Dichloropropene-1

BY ERNEST H. HUNTRESS AND F. SANCHEZ-NIEVA[1]

In view of the extent of recent studies of chloro- and polychloro-olefins the paucity of reports on 1,2-dichloropropene is remarkable. This compound should exist in two geometrically stereoisomeric forms. The only record of the lower boiling stereomer is an ancient report[2] claiming its preparation from 1,2,2-trichloropropane by dehydrochlorination with alcoholic potassium hydroxide. A liquid regarded as the higher boiling stereomer was subsequently obtained[3] from α,β,β-trichloro-*n*-butyric acid by solution and heating in aqueous sodium carbonate. None of the cited papers give satisfactory details.

We have developed the preparation of the lower boiling stereomer to give readily 55–58% yields, have established certain needed physical constants, have shown that upon ozonolysis the compound yields formic and acetic acids, and that with methanol it gives an azeotrope. We did not, in this work, study the preparation of the supposed higher boiling stereomer[3] but all attempts to isomerize the lower boiling material were unsuccessful. The configuration of the two stereomers is still undetermined.

1,2-Dichloropropene-1 (*lower boiling stereomer*).—One mole of 1,2,2-trichloropropane (b. p. 123–125° at 762.4 mm., $n^{25}D$ 1.4609, obtained from 2-chloropropene-1 by addition of chlorine) was added dropwise with frequent shaking to a 25% solution of sodium methoxide (1.3–1.5 moles) in methanol kept cold in ice water. After completion of the vigorous reaction the solution was poured into a large volume of water, and the heavy insoluble layer washed, dried and distilled. Because of its much higher boiling point any unreacted trichloropropane was easily separated from the desired dichloropropene (55–58% yield).

Redistillation of the crude product through a ten theoretical plate column gave the lower boiling 1,2-dichloropropene-1, b. p. 76.8–77.0° at 757.0 mm.; d^{25}_4 1.1755, d^{20}_4 1.1818, $n^{25}D$ 1.4451, $n^{20}D$ 1.4471.

This product formed with anhydrous methanol an azeo-

(1) From part of a thesis submitted by Mr. Sanchez-Nieva in October, 1945, in partial fulfillment of the requirements for the degree of Master of Science at M. I. T.

(2) Friedel and Silva, *Compt. rend.*, **74**, 807 (1872); **75**, 81 (1872); *Bull. soc. chim.*, [2] **17**, 386 (1872); *Jahresber.*, 322, 329 (1871).

(3) Szenic and Taggesell, *Ber.*, **28**, 2667–2668 (1895).

trope, b. p. 56.5–56.8° at 760.5 mm., $n^{25}D$ 1.4030, found by comparison with a plot of $n^{25}D$/% composition for known mixtures to contain 75 weight % of lower boiling 1,2-dichloropropene.

Ozonization of the above 1,2-dichloropropene-1 in carbon tetrachloride solution at −15° followed by treatment with boiling water gave a mixture of hydrochloric, formic and acetic acids. Treatment with silver hydroxide precipitated silver chloride, oxidized the formic to carbonic acid, and thus permitted identification by the Duclaux method of the acetate in the filtrate.

The structure of the 1,2-dichloropropene-1 was confirmed by addition of chlorine at 0° in light from a 200-watt clear glass lamp, giving the saturated 1,1,2,2-tetrachloropropane, b. p. 153–155° at 774 mm., $n^{25}D$ 1.4850.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 16, 1948

The Structure of C_3F_6

BY EDMOND G. YOUNG AND WILLIAM S. MURRAY

Studies in this Laboratory involving methods of commercial feasibility for the synthesis of $CF_3CF{=}CF_2$ brought to the fore the question of the proper structure of C_3F_6 as prepared by several methods. In particular, Benning, Downing and Park[1] reported the structure of the C_3F_6 obtained from pyrolysis of "Teflon" tetrafluoroethylene polymer as being a cyclic compound. It is to be noted that Lewis and Naylor[2] report the difficult oxidation of this product to acidic substances which also suggests the cyclic structure.

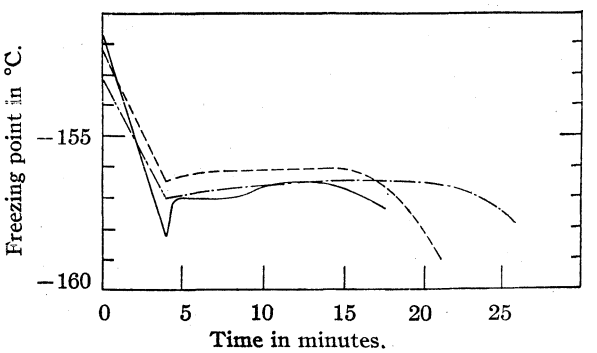


Fig. 1.—C_3F_6 products: ---, pyrolysis product; —·—, dechlorination product; ——, mixed.

It has been the purpose of this work now being reported, to establish the structure of C_3F_6 firmly and to correct any errors which have appeared in the literature.

A sample of C_3F_6 prepared by pyrolysis of tetrafluoroethylene polymer was compared with a sample of C_3F_6 prepared by the dechlorination of $CF_3CFClCF_2Cl$ with zinc and alcohol.[3] The marked similarity of these products is shown in Table I.

TABLE I

Product source	"Teflon" pyrolysis	$CF_3CFClCF_2Cl$ dechlorination
Molecular weight from vapor density	151	153
Boiling point, °C.	− 29.8	− 29.6
Freezing point, °C.	−156.2	−156.5
Mixed freezing point, °C.	156.6	

Not only is the mixed freezing point datum excellent evidence for the identity of these products (see Fig. 1), but also the infrared absorption curves of these two preparations were found to be identical. The curve for C_3F_6 is given in Fig. 2. The maximum at 5.55 microns is a positive indication of the existence of a double bond in the molecule.

Chlorination in light of the two C_3F_6 products (A) from polymer and (B) from $CF_3CFClCF_2Cl$ gave the corresponding dichlorides which were identical to each other and different from the dichloride obtained (C) by chlorination of $H(CF_2)_3$-

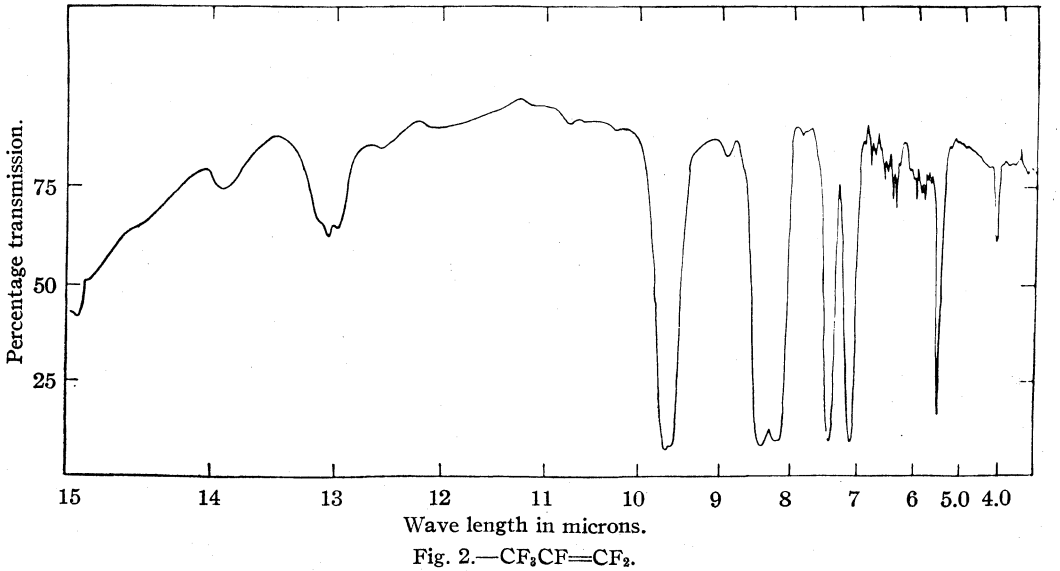


Fig. 2.—$CF_3CF{=}CF_2$.

(1) Benning, Downing and Park, U. S. Patent 2,394,581.
(2) Lewis and Naylor, THIS JOURNAL, **69**, 1968 (1947).
(3) Henne and Waalkes, *ibid.*, **68**, 496 (1946).

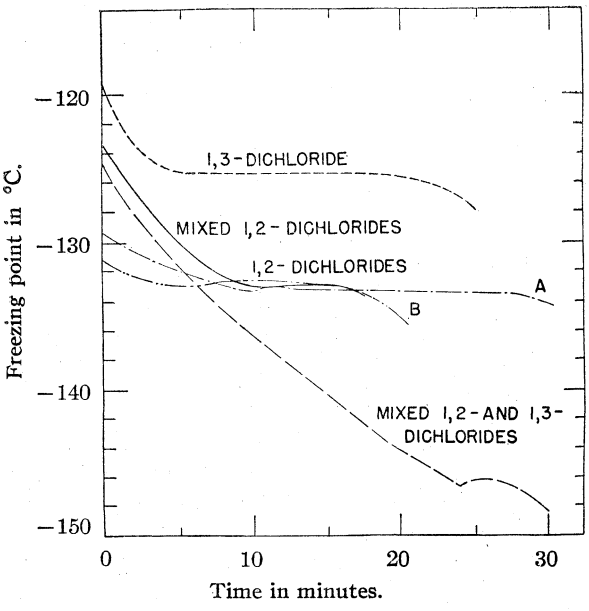


Fig. 3.—$C_3F_6Cl_2$ products.

in Fig. 4 where both A and B are represented by the single solid line.

TABLE II

COMPARISON OF $C_3F_6Cl_2$ PRODUCTS

Product	Molecular weight	Boiling point, °C.	Freezing point, °C.	Mixed freezing point, °C.
A	227.1	34.5	−132.7	−133.0
B	226.1	34.5	−133.3	
C	227.8	35.8	−125.4	−146.5
D	224.8	35.6	−126.3	−126.0

The reactions of the 1,2 and 1,3-dichlorohexafluoropropane with zinc in alcohol likewise differ in the products obtained. Although the 1,2-dichloride gave the original C_3F_6, the 1,3-dichloride gave a C_3F_6HCl which has identical infrared absorption with that of $CF_2HCF_2CF_2Cl$. The statement of Park, *et al.*,[5] that $CF_2ClCF_2CF_2Cl$ reacted with zinc to give a cyclic product must have been based upon the reaction of $CF_3CFClCF_2Cl$ obtained from pyrolysis of tetrafluoroethylene polymer, which at that time was thought to be the

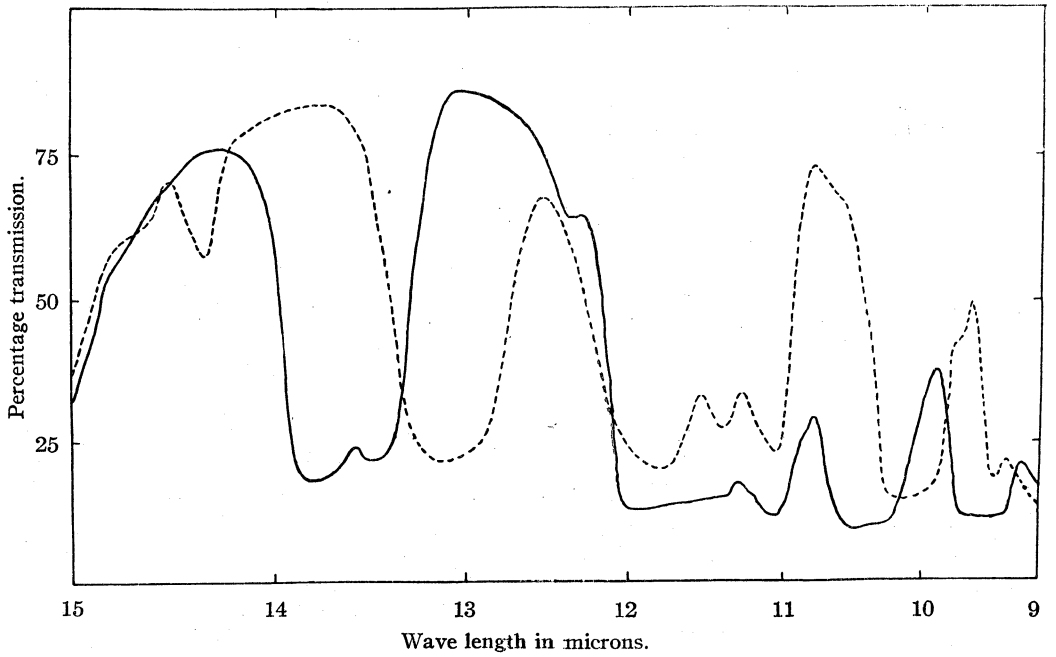


Fig. 4.— ----, 1,3-$C_3F_6Cl_2$; ——, 1,2-$C_3F_6Cl_2$.

Cl[4] and (D) by fluorination of $CFCl_2CF_2CFCl_2$. This is shown by the data given in Table II.

The freezing point curves shown in Fig. 3 not only verify the identity of A and B but also assure that the dichloride from the pyrolysis product of "Teflon" is not the same as the 1,3-dichloride. This is further corroborated by infrared absorption curves of the three $C_3F_6Cl_2$ molecules as shown

(4) Downing, Benning and McHarness, U. S. Patent 2,384,821.

1,3-dichloride, to give $CF_3CF{=}CF_2$ boiling at −30°.

There remains no doubt that C_3F_6 prepared by the pyrolysis of tetrafluoroethylene polymer is $CF_3CF{=}CF_2$ and not $\underline{CF_2CF_2CF_2}$.

JACKSON LABORATORY
E. I. DU PONT DE NEMOURS AND CO.
WILMINGTON, DEL.

RECEIVED APRIL 1, 1948

(5) Park, *et al.*, *Ind. Eng. Chem.*, **39**, 354 (1947).

On the Molecular Structure of ("Cyclic") C_3F_6

BY WALTER F. EDGELL

In line with our interest in fluorocarbons the Raman spectrum of "cyclic" C_3F_6 was determined early in 1946. The results were not published then because they were at variance with the reported "definite chemical evidence" for the cyclic structure which was later published.[1,2] Recently F. A. M. Buck and R. L. Livingston have made electron diffraction studies on this compound which also could not be interpreted with a ring model.[3] These two independent studies show clearly that this material does not have the cyclopropane structure—a conclusion also reached by other workers.[4]

Experimental Details

The Raman effect was determined in the liquid state using the spectrographic arrangement reported elsewhere.[5] The Raman tube was surrounded by an unsilvered Dewar which was maintained at low temperatures by dry air that had been passed through coils immersed in a Dry Ice–acetone slush and liquid air. The twenty Raman lines found are listed in Table I. The usual weak scattering power of fluorocarbons was observed and two of the lines listed were so weak that it would be better to consider them uncertain at present. This in no way influences the conclusions drawn.

TABLE I

THE RAMAN SPECTRUM OF C_3F_6

Description	Frequency (cm.$^{-1}$)
C=C stretching	1790 (S-)[a]
CF_3 symm. stretching	1386 (m)
CF_2 symm. stretching	1330 (m)
CF_3 assymm. stretching	1208 (m)
CF_3 assymm. stretching	1156 (m)
CF stretching	1020 (w)
CF_2 assymm. stretching	..
CF_3 symm. deformation	764 (S)
CF_3 assymm. deformation	714 (w)
CF_3 assymm. deformation	648 (S)
CF_2 rocking	607 (m)
CF_2 deformation	560 (S)
CF_2 wagging	511 (m)
CF_2 twisting	453 (vw)
C—C stretching	360 (S)
CF_3 bending	306 (vw)
CF bending	248 (w)
CF_3 bending	213 (w)
CF bending	173 (w)
C—C=C bending	140 (m)
CF_3 twisting	84 (w)

[a] S = strong, m = medium, w = weak.

TABLE II

FUNDAMENTAL VIBRATIONS OF C_3F_6 CYCLIC MODEL (D_{3h})

Description	Species	Activity[a]
CF_2 stretching	A_1'	R, p
Ring stretching	A_1'	R, p
CF_2 deformation	A_1'	R, p
CF_2 stretching	A_2''	I, $\parallel$
CF_2 rocking	A_2''	I, $\parallel$
CF_2 wagging	A_2'	Inactive
CF_2 twisting	A_1''	Inactive
CF_2 stretching	E'	R, dp; I, $\perp$
Ring deformation	E'	R, dp; I, $\perp$
CF_2 deformation	E'	R, dp; I, $\perp$
CF_2 wagging	E'	R, dp; I, $\perp$
CF_2 stretching	E''	R, dp
CF_2 rocking	E''	R, dp
CF_2 twisting	E''	R, dp

[a] R = Raman active; I = infrared active; p = polarized; dp = depolarized; $\parallel$ = parallel; $\perp$ = perpendicular.

The C_3F_6 was kindly supplied by the Jackson Laboratory of E. I. du Pont de Nemours and Co. The infrared spectrum from 2 to 15 μ was determined by Dr. J. R. Downing of the du Pont Experiment Station and appears in Table III, column 1.

TABLE III

THE INFRARED SPECTRUM OF C_3F_6 (1800 TO 750 CM^{-1})

"Cyclic" C_3F_6[a]	$CF_3CF{=}CF_2$[b]
1801 (S)	1798 (S)
1400 (S)	1398 (S)
1333 (S)	1336 (S)
1210 (S)	1210 (S)
1179 (S)	1178 (S)
1089 (S)	1035 (S)
767 (m)	767 (m)

S = strong; m = medium. [a] Origin: J. R. Downing (see text). [b] Origin: Donald G. Weiblen (see text).

Discussion of Results

The cyclic ring model, $\overline{CF_2CF_2CF_2}$, has the symmetry D_{3h} for which the selection rules and the approximate character of the vibrations, listed in Table II, may be obtained by group theoretical considerations. In contrast to the twenty Raman lines found, this model calls for but ten. To be sure this is about the number of stronger lines observed, but their frequencies do not correspond to the order of magnitude expected of a cyclic fluorocarbon.[5] Most important is the rather strong line at 1790 cm.$^{-1}$ for which no explanation seems possible in terms of this model; also five lines between 1000 and 1400 cm.$^{-1}$ are more than can be reasonably accounted for. A consideration of the C–F stretching vibrations is very significant. Experience has shown that they are found in the region *ca.* 1000 to *ca.* 1400 cm.$^{-1}$.[5–9] This model calls for three such Raman active fundamentals plus two that are infrared active—only one of which would

(1) A. F. Benning, F. B. Downing and J. D. Park, U. S. Patent 2,394,581 (1946).

(2) J. D. Park, A. F. Benning, F. B. Downing, J. F. Laucius and R. C. McHarness, *Ind. Eng. Chem.*, **39**, 354 (1947); see also Lewis and Naylor, THIS JOURNAL, **69**, 1968 (1947).

(3) F. A. M. Buck and R. L. Livingston, THIS JOURNAL, **70**, 2817 (1948). The author wishes to thank Dr. R. L. Livingston for his kindness in making his results available in advance of publication.

(4) E. G. Young and W. S. Murray, *ibid.*, **70**, 2814 (1948).

(5) Walter F. Edgell, *ibid.*, **69**, 660 (1947).

(6) Geo. Glockler and W. F. Edgell, *J. Chem. Phys.*, **9**, 224 (1941).

(7) Geo. Glockler and G. Leader, *ibid.*, **8**, 699 (1940), and others.

(8) D. H. Rank and E. L. Pace, *ibid.*, **15**, 39 (1947).

(9) J. R. Nielsen, C. M. Richards and H. L. Murray, *ibid.*, **16**, 67 (1948).

appear in both spectra. This is in complete disagreement with the data; all five frequencies in this region appear in both the Raman and infrared spectra.

It is clear that "cyclic" C_3F_6 is not hexafluorocyclopropane.

The Raman spectrum indicates a molecule which has either no symmetry or at most one element of symmetry, in which case all 21 fundamental modes of vibration would appear individually in both the Raman and infrared spectra. Molecules containing a double bond have their stretching fundamental at *ca.* 1650 cm.$^{-1}$,[10] which is shifted in polyfluorinated ethylenes to *ca.* 1750 cm.$^{-1}$.[11,12] This corresponds to the Raman line found at 1790 cm.$^{-1}$ and the infrared band at 1798 cm.$^{-1}$. Thus the spectra indicate the structure $CF_3CF{=}CF_2$!

It is difficult to predict the character of the vibrations of this molecule because of the lack of symmetry restrictions and the complexity resulting from the large interactions between the fluorine atoms. An approximate description of them based upon the neglect of coupling between the groups is found in Table I. The correlation between the expected magnitudes[5-12] and the observations is good. No definite assignment of all the frequencies can be made yet. For example, it is not clear why only five lines are found in the region where the six C–F stretching vibrations are expected. Work now under way in this Laboratory on similar molecules should throw light on these matters, however. The correlation of Table I is given solely to show that the spectrum has the proper number of lines in the proper spectral region for such a model.

In order to conclusively demonstrate that "cyclic" C_3F_6 is in reality hexafluoropropylene, the infrared spectrum between 2 and 15μ of an authentic sample of $CF_3CF{=}CF_2$ is included in Table III, column 2. It is identical with that for "cyclic" C_3F_6. This spectrum was obtained and furnished by Mr. D. G. Weiblen of the Central Research Department, Minnesota Mining and Manufacturing Company, using material prepared by Lyle Hals of that laboratory.

It is now clear why the physical properties of $CF_3CF{=}CF_2$[13] are so close to those earlier reported for "cyclic" C_3F_6.

Acknowledgment.—The author is indebted to Dr. A. F. Benning who furnished the infrared spectrum and sample of C_3F_6. Thanks are also due to Mr. D. G. Weiblen for the infrared spectrum of hexafluoropropylene.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

RECEIVED MAY 3, 1948

(10) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Company, Inc., New York, N. Y., 1945, p. 195.

(11) J. B. Hatcher and D. M. Yost, *J. Chem. Phys.*, **5**, 992 (1937).

(12) P. Torkington and H. W. Thompson, *Trans. Faraday Soc.*, **41**, 236 (1945).

(13) Henne and Waalkes, THIS JOURNAL, **68**, 496 (1946).

The Identification of C_3F_6[1]

BY F. A. M. BUCK AND R. L. LIVINGSTON

The compound C_3F_6, obtained by pyrolysis of polytetrafluoroethylene and by pyrolysis of monochlorodifluoromethane has been reported to be hexafluorocyclopropane[2,3] although some doubt as to its identity has been expressed.[4] Interpretation of electron diffraction photographs of this compound has led us to the conclusion that the compound is not hexafluorocyclopropane but is hexafluoropropene. This conclusion has been reached independently by other workers.[5,6]

The electron diffraction photographs[7] were prepared using an apparatus built by Professor H. J. Yearian of the Purdue Physics Department. The sample of C_3F_6 was kindly supplied by Drs. Young and Benning of the Jackson Laboratory of E. I. du Pont de Nemours and Company. Diffraction maxima were observable on the photographs out to $s = 33$ ($s = 4\pi/\lambda \sin \theta/2$). A radial distribution curve (Fig. 1) was calculated using essentially a method previously described.[8] The five prominent peaks of this curve at 1.32, 2.16,

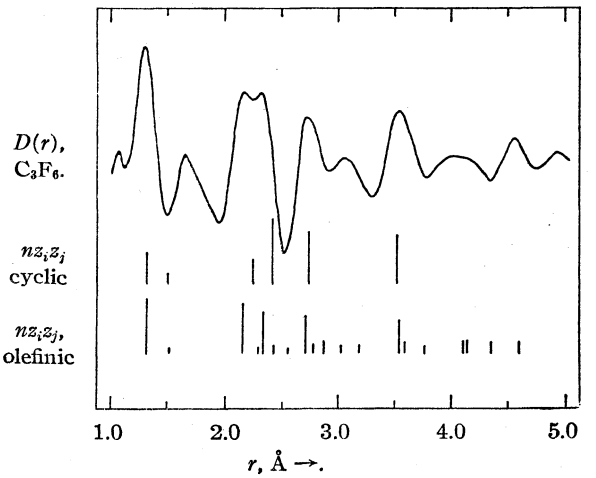


Fig. 1.—Radial distribution curve for C_3F_6. The lines under the curve correspond to bond distances in models of hexafluorocyclopropane and hexafluoropropene; the lengths of the lines indicate the relative weights, nz_iz_j, of the corresponding terms in the simplified intensity function.

(1) From the Ph. D. thesis of F. A. M. Buck, duPont Fellow in Chemistry, Purdue University.

(2) A. F. Benning, F. B. Downing and J. D. Park, U. S. Patent 2,394,581 (February 12, 1946).

(3) J. D. Park, A. F. Benning, F. B. Downing, J. F. Laucius and R. C. McHarness, *Ind. Eng. Chem.*, **39**, 354 (1947).

(4) E. E. Lewis and M. A. Naylor, THIS JOURNAL, **69**, 1968 (1947).

(5) W. F. Edgell, *ibid.*, **70**, 2816 (1948). We appreciate the cooperation of Dr. Edgell in making his data available in advance of publication.

(6) E. G. Young and W. S. Murray, *ibid.*, **70**, 2814 (1948).

(7) For a general review of the method of electron diffraction, see L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

(8) R. Spitzer, W. J. Howell and V. Schomaker, THIS JOURNAL, **64**, 62 (1942).

2.34, 2.70, and 3.54 Å. are not compatible with any cyclic model having D_{3h} symmetry. The bond distances in one cyclic model are indicated by vertical lines under the radial distribution curve; other cyclic models disagree with the curve to about the same extent or to a greater extent. Also the theoretical intensity curves for cyclic models are incompatible with the observed pattern.

We have succeeded in finding a model for hexafluoropropene which gives very good agreement with the prominent peaks on the radial distribution curve. This agreement is indicated under the curve by vertical lines representing bond distances in this model. In addition the theoretical intensity curve for this model agrees qualitatively with the photographs and the average of the $s_{calcd.}/s_{obs.}$ (for eleven features which may be confidently compared) is 0.999 with an average deviation of 0.006. Further work is necessary in order to determine the accuracy with which the various parameters in the molecule can be evaluated. The identity of the compound, however, seems clearly established.

We wish to thank Professor Yearian for the use of his diffraction apparatus and for many helpful discussions. We are also grateful to E. I. du Pont de Nemours and Company for the free grant fellowship which made this work possible.

CONTRIBUTION FROM THE
PURDUE RESEARCH FOUNDATION AND THE
DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY RECEIVED MAY 3, 1948

Maxima in Vapor Pressure Curves

BY A. E. KORVEZEE AND P. DINGEMANS

Recently N. B. Keevil[1] has given the vapor pressures of aqueous solutions of a number of salts over an extensive temperature range. In case of highly soluble salts, maxima occur in the vapor pressure curves and the author stresses the point that the maxima lie at increasing temperatures with increasing melting point of the salts.

We have found analogous results for a series of salts with lower melting points. Moreover we have derived[2] the approximate expression

$$\frac{1}{T_{max}} = \frac{1}{T_s} + 0.00021.$$

T_s = melting point of the sale (absolute temperature)
T_{max} = absolute temperature of the maximum.

This expression is derived for ideal solutions, but it proves to give also fairly trustworthy results for the temperature of the pressure maxima even for our saturated salt solutions. The relation given is also valid for vapor pressure curves of solutions saturated with respect to two or more salts, in which case T_s = the eutectic temperature of the salt mixture.[3] A number of examples are to be found in our publications.[4]

We have applied our formula to those of Keevil's curves, for which the temperature of the maximum and the melting point of the salt have been directly determined. The results are collected in Table I.

TABLE I

Salt	Melting point, °C.	Temperature of the maximum, °C. measured	calculated
NaCl	804	600	606
NaBr	755	570	573
KCl	770	565	582

From the figures given it is clear that a fairly accurate estimation of the temperature of the maximum in the vapor pressure curve can be derived from melting point data with the aid of our formula.

(1) N. B. Keevil, THIS JOURNAL, **64**, 841 (1942).

(2) A. E. Korvezee and P. Dingemans, *Rec. trav. chim.*, **62**, 653 (1943).

(3) A. E. Korvezee, P. Dingemans and L. L. Dijkgraaf, *ibid.*, **66**, 389 (1947); A. E. Korvezee, *ibid.*, **66**, 549 (1947).

(4) P. Dingemans, *et al.*, *Rec. trav. chim.*, **56**, 839 (1937); **58**, 574 (1939); **60**, 317 (1941); **61**, 605 (1942); **62**, 85 (1943); **62**, 625 and 639 (1943); **64**, 194 and 199 (1945); **65**, 477 (1946); **66**, 239 (1947).

CHEMICAL LABORATORY OF THE TECHNICAL UNIVERSITY
DELFT, HOLLAND RECEIVED APRIL 3, 1948

The Preparation of Allyl Iodide[1]

BY R. L. LETSINGER AND JAMES G. TRAYNHAM

Reported methods for the preparation of allyl iodide involve the reaction of allyl alcohol or glycerol with either hydriodic acid or phosphorus and iodine.[2] We find that preparative quantities of allyl iodide may be obtained very conveniently by the action of sodium iodide on allyl chloride in acetone. This preparation is based on a reaction investigated kinetically by Conant, Kirner and Hussey.[3]

A mixture made of 0.6 mole (45.9 g.) of allyl chloride, 0.75 mole (113 g.) of sodium iodide, and 100 cc. of acetone was warmed on the steam-bath for three hours and then poured into 500 cc. of water. The organic layer was separated, washed with both a dilute sodium bisulfite solution and with water, dried over sodium sulfate, and distilled. The yield of allyl iodide (b. p. 101–102°, d^{22}_4 1.8454, $n^{22}D$ 1.5542) was 63.1 g. (62.6%). When the reflux time was increased to twenty-four hours and 200 cc. of acetone was used as solvent, the yield was increased to 76.7%.

(1) This investigation was supported by a grant from the Abbott Fund of Northwestern University.

(2) McCullough and Cortese, THIS JOURNAL, **51**, 226 (1929); Norris, Watt and Thomas, *ibid.*, **38**, 1076 (1916); Datta, *ibid.*, **36**, 1005 (1914); Tollens and Henninger, *Ann.*, **156**, 156 (1870).

(3) Conant, Kirner and Hussey, THIS JOURNAL, **47**, 488 (1925).

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED FEBRUARY 4, 1948

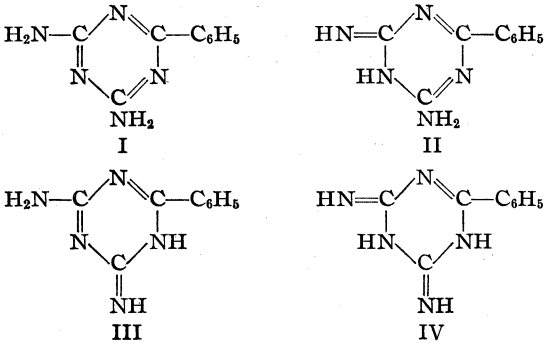
Absorption Spectra of 4,6-Diamino-2-phenyl-1,3,5-triazine

BY FREDERICK C. NACHOD AND EDGAR A. STECK

Although 1,3,5-triazine derivatives have been the subject of many investigations, relatively few

physico-chemical measurements have been made with compounds of this class.[1-7] Of these, only one group of absorption spectra has been reported,[6] referring to cyanuric acid types, as well as at an early date. As a portion of some other investigations, the spectral characteristics of 4,6-diamino-2-phenyl-1,3,5-triazine became of interest. The compound (I) was prepared by the reaction of benzonitrile with dicyandiamide in the presence of piperidine,[8] being an improvement over earlier work.[9,10]

The tautomeric states possible in 4,6-diamino-2-phenyl-1,3,5-triazine are indicated in the structures I–IV. The two mono-imino forms (II and III) are twice as likely of being the more probable



structures of the compound because only one diamino and only one di-imino structure can be formulated (I and IV). This may also account for the fact that only monohydrochlorides are formed in this type.[11,12]

Ultraviolet absorption spectra of 4,6-diamino-2-phenyl-1,3,5-triazone solutions shown in Fig. 1[13] clearly indicate that at *p*H 7 and 13 essentially the same maxima and minima are attained. On passing to *p*H 1, however, a marked batho- and hypochromic shift is to be observed. This indicates that the degree of conjugation is diminished and Table I, which lists the actual values for the maxima obtained, further emphasizes the differences in spectra. The shifting could easily be interpreted as the result of a favoring

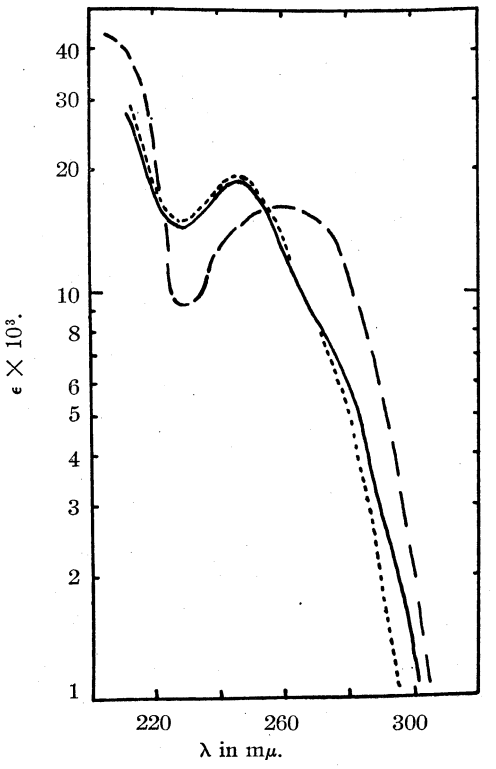


Fig. 1.—Spectrum of 4,6-diamino-2-phenyl-1,3,5-triazine monohydrochloride in — ethanol (95%) and in water, — — 0.01 *N* NaOH, ---- 0.01 *N* HCl.

of structure (IV) in strongly acidic solution as the preferential form. However, in the crystallization of the hydrochloride, the more probable forms (II) and (III) are predominant. Although the structures (II) and (III) are not equivalent, presumably they do have nearly the same energy content and may be present in a solid solution or hydrogen-bonded condition in the solid state.

TABLE I

MAXIMA OF 4,6-DIAMINO-2-PHENYL-1,3,5-TRIAZINE

Solvent	λ, in mμ	ε × 10³
95% Ethanol	244	18.6
Water	244	18.6
0.01 *N* NaOH	247	19.2
0.01 *N* HCl	255–261	16.2

THE STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK RECEIVED APRIL 20, 1948

(1) Lemoult, *Compt. rend.*, **121**, 352 (1895); **125**, 822 (1897); *Ann. chim.*, [7] **16**, 348, 372, 410 (1899); *Bull. soc. chim.*, [3] **13**, 1024 (1895).

(2) Hantzsch, *Ber.*, **39**, 145 (1906).

(3) Wightman and Jones, THIS JOURNAL, **39**, 1752 (1917).

(4) Böeseken, *Rec. trav. chim.*, **37**, 147 (1917).

(5) Wood, *J. Chem. Soc.*, **83**, 576 (1903).

(6) Hartley, *ibid.*, **41**, 48 (1882); Hartley, Dobbie and Lauder, *ibid.*, **79**, 848 (1901).

(7) Kahovec, *Monatsh.*, **72**, 364 (1939).

(8) Zerweck and Brunner, U. S. Patent 2,302,162.

(9) Ostrogovich, *Atti reale accad. Lincei*, [5] **20**, I, 182, 251 (1911).

(10) Rackmann, *Ann.*, **376**, 181 (1910).

(11) The compound was purified and used as the monohydrochloride monohydrate, needles from aqueous alcohol, m. p. 246–247°, dec. *Anal.* Calcd. for $C_9H_9N_5 \cdot HCl \cdot H_2O$; N, 28.98; Cl, 14.67. Found: N, 28.68; Cl, 14.82. Ostrogovich[9] reported this compound but gave no melting point.

(12) Ostrogovich and Gheorghiu, *Gazz. chim. ital.*, **60**, 648 (1930).

(13) The spectra were determined with a Beckman quartz spectrophotometer, Model DU, Serial No. D-377, as in our earlier studies [*e. g.*, Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946)].

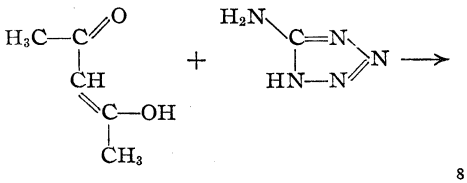
Absorption Spectra of 5,7-Dimethyltetrazolo(a)-pyrimidine

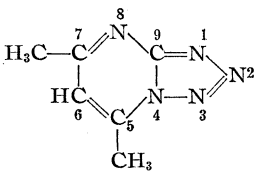
BY FREDERICK C. NACHOD AND EDGAR A. STECK

The interest in the absorption spectral behavior of 5,7-dimethyltetrazolo[a]pyrimidine resulted from certain aspects of related heterocyclic studies. The compound, named 5,7-dimethyl-1,-2,3,4-tetraazaindolizine by Bülow,[1] is now des-

(1) Bülow, *Ber.*, **42**, 4433 (1909).

ignated as above according to the system employed in the "Ring Index."[2] It has not been studied further since its preparation from 5-aminotetrazole and acetylacetone in the presence of piperidine, the method which was also employed in this work.[3]





I

From an examination of the spectra of 5,7-dimethyltetrazolo[a]pyrimidine shown in Fig. 1,[4] a tremendous batho- and hyperchromic shift is to be noted in comparing the spectrum at *p*H 13 with that in neutral and acidic solutions. As the

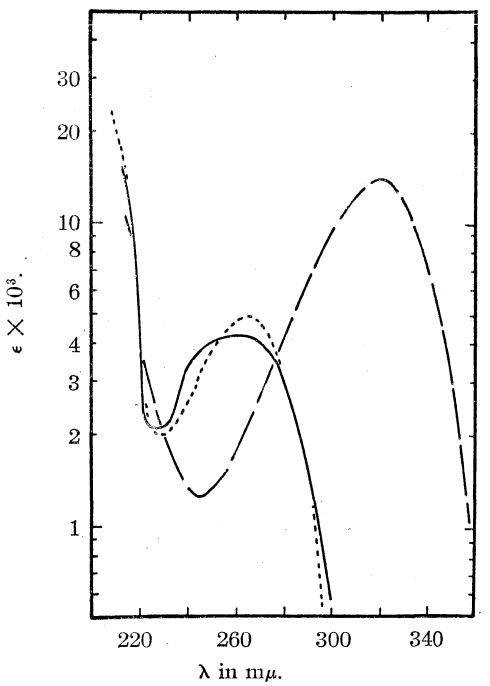
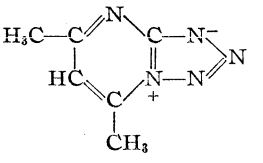
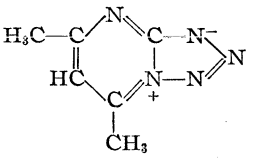


Fig. 1.—Spectra of 5,7-dimethyltetrazolo[a]pyrimidine in — ethanol (95%), ---- 0.01 *N* HCl, — — 0.01 *N* NaOH.

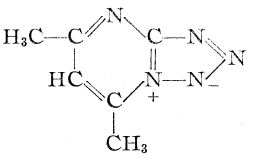
nitrogen atoms do not bear any hydrogen [atoms], a classical picture on the basis of tautomeric shifts cannot be developed. However, if one admits ionic structures,[5] this behavior can apparently be explained satisfactorily. The dipolar ions ("Zwitterions") shown in (II) to (V) contribute to the arrangement of the compound in acid, and, to a somewhat lesser extent, in neutral solution. These considerations would lead one to expect that the resulting spectrum, with respect to the position of the maximum, should be similar to that of a benzenoid ring with a conjugated double bond. Indeed, a measure of similarity to the spectra of styrene,[6] indole,[7] benzotriazole[8] and even benzoxazole[9] is observable. In alkaline medium, however, this polarization tendency, due to the addition of protons in position 1 or 3, disappears and the structure (I) is the only one remaining. Such a spectrum should more closely resemble that of a polyene and shift the absorption maximum toward the visible range. This is borne out by the similarity of the spectrum of 5,7-dimethyltetrazolo[a]pyrimidine in alkali with that of 1,3,5,7-octatetraene which was studied by Kovner[10] and Hausser.[11] Both of the compounds have four conjugated double bonds and a "maximum extinction coefficient" beyond 300 mμ.



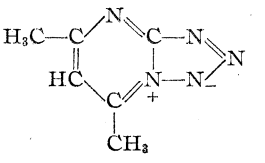
II



III



IV



V

(2) Patterson and Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940.

(3) The authors wish to express their appreciation to Miss R. Pauline Brundage for her preparation of the compound.

(4) All spectral determinations were made with a Beckman quartz spectrophotometer, Model DU, Serial No. D-377, as in earlier work [*cf.* Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946)].

(5) The authors are grateful to Dr. Elmer J. Lawson for his helpful discussion on the formation of dipolar ions.

(6) Elliott and Cook, *Ind. Eng. Chem., Anal. Ed.*, **16**, 20 (1944); Rodebush and Feldman, THIS JOURNAL, **68**, 896 (1946).

(7) Johnson, Bruce and Dutcher, *ibid.*, **65**, 2005 (1943).

(8) Specker and Gawrosch, *Ber.*, **75B**, 1338 (1942).

(9) Ramart-Lucas and Vantu, *Bull. soc. chim.*, [5] **146**, 1165 (1936).

(10) Kovner, *Acta Physicochim.* (*U.R.S.S.*), **19**, 385 (1944). *Cf.* also Ferguson and Branch, THIS JOURNAL, **66**, 1467 (1944).

(11) Hausser, *Z. techn. Physik*, **15**, 10 (1934).

THE STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y. RECEIVED APRIL 20, 1948

Remarks on the Physico-Chemical Mechanism of Muscular Contraction and Relaxation

BY JACOB RISEMAN AND JOHN G. KIRKWOOD

The physico-chemical processes underlying the contraction and relaxation of muscle have been the subject of much speculation. Recently significant analogies between the elastic behavior of muscle and that of rubber and synthetic elastomers have

been investigated by Bull[1] and others. That the structure of striated muscle, and possibly smooth muscle, is much more ordered than those of elastomeric cross-linked high polymers is clearly demonstrated by the studies of Schmitt and his collaborators.[2] Nevertheless, important aspects of structural similarity exist. The basic structural unit of the muscle fibril is considered to be the linear polypeptide chain of the myosin or actomyosin molecule. Like the segments of a polymer network, the long polypeptide chain possesses many internal rotational degrees of freedom which allow it to gain configurational entropy on contraction. Therefore it is probable that the elastic modulus of a structure composed of such elements is in part determined by the dependence of their configurational entropy upon elongation.

The contraction or relaxation of a muscle segment under constant stress is the consequence of a change in the elastic modulus arising from alteration of its structural units. Following certain ideas suggested by the work of K. H. Meyer,[3] we wish to examine the hypothesis that the essential alteration of the structural unit, leading to a change in modulus, is a change in its net electric charge. A structural unit consisting of a long polypeptide chain can gain or lose electric charge in several ways in response to changes in its physico-chemical environment. If the absolute magnitude of the charge, whatever the sign, is increased, electrostatic repulsion between the elementary charges comprising the increment will decrease the elastic modulus by destroying the balance between the external stress and the contractile force arising from configurational entropy. Conversely, if the magnitude of the charge is decreased, the modulus will increase. According to this view, the relaxed state of muscle is an electrically charged state and the contracted state one in which the polypeptide chains are in an uncharged or "isoelectric" condition. We shall presently make some rough estimates of the change in elastic modulus produced by electrostatic repulsion between charges distributed at intervals along a polypeptide chain, after discussing possible mechanisms by which it might gain or lose charge.

Since a polypeptide chain is an ampholyte, it can gain or lose charge in response to a change in the *p*H of its environment. This mechanism was proposed by K. H. Meyer[3] as a basis for the analysis of the energetics of muscular relaxation and contraction. Meyer's proposal was rejected by Weber[4] on grounds which still must be regarded as inconclusive. Adsorption of cations, for example potassium, by actomyosin segments provides a second method of charging, which the work of St. Gyorgi suggests may play a role.[5] Nevertheless, both of these charging mechanisms leave obscure the manner in which the chain of carbohydrate oxidation reactions supplies free energy for the muscular processes.

We are inclined to the view that phosphorylation of the hydroxy amino acid residues of the myosin or actomyosin molecule by adenosine triphosphate provides a charging mechanism in best accord with known facts. From its amino acid analysis, myosin is known to contain a large proportion of hydroxy amino acid residues; serine, 3.9%; and threonine, 4.95%.[6] Myosin is also considered to be one of the enzymes involved in the dephosphorylation of ATP to ADP and inorganic phosphate. Assuming that the first step in the dephosphorylation of ATP consists in the phosphorylation of the $-OH$ groups of the hydroxy amino acid residues of the myosin molecule, we conclude that at a *p*H of 7, the approximate *p*H of the sarcoplasm, each $-H_2PO_4$ group will be approximately singly ionized to $-HPO_4^-$. Thus the phosphorylation process would impart to the neutral sites originally occupied by $-OH$, approximately one unit of negative charge. The extension of the myosin chain and that of the structure of which it is the unit, resulting from electrostatic repulsion between the negatively charged $-HPO_4^-$ groups, stores up the free energy, released in the degradation of the high energy phosphate bond of ATP, in the form of negative configurational entropy of extension. Subsequent dephosphorylation of the myosin molecule with release of inorganic phosphate ion to the sarcoplasm would remove negative charge from the molecule and release the stored free energy as mechanical work in contraction of the structure. The coupling between the carbohydrate oxidation process and the mechanical processes of muscle activity is thus clarified by the proposed mechanism. ATP, regenerated in the chain of oxidation reactions, serves as a carrier of free energy released in these reactions to the myosin units of the muscle structure.

In order to examine the quantitative implications of our hypothesis, we will make some rough estimates of the change in elastic modulus E of a flexible linear molecule produced by attaching electric charges of equal magnitude at equal intervals along its length. If the terminal groups of the molecule are separated by a distance L and n charges of the same sign and magnitude e are attached to the chain at points separated by equal numbers of bonds, the random coil model of a flexible linear molecule leads to the following approximate estimate of the increment in elastic modulus ΔE, produced by the charge increment ne

(1) H. B. Bull, THIS JOURNAL, **67**, 2047 (1945).

(2) F. O. Schmitt, M. A. Jakus and C. E. Hall, *Biol. Bull.*, **90**, 32 (1946); M. A. Jakus and C. E. Hall, *J. Biol. Chem.*, **167**, 705 (1947).

(3) K. H. Meyer, *Biochem. Z.*, **214**, 1 (1929).

(4) H. H. Weber, *ibid.*, **217**, 430 (1930).

(5) A. St. Gyorgi, "Chemistry of Muscular Contraction," Academic Press, Inc., N. Y., 1947, p. 30.

(6) M. L. Anson and J. T. Edsall, "Advances in Protein Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1944, p. 310.

$$\Delta E = -\frac{8}{3}\frac{N\rho}{M}\frac{n^2e^2}{D_eL}$$

where D_e is an effective dielectric constant, N is Avogadro's number, M the molecular weight of the linear molecular unit of the structure and ρ is the density of the structure, regarded as a three-dimensional network with L the average distance between net points. Since electrostatic interactions between the charges of neighboring chain segments are neglected and other gross approximations have been employed in its derivation, Eq. (1) is intended to provide no more than an estimate of the order of magnitude of ΔE.

The elastic modulus of muscle[1] is of the order of magnitude 10^5 dynes/sq. cm. In order to produce a change of this order of magnitude by charging the structural units, we estimate from Eq. (1) a magnitude of n of the order of 100, with the rough assignments of value $\rho = 1$, $M = 10^6$, $L = 10^4$A, $D_e = 100$ to the other parameters. The values of L and M are those determined for the myosin or actomyosin molecule in solution, and D_e is assumed to be of the order of magnitude of the dielectric constant of water. The estimated number of charges would require phosphorylation sites situated at intervals of 100 Å. along the myosin or actomyosin molecule. This value is not inconsistent with the hydroxy amino acid content of myosin.

The observation of Needham[7] that the flow birefringence of myosin solutions is diminished by the addition of ATP seems at first to be in contradiction with our hypothesis. However, it seems that the effect was observed under conditions leading to the dissociation of actomyosin into actin and myosin, according to St. Gyorgi.[5]

We have deliberately avoided placing undue emphasis on hypothetical structural details of muscle and on the detailed analogy between the elastic properties of muscle and elastomers. The essential qualitative aspects of our suggestions, (a) change in the elastic modulus of the structure due to alteration of the electric charge of the structural unit, considered to be a polypeptide chain rich in hydroxy amino acid residues; (b) charging of the structural unit through phosphorylation of the hydroxyl groups by ATP, are to a large extent independent of assumed structural details.

(7) J. Needham, Shih-Chang Shen, D. Needham and A. S. C. Lawrence, *Nature*, **147**, 766 (1941).

INSTITUTE FOR HIGH POLYMER RESEARCH
BROOKLYN POLYTECHNIC INSTITUTE
BROOKLYN, NEW YORK RECEIVED APRIL 3, 1948

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA

Purification of N-Hydroxymethylphthalimide through a Molecular Compound with Pyridine

BY EUCLID J. SAKELLARIOS

In connection with the synthesis of N-alkylated phthalimides, we have prepared N-hydroxymethylphthalimide. This compound was first prepared by Sachs[1] by the hydrolysis of N-bromomethylphthalimide. It was later prepared by Sachs[2] from formaldehyde and phthalimide in sealed tubes and by Buc[3] from the same reactants at atmospheric pressure. The melting points reported by these authors were 141–142°, 139–140° and 137–141°, respectively. Buc also reported that the melting point is not improved by crystallization from ethanol.

We attempted to eliminate the impurities by adding about 1 g. of fuller's earth per 100 ml. of solution in Buc's procedure. This yielded a product melting at 144–145° which was, however, still not pure.

A product of high purity melting at 149.5° was finally obtained through an unstable, previously unreported complex formed from N-hydroxymethylphthalimide and one mole of pyridine.

Chloro-, bromo- and iodomethylphthalimides were prepared from the pure compound and the appropriate halogen acid. In all cases the products had higher melting points than those previously reported.

Procedure.—A solution obtained by warming 17.7 g. of N-hydroxymethylphthalimide[3] in 30 ml. of pure pyridine was filtered, if necessary, and left to crystallize. If crystallization did not occur, seed crystals were obtained by placing a few drops of the solution in a desiccator over sulfuric acid. As soon as the first crystals appeared, they were added to the solution. The new compound crystallized in long, bright needles which after cooling in an ice-bath were filtered with suction.

To determine the pyridine the crystals were dried briefly on a porous plate over calcium chloride. A weighed sample was then dried in vacuum over sulfuric acid. The crystals gradually lost their brightness and came to constant weight after twenty-four hours.

Anal. Calcd. for $C_6H_7O_3N \cdot C_5H_5N$: pyridine, 30.58. Found: pyridine, 30.68.

The residue melts at 148.5–149°. One crystallization from acetone brings the m. p. to 149.5°.

Anal. Calcd. for $C_6H_7O_3N$: N, 7.91. Found: N, 7.88.

The halogenomethylphthalimides were prepared essentially according to Gabriel,[4] heating at 50° for one hour after the crystals separated. The crystals were filtered, washed with the appropriate acid and then dried over sulfuric acid and potassium hydroxide. The results obtained are summarized in the table.

TABLE I

N-HALOMETHYLPHTHALIMIDES

Compound	Yield crude, %	Crystn. solvent	M. p., °C. Obs.	M. p., °C. Prev.[a]
Chloro-	93	Ethyl acetate	136.5	132–133[4]
Bromo-	91.1	Ethyl acetate	151.5	149–150[5]
Iodo-	92.3	Benzene–ethyl acet.	155.5	153[5]

[a] Best previously reported.

RESEARCH LABORATORY
THE PIRAEUS DYE WORKS
(FORMERLY S. A. OECONOMIDES AND CO.)
NEW PHALERON, NEAR PIRAEUS
ATHENS, GREECE RECEIVED FEBRUARY 24, 1948

(1) Sachs, *Ber.*, **31**, 1231 (1898).
(2) Sachs, *ibid.*, **31**, 3230 (1898).
(3) Buc, THIS JOURNAL, **69**, 254 (1947).
(4) Gabriel, *Ber.*, **41**, 242 (1908).
(5) Gabriel, *Ber.*, **31**, 1229 (1898).

Some Diacid Salts of Aminoguanidine and Methyl Aminoguanidine[1]

BY JOHN J. PITHA,[2] HARRY HUGHES, JR., AND G. B. L. SMITH[3]

There are some references in the literature to diacid salts of aminoguanidine. Lieber and Smith[4] mention aminoguanidinium dinitrate and aminoguanidinium dichloride, but give no details of the preparation. In another article, Thiele[5] also mentions the preparation of aminoguanidinium dinitrate. In this same article, Thiele also mentions the preparation of neutral aminoguanidine sulfate as well as diaminoguanidine sulfate. This present article reports a generalized method for the preparation of these and other diacid salts of aminoguanidine. This procedure is also applied in the preparation of a diacid salt α-methyl-γ-aminoguanidine. The melting points of the salts prepared are included.

Experimental

Aminoguanidinium bisulfate (0.1 mole) was dissolved in 100 ml. of hot water and to this was added a solution containing 0.1 mole of the barium salt of the acid corresponding to the diacid salt in preparation. To the above mixture was added a considerable excess of the corresponding concentrated acid. After one hour digestion on a hot plate, the barium sulfate was separated by filtration and the filtrate was evaporated on a steam-bath until crystallization started. The solution was then cooled and the crystals separated by filtration, dried *in vacuo*, and analyzed.

The methylaminoguanidine was prepared from methyl nitroguanidine by the method of Lieber and Smith.[6] Methylaminoguanidine bicarbonate was prepared by treating the methylaminoguanidine acetate obtained in the above reaction with potassium bicarbonate and carbon dioxide in isopropyl alcohol at a temperature of $-10°$. A 99% yield was obtained and the melting point of the bicarbonate was observed to be 151.5–152°.

To 6 g. of methylaminoguanidine bicarbonate (0.04 mole) in 60 g. of isopropyl alcohol was added 32 g. (0.32 mole) of 37% hydrochloric acid. The solution was treated with carbon black and filtered. After cooling to $-18°$, needle-like crystals separated out in clusters. These crystals were removed by filtration, washed with cold solvent, dried *in vacuo* for eighteen hours and analyzed. This material proved to be α-methyl-γ-aminoguanidinium dichloride.

Table I lists the diacid salts of aminoguanidine and α-methyl-γ-aminoguanidine prepared, their analyses and their melting points.

From these experiments it seems that aminoguanidine and α-methyl-γ-aminoguanidine will accept two protons in strongly acid solutions. Further work is in progress to gain more knowledge of the ionic species that exist in water solutions of these salts.

TABLE I

		% N_2H_4 Found[a]	% N_2H_4 Calcd.	% Anion Found	% Anion Calcd.	Melting point, °C.
AG.[b]	Dichloride	21.52	21.95	47.80	47.92	183–183.5
AG.	Dibromide	13.84	13.58	67.33	67.76	200–205
AG.	Diiodide	12.23	12.02	76.19	76.93	115–118
AG.	Dinitrate	16.02	16.34	61.97[c]	61.98	168 dec.
MAG.[d]	Dichloride	19.96	19.89	43.87	44.06	170.5–174

[a] By the method of Smith and Wheat.[7] [b] Aminoguanidinium. [c] By nitron precipitation. [d] α-Methyl-γ-aminoguanidinium.

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, NEW YORK RECEIVED FEBRUARY 5, 1948

(1) This paper is abstracted from the theses submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn by Mr. Pitha and Mr. Hughes in June, 1942, and June, 1944, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(2) Present address: Kedzie Chemical Laboratories, Michigan State College, East Lansing, Mich.

(3) Present address: Inorganic Chemistry Section, Science Department, U. S. Naval Ordnance Test Station, Inyokern, California.

(4) Lieber and Smith, *Chem. Rev.*, **25**, 217 (1939).

(5) Thiele, *Ann.*, **270**, 28 (1892).

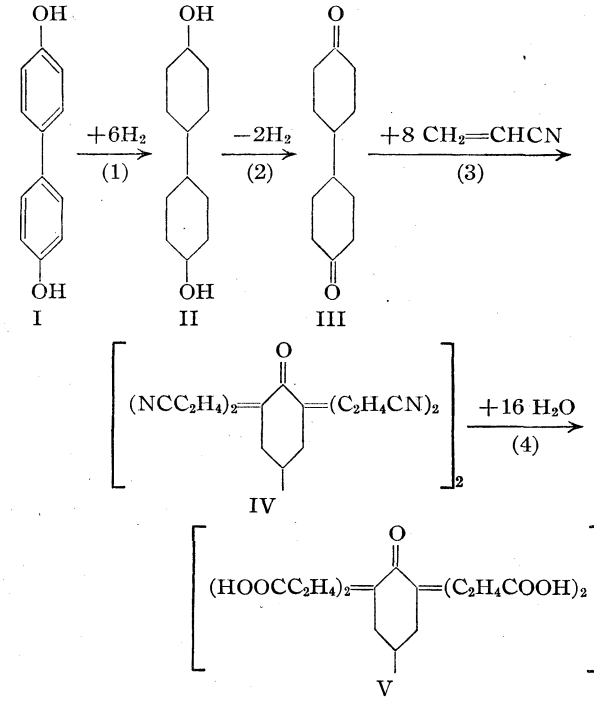
(6) Lieber and Smith, THIS JOURNAL, **59**, 2287 (1937).

(7) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

Synthesis of an Octabasic Carboxylic Acid

BY J. R. SCHAEFGEN AND P. J. FLORY

Dicyclohexanoneoctapropionic acid (V) has been prepared for use as the multifunctional reactant in the synthesis of octachain polymers.[1] This acid is of interest because, so far as we are aware, it is the first example of a stable octabasic carboxylic acid.[2] It has been synthesized from *p,p'*-diphenol (I) by the following series of reactions.



The over-all yield was about 6%. Complicating side reactions occurring in steps (1) and (2) are largely responsible for the low yield. Compounds III, IV and V are new.

(1) J. R. Schaefgen and P. J. Flory, THIS JOURNAL, **70**, 2709 (1948).

(2) Beilstein, "Handbuch der organischen Chemie," IV ed., Vol. IX, 1st Suppl., Julius Springer, Berlin, 1932, p. 446, lists diphenyloctacarboxylic acid—(2,4,5,2',4',5,'x,x) which, however, loses carbon dioxide and water when heated to 110°.

Experimental

4,4'-Diketodicyclohexyl (III).—Crude 4,4'-dihydroxydicyclohexyl (II), prepared from *p,p'*-diphenol (I) by high pressure hydrogenation over Raney nickel catalyst by the method of Adkins,[3] was converted to (III) as follows. A mixture of 50 g. of (II), 50 ml. of diphenyl ether, and 13 g. of copper chromite catalyst was heated for three hours at 260–270°. During this time 70% of the theoretical quantity of hydrogen necessary for complete conversion to the diketone (III) was evolved. The reaction mixture was cooled and dissolved in chloroform. The solution was filtered to remove catalyst, and the filtrate was distilled. The fraction boiling from 144–170° (1 mm.) (which solidified on cooling) contained the product. Several crystallizations from mixtures of acetone and *n*-hexane gave a 16.5% yield of diketone (III); m. p. 116.5–118°.[4] The purest material melted from 118–119°.

Anal.[5] Calcd. for $C_{12}H_{18}O_2$: C, 74.18; H, 9.33. Found: C, 74.62; H, 9.53.

The diketone formed a dioxime; m. p. *ca.* 290° (copper block). The dioxime was practically insoluble in all ordinary organic solvents.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.26; H, 8.98. Found: C, 64.82; H, 9.60.

bis-[3,3,5,5-Tetra-(β-cyanoethyl)-4-ketocyclohexyl] (IV).—To a solution of 18.4 g. of 4,4'-diketodicyclohexyl (III) in 80 ml. of dioxane containing 1.3 ml. of Triton B (38% aqueous solution of trimethylbenzylammonium hydroxide) there was added dropwise 41.5 g. of acrylonitrile (3% excess). The reaction mixture was vigorously stirred and maintained at room temperature by use of a water-bath during the addition. Yellow crystals were deposited as the reaction proceeded. After stirring overnight, the mixture was diluted with water and filtered, and the precipitated product was washed with acetone. Two or three crystallizations from formamide–nitromethane mixtures (*ca.* 80–20) gave 39 g. (66%) of white crystalline "octanitrile" (IV); m. p. 280–287°.

Anal. Calcd. for $C_{36}H_{42}O_2N_8$: C, 69.86; H, 6.83; N, 18.11. Found: C, 69.86; H, 7.16; N, 18.05.

bis-[3,3,5,5-Tetra-(β-carboxyethyl)-4-ketocyclohexyl] (V) (Dicyclohexanoneoctapropionic Acid).—A suspension of 6.83 g. of the "octanitrile" (IV) in 35 ml. of 85% aqueous phosphoric acid was heated for forty-eight hours on the steam-bath. Suspended matter dissolved as the hydrolysis proceeded, after which the clear solution gradually changed to a semi-solid mass. When hydrolysis was substantially complete, the reaction mixture was diluted with water, cooled and filtered. The precipitate was dissolved in alkali and the solution filtered. The filtrate on acidification gave fine white needles of the desired acid which, after recrystallization from water, weighed 5.82 g. (66% yield). Further purification consisting of (1) treating the acid with activated charcoal, (2) boiling in dilute hydrochloric acid solution (to hydrolyze any remaining nitrile groups) and (3) crystallizing from water followed by drying at 110° under reduced pressure was found necessary to secure a pure product; m. p. 274–277°, neutral equivalent 96.6, calcd. 96.3. On standing for several months in a desiccator, the melting point rose to 286–288°, probably due to a change in crystalline form.

Anal. Calcd. for $C_{36}H_{50}O_{18}$: C, 56.08; H, 6.54. Found: C, 56.05; H, 6.47.

RESEARCH LABORATORY
GOODYEAR TIRE AND RUBBER CO.
AKRON 16, OHIO

RECEIVED DECEMBER 29, 1947

(3) H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, 1937, p. 58.

(4) All melting points are corrected.

(5) Analyses by Mr. Carl Parks of this Laboratory.

Preparation of Triethylacetonitrile and Triethylacetic Acid

BY CONRAD SCHUERCH, JR.,[1,2] AND ERNEST H. HUNTRESS

Synthetic methods for the preparation of tertiary aliphatic acids or their simple relatives have not been correlated in the prior literature. They include, however, alkylation of aliphatic nitriles with alkyl bromides or chlorides in presence of sodamide,[3] and the carbonation of RMgX compounds.[4]

For tertiary acids above dimethylethylacetic, carbonation of the appropriate RMgX compounds is not generally utilizable since the Grignard reagents prepared from higher halides usually react abnormally, yielding mixtures of alkanes and alkenes. Furthermore, the required carbinols are not commercially available and simple distillation is somewhat inadequate for removal of residual traces of the carbinols from their chlorides.

Our experience (Table I) in attempting to prepare tertiary acids by carbonation of tertiary-alkyl magnesium chlorides with either gaseous or solid carbon dioxide indicates that the yields of acids become progressively more unsatisfactory. The reactions were run on Grignards derived from 200–300 g. of alkyl chloride using the usual precautions[4d]; yields are not necessarily optimal.

TABLE I

		This work		Published work		
	Acid	Carbonation with CO_2 as	Yield, %	Carbonation with CO_2 as	Yield, %	Ref.
A.	Trimethylacetic	Gas	67	Gas	61–70	4d
B.	Dimethylethylacetic	Gas	40	Gas	60	4c
					Lower than (A)	4e
C.	Methyldiethylacetic	Solid	17	Not reported	42	4a
D.	Triethylacetic	Solid	7	Not reported	Not reported	4a
E.	1-Methylcyclohexanecarboxylic	Solid	15	Gas	<25	4b

A better preparative process for triethylacetic acid was found in Ziegler's method[3] for the alkylation of acetonitrile followed by subsequent purification and hydrolysis of the resultant triethylace-

(1) This paper is constructed from part of a dissertation submitted in June, 1947, by Conrad Schuerch, Jr., to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Division of Cellulose and Industrial Chemistry, McGill University, Montreal 2, Canada.

(3) (a) Ziegler (to Schering-Kahlbaum, A. G.) U. S. Patent 1,958,653, May 15, 1933; *C. A.*, **28,** 4435 (1934); British Patent 393,955, 394,087; *C. A.*, **27,** 5755 (1933); German Patent 581,728, 583,561; *C. A.*, **28,** 1057 (1934); French Patent 728,241; *Chem. Zentr.*, **104,** I, 1197–1198 (1933); *C. A.*, **26,** 5573 (1932); (b) Ziegler and Ohlinger, *Ann.*, **495,** 84–112 (1932).

(4) (a) Whitmore and Badertscher, THIS JOURNAL, **55,** 1559–1567 (1933); (b) Gutt, *Ber.*, **40,** 2069 (1907); (c) Corson, Thomas and Waugh, THIS JOURNAL, **51,** 1950–1951 (1929); (d) Gilman, Kirby, "Organic Syntheses," Coll. Vol. I (2nd ed.), 361–364 (1941); (1st ed.) 353–356 (1932); Gilman and Parker, *ibid.*, **5,** 75–77 (1925); (e) Degnan and Shoemaker, THIS JOURNAL, **68,** 104 (1946).

tonitrile. Even when the alkylation was not carried out under pressure but merely at the boiling point of ethyl bromide where the principal reaction is dialkylation leading to diethylacetonitrile, the yield of triethylacetonitrile was sufficiently high to serve as a convenient preparative method.

In the course of our study of this procedure we also examined the behavior of acetonitrile (1 mole) with ethyl bromide (excess) and sodamide (2–2.5 moles); acetonitrile with diethyl sulfate in benzene (no alkylation); alkylation of a mixture of acetonitrile with diethylacetonitrile; and the behavior of *n*-butyronitrile with ethyl bromide (excess) in presence of sodamide (2 moles). The best conditions for the preparation of triethylacetonitrile at ordinary pressure are concisely summarized below.

Triethylacetonitrile.—To a mixture of acetonitrile (61 g., 1.5 moles), ethyl bromide (408 g., 3.75 moles) and dry ether (100 ml.) in a creased 3-liter flask with high-speed stirrer was added a slurry of sodamide (117 g., 3 moles) in dry ether. This addition was effected under slight pressure of nitrogen during a one and one-half-hour period. Although no significant reaction occurred after this period, the mixture was stirred overnight and then cautiously treated with 50 ml. of alcohol, finally with water. After washing the ether solution with dilute sulfuric acid and finally with water, it was dried over magnesium sulfate and fractionally distilled at atmospheric pressure through a one-foot packed column. The products of mono, di and trialkylation were obtained as follows:

n-Butyronitrile	24.1 g.	0.348 mole	$n^{21}D$ 1.3838
Diethylacetonitrile	35.2 g.	0.362 mole	$n^{20}D$ 1.4021
Triethylacetonitrile	28.8 g.	0.23 mole	$n^{20}D$ 1.4219

Fractionation of the intermediate material and residue gave more of all three products.

Triethylacetic Acid.—Triethylacetonitrile (60.3 g.) mixed with 75% sulfuric acid (106 g.) was raised to a temperature of 150° with constant stirring over a period of one-half hour. The temperature was then maintained at 145–150° for twenty-two more minutes after which the contents of the flask were cooled to 50°. Solid sodium nitrite (47 g.) was added from an attached flask during a period of about one hour at 50–60°. After cooling, diluting with water, and extracting with ether, the latter contained both the desired acid and its amide. The former was separated from the latter by extraction of the ether solution with aqueous 6% potassium hydroxide; yield of triethylacetic acid 56.6 g., 81.5%, purified with little loss by distillation under reduced pressure, b. p. 104–105° at 5 mm., f. p. 35.1°; yield of triethylacetamide 11.3 g., 17.6%.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 29, 1948

The Reaction of Certain β-Aminomercaptans with Iodine in Ethanol

BY H. R. SNYDER AND ERNEST L. ELIEL

In a recent report[1] on the synthesis of substituted mercaptans the derivatives obtained by reaction of certain β-aminomercaptans with iodine in alcohol were regarded as sulfenyl iodides. Shortly after the appearance of the report Professor Norman Kharasch[2] kindly called to our attention the fact that the properties of the derivatives were not those to be expected of simple sulfenyl iodides and suggested that the substances were the dihydriodides of the disulfides formed by oxidation of the aminomercaptans.

A quantitative study of the reaction of alcoholic iodine with the mercaptan[1] $[C_6H_{12}NCH_2C(CH_3)_2SH]$ obtained from β-pipecoline and isobutylene sulfide now has been made. The iodine consumption averaged 95% of that required for conversion of the mercaptan to the disulfide salt, or only 47.5% of the amount required for conversion to the sulfenyl iodide. The reaction also was carried out on a scale large enough to permit isolation of the product, conversion to the free disulfide by the action of sodium bicarbonate, distillation of the disulfide, and reconversion of the disulfide to the salt by treatment with hydriodic acid; the original salt was regenerated. The derivative previously obtained by the action of iodine on the aminomercaptan $[(C_4H_9)_2NCH_2C(CH_3)_2SH]$ from di-*n*-butylamine and isobutylene sulfide was subjected to the same cycle (except that the free disulfide was not distilled). In this instance also the regenerated substance was identical with the original sample.

It thus appears certain that all the derivatives referred to as sulfenyl iodides in the previous report[1] are dihydriodides of diaminodisulfides having the general formula $[R_2NCH_2C(CH_3)_2S]_2 \cdot 2HI$. The previously recorded analyses of the substances are in good agreement with the theoretical values calculated on the basis of this structure.

Experimental[3]

Reaction of α,α-Dimethyl-β-(β-pipecolino)-ethyl Mercaptan with Iodine in Ethanol.—Samples of about 0.5 g. of the aminomercaptan[1] were dissolved in absolute ethanol and titrated with a standardized solution of iodine (0.1 *N*) in the same solvent. In four titrations the iodine consumption was 0.949, 0.950, 0.950 and 0.954 gram atoms per mole of mercaptan. The end-point was determined by the appearance of the iodine color. The preparative reaction was carried out essentially as described previously; the product (85% yield) melted at 210.5–211.5 (dec.).

Anal. Calcd. for $C_{20}H_{42}N_2S_2I_2$: C, 38.22; H, 6.73. Found: C, 38.02; H, 7.00.

The free disulfide was obtained by the addition of 50 ml. of saturated aqueous sodium bicarbonate solution to a solution of 7 g. of the above salt in 200 ml. of hot water, extraction of the cooled solution with ether, drying of the ether solution with sodium sulfate, removal of the ether, and distillation. The liquid (yield 2.7 g., 64%) boiled at 155–156° (3 mm.); $n^{20}D$ 1.5146; mol. wt. (ebullioscopic in benzene), 328 (calcd., 372.7).

The dihydriodide was regenerated by the addition of 0.6 ml. of hydriodic acid (sp. gr. 1.5) to 0.55 g. of the disulfide in 10 ml. of absolute ethanol. The salt crystallized immediately as a solid melting at 211–212.5° (dec.); recrystallization from ethanol raised the melting point to 212–213° (dec.). A mixture of the recrystallized salt with that prepared from the aminomercaptan and iodine

(1) Snyder, Stewart and Ziegler, THIS JOURNAL, 69, 2672 (1947).

(2) Professor Norman Kharasch, the University of Southern California, Los Angeles; private communication, January 26, 1948.

(3) All melting points are corrected.

melted at 210.5–213° (dec.). The two specimens were identical in appearance under the microscope.

Experiment with the Dihydriodide of Di-[α,α-dimethyl-β-(di-*n*-butylamino)-ethyl] Disulfide.—The oil which separated when 0.15 g. of the product (previously obtained[1] by the action of iodine on the mercaptan) was treated with aqueous sodium bicarbonate was collected in ether. The solution was dried and the solvent was removed and replaced by absolute ethanol. Addition of concentrated hydriodic acid and ether caused the separation of 0.1 g. of the dihydriodide, m. p. 167.5–170.5 (dec.). After two recrystallizations from absolute ethanol and ether the salt melted at 174–176° (dec.) alone or mixed with the original salt of m. p. 173.5–175° (dec.). The two specimens were identical in appearance under the microscope.

NOYES LABORATORY
THE UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED MAY 12, 1948

Apparent Molar Volume of Sodium in Liquid Ammonia

BY A. J. STOSICK[1] AND ELTON B. HUNT

In a series of communications Ogg[2] has reported the results of experiments with the unusual solutions of alkali metals in liquid ammonia. In one of his communications[2a] he reported that at a concentration of 3×10^{-3} molar, the molar volume of sodium was 700–1000 cc. These values are ten to fifteen times greater than the values reported by Kraus and co-workers[3] for more concentrated solutions. Since the data of Kraus, while indicating an abnormal molar volume, show no trend to larger values with increasing dilution, it seemed worth repeating measurements for dilute solutions. The error in our measurements is relatively large, since we designed our apparatus to accommodate the large effect reported by Ogg. However, our results definitely are not in accord with those of Ogg, but conform to those of Kraus. The experiments consisted in a direct measurement of the increase in volume of liquid ammonia when weighed amounts of sodium were added to form a uniform solution.

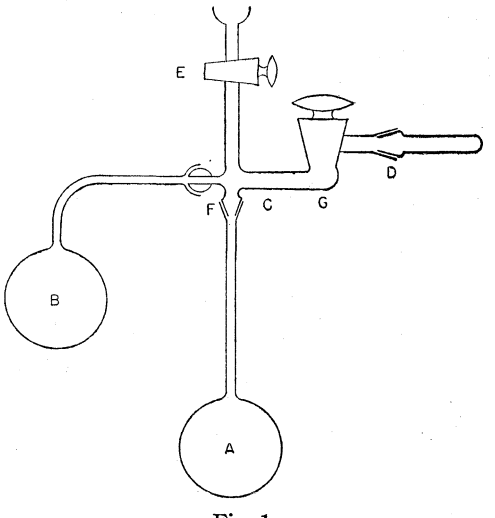


Fig. 1.

The apparatus (Fig. 1) consisted of two 100-cc. bulbs, with bulb A having a calibrated neck which served to measure the increase in volume. The whole unit was connected to a conventional vacuum line via stopcock E and a standard ball joint which permitted shaking the solution.

In the first experiment a freshly cut, massive piece of sodium (27.9 mg. in form of a cube with edge of about 3 mm.) was placed in the side-arm C and the system was quickly evacuated. Next ammonia from a concentrated sodium–ammonia solution contained in a trap on the vacuum line was distilled into bulb A. The stopcock E was then closed. The temperature of A was maintained at $-44.5 \pm 0.2°$ by means of an alcohol-bath in a large clear Dewar flask. After establishing constancy of the meniscus level, about half of the ammonia was distilled into B (previously at room temperature). This enabled the introduction of the sodium (by a magnetic pusher) to be made without splashing or "bumping" and permitted the solution to be stirred by shaking A. The ammonia in B was distilled back to A, B restored to room temperature, and A restored to −44.5°. The meniscus level was noted at intervals to be certain that constancy had been achieved. The observed rise of the meniscus, 3.0 ± 0.2 mm., the weight of the sodium, 27.9 mg., and the flask calibration lead to an apparent molar volume of 59 cc. for sodium, an excess of 36 cc. over 23 cc. for metallic sodium. The concentration of the solution was 1.1×10^{-2} molar. The precise measurements of Kraus indicate an excess volume of 41.0 to 43.5 cc. for concentrated solutions.

In the second experiment the side-arm at C was modified by the addition of an evacuable side chamber D to keep the sodium out of contact with ammonia gas until it was to be placed into solution. The side-arm had a large bore stopcock and an arrangement of magnetic pushers so that the sodium could be moved without touching stopcock grease. A second modification consisted in analyzing for the sodium remaining in A at the end of the experiment by means of a gasometric procedure. At the end of the experiment most of the ammonia was pumped from A, the temperature of A was raised to produce an ammonia pressure slightly over atmospheric. The flask A was detached at the joint F and transferred to a gasometric train where the remaining ammonia was pumped off. Dilute acid was introduced into A, the evolved hydrogen was flushed by means of carbon dioxide into a measuring vessel using concentrated potassium hydroxide as the confining fluid. Blank tests showed that this procedure introduced no gases which potassium hydroxide did not absorb.

In the second experiment the weighed amount of sodium, 5.3 mg., was placed in D and, after evacuation, was isolated by stopcock G. The subsequent steps were similar to the first experiment except for the final analysis for sodium. The temperature of A was maintained at $-42.9 \pm 0.1°$, and no change (±0.2 mm.) was noted in the level of the meniscus. When correction is made for the ammonia gas which entered the evacuated chamber D, the meniscus rise is 0.5 ± 0.2 mm. The analysis for sodium indicated 3.0 mg., which must be taken as a minimum since no allowance was made for solubility loss of hydrogen in the gasometer. These data lead to an apparent molar volume of 52 cc. (5.3 mg. of sodium by weighing) or 92 cc. (3.0 mg. of sodium by analysis). The concentration of the solution was 2.1×10^{-3} molar or 1.2×10^{-3} molar, respectively.

It is clear that these results are not in accord with those of Ogg and conform to those of Kraus. Assuming the solutions to have the same coefficient of expansion as

(1) Present address: Department of Chemistry, University of Southern California, Los Angeles 7, California.

(2) Richard A. Ogg, Jr., (a) THIS JOURNAL, **68**, 155 (1946); (b) *J. Chem. Phys.*, **14**, 114, 295, 399 (1946); (c) *Phys. Rev.*, **69**, 668 (1946).

(3) Kraus, Carney, and Johnson, THIS JOURNAL, **49**, 2206 (1927).

ammonia itself, it can easily be seen that temperature variations cannot account for the difference from Ogg's result. To agree with his results the elevation of the meniscus would have had to be about ten times the values (3.0 and 0.5 mm.) we observed.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED APRIL 7, 1948

The Preparation of Some Cyclic Acetals

BY M. SULZBACHER, E. BERGMANN AND E. R. PARISER

The present investigation of cyclic acetal derivatives of ethylene glycol (1,3-dioxolanes) was undertaken because of their possible convertibility, by hydrogenolysis, into ethylene glycol monoalkyl ethers,[1] not always available by the usual methods. It was known that aldehydes condense with ethylene glycol without catalyst[2] and that acidic substances accelerate the reaction.[3] It was also known that ketones which cannot easily be acetalated by monohydric alcohols, are capable of such zene in presence of the catalyst.[4,5,6] The time required for the liberation of the theoretically expected quantity of water gives an at least qualitative indication of the reactivity of the carbonyl compounds. From Table I in which our results are briefly summarized, the following conclusions can be drawn: Benzaldehyde has approximately the same reactivity as heptaldehyde. As in many other instances,[7] a 4-methoxy group decreases, while halogen, even in ortho-position, increases the activity of the carbonyl group. Among the ketones, those containing the $-CH_2-CO-CH_2-$ group, are most active, and in the case of cyclohexanone, even an ortho-methyl group does not affect the activity. Bulky radicals, as in the case of pinacolone, acetophenone and benzophenone deactivate the carbonyl group. Methyl isobutyl ketone shows an unexpectedly slow reaction, although it contains the group $-CH_2-CO-CH_2-$. This recalls the inactivity of that ketone in other instances, *e.g.* in the condensation with chloroform.[8] Mesityl oxide behaves in a

TABLE I

CONDENSATION PRODUCTS WITH ETHYLENE GLYCOL

Carbonyl compound	Time required, hr.	Yield, %	B. p. °C.	B. p. Mm.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Dioxolanes d^{20}_4	Dioxolanes $n^{20}D$	Mol. refraction Calcd.	Mol. refraction Found
Heptaldehyde[2]	2.5	81.0	94	20	$C_9H_{18}O_2$	..	..	..	...	0.9077[a]	1.43060[a]	44.85	44.70
Benzaldehyde[9]	2.5	82.7	101	10	$C_9H_{10}O_2$	..	..	..	...	1.1156[a]	1.52696[a,b]	41.25	41.53
4-Methoxybenzaldehyde	3.25	84.4	158–60	17	$C_{10}H_{12}O_3$	66.7	66.8	6.7	6.9	1.1776[a]	1.53622[a]	47.51	47.79
2-Chlorobenzaldehyde[10]	1.00	83.5	150–52	16	$C_9H_9O_2Cl$	58.7	58.5	4.9	5.1[c]	1.2639[i]	1.2631[i]	56.11[i]	45.99[i]
Methyl isobutyl ketone	4.0	84.0	48	10	$C_8H_{16}O_2$	66.7	66.9	11.5	11.5	0.908	1.4180	40.23	40.00
Mesityl oxide[11,d]	5.5	66.9	156	760	$C_8H_{14}O_2$	67.6	67.3	9.9	9.8	.9471[j]	1.43963[j]	39.76[j]	39.52[j]
Pinacolone[12]	4.5	80.5	139	760	$C_8H_{16}O_2$	66.7	66.9	11.1	11.4	.9239	1.42356	40.23	39.77
Cyclohexanone[13]	1.5	84.5	65	10	$C_8H_{14}O_2$	..	..	..	...	1.026[e]	1.4580[e,f]	38.07	37.67
2-Methylcyclohexanone	1.4	83.3	82	15	$C_9H_{16}O_2$	69.2	69.3	10.3	10.1	1.0000[a]	1.45579[a]	42.65	42.41
Acetophenone	3.5	85.3	110	30	$C_{10}H_{12}O_2$	73.2	73.5	7.3	7.6	.....	.....	....	....
Methyl benzyl ketone[14]	1.5	78.5	133–34	40	$C_{11}H_{14}O_2$	74.2	73.9	7.9	7.7	1.0520[a]	1.51028[a]	50.49	50.62
Dibenzyl ketone[h]	1.15	85.8	200–202	18	$C_{12}H_{18}O_2$	80.3	80.6	7.1	7.3	.....	.....	....	....
Benzophenone	5.0	81.4	168	10	$C_{15}H_{14}O_2$	79.6	80.0	6.2	6.1	1.1794[a]	1.59013[a]	65.36	65.53

[a] Temperature, 19.5°. [b] Salmi and Louhenkurru (ref. 11) give d^{20}_4 1.1116; $n^{20}D$ 1.52513. [c] Calcd.: Cl, 19.2. Found: Cl, 19.0. [d] The bromine addition product, b. p. 80–90° (30 mm.), was a purple-colored liquid which gradually split off hydrobromic acid, upon standing. [e] Temperature, 21°. [f] Salmi (ref. 4) gives d^{20}_4 1.0280; $n^{20}D$ 1.45828. [g] The acetal crystallized and had, after recrystallization from alcohol, m. p. 60°. It was described recently by Salmi, Tamminen and Louhenkurru.[15] [h] The acetal crystallized: m. p. 69° (from methanol). [i] Data by Salmi and Kyriki (ref. 4). [j] Data by Salmi and Rannikko, *Ber.*, **72**, 600 (1939).

catalyzed condensation with glycols; *p*-toluenesulfonic acid has proved to be an efficient catalyst.[4] Without catalyst, the reaction is extremely slow: in the same period in which cyclohexanone, *e.g.*, reacts completely with glycol in presence of the above acid, the reaction proceeds only to an extent of 10% in its absence.

The most convenient method for the preparation of the acetals consists in the azeotropic distillation of the mixture of the components with benmanner similar to that of its hydrogenation product, methyl isobutyl ketone.

(1) Hydrogenolysis of 2-phenyl-1,3-dioxolane and of furfural diethylacetal: Adkins, Covert and Connor, THIS JOURNAL, **54**, 1651 (1932), of ethylenimine derivatives: Karabinos and Serijan, *ibid.*, **67**, 1856 (1945); Campbell, Sommers and Campbell, *ibid.*, **68**, 140 (1946).

(2) Lochert, *Ann.*, [6] **16**, 26 (1889).

(3) Delépine, *Bull. Soc. Chim.*, [3] **23**, 915 (1900); Verley, *ibid.*, **21**, 275 (1899); Trillat and Cambier, *Compt. rend.*, **118**, 1277 (1894).

(4) Salmi, *Ber.*, **71**, 1803 (1938); Salmi and Kyrki, *C. A.*, **41**, 5480 (1947); see also Fourneau and Chantalou, *Bull. Soc. Chim.*, [5] **12**, 845 (1945).

(5) Meerwein in Houben-Weyl, Vol. 3, 3rd edition, Leipzig, 1930, p. 191.

(6) Haworth and Lapworth, *J. Chem. Soc.*, **121**, 81 (1922); see also Senkus, U. S. Patent 2,419,505 (*C. A.*, **42**, 616 (1948)).

(7) Compare, *e. g.*, Petrenko-Kritschenko, *Ann.*, **341**, 165 (1905).

(8) Ch. Weizmann, E. Bergmann and Sulzbacher, THIS JOURNAL, **70**, 1189 (1948).

(9) Hibbert and Timm, *ibid.*, **46**, 1283 (1924).

(10) Salmi and Kyrki (ref. 4).

(11) Salmi, *Ber.*, **72**, 600 (1939). The normal acetal formation of unsaturated aldehydes has already been observed by Leopold and Michael, German Patent 434,989 (*Chem. Zentr.*, **97**, II, 2846 (1926); by Senkus, U. S. Patent 2,383,622 (*C. A.*, **40**, 898 (1946), and by Fourneau and Chantalou (ref. 4). See also Salmi and Louhenkurru, *C. A.*, **42**, 537 (1948).

(12) Salmi and Rannikko (ref. 11).

(13) Salmi (ref. 4).

(14) Preparation by hydrolysis of phenylacetoacetonitrile, prepared according to "Organic Syntheses," Coll. Vol. II, p. 487.

(15) Salmi, Tamminen and Louhenkurru, *C. A.*, **42**, 537 (1948).

The acetals were purified by treatment of the reaction product with dilute sodium carbonate solution or solid magnesium carbonate, and subsequent fractionation in an efficient column. With few exceptions, they are colorless liquids; their molecular refraction is, within the limits of error, in accord with the theoretical values, as Table II shows. The same conclusion can be drawn from the date observed by Salmi and Kyrki.[4]

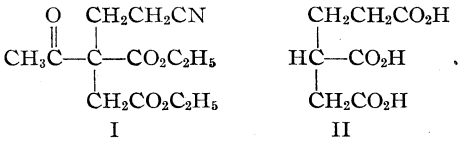
DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
THE GROSVENOR LABORATORY
LONDON S. W. 1, ENGLAND RECEIVED JANUARY 13, 1948

A New Synthesis of Butane-1,2,4-tricarboxylic Acid

BY P. O. TAWNEY AND E. J. PRILL

Butane-1,2,4-tricarboxylic acid (II) has been prepared by various methods.[1] We report herein a new synthesis of this compound.

Diethyl acetosuccinate[2] was treated with acrylonitrile in the presence of a basic catalyst to give a monocyanoethyl derivative (I). The structure of the adduct was demonstrated to be 1-cyano-3-acetyl-3,4-dicarboethoxybutane (I) through conversion to butane-1,2,4-tricarboxylic acid (II) and acetic acid by hydrolysis with concentrated, aqueous potassium hydroxide.



I II

Experimental

1-Cyano-3-acetyl-3,4-dicarboethoxybutane (I).—Potassium hydroxide (1.5 ml. of 50% aqueous solution) was added to a stirred solution of diethyl acetosuccinate[2] (164.8 g., 0.3 mole) and acrylonitrile (18.0 g., 0.34 mole). The temperature of the slightly exothermic reaction was kept at 30–35° by occasional cooling using an ice-bath. After three days at room temperature, the mixture was diluted with 2 vols. of chloroform. The resulting solution was washed successively with saturated sodium bicarbonate solution, dilute sulfuric acid and water. The solvent was removed by distillation at atmospheric pressure and the residue was fractionated at 1 mm.

Fraction I, b. p. 85–120°, 13.0 g. was recovered acetosuccinic ester. Fraction III, b. p. 154–160°, 55.0 g., (87% yield), $n^{20}D$ 1.4556, d^{20}_{20} 1.1186 was the desired 1-cyano-3-acetyl-3,4-dicarboethoxybutane.

Anal. Calcd. for $C_{13}H_{19}O_5N$: C, 58.0; H, 7.07; N, 5.2. Found: C, 58.15; H, 7.05; N, 5.07.

Butane-1,2,4-tricarboxylic Acid (II).—The ester (I) (68.0 g., 0.25 mole) was added in forty-five minutes with stirring to 120 ml. of 58% potassium hydroxide kept at 75–80°. The mixture was stirred for one hour at 75° and one hour at 100°. At the latter temperature ethanol and ammonia was removed by distillation. The solution was then cooled and acidified using 250 ml. of 35% sulfuric acid. The resulting mixture was subjected to continuous extraction with ether for forty-eight hours. After evaporation of the ether, acetic acid and water were removed from the residue by distillation under reduced pressure. The acetic acid was identified as *p*-phenylphenacyl acetate.[3] The crude product (40.5 g.) was crystallized from ethyl acetate to give 29.5 g. (62%) of white crystals, m. p. 120–121°. The reported[1] melting points for butane-1,2,4-tricarboxylic acid vary from 114° to 123–123.5°.

Anal. Calcd. for $C_7H_{10}O_6$: neut. equiv., 63.3. Found: neut. equiv., 63.5.

(1) (a) "Beilstein," Vol. II, p. 819; 1st. Supp., p. 322; 2nd. Supp., p. 683; (b) Kiliani, *Ber.*, **62B**, 640–1 (1929); (c) Ruzicka, Borges de Almeida and Brack, *Helv. Chim. Acta*, **17**, 183–200 (1934); (d) Hardegger, *ibid.*, **29**, 1195–1198 (1946).

(2) Adkins, Isbell and Wojcik, "Organic Syntheses," **14**, 38 (1934).

(3) Kamm, "Qualitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1932, p. 181.

GENERAL LABORATORIES
UNITED STATES RUBBER COMPANY
PASSAIC, NEW JERSEY RECEIVED APRIL 29, 1948

The Preparation of Fluoroacetyl Chloride

BY WILLIAM E. TRUCE

The synthesis of fluoroacetyl chloride was undertaken because of its potential value for directly introducing the group, $-COCH_2F$, into organic molecules. Such applications are being studied at this laboratory.

Experimental

Fluoroacetyl Chloride.—(Caution! Fluoroacetic acid, sodium fluoroacetate and fluoroacetyl chloride are potent poisons. The following reactions should be carried out under a hood.) Two hundred twenty grams (2.27 moles) of sodium fluoroacetate (Monsanto Chemical Co., 90% min. purity) and 530 g. (2.49 moles) of phosphorus pentachloride are mixed in a two-liter, round-bottom flask. The flask is immediately connected to a condenser arranged for downward distillation. The receiver is open to the atmosphere through a drying tube. When the initial reaction subsides, the flask is heated on a steam-bath until no further distillate comes over. The weight of distillate is 154 g. (1.60 moles). This material is redistilled through a 120-cm. helix-packed column. The fraction boiling at 70–71° (755 mm.) is collected. The colorless liquid weighs 123 g. and has $n^{27}D$ 1.3835.

Anal. Calcd. for C_2H_2ClFO: Cl, 36.7; neut. eq., 48.2. Found: Cl, 36.5; neut. eq., 47.9.

After standing for three weeks at room temperature, the compound was redistilled through the 120-cm. helix-packed column. Eighty-three per cent. of the material was recovered as a fraction boiling at 70–71° (755 mm.), signifying that fluorine–chlorine interchange was not great. A forerun, amounting to 6–7%, boiled at 62–70° (755 mm.). Since the column had a large hold-up, the rest of the material was accounted for in this way.

Fluoroacetamide.—This compound was prepared from fluoroacetyl chloride by the procedure used to make trifluoroacetamide.[1] The yield of crude fluoroacetamide is 73%. The product on recrystallization from chloroform melts at 107–108°. Fluoroacetamide has been prepared by other methods and the melting points reported are 104°,[2] 108°[3] and 108°.[4] This material gave no depression in melting point when mixed with an authentic sample of fluoroacetamide.[2]

Anal. Calcd. for C_2H_4FNO: N, 18.18. Found: N, 18.16.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA RECEIVED JANUARY 27, 1948

(1) Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

(2) Swarts, *Bull. soc. chim.*, [3] **15**, 1134 (1896).

(3) U. S. Patent 2,403,576 (1946) [*C. A.*, **40**, 6498 (1946)].

(4) U. S. Patent 2,416,607 (1947).

A New Synthesis of O-Substituted Hydroxylamines

BY PRICE TRUITT, LOREN M. LONG AND MARJORIE MATTISON

It has been reported[1] that monochloramine condenses with substances containing the =N—CS—S—Na group.

$$(CH_3)N—CS—S—Na + ClNH_2 \longrightarrow (CH_3)_2N—CS—S—NH_2 + NaCl$$

This suggested the possibility of the analogous reaction of chloroamine with sodium alcoholates to give O-substituted hydroxylamines.

$$RONa + ClNH_2 \longrightarrow RONH_2 + NaCl$$

This method has been applied with the sodium salts of β-phenoxyethanol and benzyl alcohol, giving very poor yields (1 to 5%) of the hydroxylamines. However, similar attempts with isoamyl, cyclohexyl, β-phenylethyl and 4-methoxybenzyl alcohols failed to give the desired products, ammonia (as ammonium chloride) being isolated in each case. This reaction is being studied further, using monochloroamine and various substituted chloroamines.

Experimental

An ether solution of monochloroamine was added to a stirred solution of the alcoholate in benzene, cooled in an ice-salt-bath. A white precipitate appeared at once. The reaction mixture was stirred in the ice-salt-bath for several hours (at room temperature overnight), and refluxed for one hour, cooled and poured into water. The ethereal extract was extracted with 10% hydrochloric acid and the acid layer was concentrated at reduced pressure. When white crystals appeared, the cooled mixture was filtered, the solid product washed with absolute ether and recrystallized from a mixture of absolute ethanol and ether.

One mole of β-phenoxyethanol, 0.25 mole of sodium and 0.081 mole of monochloroamine gave 0.8 g. of O-β-phenoxyethylhydroxylamine hydrochloride melting at 172–174° with decomposition.

Anal. Calcd. for $C_8H_{12}O_2NCl$: N, 7.39; Cl, 18.70. Found: N, 7.57; Cl, 18.56.

One-half mole of benzyl alcohol, 0.25 mole of sodium and 0.155 mole of monochloroamine gave 0.25 g. of O-benzylhydroxylamine hydrochloride melting at 229–235° with decomposition. Behrend[2] reported the melting point of this compound as 229–235°.

Anal. Calcd. for $C_7H_{10}ONCl$: N, 8.78. Found: N, 8.83.

(1) R. Hanslik, U. S. Patent 2,261,024, October 28, 1942.

(2) L. Behrend, *Ann.*, **257**, 207 (1890).

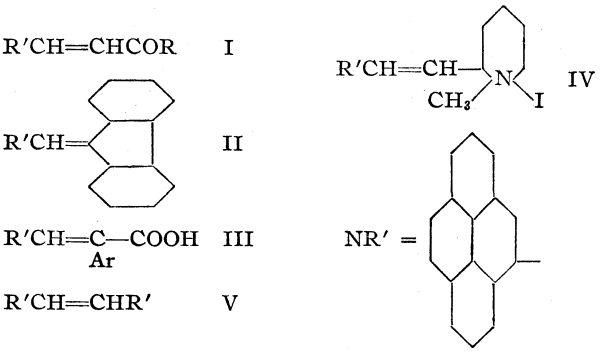
DEPARTMENT OF CHEMISTRY
NORTH TEXAS STATE COLLEGE
DENTON, TEXAS

RECEIVED JANUARY 6, 1948

Reactions of Pyrene-3-aldehyde

BY M. WEIZMANN AND E. BOGRACHOV

Pyrene-3-aldehyde reacts readily with the reactive methylene groups in malonic acid[1] and nitromethane.[2] A number of other condensation reactions have been studied, all leading to colored substances characterized by extended conjugated systems. With various methyl ketones (3-pyrenylidene)-compounds of type (I) have been obtained; fluorene gave 9-(3′-pyrenylidene)-fluorene (II) and phenylacetic and α-naphthylacetic acids condensed to form the corresponding α-aryl-β-(3-pyrenyl)-acrylic acids (III). From the methiodides of picoline, lutidine and quinaldine, stilbazole homologs were formed, *e. g.*, α-(3-pyrenyl)-β-(2′-pyridyl)-ethylene methiodide (IV). Another substance which belongs in this group is *sym*-di-(3-pyrenyl)-ethylene (V) available from (polymeric) pyrene-3-thioaldehyde by heating it in boiling ethyl benzoate or naphthalene, with or without Raney nickel.



Experimental

Condensation of Pyrene-3-aldehyde with Methyl Ketones

(a) **Acetone.**—To a solution of 4.6 g. of pyrene-3-aldehyde in 40 cc. of acetone, 1 cc. of a concentrated aqueous solution of sodium hydroxide was added with stirring. The stirring was continued for two hours, and the voluminous precipitate filtered off, washed with alcohol and acetone, and dried. The yellow 3-pyrenylideneacetone (I, R = CH_3) crystallized from acetic acid (or butanol); m. p. 152°. The yield was almost quantitative.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.9; H, 5.2. Found: C, 88.7; H, 5.1.

The phenylhydrazone, prepared in acetic acid solution, separated after twenty-four hours; the orange-yellow plates were recrystallized from butanol; m. p. 238°.

Anal. Calcd. for $C_{26}H_{20}N_2$: N, 8.0. Found: N, 7.8.

(b) **Pinacolone.**—To a concentrated solution of 4.6 g. of pyrene-3-aldehyde in absolute alcohol, gradually 1 g. of sodium metal, and then 2 g. of pinacolone were added. After a while, the yellow crystals of 3-pyrenylidenepinacolone (I, R = —$C(CH_3)_3$) began to precipitate; after recrystallization from glacial acetic acid, it melted at 155°; yield, 80%.

Anal. Calcd. for $C_{23}H_{20}O$: C, 88.5; H, 6.4. Found: C, 88.6; H, 6.4.

The picrate, prepared in glacial acetic acid solution, formed red leaflets, m. p. 150°.

Anal. Calcd. for $C_{29}H_{23}O_8N_3$; N, 7.8. Found: N, 7.8.

(c) **Acetophenone.**—In the manner described for pinacolone, 2.2 g. of acetophenone gave, in almost quantitative yield, the deep yellow 3-pyrenylideneacetophe-

(1) E. Bergmann and E. Bograchov, THIS JOURNAL, **62**, 3016 (1940).

(2) E. Bograchov, *ibid.*, **66**, 1612 (1944).

none (I, R = C_6H_5). It was recrystallized from glacial acetic acid, xylene or butanol and melted at 158°.

Anal. Calcd. for $C_{25}H_{16}O$: C, 90.4; H, 4.8. Found: C, 90.2; H, 4.8.

The yellow **phenylhydrazone**, recrystallized from xylene, melted at 236°.

Anal. Calcd. for $C_{31}H_{22}N_2$: N, 6.6. Found: N, 7.0.

(d) β-Acetylnaphthalene.—Analogously, 3.4 g. of β-acetylnaphthalene gave an almost quantitative yield of the yellow α-(2-naphthoyl)-β-(3′-pyrenyl)-ethylene (I, R = β-naphthyl). Recrystallization from xylene or glacial acetic acid gave crystals, melting at 184°.

Anal. Calcd. for $C_{29}H_{18}O$: C, 91.1; H, 4.7. Found: C, 90.9; H, 4.6.

The orange-colored **phenylhydrazone** crystallized from xylene, and melted at 246°.

Anal. Calcd. for $C_{35}H_{24}N_2$: N, 5.9. Found: N, 6.2.

9-(3′-Pyrenylidene)-fluorene.—The condensation of 4.6 g. of the aldehyde with 3.3 g. of fluorene was carried out, using sodium ethoxide as catalyst.[3] The yellow-orange fulvene (II) separated spontaneously from the solution, and melted after recrystallization from xylene, butanol or glacial acetic acid at 210°.

Anal. Calcd. for $C_{30}H_{18}$: C, 95.2; H, 4.8. Found: C, 94.9; H, 5.0.

α-Phenyl-β-(3-pyrenyl)-acrylic Acid (III, R = C_6H_5).—One mole each of pyrene-3-aldehyde and sodium phenylacetate was heated in boiling acetic anhydride (1.5 to 2 moles) for two hours. After cooling, the reaction mixture was diluted with water, and the solid residue filtered and washed with alcohol. From glacial acetic acid, the acid was obtained in yellow needles of m. p. 259°; yield, 30%.

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.2; H, 4.6. Found: C, 86.5; H, 4.9.

α-(1-Naphthyl)-β-(3′-pyrenyl)-acrylic acid (III, R = 1-naphthyl) was obtained analogously from pyrene-3-aldehyde and sodium 1-naphthylacetate; yellow needles of m. p. 290° (from nitrobenzene).

Anal. Calcd. for $C_{29}H_{18}O_2$: C, 87.4; H, 4.5. Found: C, 87.1; H, 4.7.

α-(3-Pyrenyl)-β-(2′-pyridyl)-ethylene Methiodide (IV).—To a solution of pyrene-3-aldehyde (4 g.) and α-picoline methiodide (4 g.) in a small quantity of absolute alcohol, 10 to 15 drops of piperidine was added at 180°. Heating was continued for thirty minutes; then the red precipitate was filtered, washed with alcohol, dried, and recrystallized from nitrobenzene: m. p. 295°; yield, 65%.

Anal. Calcd. for $C_{24}H_{18}IN$: C, 64.4; H, 4.0; N, 3.1. Found: C, 64.1; H, 4.0; N, 3.3.

α-(3-Pyrenyl)-β-(6′-methyl-pyridyl-2′)-ethylene methiodide was prepared in 70% yield from 2.3 g. of pyrene-3-aldehyde and 4 g. of 2,6-lutidine methiodide, as described above. It was recrystallized from nitrobenzene, and formed red shiny crystals of m. p. 275°.

Anal. Calcd. for $C_{25}H_{20}IN$: N, 3.0. Found: N, 3.1.

α-(3-Pyrenyl)-β-(2′-quinolyl)-ethylene methiodide was formed in 75% yield as a red-violet, insoluble substance from 2.3 g. of pyrene-3-aldehyde and 2.8 g. of quinaldine methiodide; m. p. 285°.

Anal. Calcd. for $C_{28}H_{20}IN$: N, 2.8. Found: N, 2.8.

***sym*-Di-(3-pyrenyl)-ethylene** (V).—(a) 10 g. of pyrene-3-aldehyde was dissolved in 100 ml. of dry benzene. Dry hydrogen chloride and hydrogen sulfide were passed simultaneously through the cold solution. The yellow precipitate was filtered and washed with water, alcohol and ether. It could not be recrystallized, as it decomposed on heating in high-boiling solvents. In its crude state the polymeric pyrene-3-thioaldehyde melted at 260–270°.

(3) Schlenk and Bergmann, *Ann.*, **479**, 56 (1930).

Anal. Calcd. for $(C_{17}H_{10}S)_x$: C, 82.9; H, 4.1. Found: C, 82.5; H, 4.4.

(b) A mixture of 2 g. of the thioaldehyde, 1 g. of Raney nickel and 20 g. of boiling naphthalene was heated for one hour. After removal of the naphthalene *in vacuo*, a brown-red residue was obtained, which was washed with alcohol and recrystallized from ethyl benzoate: m. p. 315°; yield, 75% (calculated on pyrene-3-aldehyde).

Anal. Calcd. for $C_{34}H_{20}$: C, 95.3; H, 4.7. Found: C, 95.1; H, 4.8.

DEPARTMENT OF ORGANIC CHEMISTRY
THE HEBREW UNIVERSITY, JERUSALEM
RECEIVED JANUARY 13, 1948

NEW COMPOUNDS

Hexahydrojulolidine

To a solution of julolidine,[1] 1,2,3,5,6,7-hexahydrobenzo-(i,j)-quinolizine (20 g., 0.115 mole), in alcohol (20 ml.) there was added Raney nickel (2 g.) and the mixture was shaken at 200° under a pressure of 2000 lb. of hydrogen. After removal of solvent and catalyst, the residue was distilled yielding 5 g. (low yield due to accidental loss) of a colorless oil: b. p. 76–80° at 3 mm.

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.44; H, 11.73. Found: C, 80.55; H, 11.45.

The **picrate** of hexahydrojulolidine was readily prepared using an ethereal solution of picric acid. After recrystallization from hot water the picrate was obtained as an amorphous yellow solid, m. p. 165–167°.

Anal. Calcd. for $C_{18}H_{24}N_4O_7$: C, 52.94; H, 5.88. Found: C, 52.82; H, 5.69.

The **methiodide** of hexahydrojulolidine formed readily and could be recrystallized from a solution of alcohol and ether. It was obtained as an amorphous white solid, m. p. 294–298° with decomposition.

Anal. Calcd. for $C_{13}H_{24}IN$: C, 48.50; H, 7.47. Found: C, 48.51; H, 7.45.

Hexahydrojulolidine hydrochloride and also the quaternary methiodide derivative were found to be convulsants when tested intravenously in rabbits.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK
V. BOEKELHEIDE
G. P. QUINN[2]
RECEIVED APRIL 30, 1948

(1) Glass and Weissberger, "Organic Syntheses," **26**, 40 (1946).

(2) Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

Some Derivatives of Levulinic Acid

Levulinic acid diethylamide was prepared (a) by heating 50 g. of levulinic acid with 50 g. of diethylamine at 250° for ten hours (autoclave), yield 60%; and (b) by adding 13.4 g. of γ-chlorovaleroactone[1] to a cold solution of 15 g. of diethylamine in 50 cc. of ether; the reaction was completed on the water-bath and the solution filtered from diethylamine hydrochloride and distilled, yield 70%. The amide is soluble in water and boils at 108° (0.9 mm.); $n^{22}D$ 1.457.

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.2; H, 10.0; N, 8.2. Found: C, 63.3; H, 10.2; N, 8.2.

(1) Clemo and Ramage, *J. Chem. Soc.*, 54 (1931).

Levulinic acid dibutylamide was prepared similarly in 60% yield from 40 g. of γ-chlorovaleroactone and 80 g. of *n*-butylamine in 100 cc. of ether; b. p. 140° (2 mm.); $n^{20}D$ 1.4241.

Anal. Calcd. for $C_{13}H_{25}O_2N$: C, 68.7; H, 11.0; N, 6.2. Found: C, 68.9; H, 11.4; N, 6.5.

γ-Hydroxy-*n*-valeroyl Diethylamide.—(a) Hydrogenation of 17.1 g. of levulinic acid diethylamide in 30 cc. of water with 2.3 g. of Raney nickel at room temperature and 90 atmospheres gave the product boiling at 101° (0.1 mm.) in quantitative yield.

(b) The diethylamide (34.2 g.) was heated with aluminum isopropoxide (50 g.) and isopropyl alcohol (250 g.) under a column until no more acetone was formed (four hours). The product, isolated in the usual way, boiled at 90° (0.05 mm.); $n^{23}D$ 1.4642; yield, 92%.

Anal. Calcd. for $C_9H_{19}O_2N$: C, 62.4; H, 11.0; N, 8.1. Found: C, 62.4; H, 10.9; N, 8.0.

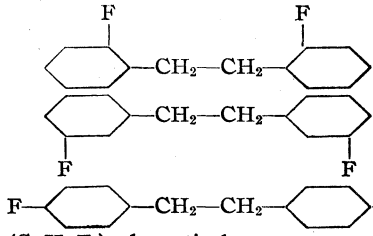
γ-Amino-*n*-valeric Acid Diethylamide.—A solution of 17.1 g. of levulinic acid diethylamide in 120 cc. of 17% alcoholic ammonia was hydrogenated at 70° and under 40 atm. pressure in presence of 2 g. of Raney nickel. Hydrogen absorption ceased after three hours: b. p. 85–90° (0.1 mm.); yield, 17 g.

Anal. Calcd. for $C_9H_{20}ON_2$: N, 16.3. Found: N, 15.9.[2]

(2) The free amino acid has been prepared similarly by Knoop and Oesterlin, *Z. physiol. Chem.*, **148**, 309 (1925).

WEIZMANN INSTITUTE OF SCIENCE
DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL L. HASKELBERG

RECEIVED JANUARY 2, 1947

Compound	M. p., °C.	B. p., °C.	%C	%H	%F	Mol. wt.
	40–41	270–271	77.7	5.7	17.2	205
	34–35	267–268	76.7	5.5	16.6	173
	90	269	77.1	5.7	17.1	175
$(C_{14}H_{12}F_2)$, theoretical			77.0	5.5	17.5	218

Ethyl 3-Halocoumarin-4-carboxylates

Ethyl 3-Chlorocoumarin-4-carboxylate.—Phenol (1.74 g., 0.0185 mole) and diethyl oxalochloroacetate[1] (4.0 g., 0.018 mole) in dioxane (4 ml.) slowly added to ice cold concentrated sulfuric acid (10 ml.), stood at room temperature for eight days and poured onto ice gave 0.7 g. (15.4% yield) of ethyl 3-chlorocoumarin-4-carboxylate. After recrystallization from 50% ethanol this product showed m. p. 116.3–116.6° uncor.; 118.1–118.4° cor.

Anal. Calcd. for $C_{12}H_9O_4Cl$: Cl, 14.06. Found: Cl, 14.2.

Ethyl 3-Bromocoumarin-4-carboxylate.—Phenol (4.32 g., 0.046 mole) and diethyl oxalobromoacetate[2] (12.0 g., 0.045 mole) in dry ether (5 ml.) was slowly added to cold concentrated sulfuric acid (30 ml.). The dark red solution stood at 0° for ninety-six hours, then at 25° for twenty hours. After pouring onto ice, extracting with ether (and removing from the resulting solution, some 29% of unreacted ester by alkaline extraction) there was obtained 1.40 g. (14.7% yield on unrecovered ester) of ethyl 3-bromocoumarin-4-carboxylate. Recrystallization from 70–80% ethanol gave yellow crystals, m. p. 120.7–121.3° uncor.; 122.2–122.8° cor.

Anal. Calcd. for $C_{12}H_9O_4Br$: Br, 26.91. Found: Br, 26.8, 26.9.

(1) Cope, THIS JOURNAL, **58**, 572 (1936).
(2) Brühl, *Ber.*, **36**, 1732 (1903).

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS. ERNEST H. HUNTRESS

CENTRAL RESEARCH LABORATORY
GENERAL ANILINE AND FILM CORPORATION
EASTON, PENNSYLVANIA ROBERT T. OLSEN

RECEIVED APRIL 8, 1948

The Di-fluorobibenzyls

The first stage in the pyrolysis of toluene was shown[1] to be the formation of the benzyl radical and a hydrogen atom. The benzyl radicals thus formed subsequently dimerized to bibenzyl.

Recent investigation of the pyrolysis of the fluorotoluenes[2] showed the same type of decomposition. The fluorobenzyl radicals produced in this way dimerized to the corresponding di-fluorobibenzyls, isolated as previously described.[1,2] The melting points, boiling points and the results of analysis of di-fluorobenzyls thus obtained are summarized in the following Table.

All these compounds have a strong smell very similar to that of bibenzyl. Boiling points were determined by the micro-method of Siwoloboff.[3] A correction of +4° was introduced by comparing the boiling point of bibenzyl actually determined in this way (280–281°) with that stated in the literature (284°). Molecular weights were estimated by the Rast method.

We are indebted to Professor M. Stacey of the University of Birmingham for the fluorine analyses.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY M. SZWARC
MANCHESTER 13, ENGLAND J. S. ROBERTS

RECEIVED MARCH 22, 1948

(1) M. Szwarc, *J. Chem. Phys.*, **16**, 128 (1948).
(2) M. Szwarc and J. S. Roberts, *ibid.*, **16**, 609 (1948).
(3) A. Siwoloboff, *Ber.*, **19**, 795 (1886).

COMMUNICATIONS TO THE EDITOR

CHAIN ELECTROLYTES[1]

Sir:

We are studying polyelectrolytes in which chain atoms carry ionic charges. Typical is the polyelectrolyte (I) formed by the addition of methyl bromide to the polyester obtained from methyldiethanolamine and succinic anhydride

(I) $HO[CO(CH_2)_2COO(CH_2)_2N^+Me_2(CH_2)_2O]_nH—nBr'$

Theoretical bromide for n infinite is 26.99%; two different preparations gave 22.73 and 23.38%, indicating incomplete addition of methyl bromide. End-group titrations gave molecular weights of 3515 and 2720. The salt hydrolyzes in water but is stable in methanol.

At 1.2 g./100 cc. in methanol, (I) has a reduced viscosity of 0.091. For comparison, polyvinylpyridine with molecular weight 80,000 has an intrinsic viscosity of only 0.15. High viscosities thus seem to be characteristic of polyelectrolytes[2] regardless of the location of the charges.

Conductance curves in methanol are shown in Fig. 1, where concentration is stoichiometric normality of bromide. The marked curvature indicates a high degree of association of counter ions to the polycations. Ordinary electrolytes, such as the addition product (II) of methyl bromide to methyldiethanolamine, are only slightly associated in solvents with high dielectric constant, as shown by the approach to the Onsager limiting slope. In our polysalts, ten positive charges are constrained to remain near each other, regardless of dilution. A bromide ion has a potential energy large compared to kT in the resulting field and therefore at finite concentrations, a certain fraction of bromide ions accompany the polycations. The polycations thus act like droplets of concentrated solution within the liquid, regardless of total dilution. The polycation configuration will, however, depend on dilution: with decreasing total concentration, probability of escape of bromide ions from the field of the polycation will increase, and intramolecular mutual repulsion between unpaired charges on chain nitrogens will then cause the chain to uncoil.

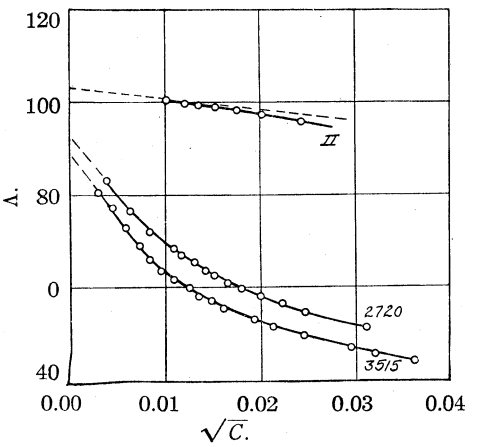


Fig. 1.—Conductance of salts I and II in methanol.

(1) Office of Naval Research, ProjectNR054-002.

(2) R. M. Fuoss and U. P. Strauss, *J. Polymer Sci.*, **3**, 246 (1948).

STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT
DAVID EDELSON
RAYMOND M. FUOSS

RECEIVED JULY 19, 1948

ULTRAVIOLET ABSORPTION BANDS OF IODINE IN AROMATIC HYDROCARBONS

Sir:

In the course of an investigation of the nature of the solvent–solute interaction in solutions of iodine now in progress, new evidence has been found for the presence of addition compounds of iodine and the solvent molecule. We find that the absorption spectrum of the violet-red solution of iodine in benzene shows in addition to the well known absorption maximum at 5000 Å. with a molar extinction coefficient of 1010, an absorption maximum in the ultraviolet region at 2970 Å. having a molar extinction coefficient (based on the iodine concentration) of 9600. This new absorption peak does not appear in solutions of iodine in hexane and carbon tetrachloride which are a pure violet with absorption peaks at 5200 Å. in the visible region. The evidence therefore points to the presence of an iodine–benzene complex. Preliminary measurements show that the height of the absorption peak at 2970 Å. is directly proportional to both the iodine concentration and the benzene concentration, indicating that the addition compound consists of one molecule of iodine bound to one molecule of benzene.

A possible explanation for the presence of such a complex appears to lie in an acid–base interaction in the electron donor–acceptor sense such as we see in the union of I^-, the base, with I_2, the acid, to form I_3^-. Evidence of basic character in benzene is its union with boron trifluoride, boron trichloride and with concentrated sulfuric acid. Additional evidence in support of this hypothesis is to be found in the recent work of Fairbrother,[1] who reports that iodine has an abnormally high dielectric polarization in such solvents as benzene, *p*-xylene, dioxane and di-isobutylene. If this basic character of benzene is also responsible for its union with iodine, then the substitution of methyl groups should increase basic strength and ability to interact with iodine. This is borne

(1) F. Fairbrother, *Nature*, **160**, 87 (1947).

out by the fact that a simple visual examination of iodine solutions of equal concentration in benzene, toluene, *o*-xylene, mesitylene and α-methylnaphthalene shows that the color shifts stepwise in that order ending with a brown solution. Preliminary measurements of the absorption spectra of these iodine solutions show an absorption band in the ultraviolet region similar to that of benzene.

This work is being continued and a complete report of the results will be given in a paper soon to be submitted for publication.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA HANS A. BENESI
BERKELEY 4, CALIFORNIA JOEL H. HILDEBRAND

RECEIVED JULY 15, 1948

β-PELTATIN, A NEW COMPONENT OF PODOPHYLLIN

Sir:

The fractionation of the drug podophyllin by chromatographic adsorption on alumina has yielded, beside podophyllotoxin and α-peltatin,[1] a new crystalline substance in about 4% yield for which the name β-peltatin is proposed. The new compound possesses about the same high necrotizing activity[2] for mouse sarcoma 37 as α-peltatin.

β-Peltatin crystallizes from alcohol in colorless, transparent prisms, m. p. 231.1–238.0° (shrinks at 225.5°) cor.; $[\alpha]^{20}D$ −115° (*c*, 1.009, absolute alcohol). *Anal.*[3] Calcd. for $C_{22}H_{22}O_8$: C, 63.75; H, 5.35. Found: C, 64.0; H, 5.6. Calcd. for three methoxyl groups: 22.5; found, 22.2. Molecular weight values (Rast) for derivatives of both α- and β-peltatin agree with the formula $C_{22}H_{22}O_8$ and indicate that the peltatins are thus isomeric with podophyllotoxin.[4] α-Peltatin has one less methoxyl group than β-peltatin and podophyllotoxin.

Beside the methoxyl content, α- and β-peltatin differ in their color reactions with sulfuric acid and in the properties of their derivatives. With concentrated sulfuric acid, both peltatins give an immediate yellow color, rapidly turning reddish brown with α-peltatin and green with β-peltatin; the final color with both peltatins is red. A series of derivatives of the peltatins has been prepared and will be reported at a later date.

Structural and biological studies with β-peltatin are in progress.

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE OF HEALTH
U. S. PUBLIC HEALTH SERVICE JONATHAN L. HARTWELL
BETHESDA, MARYLAND WENDELL E. DETTY

RECEIVED JULY 22, 1948

(1) J. L. Hartwell, THIS JOURNAL, **69**, 2918 (1947).

(2) Unpublished results of Joseph Leiter and Faith Jouvenal.

(3) By Mrs. M. M. Ledyard and Mrs. Evelyn Peake National Institute of Health.

(4) W. Borsche and J. Niemann, *Ber.*, **65**, 1633 (1932); E. Späth, F. Wessely and E. Nadler, *ibid.*, **66**, 125 (1933).

THE CRYSTALLINE TRIHYDROCHLORIDES OF STREPTOMYCIN AND MANNOSIDOSTREPTOMYCIN

Sir:

The preparation of the crystalline reineckate, sulfate,[1] helianthate,[2] and the calcium chloride double salt[2] of streptomycin and the reineckate of mannosidostreptomycin[3] has been reported. To date, there has been no published information on the crystallization of a simple mineral acid salt of either of these antibiotics. We now wish to report that, starting with relatively pure material, we have obtained the trihydrochlorides of streptomycin and mannosidostreptomycin in the crystalline state from methanol solution.

The streptomycin trihydrochloride crystallizes with two molecules of water of crystallization as monoclinic prisms showing birefringence. The crystalline material was shown to be a single substance by a modification of the Craig countercurrent distribution technique[4] and thus to be free of mannosidostreptomycin. On heating on the hot-stage, the dihydrate decomposes gradually without melting. When the trihydrochloride was dried at 55° *in vacuo*, it had the following analytical composition: C, 34.86; H, 6.36; Cl, 14.25 (Calcd. for $C_{21}H_{39}N_7O_{12}\cdot 3HCl\cdot 2H_2O$: C, 34.54; H, 6.36; Cl, 14.57). After drying at 100° *in vacuo*, the anhydrous material showed $[\alpha]^{26.6}D$ −86.1° (1.0% in water) and the following analytical data were obtained: C, 36.27; H, 6.14; N, 14.29; Cl, 15.69 (Calcd. for $C_{21}H_{39}N_7O_{12}\cdot 3HCl$; C, 36.50; H, 6.13; N, 14.19; Cl, 15.40).

When assayed with *K. pneumoniae* in a broth-dilution test,[5] the trihydrochloride dihydrate had a potency of 820 units/mg. and on this basis the anhydrous material would have an activity of 891 units/mg.[6]

The trihydrochloride of mannosidostreptomycin crystallizes in the form of hexagonal plates which are isotropic. By means of the counter-current distribution method,[4] this material was also shown to be a single entity and to be free of streptomycin.

After drying at 55° *in vacuo*, the trihydrochloride was found to have the following analysis: C, 36.45; H, 6.26; Cl, 12.14 (Calcd. for $C_{27}H_{49}N_7O_{17}\cdot 3HCl\cdot 2H_2O$: C, 36.47; H, 6.35; Cl, 11.96). When dried at 100° *in vacuo*, the anhydrous material showed $[\alpha]^{26.6}D$ −54.1° (1.0% in water)

(1) J. Fried and O. Wintersteiner, *Science*, **104**, 273 (1946).

(2) R. L. Peck, N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, A. Walti and K. Folkers, THIS JOURNAL, **67**, 1866 (1945).

(3) J. Fried and E. Titus, *J. Biol. Chem.*, **168**, 391 (1947).

(4) A modification of the counter-current distribution described by Titus and Fried (*J. Biol. Chem.*, **174**, 57 (1948)) has been developed by our colleagues Drs. Plaut and McCormack which eliminates the appearance of the tautomers of the two streptomycins in the Craig diagram.

(5) R. Donovick, D. Hamre, F. Kavanagh and G. Rake, *J. Bact.*, **50**, 623 (1945).

(6) Based on the F. D. A. working standard. Spectrophotochemical assays based on a maltol method, similar to that published by G. P. Mueller (THIS JOURNAL, **69**, 195 (1947)), have confirmed these microbiological results.

and gave analytical data: C, 38.25; H, 6.22; N, 11.31; Cl, 12.52 (Calcd. for $C_{27}H_{49}O_7O_{17}\cdot 3HCl$: C, 38.01; H, 6.14; N, 11.49; Cl, 12.47).

When assayed with *K. pneumoniae* in a broth dilution test,[5] the anhydrous mannosidostreptomycin had a potency of *circa* 210 units/mg.[6]

Additional information on the properties and activities of these crystalline hydrochlorides will be published at a later date.

We wish to express our appreciation to Dr. R. Donovick, Mr. R. Blue, and Mr. D. Lapedes for the bio-assays, Mr. F. Russo-Alesi for the countercurrent distributions, and Mr. J. Alicino for the micro-analysis.

DIVISION OF CHEMICAL DEVELOPMENT LEON J. HEUSER
E. R. SQUIBB AND SONS MORRIS A. DOLLIVER
NEW BRUNSWICK, N. J. ERIC T. STILLER

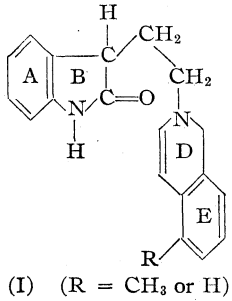
RECEIVED JULY 19, 1948

THE SYNTHESIS OF KETOYOBYRINE

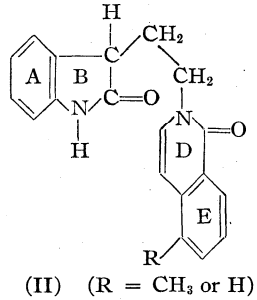
Sir:

For several years we have been investigating the possibility of synthesizing the basic ring structure of yohimbine by ring closure of isoquinolylethyl oxindoles of the type represented by formula (I).[1] The introduction of the double bond in ring D presented numerous difficulties because of the ease with which compounds of the type (I) (as well as the yohimbine molecule itself) suffer cleavage at the nitrogen atom of ring D. Moreover, we have pointed out[1] that 1,2-dihydroisoquinolines like (I) are virtually unknown.

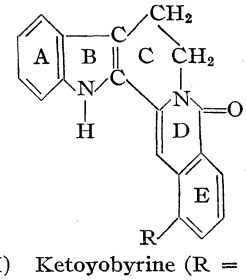
Accordingly, our efforts were later directed toward the preparation and ring closure of compounds of the type represented by formula (II)



(I) (R = CH_3 or H)



(II) (R = CH_3 or H)



(III) Ketoyobyrine (R = CH_3)

where the appropriate double bond of ring D could be introduced without difficulty. Ring closure of such a compound would lead to compounds of the structure (III), which type of structure has recently been proposed for ketoyobyrine, on the basis of an exhaustive study of its chemistry[2a] and likewise on the basis of a comparison of its absorption spectrum with that of rutaecarpine.[2b]

Pending more complete presentation of our various syntheses of the type of structure represented by (III), we wish to record our synthetic confirmation of this proposed structure for ketoyobyrine.

6-Methylhomophthalic acid, m. p. 196°, was prepared from *o*-tolylacetic acid[3] by conversion *via* the Arndt–Eistert reaction into *o*-tolylpropionic acid, which was then treated according to the method of Mercer and Robertson.[4] Condensation with tryptamine yielded N-(β-indolylethyl)-6-methylhomophthalimide, m. p. 228°. Conversion of the latter into the corresponding homophthalamic acid,[5] m. p. of picrate 147°, methylation of the acid with diazomethane, m. p. of methyl ester 222°, dec., followed by ring closure with phosphorus oxychloride, yielded ketoyobyrine, m. p. 316–318°, dec.

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.32. Found: C, 79.43; H, 5.55; N, 9.24. Comparisons of the ultraviolet absorption spectrum of synthetic ketoyobyrine with that of the product of natural origin showed the two to be identical. Absorption maxima for synthetic material: at 385, 366 and 340 mμ, log ε 4.40, 4.51 and 4.52, respectively.

(2) (a) Woodward and Witkop, THIS JOURNAL, **70**, 2409 (1948); (b) Raymond-Hamet, *Compt. rend.*, **226**, 137 (1948).

(3) Julian, Karpel, Magnani and Meyer, THIS JOURNAL, **70**, 180 (1948).

(4) Mercer and Robertson, *J. Chem. Soc.*, 288 (1936).

(5) *Cf.* Haworth, Perkin and Pink, *J. Chem. Soc.*, 1709 (1925).

THE GLIDDEN COMPANY PERCY L. JULIAN
RESEARCH LABORATORIES WILLIAM J. KARPEL
SOYA PRODUCTS DIVISION ARTHUR MAGNANI
CHICAGO, ILLINOIS EDWIN W. MEYER

RECEIVED JULY 24, 1948

THE OZONIZATION OF THE MALEIC ANHYDRIDE ADDUCT OF DEHYDROERGOSTERYL ACETATE

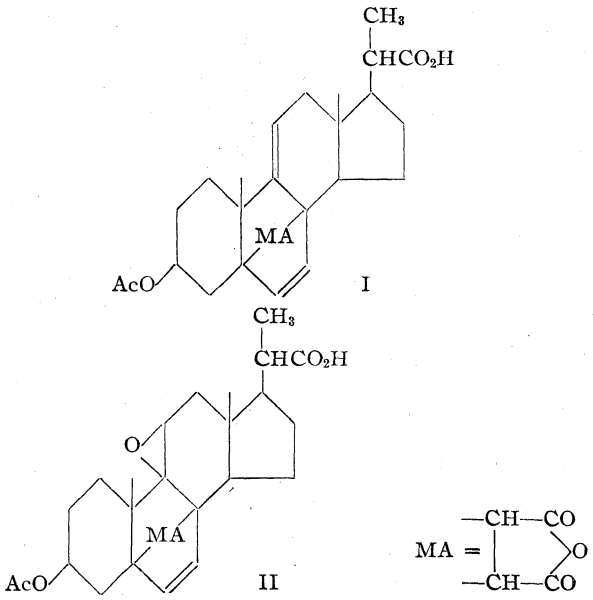
Sir:

A recent publication of Bergmann and Stevens[1] describes the preparation of the maleic anhydride adduct of 3(β)-acetoxy-9,11-oxidobisnor-5,7-choladienic acid (II) by the ozonization of 9,11-oxidoergosteryl acetate–maleic anhydride adduct. For some time previous a study of analogous reactions has been under way in our laboratories and we now wish to report the preparation of the maleic anhydride adduct of 3(β)-acetoxybisnor-5,7,9-cholatrienic acid (I) by the selective ozonization of 9,11-dehydroergosteryl acetate–maleic anhydride adduct (III).

A solution of the dehydroadduct (III) in methylene chloride was treated with two equiva-

(1) Julian, Magnani, Pikl and Karpel, THIS JOURNAL, **70**, 174 (1948).

(1) Bergmann and Stevens, *J. Org. Chem.*, **13**, 10 (1948).



lents of ozone at −30°. The methylene chloride was replaced with glacial acetic acid and the ozonide decomposed with zinc dust. After separation of the zinc, the acetic acid solution was treated with chromic acid in acetic acid at 20° for three hours and the excess chromic acid was decomposed with sodium bisulfite solution. The reaction mixture was poured into water and the precipitate of the bisnor acid (I), m.p. 226–237°, was separated by filtration. For analysis, the acid (I) was crystallized from ether–hexane, m.p. 240–243°. The yield of pure acid (I) was 55% of the theoretical.

Anal. Calcd, for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10; Found: C, 69.73; H, 7.10.

Treatment of the acid (I) with diazomethane in methylene chloride gave the maleic anhydride adduct of methyl 3(β)-acetoxybisnor-5,7,9-cholatrienate (IV), m.p. 246–248°. *Anal.* Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 69.98; H, 7.48. After saponification, methylation with diazomethane, and acetylation with acetic anhydride, the trimethyl ester of the maleic acid adduct of 3(β)-acetoxybisnor-5,7,9-cholatrienic acid (V) was obtained, m.p. 193–195°. *Anal.* Calcd. for $C_{31}H_{42}O_8$: C, 68.61; H, 7.80. Found: C, 68.66; H, 7.65. The trimethyl ester of the maleic acid adduct of 3(β)-acetoxy-9,11-oxidobisnor-5,7-choladienic acid (VI) was prepared by treating the acetoxytrimethyl ester (V) with monoperphthalic acid. It was crystallized from ether, m.p. 208–209.5°. *Anal.* Calcd. for $C_{31}H_{42}O_9$: C, 66.64; H, 7.58. Found: C, 66.76; H, 7.64.

The 9,11-oxido compound was also prepared from the methyl ester of I by perphthalic acid treatment and had a melting point of 263–265° (block), which is in fair agreement with that reported for the methyl ester of II by Bergmann and Stevens.[1]

Details of this work, together with further conversions of compound I, will be published at a later date.

RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN
ROBERT H. LEVIN
MILDRED M. WESNER
ELIZABETH M. MEINZER

RECEIVED JUNE 18, 1948

DEGRADATIVE STUDIES ON STREPTOMYCIN

Sir:

Degradation of dihydrostreptomycin with barium hydroxide under conditions which convert streptidine to streptamine[1] yielded an amorphous, antibiotically inactive product containing barium chloride. This substance was acetylated with pyridine and acetic anhydride to a crystalline compound (I), m. p. 261.5–262.5°, $[\alpha]^{23}D$ −84° (*c* 1, water).

Anal. Calcd. for $C_{16}H_{24}O_{12}N_3(CH_3C)(COCH_3)_{10}$: C, 50.92; H, 6.25; N, 4.57; O-acetyl, 7.61 cc. of 0.1 *N* NaOH per 100 mg. CH_3-C, 32.3: mol. wt., 919.9. Found: C, 50.64; H, 6.17; N, 4.47; O-acetyl,[2] 7.37 cc.; CH_3-C,[3] 32.3; mol. wt., 920 (Rast).

Methanolysis of I with subsequent reacetylation yielded hexaacetylstreptamine,[1,4] transition point[1] 250°, m. p. 341–345°, N, 6.61% (calcd. 6.50), and methyl pentaacetyldihydro-α-L-streptobiosamide,[5–8] m. p. 194–195°, unchanged on admixture with a specimen prepared from dihydrostreptomycin trihydrochloride, $[\alpha]^{23}D$ −120° (*c* 0.5, chloroform). I is designated decaacetyldideguanyldihydrostreptomycin. It was found to be readily soluble in methanol, water and hot ethanol, sparingly so in chloroform, ethyl acetate and ethanol, and insoluble in benzene and ethyl ether.

Aqueous solutions of N,N,N-tetraacetyldideguanyldihydrostreptomycin (II), N^1,N^3-diacetylstreptamine (III) and N-acetyldihydro-α-L-streptobiosaminide (IV) were prepared by partial deacetylation of the aforementioned acetyl derivatives with 0.05 *N* sodium hydroxide in water–dioxane. These N-acetates were subjected to oxidation with a large excess of buffered periodate at *p*H 4.9 and 20.0° and showed the following

(1) R. L. Peck, C. E. Hoffhine, Jr., Elizabeth W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

(2) M. L. Wolfrom, M. Konigsberg and S. Soltzberg, *ibid.*, **58**, 490 (1936).

(3) R. U. Lemieux and C. B. Purves, *Can. J. Research*, **B25**, 485 (1947).

(4) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, J. S. Meek, P. S. Skell, W. A. Strong, J. T. Alberi, Q. R. Bartz, S. B. Binkley, H. M. Crooks, I. R. Hooper and Mildred C. Rebstock, *Science*, **103**, 53 (1946).

(5) Q. R. Bartz, J. Controulis, H. M. Crooks, Jr., and Mildred C. Rebstock, *ibid.*, 2163 (1946).

(6) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn and K. Folkers, THIS JOURNAL, **68**, 2557 (1946).

(7) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, *ibid.*, **68**, 2120 (1946); **69**, 1052 (1947).

(8) J. Fried and O. Wintersteiner, *ibid.*, **69**, 79 (1947).

oxidant consumption (in moles per mole of compound) at 120, 240 and 550 minutes, respectively: II, 2.55, 3.2, 4.0; III, 2.0, 2.4, 3.0; IV, 1.1, 1.6, 2.0. These data prove the presence in II of an α-glycol which is not in III, and this α-glycol is present in the streptamine moiety of II. The presence of such a glycol group indicates that streptobiosamine is attached at C4 of streptidine, thus confirming the results of Folkers and co-workers.[9]

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY M. L. WOLFROM
COLUMBUS, OHIO W. J. POLGLASE[10]

RECEIVED JULY 26, 1948

(9) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., Elizabeth W. Peel and K. Folkers, THIS JOURNAL., **69**, 1234 (1947).

(10) Bristol Laboratories Research Fellow of the Ohio State University Research Foundation (Project 224).

NEW BOOK

The Chemistry of the Carbon Compounds. BY VICTOR VON RICHTER. Edited by the late Professor Richard Anschütz. Vol. IV. "The Heterocyclic Compounds," By F. Reindel (translated by M. F. Darken) and "Organic Free Radicals" by Ludwig Anschütz (translated by A. J. Mee). Newly translated from the Twelfth German Edition. Elsevier Publishing Co., Inc., 215 Fourth Ave., New York 3, N. Y., 1947. xv + 498 pp. 14.5 × 22.5 cm. Price, $12.00.

This volume is a literal translation of the sections on Heterocyclic Compounds and Free Radicals in the twelfth German edition of this celebrated treatise. The appearance of Volume IV makes the entire twelfth edition available in English. Users will find the new volume to be a concise and, except for the more recent work, a comprehensive guide to the literature of the subjects treated.

REYNOLD C. FUSON

BOOKS RECEIVED

June 10, 1948—July 10, 1946

RALPH M. EVANS. "An Introduction to Color." John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y. 1948. 340 pp. $6.00.

KENNETH A. KOBE. "Inorganic Process Industries." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 1948. 371 pp. $6.00.

F. A. KROEGER. "Some Aspects of the Luminescence of Solids." Elsevier Publishing Company, Inc., 215 Fourth Avenue, New York 3, N. Y. 1948. 310 pp. $5.50.

ROBERT J. MCILROY. "The Chemistry of the Polysaccharides." Longmans, Green and Co., Inc., 55 Fifth Avenue, New York, N. Y. 1948. 118 pp. $2.50.

FRANCIS J. MURRAY. "The Theory of Mathematical Machines." Ring's Crown Press, New York, N. Y. 1948. 139 pp. $3.00.

F. F. NORD. "Advances in Enzymology and Related Subjects of Biochemistry. Volume VIII." Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, N. Y. 1948. 538 pp. $8.00.

W. W. PIGMAN AND R. M. GOEPP, JR. "Chemistry of the Carbohydrates". Academic Press, Inc., Publishers, 125 East 23rd Street, New York, N. Y. 1948. 748 pp. $10.80.

W. A. WATERS. "The Chemistry of Free Radicals." Oxford University Press. 114 Fifth Avenue, New York 11, N. Y. 1948. 295 pp. $6.50.

PHILIP W. WEST. "Calculations of Quantitative Analysis." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. Copyright 1947 and 1948. 162 pp. $2.75.